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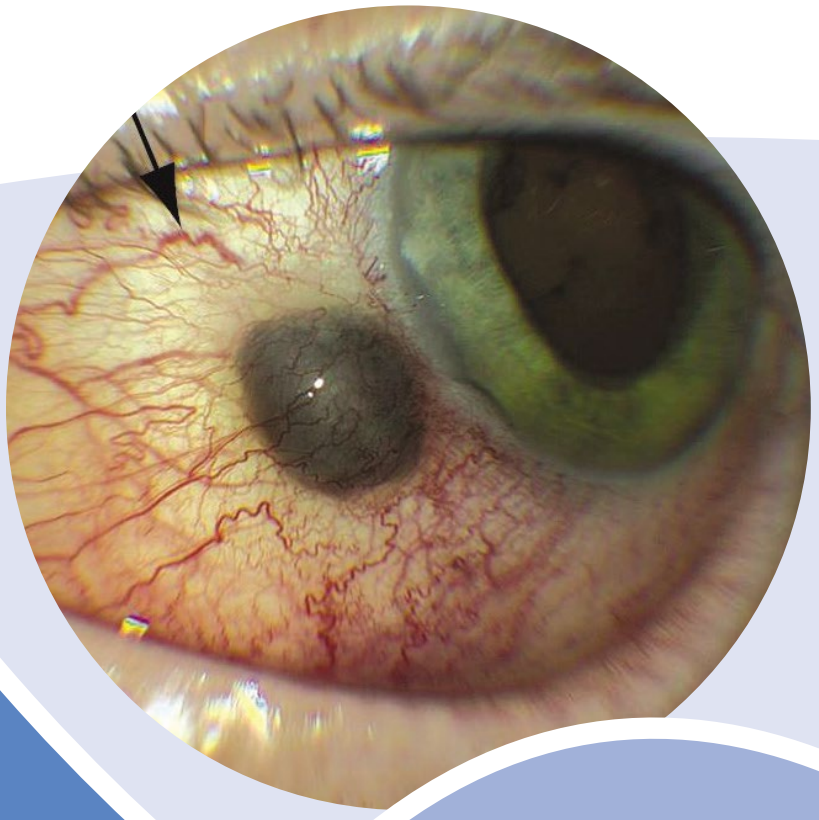

Ocular Oncology and Pathology 2023

Myth or Reality? Wide-Opening Breakthroughs in Ophthalmic Oncology and Pathology

Subspecialty Day | AAO 2023

San Francisco | Nov 3

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Ocular Oncology and Pathology 2023

Myth or Reality? Wide-Opening Breakthroughs in Ophthalmic Oncology and Pathology

Program Directors
Claudia Maria Prospero Ponce MD and Miguel A Materin MD

In conjunction with the American Association of Ophthalmic Oncologists and Pathologists

Moscone Center
San Francisco, California
Friday, Nov. 3, 2023

Presented by:
The American Academy of Ophthalmology

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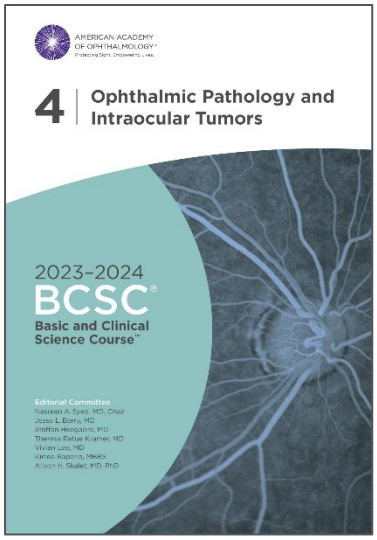

Covering all subspecialties, the BCSC books are an invaluable resource not just for residents but also for practicing ophthalmologists.

The BCSC books are authored and revised by expert ophthalmic subspecialists, ensuring that the information presented is accurate, up-to-date, and authoritative. Please join us in thanking these volunteers for their hard work and commitment to education.

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Minneapolis, Minnesota

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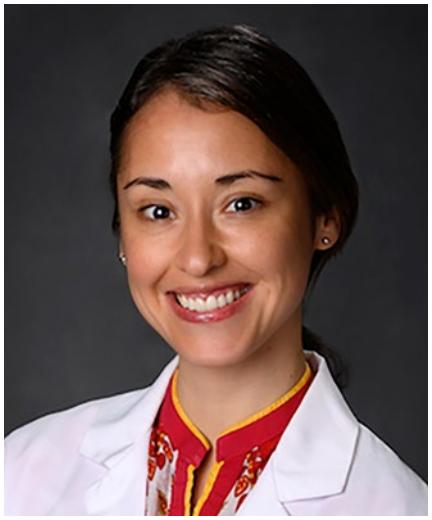
Ocular Oncology and Pathology Subspecialty Day 2023 Program Planning Group

On behalf of the American Academy of Ophthalmology and the American Association of Ophthalmic Oncologists and Pathologists (AAOOP), it is our pleasure to welcome you to San Francisco and **Ocular Oncology and Pathology 2023: Myth or Reality? Wide-Opening Breakthroughs in Ophthalmic Oncology and Pathology.**



Claudia Maria Prospero Ponce MD
Program Director

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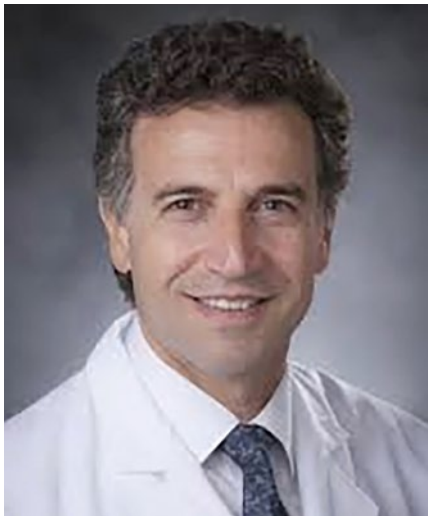

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Program Director

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Carl Zeiss Meditec: L
Castle Biosciences, Inc.: C
Ideaya Biosciences: C

Program Planning Group

Matthew W Wilson MD
Immunocore: C

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Kiora: US

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Ocular Oncology and Pathology 2023 Contents

CME Credit

The Academy's CME Mission Statement

The purpose of the American Academy of Ophthalmology's Continuing Medical Education (CME) program is to present ophthalmologists with the highest quality lifelong learning opportunities that promote improvement and change in physician practices, performance, or competence, thus enabling such physicians to maintain or improve the competence and professional performance needed to provide the best possible eye care for their patients.

Ocular Oncology and Pathology Subspecialty Day 2023 Learning Objectives

Upon completion of this activity, participants should be able to:

- Identify clinical and pathologic features of certain tumors, such as uveal melanoma, retinoblastoma, and lymphoma
- Explain current therapeutic options, including new areas of individualized targeted therapy of certain ocular tumors
- Recognize advances in solid tissue and liquid biopsies and ocular pathology
- Determine when a patient should be referred to an ocular oncology center and when to consult an ocular pathologist
- Recognize the value of diversity, equity, and inclusion in the practice of ophthalmic pathology and oncology

Ocular Oncology and Pathology Subspecialty Day 2023 Target Audience

The intended target audience for this program is practicing ophthalmologists, ocular pathologists, ocular oncologists, residents in training, and fellows.

Teaching at a Live Activity

Teaching an instruction course or delivering a scientific paper or poster is not an *AMA PRA Category 1 Credit*™ activity and should not be included when calculating your total *AMA PRA Category 1 Credits*™. Presenters may claim *AMA PRA Category 1 Credits*™ through the American Medical Association. To obtain an application form, please contact the AMA at www.ama-assn.org.

Scientific Integrity and Disclosure of Conflicts of Interest

The American Academy of Ophthalmology is committed to ensuring that all CME information is based on the application of research findings and the implementation of evidence-based medicine. The Academy seeks to promote balance, objectivity, and absence of commercial bias in its content. All persons in a position to control the content of this activity must disclose any and all financial interests. The Academy has mechanisms in place to resolve all conflicts of interest prior to an educational activity being delivered to the learners.

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Subspecialty Day 2023 CME Credit

The American Academy of Ophthalmology is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

Friday Subspecialty Day Activity: Glaucoma, Neuro-Ophthalmology, Ocular Oncology and Pathology, Refractive Surgery, Retina (Day 1)

The Academy designates this Other (blended live and enduring material) activity for a maximum of *12 AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Saturday Subspecialty Day Activity: Cornea, Oculofacial Plastic Surgery, and Retina (Day 2)

The Academy designates this Other (blended live and enduring material) activity for a maximum of *12 AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physicians registered as In Person and Virtual are eligible to claim the above CME credit.

Attendance Verification for CME Reporting

Before processing your requests for CME credit, the Academy must verify your attendance at AAO 2023 and/or Subspecialty Day. Badges are no longer mailed before the meeting. Picking up your badge onsite will verify your attendance.

How to Claim CME

Attendees can claim credits online.

For AAO 2023, you can claim CME credit multiple times, up to the 50-credit maximum, through March 29, 2024. You can claim some in 2023 and some in 2024, or all in the same year.

For 2023 Subspecialty Day, you can claim CME credit multiple times, up to the 12-credit maximum per day, through

March 29, 2024. You can claim some in 2023 and some in 2024, or all in the same year.

You do not need to track which sessions you attend, just the total number of hours you spend in sessions for each claim.

You can view content in the virtual meeting through March 1, 2024.

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CME transcripts that include AAOE Half-Day Coding Sessions, Subspecialty Day, and/or AAO 2023 credits will be available to Academy members through the Academy's CME Central web page.

The Academy transcript cannot list individual course attendance. It will list only the overall credits claimed for educational activities at AAOE Half-Day Coding Sessions, Subspecialty Day, and/or AAO 2023.

Nonmembers

The Academy provides nonmembers with verification of credits earned and reported for a single Academy-sponsored CME activity.

Proof of Attendance

You will be able to obtain a CME credit reporting/proof-of-attendance letter for reimbursement or hospital privileges, or for nonmembers who need it to report CME credit:

Academy Members

When you claim CME credits and complete the evaluation, you will be able to print a certificate/proof-of-attendance letter from your transcript page. Your certificate will also be emailed to you.

Nonmembers

When you claim CME credits and complete the evaluation, a new browser window will open with a PDF of your certificate. Please disable your pop-up blocker. Your certificate will also be emailed to you.

CME Questions

Send your questions about CME credit reporting to cme@aao.org. For Continuing Certification questions, contact the American Board of Ophthalmology at MOC@abpo.org.

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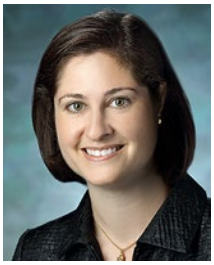

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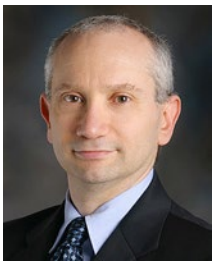

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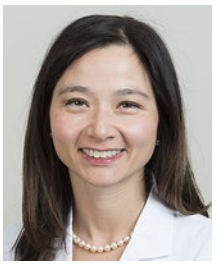

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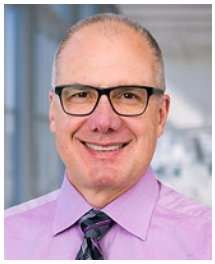

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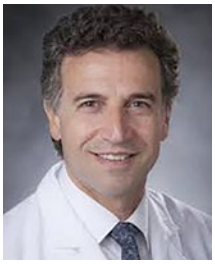

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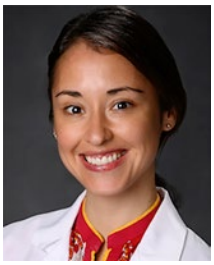

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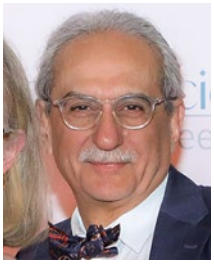

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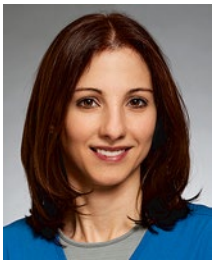

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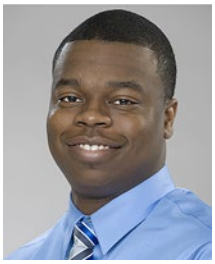


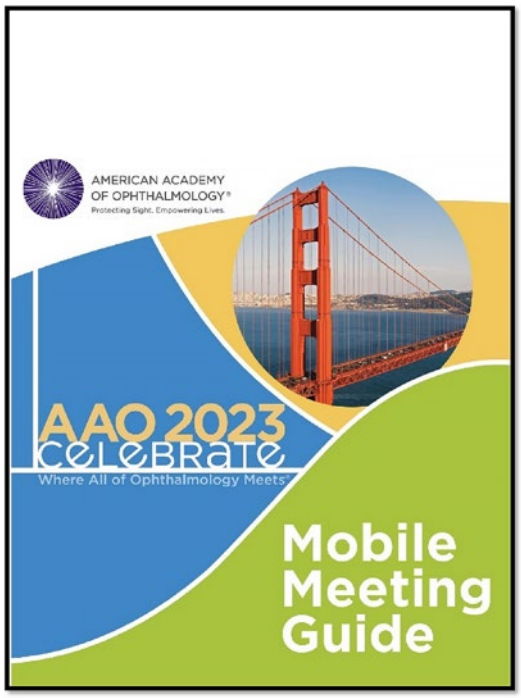
Basil K Williams MD
Miami, FL

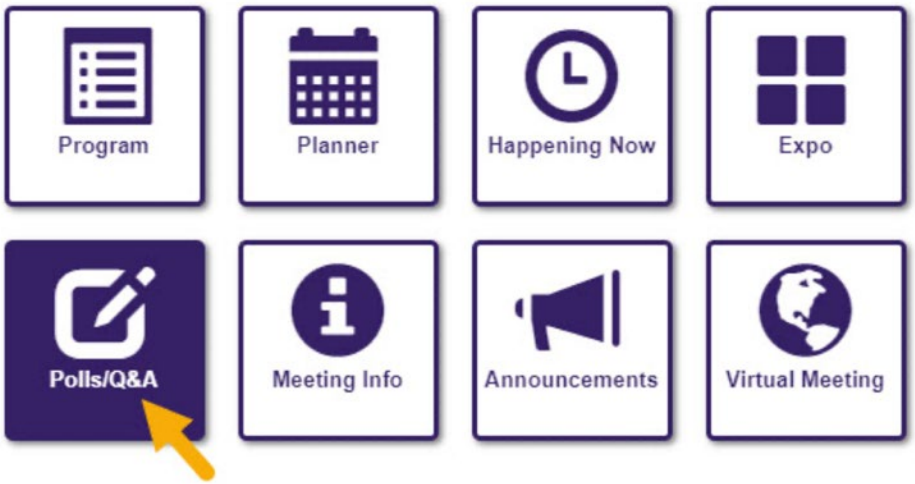
Matthew W Wilson MD
Memphis, TN

Ask a Question During the Meeting Using the Mobile Meeting Guide

To ask the moderator a question during the meeting, follow the directions below.

- Access at www.aao.org/mobile
- Select "Polls/Q&A"
- Select "Current Session"
- Select "Interact with this session (live)" to open a new window
- Choose "Ask a Question"





Ocular Oncology and Pathology Subspeciality Day 2023

Myth or Reality? Wide-Opening Breakthroughs in Ophthalmic Oncology and Pathology

FRIDAY, NOV. 3, 2023

8:00 AM	Welcome and Introductions	Claudia Maria Prospero Ponce MD Miguel A Materin MD	

Section I: Loch Ness Monster's Deep-Diving Into Liquid . . . Biopsies

Moderators: Patricia Chévez-Barrios MD and Jose S Pulido MD MS

8:05 AM	Science Behind Liquid Biopsy: Molecular Background	Debbie Rigney Walley MD	1
8:15 AM	Aqueous Humor and Vitreous Needle Biopsy Technique and Care	Tara A McCannel MD	2
8:25 AM	Retinoblastoma Liquid Biopsies: Where Are We Now?	Jesse L Berry MD	3
8:35 AM	Uveal Melanoma Liquid Biopsies: Are We Going Anywhere?	Amy C Schefler MD	4
8:45 AM	Liquid Biopsy Is Positive: Yes, It Is Vitreoretinal Lymphoma	Rajesh C Rao MD	6
8:55 AM	Liquid Biopsy Is Positive: No, It Is Not Vitreoretinal Lymphoma	John A Gonzales MD	7

Section II: Bigfoot and Its Footprints in Ocular Melanoma Diagnosis, Prognosis, and Treatments

Moderator: Prithvi Mruthyunjaya MD

9:05 AM	PRAME and Other Markers	J William Harbour MD	8
9:15 AM	Who Should Be Tested For HLA-A*02:01?	Marlana Orloff MD	9
9:25 AM	AU-011: What Have We Learned?	Brian P Marr MD	10
9:35 AM	Unresectable/Metastatic Uveal Melanoma: Treatments on the Horizon	Marlana Orloff MD	11
9:45 AM	Prospective Trial For Radiation Retinopathy	Arun D Singh MD	12
9:55 AM	Artificial Intelligence in Uveal Melanoma	Andrew W Stacey MD	16
10:05 AM	Roundtable Discussion: When, Who, and How Moderator: Prithvi Mruthyunjaya MD Panelists: J William Harbour MD, Brian P Marr MD, Marlana Orloff MD, Arun D Singh MD, and Andrew W Stacey MD		
10:20 AM	REFRESHMENT BREAK		

Section III: Giant Cyclops' Thunderstruck in Earth—Retinoblastoma Revamped

Moderator: Dan S Gombos MD

10:50 AM	What's New in Retinoblastoma Diagnoses and Treatment in the World?	Swathi Kaliki MD	17
11:00 AM	Children's Oncology Group: Current Treatment Trends	Dan S Gombos MD	18
11:10 AM	Molecular and Pathology Testing in Retinoblastoma: Why, When, and How to Test?	Patricia Chévez-Barrios MD	19
11:20 AM	Retinoblastoma Achievements Across Countries: Cybersight	Matthew W Wilson MD	20
11:30 AM	Retinoblastoma Achievements Across Countries: International Retinoblastoma Consortium	Dan S Gombos MD	21

11:40 AM	Retinoblastoma Overview in Mexico	David Arturo Ancona Lezama MD	22
11:50 AM	Is Intra-arterial Chemotherapy for Everyone? Part 1	Jasmine H Francis MD	26
12:00 PM	Is Intra-arterial Chemotherapy for Everyone? Part 2	Carol L Shields MD	27
12:10 PM	Roundtable Discussion Moderator: Dan S Gombos MD Panelists: David Arturo Ancona Lezama MD, Patricia Chévez-Barrios MD, Jasmine H Francis MD, Swathi Kaliki MD, Amish C Shah MD, Carol L Shields MD, and Matthew W Wilson MD		
12:25 PM	LUNCH and American Association of Ophthalmic Oncologists and Pathologists Business Meeting		

Section IV: Walking Over a Flat Earth—A Jump Toward Diversity, Equity, and Inclusion (DEI)

Moderator: Basil K Williams MD

1:45 PM	Baseline Comprehension and Verbiage: DEI Background	Ambar Faridi MD	28
1:53 PM	Bias: Explicit vs. Implicit (Tests Available)	César A Briceño MD	29
2:01 PM	Oculoplastics-Ocular Surgery and DEI	Nikisha Q Richards MD FACS	30
2:09 PM	Women in Ocular Oncology and Pathology	Diva R Salomao MD	31
2:17 PM	DEI's Current Application to Ocular Oncology	Basil K Williams MD	32
2:25 PM	DEI Wave: Reaching a Balance	Miguel A Materin MD	33
2:33 PM	A Look Back at American Association of Ophthalmic Oncologists and Pathologists Membership Representation: Ten-Year Projection	Patricia Chévez-Barrios MD and Claudia Maria Prospero Ponce MD	34
2:41 PM	United for Sight: A Vision for Effective Advocacy	Alison H Skalet MD PhD	35
2:46 PM	REFRESHMENT BREAK		

Section V: Kraken's Tentacles and a Spun Toward Other Tumors!

Moderator: Hans E Grossniklaus MD

3:11 PM	Ocular Surface Tumors and Advances	Carol L Karp MD	37
3:21 PM	Conjunctival Carcinomas With Goblet Cells, "Mucoepidermoid," "Adenosquamous," "Squamous," and "Adenocarcinoma": WHO Eye5 Update	Paul J Bryar MD	38
3:31 PM	Indeterminate Melanocytic Conjunctival Lesions: A Myth and Reality	Hans E Grossniklaus MD	40
3:41 PM	Conjunctival Melanocytic Intraepithelial Lesions: WHO Eye5 Update	Tatyana Milman MD	41
3:51 PM	PRAME Expression of Conjunctival Melanocytic Lesions: Is It a Magic Bullet?	Maria Miguelina de la Garza MD	43
4:01 PM	Conjunctival Melanoma Mutations and Significance in Prognosis	Mary E Aronow MD	44
4:11 PM	Uveal Metastasis: Current Approach	Arpita Suketu Maniar MBBS	45
4:21 PM	Gene Sequencing for Orbital Sarcomas: Is It Necessary?	Mukul K Divatia MBBS	46
4:31 PM	Neurogenic Orbital Tumors: Advances in Diagnoses	Fausto J Rodriguez MD	47
4:41 PM	Neurogenic Orbital Tumors: Advances in Treatments	Hakan Demirci MD	48
4:51 PM	Can Radiation Be Delivered in Less Than 4 Days?	Miguel A Materin MD	49
5:01 PM	Closing Remarks	Claudia Maria Prospero Ponce MD Miguel A Materin MD	
5:02 PM	Adjourn		

Science Behind Liquid Biopsy: Molecular Background

Debbie Rigney Walley MD

I. Circulating Cell-Free DNA (ccfDNA) Biology

A. Cell-free DNA (cfDNA) is genetic material within the body but outside of viable cells.

B. ccfDNA is cfDNA that is in the blood.

C. Half life of cfDNA is approximately 16 minutes to 2 hours.

D. cfDNA is thought to arise from necrotic or apoptotic cells.

E. cfDNA fragment length (~300-450 bp) is shorter than the fragment length of DNA extracted from tissue or whole blood.

F. Plasma levels of ccfDNA range from 10 to 100 ng/mL.

II. Circulating Tumor DNA (ctDNA)

A. ctDNA fragment length is ~150 base pairs.

B. ctDNA makes up 0.1%-10% of ccfDNA.

C. ctDNA levels vary depending on tumor burden, stage, and treatment status.

III. Liquid Biopsy Testing

A. Plasma is the preferred specimen type.

B. cfDNA is isolated and quantified; purity is assessed.

C. Sequencing methods

1. Polymerase chain reaction (PCR) based: digital droplet PCR, beads, emulsion, amplification, magnetics (BEAM), PARE, single base pair extension

a. Focused, tumor specific panel

b. Detects known gene rearrangements or gene mutations in "hot spot" regions

c. More sensitive than sequencing-based methods

d. Turnaround time: 1-3 days

2. Sequencing based: next-generation sequencing (NGS), whole exome sequencing (WES), whole-genome sequencing (WGS)

a. Large, tumor agnostic panels

b. Can detect copy number variants, translocations, point mutations, and chromosomal abnormalities depending on assay design

c. Requires bioinformatics support

d. More "discoverability"

e. Turnaround time: 1-2 weeks

D. Concordance of liquid biopsy with tissue

1. Concordance varies with tumor type.

2. In most cases tissue biopsy is more sensitive, but there are reports where liquid biopsy detects variants not identified on tissue.

IV. Clinical Use

A. Tissue biopsy is the gold standard but may not be an option.

B. Liquid biopsy is complementary to tissue biopsy—monitor cancer progression.

C. FDA-approved commercial liquid biopsy testing for solid tumors

1. Companion diagnostic: Identifies genetic variants with targeted therapy implications

2. Tumor profiling: Identifies cancer-related genetic variants

D. Sensitivity and negative predictive values vary depending on tumor type and genetic variant.

V. Liquid Biopsy of Ocular Tumors

Studies are being done but there are no concrete guidelines.

VI. Liquid Biopsy on Ocular Fluids

Research is under way.

Selected Readings

1. Decker B, Sholl LM. Cell-free DNA testing. In: Tafe LJ, Arcila ME, eds. *Genomic Medicine*. Springer; 2020:41-54.

2. FDA. Premarket Approval (PMA) for FoundationOne Liquid CDx (F1LCDx). Updated 8/21/2023. www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P190032S004.

3. Im DH, Peng C-C, Xu L, Kim ME, et al. Potential of aqueous humor as a liquid biopsy for uveal melanoma. *Int J Mol Sci*. 2022; 23(11):6226.

4. Jin E, Burnier JV. Liquid biopsy in uveal melanoma: are we there yet? *Ocul Oncol Pathol*. 2021; 7(1):1-16.

5. Lone SN, Nisar S, Masoodi T, et al. Liquid biopsy: a step closer to transform diagnosis, prognosis and future of cancer treatments. *Mol Cancer*. 2002; 21:79.

6. Martel A, Baillif S, Nahon-Esteve S, et al. Liquid biopsy for solid ophthalmic malignancies: an updated review and perspectives. *Cancers* 2020; 12(11):3284.

7. Mehrotra M, Singh RR, Loghavi S, et al. Detection of somatic mutations in cell-free DNA in plasma and correlation with overall survival in patients with solid tumors. *Oncotarget* 2018; 9:10259-10271.

Aqueous Humor and Vitreous Needle Biopsy Technique and Care

Tara A McCannel MD

I. Anterior Segment: Iris Biopsy Technique
   A. Under air for iris melanoma prognostication
   B. Use of 27-gauge instrumentation

II. Posterior Segment
   A. Transscleral approach, 30-gauge needle
   B. Vitreous needle (always in conjunction with pars plana vitrectomy): long 27-gauge under air; mainly for prognostication
   C. Vitreous cutter: under air, directly into tumor through retina

Retinoblastoma Liquid Biopsies: Where Are We Now?

Jesse Berry MD

I. Why is a liquid biopsy needed for retinoblastoma?

II. What do we know about DNA?

   A. Chromosomal alterations

   B. Mutational analysis for pathogenic variants

III. What do we know about epigenetic alterations? Methylation profiles

IV. Are there other biomarkers? Extracellular vesicles and others

V. What are the various roles of the different analytes?

   A. Blood

   B. Aqueous humor

   C. CSF

VI. This is cool, but does any of it matter?

   What current clinical tests are using liquid biopsy for retinoblastoma?

Uveal Melanoma Liquid Biopsies: Are We Going Anywhere?

Amy C Schefler MD

I. Background

II. History of Solid Tumor Biopsies for Uveal Melanoma (UM)

A. Advantages of solid tumor biopsy approach (FNAB)

1. Highly accurate and targeted, with high sensitivity and specificity and low heterogeneity when performed correctly
2. Ability to perform multiple tests on a single specimen
3. Ability to confirm tissue source with cytology and next-generation sequencing (NGS)

B. Shortcomings of solid tumor biopsy approach

1. Invasive
2. Very rare complications
   a. Vitreous hemorrhage
   b. Retinal detachment
   c. Endophthalmitis
3. It is worth noting that many potential complications (iatrogenic extraocular tumor extension, limited ability to extract quality specimen, retinal detachment) have been generally overexaggerated in the historical literature.

III. Goals of Liquid Biopsy as a Screening Tool

A. To distinguish patients at low risk from metastatic disease from patients at high risk with high sensitivity and specificity

B. To perform testing serially over time to use as a biomarker to indicate when patients have developed preradiographic metastases

C. To enrich clinical trials with high-risk patients

D. To monitor as a response to treatment for metastatic disease

IV. Potential Liquid Biopsy Sources

A. Aqueous

1. Background: Interest has been generated by previous work in retinoblastoma; however, UM is much less necrotic than retinoblastoma and less likely to generate circulating tumor DNA (ctDNA) in the anterior chamber consistently
2. Advantages
   a. Easily accessible and noninvasive, potentially even in clinic
   b. Repeatable
3. Disadvantages
4. Previous published literature: pilot studies examining differentially expressed proteins in aqueous, cytokine expression in aqueous

B. Blood

1. Background: Types
   a. Circulating tumor cells (CTCs): Cells released from the primary tumor believed to contribute to metastatic disease by seeding distant sites
   b. ctDNA: small fragments of tumor DNA released by tumor cells that enter the circulation
   c. Cell-free microRNA (miRNA): small noncoding RNAs, about 22 nucleotides, modify gene expression
   d. Tumor-derived extracellular vesicles (EVs) including exosomes: tiny particles with a lipid bilayer membrane, act as messengers between cells; thought to play a key role in metastatic tumor dissemination and progression
2. Advantages
   a. Easily accessible and noninvasive, potentially even in clinic
   b. Repeatable
   c. No complications from extraction technique expected
3. Disadvantages, CTCs
   a. CTCs are rare in peripheral blood, and concentration techniques are necessary: reverse transcription polymerase chain reaction (RT-PCR), size filtration, immunodetection
   b. Prognostic value unclear: insufficient accuracy and reproducibility
   c. Previous published literature: many studies from early 1990s to the present; very heterogeneous; varying methodologies make it very difficult to compare studies

4. Disadvantages, ctDNA
    a. Presence of large amount of normal nontumor derived cell-free DNA makes detection of ctDNA difficult.
    b. Heterogeneous: ctDNA with initiating mutations (eg, GNAQ, GNA11) can also be present in patients with nevi.
5. Disadvantages, miRNA: Must be detected by RT-PCR, microarray analysis, or deep sequencing
6. Disadvantages, EVs
    a. Not enough in-depth studies in UM
    b. Highly variable in reproducibility

C. Vitreous
1. Background
2. Advantages
    a. Large volume of fluid to draw from
    b. Repeatable
3. Disadvantages
    a. Requires invasive surgery
    b. Technically just as difficult/complex as a tumor biopsy
4. Previous published literature: Few small pilot studies examining differentially expressed proteins

D. Others: urine, CSF, ascites, saliva, tears

V. Conclusions

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Liquid Biopsy Is Positive: Yes, It Is Vitreoretinal Lymphoma

Rajesh C Rao MD

NOTES

Liquid Biopsy Is Positive: No, It's *Not* Vitreoretinal Lymphoma

John Gonzales MD

I. Introduction

Clinicians base their suspicion for vitreoretinal lymphoma (VRL) on clinical signs and imaging studies. However, definitive diagnosis has relied on identifying lymphomatous cells from a liquid biopsy. Alternatively, additional assays may be diagnostic, complementary, or in some instances, highly suggestive of a lymphoproliferative process. However, as with any test, clinical correlation is required and a positive test in and of itself does not necessarily diagnose VRL.

II. Tests Used to Diagnose Lymphoma/Pitfalls

A. Cytopathology[1,2]

1. Errors in interpretation
2. Cytopathology combined with immunohistochemistry (immunohistochemical immunophenotyping)[3]

B. Flow cytometry (for cell counting/sorting and immunophenotyping),[4,5] B or T cells, light chain restriction

C. Directed polymerase chain reaction (PCR) for IgH or TCR gene rearrangement[6-8]

D. Directed PCR for *MYD88* L265P, interleukin (IL) 10:IL6 > 1[9,10]

III. Teaching Points

A Clinical correlation is always required.

B. Rule out infection and noninfectious/autoimmune/autoinflammatory uveitis.

C. Combining tests to identify lymphoproliferative process may be necessary.

D. Some tests used alone may be insufficient to begin treatment.

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PRAME and Other Markers

J William Harbour MD

I. Introduction

A. Uveal melanoma can be divided into low-risk and high-risk groups based on the presence of RNA and DNA-based biomarkers within the tumor.

B. Tumor biomarkers are now used in routine clinical care of patients with uveal melanoma for diagnostic confirmation, prognostication, personalized surveillance, and clinical trial enrollment.

II. Gene Expression Profile and PRAME

A. Using validated 15-gene RNA-based gene expression profiling (GEP), uveal melanomas can be divided into 2 main subgroups associated with metastatic risk: class 1 (low risk) and class 2 (high risk).

B. Uveal melanomas can be further subdivided by RNA expression of the cancer-testis antigen PRAME (negative or positive) into four prognostically relevant subgroups: class 1/PRAME–, class 1/PRAME+, class 2/PRAME–, and class 2/PRAME+.

C. PRAME is normally expressed only in the testis during meiotic crossing over, and its aberrant expression in uveal melanoma leads to DNA damage and chromosomal instability that may drive further tumor evolution.

D. Specific drugs have now been developed and are in clinical trials for targeting uveal melanomas and other cancer types that express PRAME; thus, not only is detecting PRAME in uveal melanomas prognostically important but it may also determine treatment choice.

III. Driver Mutations

There are 7 canonical driver mutations in uveal melanoma that represent clinically useful biomarkers:

A. Initiating mutations: GNAQ, GNA11, CYSLTR2, and PLCB4.

These are not prognostically significant, but since 1 of these 4 genes is mutated in over 95% of uveal melanomas and nevi, and since these mutations are uncommon in other cancer types, their presence can serve as a confirmation that a uveal tumor is indeed of melanocytic origin.

B. Prognostic mutations: BAP1, SF3B1, and EIF1AX

Mutations in BAP1, SF3B1, and EIF1AX occur in a nearly mutually exclusive fashion and are associated with high, intermediate, and low metastatic risk, respectively. These mutations cannot replace the accuracy of the GEP/PRAME classification, as they are not always present and cannot always be detected. However, they may guide the choice of treatment, as an increasing number of clinical trials require that 1 of these mutations be present.

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Who Should Be Tested For HLA-A*02:01?

Marlana Orloff MD

NOTES

AU-011: What Have We Learned?

Brian P Marr MD

NOTES

Unresectable/Metastatic Uveal Melanoma: Treatments on the Horizon

Marlana Orloff MD

I. Summary of Currently Approved and Standard of Care Treatment Approaches
   A. Tebentafusp
   B. Immune checkpoint inhibitors
   C. Liver-directed therapies
II. Clinical Trials
   A. Immunotherapies
      1. Other T-cell receptor targets (ie, PRAME)
      2. Adoptive T-cell therapy
   B. Targeted therapy
      1. Protein kinase C + MEK
      2. Other targets (ie, focal adhesion kinase, vascular endothelial growth factor, histone deacetylase, receptor tyrosine kinase, poly ADP-ribose polymerase, phosphatidylinositol 3-kinase, Brahma)
   C. Liver-directed therapy
      1. Percutaneous hepatic perfusion (PHP)
   D. Combination approaches
      1. SD-101 + immune checkpoint inhibitors
      2. RP2/3 + immune checkpoint inhibitors
      3. PHP + immune checkpoint inhibitors
      4. Radiation + …
   E. Adjuvant/neoadjuvant strategies

Prospective Trial for Radiation Retinopathy

DRCR Retina Network

Arun D Singh MD

A randomized clinical trial evaluating intravitreal faricimab (6.0 mg) injections or fluocinolone acetonide (0.19 mg) intravitreal implants vs. observation for prevention of visual acuity loss due to radiation retinopathy (Protocol AL). Sponsor: Jaeb Center for Health Research (JCHR) Version 4.0.

Table 1. Protocol Summary

Item	Description
Title	An RCT evaluating intravitreal faricimab (6.0 mg) injections or FAc, 0.19 mg) intravitreal implants vs. observation for prevention of VA loss due to radiation retinopathy
Précis	This RCT will evaluate the effect of intravitreal faricimab or FAc intravitreal implant compared with observation on long-term VA following treatment of choroidal melanoma with iodine (^{125}I) plaque brachytherapy.
Investigational drugs	Faricimab (6.0 mg) intravitreal injection (Vabysmo, Genentech Inc.) FAc (0.19 mg) intravitreal implant (Iluvien, Alimera Sciences Inc.)
Objectives	Primary • To compare long-term VA outcomes in eyes that receive repeated treatment with faricimab or FAc intravitreal implants with those observed initially and treated only if ME develops Secondary • To determine whether repeated treatment with faricimab or FAc intravitreal implants vs. observation can prevent or alter the course of ME from radiation retinopathy • To evaluate the natural history of radiation retinopathy with multimodal imaging including widefield color photographs, widefield fluorescein angiography, and OCT angiography
Study design	Randomized, controlled, multicenter clinical trial
Number of sites	Approximately 30
Endpoints	Primary efficacy outcomes • Change in VA from baseline at 3 years • Loss of 15 or more letters of VA from baseline at 3 years Key secondary outcome • Development of ME on OCT, assessed beginning at 6 months following randomization Additional secondary outcomes • Development of neovascularization • Development of radiation optic neuropathy • Development of radiation retinopathy • Development of retinal ischemia • Change in VA from baseline area under the curve • Loss of 15 or more letters of VA over 3 years (time-to-event)

(table continues on next page)

Table 1. Protocol Summary (continued)

Item	Description
Population	Key inclusion criteria • Primary uveal melanoma (excluding iris melanoma) receiving primary treatment with plaque brachytherapy • Absence of unrelated cause of visual loss • Baseline VA ≥34 letters (20/200 Snellen equivalent or better) • Posterior tumor margin >0 mm from the center of the macula (ie, tumor is *not* under the geometric center of the fovea) • Posterior tumor margin >0 mm from the closest disc margin (ie, tumor is not touching the edge of the optic disc) • Calculated total dose to center of the macula ≥30 Gy Key exclusion criteria • Opaque media • Inability to undergo fluorescein angiography • Less than 18 years of age • Prior vitrectomy • IOP ≥25 mmHg or history of steroid-induced IOP elevation that required treatment at baseline • IOP ≥25 mmHg at randomization or increase in IOP ≥8 mmHg from baseline to randomization (following steroid challenge)
Sample size	600
Phase	Phase 3 trial
Treatment groups	Random assignment (1:1:1) to intravitreal faricimab (every 3 months), FAc intravitreal implants (randomization and 24 months), or observation
Participant duration	3 years of follow-up for each randomized participant
Study duration (planned)	Approximately 5.5 years from first enrollment until last participant visit
Protocol overview/synopsis	1. Informed consent will be obtained. 2. Study eligibility will be assessed, and baseline procedures will be completed. 3. Eligible participants will proceed to standard of care treatment of the tumor (^{125}I plaque placement). At this time, participants will undergo a steroid challenge consisting of a subtenon injection of steroid plus topical steroid treatment. 4. Participants will return to clinic for a randomization visit 2-4 weeks following plaque removal. At this visit IOP will be measured, and if eligible, participants will be randomly assigned 1:1:1 to faricimab, FAc intravitreal implants, or observation. If randomized to faricimab or FAc implant, the participant will receive their first study treatment. If randomized to the FAc implant, participants will have a 4-week postimplant IOP check. 5. Participants will return for follow-up visits every 3 months for 3 years. Preventive treatment will be given according to their randomized treatment group. 6. Beginning at the 6-month visit, eyes in all groups will be assessed for development of ME. If criteria for development of ME are met, the eye will initiate treatment, either with faricimab or FAc, according to their treatment group.

Abbreviations: RCT, randomized clinical trial; FAc, fluocinolone acetonide; VA, visual acuity; ME, macular edema.

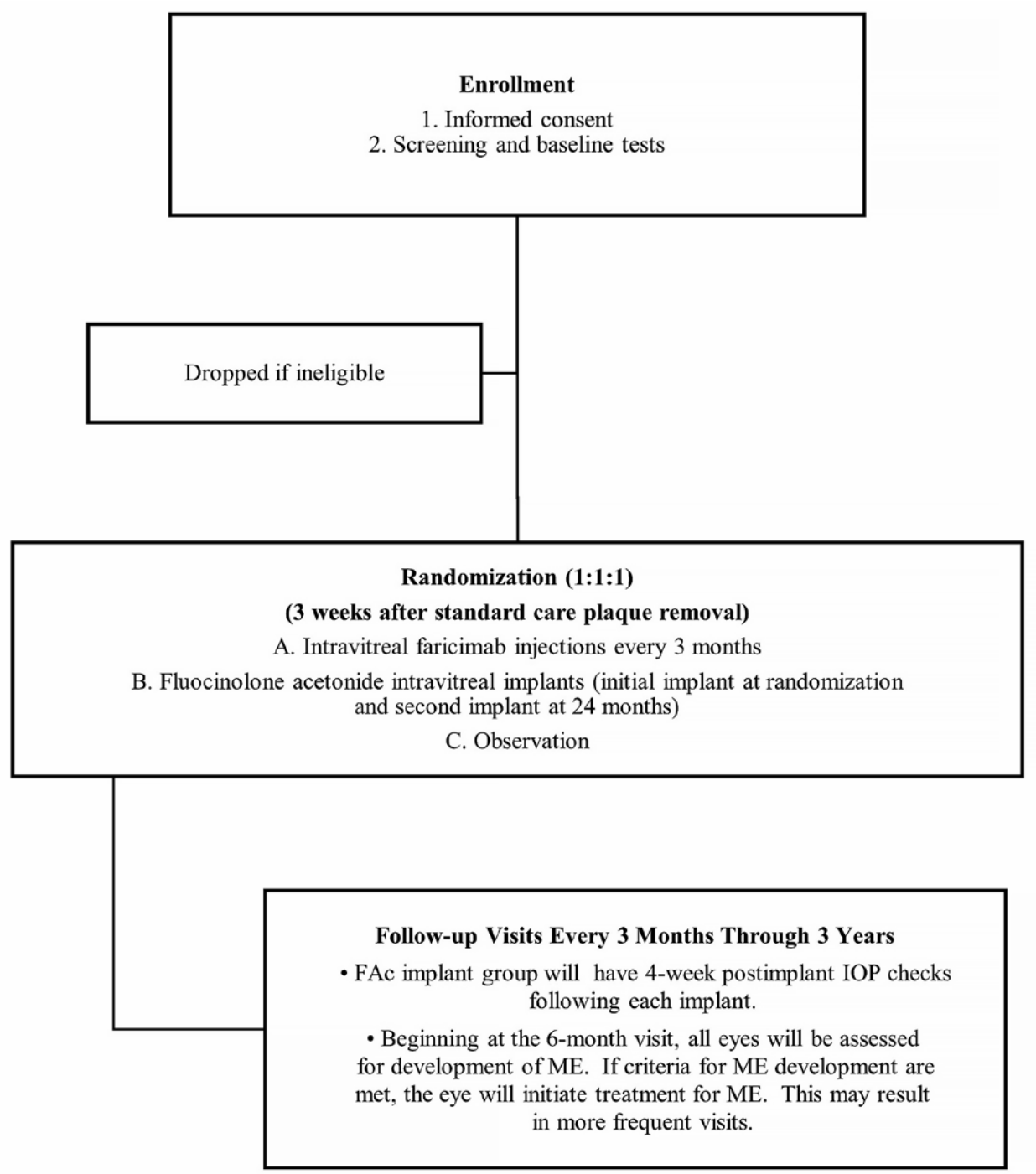

Figure 1. Schematic of study design.

Table 2. Schedule of Study Visits and Procedures

Visit	Baseline[a]	Plaque Placement (Standard of Care)	Randomization Visit	6-, 12-, 18-, 24-, 30-, 36-Month Visits	Other Study Visits (3-, 9-, 15-, 21-, 27-, 33-Month)	4-Week Postimplant IOP Check (FAc Implant Group Only)
Visit Window	Within 4 weeks prior to plaque placement	Within 4 weeks of baseline procedures	3 weeks (±1 week) after plaque removal	±12 weeks at annual visits; ±2 weeks at 6 months in between	±2 weeks	4 weeks ± 1 week post-FAc implant (following randomization and 24-month visit)
Randomization			X			
ETDRS BCVA[b]	X		X	X	X	
OCT	X		X	X	X	
Eye exam[c]	X			X	X	
IOP measurement	X		X	X	X	X
Fundus photography[d]	X			X		
Fluorescein angiography[d]	X			X		
OCT angiography[e]	X			X		
Study treatment[f]			X	X	X	
Plaque placement		X				

[a]Baseline procedures do not need to be completed on the same day provided they are completed prior to randomization and within 4 weeks prior to plaque placement.

[b]Visual acuity testing includes protocol refraction at each visit followed by electronic-ETDRS testing using the Electronic Visual Acuity Tester that has been validated against 4-meter chart ETDRS testing.

[c]Includes slit-lamp exam (including assessment of lens) and dilated ophthalmoscopy

[d]Using the widest approach available (eg, ultrawide-field imaging device)

[e]Only at sites with OCT angiography machine

[f]Study treatment will be according to treatment group: faricimab group will receive intravitreal injection every 3 months; FAc intravitreal implant group will receive an implant at randomization and 24 months; observation group will not be treated unless criteria for ME development are met. Study treatment will not be given at the final study visit (36-month visit).

Abbreviations: FAc, fluocinolone acetonide; ME, macular edema.

Artificial Intelligence in Uveal Melanoma

Andrew W Stacey MD

Introduction

Uveal melanoma (UM), the most common primary intraocular malignancy, often presents as a malignant transformation of a previously benign nevus. Patients usually present with vision symptoms, though the cancer can also be detected with routine dilated eye exam or ocular fundus photography.[1]

Though biopsy can be used in some situations, diagnosis is usually made based on clinical exam findings and clinic-based imaging modalities. The visual appearance and clinical presentation of a lesion is clinically and diagnostically relevant. Qualities within a uveal lesion increasing the risk of UM include increased thickness of the lesion, vision changes, lipofuscin formation within the tumor, and presence of subretinal fluid.

Among lesions diagnosed as UM, there are clinical findings that increase the risk that the patient will develop metastatic disease. Importantly, the thickness of the lesion has been shown to be a reliable predictor of metastatic disease, with each 1-mm increase in thickness portending a ~5% increased risk of metastases.[2] Additionally, genetic mutations within the tumor are also predictive of future metastasis. Specifically, presence of monosomy 3 and gain of chromosome 8 are both associated with increased risk of metastasis. A 15-gene expression profile from UM cells has shown to be very predictive of future metastases.[3] Although these findings are well established and easily identified by ocular oncologists, their utilization in machine learning algorithms has not been previously documented.

There are currently 2 methods for prognostication: (1) clinical staging based on size and location and (2) molecular analysis. Clinical staging can be summarized by the American Joint Commission on Cancer (AJCC) TNM (tumor, node, metastasis) staging system, information that is readily available during a routine ophthalmic examination. Molecular prognostication can be tested by various methods but requires tumor tissue, usually obtained from a fine needle aspiration. It is evident that both clinical staging and molecular prognostic studies are required to obtain the most accurate prognostic information available.[4] While AJCC staging is noninvasive, molecular prognostic information requires anesthesia, surgery, and needle aspiration, which carries some ocular risks.

Background Observations

Clinical findings in UM are the foundation for diagnosis and play an important role in disease prognosis. Yet clinical images of UM have not previously been used in artificial intelligence models for diagnosis or prognostic prediction. To date, machine learning algorithms have utilized clinical data, histopathologic information, and molecular data from biopsy to build predictive models.[5] Fundus photography and clinical imaging are routinely obtained in all patients with UM and have not been used to predict disease prognosis and mortality. If clinical images can provide prognostic information similar to what is provided by molecular prognostic testing, this would allow patients to eliminate the risk associated with surgery and biopsy.

Methods

UM is a rare disease with an incidence of approximately 5 per million. Artificial intelligence algorithms, and specifically machine learning algorithms, require many records to mature correctly. Obtaining data sufficient to perform appropriate automated algorithms on clinical images of UM requires thousands of images from thousands of patients, and a multicentered approach is necessary. Thus, an international, multicentered database was created, housed at the University of Washington. The data that are collected contain no patient identifiers and have been deemed by the University of Washington Internal Review Board to be "non-human data." Datapoints submitted include fundus photos, OCT images, ultrasound images, and fundus autofluorescence images. In addition, a small number of nonidentifiable clinical variables are also updated, including age at diagnosis, follow-up time or time to metastases, and gene expression profile result, if available.

The initial goal is to upload only images of lesions diagnosed as UM. Additional diagnoses, including nevi and nonmelanocytic lesions, will be investigated at a later date. The fundus photographs will be used to develop a training set for prognostic prediction. The Computational Ophthalmology Laboratory at the University of Washington will conduct the machine learning and prediction modelling. The images will be used to predict mortality and molecular prognosis.

Results

Currently 12 centers are submitting data from 4 countries. Over 1000 images have been uploaded. The intention is to produce an open-source database of clinical images of eye cancer that can be used by anyone who contributes to the resource. The images will remain open source after the initial models have been developed.

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What's New in Retinoblastoma Diagnoses and Treatment in the World?

Swathi Kaliki MD

Summary

Retinoblastoma is the most common intraocular tumor of childhood. The diagnosis of retinoblastoma is mainly based on clinical examination findings. In recent times, OCT emerged as a new diagnostic tool for the detection of small tumors which may sometimes be clinically invisible. Artificial intelligence is another new entrant that can aid in community screening to detect retinoblastoma and also help in its classification, thus indicating the urgency of referral to an ocular oncologist. Liquid biopsy in the form of aqueous cell-free DNA, plasma cell-free DNA, and serum exosomes is slowly gaining importance in the diagnosis and prognosis of retinoblastoma.

The treatment of retinoblastoma has evolved drastically over the years, and so have the globe salvage rates. More and more eyes with retinoblastoma are being saved now, and this is mainly attributed to newer treatment strategies. Intra-arterial chemotherapy, which has been in use for more than 10 years now, has revolutionized retinoblastoma treatment. The treatment of vitreous seeds has shifted from external beam radiotherapy to subtenon chemotherapy to intravitreal chemotherapy currently. In the past, the treatment of aqueous seeds in retinoblastoma was enucleation, while the current, newer treatment modality is intracameral chemotherapy. Intravitreal and intracameral chemotherapy are safe when performed by an experienced ocular oncologist. When intra-arterial chemotherapy is combined with intravitreal chemotherapy for vitreous seeds and intracameral chemotherapy for aqueous seeds, the globe salvage rates have further improved. In this presentation, the audience will learn about newer developments in the diagnoses and treatment of retinoblastoma.

Children's Oncology Group: Current Treatment Trends

Dan S Gombos MD

I. Background

The Children's Oncology Group (COG) was established in 2001 and serves as an umbrella for many U.S. clinical trials in pediatric oncology.

II. ARET 0332: Unilateral Retinoblastoma and the Role of Adjuvant Chemotherapy

Concomitant less than 3 mm choroidal and any prelaminar/laminar optic nerve invasion show no recurrence and may warrant no adjuvant chemotherapy. In contrast, concomitant greater than 3 mm peripapillary choroidal invasion and 1.5 mm or greater of postlaminar optic nerve invasion have the poorest outcomes, supporting the need for a more intensive adjuvant chemotherapy regimen for this subgroup.

III. ARET 0331: Systemic Neoadjuvant Chemotherapy for Group B Intraocular Retinoblastoma

In the majority of patients with Group B intraocular retinoblastoma, treatment with systemic vincristine and carboplatin provides excellent opportunity for ocular salvage.

IV. ARET 0231: Systemic and sub-Tenon Chemotherapy for Groups C and D Intraocular Retinoblastoma

Subtenon carboplatin plus systemic carboplatin, vincristine, and etoposide was partially effective in managing Group D intraocular retinoblastoma but had unacceptable ocular toxicities.

V. ARET 0321: Intensive Multimodality Therapy for Extraocular Retinoblastoma

Intensive multimodality therapy is highly effective for patients with regional extraocular retinoblastoma and stage IVa metastatic retinoblastoma.

VI. ARET 12P1: A Feasibility Study of Intra-Arterial Chemotherapy (IAC) in Children with Group D Intraocular Retinoblastoma

Within the context of this study IAC did not meet the feasibility goal of 67% success rate.

VII. ARET 2121. A Multi-Institutional Feasibility Study of Intravitreal Melphalan for Group D Retinoblastoma.

This clinical trial will explore the feasibility of incorporating intravitreal melphalan injections during Cycles 3-6 of neoadjuvant systemic chemotherapy. Open for enrollment.

Patients with either unilateral Group D or bilateral (worse eye with Group D) disease and vitreous seeding are eligible for enrollment. Patients will begin therapy with 2 cycles of systemic carboplatin, vincristine, and etoposide (CEV). All patients will be evaluated for eligibility to receive intravitreal melphalan injection concurrently with Cycle 3 and each subsequent cycle of CEV. A total of 6 injections are allowed per eye.

Molecular and Pathology Testing in Retinoblastoma: Why, When, and How to Test?

Patricia Chévez-Barrios MD

Pathology and/or genomic medicine for retinoblastoma is currently desirable in all patients undergoing treatment for retinoblastoma.

Scenario 1

Unilateral retinoblastoma group E with neovascular glaucoma undergoing enucleation

Pathology

Thorough evaluation of the enucleated eye to exclude histopathologic high-risk features for metastasis and recurrence: extraocular extension, postlaminar optic nerve invasion, massive choroidal invasion (>3 mm) and site, scleral invasion

- Genomic tumor typing (1 vs. 2)
- Retrieval of aqueous humor/blood at baseline as liquid biopsy

Genetic testing

- Tumor and blood to exclude heritable retinoblastoma: germline mutation vs. nonheritable retinoblastoma
- Final pathology and genetic classification (American Joint Commission on Cancer) reviewed to evaluate potential for adjuvant chemotherapy

Scenario 2

Unilateral or bilateral retinoblastoma treated conservatively

- Retrieval of aqueous humor/blood at baseline
- Retrieval of aqueous humor during intraocular chemotherapy for tumor seeds/other treatment
- Evaluation of therapy based on results; continue with efforts to salvage eye vs. enucleation

Scenario 3

Blood genetic testing of siblings/relatives of patients with germline heritable retinoblastoma: Ideal and probably widely available soon

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Retinoblastoma Achievements Across Countries: Cybersight

Matthew W Wilson MD

I. The Global Problem of Retinoblastoma
   A. An estimated 9,000 new cases of retinoblastoma are diagnosed each year.
   B. 80%-90% of the world's children live in low- and middle-income countries with limited capacity to diagnosis and treat.
   C. Building capacity to treat retinoblastoma is a primary objective of the St. Jude Global Retinoblastoma Program.

II. Orbis

Founded in 1982, Orbis is a nonprofit organization devoted to blindness prevention and treatment in low- and middle-income countries.

   A. Flying Eye Hospital
      1. Dedicated to ophthalmic education
      2. Surgical skill transfer between mentor and mentee
   B. Cybersight (launched in 2003)
      1. Telemedicine-based platform
      2. Fosters mentor–mentee relationships
      3. Reaches over 208 countries
      4. Facilitates over 27,000 ophthalmology consults

III. Cybersight and Retinoblastoma
   A. Approximately 1000 global retinoblastoma consults
   B. 31 countries
   C. 59 different mentees
   D. Longitudinal outcomes
      1. Patient history
      2. Clinical findings
      3. Disease assessment
      4. Available diagnostics
      5. Treatment plan
      6. Patient and ocular outcomes
   E. Longitudinal improvement in retinoblastoma-specific knowledge
   F. Longitudinal improvement in retinoblastoma patient care

Retinoblastoma Achievements Across Countries: International Retinoblastoma Consortium

Dan S Gombos MD

NOTES

Retinoblastoma Overview in Mexico

Therapeutic Approach to Patients With Retinoblastoma in Northern Mexico

David Arturo Ancona Lezama MD

Figure 1. Source: Eye Cancer Institute.

I. Retinoblastoma (RB) in Mexico.

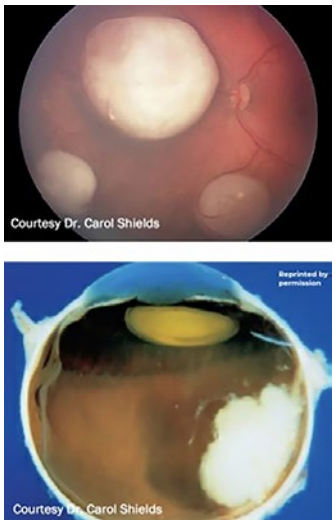

Figure 2. Reprinted by permission from Dr. Carol Shields.

A. Epidemiology (see Figure 3)

Figure 3. Source: Dr. David Ancona.

B. Relationship with Human Development Index (see Figures 4 and 5)

Figure 4. Source: Dr. David Ancona.

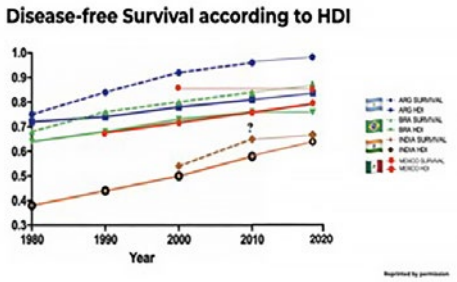

Figure 5. Source: Dr. David Ancona.

C. Classification (see Figure 6)

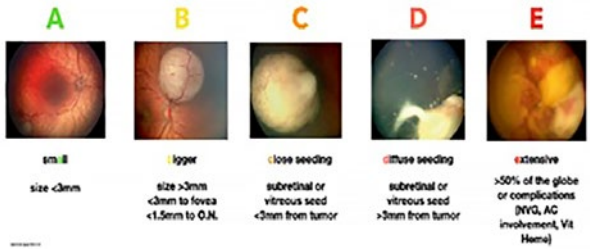

Figure 6. Source: Dr. David Ancona.

II. Research

A. Research question: Is intra-arterial chemotherapy (IAC) feasible in RB patients at a third-level private referral center in Northern Mexico?

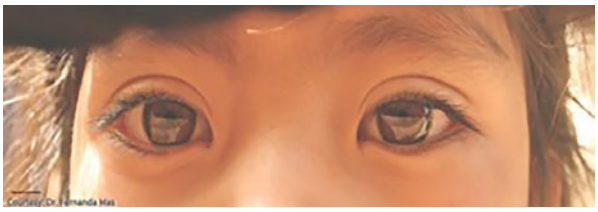

Figure 7. Reprinted by permission from Dr. Fernanda Mas.

B. Research plan

III. Published Articles

A. Challenge of RB in Mexico

Review Article

Challenge of Retinoblastoma in Mexico in 2020: Perspectives and Solutions

Lucas A. Garza-Garza,[1] Raúl E. Ruiz-Lozano,[1] Genaro Rebolledo-Méndez,[2] Ismael Ibarra-Nava,[3] Héctor J. Morales-Garza,[1] and David Ancona-Lezama[1]

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[2]*Writing Lab, TecLabs, Vicerrectoría de Investigación y Transferencia de Tecnología, Tecnológico de Monterrey, Monterrey, Mexico*
[3]*Department of Preventive Medicine and Public Health, Faculty of Medicine, Universidad Autónoma de Nuevo León, Monterrey, Mexico*

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Received 25 March 2020; Revised 28 May 2020; Accepted 29 June 2020; Published 11 August 2020

Academic Editor: Jean-Claude Mwanza

Figure 8

B. Modern treatment of RB

Review Article

Modern treatment of retinoblastoma: A 2020 review

David Ancona-Lezama, Lauren A Dalvin[1], Carol L Shields[2]

Retinoblastoma management remains complex, requiring individualized treatment based on International Classification of Retinoblastoma (ICRB) staging, germline mutation status, family psychosocial factors and cultural beliefs, and available institutional resources. For this 2020 retinoblastoma review, PubMed was searched for articles dated as early as 1931, with an emphasis on articles from 1990 to the present day, using keywords of retinoblastoma, chemotherapy, intravenous chemotherapy, chemoreduction, intra-arterial chemotherapy, ophthalmic artery chemosurgery, intravitreal chemotherapy, intracameral chemotherapy, cryotherapy, transpupillary thermotherapy, laser, radiation, external beam radiotherapy, plaque radiotherapy, brachytherapy, and enucleation. We discuss current treatment modalities as used in the year 2020, including intravenous chemotherapy (IVC), intra-arterial chemotherapy (IAC), intravitreal chemotherapy (IviC), intracameral chemotherapy (IcamC), consolidation therapies (cryotherapy and transpupillary thermotherapy [TTT]), radiation-based therapies (external beam radiotherapy [EBRT] and plaque radiotherapy), and enucleation. Additionally, we present a consensus treatment algorithm based on the agreement of three North American retinoblastoma treatment centers, and encourage further collaboration amongst the world's most expert retinoblastoma treatment centers in order to develop consensus management plans and continue advancement in the identification and treatment of this childhood cancer.

Key words Algorithm, eye, oncology, pediatric, retinoblastoma, treatment

Figure 9.

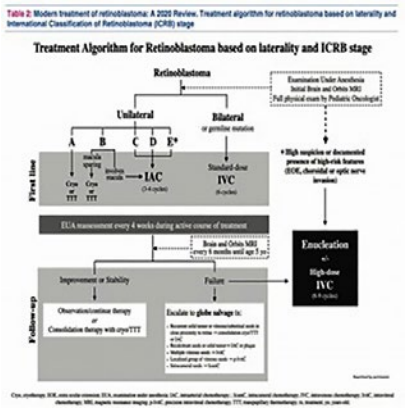


Table 2: Modern treatment of retinoblastoma: A 2020 Review. Treatment algorithm for retinoblastoma based on laterality and International Classification of Retinoblastoma (ICRB) stage

Treatment Algorithm for Retinoblastoma based on laterality and ICRB stage

Figure 10. Reprinted with permission from: Ancona-Lezama D, Dalvin LA, Shields cl. Modern treatment of retinoblastoma: a 2020 review. *Indian J Ophthalmol*. 2020; 68(11):2356-2365.

Table 1. Challenges and Possible Solutions for Improving RB Outcomes in Mexico

Challenge	Possible Solution
Differences in RB incidence, HDI, health resources, and professional availability among federal states	1. Promoting universal eye health coverage
	2. Specific direction of health resources to the most vulnerable states
	3. Twinning and telemedicine
Insufficient data and lack of subgroup analysis of RB outcomes per federal state	1. Encompassing all public and private institutions from different federal states in existing or new national registries
	2. Modification of registries to allow for complete demographic data and subsequent subgroup analysis
Insufficient medical knowledge, delayed RB diagnosis, metastatic disease at diagnosis, and cancer therapy abandonment	1. Strengthening RB programs in general medicine, academic formation
	2. Maintenance and stimulation of RB awareness campaigns for the medical and general populations
	3. Promoting universal eye health coverage
	4. Vigilance and timewise intervention in cases with risk of therapy abandonment
Maternal-fetal programs and new universal health coverage	1. An excellent program ("control del niño sano") already exists to cover child health from birth to 5 years of age; it should be maintained and strengthened.
	2. Previous universal health programs have successfully covered RB; this coverage should be maintained and strengthened.

Adapted with permission from Garza-Garza AA, Ruiz-Lozano RE, Rebolledo-Méndez G, Ibarra-Nava I, Morales-Garza HG, Ancona-Lezama D. Challenge of retinoblastoma in Mexico in 2020: perspectives and solutions. *J Ophthalmol*. 2020; 2020:1953602.

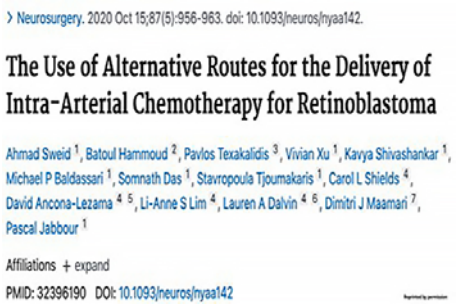
Abbreviations: RB, retinoblastoma; HDI, Human Development Index.

C. IAC

Figure 11. Interventional neurosurgeon Dr. Antonio Figueroa successfully performing an IAC procedure in Hospital Zambrano Hellion. Source: José Antonio Figueroa.

D. Initial experience in Northern Mexico

E. Alternative routes for IAC delivery



> Neurosurgery. 2020 Oct 15;87(5):956-963. doi: 10.1093/neuros/nyaa142.

The Use of Alternative Routes for the Delivery of Intra-Arterial Chemotherapy for Retinoblastoma

Ahmad Sweid [1], Batoul Hammoud [2], Pavlos Texakalidis [3], Vivian Xu [1], Kavya Shivashankar [1], Michael P Baldassari [1], Somnath Das [1], Stavropoula Tjoumakaris [1], Carol L Shields [4], David Ancona-Lezama [4 5], Li-Anne S Lim [4], Lauren A Dalvin [4 6], Dimitri J Maamari [7], Pascal Jabbour [1]

Affiliations + expand

PMID: 32396190 DOI: 10.1093/neuros/nyaa142

Figure 12

F. IAC in infants: Two groups

1. ≤10 kg
2. >10 kg

> AJNR Am J Neuroradiol. 2020 Jul;41(7):1286-1292. doi: 10.3174/ajnr.A6590. Epub 2020 Jun 25.

Intra-Arterial Chemotherapy for Retinoblastoma in Infants ≤10 kg: 74 Treated Eyes with 222 IAC Sessions

A Sweid [1], B Hammoud [2], J H Weinberg [1], P Texakalidis [3], V Xu [1], K Shivashankar [1], M P Baldassari [1], S Das [1], S Ramesh [1], S Tjoumakaris [1], C L Shields [4], D Ancona-Lezama [4 5], L-A S Lim [4], L A Dalvin [4 6], P Jabbour [7]

Affiliations + expand

PMID: 32586963 PMCID: PMC7357663 DOI: 10.3174/ajnr.A6590

Figure 13

G. Novel RB1 germline mutation

Novel RB1 germline mutation in a healthy man

Eugenia M. Ramos-Dávila, Lucas A. Garza-Garza, Rocío Villafuerte-de la Cruz, Dione Aguilar-Y-Mendez, Héctor J. Morales-Garza, Manuel Garza-Leon, Raul E. Ruiz-Lozano & David Ancona-Lezama ...show less

Received 27 Nov 2021, Accepted 30 Mar 2022, Published online: 11 Apr 2022

Download citation https://doi.org/10.1080/13816810.2022.2062390

Figure 14

IV. Research Results

V. Conclusions

VI. Future Actions

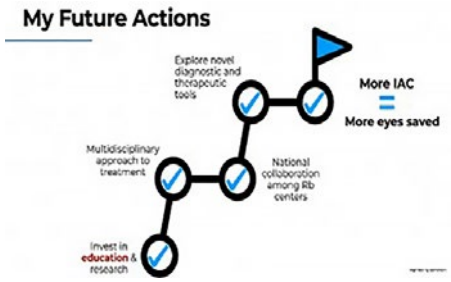


Figure 15. Source: Dr. David Ancona.

VII. Acknowledgments

Figure 16

Figure 17. Source: Dr. David Ancona.

Figure 18. Source: Dr. David Ancona.

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Is Intra-arterial Chemotherapy for Everyone? Part 1

Jasmine H Francis MD

I. Outcomes of Intra-arterial Chemotherapy for Intraocular Retinoblastoma
   A. Less advanced (International Classification of Retinoblastoma [ICRB] Groups A-C)
   B. More advanced (ICRB Group D)
   C. Most advanced (ICRB Group E)
   D. Vitreous seeds
   E. Unilateral retinoblastoma
   F. Bilateral retinoblastoma

II. When Intra-arterial Chemotherapy Is Not Indicated for Retinoblastoma
   A. Age and weight
   B. Systemic conditions
   C. Disease conditions

III. Intra-arterial Chemotherapy for Extraocular Retinoblastoma

IV. Intra-arterial Chemotherapy for Other Ocular Tumors
   A. Histiocytosis
   B. Von Hippel-Lindau syndrome
   C. Orbital tumors
   D. Other vision-threatening conditions

Is Intra-arterial Chemotherapy for Everyone? Part 2

Carol L Shields MD

I. Intra-arterial chemotherapy (IAC) for retinoblastoma (Rb) is wonderful.
   A. Excellent before and after results in experienced hands
   B. Some children demonstrate excellent visual acuity.

II. IAC for Rb—Many Concerns
   A. If germline, bilateral, we prefer intravenous chemotherapy (IVC).
      1. If IVC fails and you need IAC for both eyes, use staggered IAC (20-day interval) because you can get normal dose to each eye and don't risk bilateral NLP.
      2. Avoid tandem IAC, especially if inexperienced.
   B. If 0- to 3-month-old baby with Rb, there is 61% chance for germline mutation.
      1. Baby is too young for IAC.
      2. Avoid IAC and use IVC.
   C. If Rb is invasive into choroid or optic nerve, enucleate and give systemic IVC to prevent metastasis.
   D. Technique matters
      1. Document eye and dose with marker to assist interventional neuroradiologists. They do not do eye examination before treating.
      2. Many IAC errors lead to NLP vision. Send to an experienced center.
   E. Cost: Honavar editorial in *Indian Journal of Ophthalmology*:
      1. IAC in India costs $1000-$2000, whereas in the United States it costs $40,000.
      2. IAC costs are direct and indirect.
      3. Need to have only centers of excellence perform IAC
      4. Need to reduce direct costs
      5. Need government support

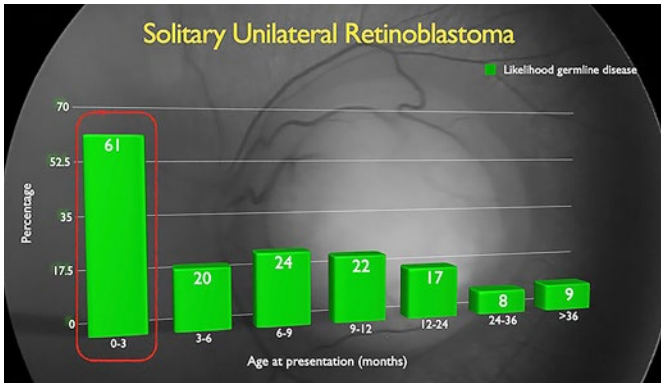

Figure 1

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Baseline Comprehension and Verbiage: DEI Background

What's DEI Got to Do With It?

Ambar Faridi MD

I. Baseline Comprehension and Verbiage
   A. Diversity, equity, and inclusion (DEI) background, awareness, and terminology
   B. The importance of DEI in medicine and ophthalmology: DEI is more than just a current-day requirement.
   C. The application and importance of utilizing inclusive language: Think about the words you use.

II. DEI in the Clinic and Work Space
   A. Recruitment and retention practices with a DEI lens
   B. Practical tips on building and maintaining an inclusive work and patient environment
   C. An eye on reducing health disparities in ophthalmology, in both patient care and research

III. DEI Progress, Pitfalls, and Priorities Summary
   A. Progress we have made
   B. Pitfalls we have to recognize
   C. Priorities we have to put into action

Bias: Explicit vs. Implicit (Tests Available)

César A Briceño MD

I. Introduction
   A. Background on bias in health care
   B. Importance of addressing bias in medical practice
   C. Overview of explicit and implicit bias
II. Understanding Explicit Bias
   A. Definition of explicit bias
   B. Examples of explicit bias in health care
   C. Impact of explicit bias on patient outcomes
   D. Recognition and self-reflection to identify explicit bias
III. Understanding Implicit Bias
   A. Definition of implicit bias
   B. Unconscious nature of implicit bias
   C. Examples of implicit bias in health care
   D. Impact of implicit bias on patient outcomes
   E. Role of cognitive biases in shaping implicit bias
IV. Assessing Bias: Tests Available
   A. Overview of tests for measuring explicit bias
   B. Commonly used explicit bias assessment tools
      1. Implicit Association Test (IAT)
      2. Modern Racism Scale (MRS)
      3. Symbolic Racism Scale (SRS)
      4. Attitudes Toward Disabled Persons (ATDP) Scale
      5. Sexism Attitudes Scale (SAS)
      6. Homophobia Scale
   C. Benefits and limitations of explicit bias tests
   D. Overview of tests for measuring implicit bias
   E. Commonly used implicit bias assessment tools
      1. Implicit Association Test (IAT)
      2. Implicit Relational Assessment Procedure (IRAP)
      3. Affect Misattribution Procedure (AMP)
      4. Single Category Implicit Association Test (SC-IAT)
      5. Go/No-Go Association Task (GNAT)
   F. Benefits and limitations of implicit bias tests
V. Addressing Bias in Medical Practice
   A. Importance of awareness and education
   B. Strategies for reducing explicit bias
      1. Bias training programs
      2. Implementing policies and guidelines
   C. Strategies for reducing implicit bias
      1. Implicit bias training
      2. Structural and systemic changes
   D. Promoting diversity and inclusion in health care
VI. Case Studies and Real-World Examples
   A. Presenting case studies illustrating the impact of bias
   B. Discussing real-world examples of bias reduction initiatives
   C. Highlighting successful interventions and outcomes
VII. Conclusion
   A. Recap of key points discussed
   B. Emphasis on the importance of addressing bias in medical practice
   C. Call to action for physicians to be proactive in combating bias

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Oculoplastics–Ocular Surgery and DEI

Nikisha Q Richards MD FACS

I. Patient Inclusivity
   A. Avoiding old dictums
   B. Fitzpatrick scale and characteristics of Fitzpatrick scale
II. Recognizing and Acknowledging Differences in Facial Structure in Those Across the Fitzpatrick Scale
III. Making the Diagnosis of Common Ocular Adnexal Lesions in those Across the Fitzpatrick Scale
   A. Basal cell
   B. Sebaceous cell
   C. Squamous cell
   D. Xanthelasma
   E. American Academy of Ophthalmology/Minority Ophthalmology Mentoring program push
IV. Pigmentation After Surgery in Those Across the Fitzpatrick Scale

Women in Ocular Oncology and Pathology

Diva Regina Salomao MD

Despite progress made in the past decades, physician gender/sex inequalities still exist in many specialties in medicine. A recent study found that the percentage of women in ophthalmology, across all levels of training, remains lower than that of the general population. Data from the Association of American Medical Colleges which evaluates yearly the mean percentage of female clinical faculty at U.S. medical schools, meaning percentage of women in academia by specialty, has consistently shown participation below 50% for both ophthalmology and pathology when compared to other clinical departments. Ocular oncology and ocular pathology are niche subspecialties within ophthalmology and pathology. Therefore, it could be assumed that the number of women physicians in these subspecialties has been lower than that of their male colleagues.

This session will evaluate the past and current participation of female physicians in the fields of ophthalmic (ocular) oncology and pathology.

The objectives are as follows:

- Review historical data of participation in national and international ophthalmic oncology and pathology societies
- Review major contributions made by female physicians to advance the field of ocular oncology and pathology
- Evaluate gender/sex gaps and progression over time
- Discuss challenges and opportunities to attract more female physicians to these subspecialties

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DEI's Current Application to Ocular Oncology

Basil K Williams Jr MD

I. Introduction
   A. What is diversity, equity, and inclusion (DEI)?
   B. What is health equity?
II. Applications Locally, Nationally, and Internationally
   A. What is your clinic like?
      1. Information for patients
      2. Social services
      3. Language assistance
      4. Staff diversity
   B. What are national trends?
      1. Patient outcomes by race and ethnicity
         a. Medical oncology
         b. Uveal melanoma
         c. Retinoblastoma
      2. Geographic access to care for patients
      3. Provider diversity by race/ethnicity, gender, and subspecialty training
   C. Global focus
      1. Treatment trends
      2. Gender trends
      3. Access to education
III. Opportunities for Improvement
IV. Conclusions

DEI Wave: Reaching a Balance

Miguel A Materin MD

Examples of Challenging Cases in DEI

1. "I can do whatever I want, they will not fire me" (from a first-year resident)

2. "34-year-old Asian male with BRCA gene and family history of breast cancer"

3. "They fired me because I am . . ."

A Look Back at American Association of Ophthalmic Oncologists and Pathologists Membership Representation: Ten-Year Projection

Claudia Maria Prospero Ponce MD and Patricia Chévez-Barrios MD

I. Introduction

Diversity, equity, and inclusion (DEI) is a powerful combination that allows groups to succeed and provide better outcomes in patient care. DEI is important because uneven access to health care and underrepresentation in ophthalmology/oncology/pathology have been known to negatively impact health quality in ophthalmologic patients. DEI requires an intentional and conscious change in order to improve the future of our profession.

II. Learning Objectives

A. Describe the importance of DEI in the AAOOP

B. Define the current status of AAOOP in the area of DEI

C. List some of the questions important for DEI achievement

D. Describe the current demographics of AAOOP

E. List the future plans of AAOOP to address DEI future

III. What Are Diversity, Equity, and Inclusion?

A. Diversity: Different characteristics in a group of members/patients

B. Equity: Each patient/member has what they need to succeed

C. Inclusion: Different individuals are culturally and socially accepted and welcomed

IV. Current AAOOP Demographics

Current AAOOP demographics may not reflect our patient population or the general population in the country.

A. AAOOP member demographics race/ethnicity, gender, orientation, disability (available at the time of presentation)

B. AAOOP member participation in committees/board/panelist/moderator

C. AAOOP areas of improvement in DEI

1. Increase diversity to enhance representation
2. Understand equity vs. equality
3. Identify implicit and explicit bias
4. Promote inclusion

V. The Future of DEI in AAOOP

A. Before addressing the future of DEI in AAOOP, we first need to identify our current status and compare it to the rest of the country and other specialties.

1. DEI survey distribution and statistical analysis

B. The final goal is to modify our approach to DEI and to intentionally make it part of our daily lives.

C. The plan

1. Educate members and learners in DEI
2. Provide statistics on DEI from our current and past members
3. Participate in inclusion of minorities (students and patients)
4. Increase representation in leadership from diverse individuals

Selected Readings

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United for Sight: A Vision for Effective Advocacy

Ocular Oncology and Pathology Subspecialty Day 2023

Alison H Skalet MD PhD

Action Requested: *Donate to strengthen ophthalmology's legislative voice and protect patients and your profession*

Please respond to your Academy colleagues and join the community that advocates for ophthalmology: OPHTHPAC, the Surgical Scope Fund, and your State Eye PAC. Ensure you and your patients are heard by our nation's lawmakers by giving to each of these funds.

Where and How to Contribute

During AAO 2023 in San Francisco, please contribute to OPHTHPAC® and Surgical Scope Fund at one of our two convention center booths or online. You may also donate via phone to both funds by sending two texts:

- Text **MDEYE** to **41444** for OPHTHPAC
- Text **GIVESSF** to same number (**41444**) for the Surgical Scope Fund

We also encourage you to support our congressional champions by making a personal investment via OPHTHPAC Direct, a unique and award-winning program that lets *you decide* who receives your political support.

Surgical Scope Fund contributions are *completely confidential* and may be made with corporate checks or credit cards. PAC contributions may be subject to reporting requirements.

Why Should You Contribute?

Member support of the Academy's advocacy funds—OPHTHPAC and the Surgical Scope Fund—powers our advocacy efforts at the federal and state levels. When you give to OPHTHPAC, you give ophthalmology a voice on Capitol Hill on critical issues like Medicare payment, optometry's scope expansion efforts in the VA, and prior authorization and step therapy burdens. When you give to the Surgical Scope Fund, you're funding our efforts to fight dangerous optometric surgery initiatives at the state level, whenever and wherever they arise. And finally, when you give to your state Eye PAC, you help elect officials in your state who will support the interests of you and your patients. Giving to *each* of these three funds is essential to helping protect sight and empower lives.

Protecting quality patient eye care and high surgical standards is a "must" for everybody. Our mission of "protecting sight and empowering lives" requires robust funding of both OPHTHPAC and the Surgical Scope Fund. Each of us has a responsibility to ensure that these funds are strong so that ophthalmology continues to thrive and patients receive optimal care.

OPHTHPAC for Federal Advocacy

OPHTHPAC is the Academy's award-winning, non-partisan political action committee representing ophthalmology on Capitol Hill. OPHTHPAC works to build invaluable relationships with our federal lawmakers to garner their support on issues such as:

- **Improving** the Medicare payment system, so ophthalmologists are fairly compensated for their services, and working to prevent impending payment cuts of 3.36% scheduled to take effect in 2024
- **Securing** payment equity for postoperative visits, which will increase global surgical payments
- **Stopping** optometry from obtaining surgical laser privileges in the veterans' health-care system
- **Increasing** patient access to treatment and care by reducing prior authorization and step therapy burdens

Academy member support of OPHTHPAC makes all this possible. Your support provides OPHTHPAC with the resources needed to engage and educate Congress on our issues, helping advance ophthalmology's federal priorities. Your support also ensures that we have a voice in helping shape the policies and regulations governing the care we provide. Academy member support of OPHTHPAC is the driving factor behind our advocacy push, and we ask that you get engaged to help strengthen our efforts and make sure that the ophthalmology specialty has a seat at the table for the critical decisions being made that affect our ability to care for our patients.

At the Academy's annual Mid-Year Forum, the Academy and the American Association of Ophthalmic Oncologists and Pathologists (AAOOP) ensure a strong presence of ocular oncology and pathology specialists to support ophthalmology's priorities. As part of this year's meeting, AAOOP supported participation of fellowship trainees via the Academy's Advocacy Ambassador Program. During Congressional Advocacy Day, they visited Members of Congress and their key health care staff to discuss ophthalmology priorities. The AAOOP remains a crucial partner with the Academy in its ongoing federal and state advocacy initiatives.

Surgical Scope Fund (SSF) for State Advocacy

The Surgical Scope Fund works in partnership with state ophthalmic societies to protect patient safety from dangerous optometric surgery proposals through advocacy. The Fund's mission is to ensure surgery by surgeons, and since its inception, it has helped 43 state/territorial ophthalmology societies reject optometric scope-of-practice expansions into surgery.

Support for the Surgical Scope Fund from ophthalmic interest societies like the American Association of Ophthalmic Oncologists and Pathologists makes our advocacy efforts

Surgical Scope Fund	OPHTHPAC®	State EyePAC
To protect patient safety by defeating optometric *surgical* scope-of-practice initiatives that threaten quality surgical care	Working across the political spectrum to advance ophthalmology and protect its members and patients at the federal level	Support for candidates for state House, Senate, and governor
	Support for candidates for U.S. Congress	
Political grassroots activities, government relations, PR and media campaigns	Campaign contributions, legislative education	Campaign contributions, legislative education
No funds may be used for campaign contributions or PACs.		
Contributions: Unlimited	Contributions: Personal contributions are limited to $5,000. Corporate contributions are confidential.	Contribution limits vary based on state regulations.
Individual, practice, corporate, and organization		
Contributions are 100% confidential.	Personal contributions of $199 or less and all corporate contributions are confidential. Personal contributions of $200 and above are public record.	Contributions are on the public record depending upon state statutes.

possible. These efforts include research, lobbyists, political organization, polling, advertising, social media, digital communications, and grassroots mobilization. However, the number of states facing aggressive optometric surgery legislation each year has grown exponentially. And with organized optometry's vast wealth of resources, these advocacy initiatives are becoming more intense—and more expensive. That's why ophthalmologists must join together and donate to the Surgical Scope Fund to fight for patient safety.

The Academy's Secretariat for State Affairs thanks the AAOOP for its ongoing commitment to the Surgical Scope Fund. The AAOOP's support for the Surgical Scope Fund is essential to fighting for patient safety and quality eye care!

State Eye PAC

The presence of a strong state Eye PAC providing financial support for campaign contributions and legislative education to elect ophthalmology-friendly candidates to the state legislature is critical, as scope of practice battles and many regulatory issues are all fought on the state level.

Support Your Colleagues Who Are Working on Your Behalf

Two Academy committees made up of your ophthalmology colleagues are working hard on your behalf. The OPHTHPAC Committee continues to identify Congressional Advocates in each state to maintain close relationships with federal legislators to advance ophthalmology and patient causes. The Surgical Scope Fund Committee is raising funds used to protect Surgery by Surgeons during scope battles at the state level.

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Ocular Surface Tumors and Advances

Carol L Karp MD

Conjunctival and corneal intraepithelial neoplasia and squamous cell carcinoma of the conjunctiva are a spectrum of diseases known as ocular surface squamous neoplasia (OSSN). Risk factors include human papilloma virus, ultraviolet light exposure, heavy cigarette smoking, and human immunodeficiency virus.

The main therapy for these lesions has been surgical excision, with "no-touch" technique and adjunctive cryotherapy. The advantages of surgery are that it provides rapid resolution of the tumor, provides tissue for diagnostic confirmation, and is covered by most insurance companies. The problem with surgical therapy is that recurrence rates can be high. Tabin reported up to 33% recurrence rates on surgical excisions, even with clear surgical margins. This rose to up to 56% recurrence with positive margins. Wide excisions may cause stem cell issues. Advances in techniques, including the use of high-resolution OCT (HR-OCT) perioperatively, will be discussed, as will limbal stem cell allograft in selected cases.

Medical therapy has taken on a key role in the treatment of these OSSN lesions. Medical therapy has the theoretical advantage of treating the entire ocular surface and treating "invisible" or microscopic disease. Furthermore, it can avoid stem cell deficiency associated with extensive surgical excisions. Mitomycin C, 5-fluorouracil, and interferon will all be discussed. Novel advances in medical therapies will be discussed.

The last advance to be discussed is HR-OCT. This is a powerful, noninvasive, rapid, and reproducible adjunct to the clinical examination. We will discuss what we have learned with OCT angiography for OSSN. HR-OCT has been most helpful in the diagnosis of various benign and neoplastic ocular surface lesions. Its applications are numerous and can enable clinicians to obtain "optical" biopsies in the clinic setting.

Conjunctival Carcinomas With Goblet Cells, "Mucoepidermoid," "Adenosquamous," "Squamous," and "Adenocarcinoma": WHO Eye5 Update

Paul J Bryar MD

I. Mucoepidermoid Carcinoma and Adenosquamous Carcinoma of the Conjunctiva

A. Nomenclature

1. Starting with WHO 4th edition, "adenosquamous carcinoma" (ASC) was the preferred term for conjunctival mucoepidermoid carcinoma.
2. In WHO 5, the term "adenosquamous carcinoma" should be used only for neoplasms with a biphenotypic differentiation comprised of squamous cell carcinoma (SCC) and adenocarcinoma.
3. The terms "mucoepidermoid carcinoma" and "squamous carcinoma with mucinous differentiation" are not recommended.

B. Clinical features

1. Can occur anywhere on the conjunctiva: limbus, fornix, palpebral, and bulbar. Up to 60% are in the fornix or on tarsal conjunctiva, so examination of these areas is important.
2. Usually conjunctival mass of short duration
3. Similar to SCC, may have a varied appearance: nodular, multinodular, leukoplakic, papillomatous, or ulcerative
4. Rare tumor, male predilection. Mean age at presentation is 64; UV exposure is risk factor.

C. Histopathology: biphasic SCC and adenocarcinoma, varying ratio of these components in each lesion

1. ASC squamous component: cords or sheets of squamous cells with varying keratinization
2. ASC adenocarcinoma component: tubule-glandular structures or confluent sheets of atypical cells with intracytoplasmic mucin with positive mucicarmine, Alcian blue, and periodic acid Schiff (PAS) with diastase staining
3. Immunohistochemistry
   a. SCC component: positive p40, CK5/6, and CK17
   b. Adenocarcinoma component: positive CK7, BerEP4, MUC-1, and CEA
4. Pathologic differential diagnosis includes SCC with mucinous differentiation and pseudoglandular hyperplasia. SCC with mucinous differentiation will not have true glandular structures or confluent sheets of mucinous cells; rather, it will have small clusters of cells in a mucinous background. (See Part III, SCC, below.)

D. Prognosis: Local recurrence is common; rare involvement of globe or orbit. Death from ASC is rare.

II. Conjunctival Squamous Intraepithelial Neoplasia (CSIN)

A. Nomenclature

1. Also known as conjunctival intraepithelial neoplasia (CIN)
2. Subtypes also include pigmented CIN and CIN with mucinous differentiation (CIN-Muc)

B. Clinical features

1. Mostly on conjunctiva that is exposed to sun; can show corneal invasion
2. Like conjunctival SCC, CSIN can have gelatinous (most common), papilliform, or leukoplakic appearance.
3. Freely mobile, which helps differentiate from invasive SCC which can be fixed to episclera
4. Etiology: UV light, immunosuppression, and in certain subtypes human papillomavirus (HPV) can be a factor.

C. Histopathology

1. Architectural (loss of polarity) and cytological: atypical squamous cells with nuclear pleomorphism/enlargement, high nuclear-to-cytoplasmic (NC) ratio, prominent nucleoli, mitoses, and sometimes foci of dyskeratosis and apoptosis. All changes are within the epithelium.
2. Degrees of dysplasia: mild (less than 1/3 of epithelium in basal layer), moderate (extending to middle third of epithelium), and severe (>2/3 of epithelium); carcinoma in situ (full thickness)
3. Immunohistochemistry: p53 and CK17 are positive; loss of CK7

D. Prognosis

1. Usually indolent but can recur or progress to SCC
2. Recurrence reduced with adjuvant cryo- or chemotherapy

III. Conjunctival SCC

A. Nomenclature: conjunctival SCC (see morphologic patterns below)

B. Clinical features

1. Occurs in interpalpebral conjunctiva and limbus (nasal > temporal) and can involve cornea
2. Less commonly involves tarsal and fornix and caruncle. Intraocular invasion is rare.
3. Can appear as nodular, papilliform, gelatinous, or leukoplakic with none or variable pigment
4. OCT, confocal microscopy, and MRI may aid in diagnosis and assessment for spread beyond the conjunctiva.
5. Etiology: Sunlight exposure, HIV, HPV, and immunosuppression are risk factors.

C. Histopathology: morphologic patterns

1. Conventional SCC
   a. Well differentiated: cells with eosinophilic cytoplasm, intercellular bridges, dyskeratosis, hyperchromatic nuclei, minimal pleomorphism, and sparse mitoses
   b. Moderately differentiated: some pleomorphic nuclei, keratinization, more mitoses
   c. Poorly differentiated: higher degrees of nuclear pleomorphism, increased mitoses and NC ratio, little or no keratinization, with invasion beneath the epithelial basement membrane.
2. Basaloid SCC
   a. Poorly differentiated SCC with scant basophilic cytoplasm, high NC ratio, oval to spindle hyperchromatic nuclei
   b. May have necrosis
3. Spindle SCC
   a. Sheets of spindle shaped cells with eosinophilic cytoplasm, mitoses
   b. May also have areas of conventional SCC
4. SCC with mucinous differentiation (formerly called mucoepidermoid carcinoma)
   a. Areas of conventional SCC with cells with mucinous cytoplasm, no glandular structures (as opposed to adenosquamous CA which has glandular structures)
5. Pigmented SCC
   a. Conventional SCC with hyperplastic melanocytes and melanophages
   b. Some melanosomes may be found in squamous carcinoma cells.
6. Acantholytic SCC
   a. Pseudolumens with acantholytic and dyskeratotic cells/debris
7. Immunohistochemistry: Useful in poorly differentiated tumors
   a. Positive high molecular weight cytokeratin stains, EMA, p63. Negative for androgen receptor.
   b. In spindle variant, focal cytokeratin positivity; smooth muscle actin and calponin may be positive.
8. Pathologic differential diagnoses
   a. For SCC with mucinous differentiation: adenosquamous carcinoma
   b. For spindle SCC: spindle melanoma, atypical fibroxanthoma
   c. For basaloid SCC: basal cell carcinoma extension from eyelid

D. Prognosis

1. Low risk of tumor-related death
2. High rate of recurrence
3. Rare lymph node metastasis
4. Spindle SCC may have more aggressive tumor behavior.

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Indeterminate Melanocytic Conjunctival Lesions: A Myth and Reality

Hans E Grossniklaus MD

I. Background
   A. First described in 1999
   B. Benign and malignant features
   C. Impossible to classify further in existing schemes
   D. Since first described, subclassifications have emerged based on immunohistochemistry (IHC) and molecular genetics.

II. WNT-Activated Deep Penetrating/Plexiform Melanocytoma (Nevus) (DPN)
   A. Darkly pigmented area withing pre-existing nevus
   B. Combined nevocellular and deep penetrating nevus
   C. Intensely pigmented melanophages
   D. IHC
      1. Beta catenin
      2. Cyclin D1
      3. BRAFV600E
      4. HMB45
      5. Ki67 (low)
   E. Molecular profile
      1. *BRAF V600E*
      2. *CTNNB1* c. 134C>T

III. Granular Cell Nevus (GCN)
   A. May be variant of DPN
   B. Dense cytoplasmic positivity for periodic acid Schiff staining
   C. Absence of nuclear positivity for beta-catenin
   D. Positive for cyclin D1

IV. Nevoid Melanoma
   A. Lack of junctional component peripheral to subepithelial component
   B. Poorly demarcated tumor base
   C. Sharp lateral demarcation
   D. "Puffy shirt" appearance
   E. IHC
      1. Loss of p16
      2. Negative for HMB45
      3. Negative for PRAME
      4. Low Ki-67 index
   F. Melanoma fluorescence in situ hybridization (FISH) positive for one
      1. *RREB1* (6p25)
      2. *MYB* (6q23)
      3. *CCND1* (11q13)
      4. *MYC* (8q24)
      5. Centromeres 6 and 8

V. Indeterminate Melanocytic Proliferations
   A. With nevus features
   B. With primary acquired melanosis features
   C. With nevoid melanoma features

VI. Conclusion
   A. Indeterminate melanocytic proliferations of conjunctiva exist.
   B. Since the original description, some may be reclassified as nevus or melanoma.
   C. Treatment is excision/cryotherapy and close follow-up.

Conjunctival Melanocytic Intraepithelial Lesions: WHO Eye5 Update

Tatyana Milman MD

Conjunctival melanocytic intraepithelial lesions (C-MIL) represent a spectrum of melanocytic hyperplasia with varying degrees of melanocytic atypia to melanoma in situ. Terminologies commonly used to classify these lesions include "primary acquired melanosis" (PAM) and "conjunctival melanocytic intraepithelial neoplasia" (C-MIN), along with the C-MIL classification proposed in the 4th edition of the World Health Organization Tumours of the Eye (WHO Eye4). In the WHO Eye4, C-MIL are classified as:

1. Low-grade C-MIL: Corresponding to PAM with or without mild atypia and lesions with C-MIN scores 1-2
2. High-grade C-MIL: Corresponding to PAM with moderate to severe atypia and C-MIN scores 3-5
3. Conjunctival melanoma in situ: Corresponding to PAM with severe atypia generally involving >75% of the epithelium and a C-MIN score >5.

This C-MIL system results in similar interobserver agreement when compared with PAM and C-MIN classification systems.

In a recent WHO Tumours of the Eye and Orbit 5th edition (WHO Eye5) consensus editorial meeting between dermatopathologists and ophthalmic pathologists, a refinement of the C-MIL classification was proposed, as outlined in Table 1.

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Table 1

WHO	Acceptable Alternative Terminology	Increased Cellularity	Histologic Features	Risk of Association With or Progression to Invasive Melanoma
Not applicable	• Benign melanosis • C-MIN (grades (0-1) • PAM without atypia	No/minimal	• Conjunctival hypermelanosis (increased pigment in epithelial cells without melanocytic hyperplasia or atypia) • Slight or focal melanocytic hyperplasia without atypia (parabasal melanocytes with condensed round nuclei, smaller than basal epithelial cell, inconspicuous nucleoli, and inconspicuous cytoplasm) may be seen.	None
Low-grade C-MIL	• PAM with mild atypia • C-MIN (grades 2-4)	Yes	Predominantly basilar melanocytic proliferation with low-grade atypia (dendritic or small to moderate size polyhedral, usually nonepithelioid melanocytes with round to irregular nuclear contours, often nuclear hyperchromasia, inconspicuous nucleoli, and inconspicuous or scant cytoplasm)	Lower
High-grade C-MIL	• PAM with moderate to severe atypia • C-MIN (grade 5-10)	Yes	More confluent basilar and significant nonbasilar proliferation of melanocytes with high-grade atypia (moderate to severe), evidence of intraepithelial nested and/or pagetoid growth, and epithelioid cell cytomorphology	Higher
	Melanoma in situ	Yes	The term "melanoma in situ" may be used for • The most atypical high-grade C-MILs involving close to full-thickness of the epithelium • Histologically obvious melanomas without documented evidence of subepithelial invasion	Highest

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Abbreviations: C-MIN, conjunctival melanocytic intraepithelial neoplasia; PAM, primary acquired melanosis; C-MIL, conjunctival melanocytic intraepithelial lesion.

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PRAME Expression of Conjunctival Melanocytic Lesions: Is It a Magic Bullet?

Maria Miguelina de la Garza Bravo MD

PRAME immunohistochemical stain is the new kid on the block in the evaluation of melanocytic lesions of the skin and eye. After the original paper, published in 2018, numerous publications have followed. However, is the stain useful in distinguishing benign from malignant in conjunctival melanocytic lesions? We will present our experience using PRAME in conjunctival lesions.

Pathology

We will show the histological features of interesting cases in conjunctival melanocytic lesions, the immunohistochemical profile (including PRAME), and the final diagnosis.

After the presentation of our findings, attendees will draw their own conclusions about whether PRAME is the magic bullet we have all been waiting for or if it is another tool that needs to be put in context with age, location of the lesion, histological findings, and results of other immunohistochemical stains that were once also called "the new kid on the block."

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Conjunctival Melanoma Mutations and Significance in Prognosis

Mary E Aronow MD

I. Introduction
   A. Incidence
   B. Demographics

II. Clinical and Histopathologic Prognostic Features

Indicators such as tumor thickness, location, degree of pigmentation, other clinical and histologic features will be briefly reviewed.

III. Mutational Landscape and Significance in Prognosis

Mutations in genes including *BRAF*, *NRAS*, *KIT*, *TERT*, *NF1*, *PTEN*, *ATRX*, and others, as well as their prognostic significance, will be discussed.

IV. Future Impact
   A. Identification of clinically actionable mutations for new potential therapies
   B. Future opportunities for precision medicine

Selected Readings

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Uveal Metastasis: Current Approach

Arpita Suketu Maniar MBBS

I. Various Presentations of Uveal Metastasis
   Common and atypical presentations
II. Noninvasive Diagnostic Modalities
   A. AF
   B. Fluorescein angiography
   C. Ultrasound
   D. OCT
III. Fine Needle Aspiration Biopsy
   A. Cytology
   B. Next-generation sequencing
IV. Systemic Screening Modalities
V. Treatment Modalities
   A. Local treatment
      1. Photodynamic therapy
      2. Transpupillary thermotherapy
      3. External beam radiotherapy
      4. Proton beam radiotherapy
   B. Systemic treatment/immunotherapy
VI. Newer Modalities

Gene Sequencing for Orbital Sarcomas: Is It Necessary?

Mukul K Divatia MBBS

Orbital soft tissue sarcomas are a group of mesenchymal malignancies with significant genetic, biologic, and clinical heterogeneity, thus posing a challenge for identification of targeted therapies and optimization of clinical outcomes and advanced patient treatment. Accurate classification of these tumors is often made challenging by overlapping histologic and immunohistochemical features, resulting in potential misdiagnoses of these neoplasms, which presently include more than 100 subtypes recognized by the World Health Organization.

Sarcomas may be broadly categorized into 2 groups based on genetic analyses:

1. tumors with simple karyotypes, exhibiting genetic translocations or activating mutations, and
2. tumors with highly complex karyotypes, including numerous genomic rearrangements and large chromosomal gains and losses, frequently involving cell cycle genes.

Next-generation sequencing (NGS), including whole-genome profiling as RNA and DNA sequencing analyses, tremendously aids pathological classification not only by detecting diagnostic mutations and translocations between partner genes but also by identifying actionable mutations for biomarker-based targeted treatment. Additionally, NGS also recognizes frequently underreported pathogenic germline variants present in approximately 10% of sarcoma cases.

NGS is an extremely valuable tool in appropriately guiding patients to mutation-specific clinical trials. Genomic characterization is imperative to avoid misdiagnosis, identify potential treatment options, and detect underrecognized hereditary diseases. NGS analysis of sarcomas is already facilitating improved diagnostic precision, identifying prognostic biomarkers, and vastly aiding in the understanding of sarcoma pathophysiology disease mechanisms to allow for better drug development to treat these malignancies and provide optimized patient care.

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Neurogenic Orbital Tumors: Advances in Diagnoses

Fausto Rodriguez MD

I. Introduction

A variety of neurogenic tumors may arise in the orbit. With some exceptions, these are primarily benign/low grade and include a variety of sporadic or familial tumors of nerve sheath derivation. Peripheral nerve sheath tumors (PNSTs), which are common soft tissue and cutaneous neoplasms accounting for approximately 4% of all orbital tumors, are presumed to arise from orbital sensory nerves. Additionally, gliomas and glial proliferations as well as meningiomas may present as primary orbital masses and present diagnostic challenges. In this presentation the pathology of selected cases will be discussed, as well as the utility of high-throughput molecular techniques for diagnosis in the context of the recent World Health Organization (WHO) Classification of Tumors of the Eye and Orbit.

II Tumor Categories

A. Nerve sheath tumors

1. Benign nerve sheath tumors (schwannoma, neurofibroma, mixed nerve sheath tumors)
2. Malignant peripheral nerve sheath tumors

B. Glioma and glial proliferations

C. Meningioma

III. Molecular Markers for Tumor Classification

High-throughput molecular platforms have found increased utility in the diagnosis of sporadic and familial neurogenic tumors. These include next-generation sequencing for pathogenic gene variants and array techniques for copy number changes and methylation profiling.

Selected Readings

1. Zhang ML, Suarez MJ, Bosley TM, Rodriguez FJ. Clinicopathological features of peripheral nerve sheath tumors involving the eye and ocular adnexa. *Hum Pathol.* 2017; 63:70-78.
2. WHO Classification of Tumours Editorial Board. Eye tumours. 5th ed. Beta version online ahead of print. Lyon (France): International Agency for Research on Cancer; 2023. WHO Classification of Tumours series, vol. 13.

Neurogenic Orbital Tumors: Advances in Treatments

Hakan Demirci MD

Primary neurogenic orbital tumors are responsible for about 10% of all orbital tumors. The neurogenic orbital tumors include meningiomas, optic nerve gliomas, neurofibromas, schwannomas, malignant peripheral nerve sheath tumors, and granular cell tumors.

In recent years, there were significant advances in the diagnosis and management of orbital neurogenic tumors. Nonsurgical management of orbital neurogenic tumors usually included external beam radiotherapy. Recently, selumetinib, a MEK inhibitor, was USFDA-approved for an inoperable, symptomatic plexiform neurofibroma and evaluated in clinical trials for gliomas, with some good results.

With recent advances in surgical techniques, a combined endoscopic approach to the sphenoid bone and orbitotomy allowed for the surgical excision of sphenoid wing meningiomas and orbital apex nerve tumors with less morbidity. Similarly, the developments in surgical instrumentation, such as navigation systems and ultrasonic surgical aspirators, allowed for the debulking of orbital neurogenic tumors with significantly less morbidity.

In this presentation, the nonsurgical treatment of orbital neurogenic tumors, including external beam radiotherapy and targeted therapy with MEK inhibitors, as well as new surgical techniques with combined endoscopic and orbitotomy approaches and ultrasonic surgical aspirator, will be reviewed.

Can Radiation Be Delivered in Less than 4 Days?

Miguel A Materin MD

- Yttrium 90 brachytherapy (Y-90 Disc)
- Anterior and surface tumors
- Posterior tumors
- Delivery time (in minutes)

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