Glaucoma 2017
Inspirations and Innovations—New Insights in Glaucoma Care

Under Pressure®

Program Directors
Jody R Piltz-Seymour MD and Shan C Lin MD

In conjunction with the American Glaucoma Society

Ernest N Morial Convention Center
New Orleans, Louisiana
Saturday, Nov. 11, 2017

Presented by:
The American Academy of Ophthalmology

Supported in part by an unrestricted educational grant from Aerie Pharmaceuticals

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2017 Glaucoma Subspecialty Day Planning Group

On behalf of the American Academy of Ophthalmology and the American Glaucoma Society (AGS), it is our pleasure to welcome you to Chicago and Glaucoma 2017: Inspirations and Innovations—New Insights in Glaucoma Care.

Jody R Piltz-Seymour MD
Program Director
Aerie Pharmaceuticals: S
Allergan: C

Shan C Lin MD
Program Director
Aerie Pharmaceuticals: C
AlEyegn: C
Allergan: C
Iridex: C

Meenakshi Chaku MD
None

Andrew Crichton MD FRCS
Aerie Pharmaceuticals: S,C
Alcon Laboratories Inc.: S,L,C
Allergan: S,L,C

David G Godfrey MD
Bausch + Lomb: C
Gregg A Heatley MD
None

Malik Y Kahook MD
Abbott Medical Optics: P,S
Aerie: C
Alcon Laboratories Inc.: C,L,S
Allergan Inc.: C,L,S
ClarVista Medical: C,P
Mile High Ophthalmics: O,P
New World Medical Inc.: P
Oasis Medical Inc.: P
Shape Ophthalmics LLC: O,P
ShapeTech LLC: O,P
Shire: C

Cynthia Mattox MD FACS
Aerie: C
Alcon Laboratories Inc.: C
Allergan: C,S
National Eye Institute: S
New World Medical Inc.: C
Novartis Pharmaceuticals Corp.: C,S
Ocular Therapeutix: C

Anup K Khatana MD
Glaucos Corp.: C,S
Gore: C
InnFocus: S
NeoMedix Corp.: L
Transcend Medical Inc.: S

Kelly Walton Muir MD
None

Arthur J Sit MS MD
Aerie Pharmaceuticals Inc.: S
Allergan: C
Glaucos Corp.: S
InjectSense Inc.: C,O

Nils A Loewen MD PhD
NeoMedix Corp.: L
2017 Subspecialty Day
Advisory Committee

Daniel S Durrie MD, Chair
(Refractive Surgery)
Abbott Medical Optics: L,C
AcuFocus, Inc.: C,L,O
Alcon Laboratories, Inc.: C
Alphaeon: C,L,O
Avedro: L,O,C
Hoopes Durrie Rivera Research Center: C
Strathspey Crown LLC: C,L,O

Julia A Haller MD (Retina)
Celgene: O | Janssen: C
KalVista: C
Merck & Co., Inc.: C
Novartis Pharmaceuticals Corporation: C
ThromboGenics, Inc.: S

Francis S Mah MD (Cornea)
Abbott Medical Optics Inc.: C,L,S
Aerie: C
Alcon Laboratories, Inc.: C,L,S
Allergan: C,L,S
Bausch Lomb: C,L
CoDa: C | ForeSight: C
NovaBay: C
Ocular Science: C,O
Ocular Therapeutix: C,S
PolyActiva: C | Shire: C
Slack Publishing: C
Sun Pharma: C
Syndexis: C | TearLab: C

R Michael Siatkowski MD
(Pediatric Ophthalmology)
National Eye Institute: S

Kuldev Singh MD (Glaucoma)
Abbott Medical Optics Inc.: C
Aerie: C
Alcon Laboratories, Inc.: C
Allergan: C
Belkin Laser Ltd: C
Glaukos Corporation: C
InjectSense: C
Ivantis: C
Mynosys: C
National Eye Institute: S
Novartis Institute for Biomedical Research: C
Santen, Inc.: C
Shire: C
Thieme Medical Publishers: C
U.S. Food and Drug Administration: S,C

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(Neuro-Ophthalmology)
Ophthotech: C
Opticent Inc.: O

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None

Melanie Rafaty
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Debra Rosencrance
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Beth Wilson
None
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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.

2017 Glaucoma Subspecialty Day Meeting Learning Objectives
Upon completion of this activity, participants should be able to:

- Describe innovations in the diagnosis and management of glaucoma within their historical context
- Manage complex cases of glaucoma when other eye diseases (eg, uveitis) are present
- Evaluate the current status of optic disc and retinal nerve fiber layer imaging and its role in diagnosing and managing glaucoma
- Demonstrate familiarity with current issues in medical and surgical therapy for glaucoma, both open-angle and angle-closure variants
- Identify and manage glaucoma surgical complications

2017 Glaucoma Subspecialty Day Meeting Target Audience
This activity has been designed to meet the educational needs of general ophthalmologists, glaucoma specialists and other ophthalmologic subspecialists, and allied health personnel who are involved in the management of glaucoma patients.

2017 Glaucoma Subspecialty Day CME Credit
The American Academy of Ophthalmology is accredited by the Accreditation Council for Continuing Medical Education to provide CME for physicians.

The Academy designates this live activity for a maximum of 7 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Teaching at a Live Activity
Teaching instruction courses 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 Financial 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. It 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.

The Academy requires all presenters to disclose on their first slide whether they have any financial interests from the past 12 months. Presenters are required to verbally disclose any financial interests that specifically pertain to their presentation.

Control of Content
The American Academy of Ophthalmology considers presenting authors, not coauthors, to be in control of the educational content. It is Academy policy and traditional scientific publishing and professional courtesy to acknowledge all people contributing to the research, regardless of CME control of the live presentation of that content. This acknowledgment is made in a similar way in other Academy CME activities. Though they are acknowledged, coauthors do not have control of the CME content, and their disclosures are not published or resolved.

Attendance Verification for CME Reporting
Before processing your requests for CME credit, the American Academy of Ophthalmology must verify your attendance at Subspecialty Day and/or AAO 2017. In order to be verified for CME or auditing purposes, you must either:

- Register in advance, receive materials in the mail, and turn in the Subspecialty Day Syllabi exchange voucher(s) onsite;
- Register in advance and pick up your badge onsite if materials did not arrive before you traveled to the meeting;
- Register onsite; or
- Scan the barcode on your badge as you enter an AAO 2017 course or session room.

CME Credit Reporting
Lobby B and Lobby G and Academy Resource Center, Hall G – Booth 3140
Attendees whose attendance has been verified (see above) at AAO 2017 can claim their CME credit online during the meeting. Registrants will receive an email during the meeting with the link and instructions on how to claim credit.

Onsite, you may report credits earned during Subspecialty Day and/or AAO 2017 at the CME Credit Reporting booth.
Academy Members: The CME credit reporting receipt is not a CME transcript. CME transcripts that include AAO 2017 credits entered onsite will be available to Academy members on the Academy’s website beginning Dec. 7, 2017.

After AAO 2017, credits can be claimed at www.aao.org. The Academy transcript cannot list individual course attendance. It will list only the overall credits spent in educational activities at Subspecialty Day and/or AAO 2017.

Nonmembers: The Academy will provide nonmembers with verification of credits earned and reported for a single Academy-sponsored CME activity, but it does not provide CME credit transcripts. To obtain a printed record of your credits, you must report your CME credits onsite at the CME Credit Reporting booths.

Proof of Attendance

The following types of attendance verification will be available during AAO 2017 and Subspecialty Day for those who need it for reimbursement or hospital privileges, or for nonmembers who need it to report CME credit:

- CME credit reporting/proof-of-attendance letters
- Onsite registration receipt
- Instruction course and session verification

Visit www.aao.org/cme for detailed CME reporting information.
The American Glaucoma Society (AGS) Subspecialty Day Lecture
The Glaucoma Renaissance
Saturday, Nov. 11, 2017
11:30 AM – 12:00 PM

Kuldev Singh MD MPH

Kuldev Singh was born in Washington D.C. and spent approximately half of his childhood in India. After finishing high school in Maryland, he attended McGill University where he completed the honors program in Economics while obtaining a degree in Biological Sciences and playing intercollegiate tennis. Kuldev then completed his MD and MPH degrees from the Johns Hopkins University as well as a one year Epidemiologic and Preventive Ophthalmology Fellowship at the Wilmer Eye Institute with Dr. Alfred Sommer and colleagues. His residency training at the Casey Eye Institute in Portland was followed by a Heed Foundation Fellowship under the guidance of Dr. Douglas Anderson and the glaucoma faculty at the Bascom Palmer Eye Institute. Kuldev then joined the ophthalmology faculty at Stanford University in 1992 and subsequently rose to the rank of Professor in 2003, serving as Residency Director and Academic Advising Dean along with various other leadership roles along the way. At Stanford, he has received several awards including the Franklin G. Ebaugh Jr. Award for mentorship and the University wide Asian American Faculty Award.

Kuldev’s clinical practice over the past 26 years has focused on the medical, laser and surgical management of glaucoma and cataract. His primary research interests have been epidemiologic including clinical trials and other longitudinal as well as cross sectional studies. Much of his research has targeted underserved communities in the U.S. and overseas. Kuldev has served as an investigator in the NEI Glaucoma Human Genetics Collaboration and is funded by the U.S. FDA to study patient related outcomes related to glaucoma surgery. His research has resulted in over 300 publications including over 175 original peer-reviewed articles. Kuldev has delivered numerous keynote and named lectures throughout the world, edited two textbooks, co-founded a journal and served on the editorial boards of ten ophthalmic publications. Kuldev continues to serve on an FDA Advisory Committee as well as on the Executive Committee of the UCSF Stanford Center for Excellence in Regulatory Science and Innovation, a joint initiative with the FDA.

Kuldev has served as President of the American Glaucoma Society, Executive Vice President, of the World Glaucoma Association (WGA), Chairman of the Board of Directors of the Glaucoma Research Foundation and Co-chair of the ARVO Asia Translational Vision Summit Steering Committee. He has received the WGA Founder’s Award, the AAO Life Achievement Honor Award and has been inducted into the Delta Omega Public Health Honor Society at the Johns Hopkins University Bloomberg School of Public Health as a distinguished alumnus. Kuldev and his family continue to enjoy time on the Stanford campus and outdoor activities in their hometown of Los Altos Hills, CA.
Facility

Iqbal K Ahmed MD
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John P Berdahl MD
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E Randy Craven MD
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C Stephen Foster MD
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Durham, NC

Kelly Walton Muir MD
Durham, NC

Robert N Weinreb MD
La Jolla, CA

Janey Lee Wiggs MD PhD
Boston, MA
Ask a Question Live During the Meeting Using the Mobile Meeting Guide

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

- Access at www.aao.org/mobile
- Select “Program Handouts & Evaluations”
- Filter by Meeting—Glaucoma Meeting
- Select Current Session
- Select “Ask the presenter a question (live)” Link
- Click Submit Question
Glaucoma Subspecialty Day 2017: Inspirations and Innovations—New Insights in Glaucoma Care
In conjunction with the American Glaucoma Society

SATURDAY, NOV. 11

7:00 AM CONTINENTAL BREAKFAST

8:00 AM Welcome and Introductions Jody R Piltz-Seymour MD*

8:03 AM American Glaucoma Society Introduction Cynthia Mattox MD FACS*

8:05 AM American Glaucoma Society Cares Joshua D Stein MD MS

8:07 AM Announcements Shan C Lin MD*

Section I: What’s Up Doc? New Therapeutics and Delivery Systems on the Horizon
Moderators: Robert D Fechtner MD FACS* and Malik Y Kahook MD*

8:09 AM New Molecules in Clinical Development Gary D Novack PhD* 1

8:19 AM Preclinical Investigation: Molecules of Interest Joel S Schuman MD* 3

8:24 AM Herbs and Supplements Lisa S Gamell MD 6

8:29 AM Intraocular Drug Delivery Systems Jonathan S Myers MD* 7

8:35 AM Extraocular Drug Delivery Systems Janet B Serle MD* 9

8:41 AM Punctal Plug Delivery Systems Marlene R Moster MD* 10

8:47 AM Panel Discussion

Section II: Latest in Diagnostics
Moderators: Nils A Loewen MD* and Lucy Q Shen MD

9:07 AM Case 1: Early (Pre-perimetric) Glaucoma Nils A Loewen MD PhD* 11

9:09 AM Best Approach to Diagnosing Early Glaucoma Angelo P Tanna MD* 12

9:14 AM Artefacts and Nonglaucomatous Abnormalities—OCT Teresa C Chen MD 13

9:19 AM Case 2: Moderate Glaucoma Mildred M G Olivier MD 15

9:21 AM Structure–Function Correlation Felipe A Medeiros MD* 16

9:27 AM Artefacts and Nonglaucomatous Abnormalities—Visual Field Annapurna Singh MD 18

9:32 AM Case 3: Advanced Glaucoma Sarwat Salim MD 19

9:34 AM The Role of Imaging in Severe Glaucoma David S Greenfield MD* 20

9:39 AM The Role of Perimetry in Severe Glaucoma Kouros Nouri-Mahdavi MD* 23

9:44 AM Wrap-up: Best Approach to Diagnosing Glaucoma Progression Robert N Weinreb MD* 25

9:50 AM Panel Discussion

9:58 AM REFRESHMENT BREAK and AAO 2017 EXHIBITS

* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.
Section III: Inflammation Nation—Uveitic and Steroid Glaucoma Diagnosis and Management
Moderators: Meenakshi Chaku MD and Kelly Walton Muir MD

10:28 AM Introduction of Session and Panelists
Meenakshi Chaku MD

10:30 AM Case Presentation: Doc, My Eye Is on Fire!
Anupama R Anchala MD

10:32 AM Panel Discussion: When to Phone a Friend—Your Neighborhood Rheumatologist / Uveitis Specialist

10:37 AM Case Progression: Bombe or Bust
Anupama R Anchala MD

10:40 AM Panel Discussion: Walking the Fine Line between Treatment Options—How to Go Low but Not Too Low?

Peter Andreas Netland MD PhD*

10:52 AM Everything Is More Challenging in Children: A Case of Pediatric Uveitic Glaucoma
Brenda L Bohnsack MD PhD*

10:55 AM Panel Discussion: The Ups and Downs of Steroids

11:00 AM Case Progression: The Plot Thickens
Brenda L Bohnsack MD PhD*

11:03 AM Panel Discussion: When to Cut, What to Cut

11:10 AM Case Progression: Happy Ending?
Brenda L Bohnsack MD PhD*

11:11 AM Goniotomy in Uveitic Glaucoma: What Is the Evidence?
Allen Dale Beck MD*

11:16 AM Panel Discussion and Audience Questions

11:23 AM Advocating for Patients
Jeff S Maltzman MD

The American Glaucoma Society Subspecialty Day Lecture

11:28 AM Introduction of the Lecturer
Cynthia Mattox MD FACS*

11:30 AM The Glaucoma Renaissance
Kuldev Singh MD MPH*

12:00 PM Presentation of the Award
Cynthia Mattox MD FACS*

12:01 PM LUNCH and AAO 2017 EXHIBITS

Section IV: Mastering MIGS
Moderators: Andrew Crichton MD* and Dale K Heuer MD*

1:31 PM Angle Considerations for Surgery
E Randy Craven MD*

1:38 PM Canalizing
Davinder S Grover MD*

1:45 PM Canal Stenting
Paul J Harasymowycz MD*

1:52 PM Canal Nonstenting
Nathan M Radcliffe MD*

1:59 PM Suprachoroidal
Iqbal K Ahmed MD*

2:06 PM Ab Interno Subconjunctival
Hady Saheb MD*

2:13 PM Panel Discussion
## Section V: The Edge of Cutting Edge—Frontiers of Glaucoma Research

**Moderators:** Ta Chen Chang MD* and Arthur J Sit MD*

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<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker and Affiliation</th>
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<tr>
<td>2:28 PM</td>
<td>Introduction</td>
<td>Arthur J Sit MD*</td>
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<td>2:29 PM</td>
<td>Should We Be Treating CSF Pressure in Glaucoma?</td>
<td>John P Berdahl MD</td>
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<td>2:36 PM</td>
<td>Understanding Glaucoma through Ocular Biomechanics</td>
<td>C Ross Ethier PhD</td>
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<td>Environmental Risks: Can Glaucoma Be Prevented?</td>
<td>Louis R Pasquale MD</td>
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<td>In Vivo Imaging of Retinal Ganglion Cells</td>
<td>Christopher Kai-shun Leung MD MBChB*</td>
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<td>2:57 PM</td>
<td>Gene Therapy for Glaucoma: Where Are We Now?</td>
<td>Janey Lee Wiggs MD PhD*</td>
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<td>3:04 PM</td>
<td>Neuregeneration and Stem Cells in Glaucoma Therapy</td>
<td>Jeffrey L. Goldberg MD PhD*</td>
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<td>3:11 PM</td>
<td>Wrap-up</td>
<td>Ta Chen Chang MD*</td>
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<td>3:12 PM</td>
<td>REFRESHMENT BREAK and AAO 2017 EXHIBITS</td>
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## Section VI: Under Pressure—All Things IOP

**Moderators:** David G Godfrey MD* and Gregg A Heatley MD

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<tr>
<td>3:42 PM</td>
<td>Case Presentation</td>
<td>Molly Walsh MD MPH*</td>
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<td>3:45 PM</td>
<td>Circadian Factors in Glaucoma Progression: Daytime</td>
<td>Anne Louise Coleman MD PhD*</td>
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<tr>
<td>3:55 PM</td>
<td>Circadian Factors in Glaucoma Progression: Night-time</td>
<td>JoAnn A Giaconi MD*</td>
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<td>4:02 PM</td>
<td>Innovations in Tonometry</td>
<td>Yvonne M Buys MD*</td>
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<td>4:09 PM</td>
<td>Innovations in Controlling IOP</td>
<td>Sayoko E Moroi MD PhD*</td>
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<tr>
<td>4:16 PM</td>
<td>Panel Discussion</td>
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## Section VII: Cataract Controversies—What Now?!?!?

**Moderators:** Anna K Junk MD and Anup K Khatana MD*

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<tr>
<td>4:24 PM</td>
<td>Case 1: Still Narrow After Laser Peripheral Iridotomy— Is Clear Lens Extraction on the Table?</td>
<td>Sunita Radhakrishnan MD*</td>
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<td>4:26 PM</td>
<td>Discussion</td>
<td>Ian P Conner MD PhD*</td>
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<td>4:31 PM</td>
<td>Case 1: Case Progression</td>
<td>Sunita Radhakrishnan MD*</td>
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<td>4:32 PM</td>
<td>Case 1: Panel Discussion</td>
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<td>4:39 PM</td>
<td>Case 2: Premium IOLs in Glaucoma Patients— The Role of Toric and Presbyopia-Correcting Lenses</td>
<td>Regine S Pappas MD</td>
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<td>Discussion</td>
<td>Steven D Vold MD*</td>
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<td>Case 2: Case Progression</td>
<td>Regine S Pappas MD</td>
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<td>Case 2: Panel Discussion</td>
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<td>4:54 PM</td>
<td>Case 3: Cataract in Pseudoexfoliation— IOL Type, Capsular Tension Ring, Role of Femtosecond Laser</td>
<td>Michael Greenwood MD*</td>
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<td>4:56 PM</td>
<td>Discussion</td>
<td>Alan S Crandall MD*</td>
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<tr>
<td>5:01 PM</td>
<td>Case 3: Case Progression</td>
<td>Michael Greenwood MD*</td>
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<td>5:02 PM</td>
<td>Case 3: Panel Discussion</td>
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* Indicates that the presenter has financial interest. No asterisk indicates that the presenter has no financial interest.
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<tr>
<td>5:09 PM</td>
<td>Case 4: IOL Selection With Post-trab Hypotony—How to Choose the Best Fit?</td>
<td>Michele C Lim MD</td>
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<tr>
<td>5:11 PM</td>
<td>Discussion</td>
<td>Thomas W Samuelson MD*</td>
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<tr>
<td>5:16 PM</td>
<td>Case 4: Case Progression</td>
<td>Michele C Lim MD</td>
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<td>5:17 PM</td>
<td>Case 4: Panel Discussion</td>
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<tr>
<td>5:24 PM</td>
<td>Wrap-up</td>
<td>Anup K Khatana MD*</td>
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<tr>
<td>5:26 PM</td>
<td>Closing Remarks</td>
<td>Jody R Piltz-Seymour MD*</td>
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<td>Shan C Lin MD*</td>
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New Molecules in Clinical Development

Gary D Novack PhD

This information is current as of 30 May 2017.

For the purpose of this presentation, I defined “new” as a new molecular entity (NME) or salt (but not isomers). I defined “development” as the status of a product that is not currently approved in a major market, and that either has a New Drug Application (NDA) submitted and under review or is in clinical Phase 1, 2, or 3. I explicitly did not consider drug delivery products of currently available molecules.

I used my experience and knowledge, as well as searching www.ClinicalTrials.gov for the indication of glaucoma in Phase 1, 2, or 3 that were submitted from Jan. 2010 to 31 May 2017. This resulted in ~341 trials. I further restricted the status to “open,” which resulted in 53 trials. I then applied the “new” criterion above. I did not include medical devices or surgical adjuncts. I provide this information here by development stage.

Ophthalmic NDAs/Biologic License Applications (BLAs) for Any Indication Pending with the FDA

Brimonidine 0.025% (redness), cetirizine 0.24%, dexamethasone insert for intracanicular use, latanoprostene bunod 0.024%, netarsudil 0.02%, sirolimus 440 μg, voretigene neparvovec. Of these, 2 are for glaucoma: latanoprostene bunod 0.024% (a prostaglandin-releasing nitric oxide) and netarsudil 0.02%, a rho-kinase inhibitor with norepinephrine re-uptake inhibition.

The minimal requirements for an NDA in the United States for an ocular hypotensive agent are 3-month efficacy, showing either noninferiority to a marketed product (timolol, latanoprost) or superiority to a vehicle, plus 12-month safety in at least 100 patients. Studies on first-line therapy will also give the Sponsor a label for additive therapy. The requirements for a neuroprotective agent are not known yet as there is no precedent, but were discussed in the same reference. Inclusion of the drug on a reimbursement formulary, adoption by physicians, or approval in Europe or Japan may be more rigorous.

Phase 3

Trabodenoson (an adenosine modulator), netarsudil / latanoprost in a fixed-dose combination (FDC)

Phase 1/2


This is a rather short list. Development time for a chronic ocular hypotensive agent is ~10 years from invention to approval, 3-4 years of which is the time from start of Phase 3 until approval. Treatments for neuroprotection, of which none is approved, would take at least this long, if not longer.

Why is this list so short? As I have previously published, it is not because there are no good research ideas, or because there is a floor effect on the Goldmann equation. Rather, it would seem that the reason is financial. I recently published a paper regarding the factors that determine what a patient with pharmaceutical insurance pays for out-patient branded pharmaceuticals. There are major factors that are invisible to the physician and patient. Further, as of the time of this outline (30 May 2017), there are generic alternatives (although not necessarily equivalents) for our topical ocular hypotensive medications.

Many of my colleagues on the commercial side of pharmaceutical business talk about 2 maxims: (1) premium pricing will demand premium performance and (2) pricing moves from east to west (ie, America will look more like Europe on pharmaceutical pricing).

While I am not talking about drug delivery, I will note that this is a move to take therapy from the patients to the physician. I consider how a millennial would design a drug delivery system. While I am certainly not of that generation, I think it would have a drug reservoir, with a computer-controlled variable release. There would be a continuous in vivo measure of efficacy (IOP, visual fields, etc.), and a feedback system that would change drug delivery based upon the outcome. Alas, of the many glaucoma delivery systems in Phase 2 and 3 development, none quite meet this standard.

There is hope! A new class of agent, topical ripasudil, was approved in Japan in 2014. Also, there are many ideas in research, including gene therapy. Finally, today, you and your patient can improve therapeutics with relatively low cost and risk—eg, training in eye drop instillation, nasolacrimal occlusion, etc.

References

2. Weinreb RN, Scassellati Sforzolini B, Vitrinow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO Study. Ophthalmology 2015; 122(2):302-307.


I. Introduction

A common initial glaucoma management choice is medical therapy. Often more than one class of drugs is required to lower the IOP. The burden of treatment, including side effects, results in suboptimal adherence that will impact the outcomes. An additional challenge is to develop drugs with targets other than IOP reduction.

II. Novel IOP-Lowering Agents (Including Agents Undergoing Clinical Trials)

A. Rho-associated protein kinase (ROCK) inhibitors: Netarsudil (AR-13324, Aerie Pharmaceuticals; Durham, North Carolina, USA): A Rho kinase inhibitor and norepinephrine transporter (NET) inhibitor. Rho kinases are serine / threonine protein kinases expressed in the trabecular meshwork (TM). A fixed-dosed combination of netarsudil / latanoprost fixed-dose is also being designed. Ripasudil (Glantec, Kowa Company Ltd; Nagoya, Aichi, Japan), another Rho kinase inhibitor, is approved in Japan for glaucoma and ocular hypertension.

B. Nitric oxide–donating prostaglandin analogue: Latanoprostene bunod (Bausch + Lomb; Bridgewater, NJ, USA): A prostaglandin F2-alpha analog that donates nitric oxide postulated to act on both the conventional and IOP-independent outflow pathways.

C. Adenosine receptor agonists—Examples: ATL313 (adenosine 2a receptor agonist), INO 8875 (adenosine A1 receptor agonist), and OPA-6566.

D. Trabodenoson (INO-8875) (Inotek Pharmaceuticals; Lexington, MA, USA): Acts as an agonist for the adenosine A1 receptor subtype, improving the TM outflow. A possible neuroprotection was suggested in animal preclinical models.

E. DE-117 (Santen Pharmaceutical; Ofuka-cho, Osaka, Japan) and ONO-905 (Ono Pharmaceuticals; Chuo-Ku, Osaka Japan): Ep2 is another prostaglandin F2 alpha analog that donates nitric oxide postulated to act on both the conventional and IOP-independent outflow pathways.

F. SiRNA targeting beta2 receptors: Bamosiran (SYL040012, Sylenis SA; Tres Cantos, Madrid, Spain): A naked siRNA that blocks by gene silencing the β2-adrenegic receptor (ADRB2), thus reducing the aqueous humor production at the ciliary body.

G. Latrunculin: Macrolides from marine sponges that inhibit actin polymerization. Studies in nonhuman primates and post-mortem: increased TM outflow via a mechanism that disrupts actin cytoskeleton of the TM.

III. Neuroprotective Agents

A. Neurotrophic factors: Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and ciliary neurotrophic factor (CNTF) are prosurvival factors. Axon damage apoptosis can be blocked with caspase inhibitors. Intercellular signaling of axonal damage can be interrupted with dual leucine zipper kinase (DLK) inhibitors. Reduction in reactive oxygen species can also be neuroprotective.

B. Tozasertib: Inhibits the work of DLK, which provides a major injury signal and might be neuroprotective, being found to be highly protective against glaucoma in rats.

C. Angiotensin II type 1 receptor agonists

1. Olmeartan: Ability to lower IOP by increasing outflow

2. Losartan: An angiotensin-converting enzyme inhibitor that inhibits activation of TGF-β in patients with Marfan syndrome. In an animal model, mice treated with oral losartan lost 10% of ganglion cells, while mice treated with only water lost 30% of ganglion cells.

D. ROCK inhibitors: In experimental glaucoma models also showed observable axon outgrowth / regenerative effects

E. AL-8398B: Topical selective agonist of the 5-hydroxytryptamine 1A receptor (5-HT1A) showed neuroprotection in animal models. Suggested mechanisms: activation of the MAPK signaling pathway that activates anti-apoptotic factors and inhibition of caspase 3.

F. Memantine: NMDA (N-methyl-D-aspartate) glutamate receptor antagonist. In preclinical studies in primates, showed a protective effect to the retinal ganglion cells (RGCs) and the neurons in the lateral geniculate body. However, memantine failed to achieve the primary efficacy end point in a Phase 3 clinical trial.

IV. Optic Nerve Regeneration

A. Oncomodulin (Ocm): An 11 kDa Ca2+ binding protein. Appears to mediate most of the inflammatory effect of optic nerve regeneration. Zymosan elevates the levels of oncomodulin and other trophic factors.
Section I: New Therapeutics and Delivery Systems

B. Suppressors of regeneration: Combining pten and socs3 (2 suppressors of regeneration) deletion combined with CNTF promoted regeneration. C-myc transcription factor overexpression in RGGs augments long-distance regeneration induced by deleting pten and socs3 combined with CNTF.

C. Cell-extrinsic inhibitors of axonal growth: The Nogo receptor (NgR) and PirB receptors are a common site of binding to molecules inhibitory to axonal growth. Many cell-extrinsic inhibitors of axon growth converge on GTPase RhoA, and RhoA inactivation was studied for axonal regeneration. Additional factors: Taxol is another pro-regenerative treatment that stabilizes microtubules.

VI. Stem Cell–Based Therapies

A. Stem cell–derived TM cells: Recently mesenchymal stem cells from human TM were successfully propagated in vitro and could differentiate into phagocytic TM cells. Induced pluripotent stem cells also were demonstrated to differentiate to TM cells with function in an ex vivo human model.

B. Pluripotent stem cells as a source of RGCs: Similar to retinal development in vivo, RGCs are the first retinal cells to be born during the differentiation from stem cells. Models to improve the populations of RGCs are under study. Many challenges are presented for stem cell–derived RGC transplantation for visual restoration, including the axonal pathfinding through the visual pathway.

C. Other potential applications: Stem cells can be a source for neurotrophic factors such as BNDF. Stem cells can provide disease modeling to evaluate the mechanisms by which genetic factors influence glaucoma.

Selected Readings


6. Quigley HA. The contribution of the sclera and lamina cribrosa to the pathogen of glaucoma: diagnostic and treatment implications. Prog Brain Res. 2015; 220:59-86.


Herbs and Supplements for Glaucoma

Lisa S Gamell MD

I. Intro to Complementary and Alternative Medicine

II. Vitamins and Their Efficacy for Glaucoma
   A. Vitamin A
   B. B vitamins
   C. Vitamin C

III. Herbs and Their Efficacy for Glaucoma
   A. Bilberry
   B. Gingko
   C. Forskolin
   D. Marijuana

IV. Summary and Conclusions
Intraocular Drug Delivery Systems

Jonathan S Myers MD and Scott J Fudemberg MD

Successful treatment of glaucoma requires not just effective medications, but medications that reach the eye. Studies repeatedly show that medications are not taken as directed, including reduced refill rates.1,2 One study of travoprost monotherapy found that 45% of patients took less than 75% of their doses, including the almost 20% of patients who took less than 50% of their doses, even when they knew they were being electronically monitored.3

Sustained-release drug delivery has the potential to eliminate much of the adherence problem. Receiving an injection from an ophthalmologist once every few months rather than self-administering eye drops multiple times per day has the potential to dramatically change the current treatment paradigm. Additionally, intraocular delivery may reduce topical side effects and allow much lower total dosages of medication.

Currently, no FDA-approved sustained-release drug delivery systems for glaucoma are available, although the pilocarpine Ocusert was marketed in the past. The most evolved examples of commercially available ophthalmic sustained-release drug therapies outside of glaucoma are the corticosteroid implants, which include Retisert (fluocinolone acetonide; Bausch + Lomb; approved in 2005), Ozurdex (dexamethasone; Allergan; approved in 2010), and Iluvien (fluocinolone acetonide; Alimera; approved in 2014). Many companies are developing sustained-release products for glaucoma, but much of the data that have been presented at meetings has not yet been published in peer-reviewed journals.

The bimatoprost sustained-release implant (bimatoprost SR, Allergan), a depot implant injected into the anterior chamber, is currently in FDA Phase 3 trials. Phase 2 trials of the implant showed a mean IOP reduction from baseline of 7.2 to 9.5 mmHg in 75 eyes 4 months after the injection.4 The fellow eyes received once-daily topical bimatoprost 0.03% and experienced an IOP reduction of 8.4 mmHg. The implant lowered IOP in 92% of patients at 4 months and in 71% at 6 months. There were no serious ocular adverse events, and the most common adverse events were related to the injection procedure.

Another depot implant that is injected intracameraly is ENV515 (Envisia Therapeutics). ENV515 is a biodegradable polymer drug delivery system that uses an extended-release formulation of travoprost. A Phase 2a open-label, 28-day dose-ranging study of 21 patients yielded 6.7 ± 3.8 mmHg, or 26%, IOP lowering over 9 months, which was comparable to once-daily travoprost (Travatan Z ophthalmic solution; Alcon) dosing in the fellow eye.5 Envisia is planning to advance to a 12-month study to evaluate the long-term IOP-lowering effects of ENV515.

GrayBug is developing a microparticle controlled-release drug delivery system for the treatment of AMD and glaucoma based on technology the company licensed from the Wilmer Eye Institute of Johns Hopkins School of Medicine in Baltimore. Particles injected through the conjunctiva as a gel in a viscous vehicle aggregate form a subconjunctival depot. GrayBug is developing compounds with both IOP-lowering activity and neuroprotective benefits. In a recent study, an intravitreal microparticle formulation of dorzolamide lowered IOP in rats, and a similar formulation was effective when dosed subconjunctivally in rabbits.6

In contrast to the bimatoprost SR and ENV515 intracameraly injectable implants, Icon Bioscience combines a drug with a carrier platform called Verisome into a liquid injection that can be placed in the posterior or anterior segment. Icon’s most evolved product is IBI-10090, which combines dexamethasone and Verisome for treating uveitis and post-surgical inflammation. IBI-10090 is in Phase 3 trials, and a glaucoma product is in the preclinical phase.7

Glaukos is developing a depot drug delivery system called iDose based on the iStent trabecular microbypass stent. In current studies, the iDose has a reservoir of travoprost capped by a membrane to allow continuous, gradual release. A Phase 2 randomized clinical trial is under way comparing 2 travoprost elution rates to topical timolol.8

Thus the groundwork is being laid for exciting new glaucoma treatments to become available in the coming years. Topical agents are effective, but patients’ problems with adherence have limited their therapeutic success, resulting in significant vision loss and blindness in some individuals who discontinue treatment for extended periods. Depot drugs may improve adherence, and early studies show better tolerability compared to drops, which could benefit many patients. Nonetheless, any side effects that do arise after injection of medication may prove more challenging to address.

The adoption of these new mechanisms of drug administration will require interest on the part of patients and physicians. Both groups will need to balance and consider the trade-offs between depot drugs and drops in terms of efficacy, safety, and economic considerations. If widely adopted, alterations in clinic flow may be needed. Selective laser trabeculoplasty is a relatively quick and low-risk procedure with little discomfort. Nonetheless, many patients approach this treatment with trepidation, which raises the question of how patients will feel about receiving an intraocular injection multiple times per year. If the FDA approves sustained-release drug delivery systems, the ultimate success of these drugs may be based on how they are presented to patients. Widespread adoption will depend on the confidence of physicians and patients in the efficacy and safety of these new treatment modalities.

References


Extraocular Drug Delivery Systems

Janet B Serle MD

Compliance is one of the major unmet needs in treating patients with glaucoma. Many intraocular and extraocular devices to lower IOP have been suggested and explored and are currently being developed and evaluated with the goal of less frequent dosing of medications and in some instances moving the dosing from the patient to the physician. Several devices will be discussed and placed into historical context here.

The devices that will be described include the Helios ring, the topical ophthalmic drug delivery device (TODDD), drug-eluting contact lenses, and the Bionode combined contact lens, gold trace, and eyeglass device. The Helios ring, which elutes bimatoprost, is currently in Phase 3 clinical trials. In Phase 2 clinical trials IOP reductions through 6 months of wear were similar to timolol, with stable IOP reductions through 13 months. This device is replaced approximately every 6 months. The TODDD is a soft flexible device that floats on the tear film and can simultaneously deliver several different ocular hypotensive medications. An early phase clinical trial has demonstrated efficacy through 180 days. A contact lens containing a drug-polymer film that elutes latanoprost is under development. A small trial in glaucomatous monkeys demonstrated IOP efficacy greater than or equal to topical latanoprost over 8 days of wear. The Bionode is a contact lens that has been fitted with a gold trace. The gold trace receives an electromagnetic field from a specially equipped pair of glasses. The electromagnetic field is converted into a current that stimulates the muscles around the Schlemm canal, somewhat analogous to pilocarpine, and enhances trabecular outflow. In a small number of glaucoma patients IOP reductions were rapid and maintained with the Bionode system.

Early phase investigations of these devices are promising, and larger and longer clinical trials are being conducted or are being planned.
Why do we need new ways to deliver glaucoma medications?
- Glaucoma is all about adherence.
- The vast majority of patients do not use their medicines.
- In fact, patients do not use medicines as directed, do not refill them on time, and if they have any side effects, usually stop taking them. Oftentimes, if one medicine runs out, patients wait until they all run out before going to the pharmacy to renew.
- One study of glaucoma monotherapy found that 25% of patients took less than 75% of their doses and that almost 20% of patients took less than 50% of their doses, even when they knew they were being electronically monitored.

Why focus on the puncta?
- Ophthalmology has a huge experience with punctal plugs for treatment of dry eyes and punctal stenosis.
- Data from the Women’s Health Studies (WHS) and Physicians’ Health Studies (PHS) estimate that 3.2 million women and 1.6 million men aged 50 years or older in the United States suffer from moderate to severe dry eye.
- It is estimated that 8.5 million Americans spend more than 300 million dollars on artificial tear preparations and other related over-the-counter medications. Punctal plugs for dry eye have become a well-accepted therapeutic solution when topical preparations are not effective.
- The best news about punctal plugs is that they can be adapted to treat glaucoma.
  - Why?
    - Plugs can be removed.
    - Plugs can be made to dissolve.
    - If one configuration doesn’t work, another shape can be tried.
    - They can be made to fit all sizes of puncta.

How will this technology work?

There are 3 places to put the plugs:
1. External puncta
2. Vertical portion of the canalicular system
3. Horizontal portion of the canalicular system

What’s in the pipeline?
At the present time, no punctal drug delivery system has been approved for delivery of glaucoma drugs in the United States. However, there is a desire to deliver consistent doses of medications in one comfortable package. The hope is that in mild to moderate disease this will help with the compliance problem. Multiple drugs can be formulated within this delivery system to treat glaucoma.

Thus far: Ocular Therapeutix and Mati Therapeutics are already performing clinical trials related to this route.
- Mati Therapeutics: Latanoprost within the plug has been studied, and the emphasis now is on different prostaglandins.
- Ocular Therapeutix: Different travoprost preparations. Drug studies completed.

Other considerations to put in punctal drug delivery systems include:
- Beta blockers
- Alpha agonists
- Adenosine agonists
- Rho kinase inhibitors

Both Mati and Ocular Therapeutix are working on delivering glaucoma therapy via the punctal plug technology.

The Evolute Punctal Plug Delivery System (Mati)
Benefits include flexible drug delivery profile, 20% IOP lowering over 3 months, noninvasive approach. The system has 92% and 96% retention rates for 3 months in 2 separate clinical trials. Doctors can play more of a role in compliance by scheduling insertions every 3 or 6 months. Mati Therapeutics deliver the drug in a novel way as this latanoprost-punctal plug delivery system is a drug-eluting plug and is comfortable but visible to the patient and doctor.

The Ocular Therapeutix system differs in that the intracanalicular depot dissolves over time, is visible via fluorescence at the slitlamp to the doctor but is invisible to the patient.

Removal of the Mati plug is relatively easy since it is superficial, while the Ocular Therapeutix punctal plug, being intracanalicular, is more difficult to remove and may require irrigation, or physical manipulation.

Phase 2 prospective studies are ongoing in order to determine both the efficacy and patient tolerability of these new drug delivery systems.
Case 1: Early (Pre-perimetric) Glaucoma

Nils Loewen MD PhD

CASE

Chief Complaint

49-year-old male, sent in by an optometrist at Sam’s Club. Glaucoma suspect exam due to elevated IOP (26) and large cups, no vision complaints.

- No trauma, family history positive for glaucoma in mother and aunt; no steroids; maximum documented IOP 26 O.U.
- Humphrey Visual Field (HVF): high fixation loss O.D. but within normal limits; reliable and within normal limits O.S.
- OCT: 69, 68, thin superior thicker than inferior retinal nerve fiber layer (S>I) O.D., thin S/I O.S.; ganglion cell analysis within normal limits O.U.; macula within normal limits O.U.
- Pachymetry: 521, 524
- Gonioscopy: Ciliary body band 360 O.U., +3 pigment
- IOPs: O.D. 25, O.S. 22 @ 10:17 AM

Right Left

- Distance, with correction: 20/20-1, 20/20-2
- Central corneal thickness: O.D. 521, O.S. 524
- Axial length: O.D. 26.55, O.S. 26.59 mm
- Cup-to-disk ratio: O.D. 0.71, O.S. 0.68

Assessment/Plan

- Open-angle glaucoma suspect, ocular hypertension O.U. Strong family history, thinning on OCT O.U. but HVF 24-2 normal, Ocular Hypertension Treatment Study (OHTS) 5-year glaucoma risk: 23.4%
- Plan: Start latanoprost. RTC 2 months for IOP and repeat HVF.

Conclusion

This patient is actually a glaucoma suspect who was treated for presumed preperimetric glaucoma due to the relatively high risk of glaucoma (OHTS + family history). A change of structure (OCT) was not demonstrated during the time he was seen.
Best Approach to Diagnosing Early Glaucoma

Angelo P Tanna MD

The early detection and treatment of glaucoma are important for the preservation of visual function and quality of life.\textsuperscript{1,2} When imaging data are used to establish the diagnosis of glaucoma, however, the diagnostic accuracy and specificity decline as a function of disease severity.\textsuperscript{3} Indeed, any combination of diagnostic testing is likely to be associated with the same limitation—reduced diagnostic specificity at a given level of sensitivity for detection at earlier stages of glaucoma.

The best approaches to the early diagnosis of glaucoma in the modern era of imaging vary depending on the baseline characteristics of the patient in question.\textsuperscript{4} It is well known that structural changes generally precede the development of visual field defects detected using standard automated perimetry (SAP), so it is compelling to expect structural evaluation with spectral domain OCT (SD-OCT) imaging to serve as the best method for the early diagnosis of glaucoma. In many instances, SAP, perimetry using the Humphrey 10-2 algorithm,\textsuperscript{5} and frequency-doubling technology perimetry\textsuperscript{6} can add meaningful information. In this presentation, I will review the evidence and our clinical experience that can be used to determine the best strategies for the early detection of glaucoma in patients with different baseline conditions that bring them to the attention of ophthalmologists as glaucoma suspects.

Imaging of the optic disc, peripapillary retinal nerve fiber layer, and the macula will be discussed.\textsuperscript{4} The utility of imaging strategies such as wide-field OCT scanning as described by Hood et al\textsuperscript{7} and the assessment of the Bruch membrane opening minimum rim width\textsuperscript{8-10} will be discussed. The importance of test-retest variability and age-related changes in structural and functional parameters as these pertain to the early detection of glaucoma will be discussed.

References

Artefacts and Nonglaucomatous Abnormalities—OCT

Teresa C Chen MD

I. OCT Artefacts in Glaucoma Management
A. Incidence
   1. 19.9% to 46.3% of retinal nerve fiber layer (RNFL) scans had at least 1 artefact.
   2. 28.2% to 90.9% of macular scans
   3. 12% to 56.5% of optic nerve scans
B. Top 10 reasons for RNFL thickness OCT artefacts
   1. Decentration artefacts (27.8% of RNFL scans)
   2. Posterior vitreous detachment–associated error (14.4% of RNFL scans)
   3. Posterior RNFL misidentification (7.7% of RNFL scans)
   4. Poor signal (5.1% of RNFL scans)
      a. Cirrus (Carl Zeiss Meditec; Dublin, CA): Maximum signal strength 10, should be over 6
      b. RTVue (Optovue; Fremont, CA): Maximum 100, should be at least 30
      c. 3D-OCT (Topcon Medical Systems, Inc.; Oakland, NJ): Maximum 160, should be over 45
      d. Spectralis (Heidelberg Engineering; Heidelberg, Germany): Maximum 40, should be at least 15
   5. Anterior RNFL misidentification (3.2% of RNFL scans)
   6. Missing parts (1.5% of RNFL scans)
   7. Peripapillary atrophy–associated error (1.2% of RNFL scans)
   8. Incomplete segmentation (0.6% of RNFL scans)
   9. Motion artefact (0.2% of RNFL scans)
   10. Cut edge artefact (0.17% of RNFL scans)

II. Diseases Caused by OCT Machines
A. Red disease
   1. False positive diagnosis of glaucoma
   2. Red colors on OCT printout but patient is normal (or with a nonglaucoma condition)
   3. Myopia is a common cause of red disease.
   4. Some other nonglaucomatous causes of RNFL thinning besides myopia
      a. Ischemic optic neuropathy
   b. Panretinal photocoagulation
   c. Superior segmental optic nerve hypoplasia (ie, topless disc appearance)
   d. Optic nerve hypoplasia
   e. Arterial and vein occlusions
   f. Multiple sclerosis and past optic neuritis
5. Patterns of RNFL damage may suggest certain disease etiologies.
   a. Glaucoma is more likely to cause preferential inferior, superior, inferior temporal, and superior temporal RNFL thinning earlier in the disease.
   b. Nonglaucomatous causes of RNFL thinning are less likely than glaucoma to cause preferential inferior and superior damage, but these nonglaucoma diseases can still be associated with inferior and/or superior RNFL loss.
B. Green disease
   1. False negative diagnosis
   2. Green color on OCT printout but patient has glaucoma

III. Artefactual RNFL Thinning Can Occur When the Patient Switches to a Different OCT Machine
A. OCT values on different machines are not interchangeable.
B. Normative databases
   1. Different OCT machines have different normative databases.
   2. Different OCT machines have different racial distributions in their normative databases.
   3. Limited ethnicities and refractive errors in all normative databases
C. Mean RNFL thickness values on different machines (in 40 normal adult subjects with mean age 37.1 ± 11.0 years, range 21 to 61 years of age)
   1. 110.1 ± 12.8 microns (Stratus, Carl Zeiss Meditec; Dublin, CA)
   2. 98.7 ± 10.9 microns (Cirrus, Carl Zeiss Meditec; Dublin, CA)
   3. 106.6 ± 12.8 microns (Spectralis, Heidelberg Engineering; Heidelberg, Germany)
   4. 112.8 ± 13.2 microns (RTVue, Optovue; Fremont, CA)
Selected Readings


Case 2: Moderate Glaucoma
“T have elevated pressures”

Mildred M G Olivier MD

History of Present Illness

A 58-year-old white male presented to his primary ophthalmologist with intermittent blurred vision O.S. greater than O.D. The patient was also noted to have increased pressures and referred for further evaluation.

Examination

- Visual acuity: 20/20 O.D.; 20/25 O.S.
- The patient was here with his wife and oriented x 3. He was a good historian.
- Central corneal thickness 590 and 600
- External examinations were normal.
- Slitlamp exam was unremarkable.
- IOPs were noted to be 40 mmHg O.U.
- Gonioscopic evaluation of the angles showed Grade III open angles by Shaffer classification. Trabecular meshwork pigmentation was light.
- Dilated fundus examination showed optic nerve head cup/disc 0.6 O.D. with +3 pallor and 0.6 O.S. with +4 pallor.
- No disc hemorrhages were noted.
- Visual fields: Bitemporal defect (nasal portion of the field) and neurologic defect temporally. Moderate visual field loss was noted.
- Heidelberg Retina Tomography was performed.

Visual fields and posterior pole evaluation along with the pallor were not consistent with the clinical picture. Red desaturation was noted as well. An MRI with contrast was ordered due to the pallor and visual field defect, which respected the midline, and the findings returned with a mass. Patient was referred to the neurosurgeon near his home. Medical management was started, patient was told to return after the drops were started, and the neurosurgery department was called to get a timely referral.

Patient saw Neurosurgery at the university and was told he needed surgical intervention. Pre and post visual field evaluations were not significantly changed. Pallor and vision have remained the same.
Structure–Function Correlation

Felipe A Medeiros MD PhD

Frequent disagreements are seen when structural and functional tests are used to monitor glaucoma patients for progression, and this has led to confusion in the literature and among clinicians. These disagreements, however, are easily reconciled when one understands the nature of the structure and function relationship in the disease. The apparent disagreement between structural and functional measurements of the disease seem to be largely derived from the different algorithms and measurement scales, as well as the different variability characteristics of the tests commonly used to assess structural and functional losses.

Models of Structure and Function Relationship

Several different models have been proposed to explain structure and function. According to these models, structural and functional measurements in glaucoma have a nonlinear relationship when evaluated at their customary scales. In fact, a curvilinear relationship is seen when different structural measurements such as optic disc rim area or retinal nerve fiber layer thickness are plotted against visual function measures. Visual function is usually assessed by standard automated perimetry (SAP) in a logarithmic scale, the decibel (dB), whereas structure is usually reported using a linear scale. Scaling of data in clinical perimetry is necessary because the ranges of stimulus intensities cover several orders of magnitude. The logarithmic scale, however, minimizes sensitivity changes in the visual field at high decibel levels and accentuates changes at low decibel values. As expected, the scaling differences result in potential disagreements when different structural and functional tests are used to assess glaucomatous damage and may give the false impression of a weak relationship between these measures. However, previous work has shown that structural and functional tests are in close agreement as long as one uses appropriate measurement scales for neural and sensitivity losses and considers factors such as the effect of aging and eccentricity on estimates of neural losses. It is important to note, however, that although linearization of SAP measurements improves the structure and function relationship on population data, it generally does not improve the sensitivity to early losses in an individual patient. As SAP sensitivity thresholds are originally acquired using staircase procedures in dB units, the compression of the range of losses in early stages of the disease caused by the logarithmic scale will still be present.

Understanding the nature of the structure and function relationship in glaucoma is fundamental for evaluating the role of these tests in detecting disease and assessing glaucoma progression. As a result of the nonlinear structure and function relationship described above, SAP measurements will generally have poor sensitivity for detection of early glaucomatous optic neuropathy. More importantly, the lack of sensitivity of SAP for detection of early glaucomatous damage frequently translates into lack of sensitivity for detection of progression in the early stages of the disease. In fact, several longitudinal investigations have shown that imaging instruments can often detect progressive damage in the absence of apparent visual field losses. While SAP has relatively low sensitivity to identify progression at initial stages of the disease, currently available methods for structural assessment often perform poorly to identify change at advanced stages of damage. This is generally due to the presence of a floor effect on structural measurements such as those acquired by OCT. For retinal nerve fiber layer thickness, for example, floor measurements have been shown to happen at around 40-50 µm of thickness. When measurements reach those levels it will become very difficult to detect further progression. However, recent studies have shown that progression can sometimes be identified by imaging even in eyes with advanced glaucoma. There is a region along the disease continuum in which structural and functional tests seem to agree better when detecting progression. This is frequently seen in patients with moderate disease (early visual field damage).

Combining Structural and Functional Information

Several recent approaches have been described integrating structural and functional information for improving diagnosis, staging, and detection of glaucoma progression. These approaches have ranged from use of Bayesian statistical methodologies to the development of combined indexes integrating structural and functional measurements. A combined structure and function index (CSFI) has been described which uses estimates of RGC counts obtained by previously derived empirical formulas in an attempt to produce a common scale to express structural and functional data. Several previous studies have reported on its use for diagnosis, staging, and detecting glaucomatous progression.

References


Artefacts and Nonglaucomatous Abnormalities—Visual Field

Annapurna Singh MD

I. Introduction
Visual field testing is critical for assessment and to document progression of glaucoma. Being objective in nature, visual field testing is inherently prone to errors and artefacts. The decision to treat or switch to more aggressive therapy such as surgery often depends upon visual field progression, so it is important to review the artefacts and pitfalls in the interpretation of visual fields.

II. Causes of Artefacts
Artefacts in visual field interpretation can be due to several factors that can be categorized as follows:

A. Patient related
1. Poor understanding of the test procedures
2. Patient inattention
3. Patient anxiety

B. Eye related
1. Prominent brows, ptosis
2. Small pupil (less than 2.5 mm)
3. Uncorrected refractive error
4. Poor visual acuity (less than 20/80)
5. Media opacity

C. Optic disc disorders
1. Disc drusen, optic nerve pit
2. Papillitis, advanced papilledema

D. Optic nerve disorders
1. Ischemic optic neuropathy (arteritic or nor arte-
ritic)
2. Compressive optic neuropathy (pituitary tumor, aneurysm, arachnoiditis

E. Chorioretinal disorders
1. Myopic degeneration, juxtapapillary chorioret-
nitis
2. Atypical RP/retinal dystrophy
3. Branch retinal vein/artery occlusion

F. Central nervous system defects
1. Bitemporal
2. Homonymous

III. Avoiding Pitfalls in Interpretation
Pitfalls in interpretation can be avoided by using a practical checklist:

A. Fixation loss less than 33%
B. False positive errors less than 33%; false negative errors less than 33%
C. Appropriate scan: SITA Fast for screening, SITA standard for monitoring
D. Appropriate age correction (for comparison with normative database)
E. First field test considered a learning test
F. Confirm visual field abnormality in 3 consecutive abnormal and reliable visual field tests with the defect in the same location.

G. Careful assessment of structure–function correlation (disc photos, OCT, retinal nerve fiber layer)

Selected Readings
Case 3: Advanced Glaucoma

Sarwat Salim MD

CASE

Case Presentation
- A 52-year-old white female with low-tension glaucoma (LTG)
- Current medications: Lumigan O.U. q.h.s. and Cosopt O.D. b.i.d.
- Past ocular history: Trabeculectomy with mitomycin-C O.S. and selective laser trabecuoplasty O.D.
- Maximum documented IOP: 17 mmHg O.D. and 16 mm Hg O.S.
- Family history: Mother with LTG
- Past medical history: HTN; irritable bowel syndrome

Exam findings and ancillary tests will be presented.

Discussion
This case of advanced LTG will be presented to highlight the appropriate use of ancillary testing to monitor progression and guide therapeutic intervention. In advanced glaucoma, structural evaluation with OCT is often limited and functional evaluation with perimetry may be more useful. Dr. Greenfield will discuss some limitations of current imaging devices (floor effect, segmentation failure, etc.) and evaluate different types of scans (optic nerve, retinal nerve fiber layer, and macula) when monitoring patients with advanced glaucoma. Dr. Nouri-Mahdavi will review the benefits and limitations of various perimetric tests and strategies, spot sizes, and guided progression analysis software.
Glaucoma is an optic neuropathy that is the second leading cause of blindness worldwide. An irreversible disease that affects nearly 15% of the general population over the age of 85, it is characterized by progressive neurodegeneration of retinal ganglion cells (RGCs) and their axons and a specific pattern of optic nerve head (ONH) and visual field (VF) damage. The pathophysiologic mechanisms of glaucomatous neurodegeneration are incompletely understood. Elevated IOP is the most important known risk factor for disease onset and progression that is amenable to modification.

There is currently no consensus on a glaucoma classification based on severity. Most classification systems are based upon the severity of VF loss rather than the degree of structural damage to the optic nerve or retinal nerve fiber layer (RNFL). The Hoddap-Parrish-Anderson criteria of VF severity in glaucoma classifies patients based upon the VF mean deviation (MD) on the pattern deviation plot as early (MD worse than −6 dB), moderate (MD worse than −6 dB but no worse than −12 dB) and severe (MD worse than −12 dB). In 2011, new International Classification of Diseases (ICD) 9/10 staging codes were introduced that classify glaucoma severity as mild (glaucomatous optic nerve damage without detectable VF loss using white-on-white perimetry), moderate (VF loss in 1 hemisphere only and not within 5 degrees of fixation), and severe (VF loss in both hemispheres and/or VF loss within 5 degrees of fixation). A limitation of the ICD staging system is that it is not based upon an objective continuous variable such as VF MD, and therefore eyes with localized paracentral VF loss may be classified as “severe” despite having only mild-to-moderate glaucomatous optic nerve and RNFL damage.

There are important implications for patients with severe glaucoma. Patients with severe glaucoma need more frequent follow-up visits, closer IOP monitoring with lower target pressures, and more frequent VF testing, and they more often undergo incisional surgery. In 2005, average direct cost of treatment ranged from $623 per patient per year for glaucoma suspects or early glaucoma to $2,511 per patient per year for patients with advanced disease. Patients with severe VF loss experience a greater impact upon quality of life and are at increased risk for glaucoma blindness.

Both structural and functional tests are necessary for glaucoma diagnosis and monitoring. Detecting glaucoma progression using optic disc photography is subtle and challenging, and it is of limited benefit in eyes with little or no remaining neural rim tissue. Other optic nerve markers that may assist with progression detection include expansion of beta zone parapapillary atrophy and serial optic disc hemorrhage. VF testing remains the standard for progression detection in eyes with severe glaucoma. However, considerable challenges exist to using perimetry in eyes with advanced damage. Greater overall variability exists in VF regions with more depressed visual sensitivity. The Guided Progression Analysis software (GPA, Carl Zeiss Meditec Inc.; Dublin, CA) for detecting event-based VF progression cannot assess change in eyes with MD values depressed below −20 dB or individual points that are severely depressed beyond the range of the analysis software. Finally, automated statistical methods are not commercially available to compare serial 10-2 VFs and VF exams using a size 5 stimulus.

OCT is a rapidly evolving technology that enables noncontact, reproducible, high-resolution imaging of anterior and posterior segment structures. Advances in OCT technology permit imaging of structures relevant to glaucoma, including 3-D volumetric imaging of the human ONH, peripapillary RNFL, and macula.

1. Optic nerve: Eyes with late manifestations associated with severe glaucoma have advanced ONH cupping and narrowing of neuroretinal rim thickness that may preclude change detection using optic disc photography as well as computerized imaging technology. Gardiner and colleagues examined the longitudinal signal-to-noise ratio of RNFL thickness and optic disc parameters (minimum rim width and area) in 157 patients with ocular hypertension or non-endstage glaucoma (MD better than −22 dB). RNFL thickness measurements were found to be superior to optic disc parameters for change detection.

2. RNFL: Progression detection in eyes with severe glaucoma may be challenging due to the concept known as the “floor effect”—points at which no further loss can be detected. OCT measurements of the average RNFL thickness rarely go below 50 µm, which often corresponds to a VF MD below −20 dB. It is unclear whether that residual value corresponds to nerve fibers beyond the resolution limits of the technology or to non-neural tissue (eg, glial cells). Therefore, it is hard to track changes in the thin nerve fiber layer of patients with advanced disease. A patient may appear stable on OCT because the device can no longer detect changes, giving the clinician false confidence that the disease has stabilized. Therefore, statistical strategies that enable detection of localized changes are important for identifying progression and differentiating biological change from test-retest variability.

3. Macula: The macula contains the highest density of RGCs in the retina, and good structure-function relationships exist in the macular region and the central 10-2 VF. Measurements in this area tend to be thicker relative to peripapillary RNFL, even in advanced disease. Therefore, failure of macular segmentation algorithms (ganglion cell–inner plexiform layer [GC-IPL] and the ganglion cell complex [GCC], which includes the combined thickness of the GC-IPL and macular RNFL) may be less likely to occur, and greater dynamic range (eg, signal-to-noise) may enable change detection in severe glaucoma when the RNFL floor effect has been reached. Recent data suggest that in eyes with advanced glaucoma (MD < −12 dB) more GC-IPL tissue remains above the measurement floor compared with other measurements, suggesting that GC-IPL thickness is the better candidate for detecting progression. Moreover, since central vision and central VF are often preserved in eyes with severe glaucoma, assessment of the RGCs that...
reside in the macular region are of interest for detecting change. Longitudinal assessment of total macular thicknesses and GC-IPL can detect progression in advanced glaucoma. In a study investigating rates of total macular thinning over time in stable and progressing eyes with baseline MD worse than −10 dB, the rate of average macular thickness loss was significantly greater in progressing eyes (−5.12 μm/year) compared to stable eyes (−2.22 μm/year). Recently, Belghith et al demonstrated that in 35 advanced OAG eyes (MD < −21 dB) monitored for an average of 3.5 years, only the mean rate of GC-IPL change reached statistical significance, −0.18 μm/year (P = .02). The mean rates of RNFL and optic nerve minimum rim width change were not statistically different from zero.

Future Directions

1. Lamina cribrosa: The lamina cribrosa has become a topic of increasing interest in glaucoma. Advances in OCT imaging, such as enhanced depth imaging OCT and swept-source OCT, permit in vivo imaging of deep tissues of the ONH. Changes in the thickness of the lamina cribrosa, anterior surface features, microarchitecture of the lamina beams or pore size, and localized defects in the laminar insertion may prove to be useful structural endpoints for progression detection.

2. Nerve fiber bundles: Adaptive optics scanning light ophthalmoscopy (AO-SLO) imaging may present a way to further improve our interpretation of circumpapillary RNFL. Localized changes in nerve fiber bundles may be detectable that are not able to be visualized with commercial OCT systems.

3. ONH microvasculature: OCT angiography measures capillary density and shows promise as an alternative method of following patients with advanced glaucoma. Quantitative assessments of the microcirculation in the ONH and peripapillary region are highly repeatable and have been shown to differentiate healthy eyes, glaucoma suspects, and glaucomatous eyes of varying severity with a diagnostic accuracy similar to VF s and RNFL thickness. Longitudinal studies are necessary to validate their role in detecting progression.

Summary

Imaging of the RNFL and macula may detect progression in some eyes with advanced stage glaucoma. Remaining challenges include the floor effect, segmentation failure, and need for sophisticated software to generate automated analyses that differentiate true biological change from test-retest variability. OCT alone is not enough to monitor severe glaucoma, and clinicians should employ 24-2 and 10-2 VF strategies, with or without a size 5 stimulus, for progression detection. Advanced statistical models that incorporate information obtained from structural and functional tests, such as the structure function index, may improve the accuracy of change detection in severe glaucoma.

References


The Role of Perimetry in Severe Glaucoma

Kourosh Nouri-Mahdavi MD

Glaucoma is a major cause of visual disability, diminished quality of life (QoL), and blindness worldwide. The hallmark of glaucoma is progressive loss of retinal ganglion cells (RGC) and their axons. Glaucoma affects many activities of daily living. Increasing severity of glaucoma is associated with worsening QoL affecting important tasks such as reading, walking, and driving. Severity of glaucoma is directly related to measures of vision-related QoL. It has been demonstrated that a 1-dB change in mean deviation (MD) of 24-2 VF is associated with about a 1-unit change in the National Eye Institute Visual Function Questionnaire (NIH VFQ-25) composite score. A recent study found that visual loss in the inferior hemifield (between 13-24 degrees) was highly predictive of collisions in patients with advanced glaucoma. Eyes with moderately advanced to severe glaucoma are at higher risk of disease deterioration and visual loss compared with those with earlier stages of the disease. Eyes with more advanced glaucoma (ie, baseline MD worse than –4.0 dB) were at 60% higher risk of worsening in the Early Manifest Glaucoma Trial (HR: 1.58; 95% CI, 1.10-2.28).

Treatment of glaucoma can slow the rate of disease worsening and prevent further deterioration of visual disability. Timely detection of disease deterioration is of utmost importance for preventing or delaying visual disability and loss of QoL.

What Is Advanced Glaucoma?

There is no universal consensus on how to define advanced glaucoma. Most classifications are too cumbersome, but the Hodapp-Anderson-Parrish criteria that are based on visual fields (VF) are easy to understand and are frequently used. Based on these criteria, a VF mean deviation of −12.0 dB or worse, or involvement of the central 5 degrees of the VF (involvement of any of the 4 paracentral locations of the 24-2 test grid) would constitute advanced glaucoma.

Monitoring glaucoma in eyes with moderately severe to advanced disease is challenging. Both the optic nerve head (ONH) neuroretinal rim thickness and the retinal nerve fiber layer (RNFL) thickness reach their measurement floor in eyes with advanced glaucoma. Both the optic nerve head neuroretinal rim thickness and the retinal nerve fiber layer thickness reach their measurement floor in eyes with advanced glaucoma. Eyes with more advanced glaucoma (ie, baseline MD worse than –4.0 dB) were at 60% higher risk of worsening in the Early Manifest Glaucoma Trial (HR: 1.58; 95% CI, 1.10-2.28).

The Problem with Standard Achromatic Perimetry (SAP) Size III

1. Increased variability with worsening damage
   It has been suggested that by the time the VF threshold at a single location reaches 15-19 dB, the threshold could be measured as low as 0 dB on repeat measurement. In other words, even a reduction of threshold sensitivity to 0 dB at such locations may not represent true worsening. Given this nonhomogeneous variance or variability of threshold over time, it has been suggested that accounting for it statistically may improve detection of progression, although this approach has not yet been clinically adopted.

2. Fewer test locations with residual sensitivity where worsening can be detected

What Type of Perimetry to Use?

There are no good alternatives to SAP at this point. Short wavelength automated perimetry (SWAP) and frequency doubling technology perimetry (FDT) are not useful in advanced disease: either they have a too narrow dynamic range and high variability (SWAP), or there is a lack of longitudinal data (FDT). Similarly, data are scarce with regard to kinetic automated perimetry, although it has been suggested to be useful in eyes with residual central islands.

What Test to Use?

As glaucoma advances, the sensitivity to size III stimulus decreases. Hence, it is now a standard practice to use a larger test stimulus, typically a size V, in such eyes. Changing from size III to size V increases the stimulus area by x16. This in turn leads to increased dynamic range (more steps from normal to complete sensitivity loss) with as many 8 discriminable steps for detection of progression, although it is not quite clear whether the measurement floor changes with conversion to size V.

The change in stimulus size also leads to decreased variability since variability diminishes as sensitivity measurements increase.

In eyes with significant peripheral loss and residual central island, a finer central grid, such as the 10-2 strategy of the Humphrey Field Analyzer (HFA) is also helpful. The central 10 degrees of the VF is the most important region of the VF given its high impact on QoL measures. Up to 50% of eyes with mild to moderate glaucoma have defects within 3 degrees of fixation. Park et al studied 50 eyes with initial paracentral defects that were followed with both 24-2 and 10-2 VFs for more than 5 years. Progression was defined as ≥ 1 worsening point on pointwise linear regression (PLR) analyses. The average VF MD was −2.7 dB (range: −5.2 to 0.9 dB). Forty-eight percent of the eyes progressed based on the 10-2 series as compared to 22% on 24-2 VFs (P < .007). Su et al reported that initial paracentral scotomas in the superior hemifield initially had an arcuate pattern that later deepened and extended to the area 3°-5° above fixation. Field loss tended to be slightly farther from fixation point inferiorly. In another study by Rao et al, there was a significantly higher rate of progression on 10-2 vs. 24-2 VFs in eyes with an average baseline MD of −12 dB or worse. A new index has been recently proposed for detection of central field progression based on 10-2 VFs (central field index).

Issues with Available Tools

StatPac II tools available within the HFA are not available with unconventional testing strategies (10-2 or size V). Also, the event analysis tool provided by the Guided Progression Analysis software is not provided when the MD is worse than around
-15 dB. The pointwise linear regression software (Progressor) is not generally available clinically. There are controversial issues regarding the definition of “worsening” (slope, P-value, and number of changing locations) on PLR.

**Summary of Recommendations on Detection of Disease Progression in Advanced Glaucoma**

- Trend analysis on MD is helpful at all levels of glaucoma damage.
- Trend analysis on visual field index is recommended only in early to moderate glaucoma as it becomes very variable at around ~20 dB and there is no benefit to using it beyond this point compared to MD.
- Use newer techniques for unconventional tests when they become available.
- Do rely on your experience with size III SAP VFs.
- Confirm evidence of VF progression: Any possible progression needs to be confirmed before major therapeutic decisions are taken.
- Take into consideration subjective worsening of vision in later stages of the disease. This finding can sometimes be the only harbinger of disease progression.

**References**

Wrap-up: Best Approach to Diagnosing Glaucoma Progression

Robert N Weinreb MD

Progression is the rule for glaucoma; most glaucoma patients, even if treated, will show progression if followed long enough. Detecting progression in a patient with existing glaucoma is key for determining whether current management is effective or it needs to be changed.

Both optic nerve structure and function should be evaluated for detection of glaucomatous progression. Due to the imperfect nature of testing analysis, individual variability, and the structure–function relationship, progression detected by functional and structural testing may not be corroborative.

I. Visual Field Testing

Visual field (VF) testing is essential for detecting progression throughout the glaucoma continuum. It not only allows staging of the disease but also provides information about the rate of VF loss.

A. Establish a baseline: A good baseline of reliable VFs is essential for monitoring for progression. In general, select a test pattern and thresholding strategy and continue the same test throughout follow-up.

B. Establish the rate of progression: This is helpful for individualizing treatment and in identifying patient at high risk (> 2 dB/year) for progressing to visual disability.

C. Frequency of testing—much may not be better

1. Obtain 2 reliable baseline VF tests, followed by semiannual testing and confirmation of progression through repeat testing.¹

2. Patients with more advanced VF loss or presenting with mild damage at a younger age may require more frequent VF testing, and this should be guided by considering risk factors for progression, age, and life expectancy.

3. Less frequent VF testing can also be considered for patients at a lower risk of progression.

D. When progression is identified, ensure that it is consistent with glaucoma and not related to another cause.

E. Program 10-2 should be considered, particularly ...

1. If OCT macula vulnerability zone (superotemporal and inferotemporal) is affected²

2. For advanced disease

II. Structural Testing

A. Optic disc stereo-photography is a valuable and enduring method for monitoring progression, particularly when obtained at baseline for comparison with subsequent clinical examination. It is particularly useful for identifying hemorrhages and beta zone parapapillary atrophy (both known risk factors for glaucoma progression).

B. Subjective estimates of cup/disc ratio detect only large changes in topography and are insufficient for monitoring structural changes.

C. OCT provides progression detection analyses that can determine whether change is greater than the measurement variability of an individual eye.

1. The prevailing method for reporting the rate of change of retinal nerve fiber layer (RNFL) thickness has mainly consisted of the average circumpapillary RNFL thickness profile generated from a circle scan with a diameter of ~3.45 mm.³

2. As glaucomatous RNFL defects are typically localized, analysis of the topography of the rates of RNFL thickness change is more informative. Peak and mean rates of change of RNFL thickness (but not area of thinning) are indicative of VF worsening.⁴

D. Macular ganglion cell–inner plexiform layer change is frequently detected in early glaucoma before corresponding change in circumpapillary RNFL thickness.⁵ Macula OCT imaging should be included in the serial observation of patients with glaucoma.⁶

E. OCT angiography measurements detect macula vessel density changes in primary open-angle glaucoma eyes without evidence of change in ganglion cell complex thickness.⁷

References

Case Presentation: Doc, My Eye Is on Fire!

Anupama Anchala MD

CASE

Pertinent History
A 40-year-old white male with history of redness, pain, and photophobia of his right eye. On initial presentation the patient was found to have visual acuity of 20/60 O.D. and 20/50 O.S. IOPs were 12 and 13. Of note: on exam there was 3+ injection, Descemet folds, pigment and white blood cells in the anterior chamber with 360 posterior synechiae O.D., and O.S. there was trace endothelial pigment, 3+ pigmented cells, and some broken posterior synechiae.

Initially the patient’s uveitis was managed using prednisolone acetate every hour along with cyclogyl t.i.d. O.U. Over the following year, he had 2-3 uveitis flares and had poor medication compliance. Then he was lost to follow-up for 6 months and was then found to have CF vision in the O.D., with IOPs in the 30s, fibrin in the anterior chamber, and 360-degree posterior synechiae O.U. He was also found to be in early iris bombe configuration. Anterior segment OCT was done and confirmed bombe configuration.

Bilateral laser peripheral iridotomy (LPI) was then recommended and performed. The patient was continued on topical steroids, cyclogyl, and dorzolamide / timolol (Cosopt) b.i.d. O.U. and oral prednisone.

After his iridotomies the patient was again poorly compliant and had another uveitis flare. His left eye LPI was small but patent. The right eye LPI was patent. Soon after, he presented again with headaches and nausea with IOP of 50 in the left eye. Laser iridotomy was attempted but failed. IOP rose to 70, and the patient was admitted for IV medications to manage his IOP. The next day, LPI was successful.

Case Progression:
Bombe or Bust

Surgical Course
The patient was then taken to the operating room for surgical iridectomy and anterior chamber triamcinolone acetonide (Kenalog). After this the patient underwent posterior subtenon Kenalog O.D. and anterior subtenon Kenalog O.S. for improved uveitis control. His IOPs eventually rose to 38 and 32, and plans are to implant Ahmed valves in both eyes to manage his steroid response glaucoma.

Conclusions
Management of uveitis and the complications of the ensuing glaucoma is difficult. This patient exhibited many of the inherent complications of persistent intraocular inflammation: iris bombe, then requiring surgical iridectomy, followed by steroid-response glaucoma necessitating Ahmed valve implantation.

Peter A Netland MD PhD

I. Introduction
A. About 25% of uveitis patients will develop elevated IOP at some time.
B. The prevalence of secondary glaucoma ranges from 10% to 39%.
C. Nearly all require treatment with glaucoma medications.
D. 20%-35% require glaucoma surgery.

II. Medical Management
A. Cycloplegia
B. Corticosteroids
C. Nonsteroidal anti-inflammatory drugs
D. Immunomodulatory therapy

III. Glaucoma Medical Therapy
A. Aqueous suppressants
   1. Beta blockers
   2. Carbonic anhydrase inhibitors
B. Alpha-2-agonists
C. Hyperosmotic drugs
D. Prostaglandins

IV. Laser Therapy
A. Laser iridotomy for pupillary block
B. Limited role for laser trabeculoplasty
C. Cyclophotocoagulation

V. Incisional Surgery
A. Trabeculectomy with mitomycin C
   1. Success rate varies from 51% to 90%.
   2. Useful option, especially when uveitis is well controlled and no previous surgery
B. Glaucoma drainage implants
   1. Uncontrolled uveitic glaucoma: 31%-57% success
   2. Conventional anti-inflammatory therapy: 60%-92% success
   3. Intensive anti-uveitis therapy: 76%-94% success

VI. Other Surgical Procedures
A. Pediatric and juvenile uveitic glaucoma: Goniotomy
B. Minimally invasive glaucoma surgery may be an option in some patients.

VII. Summary
A. Current management includes aggressive and comprehensive treatment of uveitis.
B. Most patients with uveitic glaucoma require treatment with glaucoma medications.
C. Glaucoma drainage implants are effective for surgical treatment of uveitic glaucoma.
D. Prognosis has greatly improved.

Selected Readings


Everything Is More Challenging in Children: A Case of Pediatric Uveitic Glaucoma

Brenda L Bohnsack MD PhD

CASE

Eight-year-old boy with bilateral uveitis referred for uncontrolled IOP, left eye

- Bilateral idiopathic uveitis diagnosed at 6 years of age
- On methotrexate, but unable to taper off of topical steroids
- Status post cataract extraction/IOL, both eyes
- Maximum documented IOP: 32 right eye, 38 left eye
- Unable to tolerate acetazolamide due to GI upset

September 2015

Medications
- Methotrexate 20 mg/week
- Prednisolone b.i.d. both eyes
- Dorzolamide-timolol (Cosopt) b.i.d. both eyes
- Brimonidine (Alphagan) b.i.d. both eyes
- Latanoprost (Xalatan) q.h.s. left eye

Exam
- Visual acuity with correction
  - 20/25
  - 20/35
- Cycloplegic refraction
  - 0.50+1.00x80
  - plano+0.50x90
- IOP by applanation tonometer
  - 15 mmHg
  - 32 mmHg
- Cup-to-disc ratio
  - 0.4
  - 0.75
- Slitlamp exam
  - Deep and quiet, posterior chamber IOL with mild posterior capsule opacification
  - Deep and quiet, posterior chamber IOL with mild posterior capsule opacification
- Gonioscopy
  - Open, few scattered peripheral anterior synechiae

Figure 1. Case Progression: The Plot Thickens

September 2015
- Prednisolone switched to loteprednol; decrease steroid effect on IOP and maintain control of inflammation
- Discussed advancement of steroid-sparing therapy with pediatric rheumatology

October 2015

Medications
- Methotrexate 20 mg weekly
- Infliximab (Remicade) infusions initiated
- Loteprednol b.i.d. both eyes
- Dorzolamide-timolol b.i.d. both eyes
- Brimonidine b.i.d. both eyes
- Latanoprost q.h.s. left eye

Exam
- Visual acuity with correction
  - 20/25
  - 20/35
- IOP by applanation tonometer
  - 15 mmHg
  - 32 mmHg
- Slitlamp exam: 0 cells/hpf
December 2015

- Methotrexate 20 mg weekly
- Infliximab infusions every 4 weeks
- Tapered off of topical steroids
- Dorzolamide-timolol b.i.d. both eyes
- Brimonidine b.i.d. both eyes
- Latanoprost q.h.s. left eye

**Figure 2.**

Case Progression: Happy Ending?

**Case Follow-up**

- 180-degree nasal goniotomy, left eye (January 2016)
- Last follow-up (July 2017)
  - Dorzolamide-timolol and brimonidine b.i.d. right eye
  - No drops left eye
  - Infliximab infusions every 4 weeks
  - Methotrexate 1 mg weekly

**Pediatric Uveitic Glaucoma and Surgical Approach**

- “The highs are higher and the lows are lower.”
- Control of inflammation is key to success.
  - Steroid-sparing therapy
  - Systemic steroids
  - Topical steroids
- Angle configuration is important in determining surgical options.
  - Open angle: angle surgery
    - Goniotomy
    - Trabeculotomy
  - Closed angle
    - Trabeculectomy: Early hypotony leads to bleb flattening and failure.
    - Cycloablation: Increased inflammatory response, high failure rate
    - Glaucoma drainage devices

**Goniotomy**

- Advantages
  - Short operating time
  - Less inflammation
  - Conjunctiva preservation
- Disadvantages
  - Surgeon expertise
  - Open angle
  - Gonioscopic view

**Glaucoma Drainage Devices**

- Standard treatment for adult uveitic glaucoma
- Childhood uveitic glaucoma studies limited by small patient numbers and short follow-up.
- Advantages: Closed angle, less surgeon dependent
- Disadvantages: Increased inflammation, cataract, hardware problems, corneal decompensation, strabismus

**Pediatric Uveitic Glaucoma Surgeries**

**Figure 3.**

**Figure 4.**
Goniotomy in Uveitic Glaucoma: What Is the Evidence?

Allen Dale Beck MD and Sharon Freedman MD

I. Traditional Goniotomy

Ab interno procedure in which an incision is made in the trabecular meshwork under direct visualization. “Trabeculodialysis” is an older term for a procedure that is considered a modification of goniotomy (trabecular tissue is disinserted from the scleral sulcus).

II. Traditional Trabeculotomy

Ab externo procedure in which an opening is created by incising trabecular tissue using a metal trabeculotome via a Schlemm canal entry.

III. Goniosurgery for Glaucoma Associated with Uveitis: Literature Review

A. Kanski JJ, McAllister JA. Trabeculodialysis for inflammatory glaucoma in children and young adults. Ophthalmology 1985; 92:927-930: Eighteen of 30 eyes (60%) successful at 2 years; 13/18 successful eyes (72%) required medical therapy.


1. 71% success with 1 or more goniotomies at 10 years (40 eyes of 31 patients) with an average of 1.6 medications

2. Phakic patients less than 10 years of age without prior surgery and minimal PAS had significantly better outcomes.


1. 69% success at 10 years with 1 or more goniotomies (31 eyes of 31 patients) where goniotomy was the initial procedure

2. Average medication use was 1.2 meds.

3. Success did not correlate with lens status or peripheral anterior synechiae.

E. Complications:

1. Common: Transient hyphema

2. Rare: Increased cataract formation

3. Need for further glaucoma surgery noted with longer follow-up.

IV. Newer Procedures


V. Personal Experience with Angle-Based Procedures in Uveitis

A. Case presentation

B. Indications for treatment

C. Postoperative management
2017 Advocating for Patients

Jeff S Maltzman MD

Ophthalmology’s goal to protect sight and empower lives requires active participation in and commitment to advocacy from every ophthalmologist. Contributions to the following three critical funds are a part of that commitment:

- OPHTHPAC® Fund
- Surgical Scope Fund (SSF)
- State Eye PAC

Please join the dedicated community of ophthalmologists who are contributing to protect quality patient eye care for everybody. The OPHTHPAC Committee is identifying Congressional Advocates in each state to maintain close relationships with federal legislators in order to advance ophthalmology and patient causes. At Mid-Year Forum 2017, we honored nine of those legislators with the Academy's Visionary Award. This served to recognize them for addressing issues important to us and to our patients. The Secretariat for State Affairs is collaborating closely with state ophthalmology society leaders to protect Surgery by Surgeons at the state level. This year has seen an unprecedented effort by optometry to advance its scope of practice via legislation rather than education. Our mission of protecting sight and empowering lives requires robust funding of both the Surgical Scope Fund and the OPHTHPAC Fund. Each of us has a responsibility to ensure that these funds are strong.

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OPHTHPAC is a crucial part of the Academy's strategy to protect and advance ophthalmology's interests in key areas, including physician payments from Medicare and protecting ophthalmology from federal scope of practice threats. Established in 1985, OPHTHPAC is one of the oldest, largest, and most successful political action committees in the physician community. We are very successful in representing your profession to the U.S. Congress.

As one election cycle ends, a new one starts, yet the pressure to remain vocal on our issues remains. Advocating for our congressional issues is a continuous battle, and OPHTHPAC is always under financial pressure to support our incumbent friends as well as to make new friends among candidates. These relationships allow us to have a seat at the table with legislators willing to work on issues important to us and our patients.

The relationships OPHTHPAC builds with members of Congress are contingent on the financial support we receive from Academy members. Academy member support of OPHTHPAC allows us to advance ophthalmology’s federal issues. We need to increase the number of our colleagues who contribute to OPHTHPAC and the other funds. Right now, major transformations are taking place in health care. To ensure that our federal efforts and our PAC remain strong, we need the support of every ophthalmologist to better our profession and ensure quality eye care for our patients.

The significant impacts that OPHTHPAC has made include the following:

- Derailed the onerous global surgery data collection proposal
- Preserved global surgical payments
- Halted the Part B Drug Demonstration
- Continued efforts in collaboration with subspecialty societies to preserve access to compounded and repackaged drugs such as Avastin

Contributions to OPHTHPAC can be made here at AAO 2017 or online at www.aao.org/ophthpac by clicking “Join.” Leaders of the American Glaucoma Society (AGS) are part of the Academy's Ophthalmic Advocacy Leadership Group (OALG), which meets every January in the Washington, D.C., area to provide critical input and to discuss and collaborate on the Academy's advocacy agenda. The topics on the 2017 OALG agenda included panel discussions on the Merit Based Incentive Payment System (MIPS) and APM implementation, as well as Academy analysis initiatives related to the IRIS® registry. In addition, meeting participants discussed the changing paradigm for optometric scope battles, held a roundtable to discuss challenges for surgical subspecialties, and considered opportunities to ensure physician and patient choice regarding access to pharmaceuticals.

At Mid-Year Forum 2017, the Academy and the AGS ensured a strong presence of glaucoma specialists to support ophthalmology’s priorities, and a record number of ophthalmologists visited members of Congress and their key health staff to discuss ophthalmology priorities as part of Congressional Advocacy Day. The AGS remains a crucial partner with the Academy in its ongoing federal and state advocacy initiatives.

**Surgical Scope Fund**

The Surgical Scope Fund (SSF) provides grants to state ophthalmology societies to support their efforts to derail optometric surgery proposals that pose a threat to patient safety. Since its inception, the Surgery by Surgeons campaign and the SSF, in partnership with state ophthalmology societies, has helped 32 state / territorial ophthalmology societies reject optometric scope of practice expansion into surgery.

In 2017, your colleagues serving on the Academy’s Secretariat for State Affairs, along with State Governmental Affairs staff and the leaders of state ophthalmology societies, have been put to the task while dealing with an unprecedented number of simultaneous legislative battles. Eleven states have been affected so far this year:

- Alaska
- California
- Florida
- Georgia
- Illinois
- Iowa
- Maryland
- Massachusetts
- Nebraska
- North Carolina
- Pennsylvania

**Continued efforts in collaboration with subspecialty societies to preserve access to compounded and repackaged drugs such as Avastin**

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Patient safety setbacks as well as victories will be reviewed during the presentation, but do know that in each of these legislative battles, the benefits from SSF distributions are abundantly clear. The best lobbyists and public relations consultants are contracted as necessary, and media campaigns (including TV, radio, and social media) to educate the voting public are launched when needed to secure success and stop optometry from expanding its scope of practice to include surgery. Each of these endeavors is very expensive, and no one state has the resources to wage one of these battles on its own. Ophthalmologists must join together and donate to the SSF to fight for patient safety when a state faces a scope battle over optometric surgery.

The Academy relies not only on the financial contributions to the SSF from individual ophthalmologists and their practices, but also on the contributions made by ophthalmic state, subspecialty, and specialized interest societies. We thank the AGS for its contribution to the SSF in 2017 and look forward to continued collaboration. Contributions to the SSF can be made here at AAO 2017 or online at www.aao.org/ssf.

### State Eye PAC

It is also extremely important for all ophthalmologists to support their respective State Eye PACs because campaign contributions to legislators at the state level must come from individual ophthalmologists and cannot come from the Academy, OPHTHPAC, or the SSF. 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.

### Action Requested: ADVOCATE FOR YOUR PATIENTS

Academy SSF contributions are used to support the infrastructure necessary in state legislative / regulatory battles and for public education. PAC contributions are necessary at the state and federal levels to help elect officials who will support the interests of our patients. Contributions to each of these three funds are necessary and help us protect sight and empower lives. SSF contributions are completely confidential and may be made with corporate checks or credit cards, unlike PAC contributions, which must be made by individuals and are subject to reporting requirements.

Please respond to your Academy colleagues and be part of the community that contributes to OPHTHPAC, the SSF, and your State Eye PAC. Please be part of the community advocating for your patients now.

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We are in the midst of a glaucoma renaissance. Over the past two decades, we have seen an acceleration of advances in glaucoma diagnostics and therapeutics that impact patient care, and the best and brightest are being drawn to our subspecialty in this exciting era, with many more discoveries to come. This lecture will review recent glaucoma therapeutic advances and highlight the partnerships between practitioners, innovators, regulators, and others. These leaders have created a unique environment that will undoubtedly lead to better glaucoma care and continue to make glaucoma the most exciting of all subspecialties for clinicians, researchers, and educators.
Angle Considerations for Surgery

E Randy Craven MD

I. Traditional Choice of Glaucoma Surgery
   A. Considerations
   B. IOP “goal” can be achieved with surgery and 1 or 2 medications.
   C. Choice of which technique is based on other factors.

II. Most patients who need glaucoma surgery fall into 1 of 3 categories:
   A. Bad advancing glaucoma
   B. Moderate
   C. Suspect or mild
      1. Good view and closed angle
      2. Good view and open angle

III. Many minimally invasive options use an ab interno (“from inside”) approach.
   A. Endoscopic cyclophotocoagulation
   B. XEN™: Gel stent
      1. Can be gonio-free
      2. Need to see the iris and the anterior-to-posterior position when inserting
      3. XEN bypasses trabecular and scleral resistance.
         a. Subconjunctival drainage of aqueous fluid
         b. Successful IOP-lowering depends on amount of flow or drainage through the sclerostomy and extent of conjunctival wound healing.
   C. Viewing the angle: MIGS and device-based procedures
      1. Trabecular outflow: Must see
      2. iStent and “inject”
      3. Hydrus
   D. Suprachoroidal: Usually view
      1. CyPass
      2. iStent “Supra”

IV. Why Physiologic Outflow Makes Sense
   A. What is the canal of Schlemm?
   B. Role of the canal
   C. Why choose trabecular outflow?
      1. Pharmacologic options should still work.
      2. Aqueous suppressants
      3. Parasympathomimetic
      4. Prostaglandin analog
      5. Low likelihood of complications

D. Thoughts on removing the trabecular meshwork
   1. May not allow the pulsatile action to increase collector channel outflow
   2. Trabectome
   3. Gonioscopic-assisted transluminal trabeculotomy (GATT)
   4. Trabeculotomy / goniotomy

V. Algorithm for Choices
   A. Trabecular bypass
      1. Clues to viable outflow
      2. Approach to success
   B. Suprachoroidal
      1. Canal not working
      2. Not advanced disease
   C. Gel stent with subconjunctival bleb
      1. Refractory glaucoma
      2. Others not working
   D. Trabecular extirpation
      1. Indications
      2. Why not always?
Canalizing

Davinder S Grover MD

I. Introduction

II. Brief Overview of Gonioscopy-Assisted Transluminal Trabeculotomy (GATT)

III. Highlight of Key Surgical Pearls
   A. Beginning surgeon
   B. Experienced angle surgeon

IV. Typical Postoperative Management

V. Management of Common Postoperative Complications

VI. Discussion of Cost-Effective Health-Care Delivery

VII. Conclusion
Canal Stenting

Paul J Harasymowycz MD

Patient selection is an important consideration for successful canal surgery. Patients with open angles who are well controlled by medical therapy and present with concurrent cataract may benefit the most from combined surgery.

Knowing the anatomic landmarks of the angle and performing gonioscopy routinely before and after angle surgery are also important. Identifying collector channels before implantation, targeting areas of increased angle pigmentation or blood reflux into the Schlemm canal, and verifying outflow intraoperatively enhances surgical success.

It is also important to ensure excellent visualization of the angle during surgery. This will mean initially avoiding patients with head tremors, nystagmus, opaque or hazy corneas and ensuring proper angulation of the microscope and the patient’s head, as well as avoiding incising small corneal or conjunctival vessels that may bleed and obscure the fine details of the angle structures. Consideration should be given to performing the canal stenting before cataract extraction, thereby ensuring corneal clarity.

Two-year data from clinical trials has shown reduced IOP and number of medications after combined surgery.
Canal Nonstenting

*Nathan M Radcliffe MD*

I. Rationale for Removing the Outer Wall of the Canal of Schlemm
   A. Ab interno trabeculectomy
      1. Technique
      2. 12-month safety and efficacy data
   B. Ab interno trabeculotomy
      1. Technique
      2. 12-month safety and efficacy data
   C. Ab interno trabeculotomy and viscocanalostomy technique

II. Clinical Tips
   A. Patient selection / considerations
   B. Intraoperative considerations for canal surgeries
      1. Wound construction
      2. Intraoperative considerations
      3. Postoperative approach
Suprachoroidal

Iqbal K Ahmed MD
Ab Interno Subconjunctival

Hady Saheb MD

I. Preoperative Considerations
   A. Anti-inflammatories
   B. Antifibrotics: When, where and how much?
   C. Approach to anticoagulants
   D. Orbital anatomy

II. Intraoperative Considerations
   A. Marking and incision planning
   B. Visualization
   C. Too long, too short, and not visible: What to do?

III. Postoperative Considerations
   A. What to expect: Clinical trial results
   B. Unfolding the XEN: kinks, pigtails and U-turns
   C. Adjunctive medications
   D. Bleb imaging
   E. Needling: When, why, and how?
   F. Complications and reoperations

Selected Readings


Should We Be Treating CSF Pressure in Glaucoma?

John Berdahl MD

I. Why?
   A. Why does CSF pressure matter?
   B. What are the unmet needs in glaucoma?
      1. Severe glaucoma
      2. Normal-tension glaucoma

II. What?
    What is the clinical evidence that CSF pressure in glaucoma matters?
    A. Clinical studies
    B. Basic science studies

III. How?
    A. How could we treat CSF pressure in glaucoma?
       1. Drugs
       2. Surgical approaches
    B. How could we use CSF pressure to determine the target pressure?
       1. Noninvasive approaches to measuring CSF pressure
II. Why Is the Optic Nerve Head So Sensitive to Pressure?
The scleral canal is a “weak point” in an otherwise tough corneoscleral shell.

A. Computer modeling and direct measurements indicate that optic nerve head tissues experience large deformations/mechanical insults due to changes in IOP and CSFp.

B. Resident cells are mechano-sensitive (see above).

C. These findings are consistent with observations of early axonal transport blockade occurring in animal models at the level of the scleral canal.

II. What Can We Do about It?

A. A method to assess “biomechanical risk” would be helpful.

Unfortunately, there are no reliable clinical methods to assess relevant tissue properties and/or direct measures of “biomechanical risk.” Preclinical research seeks to leverage OCT imaging to make such estimates. This important area will benefit from advances in imaging and image analysis.

B. A method to modify relevant ocular biomechanics could be a useful therapeutic strategy.

Preclinical studies are investigating novel neuroprotective treatments based on mitigating biomechanical effects on optic nerve head cells and tissues. Much work remains to be done.

Selected Readings

Environmental Risks: Can Glaucoma Be Prevented?

Louis R Pasquale MD

I. Things to Consider

A. “Glaucoma” is a heterogeneous group of diseases, and some environmental risk factors may be specific for certain disease subtypes.

B. Randomized clinical trials (RCTs) provide the highest evidence about whether an environmental factor, or any factor, reduces glaucoma risk.

C. Proving that a factor lowers IOP does not necessarily mean it reduces glaucoma risk.

D. Patients have a strong interest in the subject of modifiable risk factors for glaucoma.

E. We want to adopt strategies that are consistent with overall good vision and systemic health.

II. Existing RCTs for Environmental Factors in Relation to Glaucoma

A. Black currant anthocyanins reduce risk of glaucoma compared to conventional therapy alone.1

B. Oral antioxidant supplements with or without omega-3 fatty acids are not a useful adjunctive treatment for mild / moderate glaucoma in the short term.2

C. Ginkgo biloba had no effect on mean defect or contrast sensitivity in normal-tension glaucoma patients.3

III. Candidate Environmental Risk Factors with Rationale for Reducing Glaucoma Risk

A. Dietary patterns / food groups
   1. Mediterranean diet: Improves insulin resistance, which may be important in some glaucoma subtypes.
   2. Ketogenic diet (low carbohydrate, high protein, high fat, with the latter 2 sourced from vegetables): Improves energy biogenesis in the optic nerve head4
   3. Leafy green vegetables: Excellent source of nitrates, which may improve nitric oxide signaling in glaucoma5

B. Nutrients / supplements
   1. Resveratrol: Multiple mechanisms implicated in experimental glaucoma
   2. Niacin: Improves mitochondrial dysfunction in experimental glaucoma
   3. Coenzyme Q10: Along with vitamin E, showed improved pattern electroretinogram function in open-angle glaucoma
   4. Ginkgo biloba: Improves vascular function

C. Other lifestyle factors
   1. Sleep: Keep head elevated and avoid sleeping with worse eye in dependent position; this lowers IOP and reduces visual field progression.
   2. Exercise: Lowers IOP; may depend on the type of exercise (aerobic vs. isometric vs. toning)
   3. Maintain oral hygiene6: Reduces neuroinflammation
   4. Maintain a healthy weight for age, sex, and height: Mechanism unclear
   5. Protect the eyes from solar exposure: May be important in exfoliation glaucoma

IV. Environmental Exposures for Glaucoma Patients to Consider Avoiding

NB: Even though these lifestyle behaviors elevate IOP, there is no definitive evidence that they actually produce or worsen glaucoma.

A. Head-down yoga postures are documented to produce marked elevation of IOP.7

B. Prolonged playing of high wind instruments increases IOP transiently during play.8

References


In Vivo Imaging of Retinal Ganglion Cells

Christopher Kai-shun Leung MD MBChB

I. What Technologies Are Available for Imaging Retinal Ganglion Cells and Their Axons?
   A. OCT
   B. Confocal scanning laser ophthalmoscopy
   C. Two photo microscopy

II. What Have We Learned from Imaging the Retinal Ganglion Cells and their Axons?
   A. Topography of the distribution of retinal ganglion cell axons in the retina and the patterns of disease progression in glaucoma
   B. Morphology of axon degeneration and dendritic shrinkage
   C. Bioenergetics of retinal ganglion cell degeneration

III. What Is the Promise of Retinal Ganglion Cell Imaging Research?
   A. Prediction of functional decline in glaucoma patients
   B. Development of neuroprotective/neuroregenerative therapies
   C. Understanding the metabolism and molecular mechanisms of retinal ganglion cell degeneration in glaucoma and other optic neuropathies
Gene Therapy for Glaucoma: Where Are We Now?

Janey L Wiggs MD PhD

Gene Therapy Definition
Gene therapy is the therapeutic delivery of nucleic acid polymers into a patient’s cells as a drug to treat disease. Therapeutic nucleic acids can be DNA, RNA, antisense molecules, or viruses. Genetic information may also inform non–nucleic acid therapies implementing small molecules or proteins (gene-based therapies). Gene-based therapies are generally divided into 2 categories: (1) using a gene delivery system to provide a therapeutic molecule, such as an agent to lower IOP or promote ganglion cell survival, and (2) using genes and other nucleic acids to repair mutant genes, replace genes lost to a mutation, or restore function lost due to a genetic mutation.

Advantages for Glaucoma
Delivery of therapeutic genes or other molecules can result in long-acting treatment, which would eliminate the need for frequent delivery of topical medications. Long-acting therapeutics could also reduce the need for surgical intervention. The accessibility of the eye generally and the opportunity for targeting drug delivery to the anterior chamber and/or posterior chamber is also an advantage for gene-based therapies for glaucoma.

Challenges for Glaucoma
Viral vectors and other molecules can cause inflammation, which could increase IOP. Preventative steroid delivery to reduce inflammation could also contribute to IOP elevation. Viral vectors and other molecules need to be able to be targeted to appropriate cell types. Modified adeno viral vectors have been shown to efficiently transduce the trabecular meshwork without initiating an inflammatory response in living rats and monkeys.

Gene Delivery to Lower IOP
Preclinical studies have assessed the efficacy of using gene delivery of therapeutic molecules to reduce IOP. Two general categories of genes have been employed: (1) genes altering extracellular matrix function and integrity (e.g., matrix metalloproteinases 1 and 3, and plasminogen activator tissue) and (2) genes that are involved in pathways regulating aqueous outflow (e.g., RhoA/Rho-kinase, adenosine 1 agonists, nitric oxide donors, phosphodiesterase inhibitors, prostaglandin agonists, and potassium channel openers). Adeno-viruses have been optimized as one vehicle for delivery of desired genes to the trabecular meshwork and other outflow cells.

Neuroprotection Using Gene-Based Therapies
Genes coding for neurotrophins (e.g., BDNF, CTNF, and GDNF) have been investigated as neuroprotective therapies in animal models. Other molecules that could be delivered as effective neuroprotective therapies include antiapoptotic genes and antioxidants.

Gene Therapy to Replace a Mutant Gene or to Restore Function Lost to a Genetic Mutation
Loss of function mutations in TEK (TIE2) or CYP1B1 can cause early-onset forms of glaucoma. Restoring function through delivery of a normal copy of the disease-causing gene could reduce or eliminate the need for medical and surgical therapies. Augmenting expression of the TEK binding partners (ANGPT1 and ANGPT2) could also be therapeutic in TEK mutation carriers.

Gene Editing to Repair a Genetic Defect
Myocilin (MYOC) mutations cause intracellular stress through a “gain of function” mechanism, and gene-based therapies need to remove the responsible mutations. Antisense molecules can reduce expression of mutant MYOC, and gene editing approaches such as CRISPR/cas 9 could remove MYOC mutations.

Future Directions
Preclinical studies are suggesting that gene-based therapies for glaucoma could be developed as successful therapeutics and could reach the clinic in the next few years. Prior to initiating human clinical trials, novel therapies need to be tested for efficacy and toxicity in relevant animal models. Human studies will also need to establish safety, as well as showing efficacy that meets or exceeds current medical and surgical therapies. Repairing genetic mutations underlying early-onset glaucomas, such as congenital and juvenile glaucoma, could be initial targets, as these are severe diseases that typically require surgery early in life for management.

Selected Readings


Neuroregeneration and Stem Cells in Glaucoma Therapy

Jeffrey L Goldberg MD PhD

What are the prospects for using stem cells in glaucoma therapy? The premise of replacing trabecular meshwork cells to elicit long-term IOP control is one area of study I will not review here. Instead, I will focus on the question of whether retinal ganglion cells can be replaced to restore vision in glaucoma.

In glaucoma as in other optic neuropathies, retinal ganglion cell loss is permanent, as the adult mammalian retina cannot endogenously generate or replace retinal ganglion cells. Therapeutic approaches in which retinal ganglion cells are produced in vitro and subsequently transplanted into the retina may provide a hope for vision loss in the most severe cases of glaucoma. There are two key elements to bring this forward with strong scientific premise: differentiating stem cells into retinal ganglion cell–like progeny, and transplanting cells with successful integration into the retina, including axon growth down the optic nerve and back to the brain.

Various embryonic or induced pluripotent stem cells can be driven to differentiate into retinal ganglion cells and other specific cell types. What are the molecular mechanisms that regulate retinal ganglion cell development? Recent work establishes SoxC transcription factors as key for specifying retinal ganglion cell differentiation from rodent retinal progenitors and from human-induced pluripotent stem cells. These cells express retinal ganglion cell markers and are able to fire action potentials similar to endogenous retinal ganglion cells. These and other developmental factors missing in previous stem cell–derived retinal ganglion cell differentiation are now able to increase efficiency in generating human retinal ganglion cells.

How to integrate retinal ganglion cells after transplant into the vitreous? Recent work has demonstrated significant improvements in retinal ganglion cell integration in animal models. In these experiments, transplanted retinal ganglion cells extended axons toward the optic nerve head and into the optic nerve. They received synapses from the host retina, and when probed with electrophysiological techniques, transplanted retinal ganglion cells were responsive to light in a fashion similar to normal retinal ganglion cells.

Such studies provide encouraging evidence supporting the potential for retinal ganglion cell replacement therapies, but many questions remain. Advances are needed in understanding the basic biology of human-induced pluripotent and other stem cells, together with further progress in understanding the regulation of retinal ganglion cell development and circuit integration into the adult retina. Together these give hope for the possibility of vision restoration after stem cell–derived replacement therapies in glaucoma and other optic neuropathies.
Case Presentation

Molly Walsh MD MPH
Circadian Factors in Glaucoma Progression: Daytime

Anne L Coleman MD PhD

There is growing interest in the role of dietary and lifestyle factors in glaucoma. Identifying such factors will provide insight into the pathogenesis of glaucoma and help find preventive measures focused on altering certain habits. In light of the strong positive relation between IOP and open-angle glaucoma (OAG), it is posited that factors altering IOP have the potential to also modify the risk of OAG. Therefore, studies in this area may be focused either on modifiable IOP-dependent or IOP-independent risk factors for the development and progression of glaucoma. In this presentation, I would like to present a summary of the current literature looking into daytime factors attributed to IOP fluctuation, and possibly, glaucoma progression.

Among dietary factors, perhaps caffeine is the most commonly studied substance, and publications on this topic date back to 1952. Overall results indicate that the consumption of coffee causes a clinically insignificant transient increase in IOP of 2 mmHg for a 2-hour period in OAG and ocular hypertension (OHT) patients, but has no significant effect on normal subjects. In clinical practice, physicians should consider advising glaucoma patients to moderate caffeine consumption and to avoid caffeine intake prior to visits requiring IOP evaluation. A transient IOP elevation also occurs after acute oral water intake, which may be attributable to factors affecting aqueous drainage.

To examine the potentially beneficial effect of increasing total dietary antioxidant, Kang and colleagues applied the Food Frequency Questionnaires to the large samples in the Nurses’ Health and the Health Professionals Follow-up studies. While their results showed no strong associations overall, they found a 33% decreased risk of OAG in highest quintile of vitamin E intake compared to lowest (RR = 0.67, 95% CI, 0.50–0.90). The Study of Osteoporotic Fractures demonstrated that higher intake of certain fruits and vegetables may be associated with a decreased risk of glaucoma in older women, and that daily consumption of fruit and dark-green leafy vegetables may decrease the likelihood of having glaucoma in older African American women.

A number of studies looking at the possible effect of exercise on IOP, conducted between the 1960s and 1990s, demonstrated that exercising and physical activity could temporarily lower IOP. The IOP-lowering effect of physical activity was observed in subjects with and without glaucoma. In glaucoma patients, the percentage reduction reported in various studies ranges between 17.5% and 51%. Proposed reasons for this variation include duration and type of exercise, timing of IOP assessment, demographic characteristics, and seasonal differences. Roddy et al conducted a meta-analysis to verify the influence of participant characteristics, exercise intensity, and duration. Although they found an almost 2-fold greater effect for sedentary populations than for normally active populations, intensity and duration did not explain the difference between these 2 groups.

To examine the relationship between physical activity and ocular perfusion pressure (OPP), the European Prospective Investigation into Cancer (EPIC)-Norfolk study categorized participating individuals as inactive, moderately inactive, moderately active, or active. Active people had a lower risk of mean OPP ≤ 40 mmHg and diastolic OPP ≤ 50 mmHg after adjusting for age, sex, social class, and body mass index. The association between physical activity and perfusion pressure was independent of IOP, but largely mediated through diastolic blood pressure. The literature also contains evidence pointing to the “transiently” elevated IOP readings associated with playing high wind instruments (such as the oboe), and the effect of the Valsalva maneuver on anterior chamber parameters. Studies have also examined changes in IOP, OPP, and ocular hemodynamics as a result of wearing swimming goggles, diving masks, and tight neckties.

Selected Readings

Circadian Factors in Glaucoma Progression: Night-time

JoAnn Giaconi MD

We spend up to a third of our day in the important physiologic state of sleep, which takes place in a supine position. Multiple studies have evaluated the effect of body position on IOP. In healthy subjects, Linder et al found that IOP increased within a minute of changing position from upright to supine or inverted. Full inversion produced a 3-fold increase in IOP, and intermediate angles produced smaller elevations. This increase in IOP is assumed to be due to an immediate increase in episcleral venous pressure.

Multiple studies have examined IOP over a 24-hour period. Sleep lab studies measuring IOP every 2 hours in the habitual sitting position during the day and supine position at night found IOP to be elevated in the nocturnal period in normal, ocular hypertensive, and glaucoma patients. However, there is also an increasing number of studies in healthy individuals showing that peak IOP does not necessarily occur at night. A study of 206 healthy individuals in the Handan Eye Study in whom IOP was measured every 3 hours showed that 52% of subjects had a nocturnal peak IOP, 17% a diurnal peak, and 31% had no evident pattern of IOP peaking. Song and colleagues prospectively studied 10 healthy subjects in a sleep lab once weekly for 5 weeks and found that 24-hour IOP fluctuations were not reproducible from week to week in individual subjects, with peaks occurring at different times of the 24-hour period. Renard et al studying normal-tension glaucoma subjects found that 54.4% had a diurnal peak IOP, 36.5% had a nocturnal peak, and 9.1% had no 24-hour rhythm.

The data on nocturnal IOP elevation above is possibly flawed due to the nonphysiologic waking of subjects for measurements. To overcome this, a contact lens sensor (CLS) that measures relative (not absolute) IOP in arbitrary units has been used to study IOP rhythms. Upward drift in the output over a 24-hour period of wear has been found by some investigators, which puts into question the meaningfulness of the data. In one study, CLS values were found to be higher in the wake state than in the sleeping state in primary open-angle glaucoma / NTG subjects. In another study, average CLS output did show increased values at night during sleep, and IOP-related parameters obtained with the CLS were associated with visual field progression in treated glaucoma eyes. In a CLS study in Japan comparing treated NTG subjects to normal subjects, treated NTG subjects were found to have larger fluctuation in IOP over 24 hours. The peak IOP occurred during the nocturnal period in 91.7% of normal subjects and in only 57.1% of NTG subjects. Similarly, in a study of 40 U.S. glaucoma or glaucoma-suspect patients, a repeated nocturnal IOP peak was seen in 62.9% of patients and no repeatable acrophase in 17.1%.

What does a higher supine IOP possibly mean for glaucoma development and progression? There are only a few published studies looking at this topic. Two small studies have reported worse visual field mean deviation in eyes with greater differences between their sitting and supine IOP. There is also a case report of a patient with congenital glaucoma who suffered progressive optic nerve damage attributed to years of practicing the Sirsasana posture (headstand) during yoga. Using data from the Korean National Health and Nutrition Examination Survey V, 2010 to 2012, investigators found no association between sleep duration and glaucoma in nonoverweight individuals, but they did find an association in overweight individuals between glaucoma and sleep duration < 5 hours per night or > 9 hours per night. More studies measuring multiple 24-hour periods in larger numbers of normal, glaucoma suspect, and glaucoma subjects are needed to work out what association there is between physiologic changes during sleep and glaucoma. Likely, there are compensatory mechanisms to preserve the nerve when our eye pressure increases in the supine position, which may be deranged in eyes with glaucoma.

Obstructive Sleep Apnea Syndrome (OSAS)

In obstructive sleep apnea normal sleep physiology is disturbed. Obstructive sleep apnea is characterized by intermittent episodes of partial and complete airway obstruction that lead to apneas and hyponeas. Repeated decreases in arterial oxygen saturation, fragmented sleep, and sympathetic stimulation caused by OSAS have been associated with life-threatening conditions, including hypertension, myocardial infarction, stroke, congestive heart failure, and cardiac arrhythmia. What about an association with glaucoma?

Two studies using health systems billing databases failed to find a significant association between sleep apnea and glaucoma. Many cross-sectional studies studying 30 to 250 OSA subjects do find a higher prevalence of glaucoma than expected. As well, cross-sectional studies of glaucoma subjects have reported higher than expected prevalence rates of OSA. A meta-analysis of 12 studies and 36,909 subjects reported a significantly increased risk of glaucoma in OSAS patients (odds ratio [OR] 1.65; 95% CI, 1.44-1.88). Severe OSAHS patients had an even higher glaucoma risk (OR 5.49; 95% CI, 1.04-33.83). A second meta-analysis of 6 studies involving 2,288,701 participants also found a significant association between OSA and glaucoma (OR for case-control studies 2.46; 95% CI, 1.32-4.59 and OR for cohort studies 1.43; 95% CI, 1.21-1.69). Studies have also examined an association between retinal nerve fiber layer thickness and OSA. A meta-analysis of these studies, including 9 studies with 1086 cases and 580 controls, found that average retinal nerve fiber layer thickness in moderate / severe OSAS was lower than in healthy controls. The superior and inferior quadrant thicknesses were lower than in controls, while there was no difference seen in the nasal and temporal quadrants.

In OSA there is a persistence of inspiratory effort during airflow interruptions. During the inspiratory effort there is negative intrathoracic pressure that encourages venous return to the heart. This is the opposite of what happens during a Valsalva maneuver, where elevated intrathoracic pressure decreases venous return from the head, which can transmit to the ocular venous pressure. IOP has been shown to decrease during forced inspiratory efforts or apneas, both in a lab study on healthy young adults and with continuous 24-hour CLS monitoring in
OSAS subjects. The association between glaucoma and OSAS may be pressure independent—unless continuous positive airway pressure (CPAP) contributes, since this has been found to elevate IOP. Authors have surmised that the link between OSAS and glaucoma may be due to the other physiologic changes of OSAS, such as vascular dysregulation and chronic hypoxemia, which lead to a generalized inflammatory response with release of plasma endothelin, decreases in nitric oxide, and platelet activation.

**Selected Readings**


Innovations in Tonometry

Yvonne M Buys MD

Introduction

Intraocular pressure (IOP) remains the most important objective measure in glaucoma. Although it is no longer used in the definition of glaucoma, IOP can be used to characterize the type of glaucoma, which has implications for treatment. In addition IOP is used to monitor our glaucoma patients; it is the most common outcome measure in glaucoma studies; and it is used to determine the efficacy of glaucoma medications and procedures. Most importantly IOP currently is the only modifiable risk factor in glaucoma management. The Goldmann applanation tonometer (GAT), developed in the 1950s, is the most frequently used instrument in ophthalmology and remains the current reference standard for tonometry.

GAT is based on the Imbert-Fick law, which states that the pressure within a sphere is equal to the force required to flatten a certain area. This law assumes that the wall of the sphere is perfectly thin, elastic, and flexible. Although these features are not satisfied with the eye, at an applanation diameter of 3.06 mm, corneal thickness of 550 µm, and radius of curvature of 7.8 mm the biomechanical factors of the eye and capillary attraction of the tear film essentially cancel each other, and the IOP can be measured. For eyes not satisfying these conditions GAT either under- or overestimates the “true” IOP. Aside from physiologic variation and disease-related corneal changes, corneal modifying procedures also present challenges, including LASIK, corneal rings, crosslinking, and Boston KPros. Other limitations of GAT include the fact that a static measurement is being taken of a dynamic variable. Finally, since the biprism tip contacts the eye, proper sterilization between uses is required, and the tonometer must be regularly calibrated.

Summary of Limitations of GAT

- Measurement affected by corneal biomechanical factors: central corneal thickness, corneal curvature, elasticity, rigidity
- Snapshot measurement
- Cannot be used in presence of cornea surface irregularity, Boston KPro, etc.
- Nonportable
- Sterilization of tip required (disposable tips and covers available)
- Need for regular calibration

Due to these limitations, innovations in IOP measurement technologies have resulted in several newer tonometers:

- **Rebound tonometry** (Icare ic100, 2007; Icare TAO1i, 2007; Icare HOME, 2017)
  - No anesthesia required
  - Pediatric and home version available
- **Diaton** (BiCOM Inc., 2008)
  - Transpalpebral transscleral tonometer
- **Triggerfish** (Sensimed, 2016)
  - Continuous IOP measurement
  - Records in mVeq not mmHg

These newer techniques and their limitations will be discussed, along with comparison studies to GAT.

Selected Readings

Innovations in Controlling IOP

Sayoko E Moroi MD PhD
Case 1: Still Narrow after Laser Peripheral Iridotomy—Is Clear Lens Extraction on the Table?

*Sunita Radhakrishnan MD*

**CASE**

The lens plays an important role in primary angle closure. Several studies have shown the benefit of cataract extraction in patients with primary angle-closure glaucoma, and a recent study (the EAGLE study) also demonstrated the benefit of clear lens extraction in a mixed group of patients with PACG and primary angle closure with IOP > 30 mmHg. In this presentation, a patient with closed angles despite laser peripheral iridotomy will be discussed.

**References**


Case 2: Premium IOLs in Glaucoma Patients—The Role of Toric and Presbyopia-Correcting Lenses

Regine Pappas MD

CASE

Brief History
Surgical management of a patient with mild to moderate glaucomatous loss undergoing cataract surgery with a presbyopia-correcting toric lens for moderate astigmatism in combination with a minimally invasive glaucoma procedure.

Case Summary
Patient with unaided acuity of 20/40 with glare testing of 20/70 in the left eye. Preoperative keratotomy was 41.46 @ 017 and 43.27 @ 107. Patient had nuclear sclerosis of 2-3+ with unknown maximum documented IOP (Tmax). Cup-to-disc ratio was 0.5 in the right eye and 0.6 in the left eye. Patient was on bimatoprost (Lumigan) preoperatively. Initial treated pressures were 17 and 19 mmHg, respectively. OCT using the Optovue demonstrated moderate inferior retinal nerve fiber layer changes and moderate inferior ganglion cell complex loss in both eyes. Frequency doubling technology perimetry testing demonstrated a single isolated defect in the right eye and para-central defects in the left eye. Planned procedure was canalo-plasty Visco 360 and cataract surgery with a Symfony toric lens in the left eye. Successful surgery was performed, with resultant outcome of 20/25−2 uncorrected vision at distance and 20/20 at near. Pressure postoperatively was 12 mmHg without drops at Week 1. Pressure at Month 1 was 16 mmHg.

Conclusions
Patient with mild to moderate glaucoma not well controlled on 1 medication with a visually significant cataract successfully receives presbyopia-correcting toric lens (ZXT225 lens). Uncorrected visual acuity resulted in corrected distance and near of 20/25 and 20/20, respectively, with resultant reduction of pressure to 16 mmHg without the use of glaucoma medication.
Case 3: Cataract in Pseudoexfoliation—
IOL Type, Capsular Tension Ring, Role of Femtosecond Laser

Michael Greenwood MD and Alan Crandall MD

CASE

Pseudoexfoliation syndrome (PXF or PEX) is an age-related systemic syndrome that targets mainly ocular tissues through the gradual deposition of white flaky fibrillary material from the lens, mainly on the lens capsule, ciliary body, zonules, corneal endothelium, iris, and pupillary margin. There is a higher prevalence of open-angle glaucoma in about 50% of these patients.

Challenges that can occur during cataract surgery include retained nucleus or lens fragments, zonular dialysis, phacodonesis and pseudophacodonesis, and later IOL subluxation.

During this case, we will be discussing the role of IOL selection, capsular tension rings, and femtosecond laser, along with other tools in our toolbox that can help us achieve a favorable outcome in these cases. We will also discuss what can happen following cataract surgery, and what options may be available.
Case 4: IOL Selection with Post-trab Hypotony—How to Choose the Best Fit?

Michele C Lim MD

**CASE**

Cataract surgery in a post-trabeculectomy eye presents unique challenges in IOL selection. Our modern theoretical IOL equations consider the biometric features of the eye, and past studies have shown that trabeculectomy can alter these features. For example, the axial length can be shorter in an eye with low pressure,1,2 the anterior chamber can be shallower, and the corneal curvature can be altered2,3 by the presence of a trabeculectomy. This case presentation and discussion will highlight challenges and choices made when selecting the proper IOL in a patient who needs cataract surgery in the setting of hypotony.

**Case Presentation**

J.A. is an 80-year-old Hispanic man with a history of severe primary open-angle glaucoma. He underwent trabeculectomy surgery, first in the right eye and then in the left eye. After surgery in the left eye, the chamber shallowed and his IOP was low. Special ophthalmic testing was performed; the results will be shown as part of the presentation. He developed a brunescent cataract with poor vision and requested cataract surgery for his left eye.

**Past Ocular History**

- Primary open-angle glaucoma, advanced, both eyes
- Toxoplasmosis scars, both eyes

**Brief Eye Exam**

- Vision
  - Right eye: 20/100
  - Left eye: 20/150
  - Preop refraction O.S.: −1.00+2.25x078 20/150
- Slitlamp exam, left eye
  - Low avascular bleb superiorly
  - Shallow anterior chamber
  - Poor dilation with posterior synechiae
  - 3+ brunescent cataract

**Questions to Consider**

1. What IOL calculation formula do you use?
2. In addition to standard optical biometric device measurements, do you need additional measurement techniques to plan for the IOL implant?
3. If the patient has significant astigmatism, do you offer a toric IOL?
4. Should you offer a multifocal lens in an eye with significant visual field loss?

**References**

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