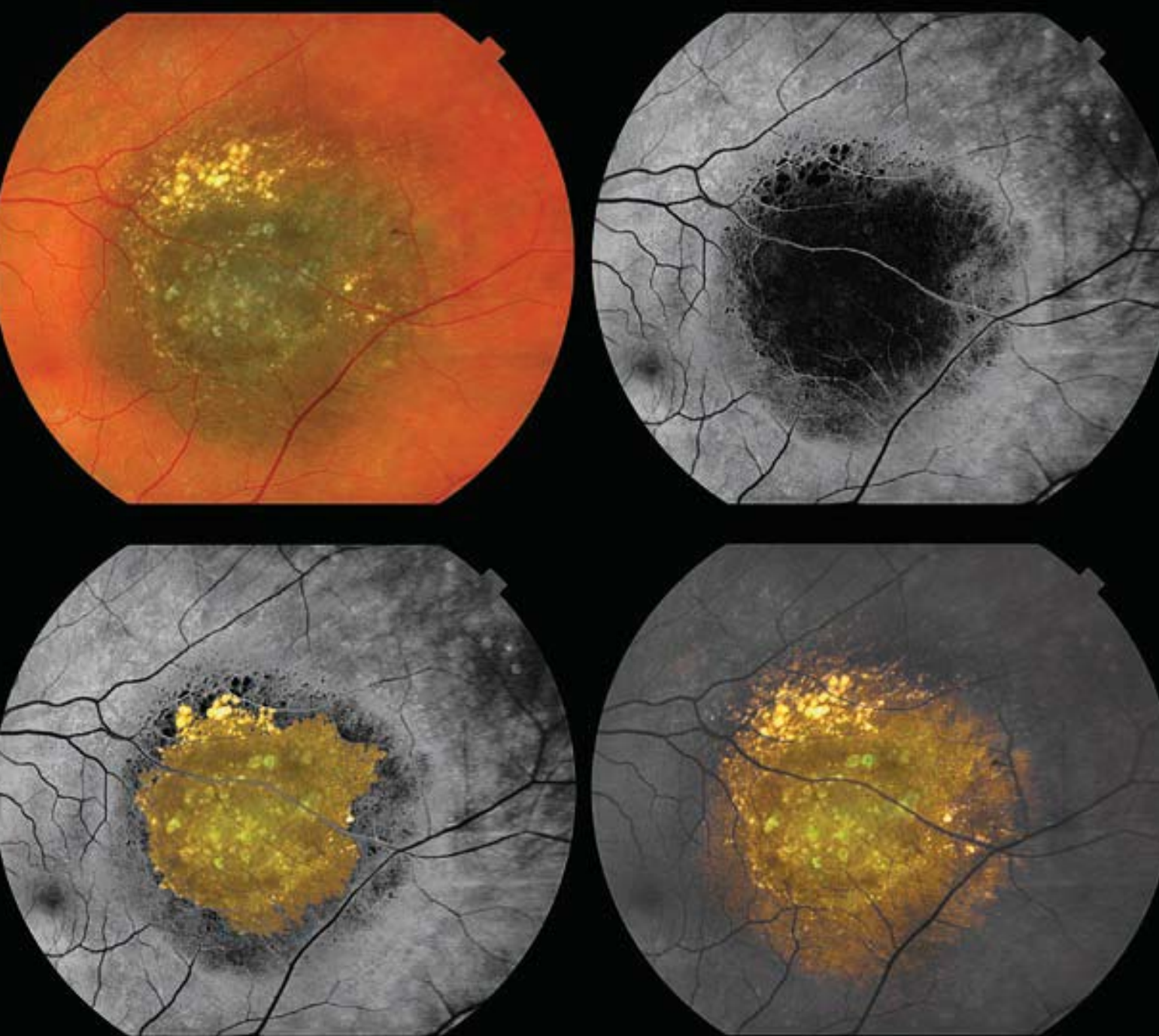
RETINA TIMES

An Official Publication of the American Society of Retina Specialists



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Retina Times (ISSN 2164-4411) is published 5 times a year by the American Society of Retina Specialists (ASRS) as a service to its membership.

The mission of the publication is to strive to be the definitive information source for ASRS members on Society news, meeting plans, socioeconomic topics, international news, and other relevant information on issues, instruments, and study updates for the practicing retina specialist.

Articles published herein are reviewed by the editor in chief and managing editor for editorial content only. The accuracy of information contained is the responsibility of the individual author. Letters and other unsolicited material are assumed to be intended for publication and are subject to rejection or editing.

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On the Cover

Choroidal nevus in a 76-year-old female. Color fundus photo taken on the TRC-50DX (Topcon Corporation, Tokyo, Japan). Image processed in Adobe Photoshop Raw, version 6.0 (Adobe Systems, Inc, San Jose, CA). Selective adjustments of saturation and luminance in narrow color bands, in combination with overall adjustments of exposure and contrast, enhance and better delineate the boundary detail and the nevus colors. Image courtesy Netan Choudhry, MD, FRCS(C). Photographer: John Golding, BA.

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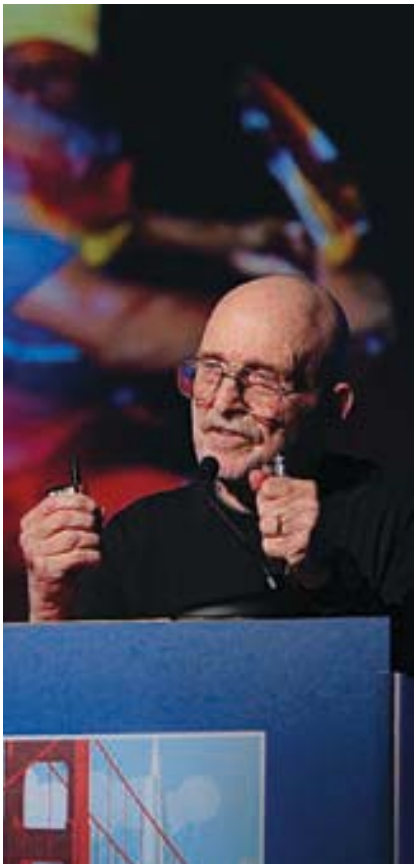

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Sunir J. Garg, MD, FACS
Editor in Chief

A Brief History of (Retina) Times

Recently, *Retina Times* Editor in Chief Mike Jumper, outgoing ASRS President Tarek Hassan, and the rest of the ASRS Board gave me the opportunity to serve you and the Society as the new editor in chief.

Mike presided over *Retina Times* for 23 issues, beginning in the spring of 2012; under his leadership, the publication grew in size and scope—the recent Annual Meeting issue was the largest ever, at 80 pages.

Mike has left an enduring legacy; he appointed 15 new section editors, creating opportunities for more new faces to get involved in this publication *by* ASRS members, *for* ASRS members. Mike and Managing Editor Susan Raef have created this current publication I love—it's beautiful to look at, intelligently laid out, teaches me useful clinical information, and helps me run a better practice.

With this issue, we have a familiar face in a new place. Mike Jumper's predecessor as editor in chief, Gaurav Shah, is back on board—this time as section editor of the International Corner in his new role as chair of the ASRS International Affairs Committee.

Mike and I would like to thank Kourous Rezaei for his dynamic leadership of the International Corner, and for his tireless work in making the Global Trends in Retina Survey a key part of the Society's international outreach. Kourous now serves as chair of the Annual Meeting Site Selection Committee—I'm sure we'll meet in some amazing places!

With this issue, Jeff Heier is stepping down as section editor of Clinical Trials: Future Pathways, which he and Chirag Shah have collaborated on since its inception in 2009. Mike Jumper and I are grateful to Jeff for helping make that section one of the highlights of *Retina Times*—and to Chirag for his continued fine work.

Over the years, so many people have left a lasting imprint on *Retina Times*. I recently was reading the Society's 25th anniversary book and got a deeper appreciation of how the publication you hold in your hands has evolved from a 4-page, black-and-white newsletter first published on copy paper in 1990. Back then, *Vitreous Society News* was produced quarterly by Society Co-founder Allen Verne and the Society's original administrator, Gerry Lewis.

In 1998, Kirk Packo suggested that the Society make a "one-time glossy publication" with the high production values for which he is known. Over the next few years, the magazine came out 2 to 3 times a year with a newer format that included more features.

In 2001, Kirk became president of the Vitreous Society, which had by then become the largest retina society in the world, with more than 1400 members. He felt the Society needed more than just a newsletter—it required a publication that engaged members by providing not only Society news, but practical content relevant to the health of our patients and to our practices.

Brett Foxman became the editor in chief of *The Vitreous Society Times,* the name of the publication until 2002, when it became *Retina Times* to reflect the change in the name of the Society to the American Society of Retina Specialists. Under the leadership of Brett and Cordie Miller, then the managing director of the ASRS, the magazine took on its artistic cover; multiple physician members joined the editorial board as section editors; and many of the columns we love to read (the ASRS X-Files, Preferences and Trends Survey results, and business articles) debuted. Brett viewed the magazine during this time as a "…mom-and-pop production. Cordie was the mom; I (Brett) was the pop."

'The publication you hold in your hands has evolved from a 4-page, black-and-white newsletter first published on copy paper in 1990.'

Tom Chang became editor in chief in 2004. Under his guidance, *Retina Times* became a standalone periodical that solicited advertising, added several new sections, and for the first time, brought on a managing editor, Steve Lenier. In many ways, Tom created the basic structure of the publication you are holding. He remained editor in chief until he was succeeded by Gaurav Shah in 2009.

Gaurav added several new sections, including Retina Genetics, Literature Roundup, and Clinical Trials: Future Pathways. He started the email blasts produced by an army of our colleagues during the Annual Meeting, and he increased the annual number of issues from 4 to 5 when he launched the Annual Meeting Issue.

It is an honor to serve as the new leader of a publication that has grown along with the Society for more than a quarter-century. *Retina Times* is mailed to nearly 3000 ASRS members in the United States and 59 other countries. We have a fantastic editorial board of 41 people, and the support of the largest organization of retina specialists in the world.

We hope to continue to bring you timely, relevant, and engaging articles that help you practice better medicine more efficiently. If you have any comments, suggestions, or ideas, please email me at sunirgarg@yahoo.com.

Financial Disclosures

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Mark S. Humayun, MD, PhD
ASRS President and
Scientific Program Chair

Stacy Kiff
ASRS Vice President
of Education

ASRS 34th Annual Meeting in San Francisco Sets New Attendance Record

Incoming ASRS President and Program Chair Mark S. Humayun, MD, PhD, welcomes attendees to the 34th Annual Meeting.

Ehab N. El-Rayes, MD, PhD; Praveen J. Patel, MBBChir, MA, FRCOphth; PAT Survey Editor Thomas W. Stone, MD; Makoto Inoue, MD; outgoing International Affairs Committee Chair Kourous A. Rezaei, MD; and J. Fernando Arevalo, MD, FACS, discuss the results of the 2016 Global Trends in Retina Survey.

The 2016 ASRS Annual Meeting, August 9-14 in San Francisco, was focused on promoting the ASRS mission: to provide a collegial open forum for education, to advance the understanding and treatment of vitreoretinal diseases, and to enhance our members' ability to provide the highest quality of patient care.

The meeting drew an unprecedented 1902 attendees from around the world. ASRS members presented 120 papers, 219 posters, 19 instructional courses, and 44 papers on demand (an enduring digital presentation format).

Expert panels presided over 19 presentations with lively discussion, including questions submitted verbally and electronically from the audience, during 6 days of rigorous scientific programming at the San Francisco Marriott Marquis. The meeting also showcased 57 films and 12 3D videos.

As president elect, it was my pleasure to organize this meeting with the help of ASRS Vice President of Education Stacy Kiff and the ASRS staff, as well as the ASRS Executive Committee. I would also like to thank the ASRS Board members and corporate partners for participating and making this meeting a tremendous success.

Mark S. Humayun, MD, PhD

34th Annual Meeting Highlights

Tuesday: Pre-Meeting Instructional Courses

Uveitis Controversies by the Bay, **Steven Yeh, MD**

The Scleral Buckle: New Light on the Lost Workhorse of Retinal Detachment Surgery, **Kamal Kishore, MD, MBBS; Raja Narayanan, MD, MBA; Christina Y. Weng, MD, MBA**

Combined Phacovitrectomy in the Era of MIVS and COMICS, **Shobhit Chawla, MS and Edmund Y.M. Wong, MBBS, MMed, FRCS**

Advanced Macular Surgery—"Tell It Like It Is ..." **Malhar Soni, DO, MS, DNB, FRCS**

Newer Advances in Vitreo-Retinal Surgeries: Tools and Techniques, **S. Natarajan, MD**

Secondary IOL Implantation and Fixation for Retina Specialists—Review of Techniques, Pros and Cons, Tips and Tricks, **Gennady Landa, MD, and Matthew P. Ohr, MD**

See all Annual Meeting video presentations

The ASRS 34th Annual Meeting video archives are now available at www.asrs.org/annual-meeting/talks.

Pneumatic Retinopexy: All You Need to Know and Beyond, **Wai-Ching Lam, MD, FRCS(C)**

Uveitis for the Retina Specialist: What Do I Do Now? **Sam Dahr, MD, and Sumit Sharma, MD**

Challenge the Masters Course, **Gabriela Lopezcarasa Hernandez, MD; Calvin E. Mein, MD; Virgilio Morales-Canton, MD; Hugo Quiroz-Mercado, MD**

Wednesday: Awards, Symposia, Expert Panels, Case Conferences

Donald J. D'Amico, MD, accepted the Gertrude D. Pyron Award from outgoing ASRS President Tarek S. Hassan, MD.

Carol L. Shields, MD, accepted the Founders Award from incoming ASRS President Mark S. Humayun, MD, PhD.

Lee M. Jampol, MD, accepted the Young Physician Section's (YPS) Crystal Apple Award from YPS Co-chairs Netan Choudhry, MD, FRCS(C), and Vincent S. Hau, MD, PhD.

Jayakrishna Ambati, MD, accepted the ASRS Presidents' Retina Young Investigator Award from outgoing ASRS Foundation President John T. Thompson, MD.

Practice Management Symposium

Moderators: Reginald J. Sanders, MD, and Trexler M. Topping, MD

Donald J. D'Amico, MD, accepts the Gertrude D. Pyron Award from outgoing ASRS President Tarek S. Hassan, MD.

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An audience member poses a question for one of the expert panels.

Survey of Patient Utilization of Web-Based Health Data Management Technology in an Outpatient Ophthalmology Practice Setting, **Robert Wong, MD**

Retina PractiCare: Coding Benchmarks for Retina Specialists, **John Thompson, MD**

AMD Neovascular 1 Symposium

Moderators: David F. Williams, MD, MBA, and David M. Brown, MD

Response to Ranibizumab of Eyes With Pigment Epithelial Detachments, Including Eyes That Developed RPE Tears: Data From the HARBOR Study, **David Eichenbaum, MD**

Gene Expression Modifications in Anti-VEGF-Treated Retinal Müller Cells, **Baruch Kuppermann, MD, PhD**

"Real-World" US Outcomes of Anti-VEGF Therapy in Neovascular AMD: Risk of Vision Loss Is Greatest in Patients With Better Baseline Visual Acuity, **Thomas Ciulla, MD, MBA**

Long-Term Results of Pro Re Nata Regimen of Aflibercept Treatment in Recurrent or Persistent Neovascular Age-Related Macular Degeneration, **Ilkay Kilic Muftuoglu, MD**

Interim Results and Key Learnings from an Ongoing Phase 2 Study of Encapsulated Cell Therapy Compared to Aflibercept in Patients With Wet AMD, **Szilárd Kiss, MD**

Treatment Response to Antioxidant Supplementation Based on *CFH* and *ARMS2* Genetic Risk Allele Number in AREDS Patients With No AMD at Baseline, **Carl Awh, MD**

AMD Neovascular Expert Panel

Moderator: Robert L. Avery, MD

Macular Atrophy in Neovascular Age-Related Macular Degeneration Eyes Treated with Monthly or Treat-and-Extend Ranibizumab: TREX-AMD Report No. 2, **Nizar Abdelfattah, MD**

Genetic Variants Associated With Anti-VEGF Drug Response in Neovascular AMD Patients in the VIEW Trial, **Nancy Holekamp, MD**

Baseline Lesion Features Are Predictive of Visual Response in Patients With Neovascular AMD Treated With Topical Squalamine and Ranibizumab, **Peter Kaiser, MD**

A Novel Anti-VEGF/Anti-Angiopoietin2 Bispecific Monoclonal Antibody for Wet Age-Related Macular Degeneration and Diabetic Macular Edema, **Pravin Dugel, MD**

Macular Surgery Symposium

Moderators: Francesco Boscia, MD, and Carl Claes, MD

ORBIT: A Phase IV Clinical Study—Lessons Learned From Patient Selection Criteria for Ocriplasmin Intravitreal Injection, **Mathew MacCumber, MD, PhD**

Differences in Surgical Performance in Peeling the ILM for Macular Holes Between Fellows in Training and Experienced Vitreoretinal Surgeons, **Robert Gizicki, MD**

T-Shaped Macular Buckling Combined With 25-Gauge Pars Plana Vitrectomy for Macular Hole, Macular Schisis, and Macular Detachment in Highly Myopic Eyes, **Marco Mura, MD**

The Evolution of Pre-Existing Epiretinal Membranes Following Cataract Extraction, **Gayatri Reilly, MD**

Macular Surgery Symposium—Rapid-Fire Papers

Moderators: Christine Gonzales, MD, and Gaurav K. Shah, MD

The OASIS Trial: Natural History of Symptomatic Vitreomacular Adhesion, **Joseph Coney, MD**

The OASIS Trial: Efficacy and Safety Outcomes in Subjects With Full-Thickness Macular Hole, **Michael Tolentino, MD**

Correlation of Intraoperative Optical Coherence Tomographic Images With Postoperative Foveal Microstructure in Eyes With Idiopathic Macular Hole, **Makoto Inoue, MD**

Macular Surgery Expert Panel

Moderator: Carl C. Awh, MD

Anatomic and Functional Outcome After Surgery for Myopic Macular Hole: Internal Limiting Membrane (ILM) Flap Technique Versus Complete ILM Removal, **Grazia Pertile, MD**

Mechanism of "Flap Closure" After the Inverted Internal Limiting Membrane Flap Technique, **Zofia Michalewska, MD, PhD**

Autologous and Allogeneic Lens Capsular Flap Transplantation in the Management of Refractory Macular Hole, **Peiquan Zhao, MD**

Autologous Retinal Transplant With and Without Choroidal Transplant in Chronic Refractory Macular Holes, **Tamer Mahmoud, MD, PhD**

Pediatric Symposium

Moderators: Antonio Capone Jr, MD, and Darius M. Moshfeghi, MD

Retinal Detachment in a Pediatric Population: A Retrospective Review of Etiology and Outcome at the Bascom Palmer Eye Institute, **Audina Berrocal, MD**

Computer-Based Image Analysis in Retinopathy of Prematurity: Are We There Yet? **J. Campbell, MD, MPH**

Fluorescein Angiographic Evaluation of Peripheral Retinal Vasculature After Ranibizumab Injection for Type I Retinopathy of Prematurity, **Clio Harper, MD**

Pediatric Symposium—Rapid-Fire Papers

Moderators: Audina M. Berrocal, MD, and Kimberly A. Drenser, MD

HIPAA and Malpractice Pitfalls in Providing Care to Infants at Risk for Retinopathy of Prematurity (ROP) for Physicians Employing Digital Imaging Technologies, **Antonio Capone, MD**

Longitudinal Changes of Peripapillary Pigmentation and Optic Nerve Area in the SUNDROP Preterm Infants: The Influence of Treatment-Warranted ROP, **Darius Moshfeghi, MD**

Bilateral Simultaneous Vitrectomy in Stage 4-5 ROP, **Sengul Ozdek, MD**

Medical Case Conference

Moderators: Neil M. Bressler, MD, and William F. Mieler, MD

Presenters: John Allen, MD; Netan Choudhry, MD, FRCS(C); Ananda Kalevar, MD, FRCS(C); Rahul Khurana, MD; Min Kim, MD; Colin McCannel, MD; Tara McCannel MD, PhD; Prithvi Mruthyunjaya, MD; Quan Nguyen, MD, MSc; Sandeep Randhawa, MD; Soraya Rofagha, MD, MPH; Christina Weng, MD, MBA; and Fatoumata Yanoga, MD

Surgical Case Conference

Moderators: Carl C. Awh, MD, and Kourous A. Rezaei, MD

Panelists: Maria H. Berrocal, MD; David R. Chow, MD, FRCS(C); Jay S. Duker, MD; Akito Hirakata, MD; J. Michael Jumper, MD; Judy E. Kim, MD; and Stanislao Rizzo, MD

Presenters: Apoorva Ayachit, MS; Boris Bajaire, MD; Jonathan Chang, MD; Vaidehi Dedania, MD; Dilraj Grewal, MD; Amir Reza Hajrasouliha, MD; Kamal Kishore, MD, MBBS; Emmanouil Mavrikakis, MD, PhD; Manish Nagpal, MD, FRCS (UK); Aleksandra Rachitskaya, MD; Jay Stewart, MD; and Homayoun Tabandeh, MD

Thursday: Symposia, Expert Panels, Instructional Courses

Imaging, Digital, and Angiography Symposium

Moderators: Jay S. Duker, MD, and Amir H. Kashani, MD, PhD

The "Double-Layer Sign" on Spectral-Domain Optical Coherence Tomography, **Giridhar Anantharaman, MS**

Evaluation of Choroidal Neovascularization Response to Anti-Vascular Endothelial Growth Factor Treatment With Quantitative OCT Angiography, **Steven Bailey, MD**

Qualitative and Quantitative Spectral Domain OCT Angiography (SD-OCTA) of Diabetic Retinopathy, **Amir Kashani, MD, PhD**

Quantitative Microscopic Validation of OCT Angiography Using Adaptive Optics Scanning Light Ophthalmoscope Fluorescein Angiography (AOSLO-FA), **Richard Rosen, MD, DSc(Hon)**

Analysis of Vascular Dilation and Tortuosity Using the ROPtool, **Kimberly Drenser, MD**

Imaging Expert Panel

Moderator: John S. Pollack, MD

Ultra-Widefield Steering-Based SD-OCT Imaging of the Retinal Periphery, **Netan Choudhry, MD, FRCS(C)**

ASRS and SAGE Publishing Launch the *Journal of VitreoRetinal Diseases*

At the Annual Meeting, Outgoing ASRS President Tarek S. Hassan, MD, announced the launch of the *Journal of VitreoRetinal Diseases (JVRD)*—a peer-reviewed Society publication that will provide unparalleled coverage of the rapidly growing universe of retina research.

JVRD will focus exclusively on publishing original basic, translational, and clinical research papers across the spectrum of vitreoretinal diseases. Submissions will include original manuscripts, reviews (both invited and submitted), letters to the editor, case series, clinical trials, research briefs, editorials, and retinal controversies—pro and con—to bring the retina community high-quality, trustworthy scientific material. These articles will be rigorously peer-reviewed and submissions are welcome from across the global retina community.

Donald J. D'Amico, MD, will serve as *JVRD*'s editor-in-chief, leading a distinguished editorial board. Dr. D'Amico is professor and chairman of ophthalmology at Weill Cornell Medical College and ophthalmologist in chief at New York-Presbyterian Hospital. He has served as president of both the Retina Society and Club Jules Gonin.

Dr. D'Amico has published over 200 scholarly works on vitreoretinal diseases and has co-edited 2 books covering comprehensive retinal themes. He serves on the boards of 4 major journals and is a distinguished national and international lecturer.

The new print and online peer-reviewed journal will publish its first articles early in 2017. For information on the submission process, visit https://mc.manuscriptcentral.com/jvrd.

Philip Rosenfeld, MD, PhD; Vincent Hau, MD, PhD; and moderators Larry Halperin, MD; and ASRS Past President Julia Haller, MD, engage in a lively discussion during the AMD Non-neovascular Symposium.

Drs. Susan and Neil Bressler answer questions from the audience during the Diabetic Retinopathy 2 Symposium.

Lessons for the High-Volume Clinic From an Initial Experience of Optical Coherence Tomography Angiography (OCTA), **Catherine Egan, FRANZCO**

Will Optical Coherence Tomography Angiography Shine When Traditional Ophthalmic Imaging Failed? **Ching Chen, MD**

Computerized Automated Characterization of Ultra-Widefield Fluorescein Angiography Features, **Justis Ehlers, MD**

Retinal Vascular Symposium

Moderators: Suber S. Huang, MD, MBA, and Anat Loewenstein, MD

Individualized Ranibizumab Treatment in Patients With RVO Leads to Visual Acuity Outcomes Consistent With a Monthly Dosing Regimen, **W. Clark, MD**

Baseline OCT Predictors in Macular Edema Due to BRVO: MARVEL Report No. 3, **Raja Narayanan, MD**

Selective Retina Therapy for Chronic Central Serous Chorioretinopathy, **Young Jung Roh, MD**

Intravitreal Aflibercept for Previously Treated Macular Edema Associated With Central Retinal Vein Occlusions: 1-Year Results From the NEWTON Study, **Rahul Khurana, MD**

Evaluation of Macular Vascular Abnormalities Identified With Optical Coherence Tomography Angiography in Patients With Various Sickle Cell Genotypes, **Adrienne Scott, MD**

Retinal Vascular Symposium—Rapid-Fire Papers

Moderators: Paul Hahn, MD, PhD, and Linda A. Lam, MD

Top 10 Pearls From the SHORE Study: Ranibizumab Treatment for Central and Branch Retinal Vein Occlusion, **Robert Johnson, MD**

Impact of Retinal Ischemia on Visual Acuity Outcomes Following Ranibizumab Treatment Over 24 Months in Patients With Retinal Vein Occlusion, **Michael Fielden, MD, FRCS(C)**

The Effect of Intravitreal Aflibercept on Perfusion Status in Patients With Retinal Vascular Disease: The ANDROID Study, **Jeffrey Heier, MD**

Diabetic Retinopathy 1 Symposium

Moderators: Mathew W. MacCumber, MD, and Judy E. Kim, MD

Deep Capillary Macular Flow Index and Degree of Vessel Density Obtained With OCT Angiography Strongly Correlate With Severity of Diabetic Retinopathy, **K. Chalam, MD, PhD, MBA, FRCS(C)**

Baseline Characteristics Associated With Changes in Diabetic Retinopathy Severity Scale (DRSS) Score: Analyses From the VISTA and VIVID Studies, **Dilsher Dhoot, MD**

Effect of Vitreomacular Adhesion on Treatment Outcomes in the Ranibizumab for Edema of the Macula in Diabetes (READ-3) Study, **Diana Do, MD**

Diabetic Retinopathy 2 Symposium

Moderators: Rajendra S. Apte, MD, PhD, and Peter K. Kaiser, MD

Prospective Trial Comparing Ranibizumab Monthly to Treat and Extend With and Without Angiography-Guided Laser for DME: TREX-DME 1 Year Outcomes, **John Payne, MD**

Vision Gains With Ranibizumab in Eyes With Diabetic Macular Edema and Retinal Nonperfusion at the Macula, **Rahul Reddy, MD, MHS**

Ranibizumab Induces Regression of Diabetic Retinopathy (DR), Prevents Retinal Nonperfusion in Patients at High Risk of Conversion to Proliferative DR, **Charles Wykoff, MD, PhD**

Optical Coherence Tomography Angiography of Diabetic Macular Edema and its Association With Anti-VEGF Treatment Response, **Young Hee Yoon, MD**

Cost-Effectiveness of Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Analysis From a DRCR.net Comparative Effectiveness Trial, **Neil Bressler, MD**

An Exploratory Analysis of Persistent Macular Thickening Following Intravitreous Ranibizumab for Center-Involved DME With Vision Impairment, **Susan Bressler, MD**

Multiplex Vitreous Cytokine Analysis From Office-Based Vitreous Aspiration, **Vaidehi S. Dedania, MD**

AKB-9778 in the Treatment of Diabetic Macular Edema: Results From the TIME-2 Study, **Arshad Khanani, MD**

The Top 10 Insights From the RIDE/RISE Trials of Ranibizumab in Patients With Diabetic Macular Edema, **Rishi Singh, MD**

Real-World Data Regarding Initial Visual Acuity In Diabetic Macular Edema (DME), **Nathan Steinle, MD**

Attendees don their 3D glasses during Saturday's Vitreoretinal Surgical Techniques instructional course, "How Do I Do It?" led by Ehab El-Rayes, MD, PhD.

Jennifer Lim, MD, presents during Saturday's Pharmacology Symposium.

Diabetic Retinopathy Expert Panel

Moderator: Tarek S. Hassan, MD

Panretinal Photocoagulation Versus Ranibizumab for Proliferative Diabetic Retinopathy: Patient-Centered Outcomes in a Randomized Clinical Trial, **Calvin Mein, MD**

Randomized Trial of PRP vs Intravitreal Ranibizumab Plus Deferred PRP for Proliferative Diabetic Retinopathy: Treatment Algorithm and Outcomes, **Andrew Antoszyk, MD**

Cost Utility Comparsion Between Panretinal Photocoagulation vs Intravitreal Ranibizumab for Proliferative Diabetic Retinopathy, **Jonathan Chang, MD**

Instructional Courses

OCT Angiography in Clinical Practice, **Sophie J. Bakri, MD**

ASRS Research and Therapeutics (ReST) Committee Symposium: Clinical Trials "Unplugged": Real, Practical Questions and Answers, **Jeffrey S. Heier, MD**

Friday: Symposia, Instructional Courses

AMD Neovascular 2 Symposium

Moderators: Jeffrey S. Heier, MD, and John T. Thompson, MD

Autologous RPE Transplantation in Cases of Long-Standing, Refractory Wet AMD, **Nikoloz Labauri, MD, FVRS**

Prospective, Randomized, Subject-Masked Evaluation of Intravitreal Sirolimus vs Anti-VEGF in Chronic Neovascular AMD With Persistent Retinal Fluid, **Raj Maturi, MD**

Comparison of Treatment Outcomes Among Subtypes of Polypoidal Choroidal Vasculopathy in a Multicenter Randomized Controlled Study (EVEREST Study), **Colin Tan, MBBS, MMed (Ophth), FRCSEd (Ophth)**

High-Dose Ranibizumab Treatment in Polypoidal Choroidal Vasculopathy: PEARL 2 Trial (Polypoidal Choroidal Vasculopathy With Intravitreal Ranibizumab), **Raymond Wee, MD**

Outcomes and Practice Preferences After Anti-VEGF Injection Endophthalmitis, **Yicheng Chen, MD**

Effects of Aflibercept in Patients With Polypoidal Choroidal Vasculopathy: One-Year Results of the VAULT Study, **Joo Eun Lee, MD**

Previous Intravitreal Therapy Is Associated With Increased Risk of Posterior Capsule Rupture During Cataract Surgery, **Aaron Lee, MD, MSCI**

Topical Dorzolamide-Timolol With Intravitreal Anti-Vascular Endothelial Growth Factor for Neovascular Age-Related Macular Degeneration: A Pilot Study, **Jason Hsu, MD**

Ocular Oncology Symposium

Moderators: Prithvi Mruthyunjaya, MD, and Rishi Singh, MD

Next-Generation Sequencing of Uveal Melanoma, **Armin Afshar, MD, MBA**

Randomized, Prospective Study of Aflibercept for Visually Significant Radiation Maculopathy—Interim Analysis, **Timothy Murray, MD, MBA**

Ocular Oncology Study Consortium (OOSC) Report No 2: Effect of Clinical and Pathologic Variables on Biopsy Complication Rates, **Amy Schefler, MD**

Ocular Oncology Symposium—Rapid-Fire Papers

Moderators: Prithvi Mruthyunjaya, MD, and Rishi Singh, MD

Correlation Between Largest Basal Diameter, Gene Expression Profile, and Survival of Patients With Posterior Uveal Melanoma Evaluated by FNAB, **Zélia Corrêa, MD, PhD**

Outcomes of Chorioretinal Biopsy Using 27-Gauge Microincision Vitrectomy, **Prithvi Mruthyunjaya, MD**

Retinal Astrocytic Hamartoma Arises Within Nerve Fiber Layer and Demonstrates Optically Empty Spaces on Spectral-Domain Optical Coherence Tomography, **Emil Anthony Say, MD**

Prognostic Choroidal Melanoma Biopsy After Proton Beam Radiotherapy, **Bertil Damato, MD, PhD, FRCOphth**

Visual Benefit of Iodine-125 Brachytherapy With Vitrectomy and Silicone Oil for Large Choroidal Melanoma: 1-to-1 Matched Case-Control Series, **Tara McCannel, MD, PhD**

AMD Non-neovascular Symposium

Moderators: Julia A. Haller, MD, and Lawrence Halperin, MD

Remote Home Monitoring of Early to Intermediate Age-Related Macular Degeneration, **Vincent Hau, MD, PhD**

Detection of Asymptomatic Neovascularization in Intermediate Age-Related Macular Degeneration Using Swept-Source Optical Coherence Tomography Angiography, **Philip Rosenfeld, MD, PhD**

Nucleoside Analogs and Derivatives as Therapies for AMD, **Jayakrishna Ambati, MD**

Severe Vision Loss After Intravitreal Injections of Autologous Adipose Tissue-Derived Stem Cells for Age-Related Macular Degeneration, **Ajay Kuriyan, MD, MSc**

Surgical Techniques and Maneuvers Symposium

Moderators: Kirk H. Packo, MD, and Stanislao Rizzo, MD

Transitioning Vitreoretinal Surgery From Microscope to Stereoscopic Display: No Negative Impact on Surgical Times or Outcomes, **Mark Barakat, MD**

The Impact of Intraoperative OCT on Vitreoretinal Surgery for Proliferative Diabetic Retinopathy: Findings From the DISCOVER Study, **Mehnaz Khan, MD**

Comparison of Ocular Aberrations Measured by Wavefront Aberrometry Before and After Vitrectomy for Floaters, **Daniel Adelberg, MD**

Primary Rhegmatogenous Retinal Detachment With Inferior Retinal Breaks Postoperative Prone Positioning Results: 1 Day vs 7 Days, **Radwan Ajlan, MBBCh, FRCS(C)**

Nonvitrectomizing Vitreous Surgery in Retinal Diseases Requiring Anti-VEGF Treatment, **Andre Principe de Oliveira, MD**

Surgical and Visual Outcomes of Pars Plana Lensectomy, With or Without Scleral Fixated Lens Implantation in Microspherophakia, **Vishal Raval, MBBS, DNB, FMRF**

Refractive Vitreoretinal Surgery: Femtosecond Laser-Assisted Cataract and Vitrectomy Surgery, **Stanislao Rizzo, MD**

27-Gauge vs 25-Gauge Vitrectomy for Different Retinal Pathologies, **Francesco Boscia, MD**

Macular Hole Surgery Assisted by Perfluorocarbon Liquids, **Virgilio Morales-Canton, MD**

A Novel Technique for IOL Fixation Utilizing Gore-Tex Suture, **Jonathan Prenner, MD**

The Removable Scleral Buckle—Back to the Future? **Paul Tornambe, MD**

Instructional Courses

RETINAWS: When the Going Gets Tough, the Tough Get Going—Challenging Cases in Vitreoretlnal Surgery, **Kourous A. Rezaei, MD**

Pediatric Vitreoretinal Surgical Techniques: An Interactive Video Panel, **Cynthia A. Toth, MD**

Saturday: Symposia, Expert Panels, Late-Breaking Abstracts, Instructional Courses

Instrumentation and Devices Symposium

Moderators: Pravin U. Dugel, MD, and Raymond Iezzi, MD, MS

Vitrectomy Infusion Control Based on Ophthalmic Artery Perfusion Pressure: A Novel Device, **Tommaso Rossi, MD, EBOD**

Sight Recovery Project for Argus II Implanted Patients Affected by Retinitis Pigmentosa, **Fabio Patelli, MD**

Instrumentation and Devices Expert Panel

Moderator: Philip J. Ferrone, MD

Digital Electro-Optical Surgical Platform for Retina Surgery as a Replacement of Operational Microscopes, **Adiel Barak, MD**

Thermal Profile of a Novel Hypersonic Vitrector (HV), **Victor Gonzalez, MD**

Engineered Biopolymer Thin-Films for Extended Intravitreal Drug Delivery: Preclinical Feasibility Studies, **Robert Bhisitkul, MD, PhD**

Argus I vs Argus II: A Comparison of Two Epiretinal Prostheses, **Mark Humayun, MD, PhD**

Diabetic Retinopathy 3 Symposium

Moderators: Vincent S. Hau, MD, PhD, and Andrew Moshfeghi, MD

Automated Diabetic Retinopathy Image Assessment Software: Study of Diagnostic Accuracy and Cost-Effectiveness of Available Systems, **Adnan Tufail, MBBS, MD, FRCOphth**

Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial, **John Wells, MD, FACS**

Automated Detection of Diabetic Retinopathy Lesions on Ultra-Widefield Pseudocolor Images, **Srinivas Sadda, MD**

Pharmacology Symposium

Moderators: Daniel F. Martin, MD, and Jonathan L. Prenner, MD

Macula Society Collaborative Retrospective Study of Ocriplasmin for Vitreomacular Traction, **Jennifer Lim, MD**

A New Biosimilar Ranibizumab for Retinal Diseases, **Alay Banker, MD**

Secondary Ocular Hypertension and the Need for Glaucoma Surgery After Dexamethasone Intravitreal Implant in Routine Clinical Practice, **Jay Stewart, MD**

Late-Phase Fluorescein Angiographic Findings Which Can Predict Capillary Dropout and Drug Treatment Which Can Lead to Capillary Preservation, **Michael Trese, MD**

Retinal Detachment Symposium

Moderators: Dean Eliott, MD, and Geoffrey G. Emerson, MD, PhD

Management of Degenerative Retinoschisis-Associated Retina Detachment, **Abdallah Jeroudi, MD**

Suprachoroidal Buckling for Retinal Detachment 4-Year Data, **Ehab N. EI-Rayes, MD, PhD**

Are We Better Than We Were 10 Years Ago? An Analysis of Retinal Detachment Outcomes, **Paul Hahn, MD, PhD**

Late-Breaking Abstracts

Moderators: Netan Choudhry, MD, FRCS(C), and Timothy G. Murray, MD, MBA

Ocular Hypertension After lntravitreal Dexamethasone Sustained-Release Implant, **Eric K. Chin, MD**

Pneumatic Vitreolysis for Effective Treatment of Vitreomacular Traction Syndrome, **Clement K. Chan, MD, FACS**

Safety and Efficacy of Razumab (Ranibizumab)—the New Biosimilar in India: Our Experience, **Srinivas Joshi, MD**

5-Year Outcomes After Initiating Anti-VEGF Therapy for Neovascular AMD in the Comparison of AMD Treatments Trials (CATT), **Daniel F. Martin, MD**

Global Trends in Retina Symposium

Moderator: Kourous A. Rezaei, MD

Instructional Courses

Vitreoretinal Surgical Techniques (How Do I Do It?) 3D Video Panel, **Ehab N. El-Rayes, MD, PhD**

Hands-On Introduction to Argus II Retinal Prosthesis Implantation, **Ninel Z. Gregori, MD**

Advances in the Treatment of Blinding Retinal Disease: Clinical Perspectives on Gene, Stem Cell, Cell-Based Rescue Therapies and Drug Delivery, **Suber Huang, MD, MBA**

Continued on page 63

Dante J. Pieramici, MD
Section Editor

Dilsher S. Dhoot, MD
Section Editor

Annual Meeting Attendees Revel in the City by the Bay

Mark Twain is rumored to have said, "The coldest winter I ever spent was a summer in San Francisco." For the ASRS 34th Annual Meeting held in the City by the Bay, this sentiment could not have been farther from the truth. The weather was downright Mediterranean—and a welcome relief for the Midwestern and East Coast retina specialists who had been fighting record heat and humidity at home.

ASRS was one of the first groups to hold an event at the newly expanded San Francisco Museum of Modern Art (SFMOMA).

SFMOMA provided a spacious venue for the opening reception.

ASRS Past President David Williams, MD, MBA; Robert Wendel, MD; Barbara Karpel Verne, MD; Linda Lam, MD, MBA; and ASRS Co-founders Allen Verne, MD, and Jerald Bovino, MD, enjoy the opening reception.

Brett Foxman, MD, Leonard Ginsburg, MD, and fellows Pooja Garg, MD, and Sundeep Kasi, MD, meet at the Fellows-in-Training Section's networking reception.

Once again, ASRS members from all over the world gathered to learn, teach, and discuss the latest advances in retinal disease management and the rapidly changing socioeconomics of medical practice today. The sunny days and cool summer nights of the streets of San Francisco served as the perfect backdrop to this meeting, and attendees enthusiastically took advantage, experiencing the diverse cultural opportunities of this unique city.

ASRS name badges were spotted all over (and at all hours) at tourist locations including Fisherman's Wharf, the Golden Gate Bridge, and even the notorious Alcatraz Island—"the Rock"—site of the former maximum-security federal prison where gangster Al Capone was confined.

Living up to the high expectations of previous meetings, the ASRS did not disappoint, hosting several social events taking full advantage of beautiful, energetic San Francisco.

Meeting attendees from all over the world gather for the International Members Reception.

Meeting attendees enjoy the gala dinner at San Francisco's historic Palace Hotel.

Revelers don glowing eyeglasses at the Umbo Lounge following the gala dinner.

On Tuesday, August 9, the ASRS welcome reception was held at the San Francisco Museum of Modern Art (SFMOMA). The museum, recently reopened following a major 3-year expansion, is home to one of the largest collections of modern art in the world. Fine wine and hors d'oeuvres helped satiate the palate as meeting attendees mingled with their ASRS friends.

The SFMOMA gallery permanent collection was on display in the exhibit halls, featuring works by many notable artists including Paul Klee, Frida Kahlo, and Mark Rothko. Among the many extraordinary pieces, *Frida and Diego Rivera* by Frida Kahlo and *Number 14, 1960* by Mark Rothko were particularly big hits with the ASRS reception attendees.

On Wednesday, August 10, the ASRS Young Physician Section hosted its luncheon at the Marriott Marquis. Here, Lee Jampol, MD, was honored with the ASRS Crystal Apple Award for his efforts in advancing the development of young retina physicians. Dr. Jampol, chair of the Diabetic Retinopathy Clinical Research Network (DRCR.net), reviewed the year 2 Protocol T data and finished with his famous tour of white-dot chorioretinal diseases.

On Thursday, August 11, the International Affairs Committee hosted a reception for retina specialists from all over the world who attended the Annual Meeting.

On Friday night, August 12, the Fellows-in-Training Section hosted a networking session for hungry fellows in need of work and seasoned, more well-fed ASRS members looking to grow their practices. This event turned out to be a hit with fellows and potential employers, each donning different color ribbons to help facilitate possible matches as members casually mingled over drinks and appetizers.

The ASRS 34th Annual Meeting concluded on Saturday, August 13, in grand style at the gala dinner held at the historic San Francisco Palace Hotel. The original 1875 Palace Hotel was demolished following a fire resulting from the 1906 San Francisco earthquake. The current Palace Hotel opened in 1909 and has hosted many notable events, including Woodrow Wilson's speeches in support of the Treaty of Versailles and the League of Nations, and the banquet marking the opening session of the United Nations.

ASRS members were wined and dined in these historic halls and then took a short stroll back to the Marriott Marquis for the annual Umbo Lounge after-hours dance party. Here members showcased their newest dance moves to a variety of contemporary tunes. The partying continued on into the late night/early morning in true ASRS fashion!

San Francisco welcomed the ASRS Annual Meeting for a memorable time with friends and colleagues. The social events allowed members to experience this hip California city while making new memories with friends. To quote another famous writer, Rudyard Kipling, "San Francisco has only one drawback—'tis hard to leave."

We look forward to next year's social events on the right coast of the United States, in Boston.

Financial Disclosures

Dr. Dhoot – REGENERON PHARMACEUTICALS, INC: Speaker, Honoraria.

Dr. Pieramici – ALLEGRO OPHTHALMICS, LLC: Investigator, Grants; ALLERGAN, INC: Investigator, Grants; GENENTECH, INC: Advisory Board, Consultant, Investigator, Grants, Honoraria; REGENERON PHARMACEUTICALS, INC: Investigator, Grants; SANTEN PHARMACEUTICAL CO, LTD: Consultant, Honoraria; THROMBOGENICS, INC: Advisory Board, Investigator, Grants, Honoraria.

The Foundation
American Society of Retina Specialists

Tarek S. Hassan, MD
President, Foundation of the ASRS

Service by Us, for Others

I am honored to write my first column as president of the Foundation of the American Society of Retina Specialists. As the immediate past president of the ASRS, I am keenly aware of the intimate, intertwined relationship between the missions of the Society and Foundation, and of the many ways they are synergistic.

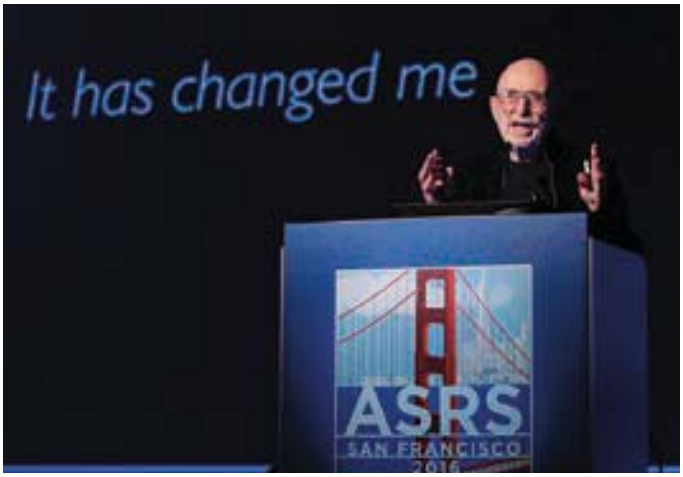
The primary mission of the Foundation is to improve the quality of life of those afflicted with retinal disease through fundraising and educational service to patients and the people who care for them. In recent years, this has been successfully done through a variety of initiatives, and with our continued growth and maturation, the Foundation now looks to increase the scope of these efforts in the coming years … and we need your help. The ASRS and its Foundation function as 2 sides of the same coin; we need contributions of time and effort from you and your ASRS colleagues to ensure both are robust and always fully functional.

Foundation initiatives were proudly on display in August at the ASRS Annual Meeting in San Francisco. At a special event, former retina specialist and now award-winning, internationally acclaimed photographer Howard Schatz, MD, shared personal insights and amazing photographs from his brilliant career with an enthralled audience. This highlight enriched us all, and we are grateful to Dr. Schatz for his contribution to the ASRS and its Foundation.

Each year, the Foundation presents the ASRS Presidents' Retina Young Investigator Award to a retina specialist under age 45 who has made outstanding contributions to retinal science during his or her early career.

This year, the Foundation had the great honor to present this prestigious award to a most deserving Jayakrishna Ambati, MD, who has had a stellar career to date and who gave a brilliant, thought-provoking talk entitled, "Solving AMD: Moving Forward by Stepping Back" during the awards ceremony. We look forward to seeing Dr. Ambati's many future contributions to our field.

Outgoing Foundation President John T. Thompson, MD (right) presents the 2016 ASRS Presidents' Young Investigator Award to Jayakrishna Ambati, MD.



Retina-specialist-turned-professional-photographer Howard Schatz, MD, captivated Annual Meeting attendees with a presentation of his award-winning photography and the philosophy behind it.

The Foundation is grateful for support of this award through a grant from Regeneron Pharmaceuticals, Inc.

Besides hosting an event at the Annual Meeting and giving the ASRS Presidents' Young Investigator Award, the Foundation engages in a variety of ongoing efforts that promote educational outreach and assistance, predominantly to our patients.

On our website, savingvision.org, retina specialists and their patients can access the Foundation's **Retina Health Series**, a collection of web pages with downloadable and printable PDF files that discuss causes, symptoms, risk factors, diagnostic testing, treatment, and prognosis of a number of retinal disorders in clearly understandable layman's terms to improve our patients' understanding of their conditions. On the same website, patients can find **low-vision apps** to use on their smartphones to better see printed material.

To further its ultimate mission of saving sight, the ASRS has, over the past several years, distributed many Foundation-funded AMD public awareness posters to member practices, senior citizen facilities, low-vision rehabilitation clinics, community health centers, and Veterans Administration facilities across the country to encourage those at risk or those with macular degeneration to be examined or seek treatment.

Going forward, the Foundation is looking to broaden its public disease awareness campaigns to reach larger audiences through a variety of media resources, social media, and associations with other philanthropic entities. As treatments for a number of significant causes of blindness improve, we hope to engage patients at the earliest possible opportunity by informing them about common retinal diseases and encouraging them to seek our attention if they have concerns or experience symptoms. We want to "get the word out" effectively and comprehensively to save as much vision as possible and maximally improve the quality of our patients' lives.

To that end, the Foundation is looking to you for help in a variety of ways. Most obviously, we want to encourage you and your ASRS colleagues to personally donate to your Society's philanthropic effort. Your tax-deductible contributions can be of any size, made at any time, be given as a recurring donation, or customized to fit your preferences.

'The ASRS and its Foundation function as 2 sides of the same coin; we need contributions of time and effort from you and your ASRS colleagues to ensure both are robust and always fully functional.'

You can also contribute to the Foundation whenever you make a purchase on Amazon.com. Rather than using Amazon.com, visit www.Smile.Amazon.com to make your purchases. There, you can register a preferred charity—select Foundation of the American Society of Retina Specialists—and then bookmark www.smile.amazon.com to make all your Amazon purchases. Prices are exactly the same as on Amazon.com. For every dollar you spend on Amazon Smile, the Foundation receives $.005. Sounds small, but the donations add up; the Foundation currently receives checks from Amazon every quarter. There is no easier way for a modern-day shopper to donate to our mission.

We also want you to talk to your colleagues and be an advocate for the Foundation with them and with other potential donating entities, such as industry supporters. We would like you to assist us in guiding the priorities of the Foundation; help us raise money and help us give it away so we can improve the lives of others.

It is our goal to build the brand of the Foundation of the ASRS so we can be most effective in our funding efforts. Many of you give to charity in a myriad of ways. Please contact me with your thoughts and ideas and become an active participant in the wonderful giving arm of your Society, the Foundation of the ASRS.

Financial Disclosures

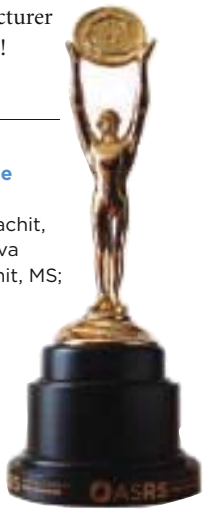
Dr. Hassan – ALCON LABORATORIES, INC: Consultant, Honoraria; ALLERGAN, INC: Advisory Board, Honoraria; ARCTICDX: Consultant, Stockholder, Stock Options; GENENTECH, INC: Advisory Board, Consultant, Honoraria; INSIGHT INSTRUMENTS, INC: Consultant, Other, Honoraria, Intellectual Property Rights; NOVARTIS, INC: Consultant, Honoraria; REGENERON PHARMACEUTICALS, INC: Advisory Board, Consultant, Honoraria; ROCHE USA: Consultant, Honoraria.

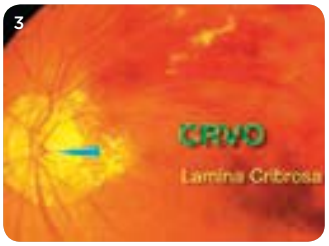
Brett T. Foxman MD
Chair, ASRS Film Festival

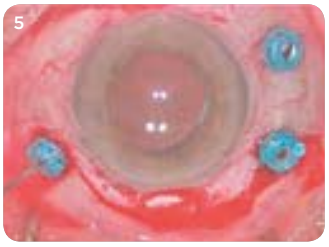
18th Annual Film Festival Spotlights Worldwide Talent

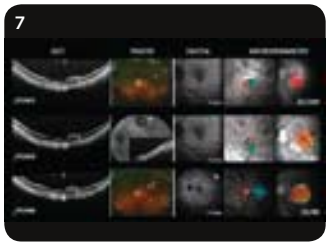
THE 2016 FILM FESTIVAL featured 59 films from countries around the world. We thank our 38 volunteer judges who devoted many hours to watching, reviewing, and grading the films for the awards presented at the Annual Meeting in San Francisco. To view the films, visit www.asrs.org/film-festival/films.

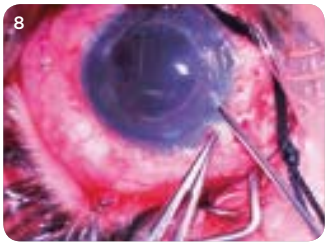
Eleven winning films earned the coveted Rhett Buckler Award, an impressive 8-pound, 24-carat-gold-plated statuette custom sculpted by RS Owens & Company in Chicago, manufacturer of the famous Oscar. Congratulations to all the winners!

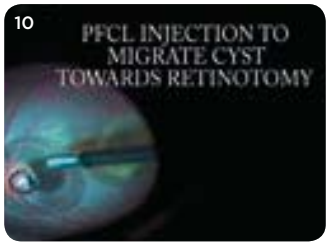


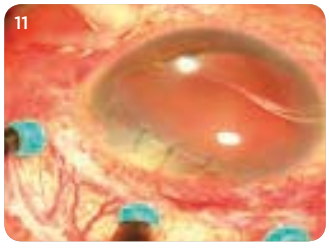












BEST OF SHOW

1 | The Evolution of Scleral Buckling: A Look at a Surgical Method Throughout the Years
Brooke LW Nesmith, MD, JD; Jeanne L. Rosenthal, MD, MPOD; Thomas O. Muldoon, MD; Seymour Fradin; Richard B. Rosen, MD, DSc (Hon); Ronald C. Gentile, MD; Vincent S. Reppucci, MD; Joseph D. Benevento, MD; Gennady Landa, MD; Aryeh L. Pollack, MD; Meenakashi Gupta, MD; Avnish Deobhakta, MD; E. Alfonso Ponce, MD; Steven A. Agemy, MD; Jessica G. Lee, MD; Fatoumata Yanoga, MD

3D VIDEO AWARD

2 | Why Digital Microscopy Will Rule the Operating Rooms of Tomorrow
Christopher Riemann, MD; Michael E. Snyder, MD

3 | Endovascular Catheter for Removing Clots in Branch Retinal Vein Occlusion
Tetsu Asami, MD, PhD

4 | Conquering the Maze of PVR
Guruprasad S. Ayachit, MBBS, MS; Apoorva Guruprasad Ayachit, MS; Srinivas Joshi, MD

5 | Star Wars Episode VIII: The Subluxated IOL Arises
Martin Charles, MD; Daniel E. Charles, MD

6 | Exoresection of Choroidal Melanoma
Bertil E. Damato, MD, PhD, FRCOphth

7 | Autologous Neurosensory Retinal Flap for Refractory Macular Holes
Dilraj S. Grewal, MD; Tamer H. Mahmoud, MD, PhD

8 | An Extreme Case of Post-Operative Complication
Wai-Ching Lam, MD, FRCS(C); Peng Yan, MD; Daniel C. Warder, MD, FRCS(C)

9 | Endoscopic View of ARGUS II Retinal Prosthesis Insertion
Flavio A. Rezende, MD, PhD; Renaud Duval, MD, FRCS(C)

10 | Subfoveal Cysticercus Removal: The Exquisite Original and the Explosive Sequel
Cyrus M. Shroff, MD; Gagan Bhatia, MBBS, DO; Charu Gupta, MBBS, MS; Daraius N. Shroff, MS, FMRF, FRCS

11 | The Agony and the Ecstasy!
Daraius N. Shroff, MS, FMRF, FRCS; Gagan Bhatia, MBBS, DO, DNB; Charu Gupta, MBBS, MS; Cyrus M. Shroff, MD

Financial Disclosures

Dr. Foxman – F. HOFFMAN-LA ROCHE AG: Investigator, Other Financial Benefit; GLAXOSMITHKLINE: Investigator, Other Financial Benefit; INVENTIVE HEALTH CLINICAL LLC: Investigator, Other Financial Benefit; OHR PHARMACEUTICAL: Investigator, Other Financial Benefit; OPHTHOTECH CORPORATION: Investigator, Other Financial Benefit; QUINTILES/JETREA: Investigator, Other Financial Benefit; REGENERON PHARMACEUTICALS, INC: Investigator, Other Financial Benefit.

WOMEN IN RETINA >>

WinR WOMEN in RETINA

Jennifer I. Lim, MD
Chair, ASRS Women in Retina Section

Women in Retina Section Hosts Events at ASRS Annual Meeting, AVTT Symposium

Women in Retina (WinR) hosted 2 events at the ASRS 34th Annual Meeting in San Francisco. Katherine High, MD, co-founder and chief scientific officer of Spark Therapeutics, Inc, presented an inspiring keynote lecture at the WinR luncheon.

Sixty WinR members gathered at a luncheon at the ASRS Annual Meeting in San Francisco. Pictured: The leadership team—Mina Chung, MD, treasurer; Judy E. Kim, MD, secretary; Jennifer I. Lim, MD, chair; Katherine High, MD, keynote speaker; Alice Lyon, MD, immediate past chair; Pauline Merrill, MD, founding member; Nancy Holekamp, MD, vice chair.

Dr. High has led pioneering bench-to-bedside studies of gene therapy for hemophilia and a series of studies that characterized the human immune response to adeno-associated virus (AAV) vectors in a variety of target tissues.

Dr. High told the story of her discovery of gene therapy for hemophilia and of her role in the development of AAV *RPE65* gene therapy for Leber's congenital amaurosis. Her talk was thought provoking, stimulating, and well received.

Also during the ASRS Annual Meeting, members presented compelling cases at the WinR case conference moderated by Caroline Baumal, MD, and Diana Do, MD.

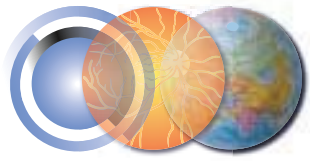
More recently, at the 15th Annual Advanced Vitreoretinal Techniques & Technology (AVTT) Symposium, Chicago-area WinR members mentored WinR fellows; WinR hosted a dinner for them at Chicago's Seven Lions Restaurant on August 24.

Financial Disclosures

Dr. Lim – ALCON LABORATORIES, INC: Consultant, Honoraria; GENENTECH, INC: Advisory Board, Speaker, Honoraria; HOSPIRA/PFIZER: Consultant, Honoraria; ICON BIOSCIENCE INC: Consultant, Honoraria; LUMENIS LTD: Consultant, Honoraria; QLT, INC: Advisory Board, Other, Unrestricted Research Grant, Honoraria; REGENERON PHARMACEUTICALS, INC: Investigator, Speaker, Grants, Honoraria; SANTEN INC: Advisory Board, Consultant, Honoraria.

Plan to Attend the WinR Winter Brunch in Chicago

Join us at Shaw's Crab House in Chicago for the WinR Winter Brunch on Sunday, January 29, 2017 (the weekend of the Retina Fellows' Forum). For more information, email Caroline Bozell at caroline.bozell@asrs.org.



Gaurav K. Shah, MD
Chair, International Affairs Committee

2016 Global Trends in Retina Survey Yields a Record 1127 Responses

In conjunction with the 18th Annual Preferences and Trends (PAT) Survey, the ASRS International Affairs Committee invited retina societies from around the world to participate in the 2016 Global Trends in Retina Survey. A total of 1127 members from 39 retina societies participated in this year's survey—the widest-reaching retina survey ever conducted.

PART 1: MEDICAL RETINA HIGHLIGHTS

Panelists

Africa/Middle East
Ehab N. El Rayes, MD, PhD
Institute of Ophthalmology
The Retina Clinic
Cairo, Egypt

Asia/Pacific
Alay S. Banker, MD
Banker's Retina Clinic
and Laser Center
Gujarat, India

Europe
José Garcia-Arumi, MD, PhD
Autonomous University
of Barcelona
Ocular Microsurgery Institute
Barcelona, Spain

Latin America
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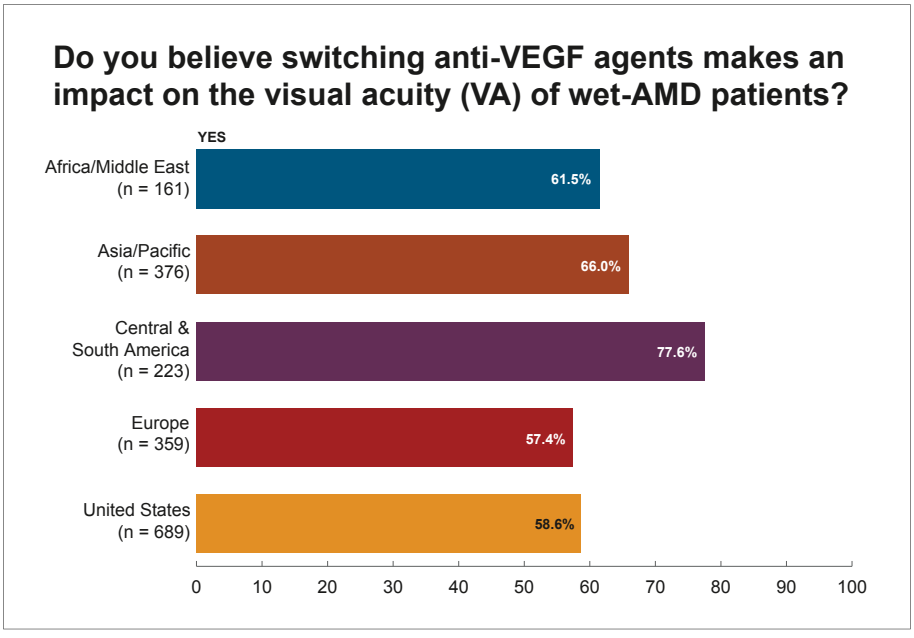
Member responses from the 39 participating retina societies were compared with those of 689 ASRS members practicing in the United States who answered the same 15 clinical questions in the 2016 PAT Survey. Here are some data highlights.

Survey responses are grouped into 5 regions for ease of analysis. We thank our thought leaders for participating in the following roundtable discussion of this year's survey.

Do you believe switching anti-VEGF agents makes an impact on the visual acuity (VA) of wet-AMD patients?

Ehab El-Rayes—Africa/Middle East: More than 55% of survey respondents around the world believe that switching anti-VEGF agents has an effect on VA through improvement in the leakage pattern of AMD.



Africa/Middle East

Changing anti-VEGF agents in response to tachyphylaxis seems to have an effect on the leakage and thus the VA. Sometimes this effect is seen only following the initial couple of injections after switching. Similar switching strategies are also seen with glaucoma medications, so VA may be affected by tachyphylaxis as well as a patient's better response to one drug than another.

Alay Banker—Asia/Pacific: In Asia, a subset of patients with wet AMD actually have polypoidal choroidal vasculopathy (PCV). Studies have shown that PCV lesions respond better to ranibizumab than to bevacizumab, and respond best to aflibercept; hence, there is a recent trend in Asia to switch patients with PCV to these drugs. Also, the genetic characteristics of AMD in the Asian population seem to be different from those in the Western population.

José Garcia-Arumi—Europe: The European response to this question does not differ from that of the other geographic regions; switching anti-VEGF drugs can increase VA in our patients. Sometimes after chronic injections, an anti-VEGF drug may present phenomena of tolerance and tachyphylaxis. The physiological mechanisms for these events are not well known, but empirically we have seen a better response by switching the drug.

We can find a few papers in the literature about switching from ranibizumab or bevacizumab to aflibercept, but in our experience, patients could also show improvement after switching from aflibercept to ranibizumab in cases of chronic treatment with aflibercept. Normally we switch the drug after chronic treatment (more than one year) in patients who at baseline were responders and become nonresponders over time.

Fernando Arevalo—Latin America: Three out of 4 Central and South American respondents feel that switching anti-VEGF agents makes an impact on VA. Lack of response to an anti-VEGF agent may be a result of the ongoing disease activity or due to tachyphylaxis or tolerance to the medication.

(Tachyphylaxis is a lack of response when a drug is used at short intervals and no response can be achieved upon dose escalation. However, when treatment is interrupted for a short time, the efficacy of the drug is regained. In contrast, tolerance is a reduction in the extent and duration of a drug's efficacy over time as a result of long-term use. The efficacy of a drug may be improved when the dose is increased or is administered at shorter intervals.)

We more often see a response when switching to aflibercept (from ranibizumab or bevacizumab) due to its high binding affinity, and that aflibercept also inhibits other factors that affect neovascularization, such as VEGF-B and placental growth factor. The second reason may be based on studies that suggest that patients treated with repeated intravitreal injections of bevacizumab or ranibizumab may have developed an immunity (antibodies). By switching to aflibercept, lesser immunogenicity associated with a new agent theoretically may lead to sustained anatomic outcomes in eyes refractory to ranibizumab or bevacizumab.

Nevertheless, we have all seen patients who responded favorably after switching from either ranibizumab to bevacizumab or vice versa.

The survey shows that 60% to 77% of retina specialists worldwide believe that patients do respond well to switching anti-VEGF agents if there is no good response to the first agent.

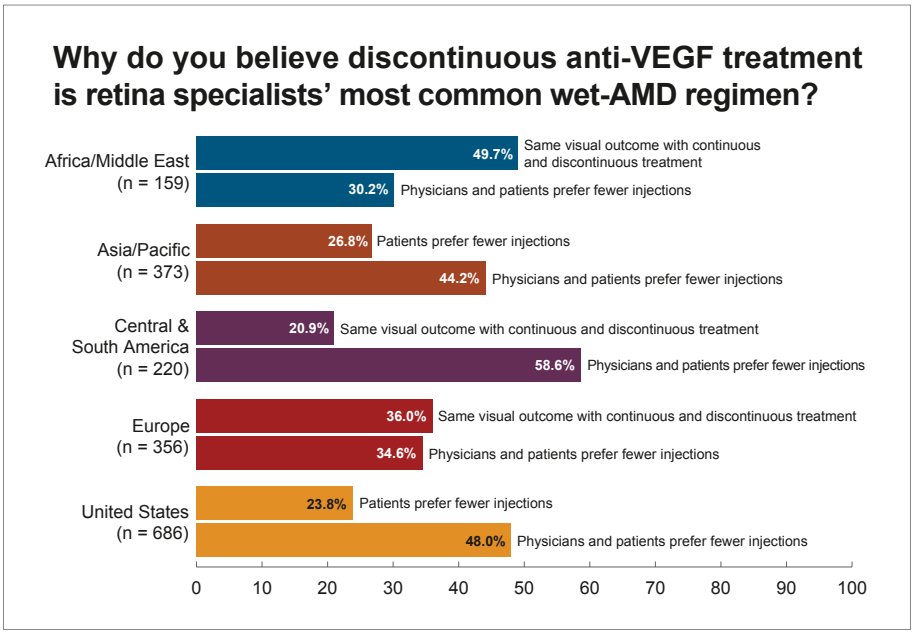
David Sarraf—United States: There appears to be supportive data from studies (eg, CATT, Protocol T) of various retinal diseases that indicate that bevacizumab is a weaker agent than ranibizumab and aflibercept in terms of anatomical outcomes. The differences in visual outcomes are smaller and this may explain the lack of an overwhelming response in support of this statement from each region.

Perhaps in Central and South America, the perception of these differences is even greater than in the other regions. Greater administration of bevacizumab as a first-line drug with the option to switch may accentuate this perception.

Why do you believe discontinuous anti-VEGF treatment is retina specialists' most common wet-AMD regimen?

Ehab El-Rayes—Africa/Middle East: Once it comes to stable or same VA after repeated injections, the physician has to explain to the patient why the last injection did not improve vision as much as when we started. Though we tell the patients that stability is a definite plus, the treat-and-extend regimen becomes the more acceptable scenario for both the patient and the physician, particularly where cost plays a major role in planning the treatment strategy. It is interesting to see that this pattern is similar in Europe as well.

Alay Banker—Asia/Pacific: None of the anti-VEGF injections are reimbursed in India;



Asia/Pacific

hence, cost is a major issue when it comes to continuous therapy. Also, as compared to the Western population, AMD lesions in Asian patients seem to respond better with fewer treatments. Most Asia/Pacific surgeons prefer either PRN or treat-and-extend therapy. Also, compliance is an issue for long-term continuous therapy.

José Garcia-Arumi—Europe: We think we can find 2 reasons in our geographical region to justify why discontinuous treatment regimen is most commonly used. First, a discontinuous treatment regimen is much easier for patients and much easier for us to explain to them—when we find disease activity, we treat. Some patients find it difficult to understand why they would need new injections if they are seeing properly.

The second reason for the popularity of discontinuous treatment is the economic burden of wet AMD; fixed regimens are normally much more expensive than others and are very difficult to maintain—in both private and public practice.

Fernando Arevalo—Latin America: The survey showed 3 out of 5 respondents from Central and South America feel that physicians and patients prefer fewer injections; that is true due to the burden on our clinics and the high cost for patients. Even with flexible follow-up protocols such as treat and extend, significant barriers to adequate management of exudative AMD remain, including the advanced age and significant co-morbidities of our patients, the high costs of drugs, and patients' lack of independence, which frequently makes them dependent on family members to return for injections.

If we look at the data from Central and South America, 20.9% think that VA is the same with continuous and discontinuous AMD treatment—but unfortunately, that is not true. The PACORES group and many others have demonstrated that in real world data patients with lower number of injections than in clinical trials will do worse and the gains obtained in years 1, 2, and 3 are lost in years 4 and 5 of follow up. These results call into question the sustainability of long-term anti-VEGF treatment in eyes with chronic conditions like exudative AMD. It appears that applying clinical trial protocols to daily clinical practice may not be feasible.

Similar misconceptions and obstacles may be the reasons why discontinuous anti-VEGF therapy is most commonly used worldwide.

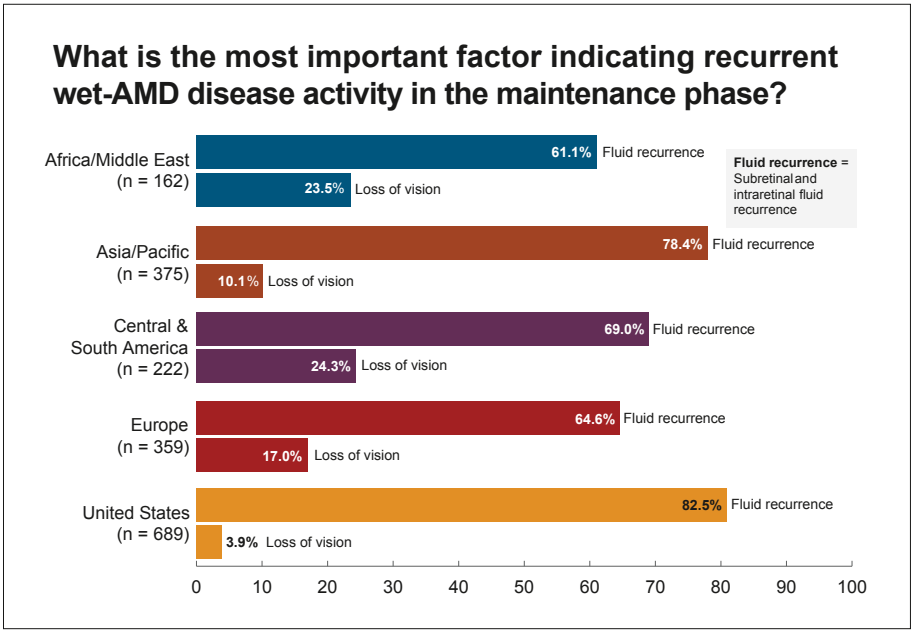
David Sarraf—United States: Several studies have validated the greater incidence of macular atrophy with a continuous monthly injection regimen including the CATT, HARBOR, and IVAN trials. Macular atrophy was identified as the most important factor associated with long-term vision loss in the SEVEN UP study, a long-term analysis of patients from ANCHOR and MARINA (and HORIZON). The US response focuses on patient and physician issues related to the burden of injections, which has become an important concern in many countries, especially the United States. Limitations and guidelines for injection regimens may vary from region to region and may determine physician practice patterns.

What is the most important factor indicating recurrent wet-AMD disease activity in the maintenance phase?

Ehab El-Rayes—Africa/Middle East: In Africa and the Middle East, 4 out of 5 respondents believe fluid recurrence in the maintenance phase means recurrent wet-AMD disease activity; this usually precedes visual drop. We as physicians often see that on regular follow-up OCT before the patients notice a significant change in their VA. More than 60% of all participating physicians around the world agree that fluid recurrence is the most important factor.

Alay Banker—Asia/Pacific: As anywhere else, most surgeons in the Asia/Pacific region rely on repeat OCT to find presence of intra/subretinal fluid, which they consider the single most important biomarker to treat. Unlike other retinal diseases such as diabetic macular edema and retinal vein occlusion, most surgeons are very intolerant to even mild presence of intra/subretinal fluid in patients with AMD.

José Garcia-Arumi—Europe: When we are evaluating the presence of wet-AMD activity, we need an easy, fast, and reliable test—a non-invasive test we can perform on all patients, every month or 2. At this point, the OCT is our best test. The fluid recurrence



Europe

AUSTRIAN OPHTHALMOLOGICAL SOCIETY

BRITISH AND EIRE ASSOCIATION OF VITREORETINAL SURGEONS

DUTCH MEDICAL RETINA SOCIETY

EUROPEAN SOCIETY OF RETINA SPECIALISTS

FRENCH SOCIETY OF RETINA SPECIALISTS

GREEK VITREO-RETINAL SOCIETY

ITALIAN VITREORETINAL SURGERY GROUP

KIEV SOCIETY OF OPHTHALMOLOGY

ROSENGREN CLUB–SWEDISH VITREORETINAL SOCIETY

SPANISH RETINA AND VITREOUS SOCIETY

TURKISH OPHTHALMOLOGICAL SOCIETY

in the tomography is, in our mind, the most useful factor for indicating wet-AMD activity. We can compare easily with past examinations and we can also measure.

VA is a subjective test and its results may vary depending on the tester, the chart used, and other reasons aside from AMD. Other signs such as retinal hemorrhages are difficult to measure and are not always related to active neovascular disease. Respondents from all 5 geographic regions consider OCT the most important factor, especially the United States. VA is the most important factor for the patient, which accounts for 17% of the response from Europe.

Fernando Arevalo—Latin America: Almost 70% of survey respondents from Central and South America agree that recurrence of fluid is of utmost importance. The survey shows worldwide agreement that fluid recurrence is a more important indicator of recurrent wet-AMD disease activity than other factors such as VA.

It is well known that there is no good correlation between anatomy (OCT) and function (VA); therefore, many patients may develop fluid recurrence before their VA is affected. Those patients should be considered as having recurrent wet AMD and treated accordingly. The consensus worldwide would be to treat those cases.

David Sarraf—United States: There is overwhelming consensus between the various regions with this question, indicating that fluid recurrence (intraretinal or subretinal), optimally detected with the aid of spectral domain OCT, is the most important biomarker of recurrent neovascular activity in AMD. Visual acuity may be affected by many other factors, including atrophy, fibrosis, or media opacity; therefore, VA is not as reliable a biomarker of recurrent neovascular activity.

What is your experience during chronic treatment for wet AMD (2 or more years) with anti-VEGF agents?

Ehab El-Rayes—Africa/Middle East: In my region, 60% of respondents believe that improvement with eventual stabilization is the scenario within 2 years of treatment. However, we know that other factors like progressing geographic lesions can also contribute to visual instability after 2 years of anti-VEGF therapy. That factor might also account for some of the difference in worldwide response as in Asia and Europe, where regression is more than 30%. It is also possible that different associated dietary regimens might be contributing factors. That is interesting to see, considering that we all share the same 3 available anti-VEGF agents.

Alay Banker—Asia/Pacific: Patients with regular follow-up and repeated OCT examinations undergoing either PRN or treat-and-extend therapy usually show initial improvement with good VA stabilization. However, patients who miss their regular and scheduled follow-up who tend to have recurrences in the window of their missed follow-up tend to show deterioration of vision and regression to baseline vision. However, the longer you follow up with patients, the more you will find the vision tends to decline—and that could be due to other factors like geographic atrophy or scarring.

José Garcia-Arumi—Europe: European retina specialists believe chronic treatments usually improve vision, then stabilize it. The problem sometimes is that when we stop treatment, some patients could have a decrease in VA due to reactivation of the disease; for this reason, we in Europe are recommending treat-and-extend regimens during the first 2 years, extending injections over 12 to 14 weeks.

When the injection interval exceeds 16 weeks, we propose changing the regimen to a "wait and extend" protocol—in some cases prolonging the interval between injections to as long as 1 or 2 more years. We stop retina specialist controls when we observe 1 year without any activity. In some patients however, even without any kind of activity, VA decreases due to retinal and retinal pigment epithelium (RPE) atrophy and fibrosis; that's why in Europe, regression to baseline occurs quite often.

Fernando Arevalo—Latin America: In Central and South America, 68.5% feel that VA improves and then stabilizes. The numbers

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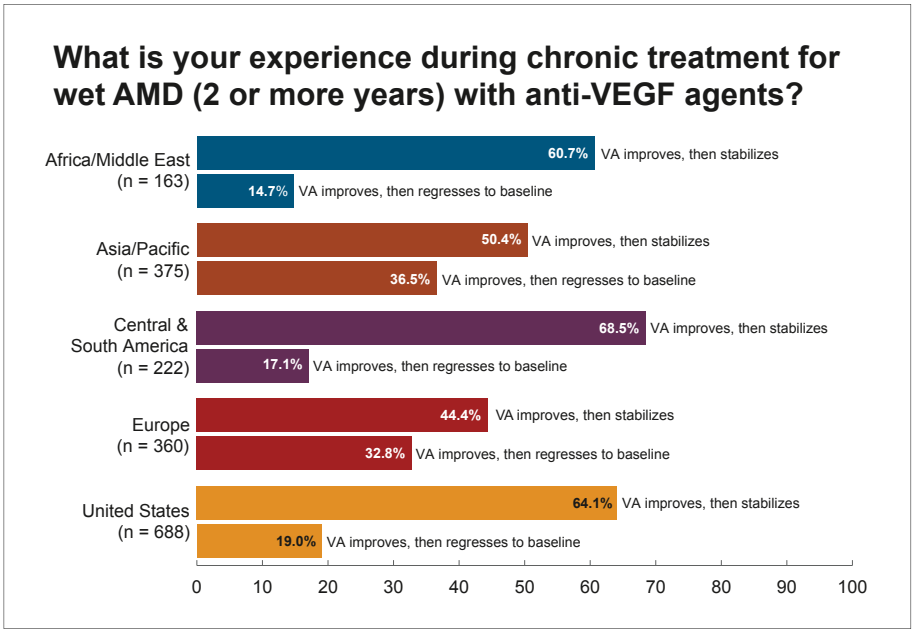

Latin America

ARGENTINE RETINA AND VITREOUS SOCIETY
BRAVS BRAZILIAN RETINA AND VITREOUS SOCIETY
ACOREV ASOCIACIÓN COLOMBIANA DE RETINA Y VITREO
COLOMBIAN RETINA AND VITREOUS ASSOCIATION
AOCR Asociación Oftalmológica de Costa Rica
COSTA RICAN ASSOCIATION OF OPHTHALMOLOGY
MEXICAN RETINA ASSOCIATION
PAN-AMERICAN RETINA AND VITREOUS SOCIETY
PERUVIAN SOCIETY OF OPHTHALMOLOGY
SALVADORAN RETINA AND VITREOUS ASSOCIATION
CENTRAL AMERICAN RETINA AND VITREOUS SOCIETY (SCRV)
asuo Asociación Uruguaya de Oftalmólogos
URUGUAYAN ASSOCIATION OF OPHTHALMOLOGY

Lee M. Jampol, MD
Chair, Diabetic Retinopathy
Clinical Research Network

Vincent S. Hau, MD, PhD
Co-Chair, ASRS
Young Physicians Section

Making an Impact in Clinical Research Early in Your Career With the DRCR.net

Since 2002, the National Eye Institute-funded Diabetic Retinopathy Clinical Research Network (DRCR.net) has made important advances in understanding diabetic retinopathy, changing the way all ophthalmologists view and treat this disease. Equally important is the Network's impact on the development of new retina clinician-scientists.

The DRCR.net has inspired and guided many early-career retina specialists to become involved in clinical trials; its open-network policy welcomes any potential investigator with an interest and strong motivation for clinical trials.

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Houston, Texas

Diabetic Retinopathy: A National Research Priority

Diabetic retinopathy is a leading cause of blindness in America. According to projections by the National Institutes of Health, the number of patients with diabetic retinopathy will nearly double from 2010 to 2050, affecting nearly 14.6 million Americans. It is therefore imperative to make combating and treating diabetic retinopathy a priority in our national research efforts.

The objective of the Diabetic Retinopathy Clinical Research Network (DRCR.net) is to develop a collaborative network to facilitate multicenter clinical research focused on diabetic retinopathy and associated conditions like diabetic macular edema (DME).

Since 2002, the DRCR.net has involved over 300 sites and 1100 investigators, spanning 48 states and 4 Canadian provinces, with nearly two-thirds of participants from private practice.

DRCR.net Chair Lee M. Jampol, MD, actively encourages the participation of young retina specialists—our specialty's future leaders. When retina specialists are just beginning to build their own practice, they "may not be maximally busy, so they have time to be involved," he explains. Dr. Jampol enjoys working with young people; it "keeps me young and maintains my mental clarity and enthusiasm," he adds.

Senior DRCR.net investigators work closely with junior investigators to train them as potential future leaders. Young investigators are regularly appointed to leadership positions, giving them invaluable experience early in their careers.

We have interviewed 4 active network leaders—retina specialists who got involved immediately after fellowship training. Jennifer Sun, MD, MPH, a former vice chair of the Network, serves as the DRCR.net protocol working investigator; she practices at Beetham Eye Institute at Joslin Diabetes Center in Boston and is an associate professor at Harvard Medical School.

Chirag Jhaveri, MD, is a Network vice chair who practices at Retina Consultants of Austin in Austin, Texas. Omar Punjabi, MD, practices at Charlotte Eye, Ear, Nose & Throat Associates, PA, in Charlotte, North Carolina and serves on the research committee of South Eastern Clinical Research Associates (SCRA), based in Charlotte, North Carolina.

Charles Wykoff, MD, PhD, is a member of the DRCR.net protocol development and writing committees and practices in Houston, Texas, as co-director of the Greater Houston Retina Research Foundation; he also serves as the deputy chair of ophthalmology for the Blanton Eye Institute.

Drs. Jhaveri, Punjabi, and Wykoff are still less than 7 years out of fellowship, so they are members of the Young Physicians Section (YPS) of the ASRS. They each provide unique insight on how their experience with the DRCR.net has helped their careers—and they share great advice on how to become a part of the Network.

How and why did you get involved in the DRCR.net?

Jennifer Sun: I got involved in the DRCR.net soon after I joined the Joslin Diabetes Center as a new attending right out of fellowship. The goals of the Network fit closely with my clinical and research interests in improving our understanding and treatment of diabetic eye disease. Lloyd Paul Aiello, MD, PhD, was my mentor at the time in the NIH-sponsored Harvard Vision Clinical Scientist K12 program; he was the founding chair of the Network, so his mentorship also played a role in fostering my involvement with the DRCR.net.

Initially I got involved by simply recruiting for the Network studies. Being a highly active recruiter is the best way to gain familiarity with the Network policies and protocols. It also leads quickly to other opportunities, such as participation on protocol development and

manuscript writing committees. Over time, I broadened my roles in the Network, having served as one of the vice chairs and as the protocol working investigator. In my current protocol role, I help shepherd all new study ideas from inception through approval, development, and implementation.

Chirag Jhaveri: I was introduced to the DRCR.net by my mentors in fellowship and by my partner in practice. I saw the Network as an excellent opportunity to participate in collaborative efforts that will likely influence the way I will manage patients with diabetic retinopathy throughout my career. In addition, the DRCR.net has been a great resource for becoming involved in clinical trials and research as a new physician.

Omar Punjabi: I had the opportunity to be exposed to research very early on in my career. During residency training at Northwestern University, I was fortunate to have worked with Lee Jampol, MD, the current chair of the DRCR.net. My retina fellowship was at the Cleveland Clinic's Cole Eye Institute, where there was a heavy emphasis on research by Chairman Daniel Martin, MD. These formative years piqued my interest in clinical research.

One of the reasons I joined Charlotte Eye Ear Nose & Throat Associates, PA (CEENTA) was because it has an established research setup, and a long history of dedication to clinical research. My retina colleagues at CEENTA have been active with the DRCR.net for several years and have served in leadership roles in the organization.

> **'The DRCR.net has been a great resource for becoming involved in clinical trials and research as a new physician.'**
>
> —Chirag Jhaveri, MD

Charles Wykoff: Harry Flynn, MD, a key mentor of mine as a resident and fellow, encouraged me to get involved with the DRCR.net early in my career. When I joined a retina-only practice with 10 doctors to help lead our research efforts, we had no presence in the Network, and I decided to engage our group. Involvement with the DRCR.net has proven incredibly productive and valuable.

What have you learned from participating in the DRCR.net, and how has it shaped your career?

Jennifer Sun: I have learned a tremendous amount from my co-investigators and from working with the Network coordinating center. The open discussions in the DRCR.net have helped me learn how to design clinical studies and how to evaluate clinical research thoughtfully. As a young investigator, I have had a great opportunity for ready access to experts in the field.

It has also been very exciting to be involved in an organization that has dramatically changed best practices for management of diabetic retinopathy and DME over the last few years. Being a DRCR.net investigator gave me early access to and a deeper understanding of results from clinical trials that established anti-VEGF therapy as first-line treatment for DME and as a safe, effective therapy for proliferative diabetic retinopathy (PDR).

Chirag Jhaveri: Because the DRCR.net is an open network, it is an excellent tool to learn how complex multicenter trials are planned and implemented. From the beginning, the team at the Jaeb Center for Health Research, the Network's coordinating center, is extremely helpful for a new clinician wanting to understand the steps required to participate in a clinical trial.

As I became more involved, I was not only learning; I also was able to participate in the decision making for protocol development. At DRCR.net meetings, there is a collaborative discussion when new protocols are being considered, and it's a great opportunity to brainstorm with your colleagues. This open and collective effort is what I think makes the DRCR.net special.

Omar Punjabi: The first few years as a retina specialist involve a lot of hard work, patience, and flexibility. I trained in a very busy fellowship program, but there was still a very steep learning curve during my first few years in practice. It can be hard to find time for research.

I tried to get involved in research from day one. I keep a summary of ongoing clinical trials (key inclusion and exclusion criteria, protocol schedules, etc), and have it handy in each clinic lane. This allows me to quickly determine if a patient is eligible for clinical trials. Research patients now encompass approximately 10% of my patient volume.

Since we are involved in all the DRCR.net trials, I have learned how research studies are formulated and how inclusion and exclusion criteria are used to determine subject eligibility. Understanding how clinical trials are structured has also helped me fine-tune my treatment algorithm for some retinal diseases.

The Network recognizes sites and investigators who recruit heavily, and we were thrilled when our site was named the 2015 DRCR.net Site of the Year. The DRCR.net invites sites that are heavily involved in recruitment to important meetings and to serve in larger roles within the organization.

The DRCR.net provides us with financially unbiased scientific data that helps us treat patients better, and become better doctors. I feel like I have improved a lot as a physician by being part of the DRCR.net.

> **'We were thrilled when our site was named the 2015 DRCR.net Site of the Year.'**
>
> —Omar S. Punjabi, MD

Dr. Wykoff: Before starting practice, I had substantial experience with basic science research and single-center studies, but had little exposure to large, prospective clinical trials. That changed rapidly after joining the DRCR.net. There are many steps to a successful prospective study, including trial design; institutional review board (IRB), Food and Drug Administration (FDA), and industry interaction; consenting and educating patients; data collection; and data analysis. Every step is vital and unique, involving complementary skill sets.

Beyond learning the nuts and bolts of trials, there are innumerable benefits to embracing the world of clinical research and participating with the DRCR.net. The relationships built with collaborators across the country and around the world have spawned multiple subsequent projects. It's motivating to collaborate with retina colleagues similarly dedicated to pursuing a deeper understanding of retinal diseases and their management.

What are the pros and cons of being a part of a multicenter clinical trial investigation?

Jennifer Sun: One of the pros of being part of a multicenter clinical trial investigation is that you immediately have access to protocols and procedures designed by leaders in the field. As a young investigator, you will learn a lot just from access to these study protocols,

since they generally incorporate current best practices in the field.

Multicenter trial involvement will also give you exposure to a variety of other clinical sites and patient populations. This is helpful in understanding the variations in practice between sites. Over time, it also helps you extrapolate why results from a particular study might be more or less applicable to your own patient population based on how comparable your patients are to the study cohort.

In the DRCR.net, you have the opportunity to discuss our studies in depth with the whole group on monthly investigator calls and in person during semiannual investigator meetings. It is exciting to participate in the often-spirited discussions at these meetings. We learn a lot from one another as we discuss how to design studies that best answer our key clinical questions. The Network is open to participation and feedback from investigators, so it is easy to get involved in nearly any aspect of our protocols, from development to writing manuscripts, especially if you can recruit successfully for the studies.

Chirag Jhaveri: It is a benefit to be able to include patients across many sites to help power larger trials, and to answer questions that may be difficult to investigate individually at academic centers. There can be challenges, however, in creating a protocol that can address the unique differences between regions and practices.

> 'The Network is open to participation and feedback from investigators, so it is easy to get involved in nearly any aspect of our protocols ...'
>
> —Jennifer K. Sun, MD, MPH

As retina specialists, although we look to evidence-based medicine, we may have our own specific practice patterns. When participating in a protocol, we have to feel comfortable following the protocol guidelines. Navigating those differences can be challenging for some, but every investigator is asked to participate only in protocols that seem scientifically sound and reasonable to them.

Dr. Punjabi: There are many benefits of participating in a multicenter trial:

- Multicenter clinical trials help us young investigators build our practices faster and get busier quicker. It is useful for referring eye doctors and primary care physicians to know we are involved in clinical trials; this can accelerate referrals and build trust and respect in the medical community.
- A number of multicenter research studies are well funded, which helps boost revenues in an age of declining insurance reimbursements. Also, the DRCR.net receives most of its funding from the NEI, so there is little to no bias involved in research methodology and results. The Network is highly respected in the retina community.
- Our patients get access to many investigational drugs and devices, sometimes even prior to FDA approval. We have excellent drugs available for many retinal diseases, but there are still many conditions with no commercially available treatment. By being involved in investigational drug studies, we can witness their results firsthand in our own patients.
- It is prestigious for us as young physicians to have our names in research publications, which can quickly accelerate our academic and research careers. Often, these studies get published in distinguished journals with a high impact factor.

> 'The DRCR.net receives most of its funding from the NEI, so there is little to no bias involved in research methodology and results.'
>
> —Omar S. Punjabi, MD

Participating in a multicenter research study also has a few drawbacks:

- Research patients need extra time and additional documentation. It takes a fair amount of work and effort to counsel patients considering a clinical trial. They usually have many questions, which can slow you down during a busy retina clinic.
- Additional visits are needed for research patients, and often it is frustrating for patients and investigators when they screen-fail for a clinical trial. Many of these patients are older and need their family members to take time off work to bring them into the office. It can be disappointing when they are not accepted into a trial.
- Conference calls and research meetings can last for a few days and take time away from our busy clinical and surgical schedules. This can be difficult when we are trying to build a practice.

Dr. Wykoff: Being intimately involved with research requires significant time and resources.

If you're not passionate about research, don't do it. Across a career, there are too many directions to pursue to spend time doing something for which you are not passionate.

I have experienced firsthand the obvious point that data integrity is critical. As an investigator, you have substantial control of how data is collected and analyzed, but much of the actual data collection itself is performed by team members such as research coordinators and certified photographers. These personnel are essential to the success of a prospective research endeavor; they need to know that the data they collect is important and that it is crucial that every piece be as accurate as possible. Protocols must be followed closely and accuracy must trump efficiency.

What advice would you offer other young retina specialists interested in incorporating research in their career?

Dr. Sun: Getting involved in the DRCR.net is a terrific way to get exposed to high-quality clinical research as a young investigator, whether you are based at an academic or private practice. My advice is to focus not only on participating by recruiting well, but also by making sure the quality of study participation in your group is excellent. I'd also advise you to find key mentors in the field early and to actively seek out opportunities for collaboration and participation in projects that interest you.

Be proactive in approaching more-experienced colleagues for advice and support; they can often give you a broader perspective invaluable in helping you to focus your efforts where they might be most fruitful. Experienced advisors can also help you design your own studies carefully so the final outcomes are informative, whether or not the results are positive.

Finally, realize that most successful research careers are built slowly over time, with patience and persistence. Don't be discouraged by early setbacks—especially in clinical research, where studies can take a lot of resources to get off the ground, be slow to recruit, and then generate data that is complicated to interpret. Enjoy the research for the sake of learning something new with each study. And remember, the studies in which you participate may lead to sweeping changes in standards of care for patients across the world.

Dr. Jhaveri: A physician has to have the enthusiasm and work ethic to become involved in clinical research. Having an excellent coordinator is the next important criterion. This may come from external hiring or finding a motivated employee who has great attention to detail. I recommend joining the DRCR.net—it is a great resource and can help guide a motivated team through all the regulatory, logistical, and practical aspects of participating in clinical trials. Active involvement will then solidify the knowledge and analytical criteria for maintaining a research center to participate in additional trials.

Dr. Punjabi: A number of retina fellowships, both academic and private, are heavily involved in research and include fellows on their research teams. Once you finish fellowship, you do not have to be part of an academic center to be involved in clinical trials. If you are a young retina physician with a keen interest and a strong motivation, it is not difficult to incorporate research into your practice.

> **'A physician has to have the enthusiasm and work ethic to become involved in clinical research.'**
>
> —Chirag Jhaveri, MD

Ideas and advice for young investigators:

- Being a principal investigator (PI) for a clinical trial is lucrative. Try to get involved as a sub-investigator and be active in recruitment. Over time, we young physicians will be given more responsibility and eventually will be trusted as a PI. Many times, we may be asked to be a PI within the first few years of practice, and it is important to take advantage of the opportunities presented to us.
- Attend investigator meetings and get to know your retina colleagues. A lot of gatherings are conveniently held at the annual meetings of ASRS, the American Academy of Ophthalmology (AAO), and the Association for Research in Vision and Ophthalmology (ARVO).
- Attend investigator conference calls and be active—have your voice heard and your ideas expressed.
- Be active in recruiting patients in clinical trials.
- In each clinic lane, have a handy summary of clinical trials in which your site is involved (key inclusion and exclusion criteria, protocol schedules, etc). This allows you to quickly determine whether a patient is eligible for clinical trials.
- Be supportive and respectful of your research coordinators—they work hard and have a stressful job. They also do a lot of the behind-the-scenes work that can go unappreciated.
- Have frequent meetings and communicate with your research team regularly.

Dr. Wykoff: If you desire to be involved, don't let the abundance of data already available dissuade you into thinking there's no way to contribute. There are a multitude of opportunities that span everything from basic science to clinical applications to data interpretation to device design. Try to think beyond what is routine, look from a new perspective, and be innovative.

If you have no experience with research, start small and read the journals. Let your clinical experiences and patients stimulate research questions. Present an interesting case or case series at local or regional meetings and consider publishing the work. Know your local IRB regulations and make sure you follow them when compiling patient information for analysis.

> **'If you desire to be involved, don't let the abundance of data already available dissuade you …'**
>
> —Charles C. Wykoff, MD, PhD

We have many excellent peer-reviewed and non-peer-reviewed journals. It's easy to feel overwhelmed by the amount of literature available—don't be. Jump in and read what you find interesting. Browse the abstracts of our major

How to Get Involved in the DRCR.net

All retina specialists are welcome to apply.

- Visit www.DRCR.net
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Your request will be reviewed and, if approved, the necessary paperwork will be sent to you.

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journals. I skim emails from the top journals when a new issue is released to identify papers to read.

To evolve to the next level, join or start a collaborative effort. The retina research community is small and full of exceptionally insightful and hard-working colleagues. Get your friends together and brainstorm about interesting topics and questions to pursue.

I see 3 broad avenues for physicians to readily pursue prospective clinical research:

- Collaborative non-industry-sponsored trials
- Industry-initiated trials
- Investigator-initiated trials

The DRCR.net is an inspiring organization. It has successfully created a unique, enduring collaboration of academically oriented practitioners across North America committed to advancing the care of diabetic patients.

One of the most exciting aspects of the DRCR.net is its flexibility. We are always in need of sites and individuals interested in working toward the common goal of improving patient outcomes. The DRCR.net is an excellent avenue for retina physicians of any age interested in getting more involved with research. The Network is genuinely interested in new ideas and is an excellent forum to learn the intricacies of clinical trials from start to finish.

Collaboration with industry is essential to the process of bringing new pharmaceuticals and devices to market for patients' benefit. I have found interaction with the science side of industry incredibly insightful and productive. On a related note, many pharmaceutical and device companies are interested in ideas about how their products could be used in innovative ways, and are often willing to sponsor investigator-initiated trials addressing an unmet need.

> 'The Network is genuinely interested in new ideas and is an excellent forum to learn the intricacies of clinical trials ...'
>
> —Charles C. Wykoff, MD, PhD

What recent DRCR.net studies you feel have made a large impact, and how are you using that information in your practice?

Dr. Sun: Protocol T, the DRCR.net comparative-effectiveness study of aflibercept, bevacizumab, and ranibizumab for eyes with DME, made a huge impact on the practice of many retina specialists by identifying that aflibercept leads to the best outcomes in eyes with worse starting vision through 1 year, although all 3 agents are similarly effective in eyes with good baseline vision and DME.

The study certainly influenced me to increase my use of aflibercept as a first-line agent in patients with vision of 20/50 or worse who are beginning anti-VEGF treatment for DME. It was reassuring, however, to see that the majority of eyes, even in the bevacizumab group, did extremely well throughout the study. Thus, I am very comfortable using the other agents for patients with DME who do not have access to aflibercept or who have previously been successful with bevacizumab or ranibizumab.

I think the results of Protocol S will also continue to inform and change the landscape of care for patients with proliferative diabetic retinopathy (PDR) as we further investigate long-term outcomes of anti-VEGF vs panretinal photocoagulation (PRP) in eyes with PDR.

Dr. Jhaveri: Both Protocol T and Protocol S have greatly influenced my practice. After explaining the results of Protocol S, I often initiate therapy with anti-VEGF instead of PRP for PDR with patients who are amenable to the treatment regimen. Protocol T influences the anti-VEGF I start with, depending on a patient's baseline vision.

I am also looking forward to learning the results of Protocol V and Protocol U, which are looking at 2 ends of the spectrum of DME—patients with very good vision and patients who have persistent edema despite anti-VEGF therapy, respectively.

Dr. Punjabi: I really like that that DRCR.net tries to formulate important questions and that it answers them in a scientific and unbiased manner. All the studies have meaningful results, but I feel the Protocol I and Protocol T data has given us some key information on how to better treat DME.

Visual acuity outcomes are always the priority, but in the real world, we have to be mindful of drug costs and patient compliance. I feel that having data from excellently structured clinical trials allows us to counsel patients better and come up with a customized plan for each patient.

Dr. Wykoff: Many of the trials having a relevant impact on clinical care delivery over the last decade have been performed by the DRCR.net. Protocol I, Protocol T, and Protocol S are great examples. Protocol T is, and will likely remain, the only well-powered, prospective trial comparing the 3 anti-VEGF agents.

Other trials in progress that I believe may have a substantial impact on guiding clinical care include Protocol V and Protocol AA. Protocol V may be particularly relevant, as it evaluates patients who previously have been excluded from our large anti-VEGF trials—those with visual acuity of 20/25 or better—and directly compares focal laser vs aflibercept vs observation.

> 'Protocol T ... made a huge impact on the practice of many retina specialists ...'
>
> —Jennifer K. Sun, MD, MPH

Leading the way

Participating in clinical trials may not be as difficult as you expect, as long as you have the motivation and initial resources. Joining the DRCR.net is a great way to get started early on in your career. The above physicians have demonstrated this and now are better doctors to their patients and are leaders in our field, shaping the way we treat our own patients as retina physicians.

Financial Disclosures

Dr. Hau – None.

Dr. Jampol – QUINTILES/JANSSEN PHARMACEUTICALS: Other, Honoraria.

Dr. Jhaveri – ALCON LABORATORIES, INC: Investigator, Other Financial Benefit; DRCR.net: Investigator, Equipment (Department or Practice), Other Financial Benefit; GENENTECH, INC: Investigator, Other Financial Benefit; REGENERON PHARMACEUTICALS, INC: Investigator, Other Financial Benefit.

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Dr. Sun – BOSTON MICROMACHINES CORPORATION: Investigator, Equipment (Department or Practice); ELEVEN BIOTHERAPEUTICS: Consultant, Honoraria; GENENTECH, INC: Investigator, Grants; NOVARTIS PHARMACEUTICALS CORPORATION: Consultant, Honoraria; OPTOVUE INC: Investigator, Equipment (Department or Practice).

Dr. Wykoff – ACUCELA INC: Investigator, Grants; ALCON LABORATORIES, INC: Consultant, Investigator, Grants, Honoraria; ALIMERA SCIENCES: Consultant, Honoraria; ALLEGRO OPHTHALMICS, LLC: Investigator, Grants; ALLERGAN, INC: Consultant, Investigator, Speaker, Grants, Honoraria; AMPIO PHARMACEUTICALS, INC: Investigator, Grants; APPELLIS PHARMACEUTICALS: Investigator, Grants; BAYER HEALTHCARE: Consultant, Investigator, Grants, Honoraria; CLEARSIDE BIOMEDICAL, INC: Consultant, Investigator, Grants, Honoraria; DORC: Consultant, Honoraria; GENENTECH, INC: Consultant, Investigator, Grants, Honoraria; ICONIC THERAPEUTICS, INC: Investigator, Grants; ONL THERAPEUTICS: Consultant, Honoraria; NATIONAL EYE INSTITUTE: Investigator, Grants; NOVARTIS PHARMACEUTICALS CORPORATION: Investigator, Grants; OPHTHOTECH CORPORATION: Investigator, Grants; PFIZER, INC: Investigator, Grants; PSIVIDA: Investigator, Grants; REGENERON PHARMACEUTICALS, INC: Consultant, Investigator, Speaker, Grants, Honoraria; ROCHE USA: Investigator, Grants; SANTEN, INC: Investigator, Grants; THROMBOGENICS, INC: Consultant, Investigator, Grants, Honoraria; XOMA CORPORATION: Investigator, Grants.

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Delivering Military Retina Care: Everywhere, Anytime

The US Military Health System's Defense Health Agency provides health care through its TRICARE program to active-duty service members, dependents, retirees, and eligible civilians—not only in the continental United States but throughout the world. The military ophthalmology system faces unique challenges in delivering care to its patients.

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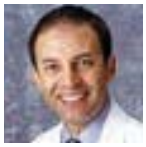

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While all TRICARE beneficiaries in the Military Health System have some form of insurance, many civilian ophthalmology practices limit their TRICARE acceptance. This is less of an issue for patients age 65 or older who have dual coverage with Medicare and TRICARE.

Regions that the Military Health System must cover include the Pacific, Europe, and the Middle East, as well as remote regions of the United States, such as Alaska. Military vitreoretinal surgeons face unique dilemmas in delivering care to patients. One challenging aspect of retina practice in the military system is coordinating patient care from great distances—often bypassing several civilian centers with retina capabilities because of the vagaries of insurance coverage. This places a premium on good communication between retina and ophthalmology providers in the military system to initiate therapy at the earliest possible opportunity during a patient's transfer.

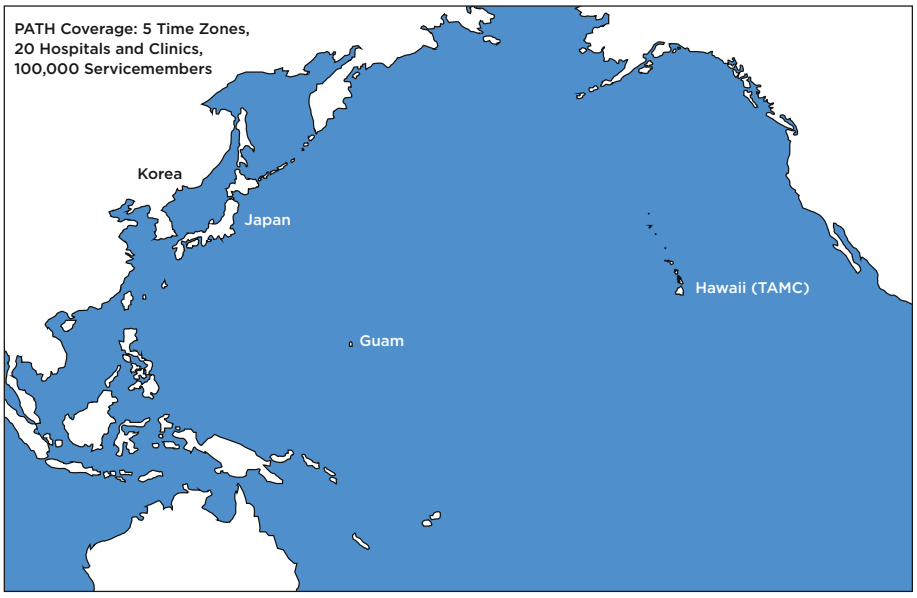

Figure 1. Distance between Hawaii and nations in the Pacific Rim: Guam (3,950 miles), Japan (4,100 miles), and Korea (4,694 miles).

Case in point: Serving the Pacific region

Several unique issues are germane to providing subspecialty ocular care to US Department of Defense (DoD) beneficiaries over a wide geographic area such as the Pacific region. The Pacific Region Healthcare System serves over 100,000 active-duty service members, their dependents, retirees, veterans, and other beneficiaries throughout the Pacific Basin.

This system encompasses more than 20 hospitals and clinics spanning 5 time zones, the International Date Line, and a geographic area including Japan, Korea, Australia, and Guam. Tripler Army Medical Center (TAMC) on the Hawaiian island of Oahu serves as the main tertiary care center for this region (see Figure 1).

> 'One challenging aspect of retina practice in the military system is coordinating patient care from great distances ...'

Alaska also is home to several military installations serving tens of thousands of military beneficiaries. Madigan Army Medical Center (MAMC) near Seattle, Washington, serves as the main tertiary care center for Alaska.

Eye care in these remote locations is often centered on treatment by primary care providers, optometrists, and a few general ophthalmologists. TAMC and MAMC are charged with providing subspecialty expertise for these regions. However, travel to Hawaii and Washington state is expensive and time-consuming. Host-nation

subspecialty care may be available in some major urban areas; however, access to such care is impeded by cultural/language barriers, out-of-pocket costs associated with treatment, and social and family concerns.

Providing subspecialty retina care to geographically isolated beneficiaries represents a significant cost to the DoD. Methods have been devised to mitigate some of the costs and logistical barriers associated with subspecialty care. In the Pacific area of operation, the DoD uses a computerized teleconsultation service called the Pacific Asynchronous TeleHealth (PATH) System.

The PATH System is a teleconsultation network encompassing all military hospitals and clinics in the Pacific Region including Hawaii, Korea, Japan, and Guam. PATH is an easy-to-use, provider-to-provider, asynchronous, electronic bulletin board that enables quick, efficient, and effective access to subspecialty expertise. The software uses store-and-push technology where consult requests are stored and forwarded to specialists for review (see Figure 2). The requesting physician and consultant do not have to be online at the same time to communicate.

'In the Pacific area of operation, the DoD uses a computerized teleconsultation service called the Pacific Asynchronous TeleHealth (PATH) System.'

Primary care providers, physician extenders, optometrists, and comprehensive ophthalmologists in remote locations, using their own computers and Internet browsers, can create and post-ophthalmology consultation requests including clinical notes as well as audio, video, and diagnostic images. PATH is maintained at Tripler Army Medical Center on secure servers, and access to PATH is password protected, encrypted, and HIPAA compliant. Access is granted only to those in remote locations with the need for consultations, and typically is granted only to the subspecialist at TAMC.

The process for a remote provider to request a subspecialty opinion is remarkably easy. Once a provider logs into the system, he or she can create a new consult request. Information pertinent to the case is typed in an email-style interface with multimedia attached. The requesting provider supplies necessary clinical information and asks questions regarding diagnosis or management.

Relevant background information and previous clinical encounters can also be reviewed using the DoD's international electronic medical record system, the Armed Forces Health Longitudinal Technology Application (AHLTA), where every medical encounter and diagnostic test can be accessed anywhere in the world. This makes PATH a concise and easy-to-use tool.

Each submitted request is then routed to a physician case manager at TAMC, who reviews it for priority and legitimacy, then forwards the request to the appropriate subspecialist. This store-and-forward method allows for review and response at a convenient time offline for the Tripler Army Medical Center subspecialist.

All ophthalmology consult requests are reviewed several times a day by the on-call ophthalmologist at TAMC; he or she then forwards the appropriate cases to the retina specialist, who reviews the consult and refers to AHLTA for more information as necessary.

Consult requests are managed by making a recommendation for clinical management online or by requesting an in-person consultation at TAMC, at which point a medical evacuation procedure is initiated. All personnel involved in the medical evacuation process have access to the PATH consult and can monitor the consultation process at any time.

The following cases highlight some notable recent consultations through PATH:

- A 47-year-old male presented to the ophthalmology clinic in Okinawa, Japan with a horseshoe tear and macula-on rhegmatogenous retinal detachment in the superotemporal quadrant of the right eye. A consult was placed in PATH. Within a few hours, the retina specialist at TAMC responded, indicating that urgent surgical evaluation was necessary and the options of host nation retina care vs transport to TAMC were provided.

  The patient elected to travel to TAMC and was seen within 36 hours of presentation to the ophthalmologist in Okinawa. He underwent successful surgical repair and returned to Okinawa in 2 weeks after the intraocular gas had dissipated and the retina was found to be satisfactorily repaired.

'PATH is an easy-to-use, provider-to-provider, asynchronous, electronic bulletin board that enables quick, efficient, and effective access to subspecialty expertise.'

- A 14-year-old child, the son of an active-duty military member in Okinawa, Japan, was suspected to have bilateral retinal detachment by the comprehensive ophthalmologist. His vision was 20/15 in both eyes and he had no ocular symptoms. A local referral confirmed the diagnosis.

  The family requested another opinion through the PATH system, resulting in evacuation to TAMC and a diagnosis of bullous retinoschisis without detachment, and the patient was discharged home. The electronic teleconsultation resulted in a cost savings and eliminated the need for surgical treatment in this child.

- A 63-year-old retiree living in Japan was being followed for chronic uveitis and steroid-response glaucoma. In 2014, the patient underwent a complex cataract extraction procedure with intraocular lens implantation. Three months later, he developed anterior

Figure 2. Screenshot of PATH teleconsultation system.

uveitis refractory to topical therapy and showed minimal response to periocular steroid injections. His intraocular pressure (IOP) remained elevated despite maximally tolerated medical treatment.

A PATH consult was placed and the patient was evaluated at TAMC. A diagnostic pars plana vitrectomy with glaucoma drainage device surgery was performed, which resulted in resolution of symptoms and normalization of IOP.

Another Military Health System strategy to treat complex medical problems involves compassionate reassignment efforts by military personnel managers. In the western United States and in austere areas outside the continental United States, patients and family members younger than 65 years old with challenging retinal conditions are often compassionately reassigned to military hospitals with retina coverage for the treatment of these conditions.

In some cases, this reassignment entails a permanent household move for a family for the purpose of one patient's retina care. Two examples illustrate how critical retina care is for the disposition of a patient and his or her family.

- A 21-year-old female had an 18-year history of insulin-dependent diabetes mellitus. She had previously undergone limited panretinal photocoagulation to treat proliferative diabetic retinopathy in a remote location outside the continental United States. The patient's retinopathy became increasingly severe and she developed bilateral tractional retinal detachments and vitreous hemorrhage coincident with becoming pregnant (see Figure 3).

  Her husband, the active-duty service member, was transferred to Madigan Army Medical Center in Washington state for the combined care of her tractional retinal detachments and pregnancy. The process of moving a family across several states and transferring care resulted in a delay of several months. However, within 4 weeks of arriving in Washington, she had undergone pars plana vitrectomy and retinal detachment repair in each eye.

- A 38-year-old activated National Guardsman from California was deployed to Kuwait as part of continuing operations in the Middle East. While deployed, he developed unilateral acute retinal necrosis. The patient was emergently transferred back to Madigan Army Medical Center, where treatment was initiated with intravitreal injections of foscarnet and ganciclovir in addition to IV acyclovir.

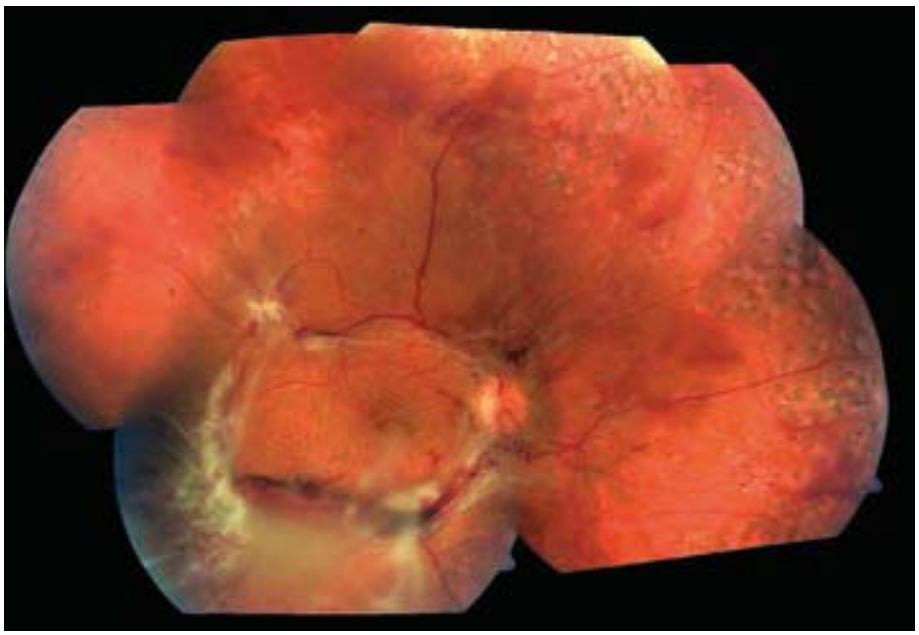

Figure 3. Diabetic tractional detachment in a 21-year-old pregnant woman. The patient's husband was compassionately reassigned so he could receive care from a military retina specialist at Madigan Army Medical Center in Tacoma, Washington.

'Another Military Health System strategy to treat complex medical problems involves compassionate reassignment efforts ...'

The patient later underwent a pars plana vitrectomy after developing a retinal detachment in the area of necrotic retina (see Figure 4). During this period, he was in a medical hold status in Washington specifically for treatment of his retinal necrosis.

In summary, military retina surgeons must balance a multitude of factors when delivering care to military beneficiaries. Importantly, they must understand the steps in the evacuation chain at their location, as well as the options available to service members and their families to ensure appropriate continuity of care—and ultimately result in a medically ready force prepared to fight and win the nation's wars.

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Dr. Colyer – None.
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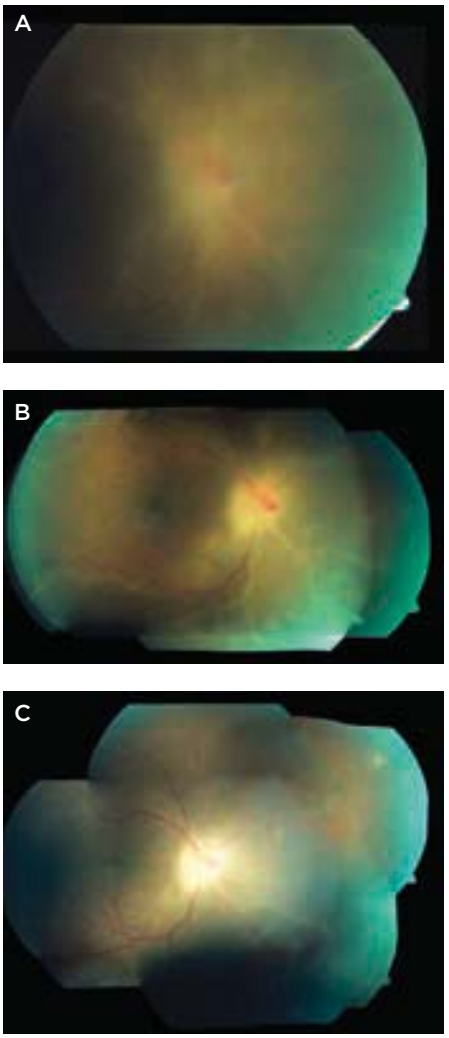

Figure 4. Serial images of National Guardsman with acute retinal necrosis on presentation (A), 3 days following arrival (B), and 1 week after arrival to Madigan Army Medical Center (C).

Roger A. Goldberg, MD, MBA

Chirag P. Shah, MD, MPH
Section Editor

A Placebo-Controlled Trial for Central Serous Chorioretinopathy

Central serous chorioretinopathy (CSC) is typically characterized by a focal retinal pigment epithelial (RPE) detachment with an associated serous neurosensory retinal detachment. For most patients, the central vision in the affected eye is blurred or distorted, and for many—often working-age, high-functioning individuals—the symptoms are distracting and hard to ignore when the disease is active.

CSC, an idiopathic condition, is estimated to be the fourth-most-common condition seen in a retina clinic—after age-related macular degeneration, diabetic retinopathy, and retinal vein occlusion—affecting 1 in 10,000 individuals over the course of their lifetime.[1] Recent studies suggest that the choroidal vessels in CSC may have excessive permeability, leading to an RPE detachment from Bruch's membrane.[2,3]

Small defects in the detached RPE then allow for a direct conduit of serous fluid into the subretinal space. When the RPE pump is overwhelmed, fluid accumulates, leading to the characteristic serous retinal detachment of CSC (Figure 1).

The role of corticosteroids in stimulating the excessive choroidal vascular permeability has not been clearly elucidated, though increases in serum corticosteroid levels are commonly associated with CSC.[3] Nearly half of patients with CSC are found to have used exogenous corticosteroids within 1 month of presentation.[4] Other risk factors for CSC include Cushing's disease, catecholamine-secreting adrenal tumors, a type A personality, and stress, all conditions characterized by excessive endogenous cortisol.[3,5]

For the majority of CSC patients, the subretinal fluid resolves on its own over a 6- to 12-week period. Therefore, most physicians recommend observation as the initial treatment. In addition to observation, patients are encouraged to avoid using exogenous steroids and to try to decrease stress through relaxation techniques including exercise, meditation, or yoga.

Despite the spontaneous resolution seen in many patients, 30% to 50% will have a recurrence of the disease, and up to 15% of patients may develop chronic CSC with subretinal fluid lasting longer than 3 months.[6,7] These chronic patients can also develop intraretinal cystoid macular edema with a "sick-RPE" phenotype.

There are no on-label, FDA-approved therapies for CSC patients whose serous detachment does not resolve spontaneously or recurs frequently. Historically, thermal focal laser was used in patients to cauterize leaking hot spots seen on fluorescein angiography (FA). Focal laser leaves a residual scar that can produce a permanent scotoma; as such, it is generally inappropriate for patients with subfoveal leaks. These chorioretinal scars also can develop secondary choroidal neovascularization.

To reduce the complications of traditional thermal laser, micropulse laser has been tried more recently to treat CSC. This ultra-short-duration laser theoretically does not induce thermal damage or scar formation, and is hypothesized to possibly stimulate the RPE to increase its pump function.[8,9] The efficacy of micropulse laser in CSC is less clearly defined, though small uncontrolled case series have reported response rates ranging from 60% to 100%.[8-10]

'Nearly half of patients with CSC are found to have used exogenous corticosteroids within 1 month of presentation.'

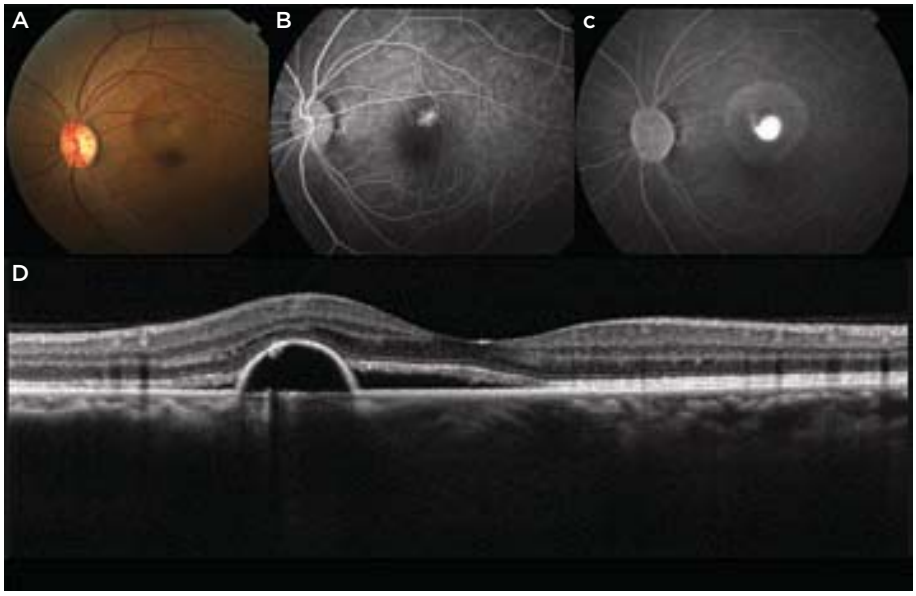

Figure 1. Color fundus photograph (A) shows a serous retinal detachment. FA (B, C) highlights a typical finding in CSC: an expansile dot with pooling of the dye into the subretinal space. SD-OCT (D) reveals a thick choroid, pigment epithelial detachment, and associated subretinal fluid.

Photodynamic therapy (PDT) can also be used to treat CSC, though it is not FDA-approved for this indication, leading to reimbursement challenges for some patients. In this treatment, verteporfin, an intravenously administered chemical, aggregates in abnormal choroidal vessels and is activated by a non-thermal laser to reduce the pathologic vascular permeability. The reported rates of reducing or eliminating subretinal fluid range from 50% to 100%.[2,11] PDT can cause RPE changes, choriocapillaris hypoperfusion, and choroidal ischemia, prompting many clinicians to use reduced-fluence PDT to treat CSC, with similar response rates and fewer complications.[12, 13]

Because of the association of CSC with excessive corticosteroid levels, orally administered steroid hormone antagonists have been investigated as possible CSC treatments. Some of these medications include mifepristone,[14] finasteride,[15] and eplerenone.[16] In general, these reports tend to be non-randomized, small case series, with variable entry criteria, outcome measures, and study durations.

Mifepristone is a potent antagonist of glucocorticoid receptor II (GR-II; the receptor for glucocorticoids), yet has no affinity for the GR-I (mineralocorticoid) receptor. It is rapidly absorbed following oral administration. Mifepristone is also a potent antagonist of the progesterone receptor and, since 2000, has been approved in the United States for early first-trimester medical abortion, administered orally in 200-mg tablets, followed by the prostaglandin analog misoprostol. In this formulation, it is sold by Danco Laboratories (New York, NY) under the trade name Mifeprex, though it is commonly called RU-486. Because of this, women who are pregnant, trying to become pregnant, or have a history of endometrial hyperplasia or endometrial (uterine) cancer should not take mifepristone.

A report from Nielsen and Jampol in 2011 described 16 patients with chronic CSC given a 200-mg daily dose of mifepristone for 12 weeks.[14] Approximately half of these patients showed evidence of anatomic and/or visual improvement, despite the fact that the average duration of CSC in their patient population was nearly 7 years, and many patients had a sick-RPE phenotype. Limited access to the 200-mg mifepristone tablets—which are expensive, distributed through a limited supplier network, and tied up in abortion politics[17]—delayed further studies from investigating mifepristone further in CSC.

However, in 2012, mifepristone 300-mg tablets (Korlym; Corcept Therapeutics, Menlo Park, CA) were approved in the United States for the treatment of Cushing's syndrome. This facilitated further study of mifepristone in CSC, and a randomized, double-masked, placebo-controlled clinical trial is underway investigating 2 doses of mifepristone in patients with CSC.[18]

The Short-Term Oral Mifepristone for Central Serous Chorioretinopathy (STOMP-CSC) is a multicenter trial that began enrolling patients in Boston and Walnut Creek, California, in January 2015. Patients are randomized in a 1:1:1 ratio to mifepristone 300-mg daily dose, 900-mg daily dose, or placebo for 4 weeks of treatment.

Inclusion criteria include:

- Diagnosis of persistent or recurrent idiopathic CSC, with symptoms ≥ 6 weeks
- Presence of subretinal fluid in the central foveal subfield on spectral-domain optical coherence tomography (SD-OCT)
- Age 18 or over
- Willingness and ability to comply with clinic visits and study-related procedures
- Ability to give written informed consent

'A randomized, double-masked, placebo-controlled clinical trial is underway investigating 2 doses of mifepristone in patients with CSC.'

Exclusion criteria include:

- Women known to be breastfeeding, pregnant, or actively trying to conceive
- Patients with active intraocular inflammation in the study eye
- Patients taking simvastatin, lovastatin, and CYP3A substrates with narrow therapeutic ranges, such as cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus
- Patients who require concomitant treatment with systemic corticosteroids for serious medical conditions or illnesses (eg, immunosuppression after organ transplantation)
- Women with a history of unexplained vaginal bleeding and women with endometrial hyperplasia with atypia or endometrial carcinoma

After the initial visit, during which baseline images are acquired and drug kits are dispensed, patients are seen at weeks 1, 2, 4, and 8; the last visit occurs 4 weeks after stopping the drug. The primary endpoint is the presence or absence of subretinal fluid on OCT after 4 weeks of treatment in those receiving mifepristone 300 or 900 mg daily, compared with placebo.

Secondary endpoints will evaluate other efficacy measures, including changes in retinal and choroidal thickness, angiography characteristics, and ETDRS best-corrected visual acuity, as well as safety and tolerability measures.

In summary, CSC is a common condition with no FDA-approved therapies. Most clinical investigations lack a placebo or sham control, which may be important in CSC, a disease that can show spontaneous improvement without intervention. Because of the strong association of CSC with elevated corticosteroid levels, glucocorticoid inhibitors such as mifepristone may offer promise to patients with CSC. The STOMP-CSC randomized controlled trial should give us valuable information regarding the efficacy and safety of this promising potential therapy.

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Continued on page 59

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Section Editor

Zélia M. Corrêa, MD, PhD
Section Editor

Suspicious Choroidal Melanocytic Tumors—How Useful Are Those Risk Factors Anyway?

Choroidal nevi are the most common neoplastic lesions encountered in the typical retina practice. At least 1 in every 15 Caucasian individuals will have a choroidal nevus.[1] While most choroidal nevi are small with minimal malignant potential, some are larger and overlap in size with choroidal melanomas such that size alone is insufficient as a diagnostic criterion.[2]

Panelists

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In the 1970s, J. Donald M. Gass, MD, conceptualized the now-familiar list of clinical risk factors for assessing suspicious small choroidal melanocytic tumors of uncertain malignant potential,[3] and other features have been suggested (Table). The ability of these features to predict the growth of indeterminate choroidal melanocytic tumors has been validated by multiple investigators,[4,5] as well as the Collaborative Ocular Melanoma Study.[6]

On the 40th anniversary of his landmark Jackson Memorial Lecture,[3] we dedicate this article to Dr. Gass' seminal contribution and have asked 4 preeminent retina-trained ocular oncologists to discuss how they use these clinical risk factors in actual practice: Drs. Thomas Aaberg Jr, Ivana Kim, Prithvi Mruthyunjaya, and Amy Schefler.

Editors: Thank you for agreeing to participate in this discussion. First, we would like to poll you on the relative weight you place on each of the clinical "risk factors" and "protective factors" currently in use.

All 4 panelists: The most important features are tumor thickness, subretinal fluid (SRF), and orange lipofuscin pigment. A "halo" around the tumor is not of much value. Angiographic hotspots are rarely helpful, partly because fluorescein angiography (FA) is infrequently used nowadays.

You each felt that other features such as symptoms, drusen, fibrous metaplasia and low internal reflectivity are useful, but you differ in the weight you would place on these.

Table

Features Associated with Increased Malignant Potential
Tumor thickness > 2 mm
Serous subretinal fluid overlying and/or surrounding the tumor
Orange (autofluorescent) lipofuscin pigment over the tumor
Low internal ultrasonographic reflectivity (acoustic hollowness)
Visual symptoms attributable to the tumor (eg, photopsias, metamorphopsia)
Juxtapapillary location
Features Associated with Decreased Malignant Potential
Drusen overlying the tumor
RPE fibrous metaplasia overlying the tumor
Choroidal neovascularization overlying the tumor
"Halo" of depigmentation around the tumor

Thomas Aaberg: I put a lot of weight on the echography findings, internal reflectivity, and choroidal excavation.

Amy Schefler: I agree. For a lesion with low internal reflectivity or acoustic hollowness, I lean toward melanoma. The rate of growth is also important. I would be more concerned about a lesion that grew a given amount over 3 months than, say, 3 years.

Ivana Kim: Evidence of prior stability based on the availability of previous imaging is very helpful in my treatment decision.

William Harbour: In addition to these factors, age is an important consideration for me. Most of these lesions do not evolve quickly (if at all) from low to high molecular risk category. In an older person with an indeterminate lesion, I am more likely to observe closely, whereas in a young person with many more years for risk to accumulate, I am more likely to treat.

Zélia Corrêa: I also consider potential for vision loss before deciding to treat small tumors with ambiguous features close to the macula and disc. In these cases, I will often observe patients closely or obtain a diagnostic biopsy prior to committing to treatment.

Next, we would like to illustrate the value of these clinical features with a discussion of 3 challenging cases. Obviously, the major caveat to our discussion is that management decisions in actual patients are made in the context of patient preference, age, ocular and general health, and tolerance for treatment.

Our first case is a 32-year-old man presenting with metamorphopsia in the right eye for the past 6 weeks (Figure 1). He is extremely bothered by the symptom, which interferes with his computer work. Examination reveals a moderately pigmented choroidal tumor superior to the macula, measuring 6 x 5 mm in basal dimensions.

There is prominent fibrous retinal pigment epithelium (RPE) metaplasia with scattered drusen over the surface of the tumor, with SRF extending into the central macula. Echography has revealed a thickness of 2.9 mm, medium internal reflectivity, and trace vascularity. What is your preliminary diagnosis?

Drs. Kim, Mruthyunjaya, and Schefler: Small choroidal melanoma.

Thomas Aaberg: I do not believe one can say with certainty whether this is a melanoma or nevus (or somewhere in between) based on clinical features alone. I would put this lesion closer to nevus based on the fibrous metaplasia and increased echographic internal reflectivity.

The SRF could be due to tumor activity, but it could also be due to choroidal neovascularization (CNV) or "sick-RPE syndrome," resulting from chronic injury to the RPE from the underlying nevus.

OCT, FA, and fundus autofluorescence (FAF) would be helpful in such a case. An OCT showing a normal overlying retina and RPE would suggest that the SRF is due to active tumor leakage. An OCT showing cystoid retinal degeneration, retinal atrophy, and abnormal RPE overlying the choroidal lesion would suggest sick-RPE syndrome.

> 'The SRF could be due to tumor activity, but it could also be due to CNV or "sick-RPE syndrome," resulting from chronic injury to the RPE ...'
>
> —Thomas M. Aaberg Jr, MD

FAF showing trough-like RPE changes would suggest prior episodes of chronic recurrent SRF and hence a long standing (likely benign) choroidal lesion. An FA would confirm the presence of CNV.

Prithvi Mruthyunjaya: I agree about the value of additional diagnostic testing. OCT can be very helpful for determining the nature of SRF, and for distinguishing SRF due to RPE dysfunction vs active tumor exudation. In

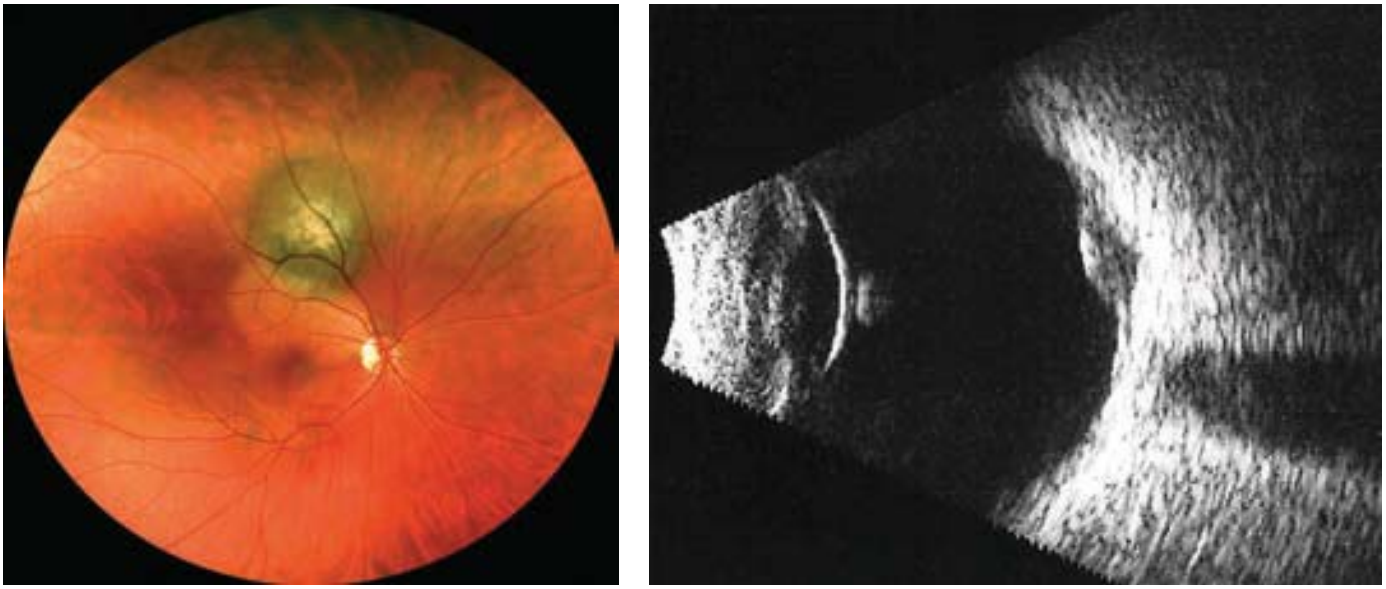

Figure 1.
Case 1. 32-year-old man with symptomatic choroidal melanocytic tumor in the right eye. Left, color fundus photograph showing the lesion located superior to the macula with secondary serous retinal detachment into the macula. Right, B-scan ultrasonography showing moderately elevated choroidal tumor with medium internal reflectivity.

addition, wide-angle FAF can show clinically subtle RPE changes arising from current or previous SRF.

William Harbour: We reported in 2004 the value of OCT for distinguishing true SRF from overlying cystic retinal degeneration.[7] These findings can be very difficult to distinguish on clinical examination and have very different prognostic implications.

OCT, FA and FAF did not show evidence of RPE dysfunction or CNV. How would you manage such a patient?

Drs. Aaberg and Mruthyunjaya: We recommend observation with follow-up evaluation in 2 to 3 months.

Ivana Kim: I would treat promptly with proton beam radiotherapy.

> 'Wide-angle FAF can show clinically subtle RPE changes arising from current or previous SRF.'
>
> —Prithvi Mruthyunjaya, MD

Amy Schefler: Given that this patient is young, the lesion is unlikely to remain stable over the course of his lifetime. Thus, I would treat now with plaque radiotherapy despite the fact that the lesion does not exhibit all of the classic high risk factors. This type of lesion will often have low-grade genomics at presentation, but may transform to high-grade genomics later. By treating promptly, we may have an opportunity to save lives, albeit at the cost of some central vision.

If your initial management was observation, what treatment would you recommend if, in 6 months, the SRF was still in the macula, and the patient was still extremely symptomatic?

Prithvi Mruthyunjaya: If the lesion had not grown, I would consider indocyanine green (ICG)-enhanced photodynamic therapy (PDT). Garcia-Arumi and colleagues reported complete resolution of SRF in more than 50% of cases using this technique.[8] Though I do not promote PDT as a primary treatment for uveal melanoma, sometimes it may play a role in fluid and symptom management while under close observation.

If definitive tumor growth were documented, I would recommend plaque brachytherapy with a notched plaque and concurrent tumor biopsy for genetic testing. Adjuvant transpupillary thermotherapy (TTT) is often needed for these juxtapapillary tumors. Proton beam radiotherapy would also be a good option.

Thomas Aaberg: I agree. While I am not advocating PDT as a primary treatment for choroidal melanoma, it can be used effectively to dry up SRF and may also induce partial regression in borderline cases like this. Of course, such a treatment does not result in definitive tumor ablation, so continued monitoring for tumor growth would be essential.

William Harbour: In an extra-macular small symptomatic tumor like this, I would consider diode laser hyperthermia (so-called TTT) with a low to medium energy to dry up the SRF, then continue to monitor the tumor for growth, in which case I would proceed to plaque radiotherapy. Dr. Corrêa, what did you do in this case?

> 'By treating promptly, we may have an opportunity to save lives, albeit at the cost of some central vision.'
>
> —Amy Schefler, MD

Zélia Corrêa: My experience with diode laser hyperthermia using low to medium energy to dry up SRF in similar cases has also been very positive. However, in this particular case, we performed a transvitreal fine needle biopsy, which showed very few cells and revealed a Class 1A gene expression profile (GEP). Based on that finding, the patient was not treated. The SRF resolved, and almost 5 years later, the vision has remained stable with no growth or metastasis.

Our second case is a 45-year-old woman presenting with metamorphopsia in the left eye for the past 2 weeks (Figure 2). She is extremely

Figure 2.
Case 2. 45-year-old woman with symptomatic choroidal melanocytic tumor in the left eye. Left, color fundus photograph showing small macular tumor with subretinal fluid and orange lipofuscin pigment. Right, fluorescein angiographic image showing late pinpoint hyperfluorescent hotspots.

bothered by the symptoms. Examination has revealed a lightly pigmented choroidal tumor in the superior macula, measuring 3 x 2.5 mm in basal dimensions. Orange lipofuscin pigment deposits and serous SRF are overlying the lesion.

There are no chronic features such as drusen or fibrous RPE metaplasia. FA has shown prominent late pinpoint hotspots but no well-developed intrinsic vasculature. Echography has revealed a thickness of 1.5 mm, low-medium internal reflectivity, and mild vascularity. What is your preliminary diagnosis?

Drs. Kim, Mruthyunjaya, and Schefler: Indeterminate choroidal melanocytic tumor.

Thomas Aaberg: I agree but would lean toward melanoma.

OCT, FA, and FAF did not show evidence of RPE dysfunction or CNV. How would you manage such a patient?

Drs. Aaberg, Kim, and Schefler: We would recommend close observation for evidence of growth, with follow-up evaluation in 2 to 3 months.

Prithvi Mruthyunjaya: I am very concerned that this lesion will grow into a melanoma. Plaque radiotherapy would carry a high risk of vision loss due to radiation maculopathy and optic neuropathy. Therefore, my initial treatment recommendation would be ICG-enhanced PDT to the leaking vasculature with close observation for growth.

If your initial management was observation, what treatment would you recommend if in 6 months the SRF was still in the macula, the patient was still extremely symptomatic, but the tumor had not grown?

Amy Schefler: I would recommend continued observation. At this small size, a reasonable proportion of lesion will not grow. If we use a threshold for radiotherapy of 1.5 mm in thickness, many benign lesions will be treated unnecessarily. That is, the number needed to treat (NNT) would be too high in this case (1.5 mm thickness), but would be reasonable in Case 1 (2.9 mm thickness).

Drs. Aaberg and Kim: We would recommend full-fluence verteporfin PDT in an attempt to reduce the SRF.

If your initial management was observation, what treatment would you recommend if, in 6 months, the tumor had increased in thickness from 1.5 mm to 3.0 mm?

Drs. Aaberg and Schefler: Plaque radiotherapy.

Prithvi Mruthyunjaya: I agree, though I would aim for a reduced apical dose of 70 Gy to try to reduce radiation-induced vision loss. Ruthenium-106 brachytherapy would also be a good option to reduce radiation exposure to the surrounding structures. To obtain a tumor sample for genetic testing, I would insert the biopsy needle at the superior aspect of the tumor, away from the fovea.

Ivana Kim: I would recommend proton beam irradiation at a dose of 50 Gy, with careful discussion about the risks and benefits of biopsy for molecular prognostic testing particularly with respect to visual prognosis.

Given the relatively young age of this patient and the small tumor size, the metastatic risk is fairly low. Therefore, the benefits of molecular prognostication have to be carefully weighed against the increased risk of visual loss from biopsy in this location. Despite the location of this tumor, our experience is that the visual prognosis after proton irradiation is not universally dismal in these cases.

William Harbour: After long discussion with this patient, we decided to monitor the lesion without treatment, and there has been no growth after 3 months. However, we have a very low threshold for proceeding to plaque radiotherapy if any growth is documented.

Our third case is a 72-year-old woman presenting with an asymptomatic choroidal lesion discovered incidentally during a routine eye exam (Figure 3). Her ocular, medical, and family histories were noncontributory.

Examination revealed a darkly pigmented choroidal tumor in the superior periphery of the right eye, measuring 12 x 10 mm in basal dimensions. There were prominent chronic features overlying and surrounding the lesion, including RPE fibrous metaplasia, intraretinal

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>
> —Ivana Kim, MD

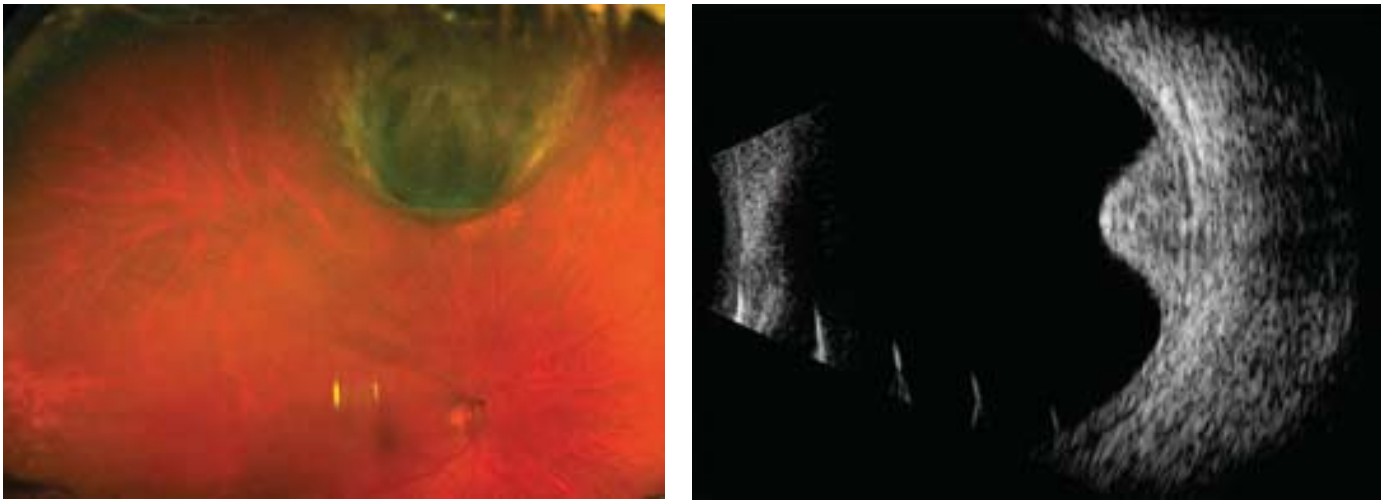

Figure 3.
Case 3. 72-year-old woman with medium-sized asymptomatic choroidal melanocytic tumor in the right eye. Left, color fundus photograph demonstrating the lesion in the superior periphery. Right, B-scan ultrasonography showing the 5-mm-thick lesion with medium to high internal.

pigment migration, and atrophy of the overlying retina.

There was no orange lipofuscin pigment, retinal detachment, or collar button configuration. Echography revealed a thickness of 5.0 mm, medium-high internal reflectivity with scattered small cavitary spaces, and no intrinsic vascularity. What is your preliminary diagnosis?

Thomas Aaberg: This is a very unusual lesion, particularly the echographic findings. The differential diagnosis would include not only a choroidal melanocytic lesion, but also an RPE adenoma. I would biopsy this lesion for both diagnostic and prognostic reasons.

Because of the atypical nature of this tumor, a biopsy was performed prior to making a management decision. Cytologic analysis revealed a diagnosis of melanocytoma without evidence of malignant transformation, and the GEP molecular classification was Class 1A. Would this additional information affect your management decision?

All 4 panelists: Yes. Given this information, we would choose observation.

Given the large size, would you still treat a melanocytoma as if it were a melanoma despite no clinical or histologic evidence of malignant transformation?

All 4 panelists: No, especially given the patient's age. The absence of active growth or histologic signs of melanoma make observation a more reassuring option, and malignant transformation of a melanocytoma is uncommon.

Does the Class 1A result have any impact on your decision?

All 4 panelists: No. It is not surprising that the gene expression profile would be Class 1A, indicating a more differentiated tumor. However, we do not have validation of this molecular classification in melanocytoma. The absence of growth or histologic evidence of melanoma are the findings that make observation a reasonable option until clinical signs consistent with malignant transformation are noted (eg, abrupt growth, retinal detachment, lipofuscin deposition).

William Harbour: This is true. However, several lines of evidence suggest that the GEP will apply to uveal melanocytomas as well. We have now analyzed several dozen melanocytomas and they have all been Class 1A. Further, colleagues have shown that melanocytomas undergoing malignant transformation acquire BAP1 mutations,[9] which are closely associated with the Class 2 GEP.

We included this case as a reminder of the importance of cytologic verification of melanoma at the time of prognostic biopsy. Some colleagues have published case reports in which they misinterpreted prognostic test results because they had made the wrong clinical diagnosis of melanoma in tumors that were actually metastatic lesions.

In general, prognostic tests are not designed to give diagnostic information. Contrary to recent claims, mutational analysis cannot substitute for good cytologic examination to confirm the diagnosis of melanoma, as melanocytomas can also harbor the characteristic GNAQ/GNA11 mutations.[9]

This patient did not want treatment, and based on these biopsy findings, we felt reasonably comfortable managing her with close observation. The tumor has not grown or changed in 4 years.

To summarize, the panelists and both editors agree that the most influential clinical features in their management of indeterminate choroidal melanocytic tumors include tumor thickness, presence of SRF, and orange lipofuscin pigment. However, none of these alone would drive the treatment decision.

Tumor thickness and internal reflectivity are best evaluated with ultrasonography. SRF can be best appreciated and distinguished from atrophic retinal separation using OCT. FAF can be very helpful in confirming the presence of orange lipofuscin pigmentation and distinguishing it from RPE atrophic changes, which can also have an orange-like color.

The discussion revealed a range of opinions regarding the treatment of small choroidal melanocytic tumors with 1 or more risk factors when the treatment decision involves a high risk of vision loss. The trade-off between vision loss and the possibility (however small) of "curing" a small melanoma can be a very challenging decision, especially since none of these clinical features is foolproof.

There is no convincing data in the literature to suggest that short periods of close observation for evidence of growth increase the risk of metastasis,[10] so this remains an attractive option in the initial management of many such cases. Indeed, tumor growth does not always indicate malignant transformation.[11] Ultimately, we continue to await more precise biomarkers to take the guesswork out of managing these small choroidal melanocytic tumors of uncertain malignant potential.

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Exploring the Role of Private Practices in Retinal Research

Historically, academic centers and pharmaceutical companies have been driving forces behind clinical trials and medical innovation. In the retina community, however, private-sector physicians also have played—and continue to play—a large role.

Benefits of conducting clinical research for private-practice physicians include, among others, diversifying the practice's revenue stream, remaining at the forefront of innovation, and offering treatment alternatives to patients in need.

This Issue's Key Opinion Leaders

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However, it is crucial to be aware of the downsides of clinical trial participation, such as increased regulation and compliance, the cost and complexity of running trials, and time spent away from routine clinical care.

Undoubtedly, clinical trials are the foundation of medical advancement and new-drug development. Recent trials have brought us retinal breakthroughs—helping validate treatments for age-related macular degeneration (AMD) and bringing us ranibizumab and aflibercept. Similarly, they have helped us determine which therapies work best for diabetic macular edema (DME).

Certain aspects of private sector-based clinical trials and research differ from those performed at academic institutions. To help us better understand the intricacies of conducting clinical trials in nonacademic practices—especially for physicians considering getting involved in clinical trials—we spoke with 2 key opinion leaders who have vast experience in conducting private practice-based clinical trials.

What factors led you to offer clinical trials as part of your retina practice?

Dante Pieramici: There are a number of reasons to consider clinical research in a busy clinical practice setting. Probably the most important is that research studies will provide your patients the opportunity to receive potentially beneficial therapies years before they are approved by the Food and Drug Administration (FDA) and are available for mass distribution.

There are still many retinal diseases with no effective therapies, and over the next few decades, myriad potential therapies will be tested. Certainly some will prove ineffective and/or unsafe, but others will provide remarkable benefits to our patients. Receiving the therapy early may change the course of some patients' lives.

> **'Research studies will provide your patients the opportunity to receive potentially beneficial therapies years before they are approved by the FDA ...'**
>
> —Dante J. Pieramici, MD

Having experienced the introduction of anti-VEGF therapy from the ground up, I still see numerous patients who are driving and reading almost a decade later because they were given the opportunity to be part of an early-phase anti-VEGF trial.

A second important reason to engage in research concerns the desire and passion for scientific inquiry. Many of us consider ourselves clinician-scientists, and active research is a key part of a satisfying, stimulating career in medicine.

Clinical practice can, at times, become monotonous, especially in the age of anti-VEGF therapy. Research allows us to step out

of the routine and explore a more creative side of medicine. It is a great way to recharge our enthusiasm about ophthalmology, especially after a week of intravitreal injections.

Most medical advances result from the work of hundreds of researchers, each contributing a small, incremental piece of information that advances our collective understanding of retinal diseases. A final benefit of research is that it is a great way of marketing your practice. Involvement in ongoing clinical research reflects your practice's commitment to providing the latest therapeutic options and emphasizes that you are keeping up with these advances.

Gaurav Shah: Our practice considers clinical trials important. As the premier retina practice in our region, we offer these trials for patients to enhance both our patient care and the education process we provide to fellows. Clinical trials allow us to offer potential therapies not available in the marketplace.

Being on the leading edge of medical and surgical trials is essential to have an enriching and educational environment for our fellows to not only learn from but, hopefully, to emulate as they get into clinical practice, in both academic and non-academic settings.

In what ways is running a research unit different in private practice than in a university setting?

Dante Pieramici: Having been a primary investigator in clinical research in the university and private-practice settings, I have concluded that clinical research is more efficient and cost effective in private practice. Deciding to be involved in a clinical trial requires far fewer levels of bureaucracy in private practice and, most of the time, needs the commitment of only a few individuals. Overhead costs in the university setting can be significant as parties not directly involved add to the overhead (eg, the "dean's tax"), while in private practice, overhead costs are minimized.

Additionally, university institutional review board (IRB) approvals may stall or halt a trial's initiation. When enrollment is competitive, such a delay may severely limit a university site's ability to enroll prior to closure of the study—so it should not be surprising that the higher-enrolling centers in most retina clinical trials during the last decade have been private practices.

On the other hand, laboratory research can be very difficult or impossible in the private-practice setting. Setting up the infrastructure, obtaining space, and hiring staff to conduct bench research is costly at best. Taking time away from clinical practice is an availability and financial opportunity cost for private practices. Despite these challenges, a number of private practitioners are able to maintain basic research efforts, though these individuals are a rare breed.

> **'Clinical research is more efficient and cost effective in private practice ... [and] ... overhead costs are minimized.'**
>
> —Dante J. Pieramici, MD

Gaurav Shah: There are many challenges in running a research unit in a hybrid practice such as ours, where we are involved in patient care, research, and education, compared to an all-university practice. The biggest difference is that we cover many satellite locations, unlike an academic practice's typical one main university campus setting.

Our clinical trial participation can be difficult as we may have multiple sites for the same study, but each site is encountered differently for both its regulatory and non-regulatory requirements. Unfortunately, trial companies and pharmaceutical companies have not adjusted to the current retina paradigm of having multiple satellite offices without one "main office."

We have several "main offices" in our practice, but sometimes it is difficult for patients to remain in those offices because they like to be seen at different locations. It would be ideal if patients could be switched between offices to make it more amenable to enroll in clinical trials.

Also, the IRB situations are different in private practice vs university settings which, in some ways, makes it easier for us to do clinical trials. There were situations in the past when having to go through a university IRB made it exceedingly difficult—the trial ended before we could get an IRB approval because of the changes required by the university IRB compared to Western IRB. This is often an issue in many universities because of the separate committees and other issues involved in certain institutions' administrative processes.

In situations where there are multiple active studies for a single disease state, how do you decide which trials to conduct, and how many studies to conduct at once?

Dante Pieramici: In general, we try not to have overlapping trials that would compete directly for patients. However, because research sites are approved by location, we might have one of our offices recruiting for a DME study with drug A, while a distant office might recruit for DME study drug B.

Differing inclusion criteria might be another reason to have 2 trials recruiting for a similar disease process at a given site. For instance, one geographic atrophy trial might exclude patients with a history of neovascular disease in the fellow eye.

Taking on too many trials can result in poor recruiting for many studies. Much of the effort in running a trial occurs during the start-up phase—getting IRB approval, training investigators and coordinators, etc. Some studies can have a learning curve, especially the surgical ones. There is a better chance of demonstrating a procedure's positive effect if the complications of learning are reduced.

Our practice functions as a democracy, and this is true for research studies as well. The research director will present studies of potential interest to the group during a lunchtime conference call. We will pursue a trial if there is clinical research interest on the part of the physicians, enough research support staff to take on another trial, evidence for patient need and interest, and we can work out a financially viable budget.

Gaurav Shah: This is a key question. We try not to have different active studies for a single disease, but there are instances where this occurs. We typically restrict the principal investigator to certain offices, making it easier for patients to get enrolled.

Also, we try to see if there is some variance in the types of patients who can be enrolled in different trials for the same disease. This has been true in some of the vein occlusion and AMD trials where we are able to offer multiple studies for the same disease, but at different offices since each office is considered an independent unit according to the clinical trial protocol.

So although we try not to have more than one active trial for a single disease state, sometimes it is hard to turn down trials we feel are going to be helpful for our patients. From a practice management perspective, it is essential to engage

your research staff in your clinical practice. I think most centers that do very well in recruitment, such as Jeffrey Heier's in Boston and David Brown's in Houston, have made trials a priority along with their clinical practice.

Make sure clinical trial study patients are given an expedited approach during office visits, because they are there for much longer than other patients. The last thing we want is to have patients drop out of studies because of the time constraints. We try to fast-track these patients because they are doing a service—to us, to the sponsor, and to society—by participating in a clinical trial. They are certainly not being reimbursed for their time. Try to integrate these patients into your schedule in a way that expedites their process.

From a practice management perspective, how do you integrate your research staff into your other clinical staff?

> **'Make sure clinical trial study patients are given an expedited approach during office visits, because they are there for much longer than other patients.'**
>
> —Gaurav K. Shah, MD

Dante Pieramici: Integrating the research staff with the clinical staff is a work in progress. Many of our coordinators began their careers in our practice as clinical technicians, so they come to research with an understanding of the logistics of our patient flow and disease management. We schedule patients into our regular physician clinics, but the research staff manage those patients from the technical side.

Angiographers work with both research and non-research patients, so it is important to schedule the research patients so they do not overlap with their regular clinic patients. Ancillary testing such as OCT and angiograms can be more labor intensive for the study patients due to the specifics of the protocols.

Under our research director's guidance, we have made efforts to open the lines of communication and build team spirit between the clinical technicians and research coordinators. The research staff will host lunches and provide education about ongoing trials for the regular clinical staff. In addition, they will pay "bounties" or small gifts to the clinical staff for identifying potential study patients. There is no hierarchy between the research and clinical staff, and no one is above jumping in to help the other side when needed.

Gaurav Shah: Sometimes it is difficult to have separate staff for studies and for clinical patients, but our practice does have separate staff. Because there is significant paperwork associated with studies, having dedicated employees makes it easier. If help is needed, our study folks are more than able to help to work up patients for the office, so ultimately a team approach is needed to ensure clinical flow and study recruitment.

What advice do you have for others thinking about initiating clinical trials in their practice?

Dante Pieramici: My advice for someone thinking about initiating clinical trials is to identify someone who is smart, energetic, and very organized to be your first coordinator. A person who is a little higher on the obsessive-compulsive scale may be a perfect fit. If he or she has no ophthalmology background, start that person working in the clinic for months to get proficient in the basics of diagnosis and management of retinal diseases.

In our research department, the more-senior coordinators teach the newer coordinators. We tend to start the new coordinators with smaller studies or investigator-initiated trials where we have more control over the protocol and data collection.

> **'Because there is significant paperwork associated with studies, having dedicated employees makes it easier.'**
>
> —Gaurav K. Shah, MD

We have also found that the Diabetic Retinopathy Clinical Research Network (DRCR.net) is a great resource for new coordinators. Given the numerous knowledgeable and helpful folks at the DRCR.net's coordinating center, a number of yearly meetings for coordinators, and readily available online information, getting into this network can significantly enhance a new coordinator's education and expertise in clinical trials while providing collegiality.

Editor's note: For more information on DRCR.net research, see the Young Physicians Section's Special Report beginning on page 24.

Gaurav Shah: I think you must do clinical trials for the right reasons. Certainly, some practices make a significant amount of money doing them. We don't at this point, but I think there are practices where it is lucrative.

Offering the best potential therapies for our patients, now and in the future, is the reason I believe it is important to participate in clinical trials. It also is crucial to look at clinical trial budgets; many practices either end up losing money or are revenue neutral. If the only goal is to do well financially with clinical trials, that may not be achievable because there are a lot of internal and external costs associated with clinical trials despite getting the "big check" at the beginning of the study. Look carefully at the budgets and the time spent for clinical trials; then determine whether you have the time, energy, and staffing to support the endeavor.

Also, it takes commitment to do clinical trials. You will need to go to investigative meetings and participate in conference calls which, in most cases, represent uncompensated time. If you think there is value in participating in a clinical trial, it is probably worth doing. Be sure to do it for the right reasons; if you are just trying to make it a lucrative process for your practice, you might be disappointed.

Financial Disclosures

Dr. Pieramici – ALLEGRO OPHTHALMICS, LLC: Investigator, Grants; ALLERGAN, INC: Investigator, Grants; GENENTECH, INC: Advisory Board, Consultant, Investigator, Grants, Honoraria; REGENERON PHARMACEUTICALS, INC: Investigator, Grants; SANTEN PHARMACEUTICAL CO, LTD: Consultant, Honoraria; THROMBOGENICS, INC: Advisory Board, Investigator, Grants, Honoraria.

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Dr. Spirn – None.

Richard A. Garfinkel, MD
Section Editor

Larry Halperin, MD
Section Editor

Take Control of Managed Care Contracting

Virtually all US retina specialists are aware of the increasing regulatory challenges thrust upon us, as well as the declining reimbursements that have to support these added costs to our practice. This imbalance can result in paralyzing frustration. Our Medicare reimbursements are cut at the whim of bureaucrats, and we can only hope to effect change at the society level.

Commercial carriers are different, however—both in terms of reimbursement and in some instances, in our ability to practice medicine in a way we deem best for our patients. How do we tackle the daunting task of negotiating better insurance contracts, and equally as important, how do we begin to retake control of patient care?

Mark Misiunas, MPH
Managed Healthcare Strategies, LLC
Atlanta, Georgia

'Back in the 1990s, the term *managed care* could have been interpreted to mean that if payers were effectively managing their costs, they were, in essence, managing care.'

—Mark Misiunas, MPH

To explore these issues, Retinomics spoke with managed care consultant Mark Misiunas of Managed Healthcare Strategies, LLC, in Atlanta. His nuanced understanding of payers' thinking is born of his previous work in managed care contracting for a major insurer and as vice president of managed care for a large physician practice management company.

Larry Halperin: How has managed care contracting evolved over the years?

Mark Misiunas: About 20 years ago, managed care primarily involved fee-for-service contracting, some risk-based contracting, and, depending on market, single-specialty and/or full-risk agreements entered into with risk-bearing entities such as independent physician associations (IPAs), physician hospital organizations (PHOs), and other similar organizations.

Larry Halperin: How has the concept of managed care itself changed?

Mark Misiunas: Back in the 1990s, the term *managed care* could have been interpreted to mean that if payers were effectively managing their costs, they were, in essence, managing care. This was under the old paradigm. That line of thinking quickly evolved as fee schedules got so low that there was no place to go. At that point, we had to look at how to tackle this beast.

Rich Garfinkel: Let's say a physician practice client has decided they've hit rock bottom with their fee schedule and they're looking to try to negotiate a contract. How do you even find out whom to contact at an insurance company to negotiate a raise in your rates?

Mark Misiunas: That's probably one of the biggest struggles facing physician practices. Things have gotten so complicated, overhead has gotten so high, and resources have been stretched so thin that, sadly, we don't know whom to contact—or in many cases, what our contractual rate is vs what we're getting paid.

First, we need to identify the top 5 private payers within our practice—a pretty easy exercise. In most cases, 4 or 5 payers represent approximately 80% of a retina practice's non-Medicare book of business. Then, once we filter out the governmental payers for which we usually don't have any control over fee schedules, assuming they are priced at 100% of the governmentally set rate, we can get to a realistic idea as to the potential re-contracting opportunities.

Rich Garfinkel: But how do you know who's the one on the payer's side of the table to negotiate and change the contract?

Mark Misiunas: To find out, your best option is to start at the top. Always try to learn the name of the director or vice president of network development and obtain his or her direct phone number. Sometimes that's hard to do, but once you identify the top person, you can work your way toward the contracting representative assigned to each specialty or to each county or statistical area. Contacting that representative is your best bet.

Larry Halperin: So the next step would be to try to find the active contract with each of those payers, which is not always easy. Then how do you go about figuring out what the payers are actually paying, so you know where you're starting?

Mark Misiunas: That is a great question. It's a challenge to gather documents that may have been signed a decade or more ago. But once you've done that—a herculean effort for most practices—you can look at just 5 or 6 key pages of those agreements.

If you want to determine where you are financially, you need to look at those reimbursement exhibits, clearly understand them, and create a spreadsheet that lists the payer and the terms. That spreadsheet can be as simple or complex as you like, but it will give you a beginning point for your analysis.

Next, conduct what can sometimes be a painful explanation of benefits (EOB) analysis showing how allowables compare to the agreements you've identified in your spreadsheet. Therein lies the great divide of what probably has been amended repeatedly, over many years, and that forms the basis point for a proper negotiation with a payer.

Larry Halperin: How often do you see practices not getting paid what they're contracted to get paid?

Mark Misiunas: Often, particularly when you compare the written agreement in your file to current allowables. When a difference is identified, it often results from amendments that the practice had no idea took place, often as a consequence of a deemed amendment. For example, there were probably notifications to the practice of fee schedule adjustments that may not have made it into the contract file. So, it is often a question of how well you've managed your payer relationship.

Rich Garfinkel: Let's say you've done your homework; you have your spreadsheet and you've successfully contacted the carrier's negotiator. Then, my experience has been that during the course of this negotiation, the carrier's negotiator ends up having to check with the director or the vice president of network development—and there's a big lag in the response time. You realize that every 6 months they postpone the negotiation is another 6 months they keep the status quo. How do you keep that process moving?

Mark Misiunas: It comes down to persistence and understanding your objectives in contracting. Let's say your contract is grossly antiquated, it's ranked among the worst in your contract portfolio, and you determine it will take a 20% increase to bring it up to what the practice feels is reasonable. If the only increase you're willing to agree to is at that level—which is potentially not achievable—that contract may never be renegotiated. It comes down to identifying what you're willing to accept, what your objectives or contracting goals are—and whether they're realistic or not. I often like to use the angle of incremental adjustments—allowing the payer to get to where you need to be through scheduled adjustments.

Larry Halperin: As opposed to jumping to where you want to be immediately?

Mark Misiunas: Correct. It is very difficult, and you'll often hear payers say their negotiations with employer groups, brokers, and stakeholders are based on projected medical costs of a forthcoming year—and they could argue that rate increases are limited to X percent per year on a network-wide or aggregate basis. The objective of the practice, of course, is to try to get the largest possible share of that, understanding that huge, one-time rate hikes are far from the norm today.

Rich Garfinkel: So are you saying that if they don't get back to you after you've made this demand they realize they can't meet, they're better off continuing to have you as a provider and not getting back to you to deny your request?

Mark Misiunas: Yes, and that's when it gets messy. While we're all struggling in the health care sector, these payer offices are grossly understaffed and the representatives are overworked. So, within the realm of re-contracting, I would err on the side of being kind and respectful, but extremely persistent. That goes a long way because the payers do need to maintain a network of quality physicians.

After you've made reasonable attempts to gain feedback to your renegotiation request, methodically go up the ladder to people higher in the organization and progress will be made.

Rich Garfinkel: How much does your approach to a negotiation depend on whether the client is willing to walk away from a contract because it is so inadequate, or whether the client simply is just probing for a better deal?

Mark Misiunas: In other words, how aggressive do you want to be and what's the success of being incredibly aggressive vs mildly aggressive? Generally speaking, I don't think anybody wins by submitting a letter of termination. Rarely would I recommend that, unless circumstances are so extreme that it's the best option. This is not to say that termination is not a viable option, it is just not how I would suggest that any negotiation begin.

The best approach is to try to work with what you've got. Payer dynamics vary substantially by market. So the question is, have you evaluated your leverage in the market and utilized that leverage to the extent required to get what you need? The biggest problem physician practices are facing is that they're not taking action where they could be.

Rich Garfinkel: How much of what you do is selling the practice, and how much is just approaching the carrier, making contact with the right people, reviewing the contract, and trying to negotiate a better one?

Mark Misiunas: Physician practices are best served when they market themselves—not only to their referring physicians, but also to the payers that drive their revenue. Much of negotiating, developing enhanced contracts, and achieving your objectives is related to how well the key players in your payer community know your practice. Successful negotiations depend, in part, on name recognition of the practice and whether a relationship exists with the payer's medical director, the director of contracting, or contracting representative.

If your payers have never heard your name, are unfamiliar with your practice, or have never received a phone call or other communication from your office, you're selling yourself short. You need to know your payers and who runs them—and whom to call when you need help.

> **'The biggest problem physician practices are facing is that they're not taking action where they could be.'**
>
> —Mark Misiunas, MPH

Larry Halperin: A significant percentage of ASRS members are in 1- or 2-person groups with a reasonably large catchment area and a decent number of plans. I know you've worked with a lot of big groups; what's been your experience in working with the small 1- and 2-person groups in urban or rural markets? Have you been successful, and is the approach different?

Mark Misiunas: The leverage a solo practitioner has—compared with a group of 4 or more physicians—varies, but keep in mind that negotiations are tough, regardless of practice size. While your options may be limited in one or more respects as a solo practitioner or small group practice, it comes down to leverage, particularly if the practice has a large catchment area or operates in a rural market. That is all

the more reason why you need to keep your name and the name of the practice in front of your payers—you need to know who your payers are in your community to gain headway.

Rich Garfinkel: So, on the other end, if you have a 7- or 10-person group, is there a way to look at market share and determine whether you're in a position where the insurance carrier has to negotiate with you?

Mark Misiunas: Yes. And that is why it is important to assess your medical marketplace. If you know your leverage in the market, and you know they need you more than you need them, there is a perfect opportunity for a renegotiation. But that circumstance is not limited to a large group—it could be the case with a small group.

If you as a solo or small group practice are the best out there and you know that, and you understand what makes your practice unique, you can enter into a proper dialog with the medical director or contracting representative of that plan. That is a perfect opportunity.

Larry Halperin: I have experience negotiating on behalf of our practices. More than 10 years ago, we did this on our own and had some success with it. Then the marketplace changed; the dynamics grew beyond my personal ability to handle and it became increasingly difficult for me to forge the necessary relationships with the people in charge of the networks in South Florida. I had no idea who they were, they didn't know who we were, and that's how we ended up needing a managed care consultant.

Mark, how would you say things have changed in the past 5 or 10 years, and what do you think will happen in the next 5 years?

Mark Misiunas: Let's go back to the early 2000s or even longer ago, when contracts were far richer, we had fee-for-service-based rate structures with little to no downward pressure, and life in the practice was, at least from a reimbursement perspective, pretty good. Then, as we all recognize, the marketplace changed rapidly.

For example, in risk-based reimbursement models, single-specialty capitation networks emerged and some networks did not survive. Issues arose because the contracts between payers, the entities accepting risk, and physicians in those networks were not based on a win-win-win model. And the losers were the physicians and—ultimately the subscribers.

Then, in markets that experienced such turmoil, we returned to fee-for-service contracts, but at grossly reduced rates or at rates significantly reduced from those we had 10 or 15 or even 20 years ago. Now, from a rate structure perspective, we have hit near rock bottom. Some in the payer world would say it's not low enough, but most would agree that things are probably about as low as they're going to get.

Rich Garfinkel: Doesn't today's consolidation, having fewer carriers in each region, enable the carriers to take advantage of the playing field more now than 10 years ago?

Mark Misiunas: Yes. A consolidation of payers in the market can ultimately result in decreased reimbursements. Couple that with the passage of the Affordable Care Act and the penetration of high-deductible plans and there is no question we've got a lot of work to do, from a physician practice perspective, to make up for lost ground.

Rich Garfinkel: We have been talking about negotiating rates based on procedures or office visits. But insurance companies seem to have an array of tactics to either delay payments or require more work from the provider so that you might not want to use an expensive therapeutic, for example, because it's such a hassle and a strain on the office. Do you have any experience in negotiating to eliminate pre-payment reviews required under certain circumstances? If so, how's that done?

Mark Misiunas: We're seeing a lot of the Medicare Advantage plans requiring a tremendous amount of oversight and medical record review. In some markets, physician practices have had success in charging the payer for gathering all of those records for, say, the last year. But most contracts we're entering into now have some limitations on how much payers are willing to pay to offset the costs of these audits. I wish we had a better answer.

Larry Halperin: Are pre-payment audits just lower and middle management doing their job because someone's breathing down their neck to make sure that all the t's are crossed and i's are dotted? Or is this the evil empire conspiring to not pay physicians for the care that they've already provided? Are they trying to figure out a scheme to not pay us?

Mark Misiunas: The payers will tell you they are obligated by the government payers they contract with to conduct audits and, as we realize, audits have become pretty widespread. I cannot overemphasize the importance of practices speaking with the payers requesting such audits about the resulting burdens to the practice. We're hearing more now about claims for in-office-administered pharmaceuticals taking 5 or more months to be paid. That's at least part of what you're getting at, right?

Rich Garfinkel: Yes—is there any recourse for the practice for the amount of time it's taking to be paid?

Mark Misiunas: It's going to take a concerted effort by the larger practices and strategically positioned physicians in each marketplace to take payers to task about slow payments.

Rich Garfinkel: Would that recourse be through an insurance commissioner? Through legal action? How would you think that might happen?

Mark Misiunas: Many payer contracts prohibit consolidation of physician groups in addressing certain matters. So I think it is best for the physician and physician group affected by slow payments to take the lead and communicate, in writing.

Payers are responsible for addressing these matters. If a particular payer issue affecting a group is resulting in harm, it is our responsibility as physician groups to take that up with each payer independently and privately. I've been noticing a lot of it lately, primarily around the Medicare Advantage plans.

> **'A consolidation of payers in the market can ultimately result in decreased reimbursements.'**
>
> —Mark Misiunas, MPH

Larry Halperin: I'd like to address the concept of tiered care, where a payer will contact a practice and try to impose using inexpensive off-label Avastin before using more expensive FDA-approved therapy. Recently a friend told me that one of his practice's major payers sent him a letter saying they would be contacting all of his referring doctors and primary care physicians in his network if he didn't stop using expensive drugs.

The payer said they were going to be directing patients to another practice that would be more compliant, which sounds illegal to me. In the case of payer-enforced tiered care, the insurance company feels they can force the treatment choice.

Mark Misiunas: We're seeing that form of a therapy policy emerge in several markets, and recently a policy was implemented by a major carrier essentially requiring the use of Avastin as first-line therapy. Physicians feel they need

ASRS Physician Choice of Medication Campaign Opposes Tiered Therapy

Since 2012, the ASRS has been closely monitoring incidents of tiered therapy (also known as *step therapy)* in which third-party payers have established policies restricting physicians' choice of medication in treating macular degeneration.

The ASRS has engaged state and national third-party payers to resolve such issues and to urge them to allow retina specialists and their patients to make wise and judicious choices based on each patient's unique risk factors and clinical appearance, as well as the availability of compounded drugs, and existing economic requirements.

Of the 3 available anti-VEGF agents, only ranibizumab (Lucentis, Genentech, Inc, South San Francisco, CA) and aflibercept (Eylea, Regeneron Pharmaceuticals, Inc, Tarrytown, NY) have specific Food and Drug Administration (FDA) approval, while lower-cost bevacizumab (Avastin, Genentech, Inc) does not, and is repackaged for off-label ophthalmic use.

ASRS believes it is inappropriate for any insurer to require the use of tiered therapy, whereby a single anti-VEGF agent (typically Avastin) is required to be used for treatment before one of the other FDA-approved agents (Lucentis or Eylea) is considered.

Based on the Society's advocacy efforts, the Centers for Medicare & Medicaid Services (CMS) has publicly reaffirmed its policy with Medicare Advantage (MA) organizations, saying in a 2012 letter, "the imposition of additional requirements for access to certain Part B drugs or services, such as step-therapy requirements, is not permitted unless also required through Original Medicare."

> 'ASRS believes it is inappropriate for any insurer to require the use of tiered therapy ...'

Because Medicare does not have a step-therapy requirement for anti-VEGFs, MA plans cannot establish their own policy.

In 2014, the agency went a step farther by agreeing to investigate MA programs that ASRS had identified as having step-therapy policies.

In 2015, additional progress was marked as large insurers, including Humana, revised their policies to address this issue.

Artificially imposed practice modifications for non-medical, financial reasons is ill advised and continues to be actively opposed by the ASRS on a national and international level, and by other societies and individuals on a state and local level.

See a tiered therapy policy? Notify ASRS

Please contact ASRS Executive Vice President Jill Blim at jill.blim@asrs.org if you have any evidence that an insurance plan has a tiered therapy policy or is restricting beneficiaries' access to Medicare Part B drugs or services.

For more information on this and other ASRS advocacy campaigns, visit www.asrs.org/advocacy-practice

to jump through hoops to utilize anything else, even if deemed more appropriate.

I think this is just going to have to play out. It's up to us to raise this as a substantive issue with the proper people in each payer office implementing or considering implementing such policies.

Larry Halperin: I have heard that some physicians have gathered together to achieve a new state law that prevents the imposition of tiered care.

Rich Garfinkel: Another ally we have in this battle are the patients. There are certainly contractual limitations to using your patients, but I know that the great fear of the insurance carriers is that subscribers will become disillusioned with their plans.

Are there strategies, based on most standard contracts, that would be helpful in educating patients to call their insurance carriers to complain that the payer is preventing the use of branded drug? What do the insurance carriers fear besides their subscribers?

Mark Misiunas: It's just that. No payer wants unsatisfied members, and no employer group funding its employee benefit plans wants to hear complaints from employees that the selected insurance vendor is implementing policies inconsistent with established, physician-recommended courses of treatment. I can virtually guarantee payers will listen when their contracted employer groups are not happy.

So the best thing patients utilizing employer-funded insurance can do is to contact their director of human resources, or whomever administers employee benefits. These individuals have direct or indirect communications with the payers and, in large or small ways, have an impact on employer decisions about insurance vendor selections. This is one important way to influence change.

Larry Halperin: Mark, are we permitted to ask patients to call their carriers to explain the problem?

Mark Misiunas: Yes, physicians should have no restrictions, and most payer contracts are explicit that a payer cannot control the dialog you may have with patients with respect to their care. It's in nearly every current payer contract. The key is handling that scenario in such a way that you remain compliant with your contract.

Rich Garfinkel: Mark, do you have any concluding advice?

Mark Misiunas: When we look at our practices and try to tackle the issue of managed care, what doesn't work is inaction—sitting back and doing nothing to improve a substantive issue needing attention. Yes this is what we see so often.

What does work is to take note of our top 4 or 5 private payers, our top Medicare Advantage plans, our top Medicaid HMOs, and determine the 1 or 2 things we could do within a year that would have a meaningful difference. That may include identifying the payers we may consider dropping. Simply investing time in review and analysis is worth its weight in gold. As always, help is available if needed.

Financial Disclosures

Dr. Garfinkel – COVALENT MEDICAL, LLC: Stockholder, Stock; NOTAL VISION: Advisory Board, Consultant, Honoraria.

Dr. Halperin – COVALENT MEDICAL, LLC: Stockholder, Stock, Other Financial Benefit; REGENERON PHARMACEUTICALS, INC: Consultant, Honoraria.

Mr. Misiunas – None.

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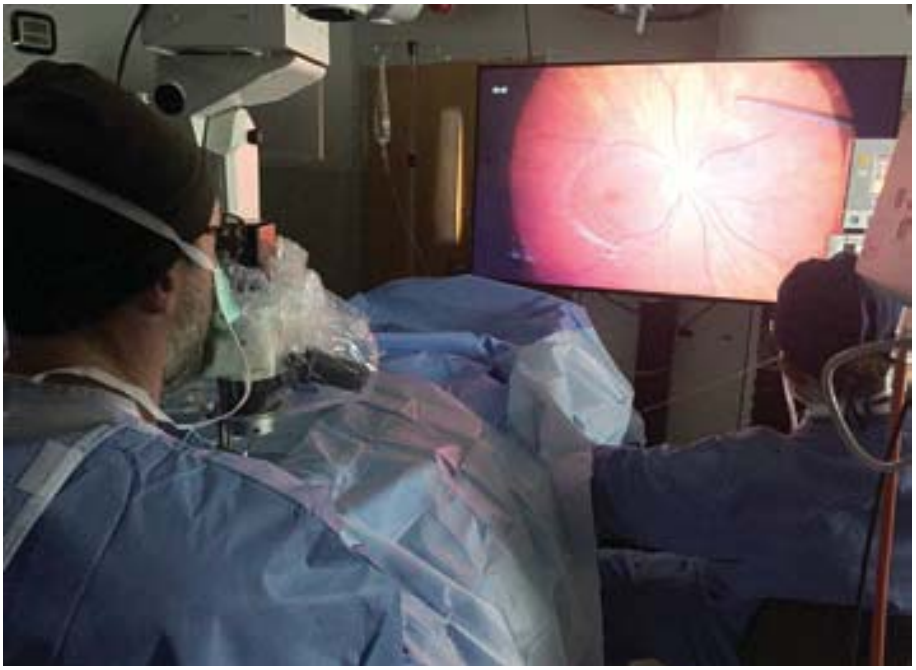
Road Testing the NGENUITY/TrueVision 3D Visualization System

In September, Alcon Laboratories, Inc (Fort Worth, TX) launched the NGENUITY 3D Visualization System in collaboration with TrueVision 3D Surgical (Santa Barbara, CA). The system features next-generation visualization technologies and an intelligent, ocular-free design for digitally assisted vitreoretinal surgery.



John Kitchens, MD, uses the heads-up viewing system with a high-definition 3D screen engineered to improve the surgeon's posture.

Road Test asked 3 retina specialists to test-drive the NGENUITY/TrueVision 3D Visualization System and to report on their experiences.

John W. Kitchens, MD
Retina Associates of Kentucky
Lexington, Kentucky

Advancements in vitreoretinal (VR) surgery tend to occur as an *evolution* rather than a *revolution*. Certainly, breakthrough technologies such as small-gauge surgery have fundamentally changed the landscape of the specialty. But for every revolutionary development, there are dozens of smaller, incremental improvements such as vented gas forced infusion (VGFI) or enhancements in illumination.

In the 11 years I have been practicing, almost all advancements have been to the vitrectomy machine itself. Outside of non-contact wide-angle viewing systems—a revolutionary change—very little advancement has been made in the realm of microscopes, surgical beds, or ancillary surgical equipment.

The NGENUITY/TrueVision 3D Visualization System (N3DVS) is one of those revolutionary technologies, with a few caveats. In many ways, this system is to teaching and surgical video creation what small-gauge instrumentation was to VR surgery. And, much like the initial version of small-gauge surgery, the system has limitations.

The fact that NGENUITY's most obvious benefit is in teaching and surgical video creation, combined with the financial considerations of purchasing the system, will likely mean that the system (in its current iteration) may not appeal to the vast majority of VR surgeons. But the untapped potential of this system and the future direction of development will make this technology indispensable for VR surgeons.

What is 3D heads-up surgery?

The N3DVS is the first device that replaces the traditional oculars of the surgical microscope with a 3D camera. That 3D camera is linked to a 4K screen positioned (ideally) at the foot of the patient's bed. The surgeon—as well as the surgical assistant, scrub nurse, and anyone else in the room—wears 3D glasses to visualize what is occurring inside the eye.

> **'In many ways, this system is to teaching and surgical video creation what small-gauge instrumentation was to VR surgery.'**
>
> —John W. Kitchens, MD

NGENUITY is the first system to utilize the advancements in technology to change the way we view and perform surgery. The system can be attached to almost any current surgical microscope and replaces the oculars and inverter device, as inversion (for wide-angle viewing systems) is now performed digitally.

Improved visualization?

One unexpected benefit of this system is the improvement over the traditional microscope in visualization achieved during surgery. This is due to a combination of factors. First, any older microscope will lose optical quality over time—particularly one shared with anterior-segment surgeons who request that inverters and laser filters be removed. NGENUITY eliminates several lenses (oculars) and prisms (inverters) as well as beam splitters (assistant scope or video camera), which can deteriorate the surgeon's view.

The N3DVS utilizes high-dynamic-range (HDR) sensors that let users adjust the color saturation, contrast, light exposure, and other variables to give the surgeon a "crisper" view. The system provides a slightly larger field of view (subjectively), allowing better visualization of the vitreous, particularly in the periphery. The NGENUITY system improved the view of our 15+ year-old Leica scope (Leica Microsystems, Wetzlar, Germany) significantly, to the point at which it rivaled a new microscope.

Postural changes

3D heads-up surgery frees the surgeon of traditional oculars. No longer is the surgeon forced into the posture of peering into the microscope. I found this system allowed me to assume a more relaxed position. As a relatively younger surgeon at 43, I found this benefit negligible for most cases, but there was a noticeable difference in longer cases—particularly in my neck and lower back. As cervical spine issues are a major cause of disability for ophthalmologists, this system may reduce these issues for some surgeons.

Surgical videos

The quality of surgical videos obtained by this system is unparalleled. NGENUITY's ability to record exactly what the surgeon is seeing during the case, with HDR cameras, provides amazing surgical video in either 3D or 2D. As someone who appreciates quality surgical videos, I can say this system provides stunning video imagery.

The downside: The file size of the surgical video is considerable, and editing 3D video is tremendously intensive on any computer system. The system comes with fairly easy-to-understand 3D video editing software called TrueEdit; this software allows the surgeon to select portions of the case, create basic video effects such as titles and transitions between clips, as well as export the edited video in either 2D or 3D.

Surgical fellowship training

The biggest benefit of this system is the ability to better train surgical fellows. As someone who loves operating and has a passion for teaching fellows the art of VR surgery, I often battle between my desire to take over and my desire to teach. This system makes me a much better educator. The fact that the fellow—or the teacher—can now see exactly what is happening in the eye is invaluable for the best training. 3D heads-up surgery is a game changer for fellowships and will become the "gold standard" for educational programs.

The negatives

Much like small-gauge surgery in its infancy, this technology has some drawbacks. The first issue is the "learning curve" associated with heads-up surgery. The traditional view through oculars is gone, and there is something "different" about seeing things in 3D. One difference is the fact that 3D glasses must be worn. These glasses can reduce the ability of the scrub nurse to load needles in a dark room and perform other essential activities outside of the microscope.

The surgeon's view, particularly depth perception during core vitrectomy, is slightly different and it may be best to perform the first few cases with this system on pseudophakic patients. Anterior-segment surgery seemed more challenging and may require more time initially as one adjusts to the view.

> **'3D heads-up surgery is a game changer for fellowships and will become the "gold standard" for educational programs.'**
>
> —John W. Kitchens, MD

The second negative is the setup required. Positioning the 3D monitor is essential for the best view during surgery. Ideally, the 3D 55-inch OLED display is positioned about 5 to 6 feet from the surgeon; this requires positioning the bed differently and may require moving the anesthesia cart. Circulating nurses must be facile with setting up the unit and moving it out of the way before and after each case. In our evaluation, there was no foot pedal to control inversion or basic camera settings, so the circulating nurse was responsible for these duties.

The final negative is the cost, which is about the same as a fully functional vitrectomy system. In an era when reimbursements are declining for surgeons and surgery centers alike, investing in a technology like this in its early stages is difficult for all but the most ardent of surgical video creators or training programs with deep pockets.

Summary

The NGENUITY system is a revolutionary change in the way VR surgeons view surgery. It has some remarkable abilities that will appeal to those who train future generations of VR surgeons and those who enjoy surgical video creation. Much like the original iPhone, the real potential of this system lies in the future development of the technology. The ability to integrate in-office diagnostics, the addition of real-time OCT imaging, improvements in 3D monitors, and other advancements will drive this technology, making it more "mainstream" as it further evolves.

Lejla Vajzovic, MD
Duke Eye Center
Durham, North Carolina

With much excitement, I recently had the opportunity to road test the NGENUITY 3D Visualization System for some of my simple and complex vitreoretinal surgery, as well as combined surgery with my anterior-segment colleagues. Overall, I was impressed by the enhanced visualization, the ease of transitioning to this system, and the collaborative environment it enabled. To me, the system has many benefits and a few of these include:

Easy setup

The setup was simple, yet important. The N3DVS consists of an HDR camera and a workstation that provides magnified 3D images of surgery. As for any camera system, white balancing and focusing were essential in providing the optimal stereoscopic image. It was worth taking a few seconds to properly set up these before starting the case—the resulting magnified, stereoscopic image on a large 3D screen in front of us was priceless.

Seamless and fast transition

The transition from the optical microscope to the 3D visualization system was fast—my fellows and I adapted to the new system

within a few hours and subsequent surgical days were seamless.

Ergonomically friendly

During vitreoretinal surgery, we are operating in a non-ergonomic position (holding our heads, extending our necks and leaning forward), and by the end of the day, we are experiencing fatigue and neck or back pain. It comes as no surprise that ophthalmologists, and particularly retina specialists, are at a high risk for neck, upper-extremity, and lower-back injury and pain. With this 3D visualization system, we remained in an ergonomically neutral position as we were operating by viewing a magnified surgical picture on a large screen in front of us.

Enables superior teaching experience and collaborative team approach

As a vitreoretinal surgeon and faculty at the University Eye Center, I find this aspect to be the most beneficial. My anxiety level was much less as I was sitting in the back and watching my fellows operate. Why? Primarily because I was seeing exactly the same thing as my fellows or anyone else in the operating room.

The panoramic screen allowed everyone—medical students, residents, circulating nurses, CRNAs, and anesthesiologists—to immerse themselves and be part of the surgical action in real time. My scrub nurse was more attentive, anticipating my next surgical step, and my CRNA was intimately involved and inquiring about surgical principles—not to mention the surgical exposure that medical students and residents received with this system.

> **'With this 3D visualization system, we remained in an ergonomically neutral position as we were operating ...'**
>
> —Lejla Vajzovic, MD

Safer surgery with digitally enhanced visualization

Even more impressive was the ability to operate in much lower light settings with this 3D system. I routinely perform small-gauge vitrectomy with my light pipe set at 35% using Alcon's Constellation System with the microscope.

With the N3DVS, I had my light pipe set at 5%—a tremendous difference that significantly decreased the risk of light toxicity. Additionally, with the NGENUITY system, you can adjust the gain or digitally apply filters (for example, red-free filter for macular pathology) and further enhance visualization of the tissues or planes.

Future advancements

The future of digitally assisted vitreoretinal surgery is even more promising, with a multi-image platform that could, for example, include preoperative testing and a live intraoperative OCT video feed. I am looking forward to these advancements.

> **'With the N3DVS, I had my light pipe set at 5%—a tremendous difference that significantly decreased the risk of light toxicity.'**
>
> —Lejla Vajzovic, MD

The only downside of this system was its latency, which was minimal at 80 milliseconds. The latency was most notable with extraocular or anterior-segment surgery, but even then, I did not think it was an issue during my scleral buckle placement/suturing, or during combined cases and glaucoma tube placement, etc. In intraocular vitreoretinal surgery, the maneuvers are very slow and cautious; therefore, latency is not relevant.

In conclusion, the N3DVS is a revolutionary technology, as it will lead to enhanced visualization during delicate vitreoretinal surgery, especially with the potential future platform additions, and therefore, it will lead to improved surgical outcomes.

Vincent S. Reppucci, MD
New York Eye and Ear Infirmary of Mount Sinai
New York, New York

After having the opportunity for a trial of Alcon's NGENUITY/TrueVision 3D Visualization System, I am very impressed, and I intend to fully incorporate this into my routine surgical technique. I predict that the N3DVS, similar to wide-angle viewing in the 1990s, will become a standard tool for vitreoretinal surgery visualization. It is that good! While there is certainly room for improvement, the N3DVS provides more than adequate visualization for just about any vitreoretinal surgical maneuver, and it does so in a more ergonomically liberating manner than our present conventional microscope ocular-based surgery (MOBS).

The N3DVS imaging system is set up by removing the microscope oculars and placing the stereo video camera directly onto the microscope objective. The 3D monitor, a 55-inch OLED screen, is placed about 5 feet away over the patient's abdomen/pelvis. Passive polarized filters are required for stereopsis. The optics are now purely a function of the microscope's objective and the field of view is not further reduced by the microscope's oculars. This allows for the initial "wow!" impression when looking at the 3D monitor—a larger image with a greater field of view than with MOBS. The operating room staff, circulators, anesthetists, technicians, and visitors all have the same 3D view, and you can imagine their initial "wow!" factor.

The following comments and observations are based on 8 surgical cases, phakic and pseudophakic, with a case mix from macular hole and puckers to anterior proliferative vitreoretinopathy (PVR). There were no diabetic cases. All procedures were performed at Danbury Hospital in Danbury, Connecticut.

The clarity, or spatial resolution, is excellent but critically dependent on parfocal focusing and the image illumination levels. Under the best of circumstances, it is about a 20/25+ equivalent, not quite the corrected 20/15 of my eye, but certainly more than adequate. This is offset by the larger image size and greater field of view mentioned above. The camera is quite light sensitive, and often I found myself reducing the fiber optic light pipe setting.

The dynamic range and tonality are quite good, but not at the level of the human eye during MOBS. There are camera setting adjustments dependent on the surgical field, eg, anterior segment, macula. Essentially, the color depth and tonality, even with proper color correction, may not be quite "correct." Purists may find fault and object to this; I will categorically state it to be a nonissue for me.

A bit more red or blue color tinge on the monitor image vs the truer color of MOBS

didn't affect my ability to identify structures and membranes. In fact, peripheral vitreous base visualization—probably due to the shorter wavelength scatter—was improved. Theoretically, there may be future potential benefits to "filtering" some wavelengths to augment specific stains and structures.

Depth perception is a function of depth of field, depth of focus, and stereopsis (binocular disparity). Unlike MOBS, the N3DVS image is on a flat monitor screen, so there is no ability to accommodate and thus no potential for depth of focus. Therefore, in N3DVS the depth perception is purely dependent on depth of field and binocular disparity.

'The clarity, or spatial resolution, is excellent but critically dependent on parfocal focusing and the image illumination levels.'

—Vincent S. Reppucci, MD

Nonetheless, depth perception is excellent during core vitrectomy and macular work, but again very dependent on image brightness. Brighter illumination means a better video image, and the smaller camera aperture allows for improved depth of field.

The stereopsis during internal limiting membrane (ILM) or pucker removal is equivalent to MOBS and free from accommodative/convergence strain. (You are looking at a fixed image several feet away.) There is also a slight hyperstereo effect that is most obvious when you look at the anterior segment and corneal curvature.

In contrast, when faced with more complex volumetric situations such as peripheral vitreous base contraction, I found the depth perception to be a bit more challenging. (This is also the case in standard MOBS). Typically the peripheral retina illumination is less homogenous (think illuminated pic) and, unless you constantly focus up or down, you are often working out of the optimal parfocal plane. Thus the N3DVS image, at least for me, has a bit less spatial resolution or clarity, a combination of increased camera gain, greater aperture openings, and less depth of field for anterior PVR work. I am sure with more experience, this would improve.

I found the adjustment from MOBS to N3VDS quite easy. With the 3D visualization system, you are not looking into the microscope, and there is a display lag on the OLED monitor of about 75 msec. I did not really notice the display lag inside the eye; most intraocular movements are deliberate and slow, but more so when placing sclerotomy sutures. It was easy to adjust to this.

Through a scheduling snafu, my first case with the N3VDS was a macular hole with ILM peel. After spending a bit of time performing the core vitrectomy to acclimate myself, and using a tenuous approach to the ILM, I was pleasantly surprised at how straightforward the peel went! I had no trouble with depth perception and visualization.

I found the learning curve for converting to N3DVS essentially nonexistent. I suspect any experienced vitreoretinal surgeon who is accustomed to operating through less-than-clear ocular media and able to control his/her accommodation will similarly have no trouble converting.

Four final observations:

1. Illumination and parfocusing at the level you wish to work, ie, retinal surface for pucker or ILM peeling, is critical to maximizing your image quality and depth perception.
2. The assistant holding a contact wide-angle lens has no ocular to look through, and is obliged to turn his or her head to look at the monitor. This was awkward and probably contributed to the peripheral retinal visualization comments mentioned above.
3. Make sure you are wearing your correct distance refraction. Often surgeons will dial their refractive error into the microscope oculars. You cannot do that with a monitor at a fixed distance from you.
4. It took several cases to lose the muscle memory of leaning forward with tense shoulder and neck muscles. By the fourth or fifth case, I was leaning back and tensing much less—a very liberating feeling! I was actually disappointed I had no more cases.

In summary, N3DVS provides excellent surgical visualization for the primary surgeon and observers, especially during posterior macular procedures. While peripheral retinal maneuvers may be a bit more challenging, I look forward to incorporating this system for all my vitreoretinal procedures in the near future. As the technology improves, I would not be surprised if it surpasses conventional microscopy visualization.

'I found the learning curve for converting to N3DVS essentially nonexistent.'

—Vincent S. Reppucci, MD

Editor's note: NGENUITY/TrueVision had the opportunity to see the reviews just prior to publication. Mark Maire, TrueVision 3D Surgical executive vice president of sales and business development, says:

The insights offered by Drs. Kitchens, Reppucci, and Vajzovic are very valuable. Disruptive technologies require early adopters' feedback and input on their use. The digital microscope platform (NGENUITY) succeeds in most areas, and we are working diligently on the others. Latency, reorientation of the room and staff, and the requirement for polarized glasses are all areas of attention.

As the surgeons point out, the NGENUITY system brings value now. The software upgrades coming in the very near future will only add to the value. Better outcomes through better visualization and information on the screen are the goal. Integration with other digital technologies and diagnostics is coming quickly and, like the iPhone, once you have a digital platform, enabling applications is limited only by imagination.

Financial Disclosures

Dr. Hassan – ALCON LABORATORIES, INC: Consultant, Honoraria; ALLERGAN, INC: Advisory Board, Honoraria; ARCTICDX: Consultant, Stockholder, Stock Options; GENENTECH, INC: Advisory Board, Consultant, Honoraria; INSIGHT INSTRUMENTS, INC: Consultant, Other, Honoraria, Intellectual Property Rights; NOVARTIS, INC: Consultant, Honoraria; REGENERON PHARMACEUTICALS, INC: Advisory Board, Consultant, Honoraria; ROCHE USA: Consultant, Honoraria.

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Mr. Maire – TRUEVISION SYSTEMS, INC: Employee, Salary, Stock, Stock Options.

Dr. Reppucci – None.

Dr. Rhee – CONNECTONCALL.COM, LLC: Founder, Stock; COVALENT MEDICAL, LLC: Stockholder, Stock.

Dr. Vajzovic – ALCON LABORATORIES, INC: Investigator, Grants; SECOND SIGHT MEDICAL PRODUCTS, INC: Investigator, Grants.

Pravin U. Dugel, MD
Research and Development
Section Editor

PART 2 IN A SERIES

So, Is Protocol S a Game Changer? The Debate Continues ...

There are several terms we throw about carelessly, to the point where they have become meaningless. In sports, the word *great* fits the bill. In retina, *game changer* may be the most overused and misused term.

The Diabetic Retinopathy Clinical Research Network's (DRCR.net) Protocol S[1] may be (at the risk of lexicon abuse) a "game changer." However, its conclusion, that anti-VEGFA monotherapy may have advantages over panretinal photocoagulation (PRP), does not occur in a vacuum.

We do have a treatment in PRP that is 90% effective and has a more than half-century history of success. The bar is indeed high. Is this study truly a "game changer"? Three internationally recognized experts opine on the potential implications of Protocol S in the second part of our discussion series.

Panelists

Susan B. Bressler, MD
Wilmer Eye Institute
Johns Hopkins University
School of Medicine
Baltimore, Maryland

Michael S. Ip, MD
Doheny Eye Institute
David Geffen School of
Medicine, UCLA
Pasadena, California

Jay S. Duker, MD
New England Eye Center
Boston, Massachusetts

Pravin Dugel: Jay, being a skeptic, I want to push you. You've said that Protocol S is a behavior changer. I can't logistically give sufficient injections for patients who are symptomatic with diabetic macular edema (DME) or neovascular macular degeneration. How do you expect me to inject an asymptomatic patient every 4 weeks for 1 year, let alone for many years?

Jay Duker: First, you need to distinguish between DME and AMD. For most patients, wet AMD is forever. Once you have it, you will require anti-VEGF injections for the rest of your life. This is not generally true for DME. Second, recurrent fluid in DME is not as worrisome as wet-AMD recurrences. Third, we don't have any proven alternative treatments to anti-VEGF monotherapy for wet AMD. We do have several effective alternatives for DME, however, including laser, corticosteroids, and surgery.

And with respect to proliferative diabetic retinopathy (PDR), we have an excellent alternative to anti-VEGF: PRP. I think PDR treatment, for now, will be characterized by an individualized approach. The therapy will be based on what the patient wants and the overall status of his or her systemic disease and retinopathy.

Pravin Dugel: Jay, what's the conversation you have if a patient has no DME, just PDR? What treatment would you recommend?

Jay Duker: What we need to talk about is, first of all, what's the visual acuity? What's going on in the fellow eye? What's the age of the patient? What are the comorbidities? But in the general conversation, I would tell the patient, "You've got a severe, sight-threatening disease that we need to treat. The treatment is going to be intensive, and you may have some side effects from it. The good news is that treatment is generally effective. There are 2 choices, and we can combine the choices if need be, and we can step in with surgery if indicated."

And then you give an informed consent about what we know about PRP and the anti-VEGF

> **'You need to distinguish between DME and AMD. For most patients, wet AMD is forever ... This is not generally true for DME.'**
>
> —Jay S. Duker, MD

regimen. If we start off with anti-VEGFs and the patient is not able to make the necessary visits, you might say right away, "Fine, we gave this a chance, but we now are switching to laser because you can't miss visits with anti-VEGF treatments."

Pravin Dugel: Susan, let's say a patient walks in today with PDR without DME. This is a typical patient who may be 27 years old, a gainfully employed young man with type 1 diabetic retinopathy. What is the conversation you're going to have with him?

Susan Bressler: Pravin, I know you've been eager to get some skepticism, and I'll introduce the one area where I would have some at the moment as I respond to your question.

The first thing I'm going to say to this diabetic patient, as Jay has already said, is, "You now have a sight-threatening disorder that needs treatment. Absence of treatment is a very poor choice because we know it's highly probable you will have severe vision loss if we do nothing."

I agree with Jay that we would then say, "We have 2 choices. One option we've had for quite some time—and we know it works in about 90% of people—is PRP. If we do PRP, we will have an excellent chance of preserving functional vision. However, PRP does have some negative characteristics that we should touch upon."

I would explain to the patient, "Following PRP, there is measurable reduction in visual field, a loss believed to have clinical relevance—and eyes that do not have DME with vision impairment at the time of PRP are more apt to develop this than if we use an alternative treatment to address the PDR. Eyes that also have DME at the time of PRP are more likely to have an exacerbation of the DME, particularly if they do not simultaneously receive anti-VEGF therapy specifically to manage the DME."

I would counsel the patient, "These adverse effects that we associate with PRP, supported by evidence from prospective clinical trials, may have short- and long-term negative effects on central vision and visual field. We need to keep these issues in consideration as we discuss types of treatment we can use to manage the PDR."

And I would also tell the patient, "If you opt for PRP, we will do this PRP treatment in 1, 2, or 3 sessions over the next 6 to 8 weeks; however, it does not mean you will be forever protected from complications of your PDR. You will still need regular follow up, particularly in the first couple of years—and there's about a 50% chance we'll need to supplement the original PRP with additional PRP because in many patients, the initial course of treatment does not appear to adequately control the disease."

I would clearly explain, "PRP is going to require office visits; it's going to mean taking time off from work, and you will need transportation to get to and from your office visits due to dilation and possible need for treatment."

Then I would introduce the anti-VEGF option: "The other treatment choice is even more visit-intensive—particularly in the first year, when I'm going to ask you to come in every single month for the next 12 months. And after the first year, I'm hopeful we'll be able to reduce the frequency of your visits, but it still may amount to about 6 visits in the second year. With this therapy you will receive intravitreal injections of an anti-VEGF medication, which will foster regression of the ocular neovascularization and reduce complications associated with PDR. The number and frequency of injections will be directly linked to the anatomic changes we see in the neovascularization. Patients without DME, such as you, receive a median of 10 injections in the first 2 years of follow up."

Pravin, now I'm going to introduce my skepticism about anti-VEGF therapy to manage PDR, which relates to the fact that, so far, Protocol S has reported outcomes through the 2-year visit—and we note that the need for repeated injections decreases in year 2 relative to year 1.

What we need to feel even more comfortable with this management strategy is longer-term data to see if all the observations we have at 2 years continue. We would like to see that at years 3, 4, and 5, eyes managed with anti-VEGF continue to have vision outcomes that are at least as good—if not better—than PRP, and that the need for repeated injections continues to decline. If we eventually learn that the need for regular intravitreal injections does not decline further, or if it rises, I would question the long-term feasibility of this approach for the majority of patients.

We're hopeful that the evolution of PDR in response to anti-VEGF therapy will be similar to that of DME. When managing DME with anti-VEGF therapy, we see continued decline in visit need and injection treatment burden. We hypothesize that there is an active period of proliferative disease that lasts 1 to 4 years in most people, and that if anti-VEGF therapy can get people through this critical period with avoidance of PRP and complications associated with PDR, then we have a contribution worthy of serious consideration.

Pravin Dugel: Susan, that's a great point. As impressive as it was, Protocol S was a 2-year study. Now if you look at RIDE and RISE—a 5-year study—clearly there were some patients whose disease was modified. However, a number of patients required more than anti-VEGFA monotherapy.

'We note [in Protocol S] that the need for repeated injections decreases in year 2 relative to year 1 ... What we need ... is longer-term data to see if all the observations we have at 2 years continue.'

—Susan B. Bressler, MD

'We're hopeful that the evolution of PDR in response to anti-VEGF therapy will be similar to that of DME.'

—Susan B. Bressler, MD

Suppose a third of Protocol S patients do extraordinarily well, but two-thirds still require additional PRP. We cannot identify such patients phenotypically. Susan, in such a scenario, where the majority of patients may still require PRP, will we do a disservice by starting these patients on anti-VEGFA monotherapy based on this 2-year data?

Susan Bressler: Pravin, anyone on whom you initiate this therapy now will be coming up on 2 years' worth of treatment at about the time Protocol S reports 5-year follow up; and during those 2 years, individuals who have agreed to have this type of management for

their proliferative disease will benefit. Why? Because for those 2 years, as we've heard, analysis of the area under the curve demonstrates that these patients will retain a level of vision superior to what they would have had if they had gone on to PRP.

So, for anyone you start now, at 24 months of their therapy, if we learn that in years 3, 4, and 5, a lot of people required additional treatment and in the big picture, this isn't going to hold people for as long as we would like, I don't think you will have done any disservice to those individuals.

In the meantime, very few eyes assigned to ranibizumab met failure or futility criteria and needed PRP in the first 2 years of follow-up. Only 6% of the ranibizumab group received PRP and most of these were performed during vitrectomy, with the PRP being a routine component of the surgeon's vitrectomy procedure.

Obviously, for eyes that needed vitrectomy there was evidence of PDR progression, which is testimony that some eyes will progress despite anti-VEGF therapy to manage PDR. However, vitrectomy was performed 4 times more frequently among eyes assigned to PRP than in the ranibizumab group. So, either way, I think, I won't feel remorseful about offering this therapy to patients now through the next 2 years. I will feel proud of what we have accomplished.

Jay Duker: I think Susan is 100% right here, and I'm going to add some clinical expertise from being in practice for 25 years. I've learned that diabetic retinopathy has a beginning, a middle, and an end. It's not a disease that goes on forever if you can control it.

We've all seen patients on whom we did PRP and maybe a focal laser 5, 10, 15 years ago. They come in now only for yearly exams; the vision is stable, and I can't even find a microaneurysm in the eye anymore. Now, that's not everybody, but I believe that for a large segment of diabetics, there's an end to their process. And so I think Susan's impression, based on the other studies she quoted, is going to be the way this will end up—that the majority of eyes will not need anti-VEGF treatment forever. But we're going to need to watch them, as we do with any diabetic patient. Is it going to be an opportunity to treat them and let them go forever?

Michael Ip: It sounds like we're all in agreement. Jay's been practicing for 25 years. I've been practicing for 17. But I get pretty much the same impression—that diabetic retinopathy has a beginning, a middle, and an end. And I think that if you look at all the data we are discussing, the anti-VEGF is modulating the DME and the diabetic retinopathy. It doesn't matter whether the anti-VEGF is actually doing that or whether the disease is just burning out—it seems that the disease comes to a conclusion.

> **'Diabetic retinopathy has a beginning, a middle, and an end. It's not a disease that goes on forever if you can control it.'**
>
> —Jay S. Duker, MD

Protocol I was beautiful in the way it showed there were 9 injections in year 1, and then it dropped to 3-4, and then to 2-3, and then to almost zero by the end of year 5 because the macular edema aspect was being modulated. If you look at the diabetic retinopathy aspect, a question that always comes up is, RIDE and RISE showed all this regression of retinopathy. What happens when you stop the injections?

And when you look at the RIDE and RISE open-label extension (OLE) study, 25% of those patients didn't require further injections. Overall, very few injections were given—a mean of about 3 annually between years 3 and 5—and the retinopathy levels did not progress. The disease is stable from what we can see. Both the retinopathy level and the DME tend to stabilize without a lot of further injections. So it is an interesting question, but I think we can predict that the disease can eventually "burn out."

> **'If you look at the diabetic retinopathy aspect, a question that always comes up is, RIDE and RISE showed all this regression of retinopathy. What happens when you stop the injections?'**
>
> —Michael S. Ip, MD

Pravin Dugel: Susan, the Protocol S data is based on ranibizumab. Community physicians are using 2 other anti-VEGFs in addition, aflibercept and bevacizumab. Can we extrapolate this data for the other anti-VEGFs?

Susan Bressler: Stay tuned. First, we can look to the literature and see that VIVID and VISTA provide data that supports the premise that aflibercept modifies the evolution of retinopathy. RIDE, RISE, Protocol I, and Protocol S provide evidence that ranibizumab can do that, too. For bevacizumab there is only a single small study that provides data consistent with the same type of behavior.

We do have Protocol T, where a cohort was randomized to each of the 3 drugs to manage DME, and we are working on a manuscript comparing the 3 drugs' modifying effects on retinopathy, specifically how each drug decreases progression and fosters regression of retinopathy levels. That's why I'm saying, "Stay tuned," because we are mining that database to show you the comparative behavior of the 3 drugs so you'll have more information as you're choosing an agent with the primary intent of modifying the retinopathy itself.

Pravin Dugel: I completely get that. However, my need is immediate: Jay, I'm in the community, and for several reasons—usually economics—I'm forced to use bevacizumab. Would you have concerns about extrapolating this data to bevacizumab?

Jay Duker: No, not unless you're unwilling to use what I would call *rescue laser.* I think it's unfair to extrapolate Protocol T to Protocol S with respect to the 3 anti-VEGFs, but it wouldn't surprise me if bevacizumab didn't do quite as well, with respect to PDR, as the labeled drugs did. Again, I have no reason to believe it wouldn't modify the disease or improve PDR. The good news is we have tried-and-true laser, so if you're not getting the results you want or expect with the anti-VEGF agent, or if the patient can't come back for the required injections, just go ahead with PRP.

Pravin Dugel: Since we're in the mood to extrapolate, should I be extrapolating this data to severe nonproliferative diabetic retinopathy as well, Michael?

Michael Ip: I don't know if we can extrapolate Protocol S exactly to that question, but extrapolation would be from some of the VIVID and VISTA, RIDE and RISE, and Protocol I data on retinopathy regression. I think that's the next game-changing question we have with respect to diabetic retinopathy. It's the question being posed for severe nonproliferative diabetic retinopathy (NPDR), and what is being looked at in Protocol W from the DRCR.net; Regeneron is doing a study looking at this as well.

> 'It wouldn't surprise me if bevacizumab didn't do quite as well, with respect to PDR, as the labeled drugs did.'
>
> —Jay S. Duker, MD

And the question is, if we apply anti-VEGF therapy at an earlier stage, for example in patients who have moderately severe to severe NPDR, can we prevent PDR from occurring in the first place, and can we prevent sight-threatening DME? And I think we will have the answer fairly soon. That's the next, as I mentioned, game-changing question to think about.

Pravin Dugel: Susan, not everything we do is supported by a twin multicenter prospective randomized trial. They say medicine is an art, and not only a science. Perhaps that allows us the license to reasonably extrapolate? Given the impressive Protocol S results, why shouldn't I extrapolate to severe NPDR?

Susan Bressler: I think the reason not to extrapolate is that patients who have proliferative disease are on the cusp of dramatic irreversible vision loss, so we must intervene with one treatment or another to decrease that risk. Patients with severe nonproliferative disease in the absence of macular edema don't have anything imminently vision-threatening.

And although we have a lot of data suggesting we can make the retina look more normal, which we interpret as making the retina look healthier, we don't know if, in the long run, it does anything that changes the vision outcome for those individuals.

So, I think the missing link, for the moment, is: In changing retinopathy level, do you extend the clock by which that person will develop vision-threatening retinopathy and, more so, develop vision impairment? The answer to that question would provide the missing link—and it's what I would want to know before I started subjecting these patients to regular intravitreal therapy.

Pravin Dugel: Jay, you get the last word. It's very tempting to extrapolate data. Should we be extrapolating this to an earlier disease state?

Jay Duker: No, I would not, and I think Susan is correct in her assessment. I'll add one more thought about the danger of extrapolation: endpoint. We know our DME treatment endpoint, and I think we know our endpoint for PDR treatment. But if you start treating nonproliferative patients with an anti-VEGF agent, when do you stop? How do you define success? We don't know that yet. So even if we are modifying disease, we don't know what the endpoint of the treatment is. Until we work that out, I would not recommend extrapolating.

Pravin Dugel: That's an excellent point. Thank you all for participating in this discussion.

In conclusion, medicine is said to be an "art," not a "science." Yet we are supposed to be data-driven physician-scientists. How do we reconcile these 2 seemingly incongruous concepts? Perhaps *that* is the real "art"!

This discussion about Protocol S highlights our challenge between science and art, between the ideal and the sustainable, between clinical trials and real life.

Is a study really a "game changer" if it is not sustainable? Do we seek only the best treatment possible, or seek the best treatment possible within the constraints of societal resources? More fundamentally, can there be a "game changer" based on a single study without confirmatory data?

Protocol S is indeed a salient study, not only for its results … but also for the compelling questions it raises.

> 'The next game-changing question … is, if we apply anti-VEGF therapy at an earlier stage … can we prevent PDR from occurring in the first place, and can we prevent sight-threatening DME?'
>
> —Michael S. Ip, MD

Reference

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PART 2 IN A SERIES

Steve Charles, MD: Portrait of a Private-Practice Innovator

Many discoveries in retina have come from physicians in private practice. In the Annual Meeting *Retina Times* (available at www.asrs.org/retina-times), part 1 of this series featured interviews with 2 innovative private-practice retina specialists—ASRS Past President Paul Tornambe, MD, and Robert Wendel, MD.

In part 2 of this 3-part series, we've spoken with another pioneer in vitreoretinal surgery, Steve Charles, MD, who can talk faster than we can think.

Steve Charles, MD
Charles Retina Institute
Germantown, Tennessee

How did you get interested in the engineering aspects of medicine?

One of my grandfathers was a surgeon, and the other was a mechanical engineer. The surgeon grandfather died before I was born. My dad's oldest brother, my godfather, was a general surgeon. I didn't think about being a doctor until halfway into engineering school. I loved design from day one.

I've never wanted to be known as an entrepreneur or a *gadgeteer* or an inventor—I hate those terms. I don't like what I call *aspirational innovation.* It isn't about, "Oh, I want to be innovative," or "I want to start a company." It's about problem solving.

So I kept asking myself, "What can I do in engineering that will help people?" I wasn't going to design a heavy-metal guitar, or a gambling machine, or a new thing to serve wine—all of which have screwed up our society. I wanted to do something with meaning. I hate Hollywood. I hate Las Vegas. I hate gambling, drinking, partying—entertainment in general.

I found meaning. When I was a junior in engineering school, I decided to go to med school and continue engineering. I did engineering all the way through 4 years of University of Miami Medical School. I virtually lived at Bascom Palmer Eye Institute, building ERG machines, ultrasound machines, a lot of instruments—all from scratch.

You're a big aviation guy. Why didn't you go into jet propulsion? There are a lot of other things that involve engineering.

Well, I wanted to be a doctor and help people. With aviation, you're in a cubicle in a room full of hundreds of engineers, and you never even see the final product. You don't fly in it. You don't talk to pilots. They give you a part, and you sit there and design a part and do finite element analysis. That's not me. I don't know if I have people skills, but I wanted to be around actual humans, not just staring at a screen all day with a mouse in my hand.

But here is the core difference: There's a philosophical piece I've thought a lot about because of my age, and that is, when somebody asks me, "Didn't you used to be an engineer?" I say, "No, I *am* an engineer." I have done engineering every day of my 41-year career in vitreoretinal surgery.

I've driven $5 billion in sales. I have 100-plus patents. It's not about innovation. It's not about entrepreneurship. It's not about business. Again, It's about problem solving. And so it's constantly an overlap of what I call the 3 Ts: technique, technology, and teaching. If you don't do a ton of surgery, you're not valid in the design space. If you don't keep current in

'When somebody asks me, "Didn't you used to be an engineer?" I say, "No, I *am* an engineer."'

'It's not about innovation. It's not about entrepreneurship. It's not about business ... It's about problem solving.'

engineering and push the envelope—teach yourself mechatronix, modern control theory, and field-programmable gate arrays (FPGAs)—like I've done—then you're not valid.

I built a conceptual design of the Constellation with 1200 parts in the proposed parts list before Alcon did one hour of work on it. I didn't sketch stuff on a napkin. I built a big computer-aided design (CAD) model with what the electronics should be, and the Constellation is built very much along those lines. Numerous technologies and patents on the Constellation come from me—same with the Accurus, and before that, the Ocutome 8000.

My late friend, Conor O'Malley, developed the Berkeley Bioengineering Ocutome 800, but I invented the 8000 with Carl Wang for CooperVision; that was the first machine with linear suction. I built the first real-time gray-scale B-scan with Xenotec, Inc. I built MID Labs with Carl Wang, invented the disposable cutter and high-speed fluidics. MID Labs got acquired by Alcon. Then I started InnoVision. The InnoVision ocular connection machine (OCM) is the forerunner of the Accurus and the Constellation and had every feature that's on the Constellation. InnoVision was acquired by Alcon in 1991.

Why didn't I do engineering in an academic environment? Because I wanted to see the finished product. I'm on the ARVO Foundation board of governors just to push what I think is translational research. People always use the phrase, "the bench to the bedside," and say, "It's translational research." No, it's not. It's about getting a product into widespread clinical use.

So on the technique side, I invented fluid-air exchange, internal drainage of subretinal fluid, forceps membrane peeling, endophoto-coagulation, scissors segmentation, scissors delamination, linear suction, punch-through retinotomy for subretinal bands, retinectomy instead of Robert Machemer's relaxing retinotomy, 3-port aspiration lensectomy, and anterior proliferative vitreoretinopathy (PVR) dissection.

Steve, if I can push you a bit ... My impression of Machemer is that he was a full-time faculty guy who was tinkering in his garage and then ...

Although Anton Banko patented a device similar to the VISC before the VISC was developed, it was never commercialized. Banko was the fluidics engineer for Charles Kelman, and sent a letter to Charles Schepens, Harvey Lincoff, and Edward Norton, saying, "Look what I've got. Could you guys use this? Kelman lost vitreous all the time. I invented this because I invented mechanical lensectomy, and it didn't really work as well as ultrasound. So what do you think?" And Banko's patent was issued 2 years before Machemer came out with his device.

'People always use the phrase, "the bench to the bedside," and say, "It's translational research." No, it's not. It's about getting a product into widespread clinical use.'

Machemer created the specialty of vitreo-retinal surgery. He trained a bunch of people because he was at an academic institution, and he and Jean-Marie Parel invented endoillumination. That's a big deal. And Machemer invented membrane peeling with a bent needle. That's a big deal. He technically didn't invent the vitrectomy probe because Anton Banko's patent preceded his work. But it doesn't matter. What matters is creating the field, and Machemer created the field and trained us.

Conor O'Malley was in private practice too, wasn't he?

Correct. He trained at UCLA. Conor was in San Jose and he just loved to invent things. He wasn't an engineer; to use an old-timey term I hate when they apply it to me, he was a *tinkerer.* But he hooked up with a guy named Ralph Heinz, and that's where the Ocutome came from; it had a bellows drive so it wasn't disposable, but it was the first pneumatic cutter and the first axial cutter and first 20-gauge, 3-port system.

So, when you were inventing devices and techniques and presenting at meetings, how did the retina community accept you as an engineer-doctor from Memphis? Do you think it would have been an easier road had you been at the platform of a Wills, Wilmer, or Bascom Palmer?

I've thought a lot about that. It's a great question, and I think it would have been worse for me. I'm not a committee guy. I don't want to sit in discussions at meetings—I just want to do it. And I don't want to apply for RO1 grants and walk around trying to hit people up for money. I just hate all that. I want to design and build, so I had to find a company capable of getting it out there.

Why not then say, "Okay, forget this. I'm going to go out and just take my company and do it full-time to take my engineering ..."

Because then you're not valid in the operating room. If you're not constantly doing more cases than anybody else, you don't know what you're talking about. You've got to be embedded. Guys who are in aeronautics, have a PhD in aeronautical engineering, and fly jets are the best guys to design airplanes—not guys who do one or the other, but not both.

'I'm not a committee guy. I don't want to sit in discussions at meetings—I just want to do it.'

And the technically confident guys who drive race cars, who really understand suspension systems and engine tuning, are better race car drivers. But what *don't* I do? I haven't seen a movie in 30 years. I have zero intent to see a Hollywood movie ever again.

Come on, you would have been to Titanic and shed a little tear, or something.

No, I hate all that. I haven't been to a concert. I went to one NBA game with my grandkids last November. I live in Memphis; I've never seen the Grizzlies play. I've never been to an NFL game. I don't play golf. I don't hunt. I don't fish. It's been 20 years since I've been on vacation. I don't have a house, a bird, a plant, a fish. I work and work out. That's it.

And fly planes.

So, the only things at my apartment are me and my biome—the bacteria in my gut.

I'm super-tight with my kids and grandkids, but for me, it would be morally wrong to take a vacation, go to a concert, go to a ball game, or to gamble or drink because I have a moral obligation to do what I do. I'm not a religious guy, but religious people where I live would describe what I do as a calling.

I'm super-involved with Alcon and creating the next machine. Plus, I'm the main surgeon for the National Eye Institute's stem cell project, the iPSC, and that's coming along. I'm participating in 3 Orbis International fundraiser events, one I'm running here at Memphis at FedEx, and I'm doing the first China trip on the new MD-10.

So that's what I need to be doing. It isn't about getting awards. It isn't about being an officer in any of these organizations. I'm so fortunate that people like Julia Haller do such an awesome job of making the ASRS and the Retina Society and the Macula Society happen. I'm just privileged to participate and learn and interact.

Look at Sandy Brucker; he singlehandedly built the journal, *Retina*. That's hard work, and it's an enormous contribution to our field, just like Julia's leadership and George Williams' leadership and people like that—so I get that people play different roles.

'For me, it would be morally wrong to take a vacation, go to a concert, go to a ball game, or to gamble or drink because I have a moral obligation to do what I do.'

I don't have the skill set of Julia, or Sandy, or Lee Jampol. My skill set is engineering, teaching, and operating, and they all overlap, so that's what it's about for me.

What would you suggest to fellows who are interested in doing new things?

Number one is to stay current. For example, last Monday night, I spoke to a Memphis startup. They asked, "Would you give a lecture on this subject from 6:00 to 7:00 PM, followed by Q & A?" I said, "Sure." So, when did the Q & A finish? At 10:30 PM. A bunch of young engineers are studying there, and I said, "Guys, if you get an MBA because you want to start an engineering-based company, what will follow most of the time is engineering incompetence."

I said, "Engineering and technology are exploding; you have to study every day to keep up. Because you once studied engineering, that is just a language to study going forward, and if you don't continue studying, you're not going to make a contribution."

It's mind boggling to me how guys say, "Well, I'm going to start a company."

I ask, "All right, what technology are you good in?"

"Oh, I want to start a company."

I ask, "Do you have a product in mind?"

"Well, I want to be innovative."

As I said, I call this *aspirational innovation.* It doesn't work. So, if someone says, "I want to be like Steve Charles," I say, "Okay, throw away your golf clubs. Don't go to a wine tasting. Don't go to a movie theater. Don't tell me about Spotify and Pandora. Don't tell me about Hulu or Netflix. You've got to put all that stuff aside."

Now, I didn't put aside being a daddy. I got the 15-year attendance award at my kids' elementary school. But none of that other stuff, zero, ever. That's the way I could have a career that encompasses engineering and surgery. I have no interest in being a CEO. I've been chairman of the board several times—I hated it. I hate finance. I hate negotiations. I don't like financial types. It's not me. I don't want to be that. I'm not a wheeler-dealer, venture capitalist, negotiator, businessman, Donald Trump.

I'm an engineer, and engineers who design products read 40, maybe more, engineering trade journals a month. They are throwaways like we have in retina. But I read. I say, "Oh, that company keeps cropping up. They have got a new sensor or incremental encoder. I see that company all over the place; they seem to be the best at linear amplifiers." So that's how I study.

Who are some of the unsung pioneers in our field?

Dyson Hickingbotham at Duke invented cannulas. Vitrectomy was described in Japan by Tsugio Dodo, and as I mentioned, Anton Banko patented VISC. Gholam Peyman had an early machine called the vitreophage. Dyson Hickingbotham is an engineer and a lovely guy, and he never gets proper credit. He was at Duke; then he went to Grieshaber, and later to Alcon. Now he has a one-man independent instrument development company in Wake Forest, North Carolina. He's just a spectacular guy—no ego at all, no greed, just does his work incredibly well—and he built the first cannulas.

How would you advise would-be inventors in retina?

My best advice is, don't get an MBA; don't go to entrepreneurship or innovation conferences. Learn some technology, keep current, push it, and mingle with the best and the brightest—whether it's biotech or med-tech.

'I'm not a religious guy, but religious people where I live would describe what I do as a calling.'

There's an endless list of things that bright people have launched that have been failures. It's just plain complicated, hard, expensive and time-consuming work, and if you don't enmesh yourself in the technology and meet with numerous technologists, nothing is going to happen, so that's a big problem.

Sometimes people worry, "Oh, I don't want anybody to find out my ideas." Well, your ideas won't ever get out if you don't interact. You've got to try things, develop them, push them, and find out what the limits are.

Watch for part 3 of this series in the winter Retina Times*—an interview with retina innovator Michael Trese, MD.*

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Jerald A. Bovino, MD
Section Editor

It's Always Darkest Before the Dawn

My father started taking me on fishing trips when I was still in diapers. By the time I was 7 or 8, our father-and-son trips were among the most important things in my young life. In the early 1950s, we would jump out of bed at 2 in the morning, the alarm clock causing our entire house to rattle with excitement.

We would fill our arms with rods and reels on cold November mornings and hustle across a frost-covered lawn to our 1953 two-tone, lime-green Chevy Bel Air. At the start of the trip, my mother would lovingly put my leather and wool navy blue Elmer Fudd hat on me. It was the type of hat that makes even adults look ridiculous, unless they are chopping trees in the northern Minnesota woods or hunting elk in Alaska. She would always make sure the flaps were drawn down tightly around my ears, as if to squeeze my tiny head into an even smaller cerebral sleeping bag.

Once the car was packed with hero sandwiches and a stainless steel Thermos of coffee, my dad would point the Chevy to the east along Horace Harding Boulevard, the ancient predecessor to the Long Island Expressway. I would usually start to jabber away, as little boys are known to do, but I remember my father would always remind me, "Fishermen don't talk much in the mornings," and would diplomatically suggest that I "tone it down."

I recall millions of stars twinkling across the eastern sky on moonless nights as we crossed from Queens into Nassau County on our way to the North Fork of Long Island. I would always fall into the deepest sleep during the first hour of the trip, but as we hit the Suffolk County border one black morning, I suddenly awakened and blurted out, "Everything is really dark."

My dad came back with, "It's blacker than a coal mine in a power failure," and softly added, "But it's always darkest before the dawn."

And then like magic, the sky would change in an almost imperceptible way. The darkness started to lighten, as if a single drop of milk trickled into a hundred-gallon vat of black printer's ink, and then a second drop and then a third.

When we finally reached the sleepy town of Southold at sunrise, we would pull off the blacktop into a bait shop where Mary would pack green crabs, fiddler crabs, and sandworms into white cardboard cartons. Mary had a spectacular smile but almost no teeth, as if a giant laugh had caused all her teeth to explode from her mouth. She just had one bicuspid hanging down from the right side of her gums like a misplaced and discolored albino stalactite.

At Orient Point, the marina manager would lower our skiff down a steep incline with a winch powered by an old Model-T Ford engine. The laboring engine would belch and hiss noisily as the skiff slid down the embankment and plopped into Long Island Sound. My dad showed me how to place the motor in neutral and then pull the choke to allow the fuel mixture to run full rich.

I wasn't strong enough to pull the starter cord, but I would slip the black Bakelite handle between my ring finger and middle finger, and my dad would place his powerful hand over mine. We would count 1, 2, 3—and pull in unison. I still recall the thrill of hearing the engine purr to life and start to breathe on its own, and my dad would always enjoy the sparkle in my eyes at the moment of ignition.

We would sail off parallel to the coast, trolling a June bug with its spinning brass blade and a 12-inch sandworm attached to tandem hooks. My father taught me to pilot the skiff, holding the throttle of the smoothly running Evinrude outboard as we worked toward the striped bass that fed in the shallows.

Looming eerily above us on the craggy cliffs and escarpments were the deteriorating historic mansions of the Roaring Twenties, like those in a scene at the beginning of an Alfred Hitchcock movie. My dad coached me to guide the skiff closer to the rocks. "That's where the fish are, but there's danger there too, so hold her steady with a confident hand."

Fishing teaches patience. As we sat in the boat and waited, my father would strike a wooden match along the transom, cup it between his palm and forefinger to protect it from the wind, and light up a Lucky Strike cigarette. We would talk about father and son things as if the fish were tangential to our outings.

More times than not, "the fishing was great but the catching was slow." There were quiet periods when it seemed as if every fish in the sound had left for Connecticut, as if to avoid New York taxes. But then, in an instant a slack tide would change to a flood tide, and the fish would rise in a feeding frenzy.

There is a legend about Pablo Picasso sketching in a park when a bold woman approached him and asked if he would do a portrait of her. He agreed, studied her for a moment, and then drew her portrait with a single pencil stroke. The woman was thrilled. She said, "It captured me exactly!" then asked, "How much do I owe you?"

Picasso responded, "$5,000."

The woman protested, "It took you only a second to draw it."

Picasso countered, "Madame, it took me my entire life."

When we enter the operating room, we use every bit of knowledge and all the skills we have learned through a lifetime to achieve a successful surgical result. I can recall times when I was struggling with the internal limiting membrane,

Continued on page 59

'When we enter the operating room, we use every bit of knowledge and all the skills we have learned through a lifetime to achieve a successful surgical result.'

Trexler M. Topping, MD
Section Editor

Achieving Service Excellence

You have probably been to a Ritz-Carlton Hotel; the ambience is amazing. When you walk down the hallway, a maid stops, smiles, and says, "Good morning." It really makes you feel special. A smile overtakes your face and you are a little happier. I suppose you would call this part of marketing a fine-quality product. It is also called *service excellence.*

Medicine, or I should say, medical *care,* is a service we provide for our patients. We compete for patients, in a sense, as fine hotels compete for guests, but there is a big difference. Because of physician payment rules (the Resource-Based Relative Value Scale, or RBRVS), the reimbursement is the same for every physician in your city, whether in a "Ritz" practice or a "Days Inn" practice. Hopefully, we all try to provide the highest-quality care (shall I call it *Mercedes care?)* but unfortunately, we deliver it at a Yugo price.

I know others have written about this recently, but I think service excellence is something we must always keep in the forefront of our minds, our planning, our operations, and our practice.

Who in your practice gets the lowest wage? Likely that unfortunate soul is a telephone operator, if your practice is like most. When you think of it, the first interface a new patient will have with your practice is with someone in the "phone room." Thus, it makes great logical and financial sense to educate employees in the phone room (and front-desk staff) in the best ways possible to interface with the public.

At Ophthalmic Consultants of Boston, we often found that a bright, cheery, young new employee would apply for a clinical technician job after being at the front desk for a while. As human resources and other staff found these people to be very good communicators, it became easy to switch them into technician training, and they would then evolve into very loyal members of the clinical staff. However, the front-desk interface is incredibly important, as it is often where patients are first seen and the last place they interface prior to their departure.

Let's follow this service excellence theme a bit farther. In *Sweetbitter,* a recent novel by Stephanie Danler, a restaurant owner states, "Our goal is to make the guests feel we are on their side. Any business transaction—actually any life transaction—is negotiated by how you are making the other person *feel*."[1]

As I was reading these lines, I realized they apply not just to luxury hotels, fine medical practices, or 5-star restaurants, but to most everything we do.

We just took our cat into the animal hospital, and the vet tech immediately took Judy's and my cell phone numbers and texted us to help keep track of the progress of the diagnostic workup. Then the vet called us to apprise us of the situation. Medical results were not good, but the vet tech made us feel better with good communication.

I confess I never called patients at night immediately following surgery, but one of my anterior-segment colleagues does, and he gets rave reviews on patient-satisfaction surveys for this maneuver. The more communication that occurs, the more connected the patient feels.

One of my daughters-in-law works at Charles Schwab, where special emphasis is put on client relations—the heart and soul of the company is to put the client first. They find the happier the clients are, the more likely they are to refer friends and relatives. That is certainly something we know well in medicine. Probably most of our practices' mission statements emphasize putting the patient first. We need to refresh this with our employees on occasion if we find issues, sometimes told to you by a patient, when they feel our staff is not listening.

There are so many aspects of a successful retina practice. Most of us think about making the diagnostic and therapeutic process the best possible, with outcomes top notch, the experience for patient and family comfortable and caring.

This also includes the issue of patient waiting time. Four- to 6-hour waits are not service excellence, but a sign that the system needs significant improvement.

We are proud of our surgical skills and our happy, improved patients, but it behooves us also to chart their outcomes. Computer programs and electronic medical records (EMR) permit this to be done with only a little more effort. It is imperative that we follow outcomes to make sure we are giving Mercedes results.

> **'The more communication that occurs, the more connected the patient feels.'**

We all need to keep our eyes open and observe what happens in other parts of our lives, and to think how we may incorporate clever or wonderful approaches we see into our practices. When our dog went to the vet about 8 years ago, the vet put all the information into an EMR. As we left, we were given a printout of the entire visit—and I realized they were ahead of us at the animal hospital. Less than a year later, our practice caught up (but we were required to have a specific EMR by our Accountable Care Organization).

When you see and experience clever, positive processes in other parts of your life, make a note and consider whether they could help your practice improve. These enhancements only improve us, and enhance our patients' experience!

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Financial Disclosures

Dr. Topping – OPHTHALMIC MUTUAL INSURANCE COMPANY: Board of Directors, Honoraria.

JERRY'S WISDOM >> *Continued from page 57*

and I could hear my father's voice saying, "There's danger there, but that's where the fish are, so hold her steady with a confident hand."

Each time I coached a retina fellow through internal drainage of subretinal fluid and gas-fluid exchange during vitrectomy, I would think about the gray and apparently dead retina settling back onto the pigment epithelium and springing back to life like that cold Evinrude motor of my childhood.

Like my dad savored my youthful enthusiasm, I always enjoyed the sparkle in a young doctor's eyes as we watched the retina miraculously start to breathe and turn pink and healthy—as if the pigment epithelial prince had kissed the sleeping retina beauty and awakened her from a long slumber.

Whenever I encountered a situation in the OR that seemed increasingly hopeless, I would remind myself, "It's always darkest before the dawn," and as I patiently persisted, the tide would frequently turn in the patient's favor.

Each of your patient encounters, whether in the office or the OR, is preceded by the seemingly irrelevant things you learned from your parents, your siblings, your friends, and even your high school sweetheart. You should use them all. It did not take you 12 years to learn the incredibly complex skills required of a successful retina surgeon. It took your entire life!

Financial Disclosures

Dr. Bovino – None.

INTERNATIONAL CORNER >> *Continued from page 23*

are very similar worldwide. I think that the smaller percentage of responders to the survey (17%) in Central and South America and again worldwide are correct. In reality VA improves, then regresses to baseline over time (5 years). The reason for this misconception is that most data available is from randomized clinical trials and shows that with frequent injections, VA gains can be maintained over time. However, the reality is that in real-world practices, our patients are not treated monthly or regularly.

As mentioned, the PACORES group and many others have produced real-world data showing that patients with lower number of injections than in clinical trials will do worse and the visual gains obtained at years 1-2 and 3 are lost in years 4 and 5 of follow up. These results call into question the sustainability of long-term anti-VEGF treatment in eyes with chronic conditions like exudative AMD. Again, it appears that applying clinical trial protocols to daily clinical practice may not be feasible.

Another misconception is that we can keep VA gains in clinical practice. There are many obstacles to obtaining the needed number of injections for good VA results over time.

David Sarraf—United States: Multiple US and European studies indicate an initial increase in VA during the first 3 to 4 months of monthly injections in eyes with neovascular AMD with subsequent stabilization of VA at the 1- and 2-year follow-up intervals. More recent data however from CATT and SEVEN UP indicate VA decay with longer follow up from 5 to 7 years after randomization.

While the majority of survey respondents from the various regions may be referring to the 2-year data, it appears that some others may be responding on the basis of more recent studies looking at longer follow-up intervals. This breakdown of opinion is most evident in the Asian and European response, in which a higher proportion of survey respondents indicate that VA regresses to baseline. This may reflect a more resistant disease demographic (eg, polypoidal choroidal vasculopathy in the Asian population) or perhaps a more realistic long-term outlook of the disease and its therapeutic response.

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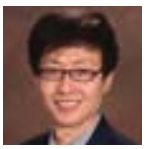
Xihui Lin, MD 

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Zika Virus Infection in Mice Causes Panuveitis With Shedding of Virus in Tears

[published online September 6, 2016]. Miner J, Sene A, Justin Richner J, et al. *Cell Reports.* 2016;16:1-11. doi:10.1016/j.celrep.2016.08.079.

Presumed congenital Zika virus infection has been suggested to cause multiple ocular diseases including chorioretinal atrophy, optic neuritis, colobomas, retina hemorrhages, and lens subluxation. Clinically, a definite association between the virus and abnormalities frequently cannot be established, as the majority of neonates with microcephaly have mothers with only presumed Zika infection. Nor have clinicians been able to establish whether the ocular abnormalities were due to direct infection or alteration of normal ocular development. The authors used a mouse Zika model to evaluate the ocular findings after an acute infection.

Zika virus does not replicate in wild mice, so the authors utilized an experimental Zika mouse model with type I interferon (IFN) receptor knockout. The authors assessed the ocular manifestations and viral RNA levels in the eye and other organs after inoculating adult IFN-knockout mice, intrauterine infection, and inoculating young wild mice. Both the French Polynesian and the Brazilian strain of the Zika virus were used, and the eyes were evaluated at different time points up to 28 days post inoculation.

The primary outcomes were ocular manifestations in adults and neonates, as well as the level of viral RNA in different ocular tissues, ocular fluids, and other organs. The researchers also studied whether the tears with viral RNA were infectious.

There were high levels of Zika RNA in the intraocular fluid, tears, lacrimal gland, and other organs 7 days after inoculation into the IFN-knockout mice with both the Brazilian and French Polynesian strands. The tears did not cause an infection when injected into IFN-knockout mice. The adult IFN-knockout mice developed panuveitis, but without significant structural damage.

In the intrauterine-inoculated group, no fetal ocular abnormalities were observed. However, in neonatal wild mice, Zika inoculation caused severe central nervous system disease and high viral load in the eye. This suggests that the ocular abnormalities seen in human neonates may be due to developmental malformations or postnatal infection.

Application to Practice: Adults infected with Zika virus must be monitored for uveitis in the first 28 days. Precautions must be taken in neonates, as Zika infection in this group may present with more severe disease.

Comparing Peripheral Vitrectomy Under Air and Fluid Infusion for Primary Rhegmatogenous Retinal Detachment

Erdogan G, Unlu C, Karasu B, MD, Kardes E, Ergin A. *Retina.* 2016;36(7):1281-1284. doi:10.1097/IAE.0000000000000898.

Extensive peripheral vitrectomy for rhegmatogenous retinal detachment (RRD) often requires scleral depression or stabilization with heavy liquid. Peripheral vitrectomy under air has the potential advantage of a wider field of view and stabilization of the retina. The authors compared peripheral vitrectomy under air vs standard peripheral vitrectomy under fluid.

The study included 80 patients with primary RRD in which half underwent peripheral vitrectomy under air and half under fluid. All surgical procedures were done with the 23-gauge Constellation System (Alcon Laboratories, Inc, Fort Worth, TX).

In the fluid group, standard core vitrectomy was performed, followed by induction of posterior vitreous detachment (PVD), peripheral shave with scleral indentation, air-fluid exchange, and laser retinopexy. The air group underwent core vitrectomy and PVD induction. After retinal reattachment with air-fluid exchange, peripheral vitreous was shaved under air infusion of 40 to 45 mmHg, cut rate of 4000 to 5000 CPM, and vacuum of 400 to 450 mmHg.

The primary outcome was rate of iatrogenic retinal breaks. Other outcomes include rate of scleral depression, visual acuity, and reattachment rate.

The rate of iatrogenic breaks in the 2 groups was comparable and occurred in 1 of 40 (2.5%) in the air group and 4 in 40 (10%) in the fluid group. Only 7 of 40 patients in the air group required scleral depression (17.5%). There were no significant differences between final visual acuity and one-operation attachment rate between the 2 groups (92.5% for air and 90% for the fluid group).

Application to Practice: Peripheral vitrectomy under air is safe and has clinical outcomes similar to traditional peripheral vitrectomy under fluid, with the potential benefit of less reliance on scleral depression.

Implications of Recurrent or Retained Fluid on Optical Coherence Tomography for Visual Acuity During Active Treatment of Neovascular Age-Related Macular Degeneration With a Treat-and-Extend Protocol

Wickremasinghe SS, Janakan V, Sandhu SS, Amirul-Islam FM, Abedi F, Guymer RH. *Retina.* 2016;36(7):1331-1339. doi:10.1097/IAE.0000000000000902.

Despite anti-VEGF treatment for exudative AMD, some patients continue to experience visual acuity loss. Both intraretinal fluid (IRF) and subretinal fluid (SRF) are associated with disease activity, but do not always predict change in visual acuity. The authors evaluated the relationship between IRF and SRF patterns and visual acuity in a treat-and-extend protocol.

The study prospectively followed 103 eyes with wet AMD undergoing treatment with ranibizumab for 12 months. After 3 monthly injections, treatment interval was extended by 2 weeks if SRF and IRF were gone, there were no new subretinal hemorrhages, and best-corrected visual acuity (BCVA) was stable. Primary outcome was change in BCVA classified as mild vision loss (5 to 9 ETDRS letters), moderate loss (10 to 14 letters) and severe loss (more than 15 letters), and OCT findings at each follow up.

During the first 12 months, there were 1.25 episodes of BCVA loss of more than 5 letters. During these episodes, IRF/SRF was present only in 37.3%. The rest were attributed to loss of ellipsoid layer (27.7%) and subretinal fibrosis (21.4%); 13.6% had no discernable cause.

Severe BCVA loss had a higher association with the presence of IRF/SRF (46.2%). New IRF or SRF is associated with more BCVA loss (33.9% and 29.6%) than when the retina is dry (16.6%) or has persistent IRF (11.9%) and SRF (14%). However, in cases of persistent fluid, new BCVA loss has a lower rate of recovery (64.3% vs 85.3%). Patients with IRF, on average, had worse BCVA (54.6 letters) than those with SRF (61.2 letters) or no fluid (59.4 letters).

Application to Practice: New IRF or SRF should be treated aggressively, but persistent fluid despite monthly treatments may be tolerated, as there are no additional risks of BCVA drop compared to patients without fluid.

Pars Plana Vitrectomy Combined with Either Secondary Scleral-Fixated or Anterior Chamber Intraocular Lens Implantation

[published online May 14, 2016]. Melamud A, Topilow JS, Cai L, He X. *Am J Ophthalmol.* 2016;168:177-182. doi:10.1016/j.ajo.2016.05.006.

In eyes following trauma or complicated cataract surgery without adequate sulcus support, an anterior-chamber intraocular lens (ACIOL) or scleral fixated intraocular lens (IOL) are effective options. Few studies have directly compared the visual acuity outcomes of the 2 approaches when combined with vitrectomy. The authors reviewed a large series comparing the 2 in terms of BCVA and complications.

After excluding eyes with previous macular pathology, retinal detachment, or an ACIOL, 57 eyes were included and followed for at least 6 months. All eyes underwent 20- to 27-gauge pars plana vitrectomy (PPV). Thirty-three patients received an ACIOL with Alcon MTA3UO or MTA4UO (Alcon Laboratories, Inc, Fort Worth, TX); 24 patients had a sutured IOL with Alcon CZ70BD. The primary outcome was the BCVA at the most recent follow up and complications.

In the ACIOL group, BCVA improved from 20/400 to 20/60 after the surgery; and for the posterior-chamber IOL (PCIOL) group, BCVA improved from 20/347 to 20/40. There was no statistically significant difference between the 2 groups in final BCVA or improvement in BCVA. There also was no difference in the rate of intraocular pressure (IOP) increase, retinal detachment, vitreous hemorrhage, lens decentration, or persistent ocular inflammation between the 2 groups. The ACIOL group had more epiretinal membrane (ERM) formation (24.2%) than the PCIOL group (0.0%, $P = .008$).

Application to Practice: ACIOL and scleral sutured IOL after vitrectomy offer similar improvements in BCVA and no significant difference in complication rates, with the exception of more ERM formation in those with ACIOL placement.

Results at 2 Years After Gene Therapy for *RPE65*-Deficient Leber Congenital Amaurosis and Severe Early-Childhood-Onset Retinal Dystrophy

Weleber RG, Pennesi ME, Wilson DJ, et al. *Ophthalmol.* 2016;123(7):1606-1620. doi:10.1016/j.ophtha.2016.03.003.

Patients with Leber congenital amaurosis (LCA) often present in infancy with profound visual impairment, nystagmus, weakly reactive pupils, fundus abnormalities, and a severely reduced or absent electroretinogram. Mutations in the *RPE65* gene account for 6% to 16% of cases of LCA. Subretinal gene therapy is an area of intense research as a possible therapeutic option for these visually debilitating eye diseases.

This nonrandomized, multicenter clinical trial evaluated 8 adults and 4 children, 6 to 39 years of age with LCA or severe early-childhood-onset retinal dystrophy (SECORD), who underwent subretinal injection of rAAV2-CB-hRPE65 in the poorer-seeing eye. Six eyes received a smaller dose (group 1) and 6 eyes a larger dose (group 2) of viral genome. Patients were followed for 2 years.

Surgical technique included a pars plana vitrectomy, injection of 0.45 mL of subretinal vector genomes using a 39-gauge microinjection cannula through a retinotomy outside the retinal vascular arcade (group 1) or inside the vascular arcade (group 2). Five patients had a subretinal bleb that involved the fovea.

Best-corrected visual acuity (BCVA) increased in 5 patients, central 30 degrees of visual field improved in 6 patients, and kinetic visual fields improved in 3 patients. In total, 9 out of 12 patients showed some form of visual improvement. The 4 pediatric patients showed the best results with 6 to 14 ETDRS letters of improvement at 2-year follow up. One patient showed a decrease in BCVA and 2 patients showed a decrease in kinetic visual field.

Application to Practice: Treatment with subretinal injection of rAAV-CB-hRPE65 had an acceptable safety profile, and showed mild improvement in 1 or more measures of visual function in 9 out of 12 patients, with younger patients receiving the most benefit. The authors note the study was too small to determine dose-related differences or the effect of subfoveal vs non-subfoveal injections.

Standard Cut Rate 25-Gauge Vitrectomy Versus Ultrahigh-speed 25-Gauge System in Core Vitrectomy. A Randomized Clinical Trial

Mariotti C, Nicolai M, Saitta A, et al. *Retina*. 2016;36(7):1271-1274. doi:10.1097/IAE.0000000000000924

Ultrahigh-speed cutters have the potential to perform a safer-shave vitrectomy because the faster cut rate reduces retinal movement, minimizing the risk of causing iatrogenic retinal breaks. However, there is concern that this increased cut rate may affect the duty cycle, diminishing the flow rate through the vitreous cutter and leading to prolonged operating time.

This randomized clinical trial compared 31 eyes undergoing 25-gauge vitrectomy with 7500 cuts per minute (CPM) vs 31 eyes with standard 25-gauge 5000 CPM probes. All surgical procedures were completed by the same surgeon performing vitrectomy for macular disease or retinal detachment without proliferative vitreoretinopathy. The Alcon Constellation Vision System (Alcon Laboratories, Inc, Fort Worth, TX), valved trocars, and maximum linear aspiration of 600 mm Hg were used. Inspection of the retina for complications was done on postoperative day 1, 1 week, 1 month, and 3 months after surgery.

The main outcome was *core* vitrectomy duration, measured from the time the probe entered the eye to the moment the surgeon performed air/fluid exchange. Further vitrectomy was completed by shaving the peripheral vitreous under air.

The surgical duration in the standard 5000 CPM group was 184.10 +/- 41.69 seconds for *core* vitrectomy vs 161.32+/-39.10 seconds in the ultrahigh-speed 7500 CPM. Both cutters were equal in their ability to

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Rosa Dolz-Marco, MD, PhD

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Section Editor

Case History A 60-year-old female was referred for a second opinion regarding a recent diagnosis of non-neovascular age-related macular degeneration (AMD). She reported noticing bilateral worsening of central vision over the prior few months.

The patient denied any other significant ocular history. She had well-controlled hypercholesterolemia and diabetes mellitus type 2. The patient had no known family history of ocular diseases. There was no history of parental consanguinity.

On examination, her visual acuity was 20/40 in her right eye and 20/25 in her left eye. The slit-lamp examination showed quiet anterior segments and mild nuclear sclerotic and inferior cortical cataracts. (Figure 1, A-B) Dilated funduscopic examination revealed bilateral macular retinal pigment epithelium (RPE) changes in a bull's-eye pattern. (Figure 1, C-D) With fundus autofluorescence (FAF), these pigmentary changes appeared as a mottled hypoautofluorescent ring surrounding a preserved fovea. (Figure 2)

Structural optical coherence tomography (OCT) demonstrated perifoveal atrophy of the ellipsoid zone and the external limiting membrane with mild hypertransmission (enhanced OCT signal penetration below the RPE). There was preservation of the outer retinal structures at the fovea. (Figure 3).

What is your diagnosis?

See discussion on page 64

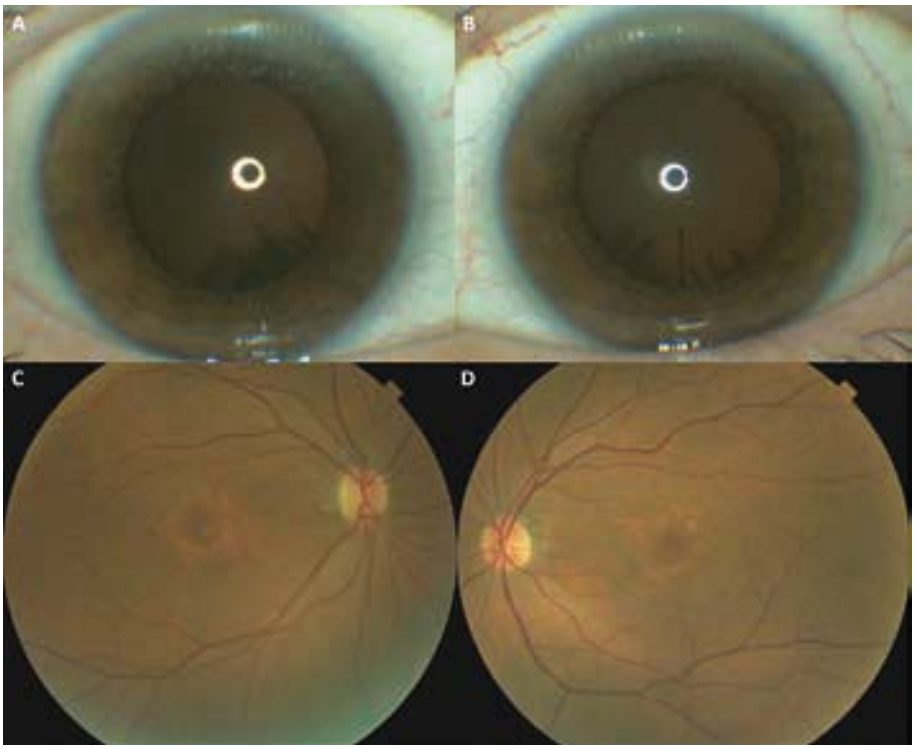

Figure 1. A, B. Anterior chamber photographs show bilateral mild nuclear sclerotic and inferior cortical cataracts. C, D. Color fundus photographs show bilateral macular pigmentary changes in a bull's-eye pattern.

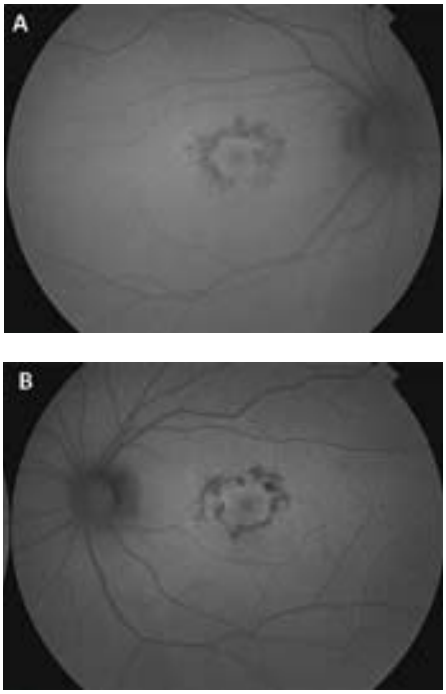

Figure 2. A, B. FAF shows a ring of mottled hypoautofluorescence surrounding the fovea with no evidence of flecks in either the paramacular or more peripheral retina.

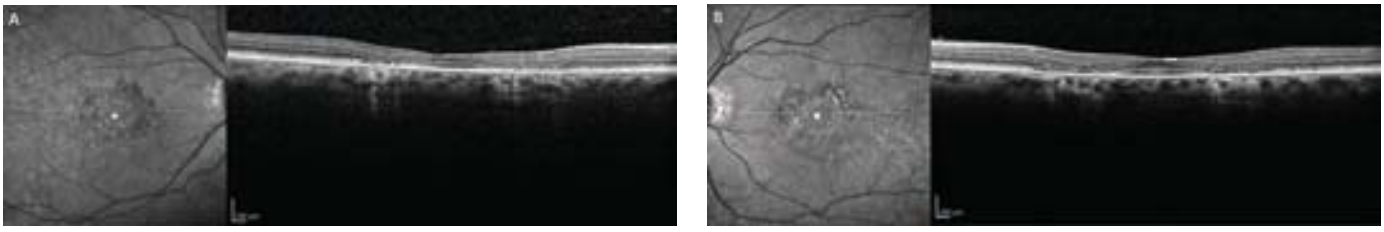

Figure 3. A, B. Near-infrared reflectance (NIR) images and corresponding structural spectral domain optical coherence tomography line scans show preservation of the retinal layers at the fovea. There is outer retinal atrophy involving the perifoveal region where there is loss of the external limiting membrane and the ellipsoid zone.

Retinal Genetics and Gene Therapy: Diagnosis, Clinical Management, and Genetic Intervention for Inherited Retinal Disease, **Christine Kay, MD**

Duke Vitreoretinal Surgical Rounds, **Lejla Vajzovic, MD**

Understanding the Business Side of Practicing Medicine: Coding, Finances, and Medical-Legal Issues, **Vincent S. Hau, MD, PhD**

Sunday: Symposia

Inflammatory and Infectious Diseases 1 Symposium

Moderators: Thomas A. Albini, MD, and Virgilio Morales-Canton, MD

Fundus Findings, SD-OCT Characteristics, Treatment and Outcomes of an Outbreak of Post-Viral Fever Retinitis in Southern India: Interim Results, **Apoorva Ayachit, MS**

Sarilumab for Non-infectious Uveitis (SARIL-NIU): Interim Results From the SATURN Study, **David Callanan, MD**

A Randomized, Masked, Controlled, Safety and Efficacy Study of an Injectable Fluocinolone Acetonide Intravitreal Insert in Non-infectious Uveitis, **Glenn Jaffe, MD**

Endophthalmitis After Vitrectomy Surgery: A Case Control Analysis, **Samuel Kim, MD**

Persistently Vitreous Culture-Positive Exogenous Endophthalmitis, **Ella Leung, MD**

The Effects of Intravitreal Sirolimus on Inflammation in Non-infectious Intermediate Uveitis: Results from SAKURA Study 1, **Pauline Merrill, MD**

Intravitreal Sirolimus Effects on Vitreous Haze and Visual Acuity in Non-infectious Uveitis of the Posterior Segment: 12-Month SAKURA Study 1 Results, **Sunil Srivastava, MD**

Suprachoroidal Administration of Triamcinolone Acetonide: Results of a Phase 2 Study of Patients With Non-infectious Uveitis, **Steven Yeh, MD**

Comparison of Microbiology and Visual Outcomes of Patients Undergoing Small-Gauge and 20-Gauge Vitrectomy for Endophthalmitis, **David Almeida, MD, MBA, PhD**

Inflammatory and Infectious Diseases 2 Symposium

Moderators: Damien C. Rodger, MD, PhD, and Steven Yeh, MD

Clinical Course and Management of a Cluster of Post Intravitreal Bevacizumab Injection Fungal Endophthalmitis in 14 Eyes, **Mallika Goyal, MD**

Suprachoroidal Administration of Triamcinolone Acetonide: Combined Results of Phase 1/2 and Phase 2 Clinical Studies, **Seenu Hariprasad, MD**

Treatment of Uveitic Macular Edema With Corticosteroids Utilizing a Novel Approach: Suprachoroidal Injector, **Shree Kurup, MD**

Fundus Abnormalities in Microcephalic Newborns Presumably Related With Congenital Zika Virus Infection During Epidemic in Brazil, **Mauricio Maia, MD, PhD**

Intravitreal Aflibercept Injection for Choroidal Neovascularization Secondary to Presumed Ocular Histoplasmosis Syndrome (POHS): HANDLE Study 1 Year Results, **Dennis Marcus, MD**

Primary Outcomes of the Study of Safety, Tolerability, and Bioactivity of Tocilizumab in Patients With Non-infectious UVEITIS (The STOP-UVEITIS Study), **Quan Nguyen, MD, MSc**

En Face Optical Coherence Tomography and OCT Angiography of MEWDS, **David Sarraf, MD**

Update on the Association of Intracameral Vancomycin and Hemorrhagic Occlusive Retinal Vasculitis (HORV), **Andre Witkin, MD**

Qualitative and Quantitative Analysis of Optical Coherence Tomography Angiography in Patients With Retinal Vasculitis, **Angela Bessette, MD**

Quantification of Blood Flow in Retinal Vasculitis Using Optical Coherence Tomography Angiography, **Monica Michelotti, MD**

Hereditary Retinal Disease and Genetics Symposium

Moderators: Hossein Ameri, MD, PhD, FRCSI, MRCOphth, and Charles C. Wykoff, MD, PhD

Subthreshold Diode Micropulse Laser (SDM) as Retinal Protective Therapy for Non-Age-Related Retinal Degenerations, **Jeffrey Luttrull, MD**

Visual Acuity Sensitivity/Subgroup Analyses From a Phase 3 Trial of AAV2-hRPE65v2 *(SPK-RPE65)* in *RPE65* Mutation-Associated Inherited Retinal Dystrophy, **Stephen Russell, MD**

North Carolina Macular Dystrophy (MCDR1): Mutations Found Affecting PRDM13, **Kent Small, MD**

Special thanks to our physician reporters

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Discussion

The differential diagnosis of a bull's-eye maculopathy includes AMD, benign concentric annular macular dystrophy, chloroquine and hydroxychloroquine maculopathy, cone dystrophy, cone-rod dystrophy, and Stargardt disease.[1]

Treatment with chloroquine or hydroxychloroquine or other drug-related retinal toxicity was ruled out in our patient. The absence of drusen and the bilateral symmetry of the pigmentary changes did not support the AMD diagnosis. The presumptive diagnosis was an inherited macular dystrophy with a strong suspicion for a late-onset *ABCA4*-related maculopathy.

The patient's blood was sent for genetic testing (Stargardt/macular dystrophy panel, Casey Eye Institute Molecular Diagnostics Laboratory, Portland, OR). Eight different genes were analyzed, including *ABCA4*, *BEST1, EFEMP1, ELOVL4, IMPG1, IMPG2, PROM1*, and *RDS*. The genetic testing showed a single homozygous pathogenic variant in exon 42 of the *ABCA4* gene (G1961E, p.Gly1961Glu, c.5882G >A).

This variant has been associated with autosomal recessive Stargardt disease. Compared with other mutations on the *ABCA4* gene, patients who are homozygous for the *G1961E* mutation show milder retinal changes, with a later onset of visual impairment. On clinical examination, the lesions are typically confined to the macula, with an absence of flecks and lack of a dark choroid on fluorescein angiography.[2] Also, it has been shown that patients who are homozygous for the same mutation in the *ABCA4* gene may have a later onset of symptoms than patients with 2 or 3 different mutations.[3]

Quantitative fundus autofluorescence (qAF) with scanning laser ophthalmoscopy is a relatively new technique that provides a more reproducible and quantifiable measure of FAF through the use of a built-in standard fluorescent reference. This technique helps adjusts for changes in FAF related to acquisition technique, ocular media, patient age, and refraction.[4] It has been reported that patients with Stargardt disease show higher levels of qAF than control eyes.[5] Interestingly, although patients with the *G1961E* mutation show increased FAF compared to normal control eyes, their qAF levels are considerably lower than those occurring with other mutations in the *ABCA4* gene (L2027F and L541P/A1038V).[6] In our patient, qAF allowed us to detect a mild increase in autofluorescence that was difficult to appreciate with other FAF techniques. (Figure 4)

When examining a patient with a presumed inherited macular dystrophy and no family history of retinal disease, establishing a diagnosis without genetic testing may be difficult. Multimodal fundus imaging, including qAF, may be helpful in establishing a presumptive diagnosis while awaiting the results of targeted genetic testing.

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Financial Disclosures

Dr. Dolz-Marco – ALCON LABORATORIES INC: Investigator, Grants; ALLERGAN INC: Investigator, Grants; ANGELINI PHARMA: Investigator, Grants; BAYER HEALTHCARE: Investigator, Grants; NOVARTIS PHARMACEUTICALS CORPORATION: Investigator, Speaker, Grants; ROCHE HOLDING AG: Investigator, Grants; THEA PHARMACEUTICALS GROUP: Investigator, Grants.

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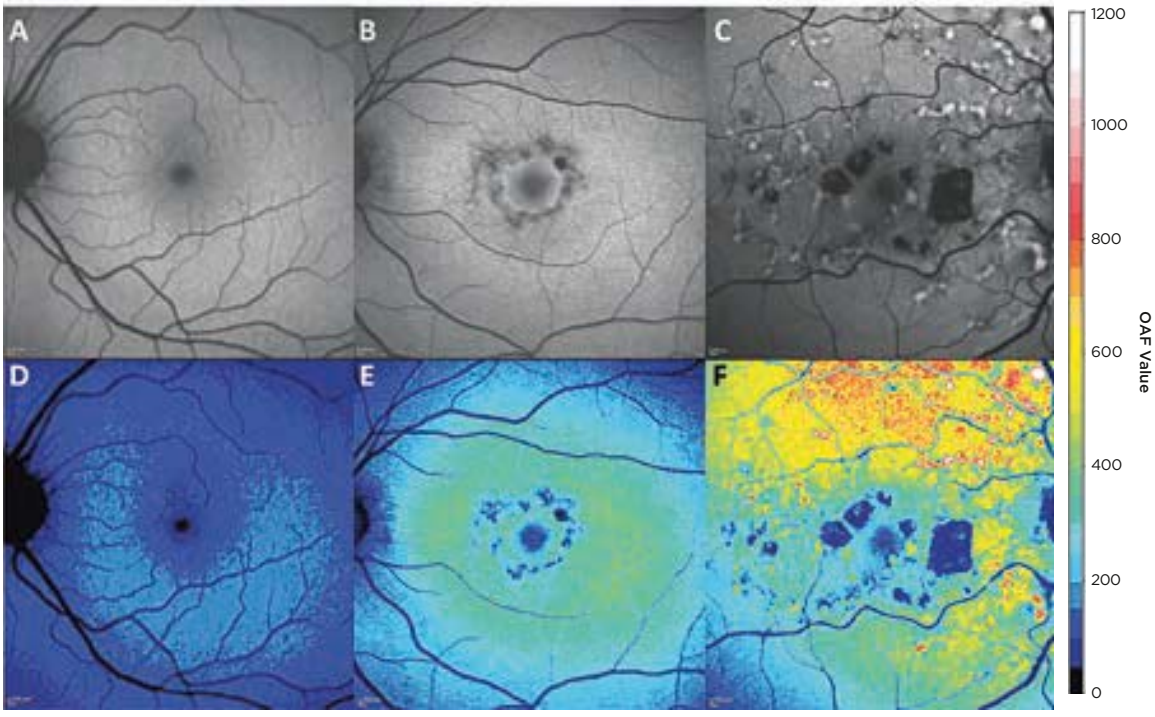

Figure 4. Quantitative autofluorescence (qAF) in 3 different patients showing the gray-scale fundus autofluorescence (FAF) (A-C) and the qAF in the color-coded maps (D-F). The qAF reference scale is shown on the right. A, D. A normal 52-year-old female. B, E. A 60-year-old female homozygous for the G1961E mutation (the patient described in this X-Files). C, F. A 69-year-old male with an inherited macular dystrophy. Genetic testing of both this patient and his brother, who has similar fundus findings, showed the same mutation in ABCA4 (p.Arg653Cys:c.1957C>T). Both patients tested heterozygous for this mutation. While the background FAF appears similar in all 3 cases, qAF reveals significant differences in the intensity of the FAF in these 3 eyes.

induce a posterior vitreous detachment with aspiration. Complication rates were not statistically different between groups, which included evaluation for macular edema, elevated intraocular pressure, iatrogenic breaks, and subsequent retinal detachment.

Application to Practice: Ultrahigh-speed 7500 CPM 25-gauge vitrectomy was found to be an effective and safe surgical procedure that does not delay surgery times for core vitrectomy when compared with standard 5000 CPM vitrectomy.

25-Gauge Pars Plana Vitrectomy and SF6 Gas for the Repair of Primary Inferior Rhegmatogenous Retinal Detachment

Duvdevan N, Mimouni M, Feigin E, Barak Y. *Retina*. 2016; 36(6):1064-1069. doi:10.1097/IAE.0000000000000853.

There is debate in the literature as to whether retinal detachments with inferior breaks have a greater risk of redetachment than detachments with superior breaks; this may lead to more-involved surgical procedures for inferior detachments, such as combined pars plana vitrectomy (PPV) with scleral buckle, or the use of silicone oil or longer-acting gases for tamponade.

This retrospective cohort study compared the anatomical and functional success rates between retinal detachment repair in 25 eyes with an inferior tear (between 4 and 8 clock hours) vs 34 eyes with a superior retinal break. Eyes with tears in both locations were included in the inferior retinal tear group. A 25-gauge Alcon Constellation System (Alcon Laboratories, Inc, Fort Worth, TX) was used with 25% SF6 gas for tamponade.

All patients had 360-degree prophylactic laser and 5 days of postoperative facedown positioning. Eyes with proliferative vitreoretinopathy (PVR) grade D, giant retinal tears, recent intraocular infection, previous ocular trauma, or serous/tractional combined retinal detachments were excluded.

The single-surgery anatomical success rate was 96% (24/25) for superior breaks vs 82% (28/34) for inferior or combined retinal detachments. However, this was not statistically significant ($P = .22$). Single-surgery anatomical success was achieved in 88% of the total cases (52/59). There was no significant difference in visual outcomes or complications, including PVR, cataract, vitreous hemorrhage, and epiretinal membrane.

Application to Practice: The study found 25-gauge PPV using 25% SF6 gas is a safe and effective technique for repairing primary retinal detachments. There were no statistical differences in anatomical or functional success rates in detachments with an inferior vs a superior break.

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