



AMERICAN ACADEMY
OF OPHTHALMOLOGY®



Retina 2023

Looking to the Future

Subspecialty Day | AAO 2023

San Francisco | Nov 3 - 4

Protecting Sight. Empowering Lives.®

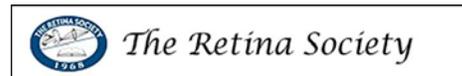
Retina 2023

Looking to the Future

Program Directors

Timothy G Murray MD MBA and Barbara Ann Blodi MD

In conjunction with the American Society of Retina Specialists, the Macula Society, the Retina Society, and Club Jules Gonin



Moscone Center
San Francisco, California
Friday – Saturday, November 3-4, 2023

Presented by:
The American Academy of Ophthalmology

Supported by an unrestricted educational grant
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Shahzad I Mian MD
Jody R Piltz MD
Sonia H Yoo MD

Bennie H Jeng MD
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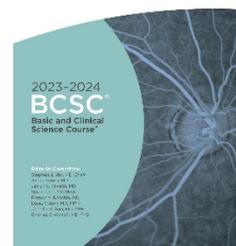
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Basic and Clinical Science Course: An Ongoing Commitment to Education

2023-2024

12 | Retina and Vitreous



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

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

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Retina Subspecialty Day 2023 Planning Group

On behalf of the American Academy of Ophthalmology and the American Society of Retina Specialists, the Macula Society, the Retina Society, and Club Jules Gonin, it is our pleasure to welcome you to San Francisco and Retina 2023: Looking to the Future.



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Program Planning Group



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Aura Biosciences, Inc.: C
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Luxa: C | NGM: S
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Spring Vision: S
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Retina 2023 Contents

	Program Planning Group	iii
	CME	vii
	The Charles L Schepens MD Lecture	ix
	Faculty Listing	x
	Using the Mobile Meeting Guide to Interact During the Meeting	xxv
	Program Schedule	xxvi
Section I:	Neovascular AMD	1
Section II:	Public Health, Education, and the Business of Retina	12
	United for Sight: A Vision for Effective Advocacy	23
	The 2023 Charles L Schepens MD Lecture	25
Section III:	My Best Medical Retina Case	27
Section IV:	Medical Retina and Chorioretinal Vascular Disease	28
Section V:	Vitreoretinal Surgery, Part I	34
Section VI:	Oncology	45
Section VII:	The 2023 Debates	51
Section VIII:	Late Breaking Developments, Part I	58
Section IX:	First-time Results of Clinical Trials	59
Section X:	Imaging	66
Section XI:	Late Breaking Developments, Part II	79
Section XII:	Nonexudative AMD	80
Section XIII:	Uveitis	92
Section XIV:	Diabetic Retinopathy	95
Section XV:	Pediatric Retina	111
Section XVI:	Gene- and Cell-Based and Neuroprotection Therapies	119
Section XVII:	Artificial Intelligence	132
Section XVIII:	Vitreoretinal Surgery, Part II	141

Section XIX: Surgical Videos—Cool Cases and Complications 148

 Faculty Financial Disclosure 149

 Presenter Index 162

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.

Retina Subspecialty Day 2023 Learning Objectives

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

- Present established and innovative approaches to the medical and surgical management of vitreoretinal diseases and disorders
- Identify imaging tests and artificial intelligence strategies that are most helpful in the diagnosis and management of retinal conditions and discuss emerging developments in retinal imaging and diagnostics
- Describe new vitreoretinal surgical techniques and instrumentation
- Identify new developments in the understanding of hereditary retinal degenerations, retinal vascular disease, AMD and other macular diseases, pediatric retinal diseases, uveitis, and ocular oncology
- Summarize current and new clinical trial data for retinal diseases such as AMD, diabetic retinopathy, hereditary retinal conditions, and retinal vein occlusion

Retina Subspecialty Day 2023 Target Audience

The intended target audience for this program is vitreoretinal specialists, members in fellowship training, and general ophthalmologists who are engaged in the diagnosis and treatment of vitreoretinal diseases.

Teaching at a Live Activity

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

Scientific Integrity and Disclosure of Conflicts of Interest

The American Academy of Ophthalmology is committed to ensuring that all CME information is based on the application

of research findings and the implementation of evidence-based medicine. 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.

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Subspecialty Day 2023 CME Credit

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

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

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

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

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

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

Attendance Verification for CME Reporting

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

How to Claim CME

Attendees can [claim credits online](#). For AAO 2023, you can claim CME credit multiple times, up to the 50-credit maximum, through March 29, 2024. You can claim some in 2023 and some in 2024, or all in the same year. For Subspecialty Day, you can claim CME credit multiple times, up to the 12-credit maximum per day, through March 29, 2024. You can claim some in 2023 and some in 2024, or all in the same year.

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

Academy Members

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

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

Nonmembers

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

Proof of Attendance

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

Academy Members

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

Nonmembers

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

CME Questions

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

The 2023 Charles L Schepens MD Lecture

Macular Telangiectasia Type 2: Tale of a Global Private and Public Collaboration

Emily Y Chew MD

FRIDAY, NOV. 3, 2023

9:40 AM – 10:00 AM



Emily Y Chew MD

Emily Y Chew MD, the director of the Division of Epidemiology and Clinical Applications at the National Eye Institute (NEI), National Institutes of Health (NIH), is also the chief of the Clinical Trials Branch. She received her medical degree and her ophthalmology training at the University of Toronto School of Medicine. She completed her fellowship in medical retina at the Wilmer Eye Institute, the Johns Hopkins Medical Institutes, and the University of Nijmegen, the Netherlands.

Emily has conducted clinical trials and epidemiologic studies in retinovascular diseases such as AMD and diabetic retinopathy, the leading causes of blindness. She has led large, randomized trials, including the Age-Related Eye Disease Study (AREDS), AREDS2, and the Actions to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. She has conducted clinical trials in rare retinal diseases, such as the international Macular Telangiectasia Project (MacTel Type 2 Project) and the recent study of belzutifan for von Hippel Lindau disease. She also collaborates with colleagues at the National Library of Medicine (NLM/NIH) on utilizing artificial intelligence/deep

learning in the detection and progression of AMD and other ocular diseases.

Emily previously served on the editorial board of *Investigative Ophthalmology and Vision* and served as the editor of the *Transactions of the American Ophthalmological Society* (2011-2018). Emily is currently a member of the editorial boards of *Ophthalmology*, *Ophthalmology Retina*, and *Retina*, and she serves as the inaugural editor-in-chief for *Ophthalmology Science*. She has also served on numerous committees in the American Academy of Ophthalmology and is the chair of the AAO IRIS[®] Registry Data Analytics Committee.

Emily has been recognized for her scientific accomplishments and mentoring efforts by numerous organizations, including National Institutes of Health, American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology, American Ophthalmological Society, Academia Ophthalmologica Internationalis, Macula Society, Retina Society, American Society of Retina Specialists, and others.

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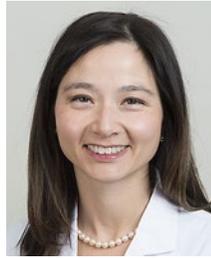
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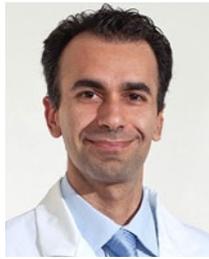
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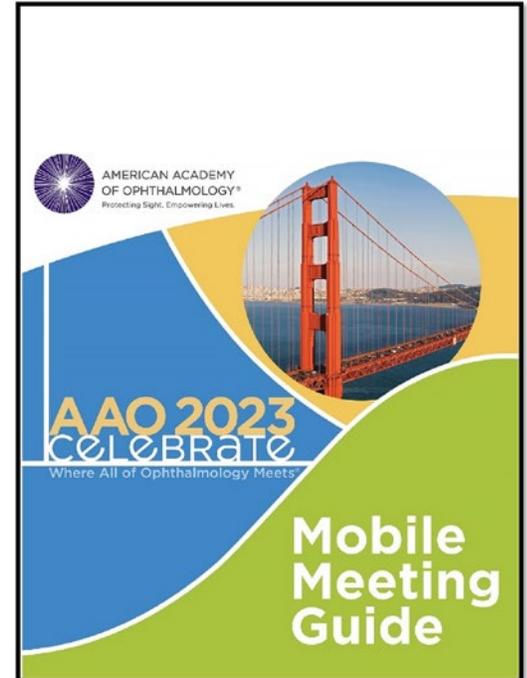


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- Select “Polls/Q&A”
- Select “Current Session”
- Select “Interact with this session (live)” to open a new window
- Choose “Answer Poll”



Retina Subspecialty Day 2023: Looking to the Future

FRIDAY, NOV. 3

7:00 AM CONTINENTAL BREAKFAST

8:00 AM Opening Remarks
Timothy G Murray MD MBA
Barbara Ann Blodi MD

Section I: Neovascular AMD

Moderator: Peter A Campochiaro MD

8:04 AM	The Importance of Classifying Macular Neovascularizations	Giovanni Staurenghi MD	1
8:10 AM	New Concepts in Atrophy and Fibrosis in Neovascular AMD	Srinivas R Sadda MD	2
8:16 AM	Biosimilars: Are They Always Similar to Originator Biologic Across Subgroups?	Susan B Bressler MD	3
8:22 AM	How Effective Is Anti-ANG2 and Anti-VEGF (Faricimab) for Neovascular AMD With Pigment Epithelial Defects?	Jennifer Irene Lim MD	4
8:28 AM	What's Next in Wet AMD?	Peter K Kaiser MD	6
8:34 AM	Drug Delivery for Posterior Segment Diseases	Baruch D Kuppermann MD PhD	7
8:40 AM	Real-world Outcomes and Treatment Patterns With Faricimab in AMD	Sophie J Bakri MD	10
8:46 AM	Acute or Chronic IOP Changes After Anti-VEGF in Patients With Unstable or Severe Glaucoma	Rajendra S Apte MD PhD	11

Section II: Public Health, Education, and the Business of Retina

Moderator: Tarek S Hassan MD

8:52 AM	The National Eye Institute in 2023: What Retina Specialists Should Know	Michael F Chiang MD	12
8:58 AM	Reimbursement of New Drugs	Ankoor R Shah MD	13
9:04 AM	Inclusion, Diversity, and Equity: Strategies for Building an Inclusive Community in Your Department, Institution, or Professional Group	Joan W Miller MD	14
9:10 AM	Compassionomics: The Science and Practice of Caring	Mark W Johnson MD	16
9:18 AM	Big Data: Identifying and Solving Unmet Needs in Retinal Practice—An IRIS® Study	Steven D Schwartz MD	19
9:24 AM	The Shifting Sands of Medicare Reimbursement for Vitreoretinal Procedures	John T Thompson MD	21
9:30 AM	United for Sight: A Vision for Effective Advocacy	Sohail J Hasan MD PhD	23

2023 Charles L Schepens MD Lecture

9:35 AM	Introduction of the 2023 Charles L Schepens MD Lecturer	Stephen D McLeod MD	
9:40 AM	Macular Telangiectasia Type 2: Tale of a Global Private and Public Collaboration	Emily Y Chew MD	25
10:00 AM	Presentation of Award	Stephen D McLeod MD	
10:01 AM	REFRESHMENT BREAK		

Section III: My Best Medical Retina Case

Moderator: William F Mieler MD

10:41 AM	Case Presentation	Rishi P Singh MD	27
10:44 AM	Discussion		
10:47 AM	Case Presentation	Lawrence J Singerman MD	27
10:50 AM	Discussion		
10:53 AM	Case Presentation	William F Mieler MD	27
10:56 AM	Discussion		
10:59 AM	Case Presentation	Jose S Pulido MD MS	27
11:02 AM	Discussion		
11:05 AM	Case Presentation	Rukhsana G Mirza MD	27
11:08 AM	Discussion		
11:11 AM	Case Presentation	J Fernando Arevalo MD PhD FACS	27
11:14 AM	Discussion		

Section IV: Medical Retina and Chorioretinal Vascular Disease

Moderator: Sobha Sivaprasad MBBS FRCS

11:17 AM	Multimodal Imaging for Foveomacular Dystrophy	Justin Gottlieb MD	28
11:23 AM	Advances in Understanding Polypoidal Choroidopathy	Gregg T Kokame MD	30
11:29 AM	Overview and Novel Approaches to Central Serous Retinopathy	Michael A Singer MD	31
11:35 AM	Central Retinal Artery Occlusion: Time to Presentation and Diagnosis	Robin A Vora MD	32
11:41 AM	Long-term Results of Anti-VEGF Therapy for Central and Branch Retinal Vein Occlusion: An Overview of Current Data	Michael S Ip MD	33
11:47 AM	LUNCH		

Section V: Vitreoretinal Surgery, Part I

Moderator: Colin A McCannel MD

1:07 PM	Spontaneous Resolution of Myopic Macular Schisis Is Not Rare and Gives Some Clues on Its Pathophysiology	Ramin Tadayoni MD PhD	34
1:13 PM	Challenging Macular Holes: From Recalcitrant to Retinal Degeneration	Elliott H Sohn MD	35
1:19 PM	Limited Membranectomy in the Management of Complex Tractional Retinal Detachments	John W Kitchens MD	36
1:25 PM	The Wisconsin Silicone Oil Vitrectomy Study: Anatomical and Vision Outcomes of Complex Retinal Detachment Repair	Michael M Altaweel MD	37
1:31 PM	Management of Complex Retinal Trauma	Dean Elliott MD	39
1:37 PM	Surgery in Uveitis Patients: What's the Difference?	Lisa J Faia MD	41
1:43 PM	Benefit of Vitreoretinal Surgery in Managing Tumor Eyes	Tara A McCannel MD	43
1:49 PM	Vitreoretinal Surgery Panel Panel Moderator: Donald J D'Amico MD Panelists: Stanley Chang MD, Manjot K Gill MD, Melissa D Neuwelt MD, and Stanislao Rizzo MD		44

Section VI: Oncology

Moderator: Amy C Scheffler MD

2:04 PM	The Controversy in Small Uveal Melanoma Treatment	Timothy G Murray MD MBA	45
2:10 PM	What's the Role of Biopsy in Uveal Melanoma? Updates and Progress on Prognostication and Liquid Biopsies	Jesse L Berry MD	46
2:16 PM	Management of Radiation Retinopathy	Ivana K Kim MD	47
2:22 PM	When to Worry About Germline Mutation in Retinoblastoma	Carol L Shields MD	49
2:28 PM	Oncology Panel Discussion Panel Moderator: Colleen M Cebulla MD PhD Panelists: Elaine M Binkley MD, J William Harbour MD, Prithvi Mruthyunjaya MD, and Arun D Singh MD		50

Section VII: The 2023 Debates

Moderator: Sunir J Garg MD FACS

2:43 PM	Early Vitrectomy in Diabetic Retinopathy: Pro	Maria H Berrocal MD	51
2:46 PM	Early Vitrectomy in Diabetic Retinopathy: Con	William E Smiddy MD	51
2:49 PM	Audience Vote		
2:50 PM	Current Complement Inhibition Therapy for Geographic Atrophy Is Acceptable: Pro	Usha Chakravarthy MBBS PhD	53
2:54 PM	Current Complement Inhibition Therapy for Geographic Atrophy Is Acceptable: Con	Richard F Spaide MD	53
2:58 PM	Audience Vote		
2:59 PM	Vitrectomy Combined With 360-Degree Extended Vitreous Base Laser vs. Scleral Buckling: Pro	Stanislao Rizzo MD	55
3:02 PM	Vitrectomy Combined With 360-Degree Extended Vitreous Base Laser vs. Scleral Buckling: Con	Edwin Hurlbut Ryan Jr MD	56
3:05 PM	Audience Vote		
3:06 PM	Private Equity: Pro	David M Brown MD	57
3:09 PM	Private Equity: Con	Richard S Kaiser MD	57
3:12 PM	Audience Vote		
3:13 PM	REFRESHMENT BREAK		

Section VIII: Late Breaking Developments, Part I

Moderator: Mark S Humayun MD PhD

Panelists: Gemmy Chui Ming Cheung MB BChir FRCOphth, Dilsher S Dhoot MD, Suber S Huang MD MBA, and Carolyn K Pan MD

3:53 PM	ALTITUDE: Suprachoroidal Delivery of ABBV-RGX-314 Investigational Gene Therapy for Diabetic Retinopathy	Mark R Barakat MD	58
3:58 PM	A 12-Week Phase 2/3 Double-Masked, Randomized, Multicenter Study of OCS-01 Eye Drops in Diabetic Macular Edema	Hani Salehi-Had MD	58
4:03 PM	Discussion		
4:08 PM	Treatment of Geographic Atrophy Secondary to AMD with Intravitreal ANX007, a Selective Classical Complement Inhibitor: Results of the ARCHER Study	David R Lally MD	58
4:13 PM	Aflibercept 8mg in Patients with Neovascular AMD: Phase 3 PULSAR Trial 96-Week Results	Jean-Francois Korobelnik MD	58
4:18 PM	Discussion		

4:23 PM	UBX1325, A Novel Senolytic Candidate for Patients with Diabetic Macular Edema: 48-Weeks Results for BEHOLD Phase 2 Study	Veeral Sheth MD	58
4:28 PM	Syfovre Initial Complication Experience	William J Johnson MD	58
4:33 PM	Discussion		

Section IX: First-time Results of Clinical Trials

Moderator: Ingrid U Scott MD MPH

Panelists: Philip J Ferrone MD, James C Folk MD, Linda A Lam MD MBA, and Paolo Lanzetta MD

4:38 PM	Diversity in Retinal Clinical Trials: Are We There Yet?	Adrienne Williams Scott MD	59
4:44 PM	Advances and Challenges in CRISPR Gene Editing for Retinal Disease	Glenn C Yiu MD PhD	60
4:50 PM	PA025 ALK-001 (C20-D3-Vitamin A) Slows the Growth of Atrophic Lesions in ABCA4-Related Stargardt Disease: Results of a Randomized, Placebo-Controlled Clinical Trial, the TEASE Study	Christine Nichols Kay MD	61
4:56 PM	Outcomes From the Randomized, Controlled Phase 3 GLOW Trial: Management of Diabetic Retinopathy With KSI-301	Charles C Wykoff MD PhD	63
5:02 PM	Aflibercept 8 mg for Diabetic Macular Edema: 96-Week Results of the PHOTON Study	Diana V Do MD	65
5:08 PM	Discussion		
5:18 PM	Closing Remarks	Timothy G Murray MD MBA Barbara Ann Blodi MD	
5:19 PM	Adjourn		

SATURDAY, NOV. 4

7:00 AM	CONTINENTAL BREAKFAST		
8:00 AM	Opening Remarks	Timothy G Murray MD MBA Barbara Ann Blodi MD	

Section X: Imaging

Moderator: Nadia Khalida Waheed MD

8:04 AM	The Key OCT Signatures and Their Histologic Correlates Every Clinician Should Recognize	K Bailey Freund MD	66
8:10 AM	Next-Generation Assessment of OCT Biomarkers for Intermediate and Advanced Dry AMD: Prognostication and Clinical Trial Utilization	Justis P Ehlers MD	67
8:16 AM	AI-Based Imaging Biomarkers in Nonexudative AMD	Frank G Holz MD	68
8:22 AM	Imaging Pearls for Distinguishing Benign From Malignant Intraocular Tumors	Jasmine H Francis MD	72
8:28 AM	Wide-field Imaging in Clinical Trials: See It to Know It	Judy E Kim MD	73
8:34 AM	Polarization-Sensitive Imaging of Scleral Abnormalities in Myopia and Dome-Shaped Macula	Kyoko Ohno-Matsui MD	74
8:40 AM	Imaging Panel Discussion		
	Panel Moderator: Jay S Duker MD		
	Panelists: Robert B Bhisitkul MD, Abigail T Fahim MD PhD, Amani Fawzi MD, and Katherine E Talcott MD		78

Section XI: Late Breaking Developments, Part II

Moderator: Dante Pieramici MD

Panelists: Dimitra Skondra MD, Demetrios Vavvas MD, Lihteh Wu MD, and David N Zacks MD PhD

8:55 AM	Intravitreal Sustained-Release Dexamethasone Implant for Diabetic Macular Edema and RVO: Six-Month Results from the First in Human Phase 2 RIPPLE-1 Trial	Sumit Sharma, MD	79
9:00 AM	First Ever Home OCT Guided Management of Treatment Experienced Neovascular AMD Patients	W Lloyd Clark MD	79
9:05 AM	Discussion		
9:10 AM	MCO-010 Optogenetic Therapy for Vision Loss in Stargardt Disease: Topline Data From the Phase 2 STARLIGHT Trial	Stephen H Tsang MD PhD	79
9:15 AM	Intravitreal Injection of “Photoswitch” Molecule (KIO 301) Improves Visual Function in Late-Stage Retinitis Pigmentosa Patients	Russell N Van Gelder MD PhD	79
9:20 AM	Discussion		
9:25 AM	REFRESHMENT BREAK and AAO 2023 EXHIBITS		

Section XII: Nonexudative AMD

Moderator: Elizabeth A Atchison MD

10:05 AM	Ocular, Systemic, and Genetic Factors That Affect Growth of Geographic Atrophy Lesions Associated With AMD	Emily Y Chew MD	80
10:11 AM	Evolution of iRORA to cRORA: A New Clinical Trial Endpoint for Geographic Atrophy Studies	David Sarraf MD	82
10:17 AM	GALE 12-Month Data: First-time Presentation of Full Cohort	Jeffrey S Heier MD	83
10:23 AM	Gather2: Two-Year Data	Arshad M Khanani MD	85
10:29 AM	How Best to Follow Geographic Atrophy Patients Receiving Anti-complement Therapy: Practical Approaches to Measure Functional Changes	Karl G Csaky MD	86
10:35 AM	Pipeline Drugs for Non-neovascular AMD	Glenn J Jaffe MD	90
10:41 AM	Nonexudative AMD Panel Panel Moderator: Jeffrey S Heier MD Panelists: Margaret A Chang MD, Robyn H Guymer MBBS PhD, Eleonora G Lad MD PhD, and George A Williams MD		91

Section XIII: Uveitis

Moderator: Steven Yeh MD

11:01 AM	Recently Described Infectious Retinochoroiditis	Anita Agarwal MD	92
11:07 AM	Tacrolimus Therapy for Noninfectious Intermediate, Posterior, or Panuveitis	Douglas A Jabs MD MBA	93
11:13 AM	Uveitis Panel Discussion Panel Moderator: Lucia Sobrin MD Panelists: Nisha Acharya MD, Thomas A Albin MD, Phoebe Lin MD PhD, and Wendy M Smith MD		94
11:28 AM	LUNCH and AAO 2023 EXHIBITS		

Section XIV: Diabetic Retinopathy

Moderator: Lisa C Olmos MD MBA

12:48 PM	Impact of the DRCR Retina Network	Daniel F Martin MD	95
12:54 PM	Potential Disparities in Real-World Treatment of Diabetic Macular Edema and Central Retinal Vein Occlusion	Julia A Haller MD	96
1:00 PM	Preventing Proliferative Diabetic Retinopathy and Diabetic Macular Edema: Two Sides of the Coin	Neil M Bressler MD	98
1:06 PM	Preventing Proliferative Diabetic Retinopathy and Diabetic Macular Edema Does Not Provide a Visual Acuity Benefit at 4 Years: Results of Protocol W	Raj K Maturi MD	99
1:12 PM	Clinical Outcomes of Diabetic Macular Edema Patients Treated With Faricimab and Aflibercept: A Subcohort Analysis of 20/50 or Worse Visual Acuity Across Faricimab Phase 3 Clinical Trials	Marco A Zarbin MD PhD FACS	101
1:18 PM	Comparison of Clarus and Optos Ultrawide-Field Imaging Systems to 7 Standard Fields in the Assessment of Diabetic Retinopathy Severity Level	Barbara Ann Blodi MD	104
1:24 PM	The Effect of GLP-1 Receptor Agonists on Diabetic Retinopathy Progression	Aleksandra V Rachitskaya MD	107
1:30 PM	New Treatments in the Pipeline for Treatment of Diabetic Macular Edema	David S Boyer MD	108
1:36 PM	Diabetes Panel Discussion Panel Moderator: Jennifer K Sun MD Panelists: Robert L Avery MD, Caroline R Baumal MD, Andrew A Moshfeghi MD MBA, and John A Wells III MD		110

Section XV: Pediatric Retina

Moderator: Kimberly A Drenser MD PhD

1:51 PM	Gene Therapy Impact in Targeted Delivery Among the Pediatric Population	Audina Berrocal MD	111
1:57 PM	Advancing in Imaging: Preoperative and Intraoperative Evaluation	Lejla Vajzovic MD	112
2:03 PM	Intravitreal Therapy in Pediatric Patients	Victor M Villegas MD	114
2:09 PM	Challenges in Managing ROP in the Evolving Neonatal Landscape	Mary Elizabeth Hartnett MD FACS	115
2:15 PM	Pediatric Retina Panel Discussion Panel Moderator: R V Paul Chan MD MBA Panelists: Antonio Capone Jr MD, Anna L Ells MD, G Baker Hubbard MD, and Yoshihiro Yonekawa MD		118

Section XVI: Gene- and Cell-Based and Neuroprotection Therapies

Moderator: Jay K Chhablani MBBS

2:30 PM	What's New in Retinal Degenerations?	Jacque L Duncan MD	119
2:36 PM	Update on Therapies for Retinitis Pigmentosa: Genes, Stem Cells, and Others	Susanna S Park MD PhD	121
2:42 PM	Gene Therapy for Neovascular AMD	Allen C Ho MD	123
2:48 PM	Subretinal Gene Therapy Surgery: Tricks of the Trade	Christina Y Weng MD MBA	127
2:54 PM	ADV-022 Intravitreal Gene Therapy for Neovascular AMD: Preliminary Data From the Phase 2 LUNA Trial and 3-Year Results From the Phase 1 OPTIC-Extension Trial	Carl D Regillo MD FACS	129
3:00 PM	Tinlarebant (LBS-008) in Adolescent Subjects With Stargardt Disease	Quan Dong Nguyen MD	131
3:06 PM	REFRESHMENT BREAK and AAO 2023 EXHIBITS		

Section XVII: Artificial Intelligence

Moderator: John P Campbell MD MPH

3:46 PM	Toward Continuous Disease Severity Scores Using Deep Learning in MacTel Type 2	Aaron Y Lee MD	132
3:52 PM	Role of AI in Fluid Quantification and Dynamics for Neovascular AMD Patients Using Home OCT	Srinivas R Sadda MD	134
3:58 PM	AI in the Management of Geographic Atrophy	Ursula M Schmidt-Erfurth MD	135
4:04 PM	Evaluation and Review of Automated Diabetic Retinopathy Screening	Roomasa Channa MD	138
4:10 PM	ChatGPT in the Modern Retina Practice	Raymond Iezzi MD	140

Section XVIII: Vitreoretinal Surgery, Part II

Moderator: Jean-Pierre Hubschman MD

4:16 PM	Advancement in Instrumentation in Retinal Surgery	David R Chow MD	141
4:22 PM	Evaluation and Necessity of Internal Limiting Membrane Peeling	Carl C Awh MD	142
4:28 PM	Internal Limiting Membrane Flap: Advantages and Techniques	Zofia Ann Nawrocka MD	143
4:34 PM	Lamellar Retinoschisis Techniques	Homayoun Tabandeh MD MS FRCP FRCOphth	145
4:40 PM	Application of 3-D Imaging in Training Vitreoretinal Fellows	Szilard Kiss MD	147

Section XIX: Surgical Videos—Cool Cases and Complications

Moderator: Kourous Rezaei MD

4:46 PM	Silicone Oil	Grazia Pertile MD	148
4:48 PM	Discussion		
4:52 PM	Retinal Fold	Martin Zinkernagel MD	148
4:54 PM	Discussion		
4:58 PM	Peeling ...	Kazuaki Kadonosono MD	148
5:00 PM	Discussion		
5:04 PM	Closing Remarks	Timothy G Murray MD MBA Barbara Ann Blodi MD	
5:05 PM	ADJOURN		

The Importance of Classifying Macular Neovascularizations

Giovanni Staurenghi MD

Introduction

Treatment of choroidal neovascularization (CNV) in AMD with the use of anti-VEGF drugs is very well established. However, it is still not possible to predict who will have the best outcome.

Macular atrophy (MA) has also been attributed to the use of anti-VEGF.

Background Observations

In the past, the classification of CNV relied on fluorescein angiography and categorized the lesions as occult or classic. However, with the introduction of indocyanine green angiography in the 1990s, 2 additional types of lesions were proposed: polypoidal lesions and retinal angiomatous proliferation (RAP).

More recently, the Consensus on Neovascular AMD Nomenclature (CONAN) Study Group, utilizing OCT, put forth a new classification system that modified the terminology from “CNV” to “macular neovascularization” (MNV). This change was made because some of these lesions do not originate from the choroid. The updated classification introduced 3 subtypes: type 1, located under the retinal pigment epithelium; type 2, located over the retinal pigment epithelium; and type 3, lesions originating from retinal vessels, corresponding to the previous RAP classification; as well as polypoidal choroidal lesions.

Studies

Following this classification update, several retrospective studies, including analyses of clinical trials, have been conducted to assess the impact of this classification on treatment outcomes and potential side effects.

- The post hoc analysis of HARBOR revealed associations between baseline MNV lesion type classified using CONAN Study Group criteria and 24-month vision outcomes among ranibizumab-treated patients with neovascular AMD.¹
- MNV type 3 was a strong risk factor for new macular atrophy (MA) development at Month 24, with fellow eye MA also being identified as a predictor. No other variables, including ranibizumab treatment, were identified as risk factors for new MA development.²
- A 24-month analysis of the Fight against Retinal Blindness! database, a web-based data collection tool that tracks real-world outcomes of treatments for neovascular AMD during routine clinical practice prospectively, showed that type 3 MNV had better visual outcomes than controls at 12 and 24 months, tended to inactivate earlier, and were less active throughout 2 years follow-up.³
- A retrospective study to evaluate the difference in the rate of survival of unaffected fellow eyes between MNVs in the first eye showed that the incidence of neovascularization in the unaffected fellow eye increases with time, and when the first eye is affected by type 3 MNV, the development of a lesion in the second eye is more premature.⁴
- The Everest I and II studies showed a difference in the treatment for polypoidal neovascularization (PCV). In particular, the 24-month data showed that the combination therapy with verteporfin photodynamic therapy added to ranibizumab achieved superior BCVA gain, increased odds of complete polypoidal lesion regression, and fewer treatment episodes compared with ranibizumab monotherapy.⁵

These retrospective studies suggest that by considering the specific subtype of MNV, clinicians can better predict the outcome and tailor treatment strategies to address individual patient needs. They shed light on the significance of the classification system in guiding treatment decisions and optimizing patient care.

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4. Bochicchio S, Xhepa A, Secondi R, et al. The incidence of neovascularization in the fellow eye of patients with unilateral choroidal lesion: a survival analysis. *Ophthalmol Retina*. 2019; 3:27-31.
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New Concepts in Atrophy and Fibrosis in Neovascular AMD

Srinivas R Sadda MD

I. Introduction

- A. Atrophy and fibrosis are generally considered to be distinct end-stage manifestations of late or advanced AMD.
- B. Although fibrosis is more commonly connected with neovascular AMD and atrophy with non-neovascular AMD, it is recognized that atrophy commonly develops in the context of neovascular AMD.
- C. Both atrophy and fibrosis are associated with vision loss.
 1. Fibrosis was the dominant cause of vision loss in wet AMD in the pre-anti-VEGF therapy era.
 2. With the advent of anti-VEGF therapy, fibrosis is less frequent or at the very least less extensive, and atrophy is more commonly apparent and more frequently the cause of late vision loss.
- D. Treatments for atrophy (anti-complement) have recently been cleared by the FDA and available for treating patients, though their relevance for treatment of atrophy in the context of wet AMD remains less certain. Atrophy in eyes with wet and dry AMD may differ.
- E. Treatments specifically targeting a further reduction or elimination of fibrosis are currently not available and are a target of interest.
- F. A challenge for developing fibrosis-specific clinical trials is the lack of consensus definitions for fibrosis on modern multimodal imaging (such as OCT), and this is topic of current research.

Subretinal hyperreflective material (SHRM) on OCT is known to be associated with poor visual outcomes in eyes with neovascular AMD and is thought to correlate with fibrosis, but the specificity is not certain.

II. Study Objective

As both atrophy and fibrosis are important causes of vision loss in neovascular AMD, we sought to better understand the relationship between SHRM and atrophy and fibrosis in this setting.

III. Study Design

- A. Post-hoc analysis of the 65 patients enrolled in the SEVEN-UP study, a multicenter cross-sectional study of patients originally enrolled in the Anti-VEGF Antibody for the Treatment of Pre-dominantly Classic Choroidal Neovascularization (ANCHOR) and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranizumab in the Treatment of Neovascular AMD (MARINA) trials of ranibizumab
- B. Color fundus photographs (CFPs) were reviewed and manually segmented to define regions of both atrophy and fibrosis.
- C. SHRM borders on OCT volume scans were manually delineated, and thickness measurements were computed and compared in corresponding regions of atrophy and fibrosis on the CFPs.

IV. Major Results

- A. 51 of the 65 eyes demonstrated atrophy and/or fibrosis on CFP.
- B. Both regions of atrophy and fibrosis demonstrated SHRM on OCT.
- C. Mean SHRM thickness on OCT was significantly greater in CFP-fibrosis regions ($44.19 \pm 46.95 \mu\text{m}$) compared to CFP-atrophy regions ($14.28 \pm 13.35 \mu\text{m}$; $P < .001$).
- D. Average maximum height of SHRM in fibrotic regions ($268.04 \pm 130.05 \mu\text{m}$) was significantly thicker than in atrophic regions ($121.95 \pm 51.17 \mu\text{m}$; $P \leq .001$).

V. Summary and Key Conclusions

- A. Although atrophy and fibrosis are thought to be different end-stage outcomes in eyes with neovascular AMD, they both demonstrate SHRM on OCT, with the main distinction being a greater thickness of SHRM in fibrosis.
- B. As a result of the greater thickness, SHRM may appear more “opaque” in fibrosis and more “translucent” in neovascular AMD-associated macular atrophy.
- C. Given these similarities, these regions of neovascular AMD-associated macular atrophy may be better termed *atrosis* to distinguish these lesions from typical geographic atrophy in the absence of neovascular disease.

Biosimilars: Are They Always Similar to Originator Biologic Across Subgroups?

Susan B Bressler MD

In 2009 the Biologics Price Competition and Innovation Act (BPCI) created an abbreviated approval pathway for biosimilar products as a way to provide the public with greater access to biological products that are shown to be biosimilar to, or interchangeable with, an FDA-licensed reference product. Biologic drugs are genetically engineered proteins that are derived from human genes and expressed in eukaryotic or prokaryotic cell lines. These large and complex agents each have their own unique manufacturing process, with acceptable in-product variation. Other than the gene sequence, little about the manufacture of originator biologics is in the public domain.

Biosimilars differ from generic drugs. A generic drug is an identical copy of a small-molecule drug, for which the same chemical formula and synthesis are used as the originator. Its development takes about 2 years, with costs of about 2 million USD. A biosimilar is not an exact copy of the originator biologic; rather, it may have minor differences in clinically inactive components, particularly since it is made in living cells and the manufacturing process is dependent on reverse engineering. Typical development spans 8-10 years, with costs of up to 200 million USD.

However, this is 5-7 years shorter and 1-2 billion USD less expensive than the development path for the originator biologic. Originator biologics require intensive investment (time/money) in clinical studies (Phases 1, 2, and 3). At least 2 Phase 3 clinical trials are required for each disease indication the developer seeks approval for in order to establish efficacy and safety vs. the standard of care in the disease-specific population.

As biosimilar agents are required to be “highly similar” to existing innovator biologics, the burden of proof lies in establishing comparable physiochemical properties, pharmacokinetics, pharmacodynamics, immunogenicity, safety, and efficacy to the originator product. The greatest investment is in the product’s design specification and demonstrating its analytical similarity to the originator. Validation of similarity is sought in a clinical trial in a sensitive patient population using a sensitive endpoint, choosing among the disease indications for which the originator has regulatory approval. The single clinical trial aims to confirm noninferior clinical outcomes, with safety signals similar to those of the originator biologic. These objectives are often met by selecting a primary endpoint of change in vision from baseline at Week 8, and this is typically accomplished with a more limited number of trial participants relative to the sample sizes needed when the originator tested relative to standard of care treatment.

Clinical trials evaluating a biosimilar candidate may adapt the eligibility criteria for trial inclusion from the originator Phase 3 trials to enroll a sensitive population to test biosimilarity while still maintaining a diverse patient population. Baseline characteristics of participants are used to describe the population and divide participants into subgroups—particularly subgroup characteristics that may affect the magnitude and/or the direction of the treatment effect. Secondary outcomes of the trial, which typically should be considered clinically relevant only if the primary outcome has been achieved, frequently include subgroup analysis to identify either consistency of or large differences in the magnitude of treatment effect among different categories of patients. RCTs generally are not powered to achieve statistical significance, even of noninferiority outcomes, within subgroup analysis, and confidence intervals around the difference in treatment groups may be large, particularly in trials evaluating biosimilarity with their smaller sample size.

Phase 3 studies of 2 FDA-approved ranibizumab biosimilar agents in neovascular AMD (Byooviz [ranibizumab-nuna] and Cimerli [ranibizumab-eqrn]) and 1 proposed aflibercept biosimilar in diabetic macular edema (MYL-1701P) will be used to illustrate these concepts.

How Effective Is Anti-ANG2 and Anti-VEGF (Faricimab) for Neovascular AMD With Persistent Epithelial Defects?

Jennifer I Lim MD

I. Pigment Epithelial Detachments (PEDs) and AMD

- A. Prevalence = 30% to 80% of neovascular AMD (nAMD) patients based on the Comparison of AMD Treatment Trial (CATT), EXCITE, and VIEW studies¹
- B. Fibrovascular PEDs sub-retinal pigment epithelial (RPE) fluid is more persistent compared with intra-retinal and subretinal fluid:
 1. VIEW studies showed 80.1% of eyes had PED at baseline; only 38% resolved with treatment.²
 2. Higher treatment burden^{1,2}
- C. Anti-VEGF therapy for PEDs in nAMD can result in improved visual acuity, although this is considered a difficult subtype to treat. Risk of RPE tear related to PED size, possibly to rapid reduction with treatment. PRN phase often associated with recurrent PED.³

II. Overview of Phase 3 TENAYA and LUCERNE Trials^{4,5}

- A. Noninferiority trial design compared faricimab up to every 16 weeks (Q16W) after 4 loading doses with aflibercept every 8 weeks (Q8W) after 3 loading doses in patients with treatment-naïve nAMD.
 1. Year 1: 1326 patients, faricimab 6.0 mg Q8/Q12/Q16 W (based on disease activity criteria at Weeks 20 and 24) vs. aflibercept 2.0 mg Q8W
 2. Year 2: treat-and-extend-based (T&E) personalized treatment interval (PTI) regimen for both arms to assess retreatment burden (based on individual patient's disease activity)
- B. Primary endpoint = mean change in BCVA at 1 year, averaged over Weeks 40, 44, 48; noninferior to aflibercept Q8W at Year 1 and Year 2
- C. Faricimab PTI arm
 1. Q12W or longer = 79.7%/77.8% Year 1 and 74.1%/81.2% Year 2
 2. Q16W = 45% for both trials Year 1 and 59%/66.9% Year 2
- D. No new safety signals and no cases of retinal vasculitis or retinal occlusive vasculitis in any of the arms

III. Post-Hoc Analysis of TENAYA and LUCERNE: PED

- A. PED defined as retinal pigment epithelium elevation with width >350 μm
- B. PED subtypes = predominantly serous (serous PED) or predominantly fibrovascular or fibrovascular only (fibrovascular PED)
- C. Baseline characteristics during head-to-head loading phase for both faricimab and aflibercept were similar.
 1. Foveal center involvement
 - a. Faricimab: 80.7%
 - b. Aflibercept: 77.5%
 2. Fibrovascular
 - a. Faricimab: 79.9%
 - b. Aflibercept: 82.1%
 3. Serous PED
 - a. Faricimab: 20.1%
 - b. Aflibercept: 17.9%
 4. Mean (standard deviation) maximum thickness within 6 mm Early Treatment Diabetic Retinopathy Study grid
 - a. Faricimab: 253 μm (189 μm)
 - b. Aflibercept: 240 μm (186 μm)
- D. Change in PED characteristics with treatment
 1. Week 4: Rapid reduction in maximum PED thickness for both faricimab and aflibercept drugs
 2. Week 12: Greater reduction in PED size and fluid with faricimab than aflibercept
 - a. Mean decrease in maximum thickness from baseline was greater with faricimab than aflibercept.
 - i. total PED reduction = -87.9 μm faricimab vs. -74.5 μm aflibercept [nominal $P = .0067$]
 - ii. serous PED reduction = -136.1 μm faricimab vs. -108.2 μm aflibercept [nominal $P = .0147$]

- b. Resolution of serous PED component was greater with faricimab than aflibercept: 95.3% [95% CI: 91.6%, 99.0%] vs. 86.6% [80.3%, 92.9%]; nominal $P < .0258$.

E. Conclusion

1. Dual Ang-2/VEGF inhibition with faricimab was associated with greater improvements in PED outcomes compared with aflibercept in the head-to-head dosing period of TENAYA/LUCERNE.
2. Findings are consistent with the greater drying of retinal fluid seen with faricimab during the head-to-head dosing period.

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Drug Delivery for Posterior Segment Diseases

Baruch D Kuppermann MD PhD

- I. Concepts of Ocular Drug Delivery: The Posterior Segment and the Blood–Ocular Barrier
 - A. Three functions
 1. Maintain tissue/fluid composition
 2. Produce aqueous
 3. Keep pathogens out
 - B. Location: Tight junctions in structures below
 1. Blood–aqueous barrier: iris vascular epithelium and nonpigmented ciliary epithelium
 2. Blood–retinal barrier: retinal vascular endothelium and retinal pigment epithelium
 - C. Consequences of blood–ocular barrier breakdown
 1. Drugs enter and leave eye more easily.
 2. Starling forces shift, which can result in macular edema.
 3. Serum leak into eye can lead to cellular proliferation.
 4. Aqueous hyphosecretion
- II. Concepts of Ocular Drug Delivery: Strategies for Delivering Drugs to the Posterior Segment
 - A. Deliver large amounts of drug systemically to achieve therapeutic levels of drug in eye
 - B. Modify the blood–ocular barrier to allow greater penetrance of drugs
 - C. Local delivery of drugs to eye
 1. Topical transcorneal
 2. Transscleral options include topical and subtenon delivery.
 3. Intravitreal
 4. Suprachoroidal
 5. Subretinal
 - D. Approaches for drug delivery to the posterior segment
 1. Topical therapy is the most common drug delivery to the eye but it is difficult for posterior segment diseases due to poor penetrance.
 2. Periocular/subtenon/juxtасcleral approach: Long used and can be effective
 3. Intravitreal injections: Long established and most commonly used, with excellent side-effect profile
 4. Drug delivery systems have been developed for longer-term drug delivery compared to intravitreal injections.
 - E. Drug delivery systems for posterior segment diseases
 1. Most common are intravitreal reservoir systems that deliver drugs implanted in reservoir system.
 - a. Biodegradable or nonbiodegradable
 - b. Surgically implanted vs. injected
 - c. Single use vs. refillable
 2. Other intravitreal approaches include cell-based delivery of neurotrophic factors and viral vector delivery systems.
 3. Suprachoroidal drug delivery and viral vector delivery systems utilize the anatomy of the suprachoroidal space as a pathway to inject in the peripheral suprachoroidal space anteriorly to treat macular disease.
 - F. Intravitreal drug delivery systems, FDA approved
 1. Vitrasert ganciclovir implant
 - a. First such system, approved in 1996
 - b. Confirmed efficacy
 - c. Surgically implanted, nonbiodegradable
 - d. Implant (5 mg)
 - i. Achieves intravitreal drug level of 4 mcg/mL
 - ii. Lasts 8 months
 - e. Intravenous
 - i. Over 100,000 mg needed for 8 months of treatment
 - ii. Achieves an intravitreal level of only 1 mcg/mL
 - f. ID50 of GCV naive viral isolates on the order of 1 mcg/mL, but increases over time
 2. Retisert fluocinolone acetonide implant
 - a. Surgically implanted
 - b. Nonbiodegradable
 3. Iluvien/Yutiq fluocinolone acetonide implant
 - a. Injected
 - b. Nonbiodegradable

4. Ozurdex dexamethasone implant
 - a. Injected
 - b. Biodegradable
5. Port Delivery System
 - a. Surgically implanted
 - b. Nonbiodegradable but refillable
- G. Intravitreal drug delivery systems under development in clinical trials
 1. Durasert implant (EyePoint)
 - a. Tyrosine kinase inhibitor vorolanib
 - b. Injected
 - c. Biodegradable
 2. Hydrogel-based implant (Ocular Therapeutix)
 - a. Tyrosine kinase inhibitor axitinib
 - b. Injected
 - c. Biodegradable
 3. Microparticle depot (Graybug)
 - a. Tyrosine kinase inhibitor sunitinib
 - b. Injected
 - c. Biodegradable
 4. Epidel implant (Ripple)
 - a. Dexamethasone
 - b. Injected
 - c. Biodegradable
 5. ABC platform (Kodiak Sciences)
 - a. Antibody Biopolymer
 - b. Conjugate Nonadsorptive
 - c. Cleared systemically
- H. Cell-based drug delivery systems
 1. Encapsulated Cell Technology, ECT (Neurotech)
 - a. Immortalized RPE cells programmed to release ciliary neurotrophic factor
 - b. Surgically implanted
 - c. Nonbiodegradable
 2. jCell (jCyte)
 - a. Retinal progenitor cells deliver a biological mixture of neurotrophic factors from immature photoreceptor cells.
 - b. Injected
 - c. Biodegradable
- I. Drug delivery using viral vectors
 1. Regenxbio uses an adenovirus-associated gene therapy viral vector (AAV8) to deliver an anti-VEGF Fab subretinally using either an intracular approach with a pars plana vitrectomy or externally using anterior suprachoroidal delivery.
 2. Adverum uses an adenovirus-associated gene therapy viral vector (AAV.7m8) to deliver aflibercept intravitreally.
 3. Many pros and cons to viral vector gene therapy but has the potential for longest durability of all drug delivery approaches
- J. Suprachoroidal drug delivery
 1. Utilizes microneedle drug delivery technology developed by Clearside Biomedical to inject drugs or viral vectors anteriorly transsclerally over the pars plana to access the suprachoroidal space anteriorly, creating a pressure gradient that moves the injected material from the anterior suprachoroidal space to the posterior suprachoroidal space near the macula
 2. Triamcinolone suprachoroidal delivery is commercially available as the first FDA-approved suprachoroidal drug delivery system (2021) utilizing the microneedle technology platform.
 3. The same microneedle suprachoroidal delivery technology developed by Clearside Biomedical is being utilized by Regenxbio to implant their AAV8 gene therapy viral vector platform to deliver anti-VEGF Fab (same product as being studied after trans pars plana subretinal delivery).
 4. Clearside Biomedical is also investigating tyrosine kinase inhibitor axitinib injected suprachoroidally using the same microneedle delivery system.
- K. Conclusion: challenges of local ocular drug delivery
 1. Many ocular diseases still seeking improved pharmacological solutions
 2. First-generation technology exists and is being further refined.
 3. Future-generation devices will allow longer duration and increased target specificity.
 4. Two fundamental approaches and philosophies
 - a. Longer-acting reservoir implants with good long-term control of disease but with potential for drug or suppressive side effects
 - b. Shorter-acting biodegradable inserts that potentially expose eye to less drug or suppressive side effects but may control disease less well
 5. Possible that each approach may have preferential uses in different diseases or with different drugs

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Acute or Chronic IOP Changes After Anti-VEGF in Patients With Unstable or Severe Glaucoma

Rajendra S Apte MD PhD

Anti-VEGF pharmacotherapy has revolutionized the treatment of diverse retinal diseases including AMD, diabetic retinopathy, and retinal vascular diseases. Although these agents significantly reduce the risk of vision loss, several challenges remain, including high treatment burden, cost, and suboptimal response or loss of initial gain in vision after long-term therapy. Other challenges include the effect of high treatment burden on patients with comorbidities such as glaucoma. All patients receiving anti-VEGF intraocular injections experience acute, transient rise in IOP immediately after the intravitreal injection procedure. A subset of patients that require multiple injections may experience chronic, albeit lower, IOP elevation. Although this may not be of high concern in patients with healthy optic nerves, it represents a unique challenge in managing patients with underlying optic neuropathy secondary to glaucoma. In addition, patients who have undergone vitrectomy may also be a high-risk group given the effects of vitrectomy on intraocular oxygen levels in these patients. Current data and treatment considerations for patients with unstable or severe glaucoma who need anti-VEGF pharmacotherapy will be discussed as part of this presentation.

The National Eye Institute in 2023: What Retina Specialists Should Know

Michael F Chiang MD

What is the National Eye Institute?

- The National Eye Institute (NEI) is the world leader in directing and funding vision research.
- The NEI was founded in 1968, when Congress and President Lyndon Johnson established it as an independent entity within the National Institutes of Health (NIH) to manage national efforts in vision science.
- The current annual NEI budget is \$896 million.
- The NEI Strategic Plan (published in November 2021) outlines our scientific directions and priorities over the next 5 years (<https://www.nei.nih.gov/about/strategic-planning>).
- It is essential for practicing ophthalmologists to stay updated about advances in research because clinical practice evolves so quickly.

What are key recent NEI-funded accomplishments in retina?

- Regenerative medicine: ocular gene therapy, retina organoids, cell-based therapies
- Imaging: adaptive optics, OCT/OCT angiography (including hand-held devices for use at bedside)
- Artificial intelligence: multiple FDA-approved systems for retinal disease, studies on retinal imaging biomarkers for systemic disease (eg, Alzheimer's, psychiatric disease, cardiac disease)
- Pharmacology: FDA approval of Syfovre (pegcetacoplan injection) for geographic atrophy, resulting from study of complement in AMD and development of compstatins (John Lambris)
- Clinical trials: DRRCR Retina Network (eg, Protocol I, Protocol S, Protocol T)

What ongoing NEI activities may be of particular interest to retina specialists?

- NIH Accelerating Medicines Partnership (AMP) Bespoke Gene Therapy Consortium
 - Public-private partnership
 - Three of 8 clinical trial awards across all fields of medicine were for ophthalmic diseases.
- Regenerative medicine initiatives: cell-based therapies, gene editing
- Artificial intelligence and data science: Bridge2AI, ocular imaging standards
- Data sharing initiatives (eg, <https://tvst.arvojournals.org/article.aspx?articleid=2776501>)
- Myopia: sponsoring National Academy of Medicine study on basic science and population health
- Quality-of-life initiatives: patient-related quality-of-life measures
- Population health: initiatives to strengthen vision workforce by increasing pipeline of underrepresented groups in medicine

How to get more information and stay updated?

- List of current NEI funding opportunities: <https://www.nei.nih.gov/grants-and-training/funding-opportunities/current-funding-opportunities>
- Follow NEI on social media for updates about policy, grant opportunities, vision research, clinical news (Twitter: @NEIDirector, <https://twitter.com/NEIDirector>)

Reimbursement of New Drugs

Ankoor R Shah MD

- I. General Reimbursement Challenges
 - A. Centers for Medicare and Medicaid Services (CMS)
 - B. Part B drugs
- II. Reimbursement Challenges of New Medications
 - A. J codes
 - B. Q codes
- III. Novel Medications
 - A. Pegcetacoplan (Syfovre)
 - B. Reimbursement challenges
 - 1. Permanent J code
 - 2. ICD-10 codes
 - 3. Frequency of 67028 edits
 - 4. Treatment of geographic atrophy with concurrent exudative AMD
- IV. Biosimilars
 - A. Unique reimbursement issues
 - B. Ranibizumab-nuna (Byooviz)
 - C. Ranibizumab-eqrn (Cimerli)
 - D. Future aflibercept biosimilars
- V. Alternative Treatment Approaches
 - A. Port delivery device (Susvimo) reimbursement challenges
 - B. Suprachoroidal injection
 - 1. CMS coding update
 - 2. Triamcinolone acetonide injectable suspension (Xipere)
- VI. Future Treatments
 - A. Reimbursement challenges of gene therapy
 - B. Cost burden for lifetime treatments
- VII. Conclusions

Inclusion, Diversity, and Equity: Strategies for Building an Inclusive Community in Your Department, Institution, or Professional Group

Joan W Miller MD, Alice Lorch MD MPH, and Ankoor S Shah MD PhD

I. Rationale

- A. Inclusion, diversity, and equity (IDE) need to be core values and central to the mission and culture.
- B. Inclusion begins with a leader who fosters a sense of belonging for all team members.
- C. By fostering inclusion, diversity is celebrated, with multiplicity of perspectives, ideas, and experiences, leading to more creativity and innovation.
- D. Promoting equity in the workforce will lead to improvement in community and in health.

II. Paradigm for Creating Inclusion and Increasing Diversity in Our Workforce

- A. Inclusion begins with local (department, institution, or group practice) programs promoting inclusion of individuals traditionally underrepresented in medicine.
- B. Increasing diversity is a natural by-product of inclusive programs on the local and national level.
- C. Local program examples

Multitiered framework at Harvard Ophthalmology: the EYE CAN Program (see Figure 1)

Purpose: To increase opportunities across the academic life cycle

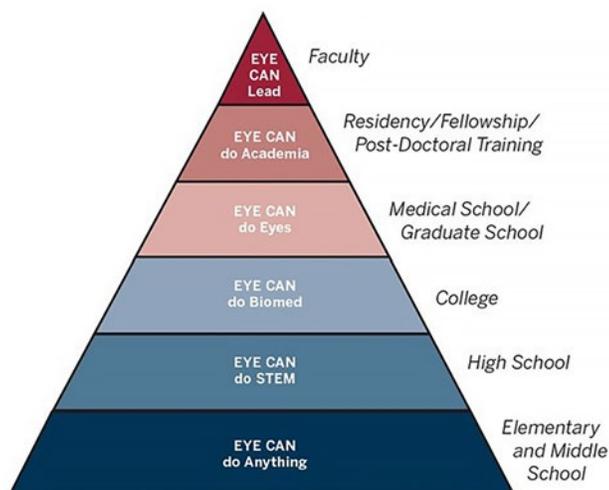


Figure 1. The EYE CAN Pyramid. The EYE CAN Program is a multitiered approach to promote inclusion and improve diversity in our faculty ranks by starting with school-aged children and encouraging them to believe “EYE CAN do anything.” As we go up the “academic life cycle,” our emphasis on EYE CAN gets more specific toward ophthalmology and visual sciences.

1. EYE CAN do Biomedical Sciences: Harvard Retinal Imaging Laboratory Undergraduate Minority Mentorship Program
 - a. Started in 2021; developed by Edward Lu MD and Augustine Bannerman and led by John B Miller MD
 - b. Initially offered to Harvard College students and expanded to include MIT students
 - c. Program provides a semester-long mentoring program to underrepresented undergraduate students to increase their exposure to biomedical sciences, specifically ophthalmology.
 - d. Didactic and experiential
 - i. Program pairs each student with a mentor.
 - ii. Opportunity to contribute to a research project, participate in laboratory meetings, critically analyze data, and write scientifically
 - e. 109 student participants thus far
 - f. Expanded faculty and mentors, with each semester involving more within the department
 - g. Feedback from participants shows increased interest in medicine and ophthalmology.
2. EYE CAN do Eyes: Harvard Ophthalmology Research Scholars Program
 - a. Started in 2021; developed by Joseph Arboleda-Velasquez MD PhD and James Chodosh MD MPH, and joined by Silas Wang MD
 - b. Provides rising second-year medical students from underrepresented and disadvantaged groups an immersive, 8-week experience in ophthalmology and vision sciences at Mass Eye and Ear
 - c. Mentored experience in a visual science laboratory: conducting a project, clinical shadowing, mentoring sessions, and writing a clinical case report
 - d. Continued support and guidance through ophthalmology residency program application

- e. Scholars are invited back to attend Annual Meeting and Alumni Reunion to cultivate network, to learn from each other, and to continue mentorship.
 - f. Interest continues to grow, with 80 applicants this year and 8 scholars selected, the largest ever.
 - g. One scholar awarded Research to Prevent Blindness (RPB) Medical Student Eye Research Fellowship
3. EYE CAN Lead: Faculty mentoring program
 - a. All junior faculty are paired with 2 senior mentors.
 - b. Mentors are encouraged to ensure that underrepresented in medicine faculty are supported and progress through the academic ranks equivalently to historical norms.
 - c. Initiating annual review of program metrics with attention to ensuring equity
 4. EYE CAN Lead: Leadership development opportunities
 - a. Nominations of faculty candidates to local programs at Harvard Medical School
 - b. Nominations of faculty candidates to national programs through the Academy (AAO) and Association of University Professors of Ophthalmology (AUPO)
 - c. Each nomination is approved by faculty committees that reference the historical lists of nominations to ensure balance across time.
- D. Coordinate efforts with national programs
1. Recruit students for the Minority Ophthalmology Mentoring (MOM) Program of the AAO/AUPO
 2. Recruit faculty to participate in the MOM program
 3. Participate in Rabb-Venable Program fireside chats and webinars
 4. Support and leverage programs developed by the NIH, Association for Research in Vision and Ophthalmology, and the National Academy of Arts, Science, Engineering and Medicine

III. Departmental Approach to Equity

Residency and fellowship application review and interview process

- A. Reducing emphasis on standardized scores
 1. USMLE Step 1 exam now Pass/Fail
 2. Avoid using Step 2 scores as a replacement for Step 1 scores
 3. AUPO modified SFMatch application to reflect changes.

- B. Program values defined prior to the interview process
- C. Committee members encouraged to incorporate appreciation for “journey travelled”
- D. Implicit bias training for interviewers
- E. Standardization of interview questions
- F. Virtual interview and open house to reduce effect of socioeconomic status on opportunity

IV. Conclusions

- A. IDE informs all aspects of our work, communication, and organization.
- B. Continue to invest in current IDE programs and encourage further conversations and innovation in IDE
- C. More diversity in the ophthalmic community creates a wider range of perspectives, ideas, and experiences, leading to increased creativity and more innovation for patients and for the broader community.

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Compassionomics: The Science and Practice of Caring

Mark W Johnson MD and Ines Lains MD PhD

- I. Objectives
 - A. Summarize the scientific evidence that compassion makes a measurable difference in patient outcomes, health-care quality and cost, and provider well-being
 - B. Briefly discuss ways providers can cultivate compassion and communicate it to their patients
- II. Definitions
 - A. Compassion: *The awareness of and emotional response to pain or suffering, coupled with an authentic desire and intention to alleviate it*
 - B. Empathy vs. compassion
 1. Empathy involves recognizing and mirroring another's emotions ("I feel your pain") and is a necessary prerequisite to compassion
 2. Compassion goes further and involves desiring/intending to take action to help
 3. Functional brain MRI imaging
 - a. Feelings of empathy light up pain centers.
 - b. Intentions of compassion (desire to alleviate another's suffering) light up reward pathways associated with affiliation and positive emotions.
- III. Evidence for a Compassion Crisis in Health Care
 - A. Surveys
 1. One half of Americans believe the U.S. health-care system is not compassionate (Harvard 2011).
 2. 35% of physicians manifest high levels of depersonalization (Mayo Clinic 2011).
 - B. Field studies
 1. Physicians miss 60%-90% of opportunities to respond to patients with compassion (multiple studies).
 2. In 74% of interactions in ICU, providers showed *zero* compassionate behaviors (Johns Hopkins 2017).
- IV. Impediments to Compassion in Health Care
 - A. Personal factors
 1. Skepticism that compassion makes a significant difference
 2. Lack of skills to consistently practice compassion
 3. Preoccupation with personal stresses, empathy fatigue, and burnout
 4. Moral judgement (blaming patient for their condition)
 5. Psychological numbing in response to large-scale suffering
 - B. Organizational factors
 1. Bureaucratic, regulatory, and documentation burdens
 2. EMR
 3. High patient volumes and inefficient workflows
 4. Compensation based entirely on productivity
- V. Benefits of Compassion in Health Care
 - A. Benefits for patients
 1. Physiological health benefits
 - a. Increases parasympathetic activity and releases oxytocin
 - b. Reduces perception of experimentally induced pain by ~50%
 - c. Accelerates wound healing
 - d. Speeds recovery after heart attack and surgery
 - e. Improves endocrine function
 - f. Enhances immune function
 2. Psychological health benefits
 - a. Alleviates anxiety and psychological distress associated with illness
 - b. Effectively raises patients' expectations for recovery (strongly associated with survival)
 - c. Highly effective in treating psychiatric conditions (depression, PTSD, suicidal ideation, etc.)
 - d. Increases patient self-compassion
 3. Enhanced patient self-care
 - a. Nonadherence to therapy is epidemic; patients with chronic disease fail to take medications as prescribed ~half the time.

- b. Care by a compassionate health care provider:
 - i. substantially increases odds of adherence to treatment and screening protocols
 - ii. motivates and enhances patient empowerment to cope with and manage their illness
- B. Benefits for health-care systems and providers
1. Increased quality and safety of health care
 - a. Physicians scoring high (vs. low) for depersonalization are 45%-50% more likely to commit major medical errors and 3 times more likely to commit major surgical errors.
 - b. Physician compassion is significantly associated with lower odds of major medical errors.
 - c. Personal physician-patient relationship is associated with 40% higher odds that prescribed treatment is consistent with best practices.
 - d. Clinical competency scores for high-compassion physicians are higher than for those with low compassion ratings.
 2. Enhancement of revenue and reduction in costs
 - a. Higher patient experience scores are associated with higher financial margins. (Systems with “compassion culture” have higher patient scores.)
 - b. In choosing physicians, patients value connection and caring over education, experience, wait time, cost, etc.
 - c. Compassionate, patient-centered care:
 - i. reduces unnecessary referrals, diagnostic testing, and office visits
 - ii. reduces costs through better patient adherence
 - iii. reduces costly medical errors and malpractice costs
 - iv. boosts productivity by cutting absenteeism and reducing burnout and turnover
 3. Prevention of provider burnout
 - a. Dissatisfaction with quality of patient relationships is associated with 22-fold higher risk of burnout.
 - b. Connecting with patients through compassion transforms a provider’s experience in a way that builds resistance to burnout.
 - i. Compassionate action triggers a “helper’s high.”
 - ii. Compassion training improves emotion regulation and reduces symptoms of burnout.
- VI. Compassion is a trainable skill.
- A. Literature shows that compassionate behaviors can be learned.
 - B. Neuroplasticity: Evidence that the adult human brain is malleable (ie, we have the ability to shape our minds and rewire our brains through intentional practice)
 - C. Meta-analyses of compassion training programs
 1. Even brief periods of compassion training can lead to measurable increases in compassion and acts of generosity.
 2. 80% of studies involving physicians demonstrate measurable increases in compassion.
- VII. Cultivating Compassion
- A. Set an intention each morning to serve patients with compassion and caring.
 - B. Consider it a duty to show compassion in every encounter. You do not have to feel compassionate before responding with compassion.
 - C. Compassionate intentions can be cultivated through daily compassion practices:
 1. Lovingkindness (metta) meditation
 2. Compassion meditation
 3. Tonglen
 - D. Formal compassion training courses for health-care professionals can be accessed online.
- VIII. Communicating Compassion to Patients
- A. RSVP mnemonic
 1. Recall intention to show compassion at the start of each patient encounter (eg, when opening door or sanitizing hands)
 2. See the patient as a real human being with worries/fears. Look them in the eye, call them by name.
 3. Validate spoken or assumed fears (eg, “I can imagine this is really frightening for you”)
 4. Provide a statement of caring and support (eg, “I’ll be with you every step of the way”)
 - B. Compassionate communications take only a few seconds to deliver and have measurable effects on patient anxiety in randomized clinical trials.
- IX. Summary
- A. Compassion is the emotional response to another’s pain or suffering, accompanied by a desire to alleviate the suffering.
 - B. Systematic review of the world’s literature shows that compassion in health care:
 1. measurably improves physical and psychological patient outcomes
 2. increases patient adherence to treatment plans

3. improves healthcare quality and safety
 4. increases revenue and cuts costs
 5. prevents physician burnout
- C. Compassion can be actively cultivated through intentional practice.
- D. Compassion-infused communications with our patients:
1. require only seconds of time
 2. should be considered an essential component of effective treatment

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Big Data: Identifying and Solving Unmet Needs in Retinal Practice—An IRIS® Study

Steven D Schwartz MD

What Is Big Data?

In medicine, “big data” refers to the large and complex sets of health care–related information that can be collected, stored, analyzed, and interpreted to gain insights and make informed decisions. It involves the use of advanced technologies and techniques to handle massive volumes of data, typically characterized by the “three Vs”: volume, velocity, and variety.

Volume

Big data in medicine encompasses enormous amounts of information generated from various sources such as EHRs, medical imaging, genomic sequencing, wearable devices, social media, and clinical trials. These data sources contribute to the massive volume of health-care data available for analysis.

Velocity

Health-care data is generated at an unprecedented speed. Rapid processing is essential for timely decision-making and interventions.

Variety

Big data in medicine encompasses diverse types of data, including structured data (eg, demographic information, lab results), unstructured data (eg, clinical notes, radiology images), and semistructured data (eg, doctor’s notes, prescription data). Additionally, it includes data from different domains such as genomics, proteomics, medical imaging, and patient-generated data. Integrating and analyzing these varied data types is a significant challenge. The American Academy of Ophthalmology continues to meet these evolving challenges on behalf of our patients, practices, and providers, improving our interactions with state and federal governing agencies.

Beyond supporting the Academy’s mission for patients and providers, the application of big data in medicine has the potential to revolutionize health care in several ways:

1. Precision medicine
2. Predictive analytics
3. Real-time monitoring and surveillance
4. Drug discovery and development
5. Population health management: Big data analytics enables health-care providers and policymakers to understand population health trends, identify disease hotspots, and design targeted interventions. It can support public health surveillance, outbreak detection, and resource allocation.

However, the utilization of big data in medicine also raises significant challenges, including data privacy and security, data quality and interoperability, ethical considerations, regulatory compliance, and the need for skilled professionals capable

of effectively managing and interpreting large datasets. The Academy continuously addresses these crucial challenges to ensure the responsible and effective use of big data in improving health-care outcomes.

Big data can have several meanings, which include the following:

1. Single deep dataset: lots of patients and providers
2. Broad datasets: lots of data points for each separate patient or patient encounter
3. Multiple smaller datasets that can interface the individual data lakes or data silos. (In other words, it can be an ophthalmology claims dataset interfacing with a clinical dataset and/or interfacing with an imaging and/or genomics dataset, or a retina dataset interfacing with a glaucoma dataset—or even interfacing with a neurology or a rheumatology dataset).

The Academy’s IRIS® Registry

The Intelligent Research in Sight (IRIS®) Registry, the nation’s first comprehensive eye disease clinical database, represents one of the largest and most advanced registry databases: over 70% of U.S. ophthalmologists contribute to the database. The power of the IRIS® Registry is that it is the only ophthalmology data set that encompasses deep, broad, and multiple interface features.

In 2022 alone, clinicians reported more than 51 million patient visits to the Academy’s IRIS® Registry.

The IRIS® Registry is a centralized data repository and reporting tool that can analyze patient data to produce easy-to-interpret national and interpractice benchmark reports and provide information to improve eye care in all areas. The reports can validate the quality of care ophthalmologists provide and pinpoint opportunities for improvement.

Eligible physicians who sign up and meet the reporting requirements can use the IRIS® Registry to report clinical quality data to the Merit-based Incentive Payment System (MIPS). The IRIS® Registry can automatically extract and submit required data for MIPS quality measures to the Centers for Medicare & Medicaid Services (CMS) on behalf of practices integrated with their EHR. Additionally, CMS has confirmed that the IRIS® Registry is considered a Clinical Data Registry, and integration of EHR systems with the IRIS® Registry will fulfill the Clinical Data Registry Reporting measure for the Public Health and Clinical Data Exchange Objective for the Promoting Interoperability Performance Category. The IRIS® Registry also is a CMS-approved Qualified Clinical Data Registry, with additional quality measures for ophthalmologists that are not included in any other registry.

New Dataset: Qdata Anti-VEGF Market Tracker

- In 2022 alone, this dataset captured 4.8M intravitreal injections from 2300 clinicians across 6 key retinal indications.
- This curated, real-world dataset actively and accurately tracks intravitreal utilization and outcomes, down to the level of specific indication and agent.
- Critical to providers, researchers, and life sciences companies investigating outcomes of indications, agents, and switching agents or evaluating the safety of biosimilar anti-VEGF agents, insights from this dataset may guide clinicians toward optimized evaluation, management, and improved patient outcomes.

Clinical Trial Opportunities for Practices and PIs

- Series of studies in pipeline across retinal conditions including neovascular AMD and geographic atrophy
- One recent case study, an example of the types of studies integrated providers can participate in, was a Phase 2 clinical trial for patients with a condition for which there was no diagnostic code. Patients had to be identified through symptoms, signs, and other details captured in clinical notes. Practices with patients who potentially fit inclusion criteria based on their EHR data in the IRIS[®] Registry were contacted to see if they were interested in participating.
- IRIS[®] Registry members are able to connect with other data-driven practices wanting to improve research and can have their practices nominated for relevant study opportunities.

Linking Ophthalmic Imaging and EHR Data from the IRIS[®] Registry for Geographic Atrophy (GA) Insights

- The number of patients with GA available in the IRIS[®] Registry has grown in recent years, from 36,000 patients in 2016 to nearly 300,000 patients in 2022. This number is still growing, as there has been previous underdiagnosis and undercoding due to the lack of available treatments.
- This dataset extracts key variables from imaging data, such as GA diagnosis, subfoveal involvement, and GA lesion size and characteristics in eyes with available images.
- AI can be applied to ophthalmic images, speeding identification and/or confirmation of treatment or study eligibility.

MIPS Advancements

- 2023 was the first reporting year that IRIS[®] Registry participants were allowed to select all measures available through the QCDR to submit to CMS.
- Nearly 3000 participating clinicians in the IRIS[®] Registry submitted via the Academy and its partner Verana Health.
- 2-3 new quality measures are being added to offer clinicians even better insight into their practice and how they may compare to other similar practices.

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The Shifting Sands of Medicare Reimbursement for Vitreoretinal Procedures

John T Thompson MD

- I. Medicare physician payments have declined 26% from 2001-2023 after inflation adjustments for procedures which maintained a constant relative value unit composed of physician work, practice expense, and liability insurance.¹
 - A. Many vitreoretinal procedures have seen much larger decreases due to revaluation by the AMA Relative Value Scale Update Committee (RUC) and independent decisions by Medicare (CMS), which may accept or reject the RUC recommendations to arrive at an alternate valuation.
 - B. It is important to understand the process by which various services performed by retina specialists are valued and the important role of physician surveys in arriving at those valuations.
 - C. The AMA RUC does a detailed analysis of time it takes to perform a procedure and all associated practice expenses to arrive at a relative value.
 1. The reimbursement pie is fixed so an increased value in one procedure results in reductions in reimbursement for all other procedures.
 2. This dynamic creates strong pressure to reduce the relative value of procedures if the time and resources to perform the procedure are reduced. The stress/complexity of the procedures have only a minor role in their valuation.
 - D. The revaluations of services by Medicare in the “final rule” published in November of each year often subsequently lead to changes in reimbursement by private insurers and Medicaid.
 - E. This effectively creates price controls for most medical services delivered by physicians in the United States, with the exception of cosmetic procedures, concierge primary care services, premium cataract surgery, or other noncovered services.
- II. Changes in Valuations for Selected Retina Services² (see Table 1)
 - A. The percentage decreases were different primarily due to differential decreases in the intraservice time and number of postoperative visits for the various procedures.
 1. The retina specialists who responded to the RUC surveys were responsible for the decreases when they reported they took less time to perform these procedures.
 2. The more efficient we become at performing procedures, the greater the downward trend for reimbursements.
 - B. Decreases for common retinal imaging services
 1. Fluorescein angiography and indocyanine angiography decreased substantially in 2017

Table 1. Reimbursement for Selected Vitreoretinal Procedures

Procedure	CPT Code ^a	2011	2020	% Absolute Change	% Inflation-Adjusted Change
Intravitreal injection	67028	\$107.37	\$100.69	-6.22	-18.95
PPV	67036	\$927.22	\$918.12	-0.98	-14.42
PPV with panretinal laser	67040	\$1372.31	\$1062.48	-22.58	-33.08
PPV with epiretinal membrane removal	67041	\$1280.91	\$1174.36	-8.32	-20.76
PPV with internal limiting membrane removal	67042	\$1465.40	\$1173.99	-19.89	-30.76
RD repair with scleral buckle	67107	\$1194.61	\$1153.78	-3.42	-16.52
RD repair by vitrectomy with or without buckle	67108	\$1553.40	\$1222.35	-21.31	-31.99
RD repair by pneumatic retinopexy	67110	\$741.03	\$829.70	+11.97	-3.23
Complex RD repair	67113	\$1686.93	\$1365.99	-19.03	-30.01
Laser to retinal tear	67145	\$476.01	\$507.06	+6.52	-7.93

Abbreviations: PPV, pars plana vitrectomy; RD, retinal detachment.

^aCPT codes are registered by the American Medical Association.

- when they were redefined as bilateral codes since retina specialists could previously charge 150% of value if both eyes were imaged. A time-driven activity-based costing study published this year found that fluorescein angiography is reimbursed less from Medicare than the cost of performing the procedure, primarily due to increasing cost of the sodium fluorescein dye.³
2. OCT, fundus photography, and B-scan ultrasounds have also decreased in value.
- C. Hospital outpatient departments and ambulatory surgicenters have not experienced reimbursement reductions this large, but many common vitreoretinal surgical procedures cost more to perform than their Medicare reimbursement, depending on where they are performed.
1. Berkowitz and colleagues performed a time-driven activity-based costing analysis at Vanderbilt University.⁴ They found that routine vitrectomy for CPT codes 67040, 67041, and 67042 cost the institution \$7169.29 per patient, but the total reimbursement was \$5115.93, creating a loss of \$2053.85 per case.
 2. The university broke even only if the case time was 26.81 minutes or less. Other published studies have found that vitrectomy for conditions such as complex retinal detachments resulted in greater losses compared to routine vitrectomy.
- D. The devaluation of vitreoretinal surgical procedures was exacerbated by a decision by CMS in 2021 to increase the value of E&M outpatient office codes (99201 to 99205 and 99212 to 99215) by 7% to 46%. This improved reimbursements for office-based examination.
1. Medicare decided to *not* apply these increases for E&M office visits embedded in 10-day and 90-day global procedures such as vitrectomy and retinal detachment repairs.
 - a. The magnitude of the decrease depended on how many postoperative visits were included in the individual surgical code.
 - b. This destroyed the relativity of all 10- and 90-day surgical codes across all of medicine compared to all other medical services, resulting in a devaluation of surgical services.
 - c. The net effect is that retina specialists are discouraged from performing retinal surgery in the OR compared to routine office examinations.
- III. Changes in Medicare reimbursements toward rewarding office-based primary care across all medical specialties create the following incentives in the shifting sands of medical care:
- A. Focus on maximizing time spent in the office efficiently delivering routine outpatient care
 - B. Emergency surgeries and treatment of complex vitreoretinal pathologies are emotionally gratifying, but unfortunately aren't reimbursed commensurate to the difficulty, time, and stress devoted to delivering these services.

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United for Sight: A Vision for Effective Advocacy

Retina Subspecialty Day 2023

Sohail J Hasan MD PhD

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

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

Where and How to Contribute

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

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

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

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

Why Should You Contribute?

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

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

OPHTHPAC for Federal Advocacy

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

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

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

At the Academy's annual Mid-Year Forum, the Academy, the American Society of Retina Specialists (ASRS), Macula Society, and Retina Society ensure a strong presence of retina specialists to support ophthalmology's priorities. As part of this year's meeting, the ASRS, Macula Society, and Retina Society supported participation of fellowship trainees via the Academy's Advocacy Ambassador Program. During Congressional Advocacy Day, they visited Members of Congress and their key health care staff to discuss ophthalmology priorities. The three retina societies remain crucial partners with the Academy in its ongoing federal and state advocacy initiatives.

Surgical Scope Fund (SSF) for State Advocacy

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

Support for the Surgical Scope Fund from ophthalmic interest societies like the American Society of Retina Specialists,

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

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

The Academy's Secretariat for State Affairs thanks these three retina societies for past support of the Surgical Scope Fund and looks forward to their 2023 contributions. Their support for the Surgical Scope Fund is essential to fighting for patient safety and quality eye care!

State Eye PAC

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

Support Your Colleagues Who Are Working on Your Behalf

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

OPHTHPAC Committee

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Macular Telangiectasia Type 2: Tale of a Global Private and Public Collaboration

**Emily Y Chew MD and the MacTel Project Research Group,
National Eye Institute/National Institutes of Health**

Introduction

In December 2003, a 41-year-old man from Australia was examined at the National Eye Institute/National Institutes of Health and diagnosed with a condition that was referred to at that time as “juxtafoveal telangiectasia,” as described by Dr. J. Donald Gass.¹ The patient was also examined at University of California, Los Angeles (UCLA) and at Moorfields Eye Hospital in London, UK. All clinicians concurred with the diagnosis. In 2004, in response to an invitation from this affected individual’s family to explore potential ways to research this rare retinovascular condition, an international group of clinicians and basic scientists met in Baltimore. Following this inaugural meeting, a consortium of 22 clinical sites from 7 different countries and 4 basic science labs was formed. Thus, the Macular Telangiectasia Type 2 Project (MacTel Project) began in 2005 with the support of the Lowy Medical Research Institute.

This presentation will discuss the proposed goals and the course of the project that have led to a greater understanding of this disease, which is now considered a degenerative neurovascular/glial condition of unknown origin. It will also highlight the milestones reached by the collaborative group and the findings that have led to a successful Phase 3 trial that will be reported at the American Academy of Ophthalmology Meeting in 2023, almost 20 years following the initial meeting with the patient. This productive collaboration of almost 2 decades provides a model for studying rare conditions.

Definition of MacTel

Macular telangiectasia type 2 (MacTel2) is a degenerative, bilateral neurovascular/glial disease with characteristic neurosensory atrophy, prominent perifoveal telangiectatic vessels that leak into a diffuse hyperfluorescence in the late phases of the fluorescein angiography. Other ocular characteristics include loss of retinal transparency, crystalline deposits, a decrease or absence of macular pigment and hyperpigmentation of the retinal pigment epithelium in the macula, and right-angle venules. OCT findings show breaks in the ellipsoid zone (EZ) and hyporeflective cavities in the inner and outer retina.

MacTel Project

The goals of this research endeavor, known as the MacTel Project (<https://www.lmri.net/mactel/the-mactel-project/>), were to elucidate the pathogenesis, to develop potential outcome measures for clinical trials, and to identify and test treatments for MacTel. The first project was to develop a natural history study to understand the course of the disease. Subsequently, 2 natural history studies were conducted: a natural history observation study (NHOS: 2005 to 2015)² and the natural history observation registry study (NHOR: 2010 to present). This multicenter prospective observational study was designed to evaluate the

structural and functional changes associated with MacTel over >5 years of follow-up. This included standardized stereoscopic color fundus photographs, fluorescein angiography, and fundus autofluorescence images, along with spectral domain OCT, which were graded by the Fundus Reading Center at Moorfields Eye Hospital, London, UK. At baseline and annual study visits, multimodal imaging and BCVA were measured by trained examiners using a standardized protocol and the logarithm of the minimum angle of resolution Early Treatment Diabetic Retinopathy Study VA charts.

From 2010 to the present, the MacTel Project conducted a registry of potential participants for clinical trials. Participants with a clinical diagnosis of MacTel were recruited for 1 study visit examination, which included a comprehensive eye exam and the required ophthalmic imaging as previously described for the natural history study. This cohort is followed with annual telephone interviews.

What Have We Learned From This Project?

Natural History Study

Visual acuity drop is slow initially, usually not below 20/50, likely due to structural changes, low-grade vascular leakage, or hyporeflective cavities in the inner retina. It is rare to see visual acuity below 20/200.³

Outcome Measurement for Clinical Trial

- Using the natural history data, the development of the “en face” methodology for measuring the EZ loss allowed for quantifying the area of the loss of the photoreceptors.⁴ Functional changes measured by microperimetry show good correlation with the structural changes.⁵ This outcome measure of en face detection of EZ loss was successfully used for both the Phase 1 and Phase 2 trials of an implant of ciliary neurotrophic factor (CNTF) for the treatment of MacTel.^{6,7} A Phase 3 clinical trial using CNTF in MacTel will be presented at AAO 2023.
- Genetic associations were investigated in a genome-wide analysis that identified common variants associated with MacTel. These variants have been associated with retinal vascular diameter, and 2 others have been implicated in the glycine/serine metabolic pathway.⁸
- A new classification of MacTel was developed using the Classification and Regression Trees (CART), a predictive nonparametric algorithm used in machine learning. These analyses used the ophthalmic imaging including the OCT findings from the NHOR study to develop a more comprehensive classification that takes into account the more recent detection of changes such as OCT hyperreflectivity.⁹

Summary

Two decades of epidemiologic studies will be presented and discussed.

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Multimodal Imaging for Foveomacular Dystrophy

Justin L Gottlieb MD

- I. Multiple Names
 - A. Foveomacular dystrophy
 - B. Adult-onset foveomacular vitelliform dystrophy (AFMVD)
 - C. Adult vitelliform dystrophy
 - D. Adult-onset foveomacular dystrophy
 - E. Pattern dystrophy
- II. Fundusoscopic Appearance
 - A. Typically bilateral symmetric, solitary 1/3 to 1 DD round to oval yellow, subretinal lesions
 - B. Central pigment spot within egg yolk–like lesions
 - C. May only have small pigment spot/clump
 - D. Pigment may enlarge and or develop associated atrophy.
- III. May Be Misdiagnosed as AMD
 - A. Early when characteristic vitelliform lesion is not visible on funduscopy exam
 - B. Late when there may be resolution of vitelliform lesion, atrophy, and appearance of “subretinal fluid”
 - C. May have coexistent drusen
- IV. Originally Described by Dr. Gass in 1974¹
 - A. Clinicopathologic study of a peculiar foveomacular dystrophy
 - B. *Stereoscopic Atlas of Macular Disease*²
 1. Grouped with autosomal dominant pattern dystrophies of the retinal pigment epithelium (RPE)
 2. Adult-onset foveomacular vitelliform dystrophy
- V. Electro-oculogram (ERG) and Full-Field ERG
 - A. Typically normal
 - B. Differentiates from Best vitelliform dystrophy
- VI. Multimodal Imaging

OCT, fluorescein angiography, infrared image, autofluorescence

 - A. OCT
 1. Heterogeneously hyperreflective subretinal material
 2. Mottled external limiting membrane and ellipsoid zone overlying hyperreflective material
 3. Irregular or atrophic retinal pigment epithelium (RPE)
 4. Subretinal spaces may become optically empty.
- B. Fluorescein angiography
 1. Early phase: Lesions may be irregularly hyperfluorescent, hypofluorescent, or hypofluorescent with surrounding rim of hyperfluorescence.
 2. Late phase: Lesions may show staining of the subretinal material.
- C. Infrared image: Central white spot surrounded by dark and bright areas
- D. Autofluorescence
 1. Due to accumulation of lipofuscin in RPE, macrophages, and photoreceptor cells
 2. Variable: increased hyperfluorescence to relative hypofluorescence as subretinal material and RPE degenerates
- VII. Genetics
 - A. Most often autosomal dominant but autosomal recessive and sporadic cases in literature
 - B. PRPH2
 1. Structural protein in outer segments of the discs of rods and cones. Abnormality may lead to breakdown of disc materials.
 2. Also found in other pattern dystrophies, pseudo-Stargardt macular dystrophy, rod-cone dystrophies
 - C. IMPG1 and IMPG2
 1. Interphotoreceptor matrix proteoglycan
- VIII. Foveomacular Dystrophy and AMD
 - A. Possibly 2 distinct diseases co-existing in 1 eye
 - B. Likely drusen are a “marker” of outer retinal disease (photoreceptors, RPE, Bruchs membrane) and hence common among diseases, both degenerative and genetic. Studies have found that eyes with AFMVD and drusen have a higher incidence of macular atrophy and even CNVM.
 - C. AMD masquerade in early stages of mild pigmentary disease and late with “subfoveal fluid” appearance. May be treated with anti-VEGF unnecessarily.

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Advances in Understanding Polypoidal Choroidopathy

Gregg T Kokame MD

Polypoidal choroidal vasculopathy (PCV), a subtype of exudative AMD, is the most important subtype of exudative AMD to diagnose due to its clinical implications.¹

The macular neovascularization is characterized by bulb-like or aneurysmal dilations, usually at the terminal ends of a branching vascular network. The location of this network is most commonly above the Bruch membrane and below the retinal pigment epithelium (RPE) (type 1 macular neovascularization), but it can also be above the RPE and below the retina (type 2 macular neovascularization).

The presentation of PCV is very similar to typical AMD. Findings include subretinal hemorrhage, subretinal fluid, intraretinal edema, cystic changes, and RPE detachment. Progressive subretinal fibrosis and disciform scarring can develop with permanent loss of central vision. Subretinal hemorrhage can be more significant and sometimes massive in PCV.²

PCV is more common in Asian populations, in which PCV makes up 50% or more of exudative AMD.³ PCV is less common in white populations but has been under-recognized. More recent studies using indocyanine green angiography (ICG-A) with the scanning laser ophthalmoscope to evaluate all cases of wet AMD in white patients have shown a prevalence as high as 25% of cases.³ PCV is also more common in male patients, whereas typical exudative AMD is more common in female patients.

PCV is also associated with a thicker choroid, whereas typical AMD usually has a thin choroid. PCV is considered part of the pachychoroid spectrum of diseases, which include central serous chorioretinopathy and pachychoroid pigment epitheliopathy.

The gold standard for the diagnosis of PCV is ICG-A. It is best seen using the scanning laser ophthalmoscope, but it can also be seen utilizing a fundus camera. The characteristic finding is a hyperfluorescent branching vascular network (BVN) associated with bulbous dilations of the choroidal neovascularization, usually at the terminal ends of the BVN. This network can also be imaged with en face OCT or OCT angiography. B-scan OCT showing inverted U-shaped elevations of the RPE, a ring-shaped lesion within the elevated RPE, or a visible red vascular network can also be reliable at making the diagnosis of PCV. Fluorescein angiography is not helpful in the differentiation of typical AMD from PCV, as both usually show occult leakage and often RPE detachment.

PCV is the most important subtype of exudative AMD to diagnose, as it is associated with anti-VEGF resistance.³ Intravitreal anti-VEGF agents are still often used as the first line of treatment, especially because PCV may often not be diagnosed. For PCV that is diagnosed, the Everest II study showed a better anatomic and visual response with fewer injections in the combination PDT and ranibizumab group than the ranibizumab monotherapy group.⁴⁻⁵ This result is significant, as this combination PDT and anti-VEGF injection is the only treatment that has shown better vision results and fewer injections in a multicenter clinical trial than anti-VEGF monotherapy. Combination PDT and anti-VEGF injection can thus be considered as a first-line treatment for PCV or as a rescue treatment for eyes with PCV and anti-VEGF resistance.

Although a PDT laser has not been available in the United States for many years, a new laser is now available in 2023.

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Overview and Novel Approaches to Central Serous Retinopathy

Michael Singer MD, Luke Mein, Abby Diamond, Ella Leung, David Chin Yee, Preston Obrien

Abstract

Central serous chorioretinopathy (CSCR) is traditionally believed to be a self-limiting disease, resolving without treatment within months. However, recent studies have shown that nonsteroidal anti-inflammatory drops, particularly Cox 2 inhibitors, can expedite the resolution process by 50%.¹ With changes in insurance and reduction in dosing for anterior chamber inflammation, the dosing of Cox 2 inhibitors has shifted from 4 times daily (q.i.d.) to once daily (q.d.). In addition, there has been an increased substitution of ketorolac instead of bromfenac or nepafenac, due to its cost-effectiveness. This is especially true when medications need to be dosed q.i.d. This research aims to compare the natural history of untreated CSCR cases to treatment and validate the time to resolution in acute cases.

Introduction

CSCR is a retinal disorder characterized by the accumulation of subretinal fluid and serous detachment of the neurosensory retina, particularly affecting the macula. Historically, CSCR has been considered to have a self-limiting course, with spontaneous resolution occurring in many cases within 3 to 6 months without any intervention.² However, recent research has challenged this assumption, revealing that nonsteroidal anti-inflammatory drops, specifically Cox 2 inhibitors like nepafenac and bromfenac, can significantly reduce the resolution time, by approximately 50%.¹

In light of changes in insurance and label modifications, the administration of Cox 2 inhibitors has transitioned from q.i.d. dosing to q.d. dosing. This shift in dosing has prompted clinicians to seek more cost-effective alternatives, leading to an increased use of Cox 1 inhibitors, such as ketorolac (q.i.d.). As a result, it is imperative to investigate whether Cox 1 inhibitors are equally effective in reducing the resolution time of acute CSCR cases compared to Cox 2 inhibitors vs. the natural history.

Methodology

A retrospective chart review was conducted on medical records from 2 ophthalmology practices, Medical Center Ophthalmology Associates (MCOA) and Georgia Retina, from November 2018 to April 2023. Patients diagnosed with CSCR who received medication-based interventions (ketorolac) were included in MCOA, while patients managed without medication interventions (observation) were included in Georgia Retina. Patients needed to be followed for at least 6 months and had to have OCT documentation at their time of diagnoses and resolution. Resolution time was defined as the time from diagnosis to complete resolution of symptoms and retinal fluid on OCT.

Results

Over 1600 charts were reviewed in the observation arm: In the Georgia Retina arm, 119 patients had 6 months of follow-

up, but only 63 patients resolved with only observation. In the MCOA arm, 26 patients met the inclusion criteria and met resolution with medication (ketorolac q.i.d.).

In the observation group the mean number of days to resolution was 133 days (40-329 days). The calculated median was 98 days.

For MCOA, 26 patients were resolved with medication. The mean was 89 days, while the median was 70 days.

Comparing the data of the 2 groups (MCOA and Georgia Retina), treatment with ketorolac q.i.d. decreased the time to resolution by 44 days vs. observation, which was statically significant with a P -value of .0295 ($P < .05$).

Discussion

In this study there is a difference in time to resolution between the use of first-generation nonsteroidal medication (ketorolac q.i.d.) vs. historical data³ of second-generation nonsteroidal medication (bromfenac and nepafenac). Second-generation medication appears to reduce the time to resolution in CSCR cases, with a mean of 42 days. The difference between the 2 classes of medication is 47 days longer with ketorolac. Although our current study is still significantly significant, it is not as strong as the previous study. In the previous study, observation time to resolution was 131 days. Although the time to resolution by observation appears to be equivalent between the 2 trials (131 days vs. 133 days), the time to resolution using nonsteroidal medication appears to be much shorter when second-generation medication is used. A hypothesis to explain the difference in results may be that it is due to the differences between first- and second-generation medications. Ketorolac is a combination Cox 1 and Cox 2 inhibitor but more selective for Cox 1, while bromfenac and nepafenac seem to be stronger inhibitors of Cox 1 and Cox 2 than ketorolac and may be more selective for Cox 2.

In conclusion, nonsteroidal medications are statistically significantly faster in resolving CSCR than observation. However, there seems to be a difference between nonsteroidal medications in terms of time to achieving resolution of acute CSCR. The substitution of first-generation medications such as ketorolac for second-generation medications such as bromfenac and nepafenac appears to increase the time to resolution of CSCR, even when given at the same frequency.

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Central Retinal Artery Occlusion: Time to Presentation and Diagnosis

Do Patient Presentation Patterns Impede Potential Treatment?

Robin Vora MD, Ronak Shah BS, Aubrey Gilbert MD PhD, Ronald Melles MD, Amar Patel MD, Timothy Do BS, and Michael Wolek MD

Introduction

Central retinal artery occlusion (CRAO) is a medical emergency, representing an acute ischemic stroke¹ that typically results in profound monocular vision loss, with literature suggesting that less than one-fifth of patients regain functional vision.² Furthermore, none of the historic treatments for CRAO, including ocular massage and inhalation of carbogen, appear to improve outcomes, and in some situations, as is the case with anterior chamber paracentesis, these can even cause harm.^{3,4} As awareness has grown recently in recognizing CRAO as a stroke and, in particular, its association with a high risk of other vascular events, it stands to reason that treatment for acute ischemic cerebral stroke may be effective for CRAO.

Currently, the undisputed standard of care for acute cerebral stroke is intravenous thrombolysis.⁵ Although there is no level 1 evidence to guide management of CRAO, thrombolytic therapy is considered a promising option when administered within 4.5 hours, as evidenced by various large meta-analyses.^{4,6} These results have been promising enough to prompt 3 current randomized controlled trials in Europe and a statement from the American Heart Association indicating that there is clinical equipoise to offer the treatment.¹ Considering the time-sensitive nature of thrombolytic administration for CRAO, we set about to characterize how soon these patients have historically presented into our system.

Observations

Of the 804 patients we captured with confirmed CRAO from 2011 to 2020, 484 patients presented within 30 days of symptom onset and had accurate documentation of time of symptom onset, time of presentation to the health-care system, and time of ophthalmologist evaluation. Notably, 51% of those patients connected with the health-care system within 4.5 hours of symptom onset, whereas 18% waited more than 24 hours. Only 32.8% of the cohort who presented within 4.5 hours saw an ophthalmologist within that same time frame; 35.5% of patients in the entire series did not see an ophthalmologist until 24 hours after symptom onset.

These results demonstrate that supplementary public health efforts are needed to emphasize the symptom of acute monocular vision loss as a possible sign of stroke. Further system-based changes are also needed to speed the time to diagnosis once a patient initially connects with a health-care provider.

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Long-term Results of Anti-VEGF Therapy for Central and Branch Retinal Vein Occlusion: An Overview of Current Data

Treatment Patterns and Outcomes

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Purpose

To evaluate treatment patterns and VA outcomes over a 5-year period in patients with macular edema secondary to branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) who were treated in routine clinical practice in the United States

Methods

An analysis of the Vestrum database and comparison with similar cohorts such as the Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2) and LUMINOUS cohorts

Results

Treatments such as grid-pattern laser and intravitreal steroids are uncommonly used as initial therapy in conjunction with anti-VEGF therapy. However, use of grid-pattern laser and intravitreal steroids increases over time. VA gains in clinical practice are lower than those reported in registrational clinical trials, possibly due to undertreatment.

Conclusions

BRVO and CRVO with macular edema are chronic and long-lasting conditions. Many patients require long-term treatment or monitoring out to at least 3-5 years. More than 2/3 of eyes (BRVO and CRVO) in the 5-year cohort were still receiving anti-VEGF. These results suggest that current therapies are effective but may be inadequate with respect to long-term outcomes and durability in a real-world environment.

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Spontaneous Resolution of Myopic Macular Schisis Is Not Rare and Gives Some Clues on Its Pathophysiology

Ramin Tadayoni MD PhD

I. Context and Interest of This Study

Myopic macular schisis affects 9%-34% of eyes with high myopia. The natural course of the disease is usually considered as a progressive worsening over time for most cases, with the rest remaining mainly stable. Patients are then operated or observed until vision decreases and surgery becomes necessary.

Spontaneous improvement of myopic macular schisis has been described only in case reports. Our study aimed to evaluate the rate of improvement or complete resolution of myopic macular schisis without vitrectomy and to describe the associated anatomical changes.

II. Methods and Results of This Study

We retrospectively included eyes with myopic macular schisis that were followed up without surgery for more than 6 months. Evolution of the myopic macular schisis was analyzed quantitatively (central foveal thickness, parafoveal thickness, maximal myopic macular schisis height) and qualitatively (presence/absence of foveal detachment, lamellar hole, epiretinal membrane, choroidal neovascularization, inner and outer retinoschisis, vitreous status) at baseline and at final visit. Improvement was defined as a decrease in central foveal thickness of at least 50 μm .

In our cohort of 74 unoperated eyes with a myopic macular schisis, during a mean follow-up of 55 ± 38 months (range: 8-138), 49 eyes (66%) were stable, 11 eyes (15%) worsened, and 14 eyes (19%) presented an improvement of their myopic macular schisis, including 9 cases (12%) of complete resolution. In improved cases, we found a significant decrease of central foveal thickness, 153 ± 166 microns (range: 24-635; $P = .005$), when the visual acuity remained stable. Most cases of improvement (64%) were associated with vitreous changes on OCT scans in the macular area. In others (36%), the improvement of the myopic macular schisis was associated with the treatment of a concomitant choroidal neovascularization.

III. Influences on Clinical Practice

In clinical practice, the possibility of improvement or resolution of myopic macular schisis in nearly 1 of 5 cases should be considered and communicated to patients. This improvement seems more likely when an attached vitreous is observed, in particular on OCT scans. The diagnosis of myopic macular schisis should not prevent the search for concomitant myopic neovascularization, which can sometimes explain the

patient's complaint and whose treatment can lead to a reduction in the retinal thickening.

IV. Clues on Pathophysiology

These findings, along with other findings—in particular in one of our recent works on postoperative sequence of anatomical resolution of myopic macular schisis after vitrectomy—suggest the role of the vitreous more than the staphyloma in the genesis and resolution of myopic macular schisis. Then, releasing the tension of the vitreous on the macula, if no membrane is present, can be enough for the resolution of myopic macular schisis, as in our spontaneously resolute cases. The peeling of the internal limiting membrane may accelerate the improvement or reduce the risk of appearance of a membrane but may not be mandatory to treat a myopic macular schisis.

V. Conclusion

This long-term follow-up analysis showed that almost one-fifth of unoperated myopic macular schises can improve without vitrectomy. In most cases, the improvement was associated with an apparent resolution of vitreous tensions on the macula, highlighting the dominant role of vitreous tension on the genesis and the resolution of myopic macular schisis.

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Challenging Macular Holes: From Recalcitrant to Retinal Degeneration

Elliott Sohn MD

The treatment of challenging macular holes—including those associated with high myopia and those that are large (>650 microns), chronic, recurrent/recalcitrant, and associated with retinal degeneration—can present difficulties for vitreoretinal surgeons. Holes in the setting of high myopia involve tractional forces and sometimes posterior staphyloma, which can make membrane peeling more difficult, occasionally require special instrumentation, and result in a lower rate of single-surgery success. Macular holes associated with retinal degeneration and macular telangiectasia involve additional pathological changes, such as progressive retinal thinning, photoreceptor and/or retinal pigment epithelium loss, and pigmentary abnormalities. Recurrent and/or recalcitrant holes can be complicated, especially when the internal limiting membrane (ILM) has already been peeled, and are associated with worse visual outcomes despite closure. These various conditions present multifaceted challenges to effective treatment and often necessitate individualized, complex surgical approaches.

Several treatments have been developed to address challenging macular holes, including both traditional and more novel surgical techniques. Vitrectomy and gas after peeling of the ILM is a standard treatment, aiding in relieving the tangential traction around the macular hole. Wide ILM peeling, which expands the peeling radius toward the arcades, can improve the success rate of hole closure, particularly for larger holes, but might result in slightly decreased visual gain compared to limited ILM peeling. The ILM flap technique, where a small piece of peeled ILM is draped over the hole, has shown promise in promoting hole closure by providing a scaffold for glial cell proliferation. The retracting door technique has been performed for myopic holes, where the ILM is peeled nasally to temporally over the hole then draped back over the hole. In cases where the ILM has already been peeled, transposition of an ILM flap over the hole with a superior base (aka SWIFT) is one approach. Other options for large, chronic, myopic, and refractory holes include amniotic membrane transplantation and autologous retinal transplantation. In the former, an amniotic membrane is placed within the macular hole to act as a scaffold for glial proliferation, which may have the benefit of growth factor release. Autologous retinal transplantation involves cutting an oversized piece of retina, often from the superior periphery, to the macular hole under perfluorocarbon liquid. A high rate of hole closure has been observed even with recurrent holes using both forms of transplantation, with improvement in visual acuity demonstrated in a number of studies.

These treatments offer various benefits and drawbacks and are chosen based on the specific characteristics of the individual patient's macular hole. This presentation will discuss some pearls and pitfalls for treating challenging macular holes with the above techniques.

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Limited Membranectomy in the Management of Complex Tractional Retinal Detachments

John Kitchens MD

Diabetic retinopathy (DR) is the leading cause of blindness in working age patients in the industrialized world. Approximately 100 million people have DR, of which one-third are estimated to have diabetic macular edema (DME), the leading cause of vision loss in patients with diabetes.^{1,2} Proliferative diabetic retinopathy (PDR) is responsible for up to 25% of vision loss in the diabetic population. Surgery is required in up to 5% of patients with PDR.^{3,4}

Diabetic tractional retinal detachment (TRD) surgery can be technically very difficult, with a high complication rate. Iatrogenic breaks are common and are more often associated with a poor visual outcome.⁵ For this reason, in some cases limiting peripheral fibrovascular membranes may be preferred to release macular traction, clear vitreous hemorrhage, and improve visual function while reducing the potential for iatrogenic retinal breaks.

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The Wisconsin Silicone Oil Vitrectomy Study: Anatomical and Vision Outcomes of Complex Retinal Detachment Repair

Michael Altaweel MD, Kathleen Schildroth MD, Justin Gottlieb MD, Jonathan Chang MD, Michael Ip MD, Paul Boeke MD, Max Wingelaar MD, and Michael Nork MD

Indications for Silicone Oil (SO) Tamponade

- Provides long-term tamponade, allowing anatomic support for the retina until it is healed sufficiently to remove the oil
- Can potentially mitigate the tractional effects of subsequent proliferative vitreoretinopathy, the primary cause of failure of retinal detachment (RD) repair
- Most common use is for eyes with RD and prior gas tamponade that failed due to proliferative vitreoretinopathy (PVR).
- Allows support of the inferior retina for patients who cannot maintain positioning (neck issues, habitus, comorbidities, children)
- In the most complex cases, long-term tamponade may reduce the risk of phthisis, with associated pain and globe loss.
- Disadvantages include need for additional surgery for SO removal.
- Long-term outcomes with SO use in eyes with complex RD are presented.

University of Wisconsin Oil Vitrectomy Study

- IRB-approved retrospective chart review, 2013-2019
- 315 SO placement surgeries, 231 eyes
- 1000 centistoke oil 98%
- 63% male
- 54% OD, 46% OS
- Average age: 55 years; range: 4 months to 90 years
- Technique: 25-gauge vitrectomy, staining, membrane peeling, subretinal fluid drain during fluid-air exchange, endolaser, perfluoro-n-octane/retinectomy 28.1%/scleral buckle as needed, oil tamponade, inferior iridotomy if aphakic, cataract surgery as required
- Silicone Oil Study retinectomy rate: 29%

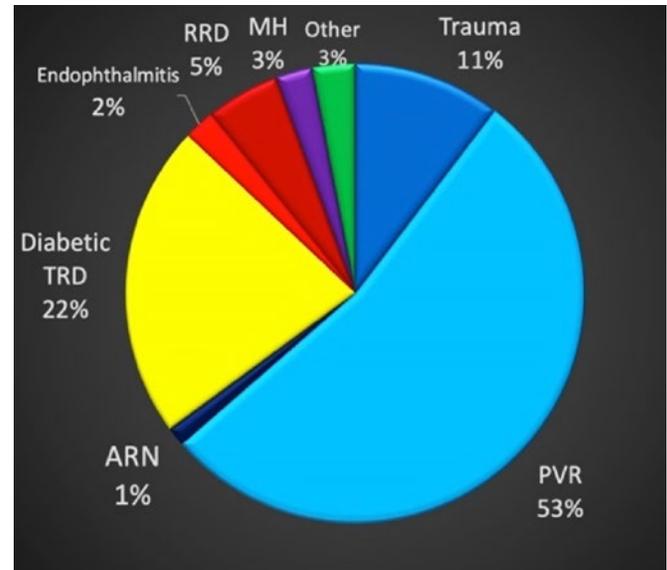


Figure 1

Anatomic Outcome (mean 26-month follow-up)

- Seventy eyes (32%) redetached under oil, 12 with repeat redetachment after later SO replacement.
- SO removed in 64.1%, mean of 7.1 months after placement. Subsequent redetachment rate: 28%
- Multiple vitreoretinal surgeries often required, 2.7 per patient
- Smokers required more surgeries (2.9) than nonsmokers (2.5, $P = .009$).
- Final anatomic success achieved in 82%; 45% of eyes SO tamponade at last follow-up.

Anatomic Success PVR Group, Final (122 Eyes, Grade C)

- Treatment-naive PVR: 93.5% (29/31)
- Previous pars plana vitrectomy/gas and PVR: 81.3% (74/91)
- RD without PVR: 91.7% (11/12)—monocular, inability to position, need to fly
- Compared with Silicone Oil Study at 18 months
 - Group 1, no prior vitrectomy: success with SO = 60.3% attached
 - Group 2, prior vitrectomy: success with SO = 59% attached, final attachment rate up to 71%

Vision Outcome (All Cases)

- Mean initial VA 20/1321 (logMAR 1.82)
- Mean final VA 20/693 (logMAR 1.54; $P = .004$)
- Attached at final visit (82%): preop 20/1262 (logMAR 1.80), improved to 20/526 (logMAR 1.42; $P < .0001$)
- Final vision 20/200 or better in 35.9% and 20/40 or better in 7.4%.
- Rhegmatogenous RD: Improved from preop logMAR 1.36 (20/458) to postop logMAR 0.57 (20/74; $P = .03$)

Vision Outcomes, PVR Group

- 35% > 20/200
- Vision $\geq 5/200$, logMAR 1.6
- Treatment-naive PVR: 50% at last follow-up (gain: 2.2 line; $P = .06$)
- Previous pars plana vitrectomy/gas PVR: 67% at last follow-up (gain: 4.2 lines; $P = .001$)

Vision vs. Number of Surgeries

- Patients undergoing a total of 3 vitreoretinal surgeries had the best final vision outcome, improving by 5.2 lines.
- Compare this with 1 or 2 surgeries: 1.1 lines of improvement ($P = .002$) (more tractional RD patients),
- Or 4+ surgeries: improvement of 0.7 lines ($P = .1$)

Preventing Ocular Hypertension (Rates of 2.2%-56% in Literature)

- Reservoir technique for controlled SO infusion; target IOP 15 mmHg
 - Fill until oil starts to egress through vent, remove vent
 - Air infusion line opened to atmospheric pressure, and SO allowed to egress up infusion line
 - Infusion line redirected to vitrectomy machine, with air infusion pressure set to 15; watch for stabilization of SO in line.
 - Trocars removed. Suture. Any SO lost during sclerotomy closure is replaced via the reservoir.
- Technique used by 2 surgeons (100 eyes); IOP estimated by digital palpation by 3 surgeons.
- Ocular hypertension (≥ 24) at Week 1
 - Reservoir: 8.7%
 - Palpation: 17.4%
 - $P = .029$
 - At 1 month: reservoir, 8.2% vs. palpation, 11.1%
- IOP ≥ 30 mmHg at 1 week and 1 month
 - Reservoir: 1.6%, 3.3%
 - Palpation: 9.3%, 6.8%
 - $P = .005$
- Overall IOP average
 - Reservoir: 13.8 mmHg
 - Palpation: 16.4 mmHg
 - $P < .001$
- Three eyes required oil removal for overfill in the palpation group.
- On medical treatment at 3+ months
 - Reservoir: 8%
 - Palpation: 17%

Conclusions

- Poor initial and final vision due to underlying pathology, though improvement is observed.
- When used for primary rhegmatogenous RD and successful repair of RD with PVR that previously failed gas, SO tamponade is associated with substantial vision improvement (7.2 lines).
- Smokers had worse vision outcomes (loss of 0.7 lines) compared with nonsmokers (improved 2.7 lines; $P = .05$).
- Redetachment is common.
 - Under SO: 32%
 - After oil removal: 28%
- Multiple surgeries often required, average 2.7
- Reservoir technique is associated with less postoperative ocular hypertension.
- Final anatomic success: 82% overall, 84% for PVR group

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Management of Complex Retinal Trauma

Dean Elliott MD

- I. Incidence of Retinal Detachment After Open Globe Injury

Based on 10-year review of ~900 open globe cases¹

 - A. 8% at presentation and within 1 day after presentation
 - B. 13% at presentation and within 1 week after presentation
 - C. 21% at presentation and within 1 month after presentation
 - D. 29% at presentation and within several years after presentation
- II. Risk Factors for Retinal Detachment After Open Globe Injury

Probability of developing retinal detachment can be predicted using open globe injury score based on the following risk factors:^{1,2}

 - A. Visual acuity at presentation
 - B. Zone of injury
 - C. Vitreous hemorrhage
- III. Indications for Vitrectomy After Open Globe Injury

Based on >60 eyes with open globe injury that underwent vitrectomy³

 - A. Retinal detachment (without retinal incarceration in wound) comprised 39% of cases.
 - B. Media opacity comprised 28% of cases.
 - C. Retinal incarceration in wound (\pm retinal detachment) comprised 13% of cases.
 - D. Progressive vitreoretinal traction comprised 11% of cases.
 - E. Intraocular foreign body comprised 5% of cases.
 - F. Endophthalmitis comprised 3% of cases.
- IV. Comorbidities Noted During Vitrectomy for Open Globe Injury

Based on >60 eyes with open globe injury that underwent vitrectomy³

 - A. Iris trauma in 62% of cases
 - B. Lens expulsion in 54% of cases
 - C. Subretinal hemorrhage in 51% of cases
 - D. Hyphema in 41% of cases
 - E. Choroidal hemorrhage in 30% of cases
 - F. Corneal trauma in 20% of cases
- V. Secondary Procedures Performed After Primary Repair of Open Globe Injury
 - A. Indications
 1. Media opacity
 2. Progressive vitreoretinal traction (\pm retinal detachment)
 3. Retinal incarceration in wound (\pm retinal detachment)
 4. Retinal detachment
 - B. Timing: typically 7-14 days after primary repair surgery
 1. Less bleeding
 2. Easier to create posterior vitreous detachment (PVD)
 - C. Goals of vitrectomy
 1. Create PVD.
 2. Relieve vitreous traction.
 3. Relieve retinal traction, in cases with incarceration and/or proliferative vitreoretinopathy (PVR).
 4. Reattach retina using any of a variety of techniques, which may include membrane peeling, scleral buckle, retinectomy, perfluorocarbon liquid, endolaser, and extended tamponade.
- VI. Surgical Technique
 - A. Retinectomy commonly used for retinal incarceration and/or PVR
 - B. General principles of retinectomy for retinal detachment after open globe injury⁵
 1. Strongly consider lensectomy in phakic eyes (lower incidence of hypotony with aphakia)
 2. Consider scleral buckle to support vitreous base (except in cases with 360-degree retinectomy)
 3. Retinectomy performed after attempted complete epiretinal membrane removal; if retinectomy is done before complete epiretinal membrane removal, further membrane removal may be difficult.
 4. Orientation: circumferential, posterior to vitreous base

5. Location
 - a. Avoid retinectomy edge near 6 o'clock position.
 - b. Most common retinectomy location is inferiorly with edges at 3 o'clock and 9 o'clock.
6. Size
 - a. Retinectomy should extend into normal retina surrounding areas of traction.
 - b. Most common retinectomy size is 6 clock hours or 180 degrees.
 - c. If greater than 270 degrees, extend the retinectomy to 360 degrees.
7. Hemostasis: Diathermy used to delineate intended edge and to prevent intraoperative bleeding
8. Instruments: vitrectomy probe (or scissors) used to cut retina
9. Adjuvants: May consider perfluorocarbon liquid to stabilize posterior retina
10. Complete excision of anterior retina to prevent postoperative proliferation with resultant traction on the retinectomy edge or ciliary body (lower incidence of hypotony with removal of anterior retina)
11. Retinopexy: confluent endolaser to the retinectomy edge \pm 360-degree endolaser
12. Extended tamponade: C₃F₈ gas or silicone oil (Silicone Oil Study showed equal efficacy in eyes with retinectomy; recent studies favor silicone oil over gas; redetachment occurs in 4%-25% after oil removal.⁶)

VII. Recurrent Retinal Detachment due to PVR After Open Globe Injury

A. Risk factors

1. Smoking⁴
2. Presence of PVR at time of initial retinal detachment repair^{3,4}
3. Subretinal hemorrhage noted at time of initial vitrectomy³
4. Absence of scleral buckle performed during initial vitrectomy⁴
5. Retinectomy performed during initial vitrectomy³

B. Incidence: ~50%^{3,4}

C. Outcomes

1. After initial retinal detachment repair³: 100% reattached intraoperatively (many with large retinectomies).
2. After initial retinal detachment repair \pm reoperations for recurrent detachment due to PVR³
 - a. 80% completely attached at last follow-up.
 - b. 14% partially attached at last follow-up.
 - c. 6% remained detached at last follow-up.

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Surgery in Uveitis Patients: What’s the Difference?

Lisa J Faia MD

- I. Posterior Segment Complications in Uveitis Patients
 - A. Visually significant vitreous opacities
 - B. Epiretinal membranes
 - C. Tractional retinal detachments
 - D. Rhegmatogenous retinal detachments
 - E. Combined detachments
 - F. Dislocated lens
- II. Indications for Surgery
 - A. Therapeutic
 - 1. Visually significant or visually threatening complications/etiologies
 - 2. Inflammatory control
 - B. Diagnostic: unknown etiologies
- III. Key Considerations Before Surgical Intervention
 - A. Proper preoperative evaluation and management
 - B. Proper preoperative inflammatory control; quiescence for 3 months
 - C. Etiology and type of uveitis dictate preoperative precautions and rate of postoperative complications.
 - D. Current regimen may dictate preoperative escalations needed before surgery.
- IV. Preoperative and Perioperative Escalations of Inflammatory Control Mechanisms
 - A. Etiology
 - 1. Anterior uveitis: Usually does not require oral steroids prophylactically unless on systemic immunomodulation already
 - 2. Posterior uveitis: 97% will require systemic steroids for prophylactic care.
 - B. Current treatment regimen
 - 1. If currently controlled with local therapies (see Figure 1), could consider subtenon Kenalog, triamcinolone acetonide injectable suspension (Xipere), dexamethasone intravitreal implant (Ozurdex), or preservative-free triamcinolone acetonide (Triescence) several days prior to or at the time of surgery.
 - 2. If patient is controlled with injections, could consider:
 - a. Injection 1 week prior and close follow-up if prone to cystoid macular edema
 - b. Oral steroids to be considered if frequent injections are needed. Usually 0.5 mg/kg 3-5 days before surgery, day of surgery, and 3 days after, and taper by 5-10 mg a day every 5-7 days depending on inflammatory response.
 - 3. If patient requires systemic medications for control (see Figure 2), could consider:
 - a. If on oral steroids for treatment, then 1 mg/kg (no greater than 60 mg PO per day needed) beginning 3-5 days prior with taper by 5-10 mg per week
 - b. If on steroid-sparing medications for control, could consider:
 - i. Solumedrol day before, day of surgery, and day after with steroid taper
 - ii. Typically ok for IV solumedrol in the OR and then steroid taper

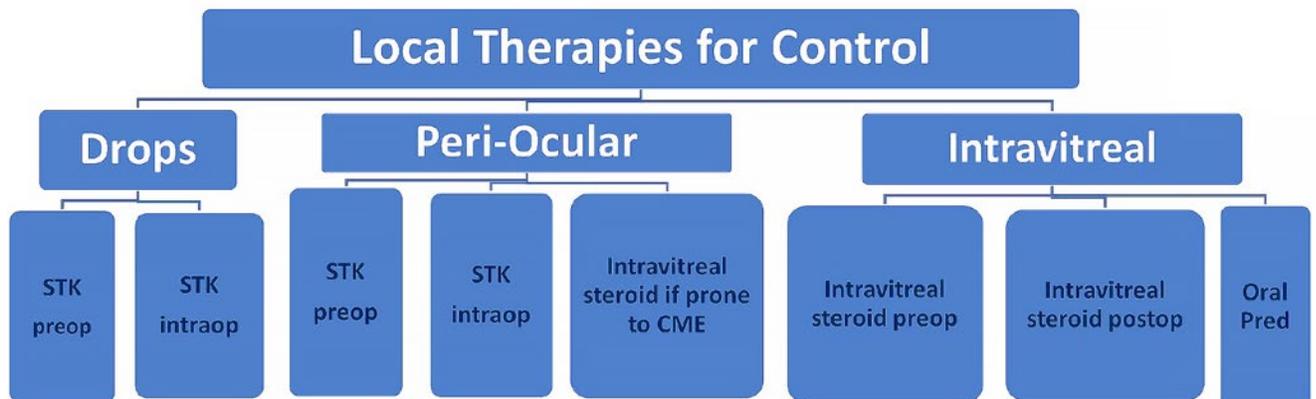


Figure 1. Suggested inflammatory prophylaxis/treatment for uveitis patients controlled with local therapies. Abbreviations: STK, subtenon Kenalog; CME, cystoid macular edema; Pred, prednisone.

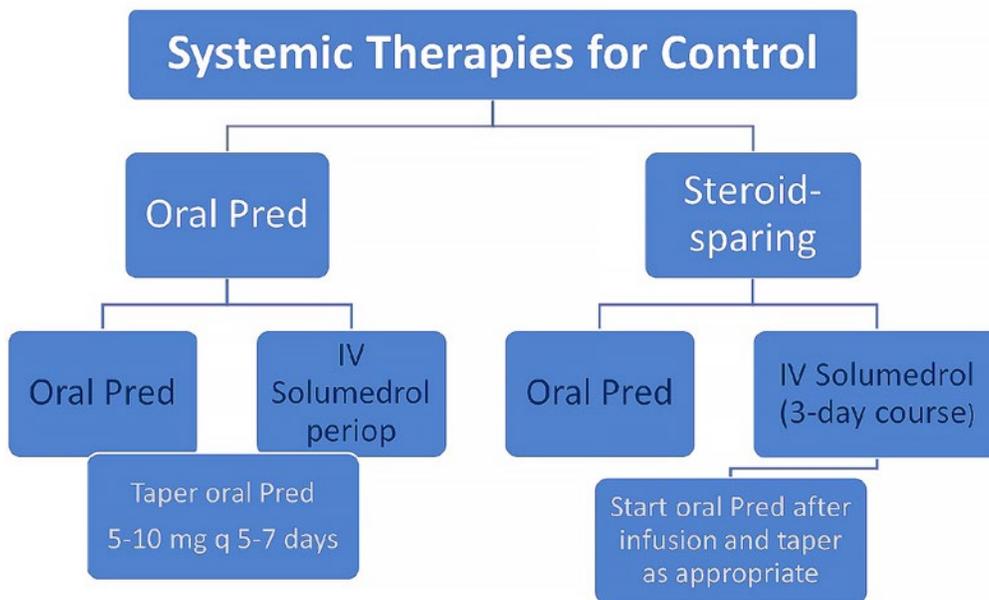


Figure 2. Suggested inflammatory prophylaxis/treatment for uveitis patients controlled with systemic therapies. Abbreviation: Pred, prednisone.

V. Do Patients Always Need Prophylaxis?

- A. It's easy to be aggressive beforehand as once inflammation erupts it can be very difficult to contain and may produce more unwanted complications.
- B. Don't be fooled by a quiet eye.

VI. Possible Postoperative Complications

- A. Cystoid macular edema
- B. Hypotony
- C. Reactivation of inflammation
- D. Endophthalmitis

Benefit of Vitreoretinal Surgery in Managing Tumor Eyes

Tara A McCannel MD

I. Introduction

A. Controversy

1. Fear that manipulation will cause tumor seeding and metastasis
2. Lack of vitreoretinal training in most ocular oncologists
3. Ocular oncologists slow to adopt novel approaches
4. Few centers with experience combining vitreoretinal approaches with tumor management

B. Critical for modern approaches to visual preservation

1. Traditional approach to uveal melanoma is focused on tumor control.
2. Preserving vision is not part of management strategy at most centers.

II. Radiation Shielding

A. Role of silicone oil

1. Rationale, data supporting improved vision
2. Palladium-103 is better shielded than iodine-125—move to palladium-103 as primary radioisotope

B. Future materials for radiation shielding

III. Management of Retinal Detachment

A. Serous retinal detachment

1. Frequently left for “observation only”
2. Vitrectomy is only path for improving vision.

B. Rhegmatogenous retinal detachment: Abnormal retinal pigment epithelium–choroid requiring different surgical approaches

IV. Management of Vitreoretinal Comorbidities: Macular Pucker and Holes

A. Frequently left for “observation only”

B. Vitrectomy required for visual improvement

V. Summary

The Controversy in Small Uveal Melanoma Treatment

Timothy G Murray MD MBA

Overview

- Uveal melanoma remains a clinical diagnosis and requires expertise in evaluation to ensure diagnostic accuracy.
- Major findings for transition to malignancy include growth, orange pigment, subretinal fluid, initial size, location, symptoms, and atypical internal echographic reflectivity.
- Primary and secondary management of small uveal melanoma holds the greatest promise to reduce melanoma-related mortality.

Controversy

- Concerns with diagnostic accuracy slowed the adoption of early treatment as a viable strategy to delayed treatment.
- Traditional approaches have focused on radiotherapy (brachytherapy or charged particle) or enucleation—neither of which is appealing in the primary management of small uveal melanoma.
- Historical treatments had unacceptable short- and long-term complications.
- Advanced molecular genomics give insight into metastatic risk and ultimately define the need for surgical management.
- Uncertainty that earlier intervention for small uveal melanoma impacts survival.

Approach

- Once established, the diagnosis of small uveal melanoma typically requires definitive therapy to minimize/eliminate metastatic risk.
- Advances in biopsy for genetic prognostication now play a major role in tumor management.
- The most controlled approach to biopsy utilizes small-gauge microincisional valved vitrectomy with fluidic control—best approached via 3-port vitrectomy and wide-field viewing.

- Microincisional valved vitrectomy surgery (MIVS) as a primary treatment strategy for small uveal melanoma has now been reported with over 5 years of follow-up in a large consecutive series.
- Technically, the approach incorporates small-gauge vitrectomy with valved fluidics, removal of vitreotumoral traction, removal of macular internal limiting membrane, confluent endolaser tumor ablation, 25-gauge multipass fine needle aspiration biopsy for gene expression profiling (GEP), and intravitreal triamcinolone acetate to modulate post-treatment inflammation. Each of these steps has proven critical to excellent tumor control with minimized morbidity.

Results: MIVS Ablation and GEP as Primary Therapy

- Local tumor control: Approximately 99% at 5 years
- GEP biopsy positive results: Approaching 98%
- Post-treatment progressive retinal detachment: 1%-2%
- Melanoma-associated metastatic disease: Less than 1% at 5 years
- Enucleation rates: None
- Endophthalmitis rates: None
- Intraocular tumor dissemination: None

Impact

- Advances in vitreoretinal surgery have now enabled a targeted microsurgical approach to small tumor management that enhances precision tumor treatment, incorporates advanced biopsy techniques, exhibits excellent tumor control, and minimizes treatment-related morbidity. Continued focus on enhanced strategies for small tumor melanoma management remains the single best approach to reduce melanoma-related mortality.

What's the Role of Biopsy in Uveal Melanoma? Updates and Progress on Prognostication and Liquid Biopsies

Jesse L Berry MD

1. Why is a liquid biopsy needed for uveal melanoma?
2. What do we know about DNA? Chromosomal alterations
3. What do we know about DNA? Mutational analysis for pathogenic variants
4. What do we know about protein analysis in liquid biopsy for uveal melanoma?
5. Are there other biomarkers? Extracellular vesicles and others
6. What are the various roles of the different analytes: blood vs. aqueous humor
7. This is cool, but does any of it matter? Will liquid biopsy ever replace traditional biopsy for uveal melanoma?

Management of Radiation Retinopathy

Ivana K Kim MD

- I. Radiation Retinopathy
 - A. Occlusive microangiopathy that occurs months to years after ocular exposure to ionizing radiation
 1. Vascular endothelial cell is primary focus of damage.
 2. Threshold dose estimated to be approximately 25 Gy at 2 Gy per fraction.¹
 - B. Manifestations of radiation retinopathy
 1. Maculopathy
 2. Optic neuropathy
 3. Proliferative retinopathy
 - II. Treatment of Radiation Maculopathy
 - A. Photocoagulation
 1. Macular grid laser may decrease edema and slow visual loss in some patients.²
 2. Benefit is not sustained.
 - B. Anti-VEGF
 1. Bevacizumab
 - a. Finger et al, 10-year experience³
 - i. 92/99 patients treated with bevacizumab, some with doses up to 3 mg
 - ii. 4-12 week intervals
 - b. Initial decrease in OCT central foveal thickness with subsequent fluctuations
 - c. Probability of vision retention within 2 lines of baseline: 69% at 5 years, 38% at 8 years
 2. Aflibercept
 - a. Murray et al, aflibercept for radiation maculopathy⁴ ($n = 40$)
 - i. Stabilization of VA
 - (a) mean VA at entry: 20/63
 - (b) mean VA at 2 years: 20/70
 - ii. Frequent injections required
 - (a) fixed every 6 weeks group: 9 injections/yr
 - (b) "treat and adjust" group: 8.4 injections/yr
 - (c) second year extension: 7.8 injections/yr
 - b. Switch from bevacizumab (Srivastava and Weis)⁵
 - i. 46% with central foveal thickness improvement of 100 μm
 - ii. 23% with VA improvement of 1 line or more
- C. Corticosteroids
 1. Intravitreal triamcinolone
 - a. 31 patients, single injection 4 mg/0.1 mL (Shields et al)⁶
 - b. VA stable (within 2 lines of baseline) or improved at 6 months in 45%
 2. Steroid implants
 - a. Dexamethasone implant (Caminal et al)⁷
 - i. Reduction in OCT thickness in both treatment-naïve patients and patients previously treated with anti-VEGF therapy
 - ii. Stabilization of vision
 - b. Fluocinolone implant (Singaravelu et al)⁸
 - i. Stabilization of vision and OCT thickness in previously treated patients
 - ii. Reduction of treatment frequency
- III. Prophylactic Treatment
 - A. Periocular triamcinolone
 1. Randomized trial of periocular triamcinolone 40 mg in 1 mL (Horgan et al)⁹
 - a. Three treatments every 4 months, starting at plaque application
 - b. 18-month follow-up
 - c. 108 patients triamcinolone, 55 patients control
 2. Moderate vision loss: 31% in triamcinolone group vs. 48% in control group ($P = .039$)
 - B. Bevacizumab
 1. Retrospective cohort study (Shields et al)¹⁰
 - a. Bevacizumab every 4 months for 2 years starting at time of plaque removal
 - b. 1131 bevacizumab-treated patients (mean follow-up 40 months) vs. 117 historical controls (mean follow-up 58 months)

2. Median logMAR visual acuity at last follow-up: 0.54 [20/70] bevacizumab group vs. 1.3 [20/200] historical controls; $P < .001$
 3. Visual acuity 20/40 or better: 37% bevacizumab group vs. 27% historical controls; $P = .002$
- C. Ranibizumab
1. Prospective study, historical control group (Kim et al)¹¹
 - a. Ranibizumab every 2 months for 24 months starting at time of tumor localization surgery for proton radiation
 - b. 25 patients with small-medium tumors within 2 disc diameters of optic disc or fovea
 - c. 100 historical controls meeting eligibility criteria with similar follow-up
 2. Moderate vision loss (≥ 3 lines) at 24 months: 20.8% in ranibizumab group vs. 45.2% in historical controls; $P = .03$
 3. Visual acuity 20/40 or better at 24 months: 88% in ranibizumab group vs. 47% in historical controls; $P < .001$
- D. DRRCR Retina Network study in development
1. Protocol AL
 2. A randomized clinical trial evaluating intravitreal faricimab (6.0 mg) injections or fluocinolone acetonide (0.19 mg) intravitreal implants vs. observation for prevention of visual acuity loss due to radiation retinopathy

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When to Worry About Germline Mutation in Retinoblastoma

Carol L Shields MD

- I. What are genetics of retinoblastoma?
 - A. Germline: 13q mutation in all cells in the body
 1. At risk for bilateral, multifocal, familial retinoblastoma
 2. At risk for pinealoblastoma
 3. At risk for secondary malignancies
 4. At risk for future children having retinoblastoma
 - B. Somatic: 13q mutation in retinoblastoma only
 1. One tumor in one eye
 2. No additional risks for other cancers or transmission to future children
- II. Can we predict germline mutation of retinoblastoma from clinical features?
 - A. Yes: The younger the patient, the greater the risk for germline mutation. See Figure 1, which shows that children ages 0 to 3 months with solitary unilateral retinoblastoma have a 61% chance for germline mutation, and the risk decreases with increasing patient age.
 - B. Yes: Macular location of tumor imparts greater risk for germline mutation than extramacular tumor (see Figure 2).

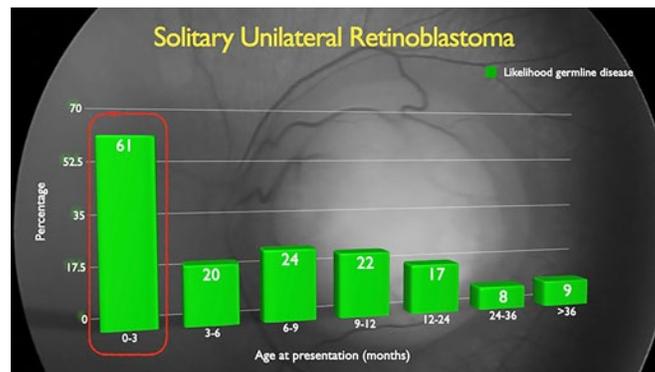


Figure 1

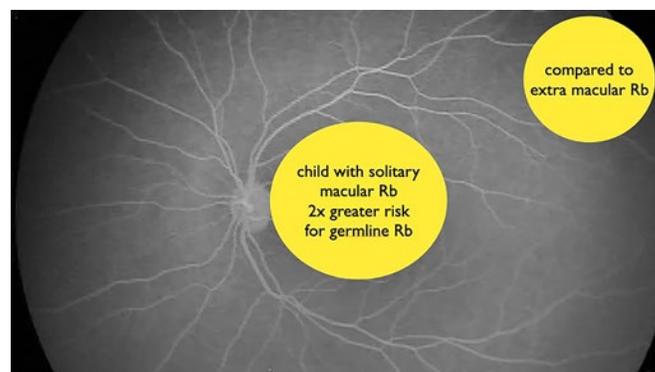


Figure 2

Selected Readings

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Early Vitrectomy in Diabetic Retinopathy: Pro

Maria H Berrocal MD

Early vitrectomy in eyes with severe proliferative diabetic retinopathy offers significant advantages. Removing the posterior hyaloid stabilizes eyes, reducing the progression of retinopathy and preventing the formation of tractional retinal detachments. Complications of pars plana vitrectomy have been significantly reduced with advances in vitrectomy technology and instrumentation. Therefore, vitrectomy should not be considered only as a treatment of last resort to treat severe complications of diabetic retinopathy.

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Early Vitrectomy in Diabetic Retinopathy: Con

William E Smiddy MD

I. Introduction

The subject of timing for diabetic vitrectomy has been debated for decades, modified for advances in medical and surgical options. Both studies and experience clearly converge on the concept that medical and surgical options are complementary, not exclusive. The relative paucity of randomized studies on this issue reflects its multifactorial nature. The Diabetic Retinopathy Vitrectomy Study (DRVS) and Diabetic Retinopathy Clinical Research Protocol AB are the only such studies in the literature. They offer valuable and enduring information that guides treatment, but individual patient factors also influence optimal patient care.

II. Definition of Early Vitrectomy (Pars Plana Vitrectomy [PPV])

- A. Immediate (<1 month)
- B. Early (1-3 months)
- C. Longer than 3 months

III. Only Randomized Trials Addressing This Question

- A. DRVS 2 and 5, vitreous hemorrhage, and 3 and 4, nonmacular traction retinal detachment: 2- and 5-year results
 1. Vitrectomy before 3 months vs. standard of later
 2. For both, benefit was higher proportion of 20/40 or better.
 3. Other parameters, equivalent results
- B. Protocol AB (vitreous hemorrhage only), 2-year results
 1. Aflibercept vs. PPV + panretinal photocoagulation (PRP)
 2. Context: Protocol N (and others) established efficacy of ranibizumab for proliferative diabetic retinopathy.
 3. Faster recovery of VA in first 3 months; no difference thereafter
 - a. All parameters similar after ~12 weeks (good, bad results; regardless of baseline VA)
 - b. About 1/3 “crossed over”
 - c. Recurrent vitreous hemorrhage rate higher in nonsurgical group

IV. Better Questions

- A. Which patients are better candidates for initial deferral of PPV?
- B. Factors to consider
 1. Medical issues: DM control, hypertension
 2. Previous degree of PRP
 3. Degree of prior FVP
 4. Fellow eye status

V. Conclusion

- A. It's not a binary answer.
- B. Current anti-VEGF era offers options, even if temporary/complementary control.
- C. Individualization is necessary, at least to some degree.

Selected Readings

1. DRVS 2: Diabetic Retinopathy Vitrectomy Study Research Group. Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy: two-year results of a randomized trial. *Arch Ophthalmol.* 1985; 103:1644-1652.
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Current Complement Inhibition Therapy for Geographic Atrophy Is Acceptable: Pro

Usha Chakravarthy MBBS PhD

The molecular pathway of complement activation represents a prime target for interventions that can ameliorate or prevent geographic atrophy (GA), a late-stage manifestation of AMD. When the area of atrophy is located in the central retina, particularly within and involving the fovea, visual function can be markedly reduced. Because GA is almost always bilateral at detection and often exhibits considerable symmetry, visual impairment in both eyes is commonly present, leading to significant handicap in those affected by this condition.¹ Until recently, GA has been untreatable as the area of atrophy expands steadily over time; data from routine care records has shown that sufferers will experience the inexorable progression toward severe visual impairment, often with the loss of ability to see well enough to drive within 2 years of initial presentation.²

However, there is a glimmer of potential success in the management of GA with 2 molecules, one that inhibits C3 and the other, C5—representing key steps in the activation of the complement cascade having been shown to reduce the expansion of GA.

In independently conducted clinical trials, treatment with pegcetacoplan injection (Syfovre by Apellis) and avacincaptad pegol (Zimura by Iveric) with intravitreal administration of drug either monthly or bimonthly has been shown to reduce the expansion of GA by around 20% compared to sham. Although corresponding reductions in mean change in measures of vision were not observed with either treatment compared to sham, in the Iveric trial a lower proportion of patients at highest risk of visual decline due to GA lost fewer than 15 or more letters

of visual acuity in the treated group compared to sham. This measure of a 15-letter loss represents a doubling of the visual angle and is an accepted clinical trial outcome, as it is a measure of clinically significant vision loss. In the Apellis trial, the subgroup of patients with extrafoveal GA similarly experienced less reduction in visual acuity in treated eyes compared to sham. These data indicate that functional benefit due to slowing of GA growth is unevenly distributed across large populations and that subgroups of patients with specific characteristics of GA may be of value. However, this begs the questions, is the effect size within such subgroups sufficient to offset potential adverse effects of repeated intravitreal injection (endophthalmitis) and the hazard of developing exudation, and also is the risk-to-benefit ratio acceptable given that GA is untreatable and leads to severe reductions in quality of life?³

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Current Complement Inhibition in the Treatment of Geographic Atrophy Is Acceptable: Con

Richard F Spaide MD and Demetrios Vavvas MD

The FDA's approval of pegcetacoplan in February 2023, despite lacking tangible patient benefits or significant improvements in visual acuity, reading speed, low luminance vision, reading speed, mean microperimetry, and other measures, stirred controversy.¹

Patients were asked to complete the National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25), a measure of vision-related quality of life that has been validated in AMD²⁻⁵ and geographic atrophy (GA).⁶⁻⁸ In the DERBY and OAKS tri-

als by Apellis, there was no difference between treated patients and sham controls in the VFQ-25. Apellis didn't announce the actual values, only that there was no statistical difference. Whatever the motivation for the lack of reporting of important outcomes, patients clearly did not perceive any quality-of-life benefit from this treatment! This lack of nonfunctional benefit was coupled with considerable risks: over 2 years of monthly injections there were reports of 12% exudation, 4% inflammation, and 1.7% ischemic optic neuropathy. Deaths were nearly

double (6.7%) in the monthly pegcetacoplan arm compared to sham (3.8%; see prescribing information package). These are important risks that have functional consequences. Yet many downplay them, especially the conversion to exudative AMD, arguing that we convert an untreated disease into a treatable one; please note that the people that converted to exudative AMD lost more letters than the people that did not convert despite treatment (as published by the FILLY report)! The idea that it is OK to induce a treatable complication is like saying it is OK for children to play with matches since we can put out fires.

The quality-adjusted life years (QALYs) metric assesses the burden of disease and its treatment. In the case of pegcetacoplan, where patients perceived no improvement in quality of life, the QALYs would be zero. Thus, the cost per QALY becomes astronomical, thereby increasing the burden on both patient and society. Overall, objective test data on the nearly 1200 patients in the study showed that the patients, in a validated quality-of-life survey, did not perceive any benefit. The patients who were treated experienced much higher rates of complications. The drug was approved because of a subtle difference in a surrogate test (autofluorescence imaging).

Some from the company argue that functional endpoints are unreliable in GA and that we should rely only on the surrogate test. However, the functional tests are the ones that form the basis of how we evaluate every disease and treatment affecting vision. Apellis picked the vision tests that were evaluated in their trials. If there were better tests, why didn't Apellis pick those? Visual acuity, reading speed, low-luminance BCVA, Functional Reading Independence Index composite score, and mean microperimetry are measures that have been used in previous retina-related studies.^{7,9-14}

One important measure is what the patients think about their own visual function and how it affects their lives. In that respect, there was no treatment benefit.

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Vitreotomy Combined With 360-Degree Extended Vitreous Base Laser vs. Scleral Buckling: Pro Prevention of Post vitrectomy Retinal Detachments

Presented by Stanislao Rizzo MD

Steve Charles MD and Adam Pflugrath MD

Reducing the rate of post vitrectomy retinal detachments in the treatment of vitreoretinal disorders is an ongoing and ever-changing endeavor. The treatment of vitreoretinal disorders, specifically the treatment of retinal detachments, has evolved rapidly, with many surgeons preferring to perform pars plana vitrectomy (PPV) over scleral buckle (SB) procedures.¹ Further, the evolution of vitrectomy technology (25-gauge, high cutting rates, advanced fluidics, endolaser photocoagulation, and wide-angle visualization) has led to expanded treatment options and opportunities for improved patient outcomes.

Several factors go into the development of post vitrectomy retinal detachments. Eyes at highest risk of developing post vitrectomy detachments are those in which a posterior vitreous detachment is created during vitrectomy, such as in macular hole repair,² non-posterior vitreous detachment (PVD)-associated detachments (young myopes with round holes), vitreomacular traction, vitreomacular schisis, and inherited collagenopathies such as Stickler syndrome or Wagner syndrome. Additionally, the interaction of residual vitreous and the air/gas or silicone bubbles may lead to new inferior retinal breaks. Further, the interaction with the superior aspect of perfluorocarbon liquid in cases of medium-term perfluoron (PFO) may cause new superior retinal breaks.

Eyes that are at low risk of post vitrectomy retinal detachment are those in which a prior PVD has occurred without retinal detachment, retinal break, or lattice degeneration, diabetic traction retinal detachments, and post-PPV eyes with sufficient vitreous removal accompanied by 360-degree scleral depression.

Some retina surgeons advocate for the use of a scleral buckle or combined scleral buckle and PPV at time of surgery for retinal detachments.³ In a recent meta-analysis comparing PPV to PPV-SB, they have similar single-surgery anatomic success rates.⁴ Further, a Cochrane Review comparing scleral buckles to PPV found low-certainty evidence favoring PPV.⁵ Additionally, a large meta-analysis comparing PPV, SB, and pneumatic retinopexy found similar outcomes with PPV and SB, with no added benefit of combined PPV-SB.⁶ Brazitikos et al's series of vitrectomy without a buckle produced better retinal detachment outcomes than the Primary Retinal Detachment Outcomes Study (PRO) series of PPV outcomes.⁷

Scleral buckles are associated with 2.75 D of induced myopia,⁸ diplopia,⁶ infection, and extrusion.⁹ The practical arguments against combining scleral buckle with PPV are that there is no induced myopia or strabismus and there are fewer ocular surface disorders due to minimal conjunctival and epithelial disruption. Further, scleral buckles induce significant Tenon capsule and conjunctival scarring, thereby creating challenges if the patient should require a glaucoma filtering procedure and limiting its efficacy.

Advocates of combining a scleral buckle with PPV for retinal detachment believe it is the buckle that reduces post-PPV retinal detachment compared to vitrectomy alone in their series. An argument can be made that it is the degree of retinopexy that provides the benefit, not the buckle.

Use of prophylactic 360-degree laser retinopexy vs. only laser retinopexy around identified retinal breaks to reduce the risk of post vitrectomy retinal detachment is an area of debate.¹⁰ A large series in Japan noted a significant reduction in risk of post-PPV retinal detachments with 360-degree laser retinopexy at the vitreous base.¹¹ Additionally, there is a 3-fold reduction in the incidence of postoperative retinal detachments with use of prophylactic 360-degree laser retinopexy.^{12,13} Further, prophylactic extended vitreous base laser significantly reduces the risk of retinal detachments in patients with Stickler syndrome.¹⁴ Thus adjunct or prophylactic 360-degree laser retinopexy appears to be advantageous in the prevention of retinal detachments.

With higher laser power, there is the potential for retinal breaks at laser edges, formation of proliferative vitreoretinopathy, and pupillary abnormalities due to damage to the ciliary nerves. However, the application of low-intensity, nearly confluent laser to the entire (extended) vitreous base should reduce these risks.

Endolaser photocoagulation is preferred to laser indirect ophthalmoscopy intraoperatively as endolaser photocoagulation improves surgeon ergonomics and prevents direct iris damage. The use of the Alcon Vektor illuminated articulated endolaser probe enables simultaneous scleral depression by the surgeon.

Scleral buckle combined with PPV is not efficacious and not indicated as an adjunct to reduce risk of post vitrectomy detachments. Prophylactic 360-degree low-intensity endolaser photocoagulation at the vitreous base reduces post vitrectomy detachments and should be utilized in high-risk cases.

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Vitrectomy Combined With 360-Degree Extended Vitreous Base Laser vs. Scleral Buckling: Con

Edwin Hurlbut Ryan Jr MD

Abstract

Fifty years ago, scleral buckling was the only option for retinal reattachment. Then pars plana vitrectomy became a useful adjunct, and success rates improved. Nowadays, vitrectomy has become ascendant, and some surgeons declare that there is no role for scleral buckling as an adjunct to vitrectomy. This argument is mistaken, as most good studies in the past 20 years show superior single-surgery success rates with the addition of a scleral buckle to vitrectomy for retinal reattachment. The newer approach sans scleral buckling is leading to deficiencies in fellow training, poor buckling skill sets, and erroneous surgical judgment, with resultant inferior outcomes. Understanding when and how to use a scleral buckle as an adjunct to vitrectomy will result in better patient outcomes.

Late Breaking Developments, Part I

Panel Moderator: Mark S Humayun MD PhD

Panelists: Gemmy Chui Ming Cheung MB BChir FRCOphth, Dilsher S Dhoot MD, Suber S Huang MD MBA, and Carolyn K Pan MD

ALTITUDE: Suprachoroidal Delivery of ABBV-RGX-314 Investigational Gene Therapy for Diabetic Retinopathy

Mark R Barakat MD

Aflibercept 8 mg in Patients With Neovascular AMD: Phase 3 PULSAR Trial 96-Week Results

Jean-Francois Korobelnik MD

A 12-Week Phase 2/3 Double-Masked, Randomized, Multicenter Study of OCS-01 Eye Drops in Diabetic Macular Edema

Hani Salehi-Had MD

UBX1325 A Novel Senolytic Candidate for Patients With Diabetic Macular Edema: 48-Weeks Results for BEHOLD Phase 2 Study

Veeral Sheth MD

Treatment of Geographic Atrophy Secondary to AMD With Intravitreal ANX007, a Selective Classical Complement Inhibitor: Results of the ARCHER Study

David R Lally MD

Syfovre Initial Complication Experience

William J Johnson MD

Diversity in Retinal Clinical Trials: Are We There Yet?

Adrienne W Scott MD

Introduction

Clinical trials inform evidence-based medical care. A diverse pool of clinical trial participants is important, as populations may differ with respect to genetic, environmental, and physiologic characteristics that may inform disease processes and response to therapy. Nonetheless, health-care disparities are well documented and persist in clinical trial enrollment.

The field of retina has led clinical medicine in the size and breadth of landmark randomized research trials; however, Black, Hispanic/Latino, and non-White populations remain underrepresented in clinical trial enrollment relative to the respective retina disease burdens, as are those from rural and socioeconomically disadvantaged backgrounds. Most retina clinical trial participants are from White, high-income countries. To promote generalizability of clinical trial findings, the NIH and the USFDA have provided standardized reporting guidelines to encourage representation of underrepresented groups in clinical trials.

Summary

Though there has been an increased awareness of the importance of enrolling a diverse clinical trial cohort and the incidence of reporting of race/ethnicity in clinical trial reporting has improved, retinal clinical trial diversity remains limited. Clinical researchers should continue to work to identify strategies to eliminate barriers that contribute to disparities in enrollment and retention of underrepresented populations in ophthalmology, and specifically in retina clinical trials. Prioritizing diversity in clinical trial representation will improve the quality of scientific evidence produced by these trials and is necessary to inform treatment guidelines, health policy, and the standard of retinal care for our patients.

Selected Readings

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Advances and Challenges in CRISPR Gene Editing for Retinal Diseases: Comparison of Gene Augmentation vs. Gene Editing, Early Termination of EDIT-101 Study for LCA10, and Preclinical Studies Using CRISPR to Target VEGF

Glenn Yiu MD PhD

Background

Recent advances in gene therapy have the potential to revolutionize the management of both rare and common retinal disorders. However, most current gene therapy strategies rely on gene augmentation by producing a functional version of the mutated gene in a rare disease, or a biofactory approach of overexpressing a biologic therapy such as an anti-VEGF agent. For example, the first FDA-approved gene therapy employed an adeno-associated viral (AAV) vector to deliver the RPE65 gene to replace the defective visual cycle isomerase in type 2 Leber congenital amaurosis (LCA).¹ At the same time, multiple clinical trials are under way using novel AAV serotypes to enable aflibercept, ranibizumab, or other anti-VEGF agents to be produced in the eye indefinitely, with the promise of putting an end to the clinical burden of frequent intraocular injections. However, these conventional gene therapies do not repair the underlying genetic defect and are often driven by strong, nonspecific promoters that produce the therapeutic protein at concentrations far exceeding physiologic or homeostatic levels.

CRISPR-based genome editing technology enables modifications of genetic materials at the DNA level, allowing precise repair of gene mutations that can restore physiologic function.² This revolutionary technology, for which a Nobel Prize was awarded to its inventors in 2020, has since expanded to different novel applications and clinical trials.³

Outline

In this presentation, I will review advances in CRISPR technology, including the development of base editors and prime editing, and how these strategies contrast with conventional gene therapies that are currently under investigation. Specifically, I will discuss the first human clinical trial using CRISPR technology—the BRILLIANCE study—a Phase 1 study evaluating the use of EDIT-101, which uses CRISPR-based gene editing to repair the splice mutation in the CEP290 gene in patients with type 10 LCA.⁴ Finally, I will provide updates on the preclinical optimization and development of a CRISPR-based strategy to ablate VEGF in mouse and nonhuman primate models.⁵⁻⁷

- I. Advances in Gene Editing
 - A. Origin of CRISPR-Cas9 technology
 - B. Base editing and prime editing
 - C. CRISPR activation or repression

II. BRILLIANCE Study

- A. EDIT-101 strategy
- B. BRILLIANCE study design
- C. BRILLIANCE study outcomes

III. Gene Editing for Neovascular AMD

- A. In vitro testing of CRISPR to suppress VEGF
- B. Comparison of Cas9 orthologues to suppress VEGF
- C. Optimizing gRNA design to suppress VEGF
- D. Preclinical testing of CRISPR platform to suppress CNV in nonhuman primates

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PA025 ALK-001 (C20-D3-Vitamin A) Slows the Growth of Atrophic Lesions in ABCA4-Related Stargardt Disease: Results of a Randomized, Placebo-Controlled Clinical Trial, the TEASE-1 Study

Christine Nichols Kay MD

- I. Stargardt disease is caused by ABCA4 mutations. Toxic vitamin A dimers form rapidly in the retina due to defective ABCA4.
 - A. Vitamin A is delivered to the retina via the bloodstream.
 - B. Enzymes of the visual cycle enable proper transport of vitamin A through the retina.
 - C. When the ABCA4 gene is defective, vitamin A dimerizes quickly, causing toxicity to the retina and vision loss.
- II. Clinical attempts at slowing vitamin A dimer formation without affecting vitamin A have been challenging, as adequate supply of vitamin A is vital for retinal health. Can replacing vitamin A with gildeuretinol slow the progression of Stargardt disease?
- III. Gildeuretinol is a chemically modified retinol (vitamin A) whereby 3 hydrogen atoms are replaced with 3 heavy hydrogen atoms (deuterium). Gildeuretinol functions like natural vitamin A and acts as vitamin A replacement. It is not a visual cycle modulator. Gildeuretinol is taken as a pill, once a day.
- IV. In preclinical studies, replacement of vitamin A with gildeuretinol results in 80% reduction in dimer formation and accumulation, preservation of retinal anatomy and ERG function.
 - A. Slows vitamin A dimerization 4-5 fold
 - B. Results in 80% dimer reduction in mice
 - C. Rescues the phenotype of pigmented ABCA4 mice
 - D. Improves dark adaptation in double knock-out mice
- V. TEASE-1 was a clinical trial designed to estimate the effects of gildeuretinol on the growth rate of atrophic lesions in Stargardt disease.
- VI. The eligibility criteria were broad to allow enrollment of nearly all Stargardt disease patients with well-delineated areas of decreased autofluorescence.
 - A. 12 to 60 years old
 - B. No restriction on visual acuity
 - C. At least 1 eye with well-delineated areas of significantly decreased autofluorescence
 - D. Clinical diagnosis of Stargardt disease, further supported by ABCA4 mutation(s)
- VII. TEASE-1 was a multicenter, randomized, double-masked, placebo-controlled clinical trial in patients with atrophic Stargardt disease.
 - A. 50 patients were randomized: 30 received gildeuretinol, 20 received placebo for 1 year. After 1 year, half of the placebo patients were randomly crossed over to gildeuretinol.
 - B. At the end of the trial, external natural history cases of atrophic Stargardt patients were prospectively added to the dataset.
 - C. The primary safety endpoint was long-term safety.
 - D. The prespecified primary efficacy endpoint was the growth rate of atrophic lesions.
- VIII. There were 7 participating sites across the United States.
- IX. Demographics and baseline characteristics were well balanced across groups.
- X. The prespecified primary efficacy outcome measure was the growth rate (slope) of well-delineated atrophic lesions (chorioretinal atrophy).
 - A. Imaging acquired on Spectralis FAF
 - B. Confirmed by OCT when needed
 - C. Two masked graders
- XI. In the intent-to-treat group, we observed a statistically significant, clinically meaningful slowing of atrophic lesions growth rate.
 - A. 21% slower growth rate ($P < .001$) when using square root transformation
 - B. 28% slower growth rate ($P < .001$) when using untransformed areas
 - C. Results remain statistically significant when excluding external natural history cases ($P = .01$).

- XII. Gildeuretinol further slowed the growth rate of atrophic lesions toward the foveal center by 34% ($P < .001$), demonstrating preservation of central retina.
- XIII. Sensitivity analyses showed no relationship of growth rates with sex, lesion multifocality, mild allele, or baseline BCVA.
- XIV. The safety profile was similar to that of taking natural vitamin A.
 - A. No clinically significant changes or trends of change seen in liver function tests over 2 years
 - B. No dark adaptation delays or night blindness
 - C. Gildeuretinol was well tolerated, with mild to moderate adverse events.

Outcomes From the Randomized, Controlled Phase 3 GLOW Trial: Management of Diabetic Retinopathy With KSI-301

Tarcocimab Tedromer (KSI-301) in Diabetic Retinopathy and Its Role in the Management of Diabetic Eye Disease

Charles C Wykoff MD PhD, Daniel Janer MD, Trinh Pham MS, J Pablo Velazquez-Martin MD, Victor Perlroth MD, and Jason Ehrlich MD PhD

Introduction

Despite the many improvements in medications available for diabetes and in the medical care of people with diabetes, diabetic retinopathy (DR) remains a leading cause of vision loss in working-aged people.¹ A patient's future risks of developing sight-threatening complications of diabetic retinopathy, such as diabetic macular edema (DME) and/or proliferative diabetic retinopathy (PDR), are related to their level of diabetic retinopathy severity and its rate of worsening, as measured on the Diabetic Retinopathy Severity Scale (DRSS) using color fundus photography.² Historically, clinical recommendations for patients focused on preventing the worsening of diabetic retinopathy severity, for instance with improvements in management of hypertension and hyperglycemia.

Several randomized clinical trials have demonstrated that locally applied therapies, such as inhibitors of vascular endothelial growth factor (VEGF) or steroids, could both markedly improve diabetic retinopathy severity and prevent worsening, at levels of benefit far exceeding those realized with the use of laser therapies or with systemic diabetes and hypertension management alone.³⁻⁷ Subsequently, 2 anti-VEGF therapies have been approved by the USFDA as primary treatments for diabetic retinopathy in patients with or without concomitant DME.

Although substantial improvements in DR severity have been demonstrated following anti-VEGF treatment, the approved dosing regimens demand a high treatment frequency on average. The burdens of treatment, associated risks, and cost are such that anti-VEGF therapies are still not widely used in the absence of sight-threatening complications such as DME or PDR.⁸ There is thus a substantial medical need for a more durable therapeutic option that allows a reduced treatment frequency, thus making it a more suitable treatment for nonproliferative PDR (NPDR) in routine clinical practice. Importantly, a more durable treatment could hopefully prevent the occurrence of more complicated/advanced stages of diabetic eye disease.

Tarcocimab tedromer (also known as KSI-301) is an antibody biopolymer conjugate (ABC) designed to potently inhibit intraocular VEGF while providing longer-lasting VEGF suppression. The antibody portion of KSI-301 binds to VEGF-A with high affinity and inhibits the ability of VEGF-A to bind and activate its cognate receptors. The biopolymer portion is an ultra-hydrophilic phosphorylcholine polymer that significantly increases the overall molecular size of KSI-301, which in turn extends its ocular half-life.

The Phase 3 GLOW Study (NTC05066230) was designed with the objective of demonstrating that KSI-301 5 mg is superior to sham treatment with respect to Diabetic Retinopathy Severity Scale (DRSS) change from baseline at Week 48 in participants with NPDR, and evaluating the benefit of KSI-301 treatment on the incidence of sight-threatening complications (DME and/or PDR) and the use of treatment for these complications when they develop.

Methods

Anti-VEGF treatment-naïve patients with moderately severe to severe NPDR were randomized 1:1 into 2 treatment arms: KSI-301 5 mg given on Day 1, Week 8, Week 20, and then every 24 weeks (Q24W); or sham injections at the same intervals. The primary efficacy endpoint is the change in DRSS from baseline at Week 48 (see Figure 1). Additional secondary endpoints evaluated at Week 48 include time to development and proportion of sight-threatening complications (PDR and DME, among others) and the incidence of ocular and non-ocular adverse events. Participants who developed any of the sight-threatening complications of DR in the study eye were treated with open-label KSI-301 5 mg, irrespective of the treatment group that they were originally randomized into (KSI-301 5 mg or sham).

Results

Fifty-two sites across the United States and Europe randomized 253 patients (146 males, 58%) into the study, with a mean age of 56.7 years. At baseline, mean BCVA was 81.5 letters and mean baseline central subfield thickness (CST) was 266.9 μm . Results for the primary endpoint and additional secondary endpoints will be presented at the meeting.

Conclusions

The adoption of approved anti-VEGF therapies for NPDR is constrained partly by the high treatment burden caused by their insufficient durability. The extended ocular half-life of tarcocimab and its associated less frequent dosing regimen lend it the potential to be a clinically relevant therapy for diabetic eye diseases broadly including NPDR and DME. Data on the Week 48 primary and secondary efficacy outcomes will be presented at the meeting.

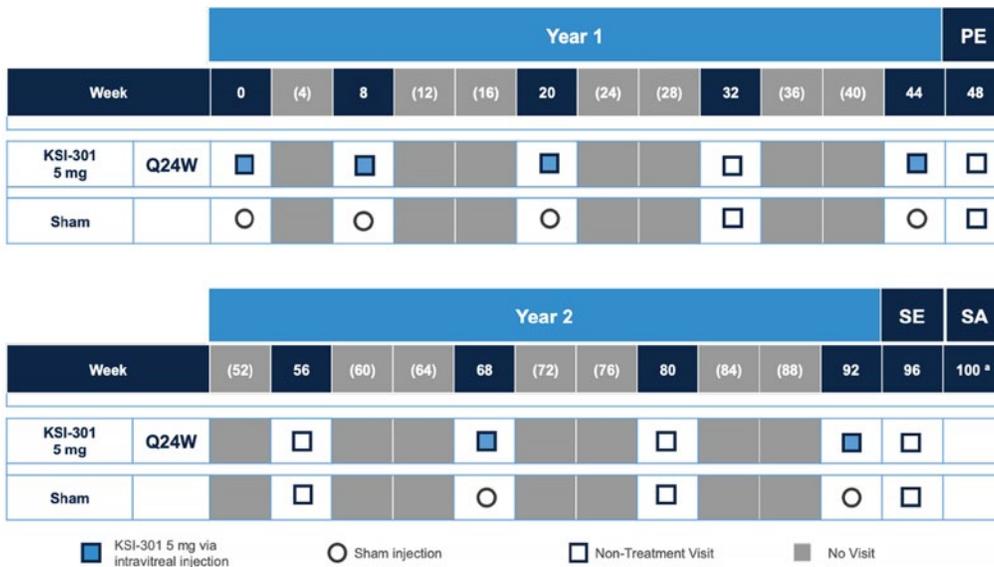


Figure 1. Phase 3 GLOW Study schematic design.

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Aflibercept 8 mg for Diabetic Macular Edema: 96-Week Results of the PHOTON Study

Diana Do MD on behalf of the PHOTON study investigators

Background Statement

Aflibercept 8 mg demonstrated comparable efficacy and safety to aflibercept 2 mg through Week 48 of the Phase 2/3 PHOTON trial. Herein, efficacy and safety results for aflibercept 8 mg and 2 mg through Week 96 will be reported.

Précis

In the Phase 2/3 PHOTON trial, aflibercept 8 mg every 12 or 16 weeks met the primary endpoint and demonstrated noninferior BCVA gains to aflibercept 2 mg every 8 weeks at Week 48. Furthermore, the safety profile of aflibercept 8 mg was similar to that of aflibercept 2 mg through Week 48. Efficacy and safety data through Week 96 will be presented.

Abstract

Purpose

To evaluate the treatment effects of aflibercept 8 mg vs. 2 mg in diabetic macular edema (DME)

Methods

PHOTON (NCT04429503) was a double-masked, 96-week, noninferiority trial that evaluated the efficacy and safety of aflibercept 8 mg every 12 or 16 weeks after 3 monthly doses (8q12, $n = 328$; or 8q16, $n = 163$) vs. aflibercept 2 mg every 8 weeks after 5 monthly doses (2q8, $n = 167$) in patients with DME.

Results

Mean BCVA change from baseline at Week 48 was +9.2, +8.8, and +7.9 letters with 2q8, 8q12, and 8q16, respectively (primary endpoint; 95% CI for 8q12 vs. 2q8: -2.26 to 1.13; 95% CI for 8q16 vs. 2q8: -3.27 to 0.39). Through Week 48, 91% of 8q12 patients and 89% of 8q16 patients maintained their original randomized dosing interval with no shortening, and in the 8 mg-combined group, 93% maintained a dosing interval ≥ 12 weeks. Safety outcomes for aflibercept 8 mg and 2 mg were similar through Week 48. New data through Week 96 will be presented.

Conclusion

Aflibercept 8 mg met the primary endpoint, demonstrating noninferiority in BCVA vs. aflibercept 2 mg, with no new safety signals through 48 weeks. The vast majority of patients maintained extended ≥ 12 -week dosing (93% in 8 mg-combined) and 16-week dosing (89% in 8q16). Data through Week 96 will be presented.

The Key OCT Signatures and Their Histologic Correlates Every Clinician Should Recognize

K Bailey Freund MD

Beginning in 2010, Drs. Freund and Curcio have collaborated on imaging-histology correlations intended to improve interpretation of clinical OCT imaging of patients with diseases of the retina and underlying choroidal vasculature, especially AMD. Goals are accomplished through microscopic analysis of human donor eyes with extensive clinical history and multimodal imaging. Eye tissues are processed for high-resolution histology and microscopy and compared to clinical images of the same eyes obtained while the patients were living. They seek histopathologic correlates of distinctive OCT signatures that appear commonly in patients with both non-neovascular and neovascular AMD.

This presentation will include multimodal retinal imaging and clinicopathologic correlates for several AMD phenotypes that can be mistaken for exudative macular neovascularization. Clinicians familiar with these findings will be less likely to initiate potentially unnecessary treatment with intravitreal anti-VEGF therapy when they encounter such cases. Manuscripts related to the findings described in this presentation are listed below.

Selected Readings

1. Messinger JD, Brinkmann M, Kimble JA, et al. Ex vivo OCT-based multimodal imaging of human donor eyes for research into age-related macular degeneration. *J Vis Exp*. 2023 May 26; (195).
2. Berlin A, Cabral D, Chen L, et al. Histology of type 3 macular neovascularization and microvascular anomalies in treated age-related macular degeneration: a case study. *Ophthalmol Sci*. 2023; 3(3):100280.
3. Berlin A, Messinger J, Ferrara D, Freund KB, Curcio CA. Optical coherence tomography features relevant to neovascular AMD management and non-neovascular age-related macular degeneration progression: clinicopathologic correlation. *Retin Cases Brief Rep*. 2023; 17(4S):S41-S46.
4. Berlin A, Cabral D, Chen L, et al. Correlation of optical coherence tomography angiography of type 3 macular neovascularization with corresponding histology. *JAMA Ophthalmol*. 2022; 140(6):628-633.
5. Brinkmann M, Bacci T, Kar D, et al. Histology and clinical life-cycle of acquired vitelliform lesion, a pathway to advanced age-related macular degeneration. *Am J Ophthalmol*. 2022; 240:99-114.
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7. Tan ACS, Pilgrim MG, Fearn S, et al. Calcified nodules in retinal drusen are associated with disease progression in age-related macular degeneration. *Sci Transl Med*. 2018; 10(466):eaat4544.
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Next-Generation Assessment of OCT Biomarkers for Intermediate and Advanced Dry AMD: Prognostication and Clinical Trial Utilization

Justis P Ehlers MD

- I. Background on Dry AMD OCT Biomarkers
 - A. Qualitative features
 - B. Importance of biomarkers for emerging therapeutics
- II. Enhanced Technology for Biomarker Characterization
 - A. Compartmental segmentation
 - B. Deep learning interrogation
- III. Function-Structure Correlation
 - Ellipsoid zone integrity features and visual function
- IV. Clinical Trial Integration
 - A. Utilization as key endpoints
 - B. Population enrichment
- V. OCT Biomarkers and Emerging Therapeutics

AI-Based Imaging Biomarkers in Nonexudative AMD

Frank G Holz MD, Leon von der Emde MD, Maximilian Pfau MD FEBO, and Thomas Ach MD FEBO

Background

Nonexudative AMD encompasses a broad spectrum of clinical subphenotypes classified into early, intermediate, and atrophic (geographic atrophy, GA) according to the fundus photography-based Beckman classification. New imaging technologies allow for a more granular characterization of a multitude of anatomical features, including drusen volume, hyperreflective foci, subretinal drusenoid deposits, ellipsoid zone reflectivity, photoreceptor degeneration, and iRORA (incomplete retinal pigment epithelium [RPE] and outer retinal atrophy) and cRORA (complete RPE and outer retinal atrophy) as precursor lesions and GA lesion size. These pathological features have been shown to possess predictive value for progression over time and are thus of clinical relevance. Detection, quantification, and manual annotation of AMD-related biomarkers (eg, in complex OCT volume scans) is not practical, either in routine clinical practice or in the context of large-scale clinical natural history studies and interventional trials. Particularly, recording the mere presence or absence of a risk feature is insufficient, as the magnitude of changes may correlate with risk for progression. So precise quantification and topographic mapping are prudent.

Artificial intelligence allows for the creation of fully automated pipelines that can segment these biomarkers in a very timely, accurate, reproducible, and quantitative fashion. These tools may allow for manifold applications, including risk assessments in clinical practice, therapy monitoring, and the development of new structural endpoints for regulatory approval of novel therapies for various disease states of nonexudative AMD.

Geographic Atrophy

Identifying areas of GA has benefited greatly from technological advancements. The so-called RegionFinder—a semiautomated software that identifies areas of GA based on fundus confocal scanning laser ophthalmoscopy autofluorescence images in patients with GA—has shown utility in tracking GA enlargement over time. More recently, multimodal deep learning networks have been able to segment GA lesions from fundus autofluorescence (FAF) images, near-infrared reflectance images, and OCT scans while yielding segmentation accuracies comparable to those of experienced human graders.¹

Multiple companies are developing AI-based tools to monitor disease progression during anti-complement therapy, with easy-to-use dashboards that plot the enlargements of GA lesions (eg, before and during treatment). Lastly, a major milestone was set with the development of convolutional neural network (CNN) models to predict the future region of growth of GA lesions, which could enhance clinical trial efficiency and improve patient counseling.

Complete outer retinal atrophy, termed GA in the context of AMD, may have various etiologies, including a multitude of monogenetic macular and retinal dystrophies. An AI-based approach has recently been shown to automatically diagnose the specific underlying disease (Eye2Gene) based on various imaging modalities, including FAF. For the differential diagnosis, this may be helpful in clinical practice for dissecting mimicking diseases and accurately selecting patients (eg, for anti-complement therapies), as there is no evidence for efficacy in atrophy from other causes than AMD.

Drusen Volume

The Beckmann classification, the most-adopted grading system for AMD staging, is based on drusen diameters in color fundus photography. Nowadays a more in-depth assessment of drusen volume is possible using 3-dimensional quantification with OCT. Algorithms for quantifying drusen volume, which make use of the RPE's high reflectivity, were among the first AI tools developed for AMD.² Quantitative drusen measurements are correlated with disease progression in AMD, and therefore serve as a risk assessment feature and structural biomarker.

Hyperreflective Foci

Similar to the hallmark drusen, pigmentary abnormalities and hyperreflective foci (HRF) on OCT represent key features and are associated with progression over time. Manual identification of HRF, however, is tedious and error prone, and thus it was more challenging to develop accurate algorithms for their quantification. First algorithms on HRF have recently been published, with promising results demonstrating that HRF quantification can predict future disease progression.³

Subretinal Drusenoid Deposits

Subretinal drusenoid deposits (SDD), in contrast to conventional sub-RPE drusen, are lesions that occur anterior to the RPE monolayer. Patients with SDD show a faster disease progression associated with more profound visual deficits, especially under scotopic conditions. SDD can be visualized in color fundus photography or even better in FAF, near-infrared reflectance imaging, and OCT. Nonetheless, the inter-reader agreement of SDD quantification may be poor. First algorithms have achieved results comparable to those of the inter-reader agreement for automated FAF-based quantification.⁴ Algorithms for automated annotation of OCT-based SDD volumes and their staging are still pending.

Photoreceptor Layers

Photoreceptor degeneration

Functional studies in AMD suggest that the degeneration of certain photoreceptor layers such as the outer nuclear layer (ONL) have a high predictive value for retinal sensitivity loss. Pfau and colleagues developed a novel biomarker of photoreceptor degeneration and demonstrated that photoreceptor thinning was indicative of future GA progression (see Figure 2).⁵ This algorithm has already crossed the threshold into clinical use and has underscored the therapeutic utility of pegcetacoplan for slowing down GA progression. Treatment with this complement C3 inhibitor was associated with a thicker ONL and thicker inner segments compared to the sham arm. Automated pipelines are also needed to quantify iRORA and cRORA (ie, precursor lesions of GA).

Ellipsoid zone reflectivity

Quantification of the relative ellipsoid zone reflectivity (rEZR) could yield additional information about the function/degenerative stage of the outer retina and has shown strong correlations with disease severity in AMD.⁶ Further studies are necessary to evaluate and compare the predictive value as well as functional correlate of this biomarker.

Inferred sensitivity

Two-color dark-adapted fundus-controlled perimetry is an excellent way to probe rod and cone function in the macula region. However, the procedure is relatively time consuming. “Inferred sensitivity” refers to the technique of using multimodal imaging to generate predictions of these extensive psychophysical examinations. This machine learning–based method has yielded excellent results and may serve as a functional surrogate endpoint in future clinical trials.^{7,8}

Perspectives

The evolving field of AI has demonstrated significant potential in enhancing the understanding, diagnosis, and management of nonexudative AMD.⁹ A range of AI-based imaging biomarkers have been developed, providing a more sophisticated and comprehensive way of tracking disease progression. Besides tracking and predicting the progression of GA, risk estimation of the progression to GA is becoming increasingly more accurate.¹⁰ As AI continues to mature, the integration of these tools into routine practice will enhance the management of these patients.

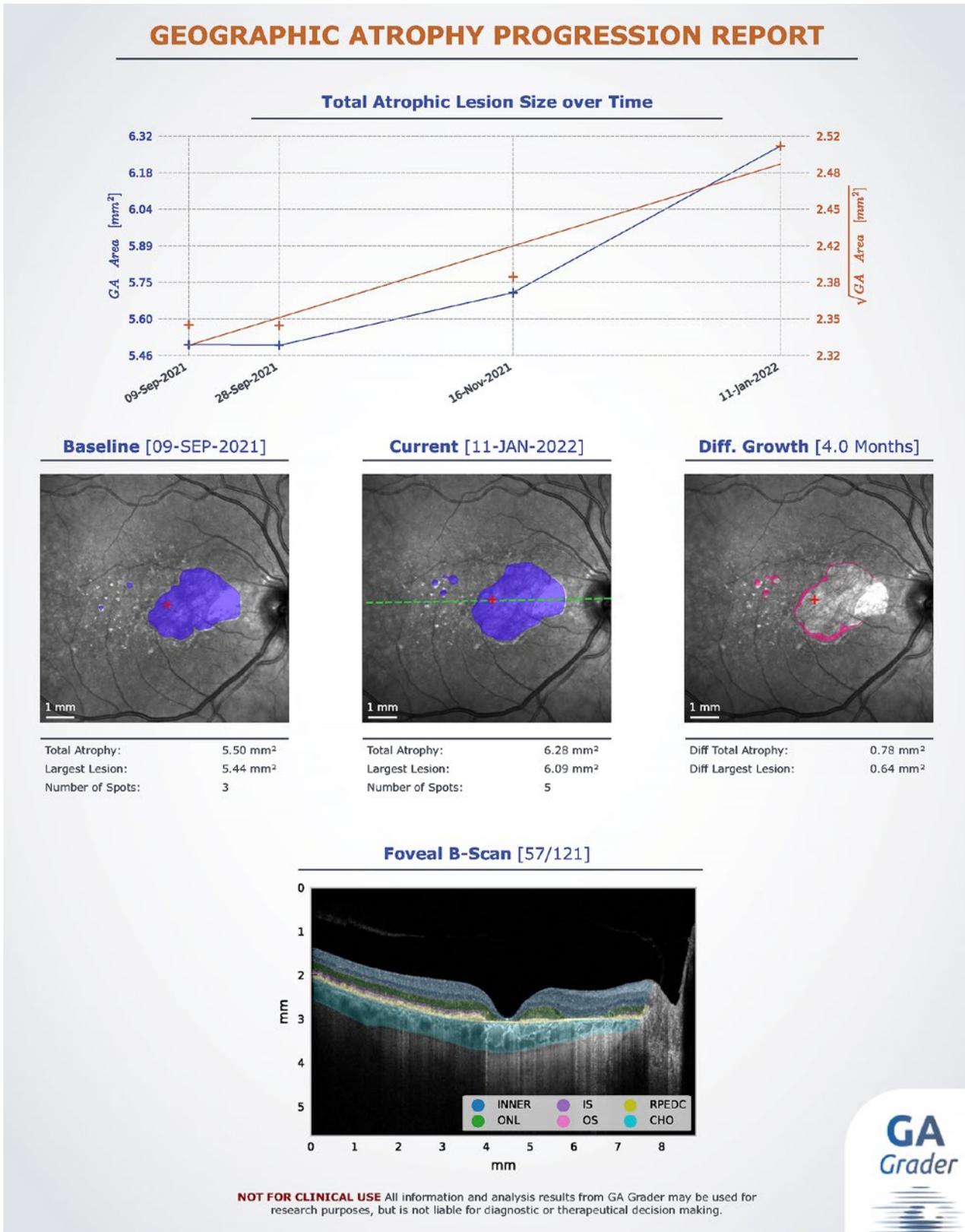


Figure 1. Geographic atrophy progression report (GA-Grader; GRADE reading center). The graph on the top shows the total GA lesion size over time. The blue line indicates the GA lesion size (in mm²). The orange line shows the square root of the GA lesion. In the middle the baseline, current, and differential growth infrared reflectance images are depicted. GA lesion size is shown in blue. In pink the difference between baseline and current image GA lesion size is visualized. The bottom image shows the automated AI-based image segmentation of the OCT B-scans from the foveal OCT scan. Retinal layers are color coded: inner retina, outer nuclear layer (ONL), photoreceptor inner and outer segments (IS, OS), retinal pigment epithelium drusen complex (RPEDC) and choroid.

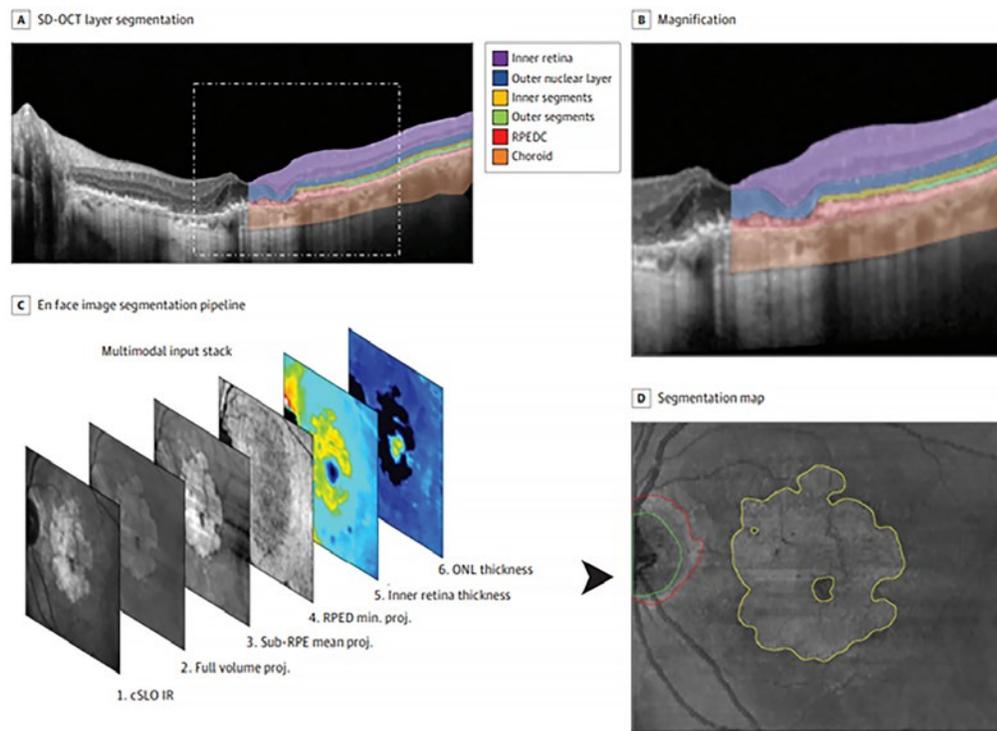


Figure 2. Image segmentation pipeline: (A) Resulting segmentation generated by the first convolutional neural network (CNN, Deeplabv3 model with a ResNet-50 backbone), providing a 6-layer segmentation: inner retina, outer nuclear layer (ONL), photoreceptor inner and outer segments, retinal pigment epithelium drusen complex (RPEDC, including reticular pseudodrusen, RPE, drusen), basal laminar deposit, and choroid. The insert on the upper right side provides a magnified view. (B) En face projections and thickness maps generated based on these segmentations as well as the confocal laser scanning laser ophthalmoscopy (cSLO) infrared reflection (IR) image were passed on as 6-layered input stack to the second CNN (Deeplabv3 model with a ResNet-50 backbone). As shown in (D), the second CNN provided an en face segmentation of geographic atrophy (yellow outline), peripapillary atrophy (red outline), and the optic nerve head (green outline).⁵

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Imaging Pearls for Distinguishing Benign From Malignant Intraocular Tumors

Jasmine H Francis MD

Using clinical characteristics based on exam, fundus photography, ultrasound, OCT, fluorescein angiography, and indocyanine green angiography, the following will be explored:

- I. Distinguishing Benign From Malignant Melanocytic Uveal Lesions
 - A. Key features of choroidal nevus
 - B. Key features of congenital hypertrophy retinal pigment epithelium
 - C. Key features of peripheral exudative hemorrhagic chorioretinopathy
 - D. Key features of choroidal hemangioma
 - E. Key features of melanocytoma
 - F. Versus key features of uveal melanoma
- II. Distinguishing Benign From Malignant Amelanotic Uveal Lesions
 - A. Key features of choroidal granuloma
 - B. Key features of sclerochoroidal calcification
 - C. Key features of choroidal histiocytosis
 - D. Key features of uveal leiomyoma
 - E. Key features of choroidal schwannoma
 - F. Versus key features of choroidal metastasis or uveal melanoma
- III. Distinguishing Uveal Lymphoid Hyperplasia From Uveal Lymphoma
- IV. Distinguishing Retinoblastoma From Its Masquerades
- V. Distinguishing Vitreous Retinal Lymphoma From Other Intraocular Inflammation

Polarization-Sensitive Imaging of Scleral Abnormalities in Myopia and Dome-Shaped Macula

Kyoko Ohno-Matsui MD, Tae Igarashi-Yokoi MD, and Masahiro Yamanari PhD

Introduction

The sclera is a major component of the outer coat of the eye and consists mainly of collagen. The scleral stroma is composed of collagen bundles and fibroblasts, along with a moderate amount of ground substance. The dimensions and course of the scleral collagen bundles are not fully understood, but they are believed to differ between the superficial and deep portions.¹ The collagen bundles in the scleral stroma vary in thickness and in shape. The collagen fiber bundles in the peripapillary region run in a concentric circular fashion around the optic disc margin. Collagen bundles in the outer region are thinner and run in a lamellar fashion, whereas those in the inner region are interwoven randomly, forming irregular and intermingled arrangements.²

Earlier studies on scleral morphology were primarily based on histological observations. However, with the advancement of OCT, we can now observe the inner part of the sclera. In highly myopic eyes with a thin choroid and sclera, we can even observe the entire thickness of the sclera. Nevertheless, most studies focus on the thickness of the sclera because observing collagen fibers in the scleral stroma in patients is still challenging.

Apart from its thinning, sclera in eyes with pathologic myopia displays several structural abnormalities, such as a decrease in collagen fibril diameter and an increase in the distance between collagen fibrils.^{3,4} McBrien et al⁴ hypothesized that the orientation of collagen fiber bundles in the eye's posterior pole might be related to the formation of a posterior staphyloma.

In this study, we employed a novel technology, polarization-sensitive OCT (PS-OCT), to visualize the birefringence and direction of scleral collagen fibers in the posterior segment of highly myopic patients. We investigated their relevance to pathologies occurring in the sclera, such as dome-shaped macula (DSM) and posterior staphyloma.

Polarization-Sensitive OCT (PS-OCT)

Sclera is a fibrous tissue with aligned collagen fiber that has a periodic structure in a nanometer scale and birefringence. Birefringence is an optical property where the refractive indices of the material depend on the state of polarized light. PS-OCT is a functional extension of conventional OCT to resolve polarization properties of the measurement target. Recent progress in PS-OCT has enabled the measurement of the local magnitude and the depth-resolved axis orientation of the birefringence. Here, we use our prototype of PS-OCT, the hardware details of which were described previously.⁵ To calculate the axis orientation of the scleral birefringence, we use our customized algorithm, which utilizes similar approaches demonstrated in several publications.⁶⁻¹⁰ To visualize the axis orientation intuitively, volume rendering of streamline is performed using an open-source software, ParaView 5.11.¹¹

PS-OCT Findings of Highly Myopic Eyes Without DSM or Staphylomas

In highly myopic eyes, it is often possible to view the entire thickness of the sclera, which enables obtaining PS-OCT images of the sclera. Images of the representative highly myopic eye without DSM or staphyloma are shown in Figure 1. The local retardation (magnitude of birefringence) images comprise fibers with different birefringence, consisting of a combination of high birefringent fibers and low birefringent fibers (Figure 1E and F). Streamline images of scleral fibers depict collagen fibers running in concentric circles around the optic nerve in the full depth of the sclera (Figure 1J and K). The image viewed from inside of the eye (Figure 1J) reveals the fibers running radially at the shallow depth of the sclera that is outside of the concentric circles around the optic nerve. In contrast, the image viewed from outside of the eye (Figure 1K) shows intertwined fibers running predominantly in the vertical direction across the macula, and the radial fibers toward the macula are not observed at this deep region of the sclera.

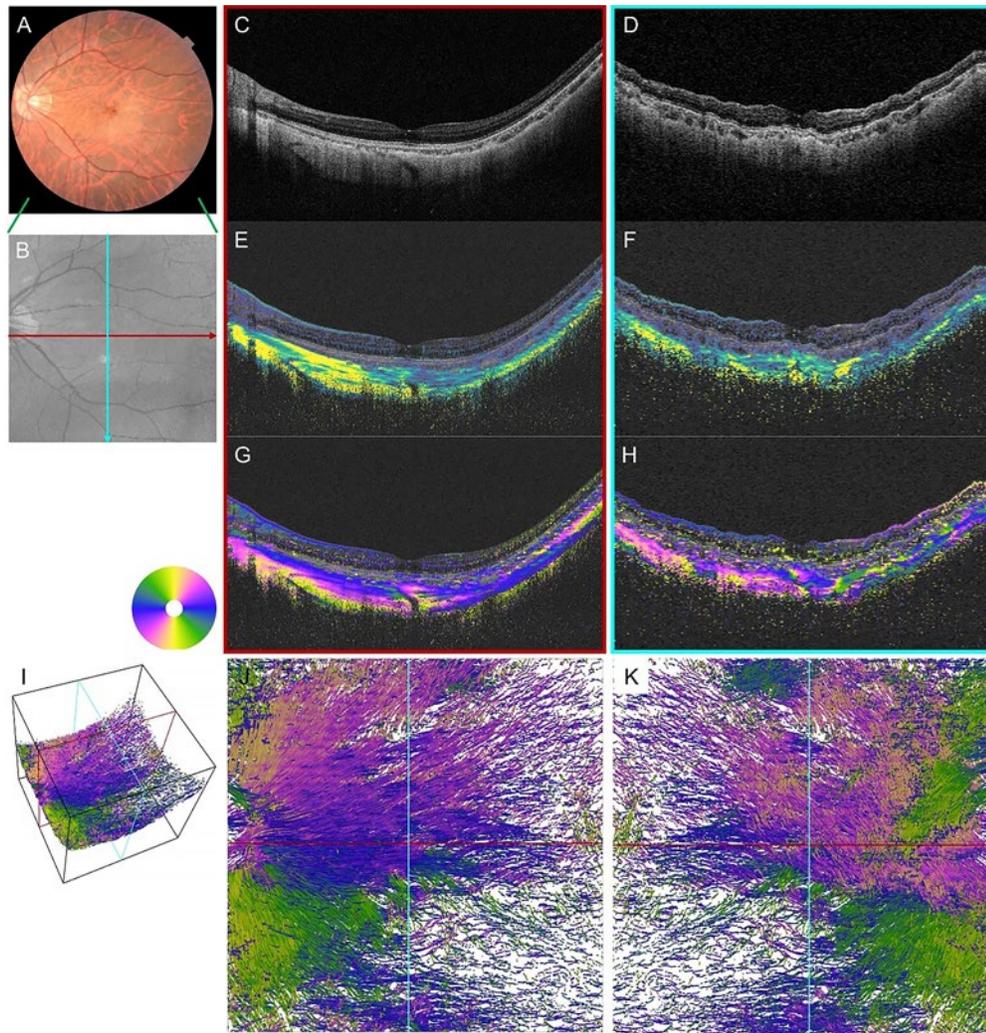


Figure 1. Images of the highly myopic eye without dome-shaped macula or staphyloma. (A) The color fundus photo. (B) En face projection of the OCT intensity image, where the horizontal and vertical arrows indicate the scanned locations of C, E, G and D, F, H, respectively. (C and D) Horizontal and vertical OCT intensity B-scan images, respectively. (E and F) Horizontal and vertical B-scan images of the local retardation, respectively. (G and H) Horizontal and vertical B-scan images of the axis orientation, respectively. (I) Volumetric streamline visualization of the scleral axis orientation. (J and K) Images of the scleral axis orientation viewed from the inside and outside of the eye globe, respectively. In I, J, and K, the location of the fovea is at the crossed point of the horizontal red line and the vertical light-blue line.

PS-OCT Findings of Highly Myopic Eyes With DSM

A dome-shaped macula (DSM) is an inward bulge in the macular area that was first identified in OCT images by Gaucher et al.¹² The prevalence of DSMs in highly myopic eyes has been reported to be as high as 20%.¹³ Imamura and Spaide¹⁴ showed that DSM was a local thickening of the foveal sclera.

In images showing magnitude of birefringence or local retardation (see Figure 2E and F), a DSM is composed of fibers with low birefringence. In areas other than the macula, fibers with low birefringence are not observed, and only fibers with high birefringence remain.

In streamline images viewed from inside the eye (Figure 2J), fibers running horizontally from the optic papilla to/beyond the macula are densely packed, and radially running fibers from the optic disc toward the upper temporal and lower temporal regions are decreased and damaged. On the other hand,

streamline images viewed from outside the eye (Figure 2K) did not show significant differences around the optic nerve from those seen in highly myopic eyes without DSM. Additionally, we notice that the fiber bundles at the deep macular sclera show highly interwoven structure. Further studies are required to investigate whether this highly interwoven structure of the deep macular sclera is characteristic of the DSM or not.

These observations suggest that of the fibers radiating from the optic disc, fibers toward the superior and inferior temporal fundus are lost, and horizontally oriented fibers toward the macula are densely squeezed. The comparison of the images viewed from outside the eye with DSM (Figure 2K) and without DSM (Figure 1K) suggests that the above changes may mainly occur in the fibers that consist of the inner layer of the sclera.

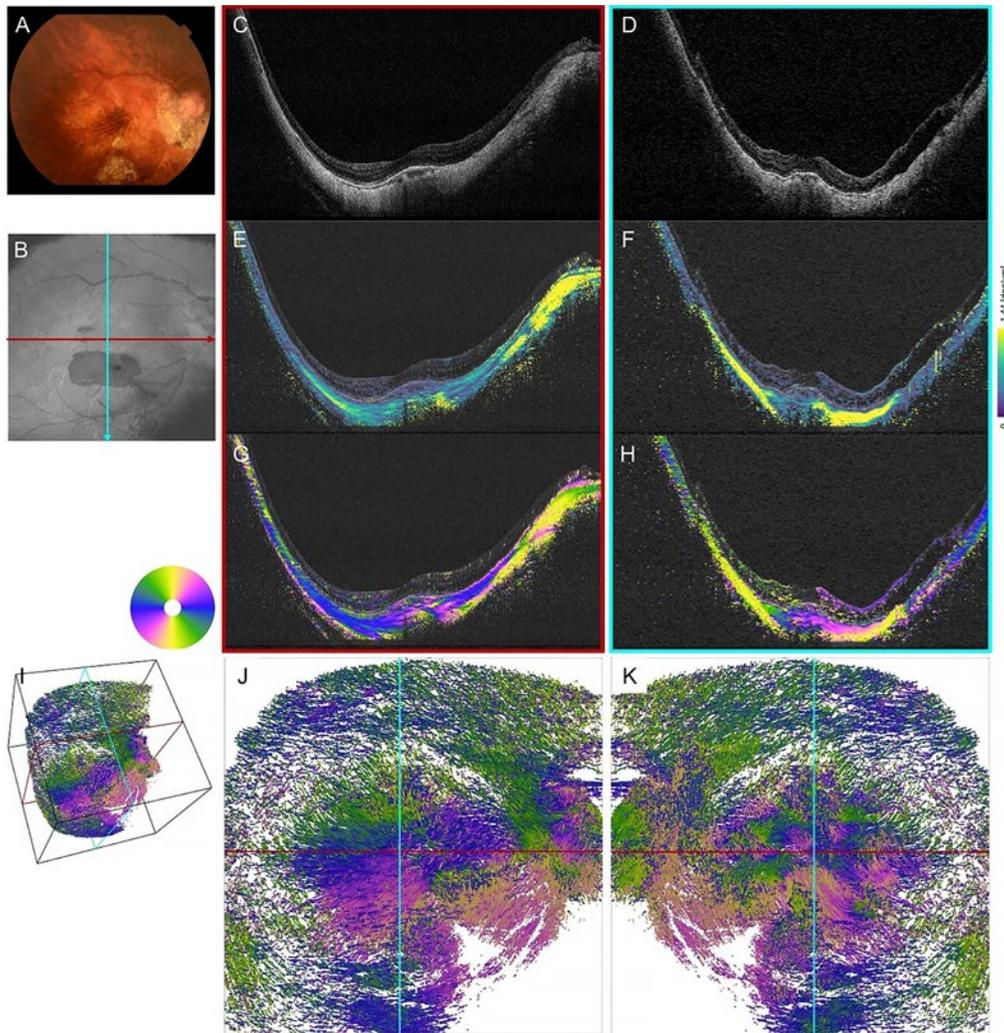


Figure 2. Images of the highly myopic eye with dome-shaped macula. Annotations of A-K are same as in Figure 1.

PS-OCT Findings of Other Pathologies in High Myopes

In highly myopic eyes, a ridge-like protrusion often develops temporal to the optic disc.^{1,2} Earlier studies have shown that eyes with such a ridge tend to exhibit visual field defects due to its impact on papillomacular nerve fibers. PS-OCT images have revealed that the ridge, as well as the edges of the staphyloma, exhibit densely packed inner scleral fibers, similar to what is observed in DSM. The structural similarities between DSM, the ridge, and staphyloma edges are intriguing.

Clinical Significance and Future Possibilities of Imaging of the Posterior Sclera With PS-OCT

PS-OCT provides a new perspective on the qualitative changes that occur in diseases causing scleral abnormalities, such as DSM and pathologic myopia. It can demonstrate different internal qualities of the sclera, which may aid in understanding the etiology of DSM and staphyloma edge, leading to potential preventive therapies. PS-OCT is also a powerful tool for developing sclera-targeted therapies to prevent and treat staphylomas, as well as for providing valuable insights into the etiology of other diseases (such as pachychoroid spectral diseases) in which the sclera is believed to play a role.

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Late Breaking Developments, Part II

Panel Moderator: Dante Pieramici MD

Panelists: Dimitra Skondra MD, Demetrios Vavvas MD, Lihteh Wu MD, and David N Zacks MD PhD

Intravitreal Sustained-Release Dexamethasone Implant for Diabetic Macular Edema and RVO: Six-Month Results From the First-in-Human Phase 2 RIPPLE-1 Trial
ALTITUDE: Suprachoroidal Delivery of ABBV-RGX-314 Investigational Gene Therapy for Diabetic Retinopathy

Sumit Sharma MD

First Ever Home OCT-Guided Management of Treatment Experienced Neovascular AMD Patients

W Lloyd Clark MD

MCO-010 Optogenetic Therapy for Vision Loss in Stargardt Disease: Topline Data From the Phase 2 STARLIGHT Trial

Stephen H Tsang MD PhD

Intravitreal Injection of “Photoswitch” Molecule (KIO 301) Improves Visual Function in Late-Stage Retinitis Pigmentosa Patients

Russell N Van Gelder MD PhD

Ocular, Systemic, and Genetic Factors That Affect Growth of Geographic Atrophy Lesions Associated With AMD

Emily Y Chew MD, Tiarnan Keenan BMBCh PhD, Catherine Cukras MD PhD, and the Age-Related Eye Disease Study (AREDS) & AREDS2 Research Groups, National Eye Institute/National Institutes of Health

Introduction

The natural course of geographic atrophy (GA) associated with AMD and the risk factors associated with expansion of GA lesions have taken on greater importance with the recent approval by the US Food and Drug Administration (FDA) of the intravitreal delivery of Syfovre (pegcetacoplan, C-3 inhibitor) developed by Apellis for the treatment for GA in February 2023¹ and the positive results of the study of Zimura (PEGylated anti-C5 aptamer) from Iveric Bio.² The complex nature of AMD is reflected in the fact that the risk factors associated with the development of GA may differ from those associated with the expansion of established GA lesions.

This presentation will review the known rates of enlargement and the recently reported associated risk factors for the rate of GA enlargement. Data from the Age-Related Eye Disease Study (AREDS) and AREDS2 suggest that these include ocular characteristics, including presence of reticular pseudodrusen (RPD), dietary modifications (specifically the Mediterranean diet), and genetic associations.

Background

General GA progression has been studied by several research groups.^{3,4} These studies demonstrated the variable rate of expansion of GA lesions in various studies. These risk factors can be summed up by the data from AREDS2 that suggest the following risk factors were important for GA lesion expansion.⁵ At baseline in the AREDS2, analyses included 517 eyes (6.2%) of 411 participants (9.8%) that had pre-existing (prevalent) GA (without neovascular AMD), with the following characteristics:

33% central, 67% noncentral; and the following configurations: 36% small, 26% solid/unifocal, 24% multifocal, 9% horseshoe/ring, and 6% indeterminate. Of the remaining 6530 eyes at risk, 1099 eyes (17.3%) of 883 participants developed incident GA without prior neovascular disease during mean follow-up of 4.4 years. Change in GA expansion was measured on color fundus photographs using the square root of GA area over time. Risk factors found to be associated with GA lesion expansion include the following:

Ocular

GA enlargement rate (following square root transformation) was similar in eyes with pre-existing GA (0.29 mm/year; 95% CI, 0.27-0.30) and incident GA (0.28 mm/year; 0.27-0.30). Since they were very similar, they combined for the analyses of GA enlargement. Risk factors that were found to be associated with faster GA enlargement were noncentricity, multifocality in configuration, intermediate baseline size, and the presence of bilateral GA ($P < .0001$ for interaction in each case) and presence of RPD. See Table 1 for association of RPD with GA enlargement.

Systemic

GA enlargement rate was significantly higher for those in the highest tertile of the Mediterranean diet, as shown in Table 2.⁶ Slower GA growth was found with dietary components of higher whole fruit, lower red meat, moderate alcohol, and higher monounsaturated/saturated ratio of fat intake. In eyes with noncentral GA, higher adherence to the Mediterranean diet was not associated with slower progression into the foveal area.

Table 1. Geographic Atrophy Lesion Enlargement According to Reticular Pseudodrusen Status

Reticular Pseudodrusen Status	Estimate (mm/year)	95% CI (mm/y)	P-Value
Absence ($n = 657$ eyes)	0.269	0.258-0.281	< .0001
Presence ($n = 114$ eyes)	0.388	0.347-0.430	

Table 2. Association Between Higher Adherence to Mediterranean Diet and Geographic Atrophy Enlargement Rate

Mediterranean Diet	Mean GA Enlargement Rate, Square Root Transformation	95% CI	P-Value
High (tertile 3)	0.256 mm/y	0.235 to 0.276	< .008
Moderate (tertile 2)	0.290 mm/y	0.268 to 0.311	
Low (tertile 1)	0.298 mm/y	0.280 to 0.317	

Table 3

RPD Status and ARMS2 Risk Alleles ^a	Estimate ⁺ (mm/year)	95% CI (mm/year)	P-Value
RPD absence/0 (GG)	0.206	0.178-0.234	< 0.0001
RPD absence/1-2 (GT+TT)	0.275	0.257-0.293	
RPD presence/0 (GG)	0.312	0.275-0.348	
RPD presence/1-2 (GT+TT)	0.372	0.348-0.396	

Abbreviations: RPD, reticular pseudodrusen; G, non-risk allele; T, risk allele.

^aP-value for interaction between characteristic (RPD status/ARMS2 risk alleles, in 4 levels) and years.

Genetic association

Enlargement was significantly faster with ARMS2 risk ($P < .0001$), C3 non-risk ($P < .0002$), and APOE non-risk ($P < 0.001$) genotypes. Since RPD is associated with ARMS2 risk alleles, they were evaluated simultaneously (see Table 3).⁷

Conclusion

The ocular characteristics of presence of RPD, bilaterality, multifocal configuration, medium baseline size, and noncentral lesions were found to have faster GA enlargement. A Mediterranean-type diet was associated with slower GA enlargement. Several components that seemed to contribute to this association with GA enlargement did so in a pattern that differed from the pattern of components most associated with decreased progression to GA, like fish consumption. Hence, the Mediterranean diet is associated with protection against both faster progression to GA and faster enlargement of GA, but probably for partially distinct reasons. GA enlargement was also found to be associated with genetic risk factors including ARMS2, C3, APOE alleles.

These data may help us further understand the underlying biology of the complex disease of AMD. These data may also aid in future secondary analyses of current studies of GA, as well as informing us of future designs on the study of therapies for GA.

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GALE 12-Month Data: First-time Presentation of Full Cohort

Long-term Efficacy and Safety of Pegcetacoplan From the GALE Open-Label Extension of the Phase 3 OAKS and DERBY Trials

Jeffrey Heier MD on behalf of the OAKS, DERBY, and GALE investigators

Background

Pegcetacoplan (Syfovre, Apellis Pharmaceuticals; Waltham, MA) is the first US Food and Drug Administration–approved intravitreal treatment for geographic atrophy (GA), based on 24-month data from the OAKS and DERBY trials. GA is an advanced form of AMD, and the prevalence of GA is projected to markedly increase over the next 2 decades.¹⁻³ GA lesion growth is progressive, constant, and irreversible, and lesions can impact nonsubfoveal and subfoveal regions. Loss of visual function can accompany lesion growth.⁴

GALE is a 3-year extension trial following the 24-month OAKS and DERBY trials, and the first 12 months of efficacy data will be presented here.

DERBY and OAKS⁵

DERBY and OAKS were 2 randomized, Phase 3, double-masked, sham-controlled, 24-month trials evaluating the efficacy and safety of the C3/C3b inhibitor pegcetacoplan in GA secondary to AMD. Inclusion criteria were age ≥60 years, BCVA of ≥24 letters (approximate Snellen equivalent 20/320), and a GA area between 2.5 and 17.5 mm², or if multifocal at baseline, at least 1 focal lesion ≥1.25 mm². Of note, nonsubfoveal and subfoveal GA lesions were included, and fellow eye

choroidal neovascularization was not exclusionary. The primary endpoint for both studies was change in GA lesion area via fundus autofluorescence imaging from baseline to Month 12. Safety measures included incidence of ocular and systemic adverse events (AEs).

In the combined OAKS and DERBY trials, 1258 patients were enrolled and randomized 2:2:1:1 to pegcetacoplan monthly (PM), pegcetacoplan every other month (PEOM), sham monthly, and sham every other month. The sham arms were pooled for all analyses.

At Month 12 in the combined studies, pegcetacoplan reduced growth of GA by 14% in PEOM and 16% in PM. In eyes with nonsubfoveal GA, lesion growth was reduced by 23% in PEOM and 26% in PM.

In OAKS and DERBY at Month 24, pegcetacoplan reduced GA lesion growth vs. sham by 17% in PEOM and 21% in PM. In patients with nonsubfoveal lesions, lesion growth reductions were 22% and 26% with PEOM and PM, respectively. A piecewise linear slope analysis of the combined studies demonstrated increasing effects over time, with 24% and 30% reductions over Months 18-24 in PEOM and PM, respectively. In the individual studies, lesion growth was reduced by up to 36% (DERBY, PM, Months 18-24). Additional studies supporting the benefits of pegcetacoplan include artificial intelligence–based OCT analy-

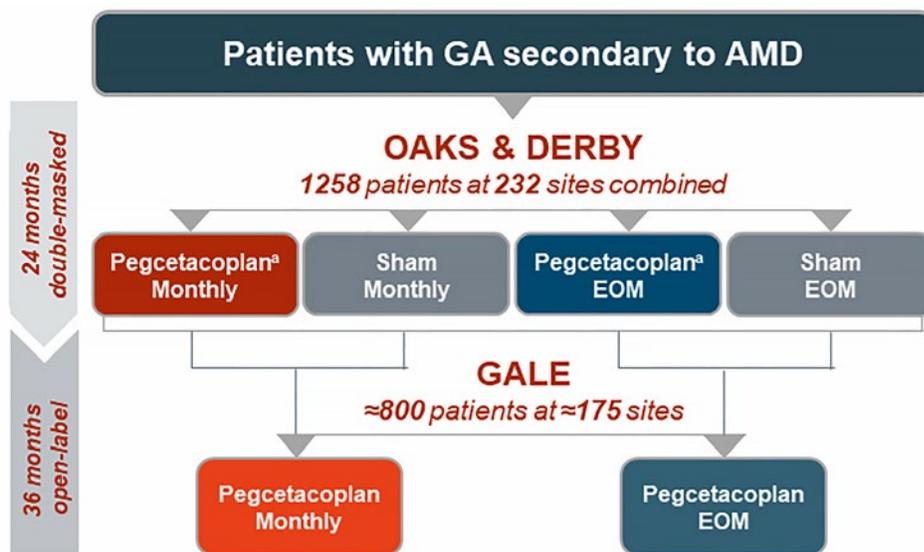


Figure 1

^a Pegcetacoplan 15 mg/0.1 mL administered by intravitreal injection. DERBY, NCT03525600; GALE, NCT04770545; OAKS, NCT03525613

ses demonstrating reduction of photoreceptor loss and covariate-adjusted subgroup analyses demonstrating preservation of BCVA and quality of life vs. sham.

Pegcetacoplan was well tolerated at 24 months; most study eye ocular AEs were classified as mild or moderate. Over 12 months, new-onset exudative AMD was observed in 4%, 6%, and 2% of patients in the PEOM, PM, and sham arms, respectively. Over 24 months, exudative AMD was observed in 7%, 12%, and 3% of patients in the PEOM, PM, and sham arms, respectively. Intraocular inflammation was observed in 1% and 2% of PEOM and PM patients over 12 months, respectively, and in 2% and 4% of PEOM and PM patients over 24 months, respectively. Most cases of intraocular inflammation were mild and resolved with topical steroids, and most patients resumed treatment. The rate of infectious endophthalmitis was consistent with other trials with intravitreal injections. There were 3 serious AEs of optic ischemic neuropathy in the PM arm.

GALE⁶

Overall, 83% ($n = 780$) of patients who completed OAKS and DERBY studies entered the GALE 3-year extension study. In GALE, patients originally randomized to PM or PEOM in OAKS and DERBY continued on pegcetacoplan at the same dosing interval. Patients originally randomized to sham monthly or every other month in the 24-month OAKS and DERBY studies transitioned to active treatment with pegcetacoplan PM or PEOM, respectively, in GALE.

In the absence of a sham arm in GALE, to assess the long-term efficacy of pegcetacoplan, lesion growth in patients on PM and PEOM continuously for 30 months was compared with a hypothetical sham arm in which lesion growth data from Months 0-24 from the sham pooled arm was projected forward to progress linearly in Months 24-30. The assumption of continued linear growth from Month 24 to Month 30 in the hypothetical sham arm of GALE is supported by the previous 24 months of linear growth in the sham arms of OAKS and DERBY, as well as by 30-month data from untreated fellow eyes of patients with bilateral GA, in whom lesion growth continued in a linear fashion over 30 months.

Between Months 24 and 30, PEOM and PM continued to demonstrate increasing effects over time, reducing lesion growth compared with the hypothetical sham arm by 32% and 39% (both $P < .0001$; nominal), respectively. Over 30 months, the absolute difference in least-squares mean lesion size vs. hypothetical sham was 1.03 mm² for PEOM and 1.16 mm² for PM, reflecting a cumulative preservation of retinal tissue of more than 1 million square microns with both PEOM and PM, and translating to preservation of thousands of photoreceptors.⁷ There were no new or unexpected safety signals. Twelve-month GALE data (results of 36 months of continuous PM and PEOM treatment) will be presented for the first time at 2023 Retina Subspecialty Day.

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GATHER2: Two-Year Data

Arshad M Khanani MD, Sunil S Patel MD, Giovanni Staurenghi MD, Ramin Tadayoni MD, Carl J Danzig MD, David A Eichenbaum MD, Jason Hsu MD, Charles C Wykoff MD, Jeffrey S Heier MD, David R Lally MD, Jordi Monés MD, Jared S Nielsen MD, Veeral S Sheth MD, Peter K Kaiser MD, Julie Clark MD, Liansheng Zhu PhD, Hersh Patel OD, Justin Tang PhD, Dhaval Desai PharmD, and Glenn J Jaffe MD on behalf on the GATHER2 Trial Investigators

I. Avacincaptad Pegol (ACP) for the Treatment of Geographic Atrophy (GA)

- A. ACP is a pegylated RNA aptamer administered through intravitreal injection. ACP binds to and inhibits complement C5, preventing formation of C5 cleavage products that play roles in inflammation and cell death.¹
- B. In the Phase 2/3 GATHER1 study, ACP 2 mg showed efficacy in slowing GA growth. The mean change in GA area was reduced by 27.4% ($P = .0072$) for ACP 2 mg compared with sham over 12 months, and treatment with ACP (2 mg and 4 mg) was generally well tolerated over 18 months.^{1,2}

II. GATHER2 Study Design

- A. GATHER2 (NCT04435366) was a randomized, double-masked, sham-controlled study to evaluate the efficacy and safety of ACP in participants with GA.³
- B. Participants were randomized 1:1 to monthly ACP 2 mg or sham. At Month 12, participants who received monthly ACP 2 mg were rerandomized 1:1 to ACP 2 mg monthly or to ACP 2 mg every other month (final follow-up at Month 24). Participants initially randomized to sham continued to receive monthly sham.³

III. Primary Objective⁴

The primary objective was the mean rate of GA growth (slope analysis, square root transformed) estimated based on GA area as assessed by fundus autofluorescence on at least 3 time points (baseline, Month 6, and Month 12) in the ACP 2 mg group vs. the sham group.

IV. Overview of GATHER2 1-Year Results^{4,5}

- A. Overall, 448 participants were randomized to ACP 2 mg or sham, and 447 ($n = 225$, ACP 2 mg; $n = 222$, sham) were included in the intent-to-treat and safety populations.
- B. The primary objective was met at 12 months. Treatment with ACP 2 mg resulted in a statistically significant reduction of 0.056 mm ($P = .0064$) in GA growth vs. sham.

- C. Over 12 months, ocular treatment-emergent adverse events in the study eye occurred in 48.9% and 37.4% of participants in the ACP 2 mg and sham groups, respectively. There were no events of endophthalmitis, intraocular inflammation, or ischemic optic neuropathy. Macular neovascularization rates in the study eye were 6.7% for ACP 2 mg and 4.1% for sham.

V. GATHER2: 2-Year Efficacy and Safety Results

- A. The efficacy of ACP 2 mg vs. sham over 24 months will be presented.
- B. All adverse events over 24 months, including treatment-emergent and serious, whether deemed related to the injection procedure or study drug or not, will be reported.

VI. Conclusions

The 24-month efficacy and safety results will provide valuable information on the continued treatment efficacy and tolerability of ACP 2 mg for GA.

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How Best to Follow Geographic Atrophy Patients Receiving Anti-complement Therapy: Practical Approaches to Measure Functional Changes

Karl G Csaky MD

Background

At 2 NEI/FDA Ophthalmic Clinical Trial Design and Endpoints Symposiums in 2007¹ and in 2016,² the FDA identified the expansion of geographic atrophy (GA) as an endpoint for trials assessing potential benefits for patients with GA associated with dry AMD. In this approval pathway the FDA, explicitly, did not require demonstration of a functional benefit between treated and control arms, such as a difference in visual acuity, scotoma size, or reading speed. However, as it had been shown that reduced fundus autofluorescence (FAF) was a reliable measure of GA area^{3,4} and correlated with eventual vision loss, FAF⁵ has become the primary measurement used in all GA clinical trials.

On February 17, 2023, the FDA announced approval of the first anti-complement drug for “the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).”⁶ Pegcetacoplan is a pegylated anti-complement 3 peptide that is injected intravitreally. The FDA approval was predicated on the results of the OAKS and DERBY Phase 3 clinical trials that demonstrated a 22% and 12% reduction,

respectively, in growth of GA lesion area when pegcetacoplan was given monthly over a 12-month period. Follow-up data at 24 months demonstrated a 22% and 19% reduction in growth of GA lesion area from baseline to 24 months in the 3 studies when pegcetacoplan was injected monthly.⁶

Functional Benefits of Pegcetacoplan

No statistically significant differences across study arms on key secondary functional endpoints at 24 months⁷

- BCVA (Figure 1)
- Maximum reading speed
- Functional Reading Independence Index
- Microperimetry: Mean threshold sensitivity (OAKS only)

Effect of Pegcetacoplan on Visual Acuity Through 24 Mos

Change in Best Correct Visual Acuity (NL-BCVA) Score in the Study Eye over 24 Months

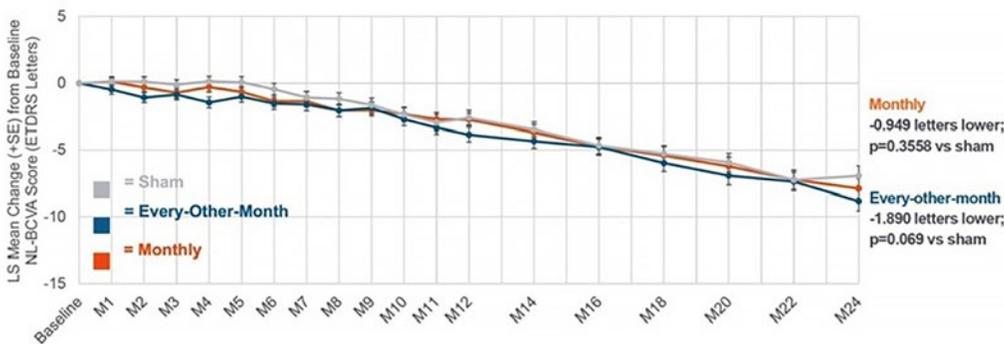


Figure 1. Vision changes over 24 months with monthly and every-other-month pegcetacoplan injections compared with sham.⁷

Possible Signal With “Focal” Microperimetry

See Figure 2.

Concept of “At Risk” GA Patient

Fast Progressors (DERBY/OAKS)

See Figures 3 and 4.

Assessment of Subjects (Spectri and Chroma)

See Figure 5.

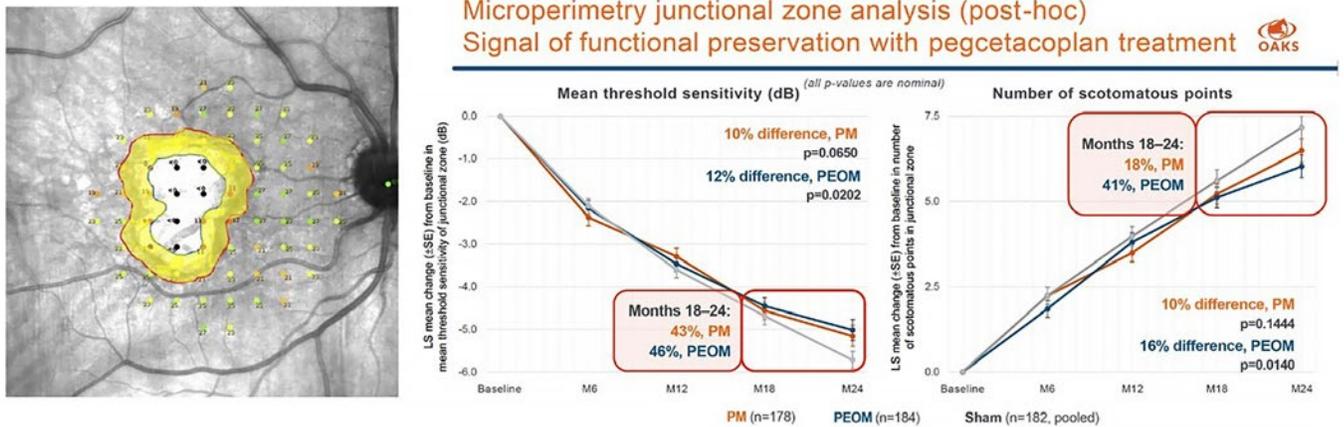


Figure 2. Results of microperimetry examining the junctional zone sensitivities demonstrated a possible effect on both mean sensitivities and number of scotomatous points with pegcetacoplan.⁸

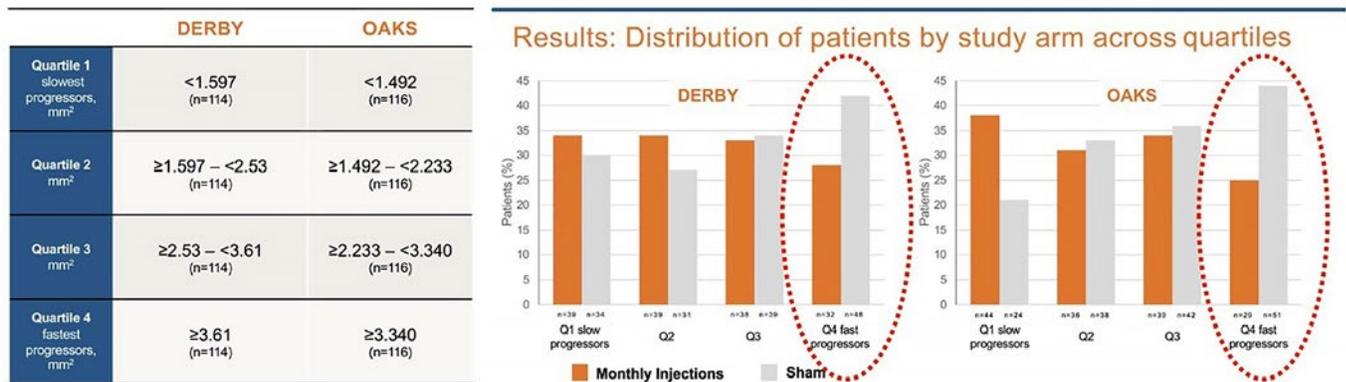


Figure 3. Segregating subjects within the DERBY and OAKS Phase 3 clinical trials as to the rate of GA expansion over 18 months comparing pegcetacoplan with sham.⁸

	Risk of progression	Slowest progressors n=24	Fastest progressors n=51
GA lesion size (mean, mm ²)	↑	5.5	9.8
Bilateral GA (%)	↑	63%	86%
Mean low luminance deficit (ETDRS letters)	↑	15	29
Foveal lesion location (%)	↓	88%	55%
Unifocal lesions (%)	↓	46%	22%
Intermediate/large drusen >20 (%)	↓	71%	33%

Figure 4. Aspects of baseline characteristics that correlate with slower and faster progressors in the DERBY and OAKS Phase 3 clinical trials of pegcetacoplan.⁸

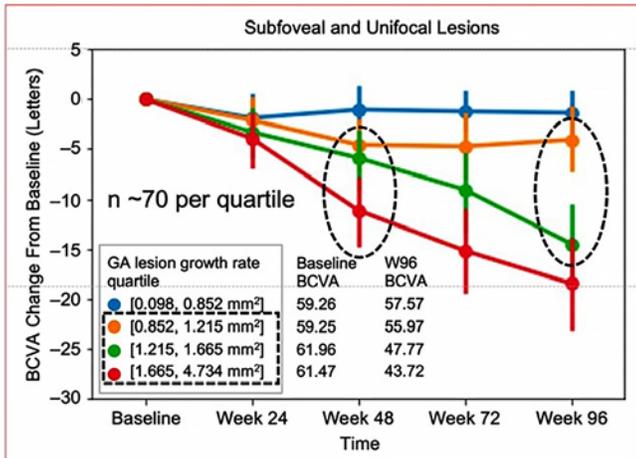


Figure 5. Retrospective analysis of vision loss from the Spectri and Chroma studies demonstrating the correlation between GA expansion and vision loss in subjects with unifocal subfoveal lesions.⁹

Focal Microperimetry in GA Patients

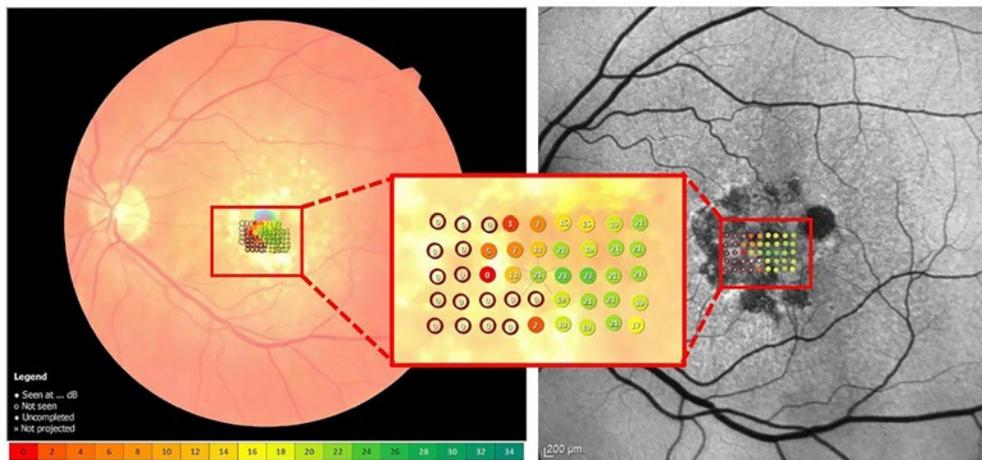


Figure 6. Results of “focal” microperimetry examining intact foveal region in a patient with GA.

Various Functional Tools Available Now

BCVA (visual acuity)

There is still the possibility of detecting changes in vision, especially in “fast” progressors and potentially in unifocal subfoveal GA lesions.^{8,9}

Low luminance visual acuity (LLVA)

LLVA is an easy function tool that simply requires that a 2 neutral density filter be placed in front of the eye under normal conditions of ETDRS visual acuity testing. Studies have shown that the extent of low luminance deficit (BCVA-LLVA) correlates to the rate of expansion of GA.¹⁰

Future Functional Tools

Microperimetry

Using white light to measure mesopic microperimetry can directly quantify retinal function.¹¹ While useful for measuring changes in scotoma sizes in GA or peri-GA retinal sensitivity

changes, these tests are time consuming and difficult to administer and are not reliable in numerous patients with dry AMD.¹² Newer and quicker approaches are under investigation (see Figure 6) using small area “focal microperimetry” that may allow quicker and more complete demonstration of benefit of anti-complement therapies.

Normal and low luminance quantitative contrast sensitivity

While older forms of assessing contrast sensitivity using Pelli-Robson plates proved to be unreliable, a newer automated form utilizing Bayesian algorithms to more quickly and precisely identify contrast sensitivity results in dry AMD patients has shown earlier success. Easy to use by patients and straightforward to administer, this approach captures a large amount of data both on spatial frequencies and contrast sensitivity. In addition, utilizing a standard 2 neutral density filter, low luminance automated contrast sensitivity can also be assessed. Preliminary data indicates dissection of varying stages of dry AMD (see Figure 7) can be achieved with good intra- and inter-patient reliability, as well as the possibility of demonstrating correlation with increasing areas of atrophic changes.¹³

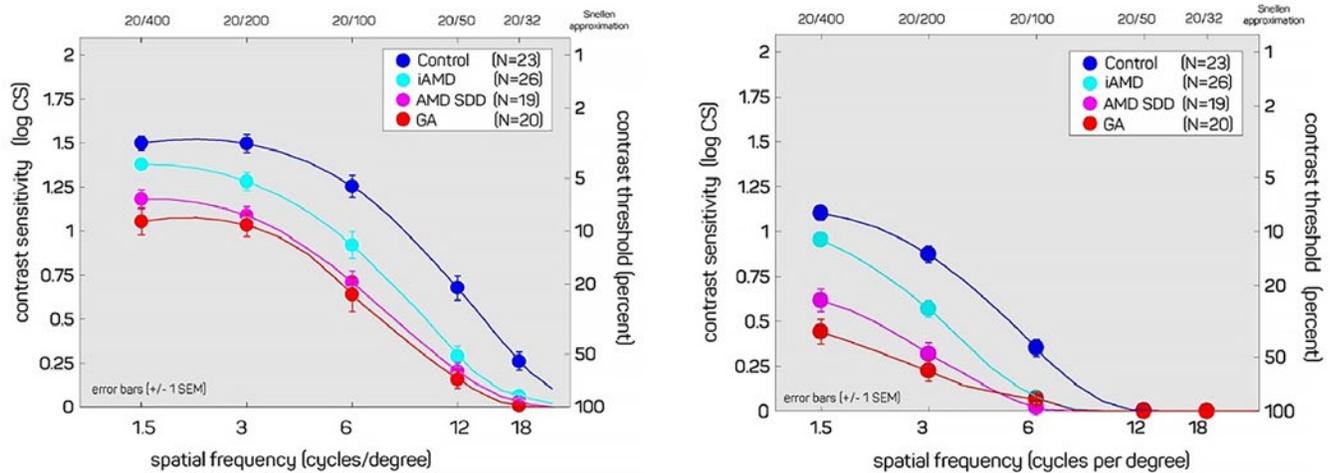


Figure 7. Contrast sensitivity functions measured under standard (left) and low (right) luminance conditions in eyes with varying stages of dry AMD, including intermediate AMD (iAMD), AMD with subretinal drusenoid deposits (AMD SDD), and geographic atrophy (GA), demonstrating stepwise losses between advanced forms of dry AMD.¹³

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Recently Described Infectious Retinochoroiditis

Anita Agarwal MD

Viral

- Dengue
- Chikungunya
- Subacute sclerosing panencephalitis (measles)

Bacterial

- Mycobacterium bovis*
- Mycobacterium chimaera*

Dengue

- Tropical and subtropical regions
- Hemorrhagic fever
- Grade 1-4 severity
- Severe: hemorrhagic shock
- Children less than 15 years of age
- Retinal heme, optic neuritis
- Self-limited

Chikungunya

- Tanzania, India, S.E Asia, recently wider
- Vascular occlusions
- Iritis
- Retinitis
- Optic neuritis
- Resembles Behçet
- IV acyclovir

Subacute Sclerosing Panencephalitis (SSPE)

- Progressive neurologic disease by a defective measles virus
- Typically follows a preceding measles infection (usually before 2 years of age) in children at a mean interval of 7 years
- Men > women 3:1
- Personality and behavior changes followed by dementia
- Visual symptoms (seen in ~50%) antedate neurologic symptoms by several weeks
- Visual loss is caused by 1 or more flat focal ragged gray-white lesions; cherry red spot may be seen, rapidly heal with gliotic atrophic scars with radiating lines
- EEG: periodic complexes of high-amplitude delta waves repeated every 4-7 seconds
- T2 MRI: focal or diffuse periventricular and subcortical white matter changes
- Interferon
- Death

Mycobacterium bovis

- Patients receiving bacillus Calmette-Guérin immune therapy for superficial bladder carcinoma
- Disseminated infection
- Fever, night sweats, malaise, weight loss,
- Lymphadenitis, pneumonia, osteomyelitis, renal mass, mycotic aneurysms, granulomatous hepatitis
- PCR from blood, organ biopsy
- Streptomycin, ethambutol, INH, and rifampicin for 12 months

Mycobacterium chimaera

- Outbreak of infection following cardiac surgery in Switzerland, 2015
- Source: heater-cooler unit water tanks during open heart surgery
- Systemic dissemination and choroid and retina
- Many reports since
- Disseminated chronic infection
- Liver, spleen, kidneys, meninges, encephalitis
- Treatment: azithromycin, ethambutol, rifabutin, amikacin, linezolid, or moxifloxacin
- Mortality: 50% or more

Summary

- Various newer infectious uveitides
- High index of suspicion
- Associated medical or surgical conditions
- Newer PCR
- Diagnostic vitrectomy

Tacrolimus Therapy for Noninfectious Intermediate, Posterior, or Panuveitis

Douglas A Jabs MD MBA

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Potential Disparities in Real-World Treatment of Diabetic Macular Edema and Central Retinal Vein Occlusion

Julia A Haller MD

Large dataset analyses, such as those available through the Intelligent Research in Sight (IRIS)[®] database and others, provide population-wide evidence of significant disparities in eye disease and care, including overall visual impairment, clinical trial access, and real-world treatment disparities.

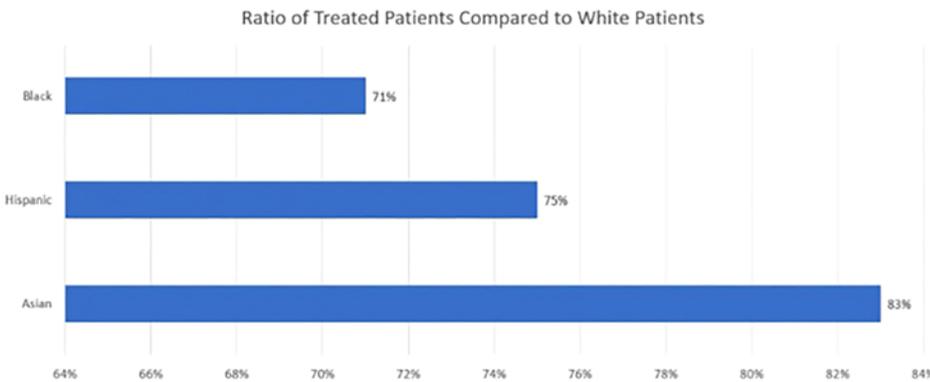
We analyzed patients in the IRIS[®] database with ICD-10 coding for retinal vein occlusion (RVO) with macular edema and found that patients with RVO present at different ages based on demographic factors. Significant differences were seen in the number of patients with RVO and macular edema in the IRIS[®] Registry treated with anti-VEGF injections in the first year after diagnosis. Black/African American and Asian patients, women, patients ≥70 years old, and patients with VA outside the <20/40 to 20/200 range were less likely to receive treatment. Awareness of this undertreatment and these disparities may encourage initiatives to ensure that all RVO patients receive timely anti-VEGF injections for optimized visual outcomes.

Part of the issue with underrepresentation is that clinical trials also exhibit disparities in inclusion of patients. Work from Khan MA, Mador M, Blotner S, Hill L, and Haller JA presented at AAO 2023 shows that there is regional variance in the enrollment of underrepresented patients in U.S. clinical trials of diabetic macular edema.

A large Komodo dataset of patients aged 65+ with diabetic macular edema (see Figure 1) showed that ethnic and racial minorities are less likely to receive anti-VEGF treatment than White patients. And even among patients receiving anti-VEGF agents, the selection of agent varies by race and ethnicity (see Figure 2). Ongoing efforts to identify and mitigate these disparities will help optimize visual outcomes for all.

For Patients Aged 65+ with DME, ethnic and racial minorities are less likely to receive anti-VEGF treatment than White patients

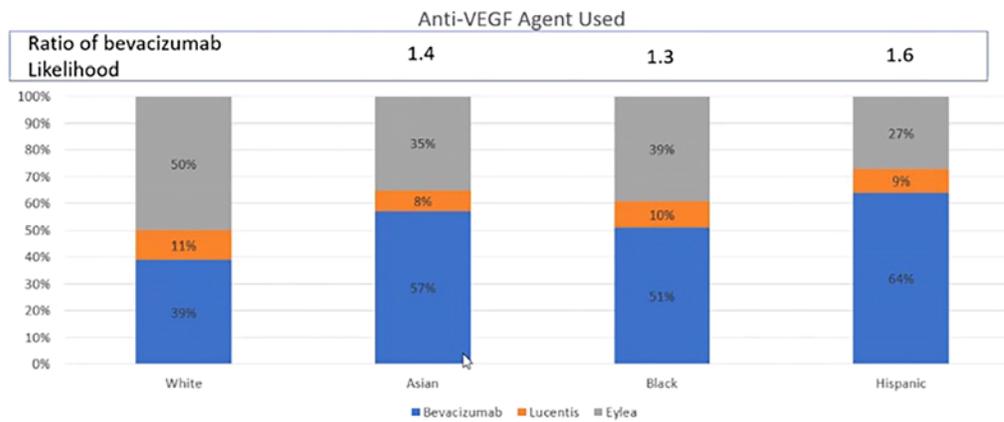
Figure 1



Source: Komodo Healthcare Map, pulled February 3, 2022
Data is drawn from 247K individual patients with DME over age 65 for whom race and ethnicity data were available

Figure 2

Even among patients receiving anti-VEGF agents, the selection of agent varies by race/ethnicity



Source: Komodo Healthcare Map, pulled February 3, 2022
 Data is drawn from 242K individual patients with DME over age 65 for whom race and ethnicity data were available.

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Preventing Proliferative Diabetic Retinopathy and Diabetic Macular Edema: Two Sides of the Coin

Neil M Bressler MD

I. Clinical Question

What is the effect of intravitreal anti-vascular endothelial growth factor (anti-VEGF, $n = 200$) vs. sham treatment ($n = 199$) for prevention of vision-threatening complications in eyes with severe nonproliferative diabetic retinopathy (NPDR) and no center-involved diabetic macular edema (DME)?

II. Relevant Definitions From DRCR Retina Network Protocol W

A. Vision-threatening complications of diabetic retinopathy

1. Center-involved DME with visual acuity (VA) loss
 - a. VA loss definition 1: Loss of 10 or more letters (approximately 2 or more lines) from baseline due to DME at 1 visit
 - b. VA loss definition 2: Loss of 5-9 letters (approximately more than 1 but less than 2 lines) from baseline due to DME at 2 consecutive visits

2. Proliferative diabetic retinopathy (PDR)

B. Treatment for vision-threatening complications of diabetic retinopathy

1. DME: Per DRCR Retina Network Protocol V
2. PDR: Per DRCR Retina Network Protocol S if high-risk PDR or vitreous hemorrhage from PDR

C. Primary outcomes

1. Vision-threatening complications of diabetic retinopathy at 2 years
2. BCVA following protocol refraction at 4 years

III. Results

A. Follow-up aflibercept and sham, respectively

1. 2-year: 80% and 84%
2. 4-year: 75% and 73%

B. Cumulative percent developing DME or PDR at 2 years: adjusted hazard ratio (aflibercept vs sham) = 0.32 (95% CI, 0.21-0.50); $P < .001$.

1. Sham: 44% (including PDR = 33%; DME = 15%)
2. Aflibercept: 16% (including PDR = 14%; DME = 4%)

C. VA change (adjusted mean difference from baseline)

1. At 2 years, aflibercept vs. sham: 0.5 (–1.0, 1.9) letter; $P = .47$

2. At 4 years, aflibercept vs. sham: –0.5 (–2.3, 1.3) letter; $P = .52$

D. Change in Diabetic Retinopathy Severity Scale (DRSS) level at 2 years

1. 2-step or more worsening, aflibercept vs. sham: 5% vs. 12%; adjusted odds ratio = 0.37 (97.5% CI, 0.13-1.01); $P = .03$
2. 2-step or more improvement = 5.91 (97.5% CI, 3.19-10.95); $P < .001$

IV. Discussion: Two Perspectives With Similar Results From the PANORAMA Trial

A. DRCR Retinal Network: Aflibercept injections reduced the development of vision-threatening complications; however, through 2 and 4 years, preventive treatment did not confer VA benefit compared with observation plus aflibercept if complications developed.

B. PANORAMA investigators: Anatomic improvement was more likely to occur in eyes with moderately severe to severe NPDR that were treated with intravitreal aflibercept injections; in Year 2, fixed dosing appeared necessary to maintain anatomic benefit.

C. Evidence-based medicine: Always take into account the patient's values—the unique preferences, concerns, and expectations each patient brings to the clinical encounter. For example: What if the fellow eye had severe NPDR and a nonclearing vitreous hemorrhage developed, resulting in vitrectomy? Might that have been prevented if prophylactic anti-VEGF were given? What if the fellow eye had severe NPDR and rapidly progressive posterior subcapsular cataract and underwent cataract surgery, and severe DME developed? Might that have been prevented if given prophylactic anti-VEGF?

Selected Readings

1. Maturi RK, Glassman AR, Josic K, et al. Effect of intravitreal anti-vascular endothelial growth factor vs sham treatment for prevention of vision-threatening complications of diabetic retinopathy: the Protocol W randomized clinical trial. *JAMA Ophthalmol.* 2021; 139(7):701-712.
2. Brown DM, Wykoff CC, Boyer D, et al. Evaluation of intravitreal aflibercept for the treatment of severe nonproliferative diabetic retinopathy: results from the PANORAMA randomized clinical trial. *JAMA Ophthalmol.* 2021; 139(9):946-955.
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Preventing Proliferative Diabetic Retinopathy and Diabetic Macular Edema Does Not Provide a Visual Acuity Benefit at 4 Years: Results of Protocol W

Four-Year Visual Outcomes in the Protocol W Randomized Trial of Intravitreal Aflibercept for Prevention of Vision-Threatening Complications of Diabetic Retinopathy

Raj K Maturi MD and the DRCR Retina Network

I. Background

- A. The 2-year results of this study showed that treatment with aflibercept (Eylea, Regeneron) anti-VEGF in eyes with moderate to severe nonproliferative diabetic retinopathy (NPDR) reduced the risk of developing proliferative diabetic retinopathy (PDR) or center-involved diabetic macular edema (CI-DME) but did not make a difference in 2-year VA when compared with eyes that received sham injections and aflibercept treatment only if disease worsened.¹
- B. Whether early treatment has a longer-term benefit on VA is unknown.
- C. Primary objective: To compare the 4-year VA and rates of disease progression between the aflibercept and sham treatment groups

II. Methods

- A. Study design
 1. Randomized clinical trial
 2. 64 sites in the United States and Canada
 3. 328 adults with at least 1 eye with moderate to severe NPDR (diabetic retinopathy severity score [DRSS] levels 43 to 53), good vision (20/25 or better), and no CI-DME followed for 4 years
 4. Study enrollment: January 2016 to March 2018
 5. Study completion: May 2022
- B. Interventions
 1. 1:1 randomization stratified by baseline diabetic retinopathy severity score (DRSS) to
 - a. Aflibercept (2 mg) injections
 - b. Sham injections
 2. Prevention injections (either aflibercept or sham)
 - a. Given at baseline and 1, 2, and 4 months, then every 4 months through 2 years

- b. Given every 4 months through Years 3 and 4 unless the eye regressed to mild NPDR or better on clinical exam. For DRSS \leq level 35 the injection could be deferred.
3. Aflibercept treatment was initiated for eyes in both groups that developed high-risk PDR or CI-DME with vision loss; re-treatment followed DRCR Retina Network algorithms.^{5,6}

C. Primary outcomes

1. Development of PDR or CI-DME with vision loss (≥ 10 letters at 1 visit or ≥ 5 letters at 2 consecutive visits)
2. Change in VA (best corrected ETDRS letter score) from baseline to 4 years

III. Baseline Results

- A. 399 eyes (328 participants, 71 bilateral with 1 eye in each treatment group) were randomized: 200 in aflibercept, 199 in sham.
- B. Median age: 57 years in aflibercept, 56 years in sham
- C. Female: 42% in aflibercept, 43% in sham
- D. Type 2 diabetes: 94% in aflibercept, 88% in sham
- E. Race/ethnicity
 1. White: 46% in aflibercept, 43% in sham
 2. Hispanic or Latino: 31% in aflibercept, 34% in sham
 3. Black/African American: 15% in aflibercept, 16% in sham
 4. Asian: 5% in aflibercept, 5% in sham
 5. Other: 2% in aflibercept, 2% in sham
- F. Median VA (Snellen equivalents of 20/20): 88 letter score in aflibercept, 88 letter score in sham

G. Median OCT central subfield thickness (Spectralis machine equivalents): 283 μm in aflibercept, 283 μm in sham

H. Prior DME treatment: 10% in aflibercept, 11% in sham

IV. Four-Year Results

A. Study treatments

1. Initiation of anti-VEGF treatment for PDR or CI-DME with vision loss: 19% in aflibercept, 41% in sham
2. Mean number of aflibercept injections: 13.0 (SD = 3.7) in aflibercept, 3.5 (SD = 5.3) in sham, 8.7 (SD = 5.1) in sham among eyes that received at least 1 aflibercept injection

B. Efficacy

1. Cumulative incidence of PDR and CI-DME with vision loss
 - a. 34% in aflibercept, 57% in sham developed PDR or CI-DME with vision loss.
 - b. 28% in aflibercept, 49% in sham developed PDR.
 - c. 11% in aflibercept, 19% in sham developed CI-DME with vision loss.
2. Adjusted hazard ratios for PDR and CI-DME with vision loss*
 - a. PDR or CI-DME with vision loss: 0.40 (97.5% CI, 0.28-0.57; $P < .001$)
 - b. PDR: 0.42 (97.5% CI, 0.29-0.61; $P < .001$)
 - c. CI-DME with vision loss: 0.51 (97.5% CI, 0.27-0.97; $P = .02$)
3. Mean change in VA from baseline
 - a. Aflibercept: -2.7 (SD = 6.5) letters
 - b. Sham: -2.4 (SD = 5.8) letters
 - c. -0.5 (97.5% CI, -2.3 to 1.3; $P = .52$) adjusted mean difference*
4. *Adjustments for baseline DRSS, study eye laterality, and correlation in participants with 2 study eyes

C. Safety outcomes

1. Endophthalmitis: 2% in aflibercept, 0 in sham
2. Antiplatelet Trialists' Collaboration cardiovascular/cerebrovascular event
 - a. Unilateral aflibercept participants: 11%
 - b. Unilateral sham participants: 8%
 - c. Bilateral participants: 10%

V. Conclusion

- A. Four-year results of preventative aflibercept treatment for NPDR compared with aflibercept treatment only if disease worsened
 1. Statistically significant anatomic improvement
 2. No difference in VA
- B. Aflibercept as a preventive strategy may not be generally warranted for patients with NPDR without CI-DME.

References

1. Maturi RK, Glassman AR, Josic K, et al. Effect of intravitreal anti-vascular endothelial growth factor vs sham treatment for prevention of vision-threatening complications of diabetic retinopathy: the Protocol W randomized clinical trial. *JAMA Ophthalmol.* 2021; 139(7):701-712.
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Clinical Outcomes of Diabetic Macular Edema Patients Treated With Faricimab and Aflibercept: A Subcohort Analysis of 20/50 or Worse Visual Acuity Across Faricimab Phase 3 Clinical Trials

A Pooled Subcohort Analysis

Marco Zarbin MD PhD FACS, David Tabano PhD, Ayesha Ahmed PharmD, Manuel Amador MD, Allan Ding PharmD, Nancy Holekamp MD, Xiao-Yu Lu, Ivaylo Stoilov MD, and Ming Yang PhD

I. Overview

- A. Faricimab is a bispecific antibody for intraocular use that independently binds and neutralizes both angiopoietin-2 and vascular endothelial growth factor-A with high specificity and potency.
- B. Post hoc analyses were conducted to assess clinical outcomes in patients with diabetic macular edema (DME) with a baseline BCVA of $\leq 20/50$ enrolled in the YOSEMITE/RHINE Phase 3 clinical trials of faricimab.
- C. Rationale for the post hoc analyses was derived from DRCR.net Protocol T methodology.

II. Protocol T Study Design¹

- A. Prospective, randomized clinical trial ($n = 660$ patients)

B. ETDRS BCVA: 24-78 letters

C. Center-involved DME (exam and OCT)

D. Mean (SD) baseline central subfield thickness (CST)

1. Aflibercept: 373 (108) μm

2. Bevacizumab: 363 (88) μm

3. Ranibizumab: 384 (99) μm

E. No anti-VEGF therapy within previous 12 months

III. Protocol T Result

Aflibercept significantly improved BCVA at Year 1 in patients with baseline BCVA of 20/50 or worse.¹

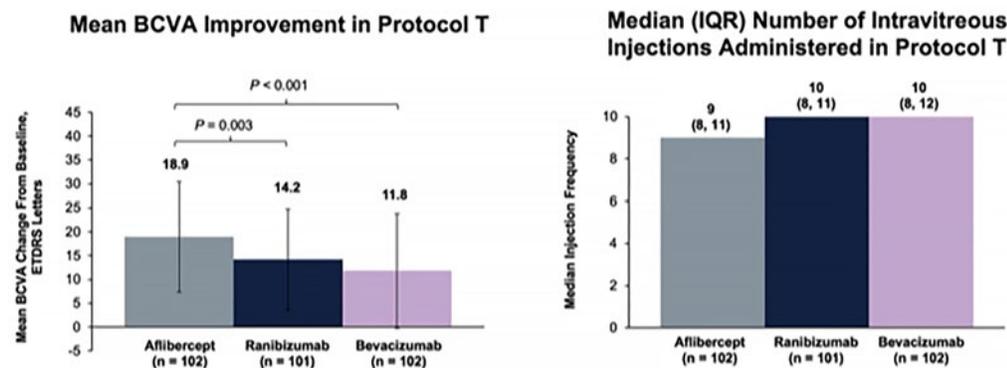


Figure 1

IV. YOSEMITE and RHINE

- A. Investigated faricimab every 8 weeks (q8w) or treat-and-extend–based personalized treatment interval (PTI) dosing with up to 16-week injection intervals²
- B. Phase 3, randomized, double-masked, active comparator-controlled trials
 - 1. Patients with center-involving DME (CST \geq 325 μ m)
 - 2. BCVA: 25-73 ETDRS letters (Snellen BCVA ~20/320 to 20/40)

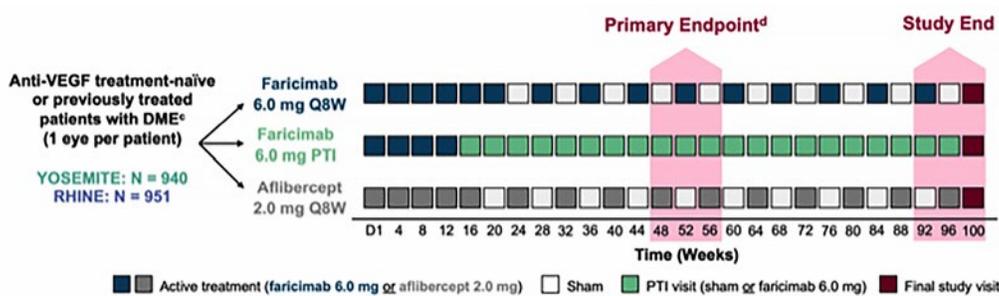


Figure 2

V. Post Hoc Analysis Methods

- A. Pooled post hoc subgroup analyses were conducted using the combined DME intent-to-treat population from YOSEMITE and RHINE trials with baseline BCVA of \leq 20/50 (letter score, < 69).
- B. Changes from baseline in BCVA and CST at Years 1 and 2 were compared between faricimab q8w, PTI dosing, and aflibercept q8w arms.
- C. Treatment intervals achieved at Years 1 and 2 for faricimab treat-and-extend arms were also explored.

VI. Changes in BCVA between faricimab and aflibercept arms were comparable in patients with baseline BCVA of \leq 20/50.

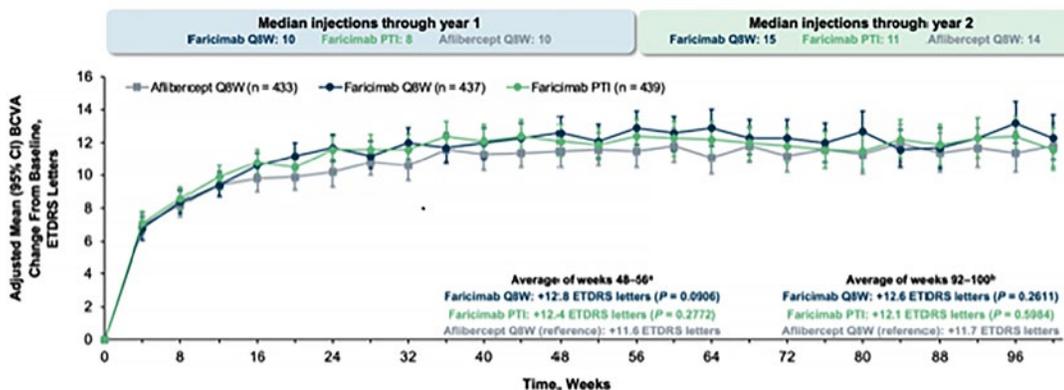


Figure 3. YOSEMITE and RHINE pooled (intent-to-treat population).

VII. Reductions in CST

Reductions in CST were numerically greater in the faricimab arms vs. aflibercept in patients with baseline BCVA of $\leq 20/50$.

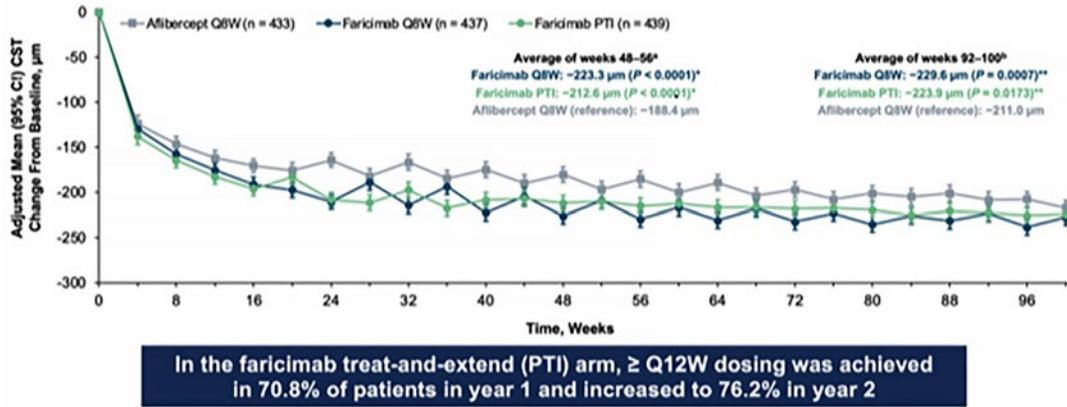


Figure 4. YOSEMITE and RHINE pooled (intent-to-treat population).

VIII. Conclusion

A. Faricimab demonstrated comparable vision outcomes with fewer injections in patients with DME with baseline BCVA of $\leq 20/50$.

1. Comparable change in BCVA between faricimab arms and aflibercept
2. Superior CST reduction for faricimab vs. aflibercept at Years 1 and 2
3. Durability achieved in the faricimab treat-and-extend arms across both clinical trials suggests vision outcomes with superior drying and fewer injections can aid in reducing treatment burden for patients, providers, and payers.

B. Caveat: Differences in Protocol T, YOSEMITE, and RHINE

1. Similar, but not identical, inclusion criteria: No history of anti-VEGF therapy in Protocol T within 12 months vs. 25% with anti-VEGF therapy history (>3 months prior to enrollment) in YOSEMITE and RHINE
2. Similar, but not identical, retreatment criteria in Protocol T vs. YOSEMITE and RHINE

References

1. Wells JA, Glassman AR, Ayala AR, et al; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med.* 2015; 372:1193-1203.
2. Wykoff CC, Abreu F, Adamis AP, et al. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, Phase 3 trials. *Lancet* 2022; 399:741-755.

Comparison of Clarus and Optos Ultrawide-Field Imaging Systems to 7 Standard Fields in the Assessment of Diabetic Retinopathy Severity Level

Comparison of Standard 7-Field, Clarus, and Optos Ultra-Widefield Imaging Systems for Diabetic Retinopathy Assessment (COCO)

Barbara Blodi MD

I. Background

In the 1980s the landmark Early Treatment of Diabetic Retinopathy Study (ETDRS) established a Diabetic Retinopathy Severity Scale (DRSS) of prespecified DR features using a 30-40 degree fundus camera. The imaging protocol was based on imaging the macula and midperipheral by mapping out 7 stereoscopic fields. Advances in imaging technology have led to ultrawide-field color (UWF-C) with a single 100-200 degree field. Two of these systems are Clarus (Carl Zeiss Meditec AG; Jena, Germany) and Optos California (Optos PLC; Dunfermline, United Kingdom).

II. Purpose

- A. To determine whether DRSS on both Clarus and Optos systems is comparable to assessment of 7-field imaging area on a fundus camera
- B. To compare the performance of Clarus and Optos for global DR level

III. Methods

After obtaining informed consent, 50 participants (97 eyes) had color photos on 3 imaging systems taken in a single visit.

- A. Imaging protocol performed on fundus camera and 2 ultrawide-field systems
 1. Topcon 35-degree fundus camera, 7-field imaging protocol

2. Clarus UWF-C system, steered superior, nasal, inferior, and temporal fields
3. Optos UWF-C imaging, steered superior, inferior fields

B. ETDRS grading

1. DRSS level was determined for the 7-field area of each image set using the ETDRS 12-step scale.
2. Global DR Severity Level was assigned on the ultrawide-field images using the entire visible retina, including both the 7-field area and the far periphery.
3. Images were evaluated by 2 independent graders and adjudicated by a third evaluator when necessary.
4. Graders had a 2-day washout period between grading the 3 sets of images from the same eye.

IV. Results

A. Distribution of ETDRS levels:

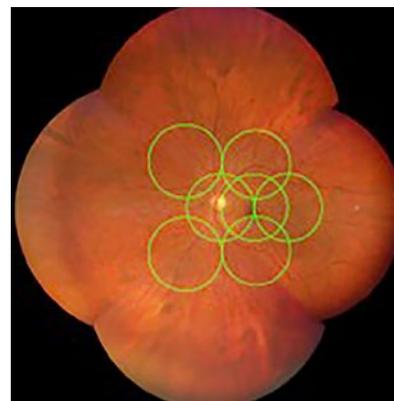
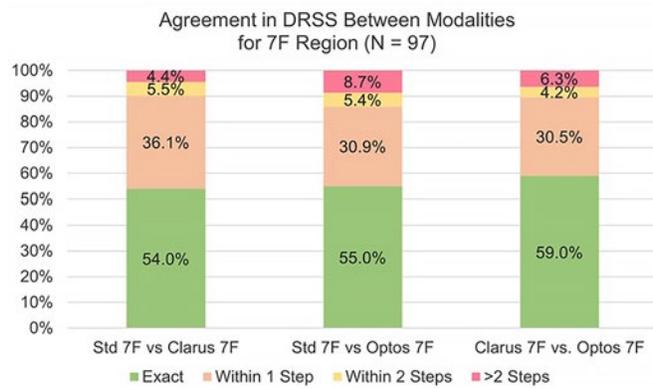
The majority of eyes in this study had mild or moderate nonproliferative DR as shown in Table 1.

Table 1

ETDRS Steps	ETDRS Level	Severity	Standard 7-Field (N = 97)	Clarus 7F (N = 97)	Optos 7F (N = 97)	Clarus Global (N = 97)	Optos Global (N = 97)
1	10, 12, 14A-C, 15, 20	Non/early DR (4.1%)	4	7	10	4	3
3	35A-F	Mild NPDR (48.5%)	47	35	37	30	35
4	43A-B	Moderate NPDR (20.6%)	18	20	22	21	25
5	47A-D		2	10	5	13	8
6	53A-E	Severe NPDR (2.0%)	2	3	2	3	2
7	60, 61A-B	Proliferative DR (19.6%)	7	8	9	8	10
8	65A-C		9	8	9	9	7
9	71A-D		3	4	2	6	4
10, 11, 12	75, 81, 85		0	0	0	0	0
90	90	Cannot grade (5.2%)	5	2	1	3	3

B. Comparison of ETDRS level within 7 fields:

Comparison of ETDRS level within 7 fields shows agreement between 3 imaging modalities. This 3-way comparison shows that over 50% of the time, there is exact agreement between the 3 imaging modalities taken of the same patient. Agreement within 2 steps occurs more than 85% of the time across all modalities.



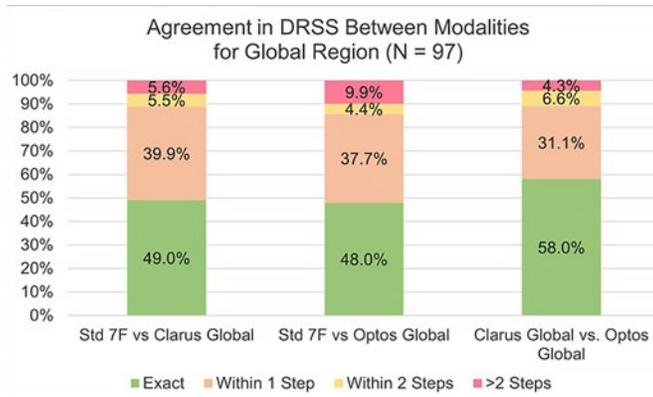
A

B

Figure 1

C. Comparison of global ETDRS level:

Comparison of global ETDRS level shows agreement between Optos and Clarus systems. Figure 2 shows findings very similar to the comparison done only within the 7 fields.



A



B

Figure 1

D. Disagreements between NPDR and PDR status:

Overall, the number of disagreements between NPDR and PDR grade were small, ranging from 2 to 7 eyes for each modality, and no specific trend was observed. Of 72 eyes graded as NPDR on standard 7-field, 3 (4.1%) were graded as PDR on Clarus within the 7F and 5 (6.9%) were graded as PDR on Optos. In 19 eyes graded as PDR on standard 7-field, 2 (10.5%) were graded as NPDR on Clarus within the 7 fields and 5 (2.6%) on Optos within the 7 fields.

V. Conclusions

Our study showed excellent 2-step agreement between graders when comparing standard 7-field, Clarus 7F, and Optos 7F for 7-field ETDRS levels. When graders viewed the entire visible retina and used a global scale, there was also excellent 2-step agreement between Clarus and Optos for the 7-field vs. global ETDRS levels. This level of agreement may support UWF-C imaging as being comparable to standard 7-field imaging for the assessment of DR severity.

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The Effect of GLP-1 Receptor Agonists on Diabetic Retinopathy Progression

Aleksandra Rachitskaya MD

Diabetic retinopathy (DR) is a common complication of diabetes that can be visually threatening and, in advanced stages, lead to irreversible blindness. The progression and development of DR has been associated with several risk factors, including the duration of diabetes, poor glycemic control, and poorly controlled hypertension.

Glucagon-like peptide-1 agonists (GLP-1RA) are a class of medications being used more frequently in the management of type 2 diabetes mellitus and obesity. However, certain GLP-1RA have been cited to be associated with early worsening of DR phenomenon. For instance, in the SUSTAIN-6 trial, semaglutide showed higher rates of retinopathy complications, including vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation. As a result, the semaglutide label included the following information:

In a 2-year trial involving patients with type 2 diabetes and high cardiovascular risk, more events of diabetic retinopathy complications occurred in patients treated with OZEMPIC® (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline (OZEMPIC® 8.2%, placebo 5.2%) than among patients without a known history of diabetic retinopathy (OZEMPIC® 0.7%, placebo 0.4%). Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

The current retrospective study analyzed the real-world effects of GLP-1RA on DR progression. Patients on SGLT2 inhibitors were used as controls. This study was conducted following approval from the Cleveland Clinic Institutional Review Board.

The study defined DR worsening as ICD-10 code worsening and development of vitreous hemorrhage, or conditions requiring treatment with an intravitreal agent or photocoagulation. Out of 692 subjects on GLP-1RA and 289 subjects on SGLT2 inhibitors, there was no statistically significant difference in DR worsening. Each case of worsening was examined individually.

The current study highlights the need for further investigation into the role of GLP-1RA, an increasingly popular class of diabetic medication, on DR early worsening.

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New Treatments in the Pipeline for Treatment of Diabetic Macular Edema

David Boyer MD

What are we trying to treat?

- Decrease in diabetic macular edema (DME)
- Improvement in Diabetic Retinopathy Severity (DRSS)
- Reduce vision-threatening complications
- Improvement in macular ischemia
- Better compliance to therapy by having longer-acting drugs

Do we need new treatments?

- Anti-VEGF therapy is very effective.
- 40% of patients with DME treated with monthly ranibizumab had minimal visual improvement.
- Important to remember!! Medical management is first line:
 - Control of blood sugar
 - Control of blood pressure
 - Smoking cessation
 - Control of lipids

Table 1. Anti-VEGF Drugs in the Pipeline, All Treating DME

Drug	Company	Route of Administration	Target	Comments
KSI-301	Kodiak	IVT	VEGF A	Longer acting
8-mg aflibercept	Regeneron	IVT	VEGF A,B Plgf	Longer acting
PDS	Susivmo; Genentech/ Roche	Surgical implant	VEGF A	Longer acting to refill
Biosimilars	Many	IVT	VEGF A	Less expensive

Abbreviations: IVT, intravitreal; PDS, port delivery system.

Table 2. Oral Drugs in the Pipeline

Drug	Company	Route of Administration	Target	Goal
APX-3330	Ocuphire	Oral	Ref-1 inhibition	Reduce vision loss
RZ-402	Rezolute	Oral	Kallkerin	DME
HCB-1019	InflammX	Oral	Connexin 43	Reduce inflammation DR
BAY1101042	Bayer	Oral	Guanylate cyclase activator	DR
AKST4290	Alkahest	Oral	CCR3 eotaxin inhibitor	DR
RG7774	Roche	Oral	CB2 receptor	DR

Abbreviations: DME, diabetic macular edema; DR, diabetic retinopathy.

Note: All oral drugs treat DR except RZ-402, which treats DME.

Table 3. Topical Treatments in the Pipeline

Drug	Company	Route of Administration	Target	Goal
OTT-166	Ocuterra	Topical	Integrin	DRSS
OCS-01	Oculus	Topical	Steroid	DME

Abbreviations: DRSS, Diabetic Retinopathy Severity Score; DME, diabetic macular edema.

Table 4. Gene Therapy in the Pipeline

Drug	Company	Route of Administration	Target	Goal
RGX-314	RegenXbio	Suprachoroidal	Anti-VEGF	DRSS

Abbreviation: DRSS, Diabetic Retinopathy Severity Score.

Table 5. Drugs in the Pipeline With Multiple New Modes of Action

Drug	Company	Route of Administration	Target	Goal
OTX-TKI	Ocular Therapeutics	IVT	Axitinib-TKI	DME longer acting
ET-1	Perfuse	IVT	Endothelin	DME
AG-77305	Allegenes	IVT	VEGF+integrins	DME
UBX-1325	Unity	IVT	Senescent cells	DME longer acting
THR-149	Oxurion	IVT	Kallikrein	DME poor responders
AR-1105	Aerie	IVT	Steroid	DME long acting
OPT-302	Opthea	IVT	Blocks VEGF C+D	In conjunction with anti-VEGF
HA-1077	Fasudil	IVT	Rho kinase inhibitor	Studied in Japan

Abbreviations: IVT, intravitreal; DME, diabetic macular edema.

Diabetic eye disease is multifactorial; hopefully, some of these drugs will reduce the frequency of injections and improve the visual acuity over current treatments.

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Gene Therapy Impact in Targeted Delivery Among the Pediatric Population

Audina M Berrocal MD, Carlos Mendoza-Santiesteban MD, Byron Lam MD, and Jesse Sengillo MD

- I. Among pediatric patients treated with voretigene at Bascom Palmer Eye Institute from 2018 to the present:
 - A. Chorioretinal scarring/atrophy was noted in patients months after treatment.
 - B. It affected central vision in 1/14 patients.
 - C. It did not affect central vision in 2/14 patients.
 - D. It was at the site of the bleb in 1/14 patients
 - E. It was not related to the site of the bleb in 2/14 patients.
- II. Pediatric patients treated with voretigene need to be monitored after treatment for possible chorioretinal complications of the treatment. We need a better understanding of gene therapy effects in the eyes of pediatric patients with inherited retinal diseases.

Advancing in Imaging: Preoperative and Intraoperative Evaluation

Lejla Vajzovic MD and Vahid Ownagh MD

I. Wide-field Fundus Photographs

Wide-field fundus photography is usually the first imaging modality supplementing indirect ophthalmoscopy in the evaluation of pediatric subjects. Commercially available imaging systems include the following:

A. Handheld contact systems

1. RetCam 3 (Clarity Medical Systems, Inc.) with field of view (FOV) up to 130 degrees¹
2. 3nethra neo (Forus Health, Inc.), FOV up to 120 degrees²
3. PanoCam (Visunex Medical Systems), FOV up to 130 degrees³
4. ICON Cart and ICON GO (NeoLight LLC), FOV of 100 degrees³

B. Noncontact table-mounted device:

Optos is a multimodal imaging system capable of wide-field fundus images, fluorescein angiography (FA), and indocyanine green angiography (ICG-A) up to 220 degrees.⁴ Imaging is possible only in upright position, restricting utility to older children.

II. Wide-field FA

- A. Intravenous fluorescein is not well tolerated in many children and infants, which may increase the number of required exams under anesthesia.
- B. Oral fluorescein angiography (off-label use, 25 mg/kg) may be an alternative to intravenous imaging in the clinic.^{5,6}

III. OCT and OCT Angiography (OCT-A)

Retinal layer-specific pathologies may not be evident with fundus images or indirect ophthalmoscopy.

OCT may provide invaluable information for evaluation of children with suboptimal vision or unexplained visual loss. OCT imaging has had a far more limited role in the care of retinal disease in infants, predominantly because of the perceived difficulties in capturing images from a nonfixating infant.⁷

- A. Heidelberg Spectralis, Flex mode, designed for supine position OCT/OCT-A imaging: The system was successfully employed to visualize infant retinal vasculature with OCT-A mode in supine position.⁸ Microvasculature of macular nodules in Coats disease was evaluated with the same device.⁹ Significant difference in some retinal microvascular parameters was observed in a study of supine vs upright positioning using Spectralis Flex mode.¹⁰

- B. Leica spectral domain OCT (SD-OCT) Envisu is a commercially available noncontact handheld system facilitating OCT imaging in the clinic and during examination under anesthesia.^{11,12}

- C. Investigational 400-kHz swept source OCT (SS-OCT) hand held bedside non-contact device developed at Duke University: The system has been deployed extensively to study microanatomy of retinal and choroidal development in infants. Now the fifth-generation (UC5) is the preferred pediatric OCT imaging modality in our retina service. Additionally, 9×9-mm OCT-A is feasible with UC5 (750 A-scans/B-scan, 750 B-scans/volume).¹³

An ergonomic research handheld SS-OCT-A system developed at Duke University is capable of image acquisition with infant in supine position or lying on the mother's lap.¹⁴ Our investigational noncontact handheld OCT has shown promise in clinical research:

1. Identifying choroidal thinning associated with ROP plus disease⁷
2. Detailed study of vascular avascular interface in ROP¹⁵
3. Distinguishing 4A from 4B ROP by revealing retinal detachment or traction¹⁶
4. Identifying morphologic differences between pediatric and adult epiretinal membrane on SD-OCT. Similar to adults, photoreceptor integrity predicts better VA changes after surgical epiretinal membrane removal.¹⁷
5. The handheld SD-OCT imaging systems was USFDA cleared in 2012 for use in supine neonates. Pediatric clinical applications are facilitated by noncontact design and near infrared scanning laser. Pupillary dilation is not mandatory.

IV. Intraoperative OCT (iOCT)

iOCT provides instant intraoperative feedback on retinal microstructures during pediatric vitreoretinal surgery. iOCT and iOCT angiography can be performed by handheld OCT devices or by newly developed microscope-integrated OCT (MI-OCT) systems.^{18,19}

- A. iOCT has been employed to detect vitreolenticular interface disorders in children undergoing congenital cataract surgery.²⁰
- B. iOCT has additional advantage in pediatric patients due to limitation of OCT acquisition at postoperative examinations.²¹

- C. A case of pediatric retinal detachment is presented to emphasize the utility of iOCT
- D. MI-OCT has shown promise in specific pediatric pathologies, like optic disc pit maculopathy, by assisting intraoperative delineation of presumed connection site between vitreous cavity and intraretinal spaces.²²
- E. For research and clinical applications, we utilized an MI-OCT prototype system developed at Duke University to image macular vitreoretinal interface and subretinal blebs created during subretinal injections for macular hole surgery or gene therapy clinical trials. The Duke MI-OCT is a 100-kHz SS-OCT system with 1050-nm scanning laser. It acquires volumetric images with 1000 A-scans/B-scan and 1000 B-scans/volume through a wide-angle contact lens.²³ The system has been successfully integrated to our clinical practice of selected pediatric vitrectomies, eg, retinal detachments with epiretinal membranes, macular holes, and puffers.

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Intravitreal Therapy in Pediatric Patients

Victor M Villegas MD

- I. Introduction
 - A. Overview of pediatric intravitreal injections
 - B. Importance of the topic in pediatric ophthalmology
 - C. Objective of the presentation
- II. Anatomy and Physiology of the Pediatric Eye
 - A. Brief review of the anatomy of the eye in children
 - B. Developmental differences in the pediatric eye compared to adults
 - C. Key considerations for intravitreal injections in pediatric patients
- III. Indications for Pediatric Intravitreal Injections
 - A. Common retinal conditions requiring intravitreal therapy in children
 1. Retinopathy of prematurity (ROP)
 2. Retinoblastoma
 3. Coats disease
 4. Familial exudative vitreoretinopathy
 5. Pediatric macular edema
 - B. Rationale for using intravitreal injections in these conditions
 - C. Evidence supporting the efficacy and safety of intravitreal injections in pediatrics
- IV. Technique and Procedure
 - A. Pre-injection assessment and preparation
 1. Patient selection and evaluation
 2. Consent and parental involvement
 3. Preoperative considerations
 - B. Administration of intravitreal injections
 1. Equipment and instruments
 2. Anesthesia options
 3. Injection technique and precautions
 - C. Post-injection care and follow-up
 1. Monitoring for complications
 2. Schedule and frequency of follow-up visits
 3. Management of adverse events
- V. Safety and Complications
 - A. Overview of potential complications associated with intravitreal injections in pediatrics
 - B. Strategies to minimize risks and improve safety
 - C. Management of complications if they arise
- VI. Special Considerations in Pediatric Intravitreal Injections
 - A. Age-specific challenges and adaptations
 - B. Psychological considerations and strategies for pediatric patients
 - C. Ethical and legal considerations in pediatric ophthalmology
- VII. Current Research and Advancements
 - A. Emerging techniques and technologies in pediatric intravitreal injections
 - B. Latest research findings and clinical trials
 - C. Future directions and potential advancements
- VIII. Conclusion
 - A. Recap of key points covered in the presentation
 - B. Importance of pediatric intravitreal injections in improving visual outcomes
 - C. Encouragement for further research and clinical practice in the field

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Challenges in Managing ROP in the Evolving Neonatal Landscape

Mary Elizabeth Hartnett MD FACS

- I. Challenge: Evolution of ROP Over Time and Across the World
 - A. Historical perspective to understand current day: Three pandemics
 1. First (1940s): Due to unrestricted oxygen without adequate monitoring (Birth weights were over 150 grams on average in United States [U.S.] and United Kingdom.)
 2. Second (1970s): Following increased survival of more preterm infants with advances in neonatal care
 3. Third (1990s): ROP emerged in middle-income countries, thought to be due to resources for monitoring and regulating as well as for education of screening ophthalmologists and to support nurses and technical staff
 - B. Potential Steps Forward: awareness and addressing public health and social needs universally
- II. Challenge: Preterm birth remains high and is increasing in some regions; ROP is a retinovascular disease of preterm infants.
 - A. “Born Too Soon” estimates from WHO: 1 in 10 infants are born preterm (<37 weeks)¹
 - B. Rates have not diminished and in some places have increased.
 - C. Premature birth remains the leading cause of childhood death.
- III. Challenge: As more premature infants survive, ROP increases.
 - A. ROP increases to varying degrees and has different appearances.
 1. ROP has increased in middle-income countries and in regions with ventilators, but there is still insufficient staff to care for infants.
 2. ROP is a growing problem in the U.S., including in low-income areas.
 - a. Possible reasons include use of high oxygen and insufficient staffing resources.
 - i. Oxygen at birth has an effect and after birth can continue to damage newly developed capillaries.
 - ii. Experimentally, high oxygen at birth damages newly developed capillaries.
 - b. Other factors include infection, nutrition, oxidative stress, and research needed.
- IV. Challenge: ROP is greater in regions with increased preterm birth and insufficient resources or workforce to optimally manage.
 - A. Further education to optimize prenatal nutrition, reduce obesity to reduce preterm birth.
 1. Population health: Studies suggest differences based on income and external factors, but factors regarding genotype may also play a role and require investigation.
 2. Experimental studies
 - a. Maternal uteroplacental insufficiency
 - b. Antioxidants (lutein and zeaxanthin), fatty acid supplements, growth factors
 - c. Testing in clinical trials
 - d. Implementation
 3. Screening of infants required in ROP
 - a. Indirect ophthalmoscopy
 - i. Challenging to teach for effective screening
 - ii. Difficult in larger or older infants
 - b. Telemedicine approaches
 - i. Patients missed if the camera cannot be angled to periphery
 - ii. Has been used successfully in other venues, including by training non-MD professionals
 - B. Potential Steps Forward: telemedicine, AI, implementation of programs using non-MD professionals

- V. Challenge: Presentation of ROP varies worldwide, with aggressive ROP (A-ROP) appearing in greater birthweight, older gestational age infants.

ROP appearances:

- A. Zone II, stage 2-3 ROP with plus disease: Slower time course
- B. A-ROP: Rapid course with poor outcomes if not treated urgently. Aggressive posterior ROP (AP-ROP) included within A-ROP.
- C. Spectrum of Plus: Allows flexibility in management of patients

- VI. Management Challenge: Anti-VEGF vs. laser is clearer in zone I than zone II.

ROP varies in appearance and pathophysiology worldwide, requiring tailored treatment.

- A. Laser has a long track record but ablates peripheral avascular retina.
 - 1. Prevents vascularization into peripheral retina with potential expanded visual field and reduced stimulus for late reactivation when infants are too large to adequately examine in clinic
 - 2. May reduce later atrophic holes and retinal detachment in teenage years
 - B. Anti-VEGF allows vascularization into peripheral avascular retina.
 - 1. May facilitate vascularization into peripheral avascular retina
 - 2. May reduce myopia
 - 3. Safety reports of neurocognitive delays require longer-standing outcomes from clinical trials.
- VII. Challenge: There is no universal agreement on reactivation vs. initiation of vascularization into peripheral avascular retina.
- A. Basic work showing that regulation at the level of VEGFR2 specifically in endothelial cells supports vascularization into peripheral retina that may expand visual field and reduce stimulus for reactivation, but clinical translation is not specific to endothelial cells or receptor.
 - B. Potential Steps Forward: research to identify more targeted and safer approaches and clinical outcomes with imaging and quantitative measures
 - 1. Different treatments: Long-term efficacy and safety outcomes remain unknown.
 - 2. Long-term outcomes following cryotherapy and laser only: Vascularization into peripheral retina was not possible or was not beneficial for potential expanded visual field.

VIII. Anti-VEGF Clinical Trials

- A. Clinical evidence and knowledge of outcomes currently
 - 1. Efficacy in zone I eyes in BEAT ROP¹⁸
 - 2. RAINBOW (ranibizumab) and FIREFLY (aflibercept) do not meet their endpoint of non-superiority or noninferiority to laser but still show effect.
 - 3. ROP1 and 2 in Pediatric Eye Disease Investigator Group studies
 - 4. Meta-analysis shows value in zone I ROP, but informed consent is important in decision.
 - 5. Differences in agents
 - a. Bevacizumab lowers systemic VEGF for at least 2 months.
 - b. Ranibizumab, with shorter half-life, does not lower systemic VEGF compared to laser but requires multiple injections.
 - c. Aflibercept may lower VEGF longer than ranibizumab based on adult studies but future data are needed.
- B. What about laser vs. anti-VEGF?
 - 1. Efficacy in zone I eyes in BEAT ROP and in meta-analysis considering this as a first-line treatment for type 1 ROP in zone I
 - 2. Based on studies and meta-analysis, laser and anti-VEGF should be considered and potentially offered in informed consent.
 - 3. Other considerations
 - a. Laser requires well-trained treaters and takes longer than anti-VEGF administration.
 - b. More long-term experience with laser than anti-VEGF
 - c. Intraocular injections have risk of cataract, endophthalmitis, retinal injury (use SAFER guidelines)

IX. Questions Persist

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What's New in Retinal Degenerations?

Jacque L Duncan MD

Retinal dystrophies and degenerations are among the most challenging diseases that ophthalmologists encounter because they are genetically, as well as clinically, diverse and heterogeneous. In addition, these conditions are rare, affecting fewer than 1 in 3000 people in the United States. Many ophthalmology residencies and retinal fellowships provide limited exposure to patients with inherited retinal degenerations, and many retinal specialists are not familiar with how to interpret the tests used to characterize these heterogeneous conditions, including genetic, psychophysical, and electrophysiological testing. The range of diseases can be overwhelming, and traditionally there have been limited to no treatments for retinal degenerations.

However, retinal specialists owe it to our patients and colleagues to understand how to diagnose, characterize, and manage patients with inherited retinal degenerations. Over 300 genes to date have been identified in patients with inherited retinal degenerations, and the number increases each year. However, genetic testing in clinical settings results in inconclusive results for nearly half of patients tested, complicating interpretation of test results for patients and providers.¹ In most cases, explanation of genetic test results is best done in partnership with a genetic counselor who can help interpret results, which are often complicated by variants of uncertain significance that may be disease causing but have not been reported in other patients. The genetic testing and genetic counseling that should be provided for patients with inherited retinal degenerations is available through sponsored programs, with support from non-profit and for-profit entities.

Genetic testing became clinically important for patients with early-onset retinal degenerations beginning in December 2017, when the U.S. Food and Drug Administration approved voretigene neparvovec for patients with retinal degeneration with biallelic pathogenic variants in *RPE65*. Long-term results becoming available now, more than 3 years after FDA-approval of voretigene neparvovec, demonstrate sustained visual benefit in the ability to navigate mobility tests in most patients.² However, some patients develop chorioretinal atrophy in the posterior pole, not always related to the region where the treatment was delivered.^{3,4} In fact, patients who develop progressive retinal pigment epithelial atrophy have been reported to show significant benefit in dark-adapted vision,⁵ perhaps indicating that chorioretinal atrophy results from restored expression of *RPE65* in patients with early-onset retinal degeneration.

The adeno-associated viral (AAV) vector that was successfully used to deliver *RPE65* can accommodate genes up to about 4 kb in size. Alternative approaches, including antisense oligonucleotide therapies, have been developed for large genes with common variants that introduce splicing defects in genes, including *CEP290* and *USH2A*.⁶ Gene editing with clustered regularly interspaced short palindromic repeats (CRISPR) may offer a new approach for genes that exceed the carrying capacity of AAV or for autosomal-dominant retinal degenerations. The first use of CRISPR to treat a patient at the site of

the disease was reported for patients with *CEP290*-related retinal degeneration, demonstrating early evidence of safety in November 2022; but sponsors of the trial decided not to pursue development of what could be a promising therapy for patients with this severe form of retinal degeneration.

The results demonstrate the critical importance of clinical trial design based on information from well-designed natural history studies and communication with regulatory agencies to ensure that the study is designed to demonstrate significant change in the specified primary outcome measure. Natural history studies of rare inherited retinal degenerations have been facilitated by a consortium of clinical centers with expertise in management of patients with retinal degenerations.

For patients who do not have identified genetic causes of their retinal degeneration, nonspecific treatments may prevent photoreceptor degeneration⁷ or reduce oxidative stress to photoreceptor survival and improve visual function.⁸ For patients with advanced disease, electrical stimulation of remaining cells may elicit some vision.⁹ Gene therapy can introduce light-sensitive proteins to make retinal cells that are not photoreceptors respond to light through optogenetics, with many approaches in clinical development to provide sight to patients with profound vision loss from retinal degeneration.¹⁰

In summary, retinal specialists must stay informed about new developments and opportunities to care for their patients with retinal degenerations, perhaps the most promising areas of unmet need in ophthalmology.

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Update on Therapies for Retinitis Pigmentosa: Genes, Stem Cells, and Others

Susanna S Park MD PhD

Retinitis pigmentosa (RP) represents a group of hereditary retinal degeneration associated with diffuse photoreceptor degeneration and vision loss in both eyes. It affects about 1:4000 individuals worldwide.¹ Patients present initially with loss of night and peripheral vision. Total blindness can result as the condition advances.

Currently, there are limited treatments for RP. Despite published research supporting the use of nutritional supplementation, such as vitamin A palmitate and DHA, the effect of these nutritional supplements on progression of RP is modest at best.² In 2013, the Argus II retinal prosthesis was approved by the Food and Drug Administration (FDA) for advanced RP. However, recently the device was discontinued.³

Thus there is a great unmet need for therapies that limit or reverse vision loss associated with RP. Currently, almost 100 different clinical trials exploring novel therapies for RP are listed in ClinicalTrials.gov. Most of them are early phase trials, exploring safety and feasibility. A couple of Phase 3 trials are under way to determine efficacy. This presentation will present highlights of novel approaches being explored in clinical trials in the United States.

Gene Therapy

Since RP is a hereditary condition, correcting the genetic defect would be a logical approach. In 2017, the FDA approved the first gene therapy for RP.⁴ Voretigene neparvovec is a one-time adeno-associated virus vector-based gene therapy indicated for the treatment of individuals with biallelic *RPE65*-mutated retinal dystrophy. It delivers a normal copy of the *RPE65* gene to the retinal cells via subretinal administration. Significant improvement in white light full-field light sensitivity threshold (FST) and multiluminance mobility testing (MLMT) was noted in a Phase 3 clinical trial, which was sustained 3 to 4 years after gene therapy.⁵

A factor limiting gene therapy for RP is the heterogeneous genetic mutation associated with RP. Over 100 different genes are associated with RP, and many more yet to be determined.⁶ Thus, the currently FDA-approved gene therapy that targets the *RPE65* gene is a treatment option for less than 1% of RP patients.⁷

Nonetheless, clinical trials continue to explore novel gene therapies. Four of these trials, including a Phase 3 clinical trial, are targeting X-linked RP, since 75% of X-linked RP is associated with mutations in the *RPGR* (retinitis pigmentosa GTPase regulator) gene, and X-linked RP accounts for 10% to 15% of RP.⁸ The *RPGR* gene, expressed in rods, is essential for cell viability. Both intravitreal and subretinal approaches are being explored. Initial results of a Phase 1/2 clinical trial showed safety and tolerability of subretinal delivery, with visual field improvement noted at 1 month and sustained.⁹

Optogenetic Therapy

In optogenetic therapy, genes for light-sensitive proteins are introduced into surviving inner retinal cells to make them sensitive to light.¹⁰ Three Phase 1/2a clinical trials and one Phase 2b clinical trial are exploring optogenetic therapy for RP via intravitreal delivery of a gene for channelrhodopsin or multi-characteristic opsin. Preclinical studies show that the cells in the inner retina become transfected with light-sensitive proteins and improve visual function.¹¹ Theoretically, this approach can restore vision even in advanced RP. The limitation is that remodeling of the retina may limit the extent of visual restoration possible using this approach.¹²

Stem Cell Therapy

Stem cells limit or reverse retinal degeneration by replacing degenerating retinal cells or via paracrine trophic effects.⁸ Two Phase 1/2 clinical trials are exploring subretinal transplantation of fetal neural progenitor cells or retinal progenitor cells for tissue replacement. Intravitreal injection of fetal retinal progenitor cells is also being explored in Phase 2 clinical trials for paracrine trophic effects. The use of cultured allogeneic stem cells is appealing since the cells can be expanded, but rejection and abnormal cellular proliferation are safety issues that can arise.¹³ Our group is completing a Phase 1 clinical trial of intravitreal injection of autologous CD34+ cells from bone marrow for RP since these natural repair cells do not proliferate and have protective effects following intravitreal injection in animal models of RP.¹⁴

Antioxidant Supplement Therapy

N-acetyl cysteine (NAC) is an oral supplement form of cysteine essential for making antioxidant glutathione. In an animal model of RP, oral administration of NAC prolonged cone survival and function since cone degeneration in RP results from oxidative stress.¹⁵ A Phase 1 clinical trial showed improved macular sensitivity on microperimetry after 6 months in the RP cohort receiving the highest dose of NAC.¹⁶ A multicenter Phase 3 trial is studying the effect of oral NAC on macular photoreceptors (NAC-Attack Clinical Study).

Novel Drug Therapies for RP

Ulteversen

Ulteversen is an antisense oligonucleotide delivered intravitreally for RP associated with mutation in exon 13 of the *USH2A* gene. The goal is to stop the mutation-containing exon 13 of *USH2A* gene from being incorporated into the mature mRNA.¹⁷ *USH2A* is one of three genes associated with Usher type II.⁸ Usher type II has later onset and a less severe pheno-

type than Usher type I, and thus is a good therapeutic target. A Phase 2/3 study is ongoing after promising Phase 1 study results.

Ocu400

A modifier gene therapy, Ocu400 targets the nuclear hormone receptor (NHR), which regulates multiple functions within the retina. Subretinal injection of Ocu400 is being explored in a Phase 1/2 clinical trial for RP resulting from mutations in the nuclear receptor subfamily 2 group E member 3 (NR2E3) and rhodopsin (RHO) genes. Preliminary results show stable or improved mobility in maximum tolerated medical therapy.¹⁸

EA-2353

EA-2353 is a novel small molecule that selectively activates endogenous retinal stem and progenitor cells to differentiate into photoreceptors. Repeat intravitreal weekly injection of EA-2353 x4 is being explored in a Phase 1/2 clinical trial.

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Gene Therapy for Neovascular AMD

Allen C Ho MD

With credit to the RGX study teams and Dr. Arshad Khannani

Summary

Human gene therapy has evolved from science fiction to science fact, and gene therapy shows potential to be a safe, effective, durable treatment for neovascular AMD. Safety and efficacy questions are being answered as we garner more and longer-term data from multiple clinical trials.

We are in a human gene therapy era of medicine across many medical conditions, with clinical trials in inherited retinal degenerations, common retinal conditions such as AMD and diabetic retinopathy (DR), blood cell diseases such as sickle cell disease and multiple myeloma, neurologic conditions, and more.¹ Importantly, this change was led by retina colleagues using a gene replacement strategy for an inherited retinal degeneration. The first-in-human gene therapy was pioneered by Drs. Jean Bennett and Albert Maguire in collaboration with Spark Therapeutics, resulting in the 2017 FDA approval of Luxturna (voretigene neparvovec) for Leber congenital amaurosis biallelic RPE65 mutation.^{2,3} As of 2023, this has sparked more than 30 clinical trials worldwide for inherited retinal degenerations and more than 20 clinical trials for common retinal conditions like AMD and DR.

Gene therapy for neovascular AMD utilizes a gene therapy biofactory approach—whereby a gene that encodes for a therapeutic protein (for example, an injectable anti-VEGF therapy) is

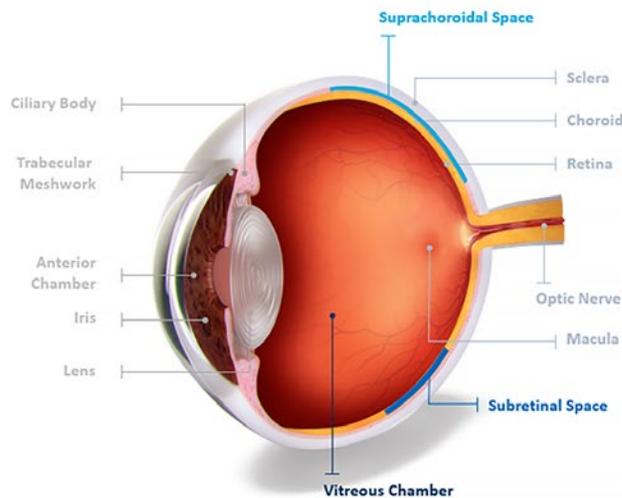
introduced into a host cell (for example, retinal cells and retinal pigment epithelial cells) so that the host cells produce the therapeutic protein. RegenXBio and Adverum programs in neovascular AMD have both documented durable therapeutic protein production over time. There are multiple gene therapy programs for neovascular AMD in progress, at different stages of clinical development, including Phase 2 4D-150, which employs a dual transgene anti-VEGF payload injected intravitreally.

Next-Generation Gene Therapy Trials for Neovascular AMD

First-generation gene therapy clinical trials for neovascular AMD revealed the potential for biofactory gene therapy; however, they lacked efficacy and showed mixed results. For example, Avalanche AVA-101 for neovascular AMD did not work, but there are multiple learnings from Avalanche and other first-generation gene therapy trials that have improved our current next-generation clinical trials.⁴⁻⁷ We are in “next-generation” clinical trials of gene therapies for wet AMD, learning from prior clinical trials on improved gene therapy vectors, refined surgical delivery techniques and hardware, and more effective transgenes, including those that encode for proteins similar to ranibizumab and aflibercept.

An important consideration of gene and cell therapy is consistent delivery to target tissues. Several delivery methods are being evaluated in clinical trials for neovascular AMD,

Ocular gene therapy delivery methods Comparative profiles



¹ Ding, K., et al. 2019 *Journal of Clinical Investigation*, ² Vandenbergh et al. 2011 *Science Translational Medicine*, ³ Maclaren et al. 2016 *Lancet*, ⁴ Yin L, et al. 2011 *JOVS*, ⁵ Bennett, J., et al., 2017 *Human Gene Therapy*, ⁶ Heier JS, et al. 2016 *Lancet*, ⁷ Kotterman M, et al. 2015 *Gene Therapy*, ⁸ Bouquet C, et al. 2019 *JAMA Ophthalmology*

Delivery Space Considerations	
	<p>Suprachoroidal Space (SCS)¹</p> <ul style="list-style-type: none"> Targeted access and broad transduction of the retinal cells observed in preclinical studies Compartmentalized AAV delivery Minimal exposure to the vitreous and anterior segment
	<p>Subretinal Space^{2,3}</p> <ul style="list-style-type: none"> Targeted access and broad transduction of the retinal cells observed in preclinical studies Compartmentalized AAV delivery Minimal exposure to the vitreous and anterior segment Low risk of immune response Low risk of inflammation
	<p>Vitreous Chamber</p> <ul style="list-style-type: none"> Inner limiting membrane (ILM) presents physical barrier, potentially limiting direct transduction of the retina² Limited transduction of the retina observed in preclinical studies⁵ Broad exposure to the vitreous and anterior segment High risk of immune response^{5,6} High risk of inflammation⁸ Typically requires prophylactic corticosteroids⁷

Figure 1

including surgical pars plana vitrectomy and subretinal delivery and office-based intravitreal injection and suprachoroidal injection. Retina specialists continue to evolve techniques and delivery hardware to achieve the most consistent delivery of gene therapy.⁸

Transvitreal Subretinal Delivery After Pars Plana Vitrectomy

This technique is used for many retinal gene and cell therapy studies— with a good safety profile, familiar procedure, direct visualization, and improved precision with MicroDose Injection Kit, by which the injection is performed with surgeon foot pedal control via a viscous fluid injection (VFI) system.

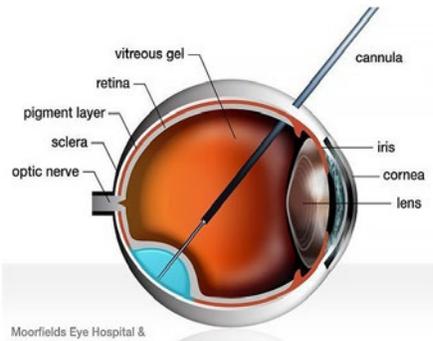


Figure 2. RegenXBio RGX-314 transvitreal subretinal delivery is in global pivotal trials for wet AMD. Credit: Moorfields Eye Hospital.

Atmosphere/Ascent Pivotal Phase 3 With Next-Generation AAV8 Vector

Long-term follow-up of subretinal RGX-314 reveals durable anti-VEGF protein production and demonstrates safety and long-term treatment effects for Cohorts 3 and 4 (out to 4 and 3 years, respectively), with stable to improved visual acuity and meaningful reductions in anti-VEGF treatment burden. Pivotal Phase 3 trials Atmosphere (RGX314 vs. ranibizumab) and Ascent (RGX-314 vs. aflibercept) are ongoing in expanded international multicenter clinical trials.

Interim Conclusions from the RGX-314 Subretinal Long-Term Follow-Up Study

- Subretinal RGX-314 continues to be **generally well-tolerated** in a Long-Term Follow-Up Study (n=37*) and will continue to be followed for a total of 5 years
- No new drug-related ocular AEs were reported in the last year of follow-up for Cohorts 3 and 4
- With a **single injection** of RGX-314, **patients demonstrate a long-term, durable treatment effect** for Cohort 3 over 4 years and Cohort 4 over 3 years
 - Stable to improved visual acuity
 - Meaningful reductions in anti-VEGF injection burden

Two pivotal trials for nAMD are now active and enrolling patients

Data cut August 29, 2022. *Patients with at least one visit in the LTFLU study

Figure 3. Interim conclusions from the RGX-314 subretinal long-term follow-up study.

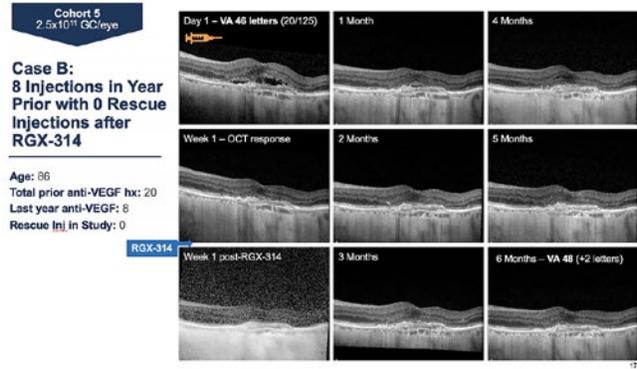


Figure 4



Two Randomized, Partially Masked, Controlled Clinical Studies (Phase 2b/3 and Phase 3) to Evaluate the Efficacy and Safety of RGX-314 Gene Therapy in Participants with nAMD

Figure 5

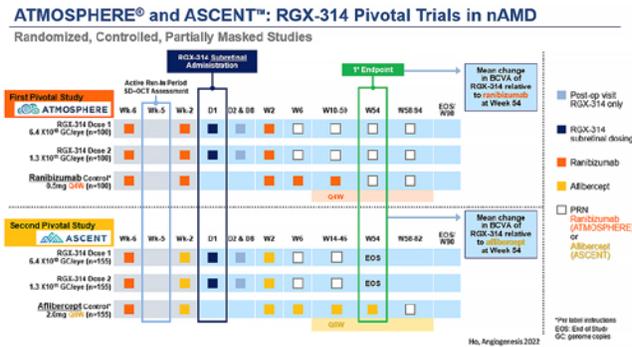


Figure 6

Suprachoroidal Injection

This technique is being explored to simplify delivery of gene and cell and other retinal therapies. It does not deliver to the subretinal space, but preclinical work suggests transfection of retinal cells. It can be an office-based procedure, avoiding OR surgery.

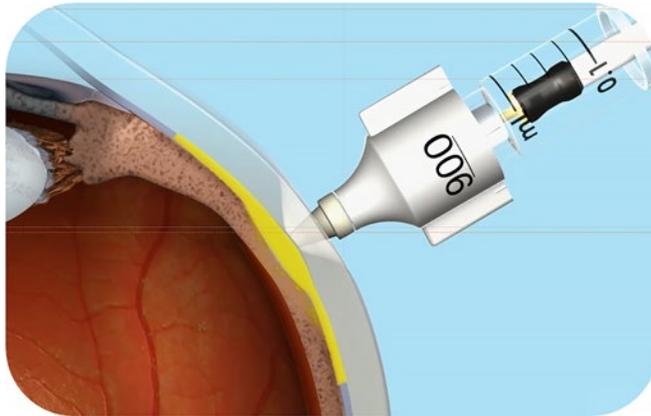


Figure 7. Regenxbio RGX-314 Suprachoroidal is in Phase 2 trials for wet AMD (and DR).

AAVIATE Phase 2 With Next-Generation AAV8 Vector

Summary of Results from the Phase II AAVIATE® nAMD Study

RGX-314 Cohorts 1-5 (n=85): Safety

- Suprachoroidal RGX-314 has been well-tolerated

RGX-314 Cohorts 1-4 (n=65): 6 Month Results

- RGX-314 treated patients had stable vision and retinal thickness, with a meaningful reduction in treatment burden across all dose levels; highest reduction in treatment burden seen in Cohort 4 (Dose 3):
 - 85% reduction in annualized injection rate
 - 67% injection-free
- No meaningful differences in patient outcomes with and without baseline AAV8 NAbS
- Intraocular inflammation (IOI) resolved with topical corticosteroids
 - Cohorts 1-3 (Dose 1 and 2) - all mild and similar incidence observed across doses
 - Cohort 4 (Dose 3) - mild to moderate with increased incidence compared to prior doses

AAVIATE is currently enrolling a new Cohort 6 to further evaluate Dose 3 (1x10¹¹ GC/eye) with short-course, ocular steroids following RGX-314

Data on file, August 2022. REGENXBIO.COM Q1 2022

Figure 8. Summary of results from the Phase 2 AAVIATE® neovascular AMD study.

Adverum-022 Intravitreal ADVM-022

This is an intravitreal injection of next-generation vector AAV.7m8, encoding for aflibercept with lower dose ($2 \times 10E11$) from Optic Phase 1, showing the best safety/efficacy profile, and moving forward in Phase 2 Luna, along with ($6 \times 10E10$) different ocular/systemic corticosteroid prophylaxis regimens. Optic Phase 1 two-year results are complete. Luna Phase 2 is ongoing.

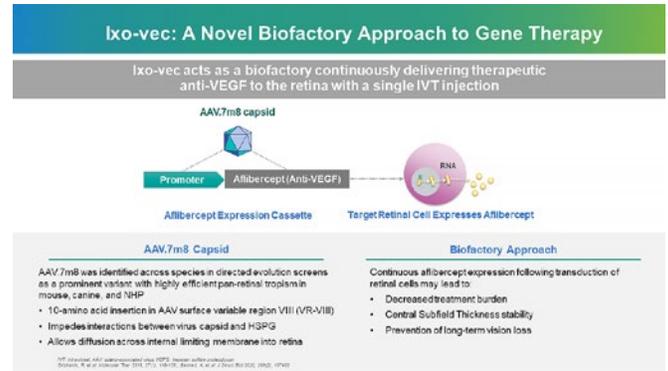


Figure 9. ADVM-022 utilizes a novel biofactory approach to gene therapy designed for continuous delivery of aflibercept following intravitreal injection.

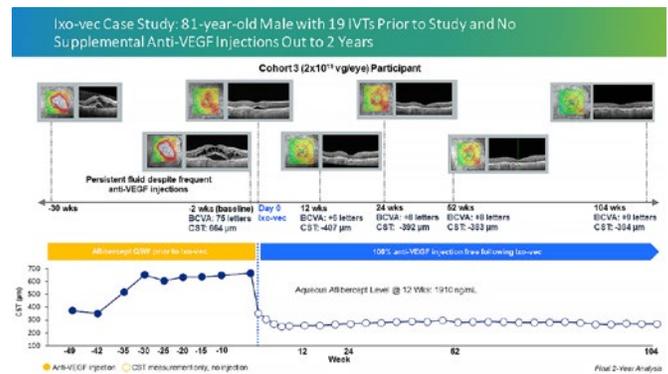


Figure 10. Case study: 81-year-old male with 19 intravitreal injections prior to study and no supplemental anti-VEGF injections out to 104 weeks.

Ixo-vec OPTIC Study Conclusions

- Ixo-vec was generally well tolerated. Mild to moderate, dose-related inflammation responsive to topical corticosteroids was the most common adverse event
 - All participants in Ixo-vec 2x10¹¹ vg/eye dose groups were inflammation free at the end of the study
- BCVA and CST were maintained or improved through two years with both doses. An extension study will follow participants through 5 years
- A single Ixo-vec IVT injection resulted in sustained therapeutic aflibercept through at least 3 years
- Mean annualized anti-VEGF injections were reduced by 80-98%, and 53% of participants who received 2x10¹¹ vg/eye did not receive any supplemental injection in two years
- The 2x10¹¹ dose demonstrated a favorable benefit/risk profile despite short duration corticosteroid prophylaxis

The ongoing Phase 2 LUNA study is evaluating 2x10¹¹ vg/eye and a lower 6x10¹⁰ vg/eye dose with enhanced prophylactic corticosteroid regimens in patients with nAMD

Final 2-Year Analysis

Figure 11. LUNA Phase 2 study in neovascular AMD: study design.

4D-150 Intravitreal, Prism Phase 1/2

An intravitreal injection of next-generation vector 4D-150 dual transgene payload encoding for aflibercept with anti-VEGF C as well shows promise on safety/efficacy.

4D-150 Design Characteristics

MULTI-MECHANISTIC, INTRAVITREAL GENE THERAPY INHIBITING 4 DISTINCT VEGF FAMILY MEMBERS

- Primate-evolved retinotropic R100 capsid carrying a dual transgene payload
 - Aflibercept and VEGF-C RNAi
- Single-dose intravitreal administration
- Widespread delivery to all major regions and layers of the retina
- Efficient transduction of retinal cells
- Robust pan-retinal transgene expression
- Inhibition of 4 distinct VEGF family members (VEGF-A, B, C, and PlGF)

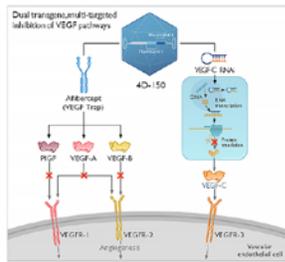


Figure 12. 4D-150 overview.

Case Study

89-YEAR-OLD FEMALE (3x10¹⁰ vg/eye)

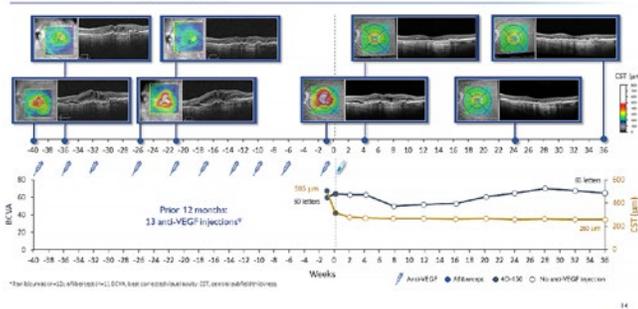


Figure 13

Conclusions

- Intravitreal administration of 4D-150 to patients with wet AMD was safe and generally well tolerated at doses ranging from 6x10⁹ to 3x10¹⁰ vg/eye through Week 24
 - No dose-limiting toxicities and no 4D-150-related serious adverse events
 - 14/15 participants with no intraocular inflammation
 - No hypotony
- Clinical activity demonstrated across all 4D-150 dose cohorts through Week 24
 - Up to 84% reduction in mean annualized anti-VEGF injection rate through Week 24, stable BCVA and CST
- 3x10¹⁰ vg/eye dose resulted in 4/5 patients (with high anti-VEGF need) injection-free at Week 36 with stable BCVA and improved CST
- Currently enrolling randomized Phase 2 dose expansion study (enrollment >50% complete)
 - 4D-150 (1x10¹⁰ vg/eye or 3x10¹⁰ vg/eye) vs aflibercept 2 mg

Figure 14

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Subretinal Gene Therapy Surgery: Tricks of the Trade

Christina Y Weng MD MBA

I. Background

- A. Retinal gene therapy holds promise in the treatment of many retinal diseases. There are 4 main retinal gene therapy delivery approaches, and no consensus on which is best.¹
 1. Intravitreal (eg, ADVM-022)
 2. Subretinal
 - a. Transvitreal-subretinal (eg, voretigene neparvovec-rzyl, currently the only FDA-approved gene therapy and the focus of this talk)
 - b. Suprachoroidal-subretinal (eg, GT005; also transvitreal-subretinal being evaluated)
 3. Suprachoroidal (eg, RGX-314; also subretinal being evaluated)
- B. Subretinal (via transvitreal) gene therapy delivery is the most well-studied method.^{2,3}
 1. Benefits
 - a. Relatively immune-privileged subretinal space may confer less immunogenic response.
 - b. Effective transduction of outer retinal/retinal pigment epithelial (RPE) cells
 2. Drawbacks
 - a. Requires surgery with concurrent vitrectomy
 - b. Greater technical demands and risks, especially if abnormal retinal-RPE adhesiveness
 - c. Effect may be limited to bleb area

II. Surgical Tips for Subretinal Gene Therapy Delivery^{4,5}

A. Preoperative

1. Patient counseling should set expectations accordingly.
2. Consider pretreatment corticosteroids.
3. Logistical planning/OR practice run (including pharmacy if drug preparation needed)

B. Intraoperative

1. Consider general anesthesia if patient movement is a concern.
2. Set up injection apparatus and prime syringe.
 - a. Can bevel the tip of the 41-gauge cannula to facilitate entry
 - b. Decide on manual vs. self-injection; self-injection utilizes a special kit connected to the silicone oil injection apparatus; set foot pedal on ~12-16 psi.
3. Surgery, as pertains to voretigene neparvovec-rzyl
 - a. Elevate hyaloid as far as safely possible; use triamcinolone to help with visualization.
 - b. Remove valve of cannula to avoid kinking of the 41-gauge cannula tip.
 - c. Target along superotemporal arcade away from vessels or obvious pathology.
 - d. Touch down on retina and look for slight blanching before injecting.
 - i. Some create prebleb with saline or air, but impact on drug concentration/localization is not well understood.
 - ii. Slow down injection velocity as bleb crosses through fovea.
 - iii. Stay within the bleb for a few seconds before withdrawing to avoid reflux.
 - iv. Entry site will self-seal.
 - e. Perform air-fluid exchange from side opposite the bleb to avoid inadvertent contact of bleb with instrument shaft; avoid directly aspirating over entry site.
 - f. Suture all sclerotomies.

C. Postoperative

1. Consider patient positioning; bleb typically absorbs within 24 hours.
2. Prescribe standard postoperative topical drops.
3. Taper corticosteroids.

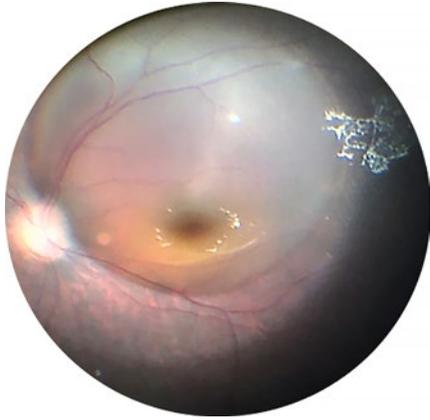


Figure 1. Subretinal bleb containing a 0.3-mL volume of voretigene neparvovec-rzyl for a young child with biallelic *RPE65* mutation-associated retinal dystrophy. Figure courtesy of Christina Y Weng MD MBA.

III. Future Surgical Considerations in Subretinal Gene Therapy

- A. Intraoperative OCT may assist in volumetric measurements for refined dosing.
- B. Robotics may facilitate greater precision in subretinal gene therapy surgery.^{6,7}
- C. Safety must be further explored (eg, pigmentary changes).⁸

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Ixo-vec (ADVM-022) Intravitreal Gene Therapy for Neovascular AMD: Preliminary Data From the Phase 2 LUNA Trial and 3-Year Results From the Phase 1 OPTIC-Extension Trial

Carl Regillo MD FACS

Purpose

Anti-VEGF therapies revolutionized treatment of neovascular AMD (nAMD), yet real-world evidence suggests that long-term anatomical and visual benefits decrease over time, in part due to an inability to maintain frequent intravitreal (IVT) injections.^{1,2} Ixo-vec (ixoberogene soroparvovec, formerly ADVM-022, AAV.7m8-aflibercept) is an investigational gene therapy designed to provide continuous stable expression of aflibercept and long-term suppression of VEGF activity following a single IVT injection. The Phase 1 OPTIC study (NCT03748784) evaluated the safety, tolerability, and efficacy of Ixo-vec in participants with nAMD through 2 years. Participants had the option to enroll in a long-term follow-up study, OPTIC EXT (NCT04645212), for an additional 3 years. Ixo-vec is currently being evaluated in the Phase 2 nAMD LUNA study (NCT05536973).

Methods

Phase 1 OPTIC/OPTIC EXT

OPTIC was a multicenter, open-label, sequential cohort, dose-ranging, 104-week study in treatment-experienced nAMD patients with a demonstrated response to anti-VEGF therapy. Participants were administered a single IVT injection of Ixo-vec at 6×10^{11} vg/eye in cohort 1 ($n = 6$) and cohort 4 ($n = 9$) and 2×10^{11} vg/eye in cohort 2 ($n = 6$) and cohort 3 ($n = 9$). Participants in cohorts 1 and 2 received oral corticosteroid prophylaxis for 13 days (initiated 3 days prior to Ixo-vec administration), while those in cohorts 3 and 4 received corticosteroid eye drop prophylaxis for 6 weeks (initiated the day of Ixo-vec administration). Incidence and severity of adverse events, change in BCVA, change in central subfield thickness (CST), and number of supplemental aflibercept injections were evaluated.

Participants who received Ixo-vec at any dose in the OPTIC parent study were eligible to enroll in OPTIC EXT, an observational 156-week extension study to evaluate the safety and efficacy of Ixo-vec. Incidence and severity of adverse events, change in BCVA, change in CST, number of supplemental aflibercept injections, and aqueous humor aflibercept protein levels over time will be evaluated.

Phase 2 LUNA

LUNA is a multicenter, randomized, double-masked, parallel group, 52-week study in treatment-experienced nAMD patients with a demonstrated response to anti-VEGF therapy. Up to 72 participants will be randomly allocated between 2

Ixo-vec doses, 2×10^{11} vg/eye and 6×10^{10} vg/eye, and across 4 prophylactic corticosteroid regimens (topical difluprednate, dexamethasone IVT implant, topical difluprednate and oral prednisone, or dexamethasone IVT implant and oral prednisone). The primary endpoints are incidence and severity of adverse events and mean change in BCVA from baseline to Week 52. Change in CST, the number of supplemental aflibercept injections, and the effectiveness of the prophylactic corticosteroid regimens in minimizing inflammation will also be evaluated. Starting at Week 14, aqueous humor samples will be collected to determine aflibercept protein levels.

Results

OPTIC participants required frequent anti-VEGF injections in the year prior to the study, with a mean annualized injection rate of 9.6-10.5 across all cohorts. Despite frequent anti-VEGF injections, several OPTIC participants had poor disease control at study entry. Mean baseline BCVA was 64.7-65.9 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, and mean baseline CST was 307.7-473.4 μm . Ixo-vec-related ocular adverse events were mild (84%) to moderate (16%). Ocular inflammation was mild to moderate, dose-dependent, and responsive to topical corticosteroids. There were no cases of retinitis, vasculitis, choroiditis, or vascular occlusive events. Both doses demonstrated sustained levels of aflibercept protein in aqueous humor from the Week 12 assessment through 2 years, with sustained aflibercept levels observed through 3 years in the samples available from OPTIC EXT. BCVA was maintained, with a mean change of +0.2 (2×10^{11} vg/eye) and -0.2 (6×10^{11} vg/eye) ETDRS letters. CST improved, with a mean change of -92.9 μm and -60.2 μm with Ixo-vec 2×10^{11} vg/eye and 6×10^{11} vg/eye, respectively. Mean annualized anti-VEGF injection frequency was reduced by 80% (2×10^{11} vg/eye) and 98% (6×10^{11} vg/eye), while 53% of 2×10^{11} vg/eye participants and 80% of 6×10^{11} vg/eye participants remained supplemental anti-VEGF injection-free through the end of the study. New safety and efficacy data, including aqueous humor aflibercept levels, from the long-term OPTIC EXT study will be presented. Initial data from the LUNA Phase 2 study will also be presented for the first time.

Conclusions

In OPTIC, sustained aflibercept expression following a single Ixo-vec IVT injection markedly reduced treatment burden, maintained BCVA, and improved CST in treatment-experienced nAMD patients through 2 years. Ixo-vec was generally

well tolerated, with mild to moderate dose-dependent inflammation responsive to topical corticosteroids. Safety and efficacy data from at least 3 years of follow-up and up to 4-year aqueous humor aflibercept protein levels from the OPTIC EXT study will be presented for the first time. Preliminary results from the ongoing Phase 2 nAMD LUNA study will also be presented.

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Tinlarebant (LBS-008) in Adolescent Subjects with Stargardt Disease

Quan Dong Nguyen MD

Tinlarebant (LBS-008) is a novel oral therapy intended as an early intervention to prevent the accumulation of vitamin A-based toxins (bisretinoids) that cause Stargardt disease (STGD1) and contribute to the pathogenesis of non-neovascular AMD. Bisretinoids are formed as by-products of vitamin A in the visual cycle. Tinlarebant acts by reducing the level of serum retinol binding protein 4 (RBP4), the carrier protein that transports retinol to the eye. By modulating the amount of retinol entering the eye, tinlarebant reduces the formation of bisretinoids to preserve the health of retinal tissues.

STGD1 is the most common inherited retinal dystrophy in both adults and children. The disease is caused by a dysfunctional retina-specific protein (ABCA4), which causes an early, aberrant accumulation of cytotoxic byproducts of vitamin A in the retina, leading to retinal cell death and progressive loss of vision. Currently no approved treatments are available for STGD1.

A two-year Phase 1b/2 study of adolescent STGD1 patients treated with tinlarebant, an orally available retinal binding protein 4 (RBP4) antagonist, has been completed with 12 subjects. Five out of 12 subjects (41.7%) remained definitely decreased autofluorescence (DDAF) lesion-free after 24 months of treatment. DDAF lesion progression rate was slowed compared to natural history data throughout the study. Maintenance of vision in the majority of subjects was also observed. Additional results will be presented at the 2023 Annual Meeting of the American Academy of Ophthalmology (November 3 to 7, San Francisco, USA).

A Phase 3 study of adolescent STGD1 patients (the DRAGON Study) was initiated in 2022. DRAGON is a multi-center, randomized, double masked, placebo-controlled study to evaluate the safety and efficacy of tinlarebant in the treatment of early-onset STGD1 patients aged 12-20 years. The primary efficacy will be evaluated by the annualized rate of change from baseline in aggregate area of atrophy as assessed by fundus autofluorescence. Other visual function outcomes, including BCVA and spectral domain OCT, are also evaluated for all subjects in this study.

The DRAGON study has enrolled approximately 100 STGD1 patients, and more than 15 subjects have received treatment with tinlarebant for more than 12 months. Similar to the Phase 1b/2 study, the majority of the treatment-related adverse events (AEs) reported in the DRAGON study can be attributed to mechanism of tinlarebant action, including delayed dark adaptation and xanthopsia. AEs reported in this study were predominantly mild in intensity. Furthermore, the baseline demographics, including lesion size and pattern, as well as the status of ABCA4 mutations and its correlation with racial backgrounds, will be presented.

In summary, tinlarebant is a safe and well-tolerated treatment in this first-ever worldwide interventional pivotal study for STGD1 adolescents.

In addition, the Phase 3 clinical trial (the PHOENIX study) to evaluate efficacy and safety of tinlarebant in patients with geographic atrophy (GA) associated with nonneovascular AMD has been launched worldwide.

Toward Continuous Disease Severity Scores Using Deep Learning in MacTel Type 2

Aaron Y Lee MD

- I. Motivation for a Continuous Severity Score in Macular Telangiectasia (MacTel)
 - A. Many diseases are graded using discrete scales, but biological processes are not discrete. Discrete scales do not allow physicians to monitor disease progression as accurately as a continuous scale.
 - B. Deep learning image analysis models may be able to provide more information about disease progression using a continuous scale.
 - C. Is it possible to use machine learning to learn a continuous severity scale from OCT images with discrete labels?
 - D. A deep learning model can contain latent representations from imaging data, which are features of the data that are not directly observable and appear only in the deeper layers of the network. These latent representations would be used by a model to classify disease severity.
 - E. The latent representations, however, are not constrained to discrete disease “grades” and contain information that may be used to generate a continuous scale of disease severity.
- II. Current MacTel Grading Systems
 - A. First grading system, developed in 1993: Gass-Blodi stage gradings^{1,2}
 1. Based on fluorescein angiography
 2. Five stages
 - Stage 1: Occult telangiectatic vessels
 - Stage 2: Loss of transparency without clinically evident telangiectatic vessels
 - Stage 3: Prominent dilated right-angle retinal venules
 - Stage 4: Retinal pigment hyperplasia into the retina
 - Stage 5: Subretinal neovascularization from proliferation of intraretinal capillaries
 - B. Current grading system, developed in 2022: Chew et al (MacTel Report Number 10) stage gradings³
 1. Based on multimodal imaging: decision tree of stereoscopic color and red-free fundus photographs, fluorescein angiography, fundus autofluorescence, and spectral-domain OCT images
 2. Seven grades corresponding to disease progression and visual acuity
 - Grade 0: No ellipsoid zone (EZ) break/no pigmentation/no OCT hyper-reflectivity (HR)
 - Grade 1: Noncentral EZ break/no pigment/no OCT HR
 - Grade 2: Central EZ break/no pigment/no OCT HR
 - Grade 3: Noncentral pigment/no, noncentral, or central EZ break/no OCT HR
 - Grade 4: OCT HR/EZ break (either central or noncentral)/no pigment
 - Grade 5: Central pigment/no exudative neovascularization/EZ present or not gradable
 - Grade 6: Neovascularization (exudative) ± central pigment
- III. Development of a Deep Learning Model for Learning Chew et al Grades Using Supervised Deep Learning
 - A. Dataset: 2003 patient visit OCTs with clinical data
 1. Mapped OCT scans to closest clinical data within last 6 months
 2. Patient-level training/validation/testing data split: 70-15-15
 - B. Model development
 1. First trained a classifier (EfficientNet-b0) to learn the 7 discrete grade labels
 - a. Basic EfficientNet-b0 backbone was modified to adopt a multiview architecture⁴ by considering different B-scans from the OCT volume to incorporate 3D information.
 - b. OCT volumes ranged from 49 to 261 scans; used central 20 OCT B-scans, center cropped.
 2. After the classifier was trained, the features the model used to distinguish the 7 grades were extracted.
 3. Dimension reduced these features with uniform manifold approximation and projection for dimension reduction (UMAP)⁵ to create a continuous MacTel severity scale.

IV. Model Results and Evaluation

- A. The classifier achieved top-1 accuracy of 63.3% (186/294) on held-out test OCT volumes.
- B. For clinical validation of model, UMAP metrics were compared against clinical experts.
 1. Five clinical experts reviewed 100 pairs of OCT volumes (test data) and decided which volume in each pair had more severe MacTel, or if too close to tell.
 - a. 35 pairs with 1-grade difference from Chew et al grades
 - b. 35 pairs with same Chew et al grades
 - c. 30 pairs with unknown Chew et al grades, but from the same patient over a 3-year period
 2. The model UMAP metric computed the MacTel severity for each pair. A smaller UMAP metric indicates more severe MacTel.
 3. The model performed comparably to all graders on all 100 volume pairs.
 4. Both human graders and the deep learning model were able to identify more granular ranges of severity within each discrete grade.

V. Conclusions

- A. The classification model with UMAP embedding (trained on discrete severity labels) generated a continuous severity scale for MacTel without requiring continuous training labels.

- B. The continuous UMAP severity scale had good correlation with the Chew et al MacTel grades and with expert human graders.
- C. Both the expert clinicians and the model were able to identify MacTel severity with more granularity in OCT images from patients diagnosed with 1 discrete MacTel severity grade.
- D. This approach may be applicable to other complex diseases, especially when combining clinical and imaging data, to develop more accurate continuous scales for measuring and understanding disease processes.

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Role of AI in Fluid Quantification and Dynamics for Neovascular AMD Patients Using Home OCT

Anat Loewenstein MD Presented by Srinivas R Sadda MD

Home OCT is an investigational technology that allows convenient self-acquisition of OCT images by patients at home. Home OCT monitoring works via referral of a patient to the monitoring program. The patient is supported by a monitoring center, facilitating near daily acquisition of the scans. This high-frequency data acquisition promises truly individualized treatment of highly heterogeneous diseases like neovascular (nAMD) and provides deeper understanding of disease dynamics.

The high volume of images produced by near daily testing requires an automated approach for fluid assessment; this enhances efficiency and reduces burden on the retina specialist. Notal OCT Analyzer (NOA) is a deep learning-based algorithm that segments and quantifies intraretinal and subretinal fluid in the home OCT scans.¹ Combined with near daily OCT scans, NOA output can be used to understand fluid dynamics in nAMD with unprecedented detail. Tiernan et al² and Liu et al³ have reported the ability of patients to perform self-imaging with a high success rate and compliance over extended periods. This work aims to use home OCT and artificial intelligence capabilities to understand fluid dynamics in nAMD and the potential clinical impact on treatment timing with respect to reactivation.

Home OCT data from 54 patients and 57 eyes was analyzed. Thirty-five reactivations and 48 responses after treatment were manually annotated by expert graders. The fluid increase rate defined by average increase per day during the annotated activation period was recorded. The maximum amount of fluid across all activation was recorded. Regarding treatment response, the rate of decrease over the annotated period of response was similarly recorded. The total decrease percentage from the treatment time was recorded. The reactivation and treatment response episodes were classified into 2 categories: (1) cases where treatment was performed within 7 days and (2) cases where treatment was performed after 7 days. The retinal fluid volume at time of treatment, total time to resolve, and area under the curve (AUC) of the fluid volume trajectories were recorded.

The mean (SD) of retinal fluid activation rates was 12.6 (18.5) nL/day. The mean (SD) of the peak fluid volume as a result of reactivation was 115 (161) nL. The mean (SD) duration from activation start to treatment was 12 (10.5) days. The response to the treatment showed a mean (SD) decrease

rate of 8.3 (8.9) nL/day. The mean (SD) decrease percentage was 91.6% (19%) from the peak value at the end of annotated response period. The mean (SD) duration from treatment to end of resolution period was 11 (8) days. Figure 1 shows a collection of reactivation and response trajectories.

The fluid level outcomes for groups within and outside the 7-day period were analyzed. The mean amount of fluid for eyes treated within 7 days was approximately 40 nL, compared to the eyes that were treated outside the 7-day period, at 140 nL, a nearly 100-nL difference. The eyes treated within 7 days achieved fluid resolution with a mean of 4 days; the eyes treated outside this period took a mean of 14 days for resolution. The area under the fluid volume curves was 80 nL · days for the group treated within 7 days, and 780 nL · days for the group treated outside 7 days.

The results here demonstrate the importance of high-frequency testing for nAMD patients. The patients with delayed treatment carried significantly high fluid burden compared to those who were promptly treated. This is assumed to be a result of a combination of factors. The fluid levels continue to increase in most nAMD patients; hence, there are higher levels of fluid after delayed treatment. In addition, the higher levels of fluid take longer to resolve after treatment.

Home OCT promises to provide this high-frequency data. Along with artificial intelligence algorithms for automated fluid quantification, it would allow retina specialists to control fluid with more precision, while keeping the burden low on both patients and practices.

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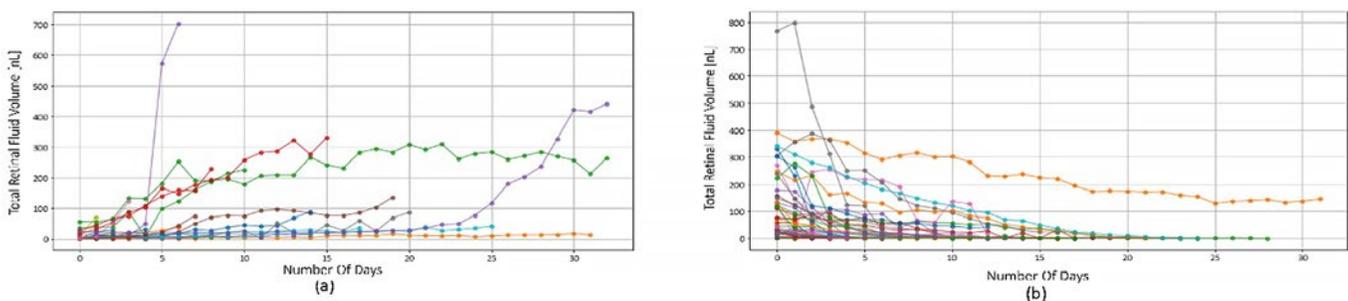


Figure 1. (a) Example of reactivations. (b) Examples of response to treatment. The examples demonstrate high heterogeneity in retinal fluid reactivation and its response to anti-VEGF treatments.

AI in the Management of Geographic Atrophy

Guiding GA Therapy From the Results of the Phase 3 Trials OAKS and DERBY and the Extension Study GALE

Ursula M Schmidt-Erfurth MD

Purpose

To identify biomarkers relevant for evaluation of the efficacy of the first approved treatment in geographic atrophy (GA) using intravitreal complement inhibition by pegcetacoplan (Syfovre) on OCT-based imaging and functional correlation with microperimetry. A detailed analysis of the available data in the Phase 3 clinical trials OAKS and DERBY, as well as their extension, GALE.

Setting

Advanced analysis of Spectralis OCT images in respect to photoreceptor (PR) degeneration and retinal pigment epithelial (RPE) loss, as well as a correlation with functional measurements obtained by microperimetry testing (MAIA) during the Phase 3 randomized controlled clinical trial OAKS and the long-term follow-up, OAKS, DERBY, GALE.

Methods

Patients with GA secondary to AMD in the Phase 3 trials were treated with intravitreal pegcetacoplan, a complement C3 and C3b inhibitor, or sham. The regimen consisted of monthly (PM), bimonthly (PEOM), and sham monthly (SM) treatment, and randomization was performed 2:2:1:1 into PM, PEOM, SM, and sham EOM treatment over 2 years. 436 and 433 eyes from OAKS and DERBY were assessed using the Spectralis OCT images acquired during the studies over 24 months and consecutively followed in GALE. Changes in RPE and PR integrity were processed by automated deep learning image analyses using validated algorithms based on convolutional neural networks. In OAKS, a 1:1 coregistration of morphologic (Spectralis) and functional (MAIA microperimetry) maps was performed. Integrity loss of RPE and PR in mm² area between arms was assessed using mixed models for repeated measurements.

OCT-Based AI Analysis

For RPE imaging, a fully automated 3D-to-2D en-face semantic segmentation was used, taking the full volumetric context into account. Ground truth was provided by validation on the clinical trial data of the Phase 2 FILLY trial, and a comprehensive correlation of automated vs. human expert RPE annotation.¹ To generate PR thickness maps, an ensemble 2D B-scan semantic segmentation incorporating 4 convolutional nets was elaborated with superior ability to quantify uncertainty in PR identification and provide highest trustworthiness.² This approach achieved accuracy on a single pixel level.³

Results

Longitudinal data from the Phase 3 trials revealed a significant reduction of PR degeneration and RPE loss under pegcetacoplan treatment monthly and also bi-monthly.

In DERBY, progression of RPE loss at Month 24 was reduced by 28.4% in PM vs. sham pooled ($P < .0001$) and by 21.2% in PEOM vs. sham pooled groups ($P = .0003$). Loss of PR integrity was reduced by 47.0% in PM vs. sham pooled ($P < .0001$) and by 45.8% in PEOM vs. sham pooled ($P < .0001$). In OAKS, loss of RPE was reduced by 23.9% ($P < .0001$) in PM vs. sham pooled and by 21.4% ($P < .0001$) in PEOM vs. sham pooled at Month 24. An even greater reduction was identified for PR integrity loss, which was reduced in PM vs. sham pooled by 52.7% ($P < .0001$), and in PEOM vs. sham pooled by 45.7% ($P < .0001$).

Comparison with the fellow eye condition demonstrated a 46%/48% (OAKS) and 44%/45% reduction in PR integrity loss in treated eyes for PM/PEOM therapy, which was significant ($P < .0001$). RPE loss was also reduced in treated vs. fellow eyes by 23%/16% (OAKS) and 30%/17% for PM/PEOM, respectively.



Figure 1. Comparison of fast growth in the fellow eye (A) compared to reduced growth in study eye (B). RPE loss in red, PR degeneration in green.

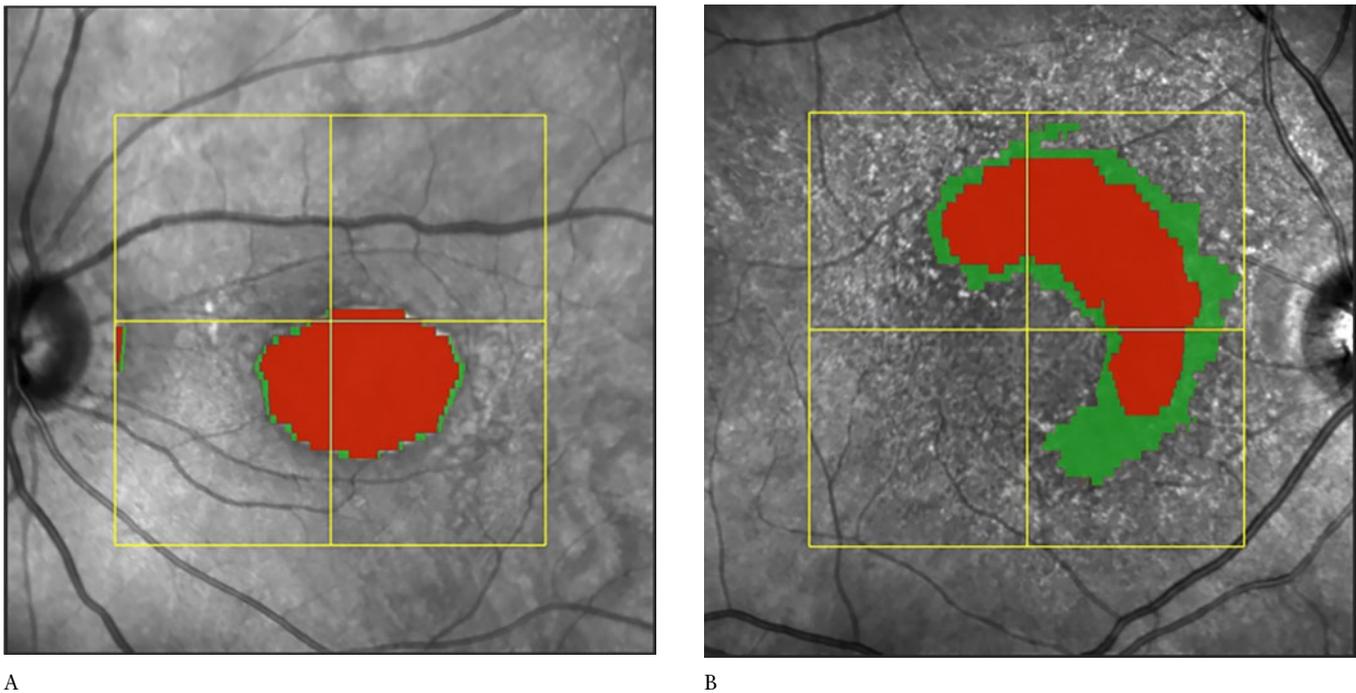


Figure 2. Comparison of low PR/RPE ratio in lower disease activity (A) and less therapeutic response and a higher ratio (B) with superior prognosis. RPE loss in red, PR degeneration in green.

The most important parameter appeared to be the ratio between PR degeneration and RPE loss. Disease activity was significantly higher in the group with a large PR/RPE loss area ratio. The therapeutic response of GA also strongly depended on the PR/RPE ratio, with significantly higher retinal maintenance in the highest ratio group over all time points. Grouping patients by quartiles of PR/RPE integrity loss ratios showed that GA lesion growth increased with higher baseline PR loss/RPE

loss ratio quartiles, which was consistent with a higher therapeutic effect. Lesions in the highest quartile showed statistically significantly increased growth of RPE loss of a mean of 284 μm (95% CI, 84-485; $P = .006$) compared with lesions in the lowest quartile. Likewise, the effect of AM treatment increased with higher PR loss/RPE loss ratio quartiles, reaching a statistically significant effect of -207 μm (95% CI, -408 to -6,5; $P = .043$).

Regarding retinal function, a point-to-point microperimetry correlation in OAKS demonstrated absolute scotoma at 0 dB in retinal sensitivity in areas with RPE loss overlying the clinical GA lesion. PR integrity loss on OCT was consistently associated with reduced mean pointwise sensitivity and an increase of the mean number of scotomatous points on MP. This structure/function correlation was also found for PR thinning, with a direct association of μm PR thinning and retinal sensitivity in dB.

Conclusions

OCT-based analysis was performed in more than 1000 patients included into the pegcetacoplan randomized controlled trials.

Advanced AI analyses of standard OCT images can be used to reliably localize and quantify RPE and PR alteration during disease activity in GA due to AMD. During long-term therapy, monitoring of therapeutic efficacy can be performed in an objective manner, demonstrating a significant reduction in RPE loss and particularly superior PR maintenance during monthly as well as every other month treatment with intravitreal pegcetacoplan; PR loss is a major biomarker for GA management.

Morphological changes detected on OCT imaging correlate directly with retinal function, highlighting preservation of retinal function by the treatment; that is, OCT morphology translates into clinical function by a corresponding relative loss in retinal sensitivity.

Assessment of the photoreceptor and RPE condition at baseline reveals a significant correlation between disease activity and therapeutic response with the extent of pre-existing integrity loss. The therapeutic efficacy of pegcetacoplan therapy can be further enhanced in patients with advanced photoreceptor integrity loss; the RPE/PR area difference is the major predictive biomarker of therapeutic benefit.⁴

Identification of patients best suited to receive pegcetacoplan treatment based on OCT and not fundus autofluorescence biomarkers will increase effectiveness in the real world and lead to improved patient selections, treatment regimens, and outcomes.

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Evaluation and Review of Automated Diabetic Retinopathy Screening

Roomasa Channa MD

I. Algorithms for Detecting Diabetic Retinopathy (DR)

There are many algorithms for detecting DR. The following are FDA-approved for autonomous detection of diabetic retinal disease.

- A. Digital Diagnostics
- B. EyeNuk
- C. AEYE Health

II. Pivotal Trials That Tested the Diagnostic Accuracy of Artificial Intelligence (AI) Algorithms

A. Abràmoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. *NPJ Digit Med.* 2018; 1:39.

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Table 1

Name of Company With FDA-Approved AI Algorithm	Date of Approval	Sensitivity/Specificity Compared to a Reference Standard	Number of Patients	Demographics of Included Patients	Inclusion Criteria
Digital Diagnostics ^a	April 11, 2018	<p><i>For mtmDR:</i></p> <p>Sensitivity: 87.2% (95% CI, 81.8%-91.2%)</p> <p>Specificity: 90.7% (95% CI, 88.3%-92.7%)</p> <p><i>For vtDR</i></p> <p>Sensitivity: 97.4% (95% CI, 86.2%-99.9%)</p>	900 participants across 10 primary care clinics	<p>47.5% of participants were male.</p> <p>Median age: 59 years (range: 22-84 years)</p> <p>Race: white (63.4%), African American (28.6%), and Asian (1.6%)</p> <p>Ethnicity: 16.1% Hispanic</p>	Asymptomatic patients with diabetes, aged 22 and older and no prior diagnosis of DR
EyeNuk ^a	August 05, 2020	<p><i>For mtmDR</i></p> <p>Sensitivity: 95.5% (95% CI, 92.4%-98.5%)</p> <p>Specificity: 85.0% (95% CI, 82.6%-87.4%)</p> <p><i>For vtDR</i></p> <p>Sensitivity: 95.1% (95% CI, 90.1%-100%)</p> <p>Specificity: 89.0% (95% CI, 87.0%-91.1%)</p>	893 participants across 15 centers, including primary care (6), general ophthalmology (6), and retina specialty (3) centers	<p>50.3% of participants were male.</p> <p>Median age: 56 years (range: 18-88 years)</p> <p>Race: white (73.3%), African American (17.8%), Asian (2.5%), American Indian or Alaska Native (0.3%), Native Hawaiian or Pacific Islander (0.4%)</p> <p>Ethnicity: 22.2%</p>	Patients with diabetes aged 18 years or older

Abbreviations: DR, diabetic retinopathy; mtmDR, more than mild DR; vtDR, vision-threatening DR.

^aReference standard was stereo photographs graded by the University of Wisconsin Reading Center, Digital Diagnostics used optical coherence tomography in addition to stereo photographs to establish presence of macular edema; mtmDR = ETDRS level 35 and higher; vtDR = ETDRS level greater than or equal to 53 but not equal to 90 and/or presence of clinically significant macular edema.

III. Reference Standards

Table 2. Different Reference Standards for Checking Diagnostic Accuracy

Level	Definition
A	A reference standard that is either a clinical outcome or an outcome that has been validated to be equivalent to clinical outcome, that is, a surrogate for a specific clinical outcome. This reference standard is derived from an independent reading center, where the clinicians or experts performing the reading are not otherwise involved in performing the study, with validated published protocols, and with reproducibility and repeatability metrics. Level A reference standard is based on at least as many modalities as the test and ideally more.
B	A reference standard derived from an independent reading center with validated published reading protocols, and with published reproducibility and repeatability metrics. Level B reference standard has not been validated to be equivalent to a clinical outcome.
C	A reference standard created by adjudicating or voting of multiple independent expert readers, documented to be masked, with published reproducibility and repeatability metrics. A Level C reference standard has not been derived from an independent reading center and has not been validated to be equivalent to a clinical outcome.
D	All other reference standards, including single readers and nonexpert readers. A Level D reference standard has not been derived from an independent reading center, has not been validated to be equivalent to a clinical outcome, readers may not be masked, and readers do not have published reproducibility and repeatability metrics.

Source: Adapted from Channa R, Wolf R, Abramoff MD. Autonomous artificial intelligence in diabetic retinopathy: from algorithm to clinical application. *J Diabetes Sci Technol.* 2021; 15(3):695-698.

IV. Going Beyond Diagnostic Efficacy to Evaluate Effectiveness of the AI at Preventing Vision Loss

Channa R, Wolf RM, Abramoff MD, Lehmann HP. Effectiveness of artificial intelligence screening in preventing vision loss from diabetes: a policy model. *NPJ Digit Med.* 2023; 6(1):53.

V. Factors to Consider in the Adoption of AI-Based DR Screening

A. Incorporating into clinic workflow

B. Potentially missing identification of concurrent ocular diseases

C. Autonomous vs. assistive algorithms

D. Impact on health equity and disparities

E. Patient and provider perspectives

F. Cost and economic considerations

G. Real-world implementation of AI-based DR screening

ChatGPT in the Modern Retina Practice

Raymond Iezzi MD

I. What is ChatGPT, and what can it do?

- A. Generative technology: examples include images, videos, deepfakes
- B. Pretraining: datasets used to train ChatGPT
 1. Open-source material on internet
 2. Possibly novels
 3. Not fully disclosed
 - a. Not clear if copyrighted material used; question of copyright infringement
 - b. Unknown if medical texts included
 - c. Unknown if peer-reviewed material used
 4. Reinforcement learning from human feedback (RLHF)
- C. Transformer
 1. Software that assigns numbers to words called “tokens”
 2. ChatGPT has a 50,000-word vocabulary.
 3. Algorithm predicts probability of most likely next words.
 - a. Depends on context of input text
 - b. Similar to how a master chess player makes the next move
 - c. Can do this for tens of thousands of next words

II. ChatGPT Language Processing

- A. Understands type-written input
- B. Responds with confident, intelligible responses

III. Relevance to Retina Practices

- A. Physicians can produce drafts of patient information handouts.
 1. Require editing
 2. Capable of translating into multiple languages
- B. Can formulate differential diagnosis lists, which must be reviewed by retina specialists
- C. Can be used to list possible testing for different diagnoses
- D. Non-physician eye care providers: Chatbots could be relied upon for:
 1. Diagnoses
 2. Referral recommendations

IV. Use of Chatbots by Patients

- A. Patients will ask chatbots medical questions that may include:
 1. Trying to self-diagnose symptoms (prone to dangerous inaccuracy)
 2. Self-triaging: If they should they seek care by a physician
 3. Looking up the credentials of physicians
- B. Fabricated or false results (called hallucinations) noted in prior testing

V. Critical Concepts

- A. This technology is here to stay.
- B. Large language models have been documented to:
 1. Produce racially biased outputs
 2. Generate misinformation
 - a. Produce false references as data sources
 - b. Produce fake PMID numbers
 3. Leak private data
- C. Ophthalmologists will need to lead efforts to educate patients and colleagues on best practices.
 1. Ophthalmology-specific training will be required.
 2. FDA oversight will be required.

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Evaluation and Necessity of Internal Limiting Membrane Peeling

Carl C Awh MD

There is no conclusive evidence that internal limiting membrane (ILM) peeling is either beneficial or harmful as an adjunct to macular epiretinal membrane (ERM) peeling. There is considerable retrospective evidence that ILM peeling increases the success rate of macular hole surgery. The literature is replete with case series, a few of which I cite below.

Given the lack of definitive evidence, it is inappropriate to state that ILM peeling is “necessary” for the surgical management of epiretinal membranes. However, I prefer to peel the ILM during almost all cases of ERM peeling. This gives me greater assurance that I’ve removed the target ERM, and I am compelled by evidence that peeling ILM results in a lower rate of ERM recurrence. I routinely peel ILM in macular hole cases, a setting in which the evidence strongly supports this maneuver.

One potential adverse outcome following ILM peeling is the development of peel-induced maculopathy (PIM), also known as dissociated optic nerve fiber layer. Although the clinical impact of PIM is unclear, there have been reports that this distinctive postoperative appearance is associated with decreased retinal sensitivity. We found that ILM peeling using a suction device that peels membranes more tangentially and methodically than typical forceps is associated with a lower incidence and severity of PIM. This may be due to reduced stress imparted to the retinal surface during ILM peeling, an outcome that could theoretically be achieved by modifications to peeling technique using conventional forceps.

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Internal Limiting Membrane Flap: Advantages and Techniques

Zofia Anna Nawrocka MD

- I. Internal Limiting Membrane (ILM) Flap Technique Description
- II. Comparison Between Inverted ILM Flap and Temporal Inverted ILM Flap Technique
- III. Temporal ILM Flap Technique Description
- IV. Explanation of Morphology of Failed Full-Thickness Macular Holes (FTMH)
 - V. Advantages of the Inverted ILM Flap Technique
 - A. Avoiding type 2 closure (flat open)
 - B. Improvement of functional and anatomical results
- VI. Indications for the Inverted ILM Flap Technique
 - A. Large and x-large MH
 - B. High myopia with and without rhegmatogenous retinal detachment (RRD)
 - C. FTMH associated with RD
 - D. FTMH associated with AMD
 - E. FTMH in trauma
 - F. FTMH in vascular diseases
 - G. Uveitis
 - H. Coats disease
- VII. ILM Peeling vs. Inverted ILM Flap Technique
 - A. Comparative studies in large MH
 - B. Comparative studies in MH associated with high myopia
- VIII. Detailed Indications for the Inverted ILM Flap Technique
 - A. Traumatic MH with subretinal fibrosis
 - B. MH with advanced soft drusen
 - C. MH after vitrectomy for RRD
 - D. MH in proliferative diabetic retinopathy
- IX. Safety and Efficacy of the Inverted ILM Flap in Small MH
- X. Flap Closure: Presentation of a New Closure Type and Visual Results
- XI. Tips and Tricks

Positioning the ILM flap on the top of the MH vs. pushing it inside
- XII. ILM Remnants and Their Consequences
- XIII. ILM Peeling vs. Inverted ILM Flap: Comparative Studies
- XIV. Repeated Surgery if ILM Peeling Used During First Attempt
- XV. Techniques Used in Repeated Surgery of Failed FTMH Closure if ILM Peeling Used as First Attempt
 - A. Autologous ILM transplantation
 - B. Lens capsule transplantation
 - C. Amniotic membrane transplantation
 - D. Subretinal injection of BSS
- XVI. Anatomical and Functional Results of Repeated Surgery Depending on Type of Primary Surgery
- XVII. Conclusions
 - A. The temporal ILM flap technique improves anatomy and function in large complicated FTMH.
 - B. Several arguments suggest benefit of ILM flap technique in small holes also.
 - C. Repeated surgery in eyes with primarily performed inverted ILM flap technique is a relatively simple procedure.

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Lamellar Retinoschisis Techniques

Macular Retinoschisis and Lamellar Hole Surgical Techniques

Homayoun Tabandeh MD MS FRCP FRCOphth

I. Introduction

Macular retinoschisis (MS) is characterized by the separation of the retinal layers that remain connected by various structures traversing the retina, including Müller cells. With the introduction of OCT, Takano and Kishi described foveal retinal detachment and foveoschisis in patients with high myopia and posterior staphylomas.¹ Subsequently, other investigators have reported on the spectrum of MS, associated features, classification, and pathomechanism.²⁻⁷ The OCT features of MS include increased thickness of the retina and separation of retinal layers, represented by a hyporeflective layer bridged by highly reflective columnar structures representing stretched Müller cells. Other associated OCT findings include partial vitreous detachment (PVD), vitreomacular traction (VMT), epiretinal membrane (ERM), internal limiting membrane (ILM) disruption, retinal folds, lamellar macular hole, ellipsoid zone defects, foveal detachment, full-thickness macular hole, and chorioretinal atrophy, among others.

MS may involve the inner or the outer retina layers or both. Inner MS predominantly affects the inner plexiform layer, the ganglion cell layer, and the nerve fiber layer. Outer MS involves the outer plexiform layer and the outer nuclear layer.

Although MS is often a part of the spectrum of myopic traction maculopathy (MTM), it may be associated with other traction-inducing conditions, such as VMT, partial PVD, ERM, proliferative retinopathies, or optic disc pit maculopathy (pseudoschisis).

II. Pathomechanism

Factors that contribute to the development of MS include the following:

- A. Anteroposterior vitreoretinal traction, such as a diffuse VMT or incomplete PVD
- B. Tangential traction with a resultant anteroposterior traction vector such as ERM
- C. Subretinal factors such as progressive outward deformation of sclera (staphyloma)^{7,8}

III. Management

A. Observation

In a study of the natural course of myopic traction maculopathy, Shimada et al noted improvement or complete resolution of the MS in 3.9% of eyes over a mean period of 36 months. Progression of the myopic traction maculopathy was observed in

11.6% of eyes, more commonly in eyes with more extensive MS (42.9%).⁶

Observation is warranted in patients with good BCVA, asymptomatic cases with uncomplicated MS, and eyes with guarded visual potential (eg, extensive myopic atrophy).

B. Surgery

Factors that influence the decision for surgery include visual acuity, visual symptoms attributable to MS, and documented progression. The surgical techniques aim to counteract the tangential and anteroposterior traction forces that contribute to schisis and to address associated pathologies that may be present.

1. Indications for surgical intervention

- a. Reduced BCVA and good visual potential
- b. Symptomatic
- c. Progressive schisis
- d. Complicated schisis: foveal detachment, macular detachment, macular hole

2. Surgical techniques

- a. Pars plana vitrectomy/membrane peel (ERM, VMT, premacular cortical vitreous)
- b. Pars plana vitrectomy/ILM peel (fovea sparing, non-foveal sparing)
- c. Pars plana vitrectomy/ILM peel/tamponade (air, gas, silicone oil)
- d. Macular buckle, scleral reinforcement, suprachoroidal tamponade (with or without pars plana vitrectomy and tamponade)

3. Surgical complications

- a. Iatrogenic full-thickness macular hole (4%-16%)
- b. Surgical trauma with progression of schisis or unroofing of the schitic layer
- c. Chorioretinal atrophy
- d. Complications of pars plana vitrectomy and scleral buckle

4. Outcomes

- a. Anatomic improvement: 70%-100%
- b. BCVA improvement: 60%-80%
- c. Improvement may continue for a year.⁹

5. Surgical pearls
 - a. Optimize intraoperative visualization.
 - b. Chromophores and triamcinolone for visualization of ILM, ERM, and other preretinal tissues
 - c. Keep forceps-tissue engagement superficial; diminished visual clues and depth perception due to hypopigmented fundus and chorioretinal atrophy, together with a structurally weak retina tissue, increase risk of surgical trauma.
 - d. Minimize centrifugal traction on the fovea; peel toward the fovea or circumferentially.
 - e. Reduce potential for phototoxicity; endoilumination intensity and duration, distance from the retinal pigment epithelium.

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Section XIX: Surgical Videos—Cool Cases and Complications

Moderator: Kourous Rezaei MD

Silicone Oil

Grazia Pertile MD

Retinal Fold

Martin Zinkernagel MD

Peeling . . .

Kazuaki Kadonosono MD

Financial Disclosure

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- Stock options and/or warrants in the producing company, even if they have not been exercised or they are not currently exercisable;
- Financial support or funding to the investigator, including research support from government agencies (e.g., NIH), device manufacturers and/or pharmaceutical companies.

Description of Financial Interests

Code	Description
C	Consultant/Advisor Consultant fee, paid advisory boards or fees for attending a meeting.
E	Employee Hired to work for compensation or received a W2 from a company.
L	Lecture Fees/Speakers Bureau Lecture fees or honoraria, travel fees or reimbursements when speaking at the invitation of a commercial company.
P	Patents/Royalty Beneficiary of patents and/or royalties for intellectual property.
S	Grant Support Grant support or other financial support from all sources, including research support from government agencies (e.g., NIH), foundations, device manufacturers and/or pharmaceutical companies. Research funding should be disclosed by the principal or named investigator even if your institution receives the grant and manages the funds.
EE	Employee, Executive Role Hired to work in an executive role for compensation or received a W2 from a company.
EO	Owner of Company Ownership or controlling interest in a company, other than stock.
SO	Stock Options Stock options in a private or public company.
PS	Equity/Stock Holder – Private Corp (not listed on the stock exchange) Equity ownership or stock in privately owned firms, excluding mutual funds.
US	Equity/Stock Holder – Public Corp (listed on the stock exchange) Equity ownership or stock in publicly traded firms, excluding mutual funds.
I	Independent Contractor Contracted work, including contracted research.

Financial Disclosures

Disclosure list contains individual's relevant disclosures with ineligible companies.
All relevant financial relationships have been mitigated.

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AbbVie: S
Hoffman La Roche, Ltd.: C
Kriya: C

Anita Agarwal MD

None

Thomas A Albini MD

Adverum Biotechnologies: C
Apellis Pharmaceuticals, Inc.: C
Applied Genetic Technologies Corp.: C
Bausch + Lomb: C
Beaver-Visitec International, Inc.: C
Clearside Biomedical, Inc.: C
EyePoint Pharmaceuticals: C
Genentech: C
Mallinckrodt Pharmaceuticals: C
Novartis, Alcon Pharmaceuticals: C
Regenxbio: C

Michael M Altaweel MD

Aura Biosciences, Inc.: S
Opsis: C
Regenxbio: S

Rajendra S Apte MD PhD

Delavie Biosciences: C
EdenROC Sciences: PS
Liberty Biosecurity: C
Metro International: P,PS
Mobius Therapeutics, LLC: P,PS
Mylan: C
QBio: C,P,US
Roche Pharmaceuticals: C

J Fernando Arevalo MD PhD FACS

AbbVie: C
Alimera Sciences, Inc.: C
DORC International, bv/Dutch
Ophthalmic, USA: C
EyePoint Pharmaceuticals: C
Genentech: C
Théa Laboratories: C
Topcon Medical Systems, Inc.: S

Elizabeth A Atchison MD

None

Robert L Avery MD

4DMT: C
Adverum: C,US
Alcon Laboratories, Inc.: C,US
Alderya Therapeutics, Inc.: US
Allergan, Inc.: C
Amgen, Inc.: C
Apellis Pharmaceuticals, Inc.: C,US
Asclex: C
Aviceda: C,SO
Bausch + Lomb: C
Cardinal Health: C
Clearside Biomedical, Inc.: C
Coherus: C
EyePoint Pharmaceuticals: C,US
Forwardvue: C,SO
Genentech: C,L,S
Glaukos Corp.: C,US
InFocus Capital Partners: C,PS
Ingenia: C,SO
Iveric Bio: US
KYS Vision: C,SO
Notal Vision, Inc.: C
Novartis: C,US
NVASC, Inc.: C,PS
Ocular Therapeutix: C
Ocuterra: C
Outlook: C,US
Oyster Point Pharma: C
Pr3vent, Inc.: C
Pulsmedica: C
Regeneron Pharmaceuticals, Inc.: US
Regenxbio: C,S
Replenish, Inc.: C,P,PS
ReVana: C,PS
Santen, Inc.: C
Tenpoint Therapeutics: C
Verana Health: PS
Vial: C
Visionary Ventures: C,PS

Carl C Awh MD

Adverum Biotechnologies: S
Apellis Pharmaceuticals, Inc.: S
ArcticDx, Inc.: PS
Bausch + Lomb: C
Carl Zeiss Meditec: C
Genentech: C,S
GlaxoSmithKline: S
Hoffman La Roche, Ltd.: S
Kodiak Sciences: S
Merck & Co., Inc.: S
Ophthotech Corp.: S
PanOptica: S
Regeneron Pharmaceuticals, Inc.: S
Stealth Biotherapeutics: S

Sophie J Bakri MD

AbbVie: C
Adverum: C
Alcon Pharmaceuticals, Ltd.: C
Alimera Sciences, Inc.: C
Allergan, Inc.: C
Apellis Pharmaceuticals, Inc.: C
Carl Zeiss Meditec: C
EyePoint Pharmaceuticals: C
Genentech: C
Ilumen: C
Iveric Bio: C
Kala Pharmaceuticals, Inc.: C
Neurotech: C
Novartis Pharmaceuticals: C
Outlook Therapeutics: C
Pixium Vision: C
Regeneron Pharmaceuticals, Inc.: C
Regenxbio: C, S
ReVana: SO
Roche Pharmaceuticals: C
VoxelCloud: SO

Mark R Barakat MD

Abbvie: C
 Adverum Biotechnologies: C,S
 Alcon Laboratories, Inc.: C,L
 Alimera Sciences, Inc.: C
 Allegro Ophthalmics, LLC: C
 Allergan, Inc.: C
 Annexon: S
 Apellis Pharmaceuticals, Inc.: C,L
 Arctic Vision: L
 Bausch + Lomb: C,L
 Biogen MA, Inc.: C
 Clearside Biomedical, Inc.: C,S
 Coherus Biosciences: C
 EyePoint Pharmaceuticals: C,S
 Genentech: C,L,S
 Graybug: C,S
 Gyroscope Therapeutics: S
 Hoffman La Roche, Ltd.: C,S
 Iveric Bio: C,L
 Kodiak Sciences: C,S
 NeuBase: US
 NeuroTech: C
 Novartis Pharma AG: C,L,S
 Ocular Therapeutix: C
 Oculis: S
 Opthea US Limited: C,S
 Outlook Therapeutics: C
 Oxular: S
 Oxurion: US,S
 Palatin Technologies: C
 Regeneron Pharmaceuticals, Inc.: C,L
 Regenxbio: C,S
 ReNeuron: S
 RevOpsis: C,PS
 Ribomic: S
 Stealth Biotherapeutics: S
 Unity Biotechnology: S

Caroline R Baumal MD

Apellis Pharmaceuticals, Inc.: EE,US
 DORC International, bv/Dutch
 Ophthalmic, USA: C
 Genentech: C
 Ocuphire Pharma, Inc.: C
 Ocuterra Therapeutics: C
 Ora: C

Audina Berrocal MD

AGTC: C
 Alcon Laboratories, Inc.: C
 Allergan, Inc.: C
 Carl Zeiss Meditec: C
 DORC International, bv/Dutch
 Ophthalmic, USA: C,L
 Oculus Surgical, Inc.: C
 ProQR Therapeutics: C
 Regenxbio: C

Maria H Berrocal MD

Alcon Laboratories, Inc.: C,L
 Genentech: C,L
 Quantel Medical: L

Jesse L Berry MD

Elsevier: P
 Provisional patent PCT US19/26221: P
 Springer: P
 UpToDate, Inc.: P

Robert B Bhisitkul MD

Feliqs: C
 Genentech: S
 Oculinea: C,SO,P
 Outlook Pharma: C
 Regenxbio: S
 Rezolute: C
 RIBOMIC: C
 Salutaris: C,SO
 Unity Biotechnology: C
 Visgenx: C

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None

Barbara Ann Blodi MD

None

David S Boyer MD

4DT: C
 Adverum Biotechnologies: C
 Aerie Pharmaceuticals, Inc.: C
 Aerpio: C
 Alcon Laboratories, Inc.: C
 Alkahest: C
 Allergan, Inc.: C
 Allgenesis: C
 Amgen, Inc.: C
 Annexon: C
 Apellis Pharmaceuticals, Inc.: C
 AsclepiX Therapeutics: C
 Bausch + Lomb: C
 Bayer Healthcare Pharmaceuticals: C
 Biogen International GmbH: C
 BioMotiv: C
 BioTime, Inc.: C
 Boehringer Ingelheim: C
 Cell Cure: C
 Chengdu Kanghong Biotec: C
 Clearside Biomedical, Inc.: C
 Coda Therapeutics, Inc.: C
 Daiichi Sankyo Co. Ltd.: C
 Duet: C
 Everads Therapy, Ltd.: C
 EyePoint Pharmaceuticals: C
 Galimedix Therapeutics, Inc.: C
 Genentech: C

GenSight Biologics: C
 Glaukos Corp.: C
 GrayBug Vision: C
 Horizon Healthcare Group: C
 Iconic Therapeutics, Inc.: C
 InflammX: C,SO
 Interface Biologics, Inc.: C
 Ionis: C
 Iveric Bio: C
 Jcyte: C
 Kala Pharmaceuticals, Inc.: C
 Lumithera: C
 Nanoscope: C
 Neurotech USA: C
 NGM Biopharma: C
 NGM: C
 Notal Vision, Inc.: C
 Novartis Pharma AG: C
 Novartis Pharmaceuticals: C
 Novartis, Alcon Pharmaceuticals: C,S
 Ocugen, Inc.: C,SO
 Ocular Therapeutix: C,S
 Ocuphire Pharma Inc.: C
 Opthea: C
 Optos, Inc.: C
 Optovue, Inc.: C
 Ora, Inc.: C
 Orbit Biomedical: C
 Oxurion: C
 Ray Vision, Inc.: C
 RecensMedical, Inc.: C
 Regeneron Pharmaceuticals, Inc.: C
 Regenxbio: C
 Regulus Therapeutics: C
 Samumed, LLC: C
 Santen, Inc.: C
 SciFluor: C
 Semathera: C
 Smilebiotek: C
 Stealth Biotherapeutics: C
 Sun Pharmaceutical Industries: C
 Taiwan Liposome Company: C
 Théa: C
 ThromboGenics: C
 Unity: C

Neil M Bressler MD

Bayer Healthcare Pharmaceuticals: S
 Biogen MA, Inc.: S
 Boehringer Ingelheim: S
 Novartis Pharmaceuticals: S
 Regeneron Pharmaceuticals, Inc.: S
 Roche Pharmaceuticals: S
 Samsung Bioepis: S

Susan B Bressler MD

Amgen, Inc.: C
 Bayer Healthcare Pharmaceuticals: S
 Biocon: S
 Biogen MA, Inc.: S
 Boehringer Ingelheim: S
 Eye Point: S
 Genentech: S
 Merck & Co., Inc.: S
 Mylan: S
 Notal Vision, Inc.: S
 Novartis, Alcon Pharmaceuticals: S
 Regeneron Pharmaceuticals, Inc.: S

David M Brown MD

4DMT: C
 Adverum: C,S
 AGTC: C
 Alderya: S
 Alexion Pharmaceuticals, Inc.: C,S
 Alimera Sciences, Inc.: S
 Alkahest: S
 Allergan, Inc.: C,S
 Amgen, Inc.: S
 Annexon: C,S
 Apellis Pharmaceuticals, Inc.: C,S
 Aura Biosciences, Inc.: S
 Bayer Healthcare Pharmaceuticals: C,S
 Biogen MA, Inc.: C
 Boehringer Ingelheim: C,S
 Boston Image Reading Center: S
 Carl Zeiss, Inc.: S
 Celltrion, Inc.: C
 Chengdu Kanghong Pharmaceutical: C
 Clearside Biomedical, Inc.: C,S
 Coherus Biosciences: C
 Eyepoint: S
 Gemini Therapeutics, Inc.: C,S
 Genentech: S
 Glaukos Corp.: C
 Graybug: S
 Gyroscope: S
 Heidelberg Engineering: C
 Ionis: S
 Irenix: S
 Iveric Bio: C,S
 Kodiak Sciences, Inc.: C,S
 Lineage Cell Therapeutics: C
 Lowery Medical Research Group: S
 Lumithera: S
 Molecular Partners AG: C
 Nanoscope: S
 Neurotech: S
 NGM: S
 Novartis, Alcon Pharmaceuticals: C,S
 Ocular Therapeutix: C,S
 Ocuphire Pharma, Inc.: S
 OHR Pharmaceutical, Inc.: C,S
 OIRRC: S

Ophthotech Corp.: S
 Opthea: S
 Optos, Inc.: C,P,S
 Oxurion: S
 Oyster Point Pharma: S
 Ray Therapeutics, Inc.: C
 Regeneron Pharmaceuticals, Inc.: C,S
 Regenix Bio: S
 Retina Consultants of America: PS
 Retinai Medical AG: C
 Samsung: C,S
 Sandoz: S
 Santen, Inc.: S
 SciNeuro Therapeutics, Inc.: C
 Senju Pharmaceutical Co., Ltd.: C,S
 Smilebiotek Zhuhai Limited: C
 Stealth Biotherapeutics: C,S
 Unity: S
 Verseon: C
 Xbrane: S

John P Campbell MD MPH

Boston AI Labs: C
 Genentech: S
 Siloam Vision: EO

Peter A Campochiaro MD

Allegro Ophthalmics, LLC: SO
 AsclipiX: C,S
 Ashvattha Therapeutics: C,S
 Bausch + Lomb: C
 Catawba Research: C
 Celanese: C,S
 Clearside Biomedical, Inc.: C
 Cove Therapeutics: C,PS,S
 ExgenesisBio: C,S
 Exonate: C
 Genentech: C,S
 Graybug Vision: SO
 Mallinckrodt Pharmaceuticals: S
 Merck & Co., Inc.: C
 Novartis, Alcon Pharmaceuticals: C
 Oxford BioMedica UK, Ltd.: S
 Perfuse: C
 Regeneron Pharmaceuticals, Inc.: C,S
 Regenxbio: S
 Roche Pharmaceuticals: C,S
 Wave Life Sciences: C

Antonio Capone Jr MD

Allergan, Inc.: C
 Aura Biosciences, Inc.: S
 Caeregen: P,PS
 Genentech: S,C
 Ionis Pharmaceuticals, Inc.: S
 Iveric Bio: S
 NeoLight: P,PS
 Novartis Pharmaceuticals: S
 Regeneron Pharmaceuticals, Inc.: S

Colleen M Cebulla MD PhD

None

Usha Chakravarthy PhD MBBS

Adverum: C
 Apellis Pharmaceuticals, Inc.: C
 Boehringer Ingelheim: C
 Isarna: C
 Iveric Bio: C
 Roche Diagnostics: C

R V Paul Chan MD MBA

Alcon Laboratories, Inc.: C
 Genentech: C
 National Institutes of Health: S
 Ocular Therapeutix: C
 Siloam Vision: EO

Margaret A Chang MD

Allergan, Inc.: S
 Genentech: C
 Iveric Bio: C
 Mylan: S
 NGM: S
 Novartis Pharma AG: S
 OcuTerra: S
 Opthea US Limited: S
 Regeneron Pharmaceuticals, Inc.: S
 Regenxbio: C

Stanley Chang MD

Alcon Laboratories, Inc.: L
 Genentech: C

Roomasa Channa MD

None

Steven T Charles MD

Alcon Laboratories, Inc.: C,P

Gemmy Chui Ming Cheung MB BChir FRCOphth

Allergan, Inc.: L
 Avirmax: SO
 Bayer Healthcare Pharmaceuticals: C,L,S
 Boehringer Ingelheim: C,S
 Carl Zeiss Meditec: S
 Janssen Pharmaceuticals, Inc.: C
 Novartis, Alcon Pharmaceuticals: C,L,S
 Roche Diagnostics: C
 Topcon Medical Systems, Inc.: S

Emily Y Chew MD

None

Jay K Chhablani MBBS

AbbVie: L
 AcuViz: SO
 Allergan, Inc.: L
 Erasca: C
 Novartis Pharma AG: C
 Ocular Therapeutix: US
 Salutaris: C

Michael F Chiang MD

None

David R Chow MD

Alcon Laboratories, Inc.: C
 Aviceda: PS
 Bayer Healthcare Pharmaceuticals: C,L
 Roche Diagnostics: C

W Lloyd Clark MD

Notal Vision, Inc.: C

Karl G Csaky MD

AbbVie: C
 Adverum Biotechnologies: C
 Annexon Biosciences: C,S
 EyeBio: C
 Genentech: C,S
 Gyroscope Therapeutics: S
 Heidelberg Engineering: C
 Hoffman La Roche, Ltd.: C
 Johnson & Johnson: C
 Merck & Co., Inc.: C
 NGM Biopharmaceuticals: C,S
 Novartis Pharma AG: C,S
 Ocular Therapeutix: C
 Regeneron Pharmaceuticals, Inc.: C
 Ribomic: C
 TenPoint Therapeutics: C

Donald J D'Amico MD

Alcon Laboratories, Inc.: C

Dilsher S Dhoot MD

Alimera Sciences, Inc.: C
 Allergan, Inc.: C
 Apellis Pharmaceuticals, Inc.: C
 Bausch + Lomb: C
 Bayer Healthcare Pharmaceuticals: C
 Coherus Biosciences: C
 EyePoint Pharmaceuticals: C
 Genentech: C
 Hoffman La Roche, Ltd.: C
 Ionis Pharmaceuticals: C
 Iveric Bio: C
 Ocular Therapeutix: C
 Outlook Therapeutics: C,PS
 Regeneron Pharmaceuticals, Inc.: C
 Regenxbio: C
 Vortex Surgical: PS

Diana V Do MD

Alimera Sciences, Inc.: C
 Apellis Pharmaceuticals, Inc.: C
 Belite Bio: C
 Boehringer Ingelheim: C,S
 Genentech: C
 Iveric Bio: C
 Kodiak Sciences, Inc.: C,US
 Kriya Therapeutics: C
 Regeneron Pharmaceuticals, Inc.: C,S

Kimberly A Drenser MD PhD

Caeregen Therapeutics: EO
 Neolight: PS

Jay S Duker MD

Aura Biosciences, Inc.: I
 EyePoint Pharmaceuticals: EE,US,SO
 Hubble Therapeutics: C

Jacque L Duncan MD

AbbVie: S
 Acucela, Inc.: S
 AGTC: C
 Biogen MA, Inc.: S
 Cone Sight: C
 DTx Therapeutics: C
 Editas: C
 Eyevensys: C
 Gyroscope Therapeutics: C
 Helios: C
 Nacuity: C
 ProQR Therapeutics: C
 PYC Therapeutics: C
 SparingVision: C
 Spark Therapeutics, Inc.: C
 Vedere Bio: C

Justis P Ehlers MD

Adverum: C,S
 Aerprio: C,S
 Alcon Laboratories, Inc.: C,S
 Allegro Ophthalmics, LLC: C
 Allergan, Inc.: C,S
 Apellis Pharmaceuticals, Inc.: C
 Bioptigen, Inc.: P
 Boehringer Ingelheim: C,S
 Carl Zeiss Meditec: S,C
 Genentech: C,S
 Iveric Bio: C,S
 Janssen Pharmaceuticals, Inc.: C
 Leica Microsystems: P
 Novartis Pharma AG: C,S
 Regeneron Pharmaceuticals, Inc.: C,S
 Regenxbio: C
 Roche Pharmaceuticals: C,S
 Stealth Biotherapeutics: C,S
 Thrombogenics: C,S

Dean Elliott MD

Alcon Laboratories, Inc.: C
 Alderya Therapeutics, Inc.: C,P,US
 Allergan, Inc.: C
 Apellis Pharmaceuticals, Inc.: C
 Asclepix: C
 Clearside Biomedical, Inc.: C
 Cocoon Biotechnology: C,SO
 DORC International, bv/Dutch
 Ophthalmic, USA: C
 EyeBio: C
 GelMedix: C
 Genentech: C
 InGel: C,SO
 Neurotech USA: C,S
 Pykus Therapeutics: C,PS
 RetMap: C,PS
 Unity Biotechnology: S

Anna L Ells MD

None

Abigail T Fahim MD PhD

Janssen Pharmaceuticals, Inc.: C

Lisa J Faia MD

AbbVie: L
 Allergan, Inc.: C,L
 EyePoint Pharmaceuticals: C,L
 Genentech: C,L
 Mallinckrodt Pharmaceuticals: C

Amani Fawzi MD

3helix: C
 Boehringer Ingelheim: C,S
 Medical Conference Planning
 International: L
 Regeneron Pharmaceuticals, Inc.: C
 Regenxbio: C
 Roche Pharmaceuticals: C
 Vindico Medical Education: L

Philip J Ferrone MD

Allergan, Inc.: C
 Apellis Pharmaceuticals, Inc.: C,S
 ArcticDx, Inc.: PS,SO
 Genentech: C,S
 Gyroscope Therapeutics: S
 Northwell Health: E
 Regeneron Pharmaceuticals, Inc.: S

James C Folk MD

Digital Diagnostics: PS

Jasmine H Francis MD

None

K Bailey Freund MD

Carl Zeiss Meditec: C
 Heidelberg Engineering: C
 Nidek, Inc.: C
 Novartis Pharma AG: C
 Regeneron Pharmaceuticals, Inc.: C

Sunir J Garg MD FACS

Allergan, Inc.: C
 Apellis Pharmaceuticals, Inc.: S
 Bausch + Lomb: C
 Boehringer Ingelheim: C,S
 Coherus: C
 Johnson & Johnson: C
 Kodiak: S
 Merck Manual: C
 NGM Bio: S
 Regeneron Pharmaceuticals, Inc.: S

Manjot K Gill MD

Genentech: C
 Regeneron Pharmaceuticals, Inc.: C

Justin Gottlieb MD

None

Robyn H Guymer MBBS PhD

Apellis Pharmaceuticals, Inc.: C
 Bayer Healthcare Pharmaceuticals: C
 Genentech: C
 Hoffman La Roche, Ltd.: C
 Janssen Pharmaceuticals, Inc.: C
 Novartis Pharma AG: C
 Ocular Therapeutix: C

Julia A Haller MD

Aura Biosciences, Inc.: C
 Bionic Sight: C
 Bristol Myers Squibb: US
 Eyenovia, Inc.: US
 Lowy Medical Research Institute: C
 Opthea: US
 Outlook Therapeutics: US
 Regeneron Pharmaceuticals, Inc.: C
 Seeing Medicine: C

J William Harbour MD

Aura Biosciences, Inc.: C
 Castle Biosciences, Inc.: C
 Immunocore: C
 Washington University In St. Louis: P

Mary Elizabeth Hartnett MD FACS

Knights Templar Eye Foundation, Inc.: C

Lippincott Williams & Wilkins: P
 Patent: P
 Regeneron Pharmaceuticals, Inc.: C,S

Sohail J Hasan MD PhD

None

Tarek S Hassan MD

Alcon Laboratories, Inc.: C
 Allergan, Inc.: C
 Apellis Pharmaceuticals, Inc.: C
 Aviceda Therapeutics: EE,PS
 Bayer Healthcare Pharmaceuticals: C
 Beaver-Visitec International, Inc.: C
 Carl Zeiss Meditec: C
 Genentech: C
 Hoffman La Roche, Ltd.: C
 ImprimisRx: C
 Iveric Bio: C
 Katalyst Surgical, LLC: C,P
 Novartis Pharmaceuticals: C
 Ocugenix: C
 Oculus Surgical, Inc.: C,P
 Ocutrx Vision Technologies, LLC: C
 Pykus Therapeutics: C
 SurgiCube International B.V.: C
 Vitreq B.V.: C

Jeffrey S Heier MD

4DMT: C
 Abpro: C
 Adverum: C,US
 Affamed: C
 AGTC: C
 Akouos: C
 Alderya Therapeutics, Inc.: US
 Allegro Ophthalmics, LLC: C,SO
 Annexon: C,S
 Apellis Pharmaceuticals, Inc.: C,S
 Asclepix: C,S
 Aviceda: C,SO
 Bausch + Lomb: C
 Bayer: S
 Biovisics: C
 Clearside Biomedical, Inc.: C
 Curacle: C,S
 DTx: C,SO
 Genentech: C,S
 Glaukos Corp.: C
 Gyroscope Therapeutics: C,S,SO
 Immunogen: C
 Iveric Bio: C,S
 Janssen Pharmaceuticals, Inc.: C,S
 jCyte: C,SO
 Kodiak: S
 Kriya: C

Nanoscope: C
 NGM: C,S
 Notal Vision, Inc.: C,S
 Novartis: C,S
 Ocular Therapeutix: C,US
 OcuPhire: C,SO
 Ocuterra Therapeutics: C
 Olix : C
 ONL Therapeutics: C
 Palatin Technologies: C
 Perceive Biotherapeutics: C,S
 Ray Therapeutics: C
 Regeneron Pharmaceuticals, Inc.: C,S
 Regenxbio: C,S
 Retinai Medical AG: C
 RevOpsis: C,PS
 Stealth Biotherapeutics: C,S
 Surrozen: C
 Théa : C
 Unity Biotherapeutics: C
 Vanotech: C
 Vinci: C,PS
 Vitranu: SO

Allen C Ho MD

AcuSurgical: C
 Adverum: C,S
 Aerie Pharmaceuticals, Inc.: C,S
 AGTC: C,S
 Alcon Laboratories, Inc.: C,S
 Alderya Therapeutics, Inc.: C,S
 Allergan, Inc.: C,S
 Apellis Pharmaceuticals, Inc.: S,C
 Asclepix: C,S
 Atsena: C,S
 Beaver-Visitec International, Inc.: C
 Clearside Biomedical, Inc.: C
 Covalent Medical, LLC: PS
 Dompe: C
 EyePoint: C
 Eyeevensys: C
 Genentech: C,S
 Gyroscope Therapeutics: C,US,S
 Iveric Bio: C,S
 Johnson & Johnson: C,S
 Kiora: C,US
 Lineage/BioTime: C,S
 Lumithera: S
 Nanoscope: C
 Notal: C,S
 Novartis: S
 Ocular Therapeutix: C
 ONL: C,PS
 Oxular: C
 ProQR Therapeutics: S
 Regeneron Pharmaceuticals, Inc.: C,S
 Regenxbio: C,S
 Stealth: C
 Vanotech: C

Frank G Holz MD

Acucela, Inc.: C,S
 Alexion: C
 Allergan, Inc.: C,S
 Alzheon: C
 Apellis Pharmaceuticals, Inc.: C,L,S
 Astellas: C
 Bayer Healthcare Pharmaceuticals: C,S
 Bioeq/Formycon: S
 Biogen MA, Inc.: C,L
 Boehringer Ingelheim: C
 Carl Zeiss Meditec: S
 Centervue, Inc.: C,S
 Cirrus: C
 Geuder AG: C,S
 Grayburg Vision: C
 Heidelberg Engineering: C,L,S
 Hoffman La Roche, Ltd.: C,L,S
 Iveric Bio: C,S
 Janssen Pharmaceuticals, Inc.: C
 LinBioscience: C
 NightStarx: S
 Novartis Pharma AG: C,L,S
 Optos, Inc.: S
 Oxurion: C
 Pixium: C,S
 Stealth BioTherapeutics: C

Suber S Huang MD MBA

Apellis Pharmaceuticals, Inc.: S
 Cell Sight Therapeutics: EO
 Genentech: S
 Goodsill: I
 Google: S
 Hoffman La Roche, Ltd.: S
 Horizon Therapeutics Plc: S
 i2i Innovative Ideas, Inc.: EO
 Lumithera/Diopsys: C,L,SO
 Lumoptik: US,C
 Lyons: I
 Nidek, Inc.: C
 NIH/NEI/NEHEP: C
 Novartis Pharma AG: S
 Outlook Therapeutics: C
 Regenerative Patch Technologies: C
 Regeneron Pharmaceuticals, Inc.: S
 Regenxbio: C
 Reminger: I
 Retina AI: S
 Retina Center of Ohio: EE
 Second Sight Medical Products: C
 State of Hawaii: I
 UAB Baltymas: C
 University of Southern California: S
 Volk Optical, Inc.: C,L
 Washington University: C

G Baker Hubbard MD

Siloam Vision: PS

Jean-Pierre Hubschman MD

Alcon Laboratories, Inc.: C
 Horizon Surgical: EO,EE
 University of California: P

Mark S Humayun MD PhD

Alcon Laboratories, Inc.: C,L
 ContactRx: C,PS,P
 Golden Eye/Intellimicro: P,PS
 Iridex: P
 Johns Hopkins University School of
 Medicine: P
 Lutronic: C,SO
 Outlook Therapeutics: SO,US
 Regenerative Patch Technologies: C,P,PS
 Replenish, Inc.: C,P,PS
 Vivani Medical, Inc.: P

Raymond Iezzi MD

None

Michael S Ip MD

4DMT: C
 Alimera Sciences, Inc.: C
 Allergan, Inc.: C
 Amgen, Inc.: C
 Apellis Pharmaceuticals, Inc.: C
 Biogen MA, Inc.: C
 Cell Lineage Therapeutics: C
 Clearside Biomedical, Inc.: C
 Genentech: C
 Iveric Bio: C
 Novartis Pharma AG: C
 Occurx: C
 ONL Therapeutics: C
 Regeneron Pharmaceuticals, Inc.: C
 Regenxbio: C

Douglas A Jabs MD MBA

None

Glenn J Jaffe MD

4DMT: C
 Adverum: C
 Annexon: C
 EyePoint Pharmaceuticals: C
 Hoffman La Roche, Ltd.: C
 Iveric Bio: C
 Neurotech USA: C
 Novartis Pharma AG: C

Mark W Johnson MD

Amgen, Inc.: C
 Apellis Pharmaceuticals, Inc.: S
 Aura Biosciences, Inc.: C

William J Johnson, MD

None

Kazuaki Kadonosono MD

None

Peter K Kaiser MD

Allegro Ophthalmics, LLC: C,SO
 Allergan, Inc.: C
 Annexon: C
 Applied Genetic Technologies Corp.: C
 Aviceda: C
 Bausch + Lomb: C
 Bayer Healthcare Pharmaceuticals: C,L
 Biogen MA, Inc.: C,L
 Boehringer Ingelheim: C
 Clearside Biomedical, Inc.: C
 Coherus Biosciences: C
 Eyevensys: C
 Formycon: C
 Galimedix Therapeutics, Inc.: C
 Irenix Medical, Inc.: C
 Iveric Bio: C
 jCyte: C
 Kala Pharmaceuticals, Inc.: C
 Nanoscope: C
 Novartis Pharmaceuticals: C,L
 Ocular Therapeutix: C,SO
 Oculis: C
 Ocuphire: C,SO
 OcuTerra: C
 Oxurion: C
 Regeneron Pharmaceuticals, Inc.: C,L
 Regenxbio: C
 Stealth Biotherapeutics: C
 Théa: C

Richard S Kaiser MD

Genentech: C
 Regeneron Pharmaceuticals, Inc.: C

Christine Nichols Kay MD

4D Therapeutics: S
 AGTC: C,S
 Alkeus: S
 Ascidian: C
 Atsena Therapeutics: C,SO
 Biogen MA, Inc.: S
 Gyroscope Therapeutics: S
 Iveric Bio: S
 Kiora: C,SO
 Meiragtx: S
 Novartis Pharma AG: C
 Opus: C
 ProQR Therapeutics: S
 Regenxbio: S
 Spark Therapeutics, Inc.: C

Arshad M Khanani MD

Adverum: C,S
 Alkahest: S
 Allergan, Inc.: C,L,S
 Genentech: C,S
 Gyroscope Therapeutics: C,S
 Iveric Bio: C,S
 Kato Pharmaceuticals, Inc.: C
 Kodiak Sciences: C,S
 Neurotech USA: S
 NGM Pharmaceuticals: S
 Novartis Pharmaceuticals: C,L,S
 Ocular Therapeutix: S
 Opthea: C,S
 Oxurion (formerly ThromboGenics):
 C,S
 Polyphotonix: C
 Recens Medical: C,S
 Regenxbio: C,S

Ivana K Kim MD

Allergan, Inc.: S
 Biophytis: C
 Genentech: C
 Kodiak Sciences: C

Judy E Kim MD

Allergan, Inc.: C
 Apellis Pharmaceuticals, Inc.: C
 Bausch + Lomb: C
 Clearside Biomedical, Inc.: C
 DORC International, bv/Dutch
 Ophthalmic, USA: C
 Genentech: C
 Notal Vision, Inc.: S
 Novartis: C
 Outlook Therapeutics: C
 Regeneron Pharmaceuticals, Inc.: C

Szilard Kiss MD

Adverum: C,SO
 Apellis Pharmaceuticals, Inc.: C
 Genentech: C
 Nanoscope: C
 Neurogene: C
 Novartis Pharma AG: C
 Optos, Inc.: C
 Outlook Therapeutics: C
 Regeneron Pharmaceuticals, Inc.: C

John W Kitchens MD

Alcon Laboratories, Inc.: C
 Alimera Sciences, Inc.: C
 Allergan, Inc.: C
 Apellis Pharmaceuticals, Inc.: C
 Bayer Healthcare Pharmaceuticals: C,L
 Biogen MA, Inc.: C
 Carl Zeiss Meditec: C
 Genentech: L,C

Kodiak Area Native Association: C,SO
 Notal Vision, Inc.: C
 Optos, Inc.: C
 Outlook: C,PS
 Regeneron Pharmaceuticals, Inc.: C

Gregg T Kokame MD

Adverum: S
 Bausch + Lomb: C
 Carl Zeiss Meditec: C
 Genentech: S
 Hoffman La Roche, Ltd.: C
 Iveric Bio: S
 Novartis: S
 Regeneron Pharmaceuticals, Inc.: S
 Regenxbio: S
 Salutaris: S

Jean-Francois Korobelnik MD

Allergan, Inc.: C
 Bayer Healthcare
 Pharmaceuticals: C
 Carl Zeiss Meditec: C
 Hoffman La Roche, Ltd.: C
 NanoRetina: C
 Novartis Pharma AG: C
 Novo Nordisk: C
 THEA: C

Baruch D Kuppermann MD PhD

Allegro Ophthalmics, LLC: C,S,SO
 Allergan, Inc.: C,L,S
 Aviceda: C,SO
 EyeBio: C,SO
 Eyedaptic: C,SO
 Genentech: C,S
 Glaukos Corp.: C
 Ionis: S
 Iveric Bio: C,S
 jCyte: C,SO
 Novartis Pharmaceuticals: C,S
 Ocular Therapeutix: C
 Regeneron Pharmaceuticals, Inc.: C,S
 ReVana Therapeutics: C,SO
 Ripple Therapeutics: C
 Theravance Biopharma: C

Eleonora G Lad MD PhD

Alexion: C
 Annexon: C
 Apellis Pharmaceuticals, Inc.: C
 Broadwing Bio: C
 Hoffman La Roche, Ltd.: S
 Hoffmann La Roche: C
 Iveric Bio: C
 Janssen Pharmaceuticals, Inc.: C
 NGM Biotherapeutics: C
 Novartis, Alcon Pharmaceuticals: S
 Osanni Bio: C,PS

Perceive Bio: C
 Retrotape: C
 Théa Laboratoires: C

David R Lally, MD

Affamed Therapeutics: S
 Alderya Therapeutics, Inc.: S
 Alimera Sciences, Inc.: C,L
 Allergan, Inc.: C,L
 Annexon Biosciences: C,S
 Apellis Pharmaceuticals, Inc.: C,L,S
 Applied Genetic Technologies Corp.: C
 Chengdu Kanghong: S
 Curacle: C,S
 DelsiTech: L
 EyePoint Pharmaceuticals: C,S
 Genentech: C,S,L
 Iveric Bio: C,S
 Kodiak Sciences: S
 Laboratories Thea: C
 LMRI: S
 Mac Tel Project: S
 Neurotech USA: S
 Notal Vision, Inc.: S,C
 Novartis Pharma AG: C,L,S
 Ocuphire Pharma Inc: US,S,C
 Opthea: S,C
 Optos, Inc.: S
 Ora Inc: S
 Outlook Therapeutics: C
 Oxurion: S
 Regeneron Pharmaceuticals, Inc.: L
 Roche Pharmaceuticals: C
 Stealth Biotherapeutics: S,C

Linda A Lam MD MBA

None

Paolo Lanzetta MD

AbbVie: C
 Aerie Pharmaceuticals, Inc.: C
 Apellis Pharmaceuticals, Inc.: C
 Bausch + Lomb: C
 Bayer Healthcare Pharmaceuticals: C,L
 Biogen International GmbH: C
 Boehringer: C
 Centervue, Inc.: C
 Genentech: C
 Novartis Pharma AG: C
 Ocular Therapeutix: C
 Outlook Therapeutics: C
 Roche Pharmaceuticals: C

Aaron Y Lee MD

Amazon: S
 Boehringer Ingelheim: C
 Carl Zeiss Meditec: S
 Genentech: C
 Gyroscope Therapeutics: C
 Heidelberg Engineering: S
 iCareWorld: S
 Johnson & Johnson Vision: C
 Meta: S
 Microsoft Corp.: S
 Santen, Inc.: S
 Topcon Medical Systems, Inc.: S

Jennifer Irene Lim MD

Adverum Biotechnologies: S
 Alderya Therapeutics, Inc.: S
 Allergan, Inc.: C
 Aura Biosciences, Inc.: C
 Chengdu Kanghong: S
 Cognition Therapeutics: C
 Eyenuk, Inc.: C
 Genentech: C,S,L
 Greybug: S
 Iveric Bio: C
 JAMA Network: C
 Janssen Pharmaceuticals, Inc.: S
 Luxa: C
 NGM: S
 Novartis Pharma AG: C
 Opthea: C
 Quark Pharmaceuticals: C
 Regeneron Pharmaceuticals, Inc.: C,S
 Santen, Inc.: C
 Spring vision: S
 Stealth Biotherapeutics: S
 Taylor & Francis (CRC Press): P
 Unity: C
 Viridian: C

Phoebe Lin MD PhD

Bausch + Lomb: C

Anat Loewenstein MD

Allergan, Inc.: C
 Annxon: C
 Bayer Healthcare Pharmaceuticals: C
 Beyeonics Surgical, Ltd.: C
 Forsight Labs: C
 IQVIA: C
 Iveric Bio: C
 Johnson & Johnson Vision: C
 Nanoretina: C
 Notal Vision, Inc.: C
 Novartis Pharmaceuticals: C
 Ocuphire Pharma: C
 Ripple Therapeutics: C
 Roche Pharmaceuticals: C
 Syneos: C
 WebMD: C

Daniel F Martin MD

None

Raj K Maturi MD

AbbVie: C
 Aiviva: C
 Boehringer Ingelheim: S
 DORC International, bv/Dutch Ophthalmic, USA: C
 Eli Lilly & Company (US): S
 ForwardVue: PS
 Gemini Therapeutics, Inc.: S
 Genentech: S
 Gyroscope Therapeutics: C,S
 NGM Biopharmaceuticals, Inc.: S
 Novartis Pharma AG: C,S
 Oxurion: C
 Regenxbio: S
 Ribomic: S
 Samsung: S
 Santen, Inc.: S
 Unity Biotechnology: C,S

Colin A McCannel MD

Alderya Therapeutics, Inc.: S
 Apple Computer: US
 DORC International, bv/Dutch Ophthalmic, USA: C,L
 Genentech: S
 Regenxbio: S
 Seyhart, LLC: EO

Tara A McCannel MD

None

Stephen D McLeod MD

None

William F Mieler MD

None

Joan W Miller MD

Aptinyx, Inc.: C,US
 Ciendias Bio: PS
 KalVista Pharmaceuticals: C
 Lowy Medical Research Institute, Ltd.: S
 ONL Therapeutics, LLC: C,PS,P
 Sunovion: C
 Valeant Pharmaceuticals: P

Rukhsana G Mirza MD

None

Andrew A Moshfeghi MD MBA

Alimera Sciences, Inc.: C
 Allergan, Inc.: C
 Genentech: C,S
 Novartis Pharma AG: C,S
 Ocular Therapeutix: C,SO
 Pr3vent: C,PS
 Regeneron Pharmaceuticals, Inc.: C,S
 Valitor: C,SO,PS
 Waldo: SO,PS,C

Prithvi Mruthyunjaya MD

Alcon Laboratories, Inc.: C
 Aura Biosciences, Inc.: C
 Castle Biosciences, Inc.: C
 Genentech: C,S

Timothy G Murray MD MBA

Alcon Laboratories, Inc.: C

Zofia Ann Nawrocka MD

None

Melissa D Neuwelt MD

None

Quan Dong Nguyen MD

Bausch + Lomb: C
 Boehringer Ingelheim: C
 Genentech: C
 Kriya Therapeutics: C
 Regeneron Pharmaceuticals, Inc.: C
 Rezolute: C

Kyoko Ohno-Matsui MD

Cooper Vision: C
 Santen, Inc.: C

Lisa C Olmos MD MBA

Alcon Laboratories, Inc.: C
 Pixium Vision: C

Carolyn K Pan MD

None

Susanna S Park MD PhD

Department of Defense: I
 Greybug Vision: S
 Opthea Limited: S
 Roche Pharmaceuticals: S

Grazia Pertile MD

None

Dante Pieramici MD

4DMT: S
 Adverum: C,S
 Alimera Sciences, Inc.: S
 Annexon: S
 Apellis Pharmaceuticals, Inc.: S
 Arrowhead Pharmaceutical: C
 Clearside Biomedical, Inc.: S,C
 EyePoint: C
 Gemini International: C,S
 Genentech: C,S
 Ionis: S
 Kodiak: S
 NGM: C,S
 Novartis Pharma AG: C,S
 Ocular Therapeutic: S
 Ophthea: S,C
 Oxurion: S
 Perceive Biotech: C
 Regeneron Pharmaceuticals, Inc.: C,S
 Regenxbio: C,S
 Stealth Biotherapeutics: S
 Unity: C,S
 Valo: S

Jose S Pulido MD MS

Lagen: PS

Aleksandra V Rachitskaya MD

AGCT: S
 Alcon Laboratories, Inc.: C
 Allergan, Inc.: C
 Apellis Pharmaceuticals, Inc.: C,L,S
 Carl Zeiss Meditec: C
 Genentech: C,L,S
 IvericBio: C
 Regeneron Pharmaceuticals, Inc.: L

Carl D Regillo MD FACS

Adverum: C,S
 Alcon Laboratories, Inc.: C,S
 Allergan, Inc.: C,S
 Apellis Pharmaceuticals, Inc.: C,S
 Clearside Biomedical, Inc.: C,S
 EyePoint Pharmaceuticals: C,S
 Genentech: C,S
 Iveric Bio: C,S,US
 Kodiak Area Native Association: C,S
 Merck & Co., Inc.: C
 Notal Vision, Inc.: C
 Novartis Pharmaceuticals: C,S
 Opthea US Limited: C,S
 Regeneron Pharmaceuticals, Inc.: S
 Regenxbio: C,S
 Théa: C

Kourous Rezaei MD

Alcon Laboratories, Inc.: C

Stanislao Rizzo MD

None

Edwin Hurlbut Ryan Jr MD

Alcon Laboratories, Inc.: C,P

Srinivas R Sadda MD

4DMT: C
 AbbVie: C
 Alexion: C
 Allergan, Inc.: C
 Alnylam Pharmaceuticals: C
 Amgen, Inc.: C
 Apellis Pharmaceuticals, Inc.: C
 Astellas: C
 Bayer Healthcare Pharmaceuticals: C
 Biogen MA, Inc.: C
 Boehringer Ingelheim: C
 Carl Zeiss Meditec: C,L,S
 Catalyst Pharmaceuticals, Inc.: C
 Centervue, Inc.: C
 EyePoint: C
 Genentech: C
 Gyroscope Therapeutics: C
 Heidelberg Engineering: C,L,S
 Hoffman La Roche, Ltd.: C
 Iveric Bio: C
 Janssen Pharmaceuticals, Inc.: C
 Merck & Co., Inc.: C
 Nanoscope: C
 Nidek Incorporated: L
 Notal Vision, Inc.: C
 Novartis Pharma AG: C,L
 Optos, Inc.: C
 OTI Tx: C
 Oxurion/Thrombogenics: C
 Oyster Point Pharma: C
 Pfizer, Inc.: C
 Regeneron Pharmaceuticals, Inc.: C
 Samsung Bioepis: C
 Topcon Medical Systems, Inc.: L
 Vertex Pharmaceuticals, Inc.: C

Hani Salehi-Had MD

None

David Sarraf MD

Amgen, Inc.: C,S
 Bayer Healthcare Pharmaceuticals: C,L
 Boehringer Ingelheim: S
 Genentech: C,S
 Heidelberg Engineering: S
 Iveric Bio: C
 Novartis Pharmaceuticals: C,L
 Optovue/Visionix: C,L,S
 Regeneron Pharmaceuticals, Inc.: S
 Topcon Medical Systems, Inc.: S

Amy C Scheffler MD

Allergan, Inc.: C
 Aura Biosciences, Inc.: C,S
 Castle Biosciences, Inc.: C,S
 Genentech: C,S
 Regeneron Pharmaceuticals, Inc.: S

Ursula M Schmidt-Erfurth MD

AbbVie: C
 Apellis Pharmaceuticals, Inc.: C,S
 Boehringer Ingelheim: C
 Heidelberg Engineering: C
 Kodiak Area Native Association: S
 Novartis Pharma AG: C,S
 RetInSight: C,S
 Roche Diagnostics: C,S
 Stealth Bio Therapeutics: C
 Topcon Medical Systems, Inc.: C

Steven D Schwartz MD

Astellas: S
 Broad Center for Regenerative
 Medicine, UCLA: S
 California Institute of Regenerative
 Medicine: S
 Horizon Surgical: PS
 Nikon, Inc.: S
 Verana Health: PS

Adrienne Williams Scott MD

Alimera Sciences, Inc.: C
 Allergan, Inc.: C
 Apellis Pharmaceuticals, Inc.: C
 Bausch + Lomb: C
 DORC International, bv/Dutch
 Ophthalmic, USA: C
 EyePoint Pharmaceuticals: C
 Genentech: C,S
 Iveric Bio: C
 Regeneron Pharmaceuticals, Inc.: C

Ingrid U Scott MD MPH

Hoffman La Roche, Ltd.: C

Ankoor R Shah MDApellis Pharmaceuticals, Inc.: US
Notal Vision, Inc.: C
Regeneron Pharmaceuticals, Inc.: C
Regenxbio: C**Sumit Sharma MD**Abbvie: C
Alimera Sciences, Inc.: C
Bausch + Lomb: C
Clearside Biomedical, Inc.: C
EyePoint Pharmaceuticals: C,S
Genentech: C,S
Gilead Sciences: S
Ionis: S
Regeneron Pharmaceuticals, Inc.: C,S
Regenxbio: C
Santen, Inc.: S**Veeral Sheth MD**4DMT: S
Alimera Sciences, Inc.: C,L,S
Allergan, Inc.: S
Apellis Pharmaceuticals, Inc.: C,L
Ashvattha: S
Chengdu Kanghong: S
DRCR: S
EyePoint Pharmaceuticals: C,S
Genentech: C,L,S
Graybug Vision: C,S
Gyroscope Therapeutics: S
Ionis: S
Iveric Bio: S
Janssen Pharmaceuticals, Inc.: S
NGM Biopharmaceuticals: S
Novartis Pharma AG: C,S
OcuTerra: S
Olix Pharmaceuticals: S
Outlook: S
Recent Medical: S
Regeneron Pharmaceuticals, Inc.: S,C
Regenxbio: S
SalutarisMD,: S
SamChungDang: S
Santen, Inc.: S
Vial: C**Carol L Shields MD**Aura Biosciences, Inc.: C
Immunocore, Inc.: C
Interveen, Inc.: C
iOnctura, Inc.: C**Michael A Singer MD**Alimera Sciences, Inc.: C,S
Allergan, Inc.: C,L,S
Apellis Pharmaceuticals, Inc.: C,L,S
Aviceda: PS
Bausch + Lomb: C,L
Biogen MA, Inc.: L
Clearside Biomedical, Inc.: C,S
EyePoint Pharmaceuticals: C,L,S
Genentech: C,L,S
Inflammasome: PS
Iveric Bio: S
Kodiak Area Native Association: C,S
Mallinckrodt Pharmaceuticals: L
Nanoscope: PS
Novartis Pharma AG: C,S
Olives: C,PS
Optos, Inc.: S
Oyster Point Pharma: S
Recent Medical: S
Regeneron Pharmaceuticals, Inc.: L,S
Santen, Inc.: C
Spark Therapeutics, Inc.: C**Lawrence J Singerman MD**Alimera Sciences, Inc.: I
Alkeus: I
Apellis Pharmaceuticals, Inc.: I
Genentech: I
Ionis: I
Kodiak Sciences: I
Neurotech Pharmaceuticals: I
NGM Biopharmaceuticals: I
Novartis Pharma AG: I
OcuTerra Pharmaceuticals: I
Oxurion: I
Regeneron Pharmaceuticals, Inc.: ID**Arun D Singh MD**Aura Biosciences, Inc.: C
Immunocore: C
ISOAID: C**Rishi P Singh MD**Alcon Laboratories, Inc.: C
Apellis Pharmaceuticals, Inc.: S
Bausch + Lomb: C
Carl Zeiss Meditec: C
Genentech: C
NGM Biopharma: S
Novartis: C
Regeneron Pharmaceuticals, Inc.: C**Sobha Sivaprasad FRCS MBBS**AbbVie: C
Apellis Pharmaceuticals, Inc.: C
Bayer Healthcare Pharmaceuticals:
C,L,S
Biogen International GmbH: C
Boehringer Ingelheim: C
Eyebiotech: C
Iveric Bio: C
Janssen Pharmaceuticals, Inc.: C
Nova Nordisk: C
Novartis Pharma AG: C,L
Ocular Therapeutix: C
OcuTerra: C
Optos, Inc.: C,S
Roche Pharmaceuticals: C**Dimitra Skondra MD**Alimera Sciences, Inc.: C
Allergan, Inc.: C
Biogen MA, Inc.: C
Focuscope: C
Keywest Health: C
Lagrippereserach: C
Lumina: C
Neurodiem: C
Trinity: C**William E Smiddy MD**

None

Wendy M Smith MD

None

Lucia Sobrin MD

None

Elliott H Sohn MD

None

Richard F Spaide MDGenentech: C
Heidelberg Engineering: C
Janssen Pharmaceuticals, Inc.: C
Regeneron Pharmaceuticals, Inc.: C
Roche Diagnostics: C
Topcon Medical Systems, Inc.: C,P

Giovanni Staurengi MD

AbbVie: C
 Apellis Pharmaceuticals, Inc.: C
 Bayer Healthcare Pharmaceuticals: C
 Boehringer: C
 Carl Zeiss Meditec: L,S
 Centervue, Inc.: C,L,S
 Genentech: C
 Heidelberg Engineering: C,L,S
 Hoffman La Roche, Ltd.: C,L,S
 Iveric Bio: C
 Medscape: C,L
 Nidek, Inc.: L,S
 Novartis Pharmaceuticals: C,L,S
 Ocular Instruments, Inc.: P
 Optos, Inc.: S
 Optovue, Inc.: S
 ORA: C
 Quantel Medical: S

Jennifer K Sun MD

Adaptive Sensory Technology: S
 American Diabetes Association: I
 American Medical Association: I
 Boehringer Ingelheim: S
 Genentech: S
 Hoffman La Roche, Ltd.: S
 Janssen Pharmaceuticals, Inc.: S
 JDRF: S
 Novartis: S
 Novo Nordisk: S
 Optovue, Inc.: S
 Physical Sciences, Inc: S

**Homayoun Tabandeh MD MS
FRCP FRCOphth**

Alimera Sciences, Inc.: US
 Coherus Biosciences: US

Ramin Tadayoni MD PhD

Alcon Laboratories, Inc.: C
 Allergan, Inc.: C
 Apellis Pharmaceuticals, Inc.: C
 Bausch + Lomb: C
 Bayer Healthcare Pharmaceuticals: C
 Carl Zeiss Meditec: C
 Genentech: C
 Hoffman La Roche, Ltd.: C
 Iveric Bio: C
 KHB: C
 Moria: C
 Novartis, Alcon Pharmaceuticals: C
 Oculis: C
 Ocuterra: C
 Théa: C
 ThromboGenics, Inc., Medical Affairs:
 C

Katherine E Talcott MD

Apellis Pharmaceuticals, Inc.: C
 EyePoint: C
 Genentech: C,L
 Regenxbio: S

John T Thompson MD

Alexion Pharmaceuticals: S
 Cognition Therapeutics, LLC: S
 Dynamic Health Records/Dhrpro: PS
 Genentech: S
 Ocutrx Vision Technologies, LLC: PS

Stephen H Tsang MD PhD

Nanoscope Therapeutics Inc: C

Lejla Vajzovic MD

AGTC: S
 Alcon Laboratories, Inc.: C,S
 Alderya Therapeutics, Inc.: S
 Alimera Sciences, Inc.: C
 Allergan, Inc.: C,L
 Apellis Pharmaceuticals, Inc.: C,L
 Bausch + Lomb: C,L
 Beaver-Visitec International, Inc.: C
 Clearside Biomedical, Inc.: C
 DORC International, bv/Dutch
 Ophthalmic, USA: C
 Genentech: C
 Gyroscope: C,S
 Heidelberg Engineering: S
 Iveric Bio: C
 Janssen Pharmaceuticals, Inc.: C
 Novartis Pharma AG: C
 Ocugen: C
 Ocular Therapeutix: C,S
 Oculus Surgical, Inc.: C
 Regenxbio: C,S

Russell N Van Gelder MD PhD

None

Demetrios Vavvas MD

Drusolv: SO
 Inhibikase: C
 Olix Pharmaceuticals: C
 Sumitomo/Sunovion: C
 TwentyTwenty: C
 Valitor: PS

Victor M Villegas MD

None

Robin A Vora MD

Iveric Bio: L
 Outlook Therapeutics: C
 Paradigm Biopharmaceuticals: C

Nadia Khalida Waheed MD

AGTC: EE
 Bayer Healthcare Pharmaceuticals: S
 Carl Zeiss Meditec: C,S
 Complement Therapeutics: C
 Iolyx: C
 Johnson & Johnson: C
 Nidek, Inc.: C,S
 Novartis Pharma AG: C
 Ocuterra: C,PS
 Saliogen: C
 Stealth: C
 Topcon Medical Systems, Inc.: C

John A Wells III MD

4DMT: C,S
 Adverum: S
 Bayer Healthcare Pharmaceuticals: S
 Genentech: C,S
 Gyroscope Therapeutics: S
 Hoffman La Roche, Ltd.: S
 Iveric Bio: S
 Kodiak: S
 Opthea US Limited: S
 Regeneron Pharmaceuticals, Inc.: S
 Regenxbio: S

Christina Y Weng MD MBA

Alcon Laboratories, Inc.: C
 Alimera Sciences, Inc.: C
 Allergan, Inc.: C
 DORC International, bv/Dutch
 Ophthalmic, USA: C
 EyePoint: C
 Genentech: C
 Iveric Bio: C
 Novartis Pharma AG: C
 Opthea US Limited: C
 Regeneron Pharmaceuticals, Inc.: C
 Regenxbio: C

George A Williams MD

Caeregen Therapeutics: PS

Lihteh Wu MD

Bayer Health: C,L
 Hoffman La Roche, Ltd.: L
 Quantel Medical: C,L

Charles C Wykoff MD PhD

4DMT: C,S
 AbbVie: C
 Adverum Biotechnologies: C,S
 Aerie Pharmaceuticals, Inc.: C
 AffaMed: S
 AGTC: C
 Alcon Laboratories, Inc.: C
 Alexion: S
 Alimera Sciences, Inc.: C,S
 Alkahest: S
 Allergan, Inc.: C
 Allgenesis: S
 Alnylam Pharmaceuticals: C
 Amgen, Inc.: S
 Annexin: S
 Annexon: C,S
 Apellis Pharmaceuticals, Inc.: C,S
 Arrowhead: C
 Asclepix: S
 Bausch + Lomb: C
 Bayer Healthcare Pharmaceuticals: C,S
 Bionic Vision Technologies Pty Ltd.: C
 Boehringer Ingelheim: C,S
 Chengdu Kanghong: S
 Cholgene: C
 Clearside Biomedical, Inc.: C,S
 Curacle: C,S
 EyePoint Pharmaceuticals: C,S
 Foresite: C
 Frontera: C
 Gemini Therapeutics, Inc.: S
 Genentech: C,S
 GlaxoSmithKline: S
 Graybug Vision: S
 Gyroscope Therapeutics: C,S
 IACTA: C
 Ionis Pharmaceuticals: S
 Irenix Medical, Inc.: S
 Iveric Bio: C,S
 Janssen Pharmaceuticals, Inc.: C,S
 Kato Pharmaceuticals, Inc.: C
 Kiora: C
 Kodiak Sciences: C,S
 Kriya: C
 Lowy Medical Research Institute, Inc.: S
 Merck & Co., Inc.: C
 Nanoscope: C,S
 Neurotech USA: S
 NGM Biopharmaceuticals: C,S
 Notal Vision, Inc.: C
 Novartis Pharmaceuticals: C,S
 OccuRx: C
 Ocular Therapeutix: C,S
 Ocuphire Pharma Inc.: C,S
 OcuTerra: C,S
 Olix Pharmaceuticals: C,S
 ONL: C,SO

Ophthotech: S
 Opthea: C,S
 Oxular: C,S
 Oxurion: S
 Oyster Point Pharma: S
 Palatin Technologies: C
 PerceiveBio: C,S
 Perfuse Therapeutics: C
 PolyPhotonix: SO
 Ray Vision, Inc.: C
 RecensMedical: C,S,SO
 Regeneron Pharmaceuticals, Inc.: C,S
 Regenxbio: C,S
 Resonance: C
 Rezolute: S
 Roche Pharmaceuticals: C,S
 SamChunDang Pharm: S
 Sandoz: S
 Sanofi: C
 SciNeuro: C
 Senju Pharmaceutical Co.,Ltd.: S
 Shanghai Henlius: S
 Stealth Biotherapeutics: C
 Surrozen: C
 Suzhou Raymon: C
 Théa: C
 TissueGen: C,SO
 Unity: S
 Valo Health: C
 Verily: S
 Visgenx: SO
 Vitranu: SO
 Xbrane Biopharma: S

Steven Yeh MD

Alcon Laboratories, Inc.: C
 Bausch + Lomb: C

Glenn C Yiu MD PhD

AbbVie: C
 Adverum: C
 Alimera Sciences, Inc.: C
 Bausch + Lomb: C
 Carl Zeiss Meditec: L
 Clearside Biomedical, Inc.: S
 Endogena: C
 Genentech: C
 Gyroscope Therapeutics: C
 Intergalactic Therapeutics: C
 Iridex: L,S
 Janssen Pharmaceuticals, Inc.: C
 Myro: C
 NGM Biopharmaceutical: C
 Novartis Pharma AG: C
 Regeneron Pharmaceuticals, Inc.: C
 Théa: C
 Topcon Medical Systems, Inc.: C

Yoshihiro Yonekawa MD

Alcon Laboratories, Inc.: C
 Bausch + Lomb: C
 EyePoint: C
 Pykus: C
 Regeneron Pharmaceuticals, Inc.: C
 Versant Health: C

David N Zacks MD PhD

ONL Therapeutics: C,SO,PS,P,S

Marco A Zarbin MD PhD FACS

Aerie Pharmaceuticals, Inc.: S
 Boehringer Ingelheim: C
 Cell Cure: C
 Chengdu Kanghong Biotechnology: C
 EdiGene: C
 Genentech: C
 Hoffman La Roche, Ltd.: C
 Iduna Therapeutics: C
 Illuminare: C
 Life Biosciences: C
 Novartis, Alcon Pharmaceuticals: C,L
 NVASC, Inc.: EO
 Ophthotech Corp.: C
 Perfuse Therapeutics: C
 Rutgers University School of Medicine:
 P
 Seeing Medicines: C
 Selphagy: C
 Smilebiotech: C
 Tamarix Pharma: C
 Tenpoint: C

Martin Zinkernagel MD

Apellis Pharmaceuticals, Inc.: C
 Bayer Healthcare Pharmaceuticals: C,S
 Hoffman La Roche, Ltd.: C
 Janssen Pharmaceuticals, Inc.: C
 Novartis Pharma AG: C,US
 Oculis: C

Presenter Index

- Acharya, Nisha 94
Agarwal, Anita 92
Albini, Thomas A 94
Altaweel, Michael M 37
Apte, Rajendra S 11
Arevalo, J Fernando 27
Avery, Robert L 110
Awh, Carl C 142
Bakri, Sophie 10
Barakat, Mark S 58
Baumal, Caroline R 110
Berrocal, Audina 111
Berrocal, Maria H 51
Berry, Jesse L 46
Bhisitkul, Robert B 78
Binkley, Elaine M 50
Blodi, Barbara Ann 104
Boyer, David S 108
Bressler, Neil M 98
Bressler, Susan B 3
Brown, David 57
Capone, Antonio 118
Cebulla, Colleen M 50
Chakravarthy, Usha 53
Chan, R V Paul 118
Chang, Margaret A 91
Chang, Stanley 44
Channa, Roomasa 138
Cheung, Gemmy Chui Ming 58
Chew, Emily Y 25, 80
Chiang, Michael F 12
Chow, David R 141
Clark, W Lloyd 79
Csaky, Karl G 86
D'Amico, Donald J 44
Dhoot, Dilsher S 58
Do, Diana V 65
Duker, Jay S 78
Duncan, Jacque L 119
Ehlers, Justis P 67
Elliott, Dean 39
Ells, Anna L 118
Fahim, Abigail T 78
Faia, Lisa J 41
Fawzi, Amani 78
Francis, Jasmine H 72
Freund, K Bailey 66
Gill, Manjot K 44
Gottlieb, Justin L 28
Guymer, Robyn H 91
Haller, Julia A 96
Harbour, J William 50
Hartnett, Mary Elizabeth 115
Hasan, Sohail J 23
Heier, Jeffrey S 83, 91
Ho, Allen C 123
Holz, Frank G 68
Huang, Suber S 58
Hubbard, G Baker 118
Humayun, Mark S 58
Iezzi, Raymond 140
Ip, Michael S 33
Jabs, Douglas A 93
Jaffe, Glenn J 90
Johnson, Mark W 16
Johnson, William J 58
Kadonosono, Kazuaki 148
Kaiser, Peter K 6
Kaiser, Richard S 57
Kay, Christine Nichols 61
Khanani, Arshad M 85
Kim, Ivana K 47
Kim, Judy E 73
Kiss, Szilard 147
Kitchens, John W 36
Kokame, Gregg T 30
Korobelnik, Jean-Francois 58
Kuppermann, Baruch D 7
Lad, Eleonora G 91
Lally, David R 58
Lee, Aaron Y 132
Lim, Jennifer Irene 4
Lin, Phoebe 94
Martin, Daniel F 95
Maturi, Raj K 99
McCannel, Tara A 43
Mieler, William F 27
Miller, Joan W 14
Mirza, Rukhsana G 27
Moshfeghi, Andrew A 110
Mruthyunjaya, Prithvi 50
Murray, Timothy G 45
Nawrocka, Zofia Ann 143
Neuwelt, Melissa D 44
Nguyen, Quan Dong 131
Ohno-Matsui, Kyoko 74
Pan, Carolyn K 58
Park, Susanna S 121
Pertile, Grazia 148
Pulido, Jose S 27
Rachitskaya, Aleksandra V 107
Regillo, Carl D 129
Rizzo, Stanislao 44, 55
Ryan, Edwin Hurlbut 56
Sadda, Srinivas R 2, 134
Salehi-Had, Hani 58
Sarraf, David 82
Schmidt-Erfurth, Ursula M 135
Schwartz, Steven D 19
Scott, Adrienne Williams 59
Shah, Ankoor R 13
Sharma, Sumit 79
Sheth, Veeral 58
Shields, Carol L 49
Singer, Michael A 31
Singerman, Lawrence J 27
Singh, Arun D 50
Singh, Rishi P 27
Skondra, Dimitra 79
Smiddy, William E 51
Smith, Wendy M 94
Sobrin, Lucia 94
Sohn, Elliott H 35
Spaide, Richard F 53
Staurengi, Giovanni 1
Sun, Jennifer K 110
Tabandeh, Homayoun 145
Tadayoni, Ramin 34
Talcott, Katherine E 78
Thompson, John T 21
Tsang, Stephen H 79
Vajzovic, Lejla 112
Van Gelder, Russell N 79
Vavvas, Demetrios 79
Villegas, Victor M 114
Vora, Robin A 32
Wells, John A, III 110
Weng, Christina Y 127
Williams, George A 91
Wu, Lihteh 79
Wykoff, Charles C 63
Yiu, Glenn C 60
Yonekawa, Yoshihiro 118
Zacks, David N 79
Zarbin, Marco A 101
Zinkernagel, Martin 148