RETINA TIMES

An Official Publication of the American Society of Retina Specialists

Winter 2019
Issue 82
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RETINA TIMES

Winter 2019 • Issue 82 • Volume 37, Number 5

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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ASRS American Society of Retina Specialists

20 North Wacker Drive, Suite 2030
Chicago, IL 60606
Phone: 312-578-8760
www.asrs.org

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Ms. Blim – None. **Ms. Nemcek** – None. **Ms. Power** – None. **Ms. Raef** – None. **Ms. Schedler** – None. **Ms. Steck** – None.

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On the Cover

Case: 43-year-old female with cone dystrophy and a new-onset branch retinal vein occlusion (BRVO) in the left eye.

Image: Asymmetric ultra-widefield fluorescein angiography montage demonstrating temporal peripheral nonperfusion in a BRVO.

Photographer: Gabriele Tai

Physician: Netan Choudhry, MD, FRCS(C), DABO
Vitreous Retina Macula Specialists of Toronto
Etobicoke, Ontario, Canada

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- Cutting-edge coding tips
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ASRS American Society of Retina Specialists

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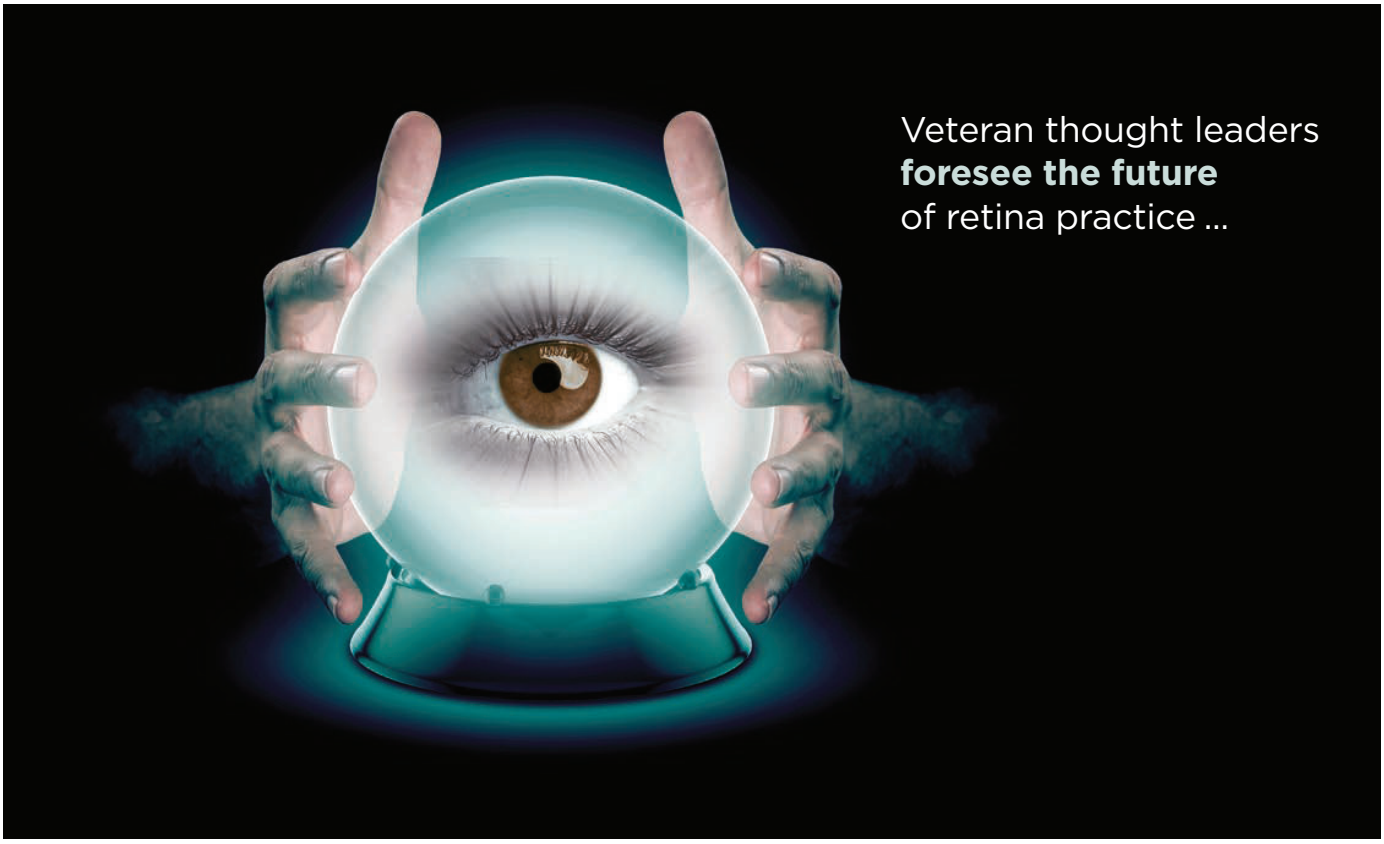

ASRS Co-founder Allen Verne, MD, invites Drs. Steve Charles, Harry Flynn, Kirk Packo, and Paul Tornambe to predict the biggest advances in the next 50 years.
See page 52.

Timothy G. Murray, MD, MBA
ASRS 2019-2020 President

ASRS: Raising Awareness, Advocating for Retina Specialists and Patients

The ASRS is poised for a banner year in 2020. One week into my presidency, Executive Vice President Jill Blim and I traveled to San Francisco to represent the ASRS at the American Academy of Ophthalmology (AAO) Annual Meeting. As always, the Preferences and Trends (PAT) Survey posters on display at the meeting highlighted retina specialists' practice patterns for those attending the AAO Retina Subspecialty Day.

The ASRS sponsored "IN THIS CORNER … The Retina Debates 2019," and our members represented retina specialists from around the globe participating in all aspects of the Academy. Also, while in San Francisco, Jill Blim and I met with W20, our partner for the upcoming Retina Specialist Campaign, to begin crafting both our focus and message for this 2020 public awareness initiative.

It is more imperative than ever for our specialty to speak for our patients with a singular voice; together, we need to advocate for personalized patient care, recognizing that early diagnosis, rapid inception of optimal therapies, and targeted follow-up are the hallmark of best practices in retina care. So much of health care policy seems directed at treatment strategies that put patients at risk by limiting or delaying access to the retina specialist, mandating treatment approaches through pre-selection of covered therapies, or equating "quality" with lower cost.

Virtually every treatment employed by retina specialists has shown significant cost utility, at both the individual level and nationally. Recent work by the ASRS has focused on the public health value of anti-VEGF therapy in neovascular AMD—no surprise to our community but clearly not appreciated at a national health policy level.

Promoting public awareness of retina specialists

At ASRS, we are moving to enhance national recognition of retina specialists through an educational campaign emphasizing that retina specialists are experts in treating all of the most prevalent blinding diseases.

In virtually no other specialty can a patient be seen in a 2-hour comprehensive office visit that incorporates patient-targeted measurements (visual acuity, intraocular pressure, anterior-segment evaluation *and* dilated indirect ophthalmoscopy), determines that individual's testing requirements (spectral-domain OCT [SD-OCT] of the macula, widefield fundus photography, and other state-of-the-art imaging), FA/ICG/OCTA, SD-OCT for RNFL, and quantitative diagnostic a/b scan echography), obtains *and* interprets results in real time, and then provides an accurate diagnosis with a treatment plan implemented *during* the office visit.

When our patients visit their primary and specialty care practitioners, they are examined, *then* scheduled for blood work, *then* for imaging, and *then* for a review and discussion of the test results. The contrast between that approach and retina's comprehensive visit model does not disparage primary or other specialty care, but *does* highlight the integration in retina care.

Get involved with our peer-reviewed journal

The ASRS has transitioned from its early years as the Vitreous Society to its current, evolving role as a patient resource and a retina specialist-focused body that must assume a policy role through initiatives that strive for best patient care. *The Journal of VitreoRetinal Diseases (JVRD)* is one of these initiatives.

For our peer-reviewed journal to thrive, it requires the backing of you, our members. This support is best manifested by your submitting quality articles, but also by your willingness to serve as timely, active reviewers. *JVRD* heralds the rigorous educational focus of our Society. Ultimately, we aim for recognition by the US National Library of Medicine's PubMed.gov online database—the gold standard for an enduring journal.

Enhancing patient-education materials

The ASRS website's patient portals will be enhanced in 2020 to improve access to, and recognition of, fellowship-trained retina specialists. Many of our members have contributed patient-focused care summaries available both to you and to your patients. (Visit asrs.org/patients/retinal-diseases.)

Advocacy: The voice of retina

ASRS Past President John Thompson, MD, and Jill Blim continue to advocate for retina specialists at both the national and regional levels. Ultimately, our 2020 public awareness campaign is focused on positioning the retina specialist as *the voice of retina*. This will be enhanced by media-trained ASRS physician leaders available as national spokespersons. ASRS plans to use this opportunity to broaden our impact on public health policy related to retinal disease.

Retina specialists are a unique subspecialty group. In the absence of formal subspecialty recognition, the ASRS has focused on identifying and documenting fellowship training through the Fellows' Activity Log; this is also an effective tool for easily and efficiently tracking retina training activities.

The ASRS Board represents the voice of the retina specialty.

Collaborating with other societies

During many ASRS activities, our members wear multiple hats, including Retina Society and Macula Society membership, Association of University Professors of Ophthalmology (AUPO) participation, and AAO leadership roles.

Participating in AAO Retina Subspecialty Day reminded me that 2 of my best friends are playing leadership roles in our sister societies. Retina Society President Allen Ho, MD, and Macula Society President Carol Shields, MD, share our commitment to ensuring the recognition of the retina specialist. I have always believed that we extend our reach, enhance our abilities, and broaden our perspective when we collaborate. I expect that Allen, Carol, and I will have much opportunity to bring each society's unique focus to ultimately better our patients' care.

Divisiveness dilutes the voice of the retina specialist, on both a national and international level. The ASRS Board, Executive Committee, and leadership have been able to speak with a collaborative voice. Over the years, and especially recently, I have had the opportunity to support members of the retina specialty community who are dealing with complex issues—many of which have been raised by disagreements within our specialty. After 20 years at Bascom Palmer Eye Institute (BPEI), I appreciate the advances that can come from differences in opinion and approach.

Early in my career at BPEI, these differences pushed me to explore novel areas of treatment, both in the laboratory and the clinic; but later in my BPEI career, differences in care became personal and the "healthy" disagreements discussed at grand rounds along with fellow/resident teaching seminars, devolved into behind-the-scenes backstabbing that positioned personal opinions and preferences as "standards of care."

As any ASRS member perusing our PAT Survey well knows, we have multiple practice patterns for virtually every aspect of retinal care. The ASRS has continued to focus on the uniqueness of patient-specific, personalized care determined by the best practices chosen by the vitreoretinal specialist and the patient. The ASRS will continue to advocate for our members, but I ask that we advocate for one another as well.

At a recent skills-transfer course, 2 of my fellow panel members discussed the concept of "staying in your lane." Both of these individuals were representing ophthalmologists in significant lawsuits as the expert witness for the surgeon. They both noted that in their cases, the "expert" witness for the plaintiff had never personally treated the condition under review, nor had he or she performed the surgical procedure at issue.

Both of these retina specialists (whom I know and respect), commented that these legal cases would not have moved forward without the "expert" witness opining on the case, as the care provided by the surgeon *was* appropriate. This leads me to ask us all to recognize that different approaches to practice are not, by definition, "wrong."

When I see patients in consultation, my objective is to drive their care forward. I focus often on the broad overlaps in care strategies, and less on the distinctions between our individual approaches. Having taught fellows and residents throughout my career, I believe that our specialty is driven by brilliant, passionate retina specialists who pride themselves on excellent patient care. Give your colleagues the benefit of the doubt when it comes to differences in practice before you suggest that their approach is below *your* "standard of care."

Finally, as my 2 daughters move through high school, having watched their father practice at Bascom Palmer and then start a private practice in Miami, I find myself wanting to leave the field of medicine a better place for them to potentially practice. Though each generation brings a different view to the practice of medicine, I believe that placing your patients' best interests first will always be the defining value in health care.

Our legacy as retina specialists is amazing, but the future holds even more promise for our patients and our specialty. Here's to a world of retina that includes artificial intelligence, gene-specific surgery, advances in imaging, telemedicine, and durable therapies for blinding diseases of the retina.

The ASRS, and we as individual members, must be tasked with integrating these advances in the future of our field, always driven by the desire to improve patient care. Retina specialists *are* the future of best patient care practices for potentially blinding retinal diseases.

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Dr. Murray – ALCON SURGICAL: Consultant, Honoraria; REGENERON PHARMACEUTICALS, INC: Investigator, Grants.

Sunir J. Garg, MD, FACS
Editor in Chief

When You're Invited to a Patient's 100th Birthday Party, *Go!*

I recently went to the 100th birthday party for a patient whom I've cared for since she was 87 years old. One of her eyes remains poor from a long-standing disciform scar, but fortunately she has maintained 20/60 vision in the other eye for more than a decade with an intravitreal anti-VEGF injection every 6 weeks. In that time, I've gotten to know this patient and her family really well.

It's amazing when we can give our patients their vision so they can enjoy their lives—and if we, and they, are so fortunate, celebrate their 100th birthday with them.

I started hitting her up somewhat jokingly for an invitation to her 100th birthday party 4 years ago—and much to everyone's delight, she celebrated her 100th birthday just after Labor Day. The surprise party was at her niece's house in New Jersey.

My patient had been making me the most amazing biscotti with chocolate chips every visit for the past 13 years. Everybody and their family loved them. I would usually bundle up some biscotti and give them to my parents; the staff would all get a certain allotment, and our son has grown up eating them.

It was a sad day in everyone's life when her trusty 35-year-old oven broke down and had to be replaced. I can attest that the new oven did not distribute the heat nearly as effectively as the old one. Some of the biscotti got burned around the edges, but nonetheless, they were still delicious.

Sadly, she wasn't so happy with the results, and her biscotti-making days unfortunately have passed. Her grandniece, however, has taken up the mantle so I still get some biscotti, but not nearly as often as my coffee would wish. Recently, I found a party invitation bundled in with the biscotti. The invitation was an opt out—I was a lock.

When the day of the birthday party arrived, I walked around the house asking my wife why I was going. She simply replied, "You have been talking about this birthday party for years!" Although I've taken care of a number of patients over the age of 100, only a few have invited me to their birthday parties, and this party was the first I'd be able to attend.

My original plan was to bring all 5 of us over—my wife, our 3 kids, and me—however, our son's friend had a birthday party that conflicted with the schedule, so my wife and children went to that one while I went to my patient's party.

The niece hosting the party lives about an hour away, and to get there, I had to cross the Delaware River (just like George Washington did—you can visit the state park where the famous boat crossing happened about an hour from Center City Philadelphia) over one of our many bridges. New Jersey is called *The Garden State* for good reason—as you leave metro Philly, the terrain gets quite rural quite rapidly.

As I was driving down the road, I was stuck behind a large flatbed trailer piled 30 feet high with hay bales. Of course, it was a beautiful

Illustration by Jeanne Nemcek

late-summer day, so I was cruising in the Corvette convertible with the top down, in a nice suit because I'd rather be overdressed than underdressed.

At first, I started wondering if I'd developed a posterior vitreous detachment, until I realized it wasn't floaters I was seeing—it was pieces of hay. Whenever the truck went by a tall tree with overhanging branches or under utility lines, pieces of the hay would be brushed off, fly through the breeze, and land in my car—and on me.

After about 3 miles, the inside of my car could've made a great manger and I would've been a shoo-in for a scarecrow. Looking in my rearview mirror, I could see the couple behind me laughing hysterically, and that laughter continued as they pulled up behind me—we all were going to the same party. They greeted me with a touch of sadness, as they had this great story to tell everyone, but I stole some of their thunder.

'At first, I started wondering if I'd developed a posterior vitreous detachment, until I realized it wasn't floaters I was seeing—it was pieces of hay.'

The party was awesome! More than 100 people were there, most from the same large Italian family. There was amazing food, and they even had a roast pig with an apple in its mouth. As a vegetarian, I was not bothered at all, but some of the people who were eating were troubled by the whole thing.

One of the family friends introduced me to the other guests. Much to my surprise, nearly everybody there knew about me because over the years, they'd all heard about this doctor who puts needles in the birthday woman's eye, but I helped her see for many years.

Several people were disappointed that I didn't bring my wife and our children to the party, as they'd hoped to meet them (a byproduct of my showing family photos to anyone who'd look). My patient knew me when I got married, and knew about the births of our children. One time, we had to cancel her appointment the morning she was to come in, as I was bringing one of our children home from the hospital.

The highlight of the party, of course, was when my patient arrived at the house (the *sell* to get her to come to the party was her nephew's famous roast lamb chops). I was overwhelmed when I was number 4 on the hugging list!

It's amazing when we can give our patients their vision so they can enjoy their lives—and if we, and they, are so fortunate, celebrate their 100th birthday with them. My recommendation: Never turn down an invitation to anyone's 100th birthday party!

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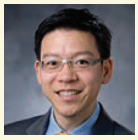
Welcome our new section editors

Lisa J. Faia, MD

With this issue, we have a few new faces on our *Retina Times* editorial team. I would like to welcome Lisa J. Faia, MD, as the new Uveitis section co-editor. She will be working along with Phoebe Lin, MD, PhD, to make the Uveitis section even more engaging to practicing retina specialists. See their article, "Uveitis or Not?" on page 26.

Dean Eliott, MD

Dean Eliott, MD, the incoming chair of the ASRS International Affairs Committee, is our new International Corner section editor, succeeding Rishi Singh, MD. Many of you have known Dean for years, and I am sure he will bring a fresh take and his wry sense of humor to this section. See his article on the worldwide educational outreach of Narsing Rao, MD, on page 20.



Paul Hahn, MD, PhD

Finally, we will be featuring the PAT Survey Deeper Dive—a new initiative spearheaded by incoming PAT Survey Editor Paul Hahn, MD, PhD, in collaboration with PAT Survey Research Consultant Mindy Schneiderman, PhD. The Deeper Dive will feature a subanalysis of PAT Survey data, providing greater context to the findings of the PAT Survey and helping make the PAT Survey data more useful and relevant to all of us. See the Deeper Dive into retina specialists and private equity on page 16.

Robert L. Avery, MD
Chair, ASRS Practice Management Committee

Tushar M. Ranchod, MD
Course Director

Stacy Kiff
ASRS Vice President of Education

Register Now for the 22nd Annual ASRS Business of Retina Meeting—March 21-22, 2020

Please join us on March 21 and 22, 2020, for the 22nd Annual ASRS Business of Retina (BOR) Meeting at the Four Seasons in Dallas.

Why should you attend?

This meeting for retina specialists and practice administrators is dedicated to the daily business challenges that retina practices face. Network with your peers from around the country and learn new ways to protect, optimize, and grow your practice. The BOR meeting is oriented toward practices of all sizes and physicians and administrators at all career stages.

What topics will the meeting cover?

- Private equity
- Clinical trials
- Medicolegal and HR issues
- Coding updates
- Decoding MIPS in 2020
- LEAN office culture

Register by February 14, 2020 to enjoy the early-bird discount: www.asrs.org/2020BOR

ASRS members: $550

Nonmembers: $725

Technicians/practice staff: $550

Fellows in training: $50

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Ms. Kiff – None.

Dr. Ranchod – None.

What are retina specialists and practice administrators saying about the Business of Retina Meeting?

"The ASRS Business of Retina Meeting is the most helpful meeting I've attended regarding the business side of medicine over the last 10 years. This meeting is designed for the managing partner and practice administrators. The topics covered each year are concise, timely, and very high yield!"

Cameron Javid, MD, Retina Associates SW, PC

"I find the Business of Retina Meeting to be the most beneficial to attend. The talks are relevant and pertain to just the issues that retina practices face, without much discussion of general ophthalmology concerns that are heard in most annual meetings. If I had to pick only one meeting to attend each year, the ASRS Business meeting would be my first choice."

Alison Ratliff, MBA, Chief Executive Officer, South Coast Retina Center

"The ASRS Business of Retina Meeting is one of a kind. As a young retina specialist, I found it gave me a wonderful opportunity to meet other physicians, practice administrators and staff around the country and learn about the ongoing issues that affect us all that are generally not discussed at other meetings.

"We all face common challenges—insurance issues, managing staff, managing drug float, changes and decline in reimbursement, interfacing with private equity. The meeting is a unique and wonderful opportunity to exchange ideas and experiences, and learn from each other about creatively dealing with these issues!"

Bozho Todorich, MD, PhD, Pennsylvania Retina Specialists

"I look forward to attending the Business of Retina Meeting each year. I believe it is an important conference for any retina practice administrator or physician to garner specific information on our specialty, and a great place to collaborate with your peers."

Stephanie Collins Mangham, MBA, COA, OCSR, Chief Operating Officer Austin Retina

Carl C. Awh, MD
Section Editor

20th Annual Retina Fellows Forum Scheduled for January 24-25

It's that time again! The 2020 Retina Fellows Forum will take place January 24-25, 2020, at The Renaissance Chicago Downtown Hotel. All second-year vitreoretinal fellows in North America are invited to add their names to the alumni roster of the granddaddy of all fellows' meetings.

The Retina Fellows Forum begins Friday night with a welcome reception followed by an academic session and continues all day (and well into the evening!) on Saturday.

Meeting goals:

- Provide an intensive review of current vitreoretinal treatments
- Allow fellows to meet and interact with peers
- Encourage research
- Introduce fellows to industry

Fellows Forum celebrates 20 years

The academic sessions feature presentations on the latest developments in the field with an emphasis on lively panel discussion. Meals and breaks allow fellows to interact with their "graduating class" and to explore the latest industry developments.

Saturday afternoon concludes with a Real-World audience and panel symposium focused on professional and personal development. Finally, we take over Chicago's 10Pin Bowling Lounge for dinner and the hotly contested Fellows Forum Bowling Tournament, with each faculty member captaining a team of decidedly amateur bowlers!

The faculty includes course director Tarek S. Hassan, MD; course co-directors Carl C. Awh, MD, and David Chow, MD, FRCSC; faculty members Tom A. Albini, MD; Sunir J. Garg, MD; Mrinali P. Gupta, MD; Aleksandra V. Rachitskaya, MD; Alan J. Ruby, MD; Amy C. Schefler, MD; Rishi P. Singh, MD; and Distinguished Guest Speaker Baruch D. Kuppermann, MD, PhD.

Each year, more than 90% of the senior vitreoretinal fellows in North America enjoy the opportunity to meet and interact with the faculty, our guest speaker, and corporate representatives in an unforgettable learning environment.

To register for the meeting or for more information, please contact Carrie Jacobowitz of Medical Conference Planners International at carrie.jacobowitz@medconfs.com.

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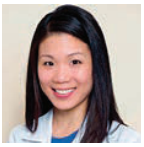
Retina fellows gather for the Real-World session at the 2019 Fellows Forum.

Dean Eliott, MD (with microphone) gets a laugh from fellow panelists Judy Kim, MD; Amy Schefler, MD; Rishi Singh, MD; and Tom Albini, MD, during the Real-World session at the 2019 Fellows Forum.

Christina Y. Weng, MD, MBA
Co-chair, ASRS Early Career Section



Ankoor R. Shah, MD
Co-chair, ASRS Early Career Section

Let's Talk About PE: Private Equity and Its Implications for Early Career Retina Specialists

Talk with any retina specialist—seasoned or early career—about the current dynamics of our field from a practice management standpoint, and private equity (PE) will surely come up. However, unlike our academic exchanges, discussions about PE seem much more muted.

Panelists

Rehan Hussain, MD
Retina Associates
Chicago, Illinois

Gregory D. Lee, MD
Georgia Retina
Atlanta, Georgia

Gaurav K. Shah, MD
The Retina Institute,
St. Louis
St. Louis, Missouri

Anonymous Retina Fellow
Academic/University-Based Fellowship
Southern United States

> 'The main disadvantage of PE is giving up control over the practice. ... [O]ur group has been very happy with our partnership, which has allowed the physicians to continue running our practice ...'
>
> —Gregory D. Lee, MD

Part of this may be due to formal limitations set by nondisclosure agreements (NDAs), but informal discretion is also often present in any sort of business transaction—especially when competing market forces are involved.

The limited conversation about PE has led to some circulating half-truths, uncertainty, and confusion—especially for early career retina specialists who have less practice management experience than our more senior colleagues.

We have elicited the perspectives of 4 colleagues at different career stages and with varying PE experience. Gaurav Shah, MD, works in an independent retina practice and has an interest in the business of retina. Gregory Lee, MD, is an ASRS Early Career Section (ECS) member who has transitioned from an academic practice to a large retina practice recently acquired by PE.

Rehan Hussain, MD, is a newly minted ECS member who just graduated from fellowship and has joined a mid-size retina practice. And we have included an anonymous retina fellow to speak on his experience with the job search thus far.

We thank all of the contributors for sharing their unique views on this sensitive subject. The contents of this article are the interviewees' own opinions, and are not representative of their groups, employers/affiliates, or the ASRS.

What are the advantages and disadvantages of PE?

Gregory Lee: Advantages of PE include economies of scale, stability, and improved administrative capabilities. The PE dynamic strengthens bargaining power with insurance companies for reimbursement rates. PE groups often make an initial capital investment to add value to the group—for example, buying 10 optical coherence tomography (OCT) machines across multiple practices is often cheaper on a per-unit basis than purchasing just 1 or 2.

From a stability standpoint, if there is a decline in reimbursement for injections or retina-specific coding, a PE retina practice's losses are hedged by being grouped with busy anterior-segment, refractive, plastic, or glaucoma specialty practices.

The main disadvantage of PE is giving up control over the practice. There are good and bad PE partnerships; fortunately, our group has been very happy with our partnership, which has allowed the physicians to continue running our practice with control over our own operations and maintenance of our culture and work-life balance. Our autonomy regarding patient care has been unaffected, a concern most physicians have about these partnerships.

Post-PE compensation structures can vary tremendously from practice to practice, but overall, new associates will likely earn less in total value over the term of a career, with more compensation front-loaded rather than back-loaded, as is the case with a traditional practice model. The reality is that we, as younger doctors, are unlikely to make what our senior partners previously earned, especially with declining reimbursement rates. Often, buy-ins and buyouts are eliminated in a PE group model, which is an advantage, but you will be an employee and never a majority owner—a disadvantage.

Rehan Hussain: Not every retina specialist is seeking the partnership track that comes with the added responsibility and stresses

of hiring and firing employees, keeping the practice expenses within budget, marketing to patients and referral sources, and much more. If you are a salaried employed physician, your job is essentially to show up and treat your patients to the best of your ability without having to worry about those additional duties.

Aside from the lower income ceiling, I think the feeling of loss of control is the biggest potential disadvantage of PE. Physicians' motivation to provide exceptional, compassionate patient care may not align with the financial priorities of the investors.

Gaurav Shah: For those with less than 5 working years remaining, a large cash payout with continued employment and retirement planning is a good deal and might outweigh the loss of control over your practice. Even if the entire operation fails and second sale doesn't materialize, you might still have a net gain—despite lost capital, you still will have had the power of those funds for the years they were invested and will also have gained equity in your new practice.

For someone who has more than 5 or 6 years remaining before retirement, the PE question becomes trickier. There are advantages to being part of a PE group, such as integration of business processes, infusion of capital for expansion, better contract negotiations with payers, and consolidation of infrastructure.

> 'For those with less than 5 working years remaining, a large cash payout with continued employment and retirement planning is a good deal ...'
>
> —Gaurav K. Shah, MD

Disadvantages include loss of decision-making control and uncertainty about the second sale, with equity being tied up in a sale that may not occur. The bottom line: Advantages and disadvantages are unique to each individual, each region, and each practice.

What are the important questions to ask when joining a group that has been acquired or will soon be acquired by PE?

Gregory Lee: First, the things within our control as potential employees or associates are often dissociated from the actual PE deal, so a new associate will have little bargaining power over the structure or terms of the PE deal. Trying to negotiate terms that guarantee partnership before another sale, or equity shares when you become a partner, may be difficult and will depend on the structure of the new partnership.

Groups that will soon be acquired may be limited in what they can share due to NDAs, but it would be fair to ask how the path to partnership, compensation, bonus structure, vacation, benefits, and expectations would change with the new partnership, in both the short and the long term. Ask to speak to junior members in the practice to hear how their practice has been affected and how they feel about the quality of the deal.

What should I do if my group is acquired by PE while I am just starting practice?

Gaurav Shah: If you signed a contract and the group sells to PE before your start date, you could ask to get out of your contract, depending on legal terms, because that is not what you signed up for. If you are already in practice as an early career associate, the situation is a bit more complicated.

Ask how your employment contract and compensation structure will change. How will staffing change? Will vacation and professional time away be different? How will future recruitment be affected? If your group has a retina fellowship, what impact will the acquisition have on it? The new contract will likely come with a higher salary dollar amount, but will be contingent on a certain duration of employment.

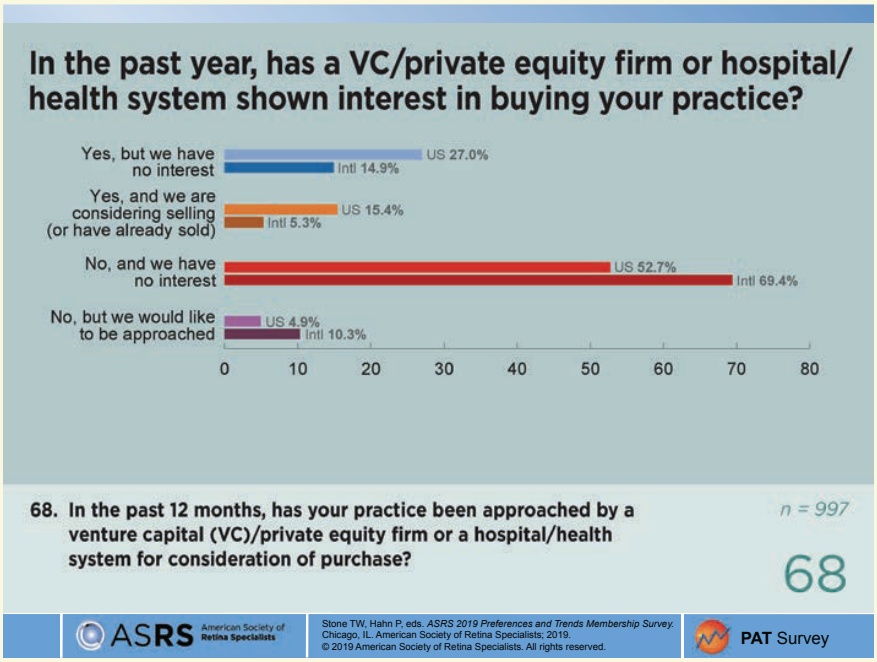
You will need to inquire about penalties for breaking the contract as well as the non-compete clause, especially since most PE non-compete clauses span state lines.

If you have equity in the practice, how will you get your cash back if you leave the group? Will you be able to choose the drugs used for your patients, or will that choice be made for you? It is well known that purchase programs can and do have a significant impact on practices, and PE firms are buying that margin when deals are negotiated.

As a fellow who has been communicating with many practices, have you found them to be forthcoming in discussing PE with you?

Continued on page 18

ASRS PAT Survey Explores Private Equity



The 2019 Preferences and Trends (PAT) Survey asked ASRS members whether their practice had been approached by a PE firm in the last year—and inquired about the practice's level of interest. For a subanalysis of this data, please see the PAT Survey Deeper Dive by PAT Survey Editor Paul Hahn, MD, PhD, on page 16.

Which Factors Influence Private Equity Experience? The PAT Survey Takes a Deeper Dive

Since 1999, the ASRS Preferences and Trends (PAT) Survey has offered a yearly snapshot of retina specialists' practice patterns—and by repeating key questions from year to year, we have shown how these practice patterns are evolving over time.

Paul Hahn, MD, PhD
ASRS PAT Survey Editor

Mindy Schneiderman, PhD
ASRS PAT Survey Research Consultant

Now, the wealth of unexplored possibilities in the PAT Survey data has led us to conduct a subanalysis—a *Deeper Dive*—to look at the factors behind the numbers. In this first Deeper Dive, we explore how 2019 PAT Survey respondents' answers to a private equity (PE) question varied by their type of practice setting, practice location, and number of years in practice.

The PAT Survey, with its anonymous and confidential responses, provides a unique window into the pulse of PE activity, which is generally otherwise not openly discussed. In the 2019 survey, 15.4% of US respondents and 5.3% of international respondents indicated that their practices had considered selling, or had sold, to PE. Given the perceived wave of PE entering ophthalmology, this number seemed surprisingly low, and we sought to dive deeper into the survey data to better understand this.

First, we excluded international responses and decided to focus on responses from US members alone. Next, we analyzed the data by demographics of survey responders—practice type, practice location, and years in practice. This analysis revealed some interesting trends, which we outline in the graphs shown.

PE activity by practice type

Figure 1 shows that, as expected, *academic + government + HMO* practices have little involvement with PE, apart from a few outlier responses. This category will be excluded from most of the subsequent analyses.

Most of the PE outreach, regardless of interest by the practice (ie, the first 2 response choices), appears to have been with group *retina-only* and *multispecialty private practices*.

Similarly, most PE deals that have closed or are being considered (response choice 2) appear to have been with *retina-only* and *multispecialty private practices*; 29.4% of *multispecialty practice* respondents indicated that they have sold or are planning to sell; this figure was 16.3% for *retina-only group practice* respondents.

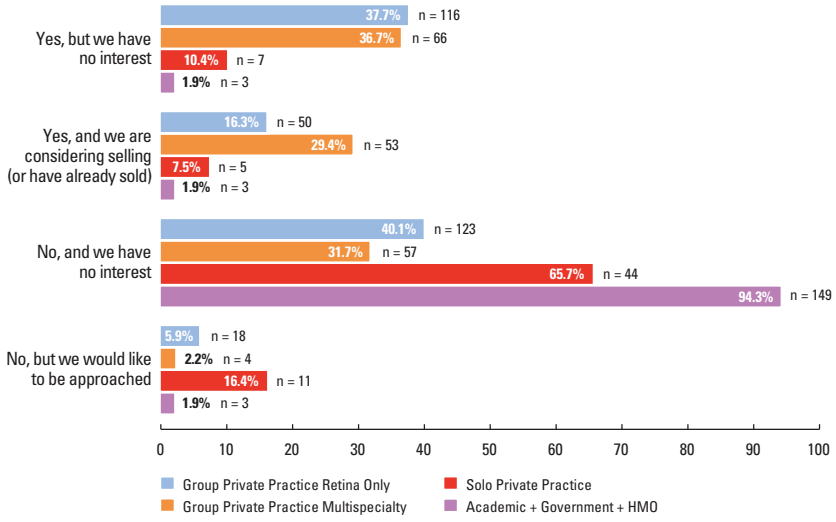


Figure 1.

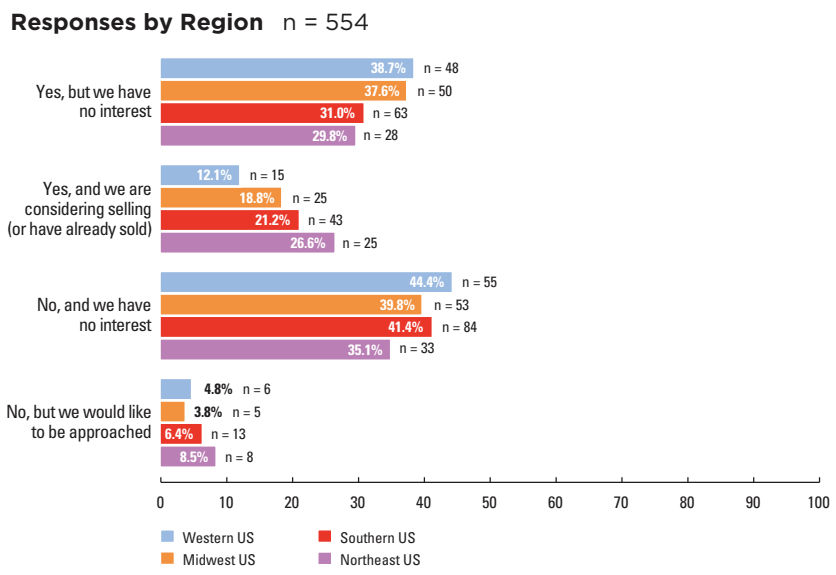


Figure 2.

However, as the number of survey respondents is greater from *retina-only* practices (310) than *multispecialty practices* (180), absolute numbers are similar, with 53 responses from *multispecialty practices* and 50 from *retina only practices* that are considering selling or have sold.

An important limitation of these data is that they measure responses of *individuals* and not *practices.*

Solo practitioners represent a small portion of PE involvement, with only 5 respondents indicating that they have sold or are considering selling.

PE activity by region

Figure 2 shows a regional breakdown suggesting the distribution of closed or considered PE deals (response choice 2). The greatest percentage of responses comes from the Northeast and the lowest percentage comes from the West.

However, due to an unequal distribution of responses from different regions, the greatest absolute number of responses indicating a closed or considered deal comes from the South (n = 43) > Midwest = Northeast (n = 25) > West (n = 15).

Figure 3 further dissects the regional analysis of these closed or considered PE deals by practice type. In *multispecialty* practices, a similar number of responses (range 19%-28%; n = 10-14) is seen across all 4 regions. In *retina-only* practices, the greatest number of responses is seen in the South (n = 27) > Midwest (n = 11) > North (n = 8) > West (n = 4).

Only 5 survey responses from *solo retina practitioners* indicated a sold or considered deal—3 were in the Northeast, and 1 each in the South and West (none in the Midwest). These data are limited but more "pure," as each response should represent a different practice.

PE interest by number of years in practice

Analysis of the response distribution by number of years in practice, shown

Continued on page 38

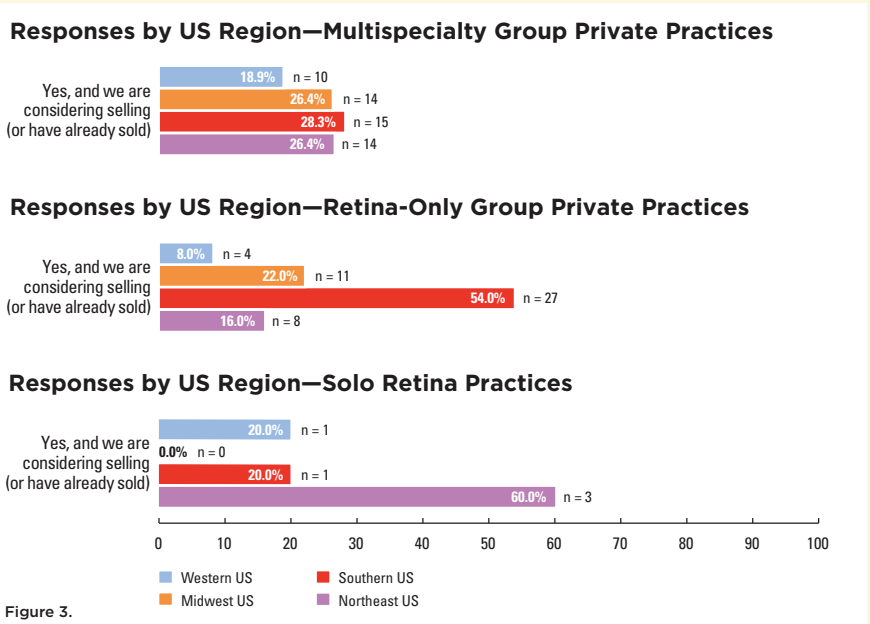


Figure 3.

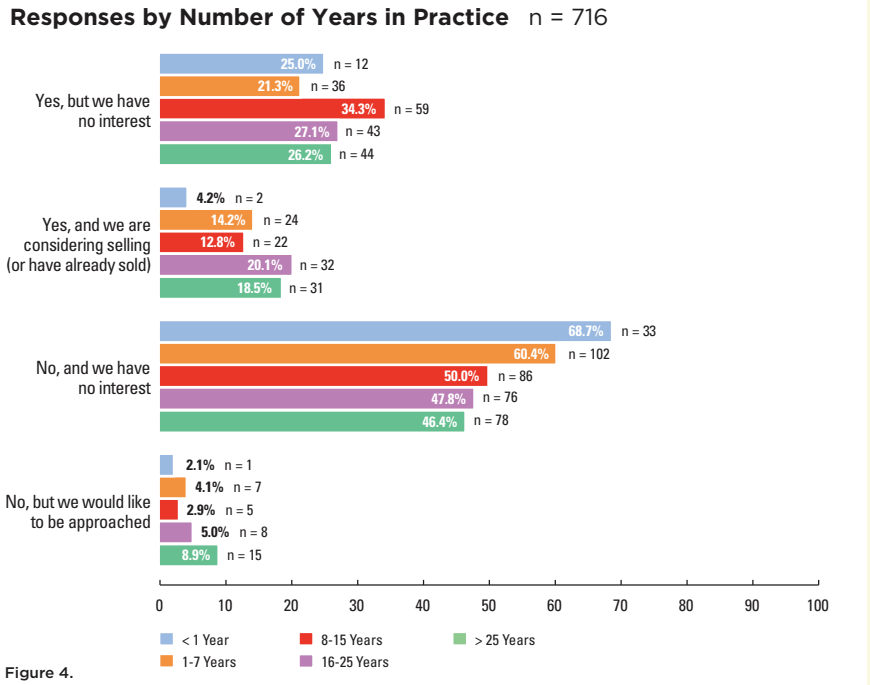


Figure 4.

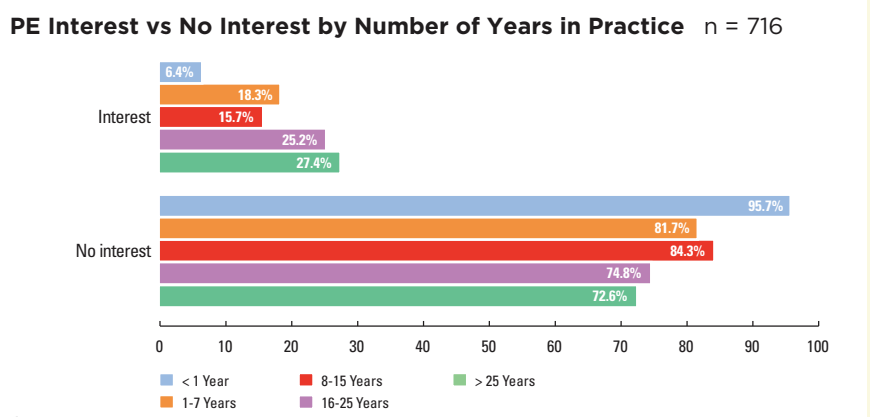


Figure 5.

Anonymous Retina Fellow: For the most part, practices have been transparent. It's difficult to predict what's going to happen in 5 years, but I've found practices to be forthcoming about PE.

What questions should fellows ask when interviewing with an independently owned group? Is there a way to tell which groups are "at risk" of being acquired?

Rehan Hussain: I asked whether the groups had been approached by PE groups, and how strong the partners' interest would be in selling if the price were right. Most of the groups denied any interest in giving up their autonomy, although of course, you must interpret their answers with some skepticism.

I think the most at-risk practices are the very large and busy groups and those where most partners are nearing the end of their careers. If many other local ophthalmology groups have sold to PE, that can be a warning sign; the referral sources could vanish since optometrists and anterior-segment surgeons are restricted to referring to retina specialists in their vertically integrated PE network. In this situation, a retina practice may have little choice but to sell in order to maintain access to referrals.

As a fellow looking for a job right now, what worries you most about the current PE movement?

Anonymous Retina Fellow: The uncertainty of the PE situation is most worrisome. We're in the middle of a PE wave and it's unclear how far it will spread, how practices and the practice landscape will be affected, and whether PE is here to stay. PE adds another variable into the mix when evaluating jobs, and unfortunately, it's difficult to predict how this variable will impact a new associate 3 to 5 years down the line.

How can earlier-career retina specialists best position themselves in case their group is sold to PE?

Rehan Hussain: Our options are somewhat limited, but I recommend attempting to add a clause to your contract about what will happen to you if a PE acquisition occurs while you are still in the vulnerable position of "associate physician." You could ask if the group would void or loosen the constraints on your non-compete clause, allow the option for a buy-in to the practice at a pro-rated price prior to the transaction, or simply give you a lump-sum payment (probably much smaller than the amount they would receive) if the group is acquired by a PE firm.

Thanks for the opportunity. Welcome, Aleksandra!

Aleksandra Rachitskaya, MD
Cole Eye Institute
Cleveland Clinic
Cleveland, Ohio

As I transition from my position of ASRS ECS co-chair, I want to express what a joy it has been to represent my ECS colleagues over the past 2 years. Thank you for your enthusiasm, ideas, and participation in the many initiatives we have spearheaded during my tenure.

I know that our membership section will be in great hands with Ankoor Shah, MD and incoming Co-chair Aleksandra Rachitskaya, MD, and am very grateful to the ASRS to have had the opportunity to serve in this capacity.

Signing off,
Christina Weng, MD, MBA

> 'The uncertainty of the PE situation is most worrisome.'
>
> —Anonymous Retina Fellow

The group may not meet any of your requests, but it can't hurt to inquire. Remember that even if a group sells to PE, they will still be highly motivated to retain you because the production you would bring to the table was part of their investor's motivation for purchasing the group.

I predict that groups eventually will not have much choice but to meet these demands, as all fellows will come to expect some degree of self-protection as an essential aspect of their contracts. Of course, having an experienced contract lawyer review your contract is an absolute must before signing!

Do you think that PE will have an increasing role in the retina world, or will it soon plateau?

Gregory Lee: With the growing number of groups consolidating, it is in many practices' best interest to at least explore the opportunity. If practices aren't joining PE, they are talking to large hospitals about acquisitions; in my opinion, this can be worse in terms of administrative burden than a well-run PE group.

Many physicians have bad memories of the consolidation efforts in the 1990s, but this round does initially appear to be different. PE firms are allowing physician groups to continue to run operations and control their own practices in ways they didn't in the '90s. I see a plateau in the future as more well-run practices are acquired and the pool of practices attractive to PE firms shrinks. Additionally, more PE groups may enter the market and have poorly run structures with unreasonable goals set for the practices, making physicians more hesitant to partner.

Gaurav Shah: The thirst for PE depends on capital availability, which is affected by many global factors including economic recession, predicted by some to occur in the next 2 to 4 years. I think that 15% to 20% of practices will go the PE route. Unfortunately, we hear only about the one deal that gets consummated, but not about the other 5 practices that decided not to go this route. Time will tell—stay tuned!

> 'I recommend attempting to add a clause to your contract about what will happen to you if a PE acquisition occurs while you are still in the vulnerable position of "associate physician."'
>
> —Rehan Hussain, MD

Financial Disclosures

Dr. Anonymous Retina Fellow – None.

Dr. Hussain – ALIMERA SCIENCES: Advisory Board, Honoraria.

Dr. Lee – GENENTECH, INC: Advisory Board, Honoraria.

Dr. Ankoor Shah – EVOLVE MEDICAL EDUCATION LLC: Speaker, Honoraria.

Dr. Gaurav Shah – ALLERGAN INC: Advisory Board, Consultant, Honoraria; BAUSCH+LOMB: Speaker, Honoraria; DUTCH OPHTHALMIC USA: Speaker, Grants, Honoraria; REGENERON PHARMACEUTCALS, INC: Advisory Board, Consultant, Speaker, Honoraria.

Dr. Weng – ALCON LABORATORIES, INC: Consultant, Honoraria; ALIMERA SCIENCES, INC: Advisory Board, Honoraria; ALLERGAN, INC: Consultant, Honoraria.

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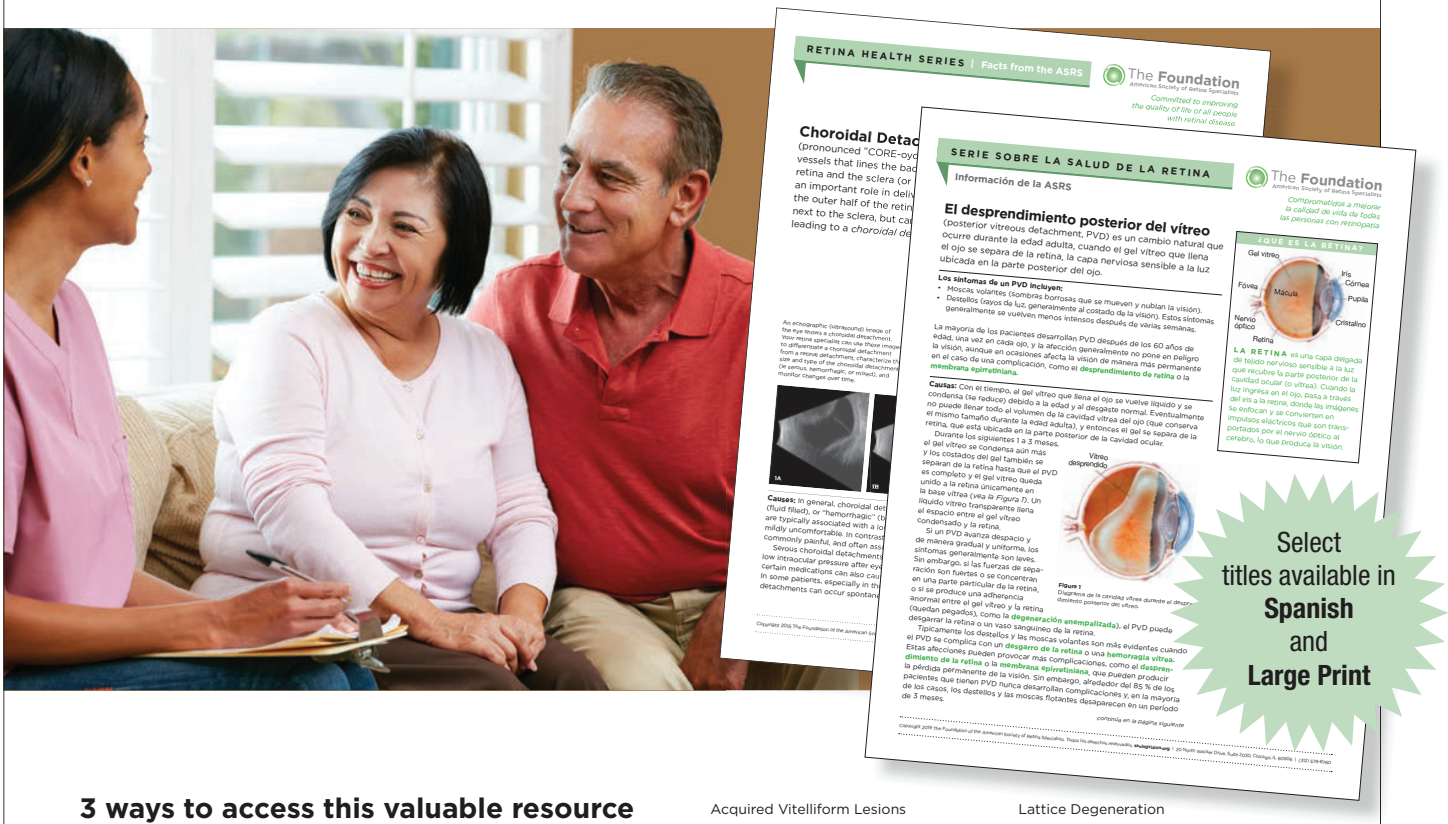

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American Society of Retina Specialists

Dean Eliott, MD
Chair, ASRS International
Affairs Committee

Narsing Rao, MD: Dedicated to Improving Inflammatory Eye Disease Treatment Worldwide

In this issue of *Retina Times*, the International Corner highlights the global educational outreach of Narsing A. Rao, MD, a beloved mentor, teacher, clinician, scientist, and role model to a generation of American and foreign students and trainees.

Dr. Rao is the Grace and Emery Beardsley Professor and chair, University of Southern California (USC) Department of Ophthalmology; co-director of the USC Roski Eye Institute; and director of the Uveitis Service and Ophthalmic Pathology Laboratory at the USC Keck School of Medicine.

Narsing A. Rao, MD

Dr. Rao came to the United States from his native India in 1968 to pursue internship training. The following year, he began a residency in pathology at Georgetown University Hospital, where he later completed his ophthalmology residency.

He then completed a fellowship in ophthalmic pathology at the Armed Forces Institute of Pathology (AFIP), one of the most prestigious programs in the country. Dr. Rao returned to Georgetown as faculty until 1983, when he joined the faculty of the Doheny Eye Institute of USC. He has since remained at USC and was appointed chair of ophthalmology in 2018.

In 2010, Dr. Rao, along with Piseth Kong, MD, of Cambodia and Somsiri Sukavatcharin, MD, of Thailand, conceived the idea of establishing an annual uveitis educational meeting in developing countries. Dr. Rao was already well known on the international scene, having been the inspiration for the founding of the Uveitis Society of India in 1999 by Drs. Amod Gupta, Jyotirmay Biswas, and Virender Singh Sangwan. The society boasts over 400 members, and Dr. Rao remains the patron in chief. Also in 1999, Dr. Rao established the biannual Global Ocular Inflammation Workshop with Masahiko Usui, MD, of Japan.

Based on his success with international education and building academic relationships, Dr. Rao wanted to extend his outreach to southeast Asia. Intraocular infections were common in this part of the world, yet most of the ophthalmic education focused on cataract, glaucoma, and diabetic retinopathy.

> ‘In 2010, Dr. Rao, along with Piseth Kong, MD, of Cambodia and Somsiri Sukavatcharin, MD, of Thailand, conceived the idea of establishing an annual uveitis educational meeting in developing countries.’

The mission of this new meeting was to establish guidelines on the medical and surgical management of ocular inflammatory diseases and to stimulate international research collaboration. Trainees and practicing physicians from developing countries often lack sufficient funds to travel to international meetings, so the concept of bringing international teachers to the students represented a novel approach.

The inaugural Indochina Ocular Inflammation and Infection Education Meeting was held in Siem Reap, Cambodia in 2012 and was an overwhelming success. Visiting faculty were from Australia, Germany, India, Japan, Singapore, Switzerland, Taiwan, Thailand, and the United States. The meeting was supported in part by the International Ocular Inflammation Society (IOIS), Save Sight Institute (Sydney, Australia), and Dr. Rao.

Subsequent meetings were held in Saigon/Ho Chi Minh City, Vietnam in 2013; Bangkok, Thailand in 2014; Yangon, Myanmar in 2015; Vientiane, Laos in 2016; Kuala Lumpur, Malaysia in 2017; Ulaanbaatar, Mongolia in 2018 (about 2000 miles from Indochina); and in 2019, the meeting returned to its original location of Siem Reap, Cambodia.

Over the years, there has been such a dramatic increase in faculty and trainee presentations from host and neighboring countries that most presentations currently involve local participants. Many of these ophthalmologists have developed a strong interest in uveitis and are now local leaders and teachers. Such change ensures the long-term sustainability of the educational mission. There has been a commensurate increase in meeting attendance, with the most recent meetings attracting well over 200 attendees.

Many local ophthalmologists who have attended for a number of years report that knowledge of ocular inflammatory diseases and clinical skills among their colleagues have flourished, and the quality of care in

their community has entered a new phase. While endemic noninfectious and infectious uveitis such as tuberculosis, toxoplasmosis, syphilis, sarcoidosis, Vogt-Koyanagi-Harada disease, Behçet's disease, and HIV-related opportunistic infections often resulted in severe visual disability, early diagnosis and timely intervention with effective treatment have now enabled better outcomes.

The success of the meetings lies in the faculty's loyalty to Dr. Rao. So many clinicians and scientists from around the world are grateful for his academic contributions and mentorship that they will travel virtually anywhere he asks. All speakers cover their own expenses and volunteer their time to participate in this worthwhile endeavor.

According to meeting co-founder Somsiri Sukavatcharin, MD, assistant professor of ophthalmology at Mahidol University in Thailand, "Dr. Rao has improved knowledge about uveitis in the Indochina region, and he treats the uveitis team as a family."

One of the regular faculty attendees, Shwu-Jiuan Sheu, MD, director and professor at Kaohsiung Medical University in Taiwan, notes, "For me, the Indochina meeting began as a mission and is now a family event, and Dr. Rao is the father of this big family."

Another regular attendee, Soon-Phaik Chee, MD, senior consultant, Ocular Inflammation and Immunology Service at Singapore National Eye Center, describes Dr. Rao as "a pioneer and champion in this underserved region, where trained doctors are now continuing his lifelong dedication to quality eye care."

Figure 1. The concept of the Indochina Ocular Inflammation and Infection Education Meeting was developed by Narsing Rao, MD, (center) with Indochina representatives, Piseth Kong, MD, of Cambodia and Somsiri Sukavatcharin, MD, of Thailand in 2010.

Jennifer Thorne, MD, PhD, Cross Family Professor of Ophthalmology and chief of the Ocular Immunology and Uveitis Division at the Wilmer Eye Institute, and professor of epidemiology at the Johns Hopkins School of Public Health (and amateur photographer extraordinaire), describes the faculty as "a wonderful group of ophthalmologists who come together each year to give a tour-de-force course on the diagnosis and treatment of ocular inflammatory disease." As one can clearly ascertain, the dedication to the mission and the gratitude to Dr. Rao are unsurpassed.

'Dr. Rao has improved knowledge about uveitis in the Indochina region, and he treats the uveitis team as a family.'

—Somsiri Sukavatcharin, MD

In the developing world, many patients suffering from ocular inflammatory diseases experienced profound visual loss because of the lack of information about modern vision-preserving standards of care. Narsing Rao has inspired faculty from almost every continent (so far, nobody from Antarctica has participated, but Dr. Rao remains hopeful) to join him annually in his educational outreach programs in southeast Asia. We are all indebted to Dr. Rao for his tremendous leadership in improving the lives of patients around the world.

Financial Disclosures

Dr. Eliott – ALCON LABORATORIES, INC: Consultant, Honoraria; ALDEYRA THERAPEUTICS, INC: Consultant, Honoraria, Intellectual Property Rights; ALIMERA SCIENCES: Consultant, Honoraria; ALLERGAN, INC: Consultant, Honoraria; COCOON BIOTECH, INC: Advisory Board, Stock Options; DUTCH OPHTHALMIC USA: Consultant, Honoraria; GENENTECH, INC: Consultant, Honoraria; NEUROTECH INC: Investigator, Grants; REGENXBIO, INC: Consultant, Honoraria.

Figure 2. In 2018, 225 ophthalmologists attended the 7th Indochina Ocular Inflammation and Infection Education Meeting in Ulaanbaatar, Mongolia.

Adam T. Chin, MD
New England Eye Center
Ophthalmic Consultants of Boston
Boston, Massachusetts

Andre J. Witkin, MD
Tufts Medical Center
Boston, Massachusetts

Chirag P. Shah, MD, MPH
Section Editor

Complement 3 Inhibition for Treatment of Geographic Atrophy in AMD

In the decade and a half since the introduction of anti-VEGF therapies, the treatment of exudative age-related macular degeneration (AMD) has dramatically changed the prognosis for patients with advanced macular degeneration. However, the lack of a similarly efficacious treatment for the large cohort of patients with advanced nonexudative AMD remains a frustrating challenge to retinal physicians and their patients.

Geographic atrophy (GA) due to late nonexudative AMD represents an ongoing challenge affecting nearly 1 million Americans.[1] While there are currently no Food and Drug Administration (FDA)-approved GA treatments, a host of potential first-in-class drugs targeting the complement system are providing hope. APL-2, ie, pegcetacoplan, (Apellis Pharmaceuticals) has become the second complement-targeting intravitreal injection to enter a phase 3 clinical trial for GA treatment.

Complement in AMD pathogenesis

AMD pathogenesis is a complex interplay between oxidative damage, retinal pigment epithelium (RPE) dysfunction, cell death, and chronic inflammation. Early in the disease, cellular debris in the form of proteins and lipids accumulates and forms drusen. Deposition of these materials activates an inflammatory process mediated in part via the complement system. Chronic inflammation is thought to contribute to the ongoing degeneration of the choriocapillaris and RPE, ultimately leading to loss of the overlying photoreceptors.[2]

> ‘While there are currently no FDA-approved GA treatments, a host of potential first-in-class drugs targeting the complement system are providing hope.’

The complement system, in particular, has been implicated in AMD pathogenesis. Immunohistochemical analysis of drusen has revealed proinflammatory proteins including those of the complement system early in AMD.[3,4] Further, elevated levels of activated complement cascade components have been found in the aqueous and systemic samples (serum) of those with advanced AMD.[5] Genome-wide association studies have linked AMD to over 50 loci related to disease risk, including complement factor genes encoding for complement factor H (CFH), complement factor I (CFI), C2, and C3 among others.[2,6]

The complement system is part of the innate immune system and is composed of dozens of soluble and cell membrane-associated proteins.[7] It is responsible for the recognition, opsonization, and destruction of pathogens. The system is activated via 3 pathways. The classical pathway responds to the presence of antigen-antibody complexes via C1. The mannose-containing polysaccharides found on bacteria activate the lectin pathway. Finally, the alternative pathway is self-activating via the slow hydrolysis of the factor C3. Each of these pathways converges with the cleavage of factor C3, which subsequently leads to a cascade promoting cell destruction.

Multiple host molecules including complement factor H and complement factor I function to inactivate and attenuate the system to protect host cells. There are also co-factors such as complement factor D that upregulate the alternative pathway. Without proper regulation, phagocytosis and apoptosis via formation of the membrane attack complex (MAC) may affect host cells.

Pharmaceuticals for AMD targeting complement

With evidence linking the complement cascade to AMD pathophysiology, a number of first-in-class pharmaceutical candidates have been or are being tested as GA treatment in AMD. Some drugs have failed to show reduction in GA growth rate, while others are currently in clinical trials. Notably, the first phase 3 trial of a complement inhibitor, lampalizumab, failed to show reduction in GA growth.[8] Current studies are evaluating the following complement-related targets: C3, C5, factor D, and properidin.[9]

> ‘The complement system, in particular, has been implicated in AMD pathogenesis.’

POT-4 (Potentia Pharmaceuticals/Alcon Laboratories, Inc) and APL-2 (Apellis Pharmaceuticals) are peptide inhibitors of C3. Phase 2 testing of POT-4 for GA was terminated early due to precipitation of the drug. APL-2, a derivative of POT-4, is currently in phase 3 testing after encouraging phase 2 results and is discussed in more detail below.

C5 inhibitors include avacincaptad pegol (Iveric Bio), eculizumab (Alexion Pharmaceuticals) and LFG316 (Novartis Pharmaceuticals Corporation). These target the breakdown of C5, which initiates MAC formation and subsequent cell lysis. Avacincaptad pegol, also known as Zimura, is currently recruiting for its phase 2b trial.

Eculizumab, another drug working on C5 inhibition, is intravenously administered monoclonal antibody. The COMPLETE phase 2 trial of eculizumab failed to show a reduction in GA growth rate and drusen volume.[10] LFG316 is a monoclonal antibody delivered intravitreally. A phase 2 study evaluating GA growth in 150 subjects did not show reduction compared to sham.

'Current studies are evaluating ... complement-related targets C3, C5, factor D, and properidin.'

Lampalizumab (Genentech, Inc/Roche Holding, AG) is an antibody fragment that binds complement factor D, the rate-limiting enzyme of the alternative pathway. Despite demonstrating a significant reduction in GA with monthly dosing in the MAHALO phase 2 trial, lampalizumab failed to show reduction in GA enlargement compared to sham in the Chroma/Spectri phase 3 trial.[8]

Properidin stabilizes the enzyme C3 convertase, responsible for cleavage of C3. CLG561 (Novartis Pharmaceuticals Corporation) is a monoclonal antibody against properidin. The efficacy and safety phase 2 study of the drug as an intravitreal monotherapy is complete, but results are not yet available.

APL-2

APL-2, pegcetacoplan, is a pegylated cyclic peptide inhibitor of C3 and C3b. With C3 at the confluence of all 3 complement activation pathways, the inhibition of C3 conversion is thought to be a potent inhibitor of the downstream cascade. Pegcetacoplan is the direct descendent of the POT-4 molecule, which had relatively low solubility in the vitreous and was found to precipitate in clinical trial subjects.[9] Polyethylene glycol has been introduced to decrease clearance and therefore reduce dosing frequency.

In addition to the trials aimed at GA, APL-2 is being tested systemically to treat complement-mediated diseases including immune nephropathies, autoimmune hemolytic anemia, and paroxysmal nocturnal hemoglobinuria.

Phase 2: FILLY

The phase 2 trial of APL-2, known as *FILLY*, enrolled 246 subjects across 40 sites in the United States, New Zealand, and Australia. The study followed subjects over 18 months. During the first 12 months, the subjects received bimonthly or monthly injections of APL-2 or sham.

Data from the phase 2 trial were encouraging. At 1 year, subjects receiving bimonthly injections of APL-2 had a 20% reduction in GA growth compared to those receiving sham. The monthly treatment arm showed a large reduction of 29% in the rate of GA growth. After stopping the medication, subjects had a GA growth rate similar to the sham arm. A post-hoc analysis demonstrated a more substantial reduction in GA growth rate during the second 6 months of the treatment with growth rate reduction of 47% and 33% in the monthly and bimonthly arms, respectively.[11]

The major complication of the trial was conversion to exudative AMD; an increased rate in conversion to exudative AMD was noted in subjects receiving APL-2 injections. Compared to 1% of the control group, 8% of subjects in the bimonthly arm and 18% of subjects in the monthly arm converted to exudative macular degeneration during the study period.[11]

Phase 3: OAKS and DERBY

APL-2 becomes only the second intravitreal GA treatment to enter phase 3 after lampalizumab. Keeping consistent with its equestrian trial acronyms, Kentucky-based Apellis Pharmaceuticals is now recruiting for the phase 3 studies—DERBY (APL2-303) and OAKS (APL2-304).[12-13] These multicenter, randomized, double-masked, sham-controlled studies began enrolling patients in North America, Europe, Russia, Brazil, Australia, and New Zealand in August 2018 with a goal of recruiting 1200 subjects between the 2 studies.

The trial is currently enrolling subjects with GA who are 60 years or older, seeing 24 letters or better on ETDRS, and whose ocular media, dilation, and fixation permit quality imaging. The total GA area must be between 1 and 7 disc areas, with the smallest focal lesion being greater than or equal to 0.5 disc areas if non-contiguous. The study excludes high myopes and patients who have undergone prior ocular surgery, intravitreal injection, or macular laser; have participated in a previous study; or have had prior choroidal neovascularization.[14]

Each study compares a 15 mg APL-2/0.1mL intravitreal injection to a sham intravitreal injection. One arm will treat on a monthly basis and the other will treat bimonthly for 24 months. The study will monitor the patients monthly over the first year and either monthly or bimonthly depending on the arm for the remainder of the study. The primary outcome is mean change in GA area from baseline to 12 months. Key functional metrics to be measured include monocular reading speed, Functional Reading Independence Index, and normal luminance best-corrected visual acuity score (NL-BCVA) in the study eye.

Conclusion

APL-2 represents the second intravitreal therapy for GA to enter phase 3 trials. Given the encouraging results of the phase 2 studies, the ophthalmic community is eagerly anticipating the findings of OAKS and DERBY. The trials are slated to be completed in December 2022. With the ongoing study of APL-2 and other complement-based therapeutics, the first drugs to treat GA in AMD may be on the near horizon.

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Kristin D. Yockus, MPH
Section Editor

Thomas W. Stone, MD
Section Editor

Telecommuting: Is It Right for Your Practice?

Working from home sounds like a dream compared with the often-frenzied activity of a busy retina clinic. Until recently, the possibility of a remote worker in a retina practice was almost unimaginable—but as technology and the employment environment change, retina practices are reconsidering.

Panelists

Stephanie Collins Mangham, MBA, COA, OCSR
Chief Operating Officer
Austin Retina Associates
Austin, Texas

Andrew M. Laverghetta, MBA
Chief Executive Officer
Southeastern
Retina Associates
Knoxville, Tennessee

The work-from-home trend is growing steadily. According to the US Bureau of Labor Statistics, 24% of all workers did some or all of their work from home in 2015, an increase from 19% in 2003. Most of these employees did some of their work from home, but an increasing number did all of it remotely.[1] Another analysis from Global Workplace Analytics reveals that since 2015, the total number of remote workers who do all of their work from home has grown from 2.9% of the workforce to 3.4%, or 4.7 million people.[2] This trend has occurred across many industries, including health care, information technology, financial services, and even manufacturing.[3]

The ability to "telecommute," however, would not have been possible without advances in technology over the past several decades. With widespread high-speed internet access, conversion to electronic health records, and easy access to communication tools such as videoconferencing, the need for an employee to be at a central office has lessened.[4]

These advances, combined with setting clear expectations, have removed some of the objections many medical practices had about employees working from home.

Protecting sensitive data

In health care, there is an especially critical need for proper security measures. Often, security policies such as not allowing printing from home can address the most obvious security holes. With such policies in place, large institutions like the Mayo Clinic have a portion of their workforce working from home.[5]

At Austin Retina Associates (ARA) in Texas, Chief Operating Officer Stephanie Collins Mangham ensures security by providing work equipment to telecommuting employees. "Everyone uses

AUSTIN RETINA ASSOCIATES

Work-From-Home Policy

Objective

Austin Retina Associates' (ARA's) work-from-home policy allows employees the option to work from home, on the road, or in a satellite location for all or part of their workweek. ARA considers working from home a viable, flexible work option when both the employee and the job are suited for it. Working from home may be appropriate for some employees and jobs, but not for others.

Eligibility

Employees requesting to work from home must be employed by ARA for a minimum of 90 days, and must have a satisfactory performance record.

Before entering into a work-from-home agreement, the employee, supervisor, IT, and HR manager will evaluate the suitability. If all above parties agree, a 3-month trial period will commence. Performance evaluation during the trial period will include regular interaction by phone and email between employee and supervisor, and monthly face-to-face meetings, or more often if needed, to discuss work progress and problems.

At the end of the trial period, the employee and supervisor will each complete an evaluation of the arrangement and make recommendations for continuance or modifications. After conclusion of the trial period, the employee and manager will communicate at a level consistent with that of employees working at the office, or in a manner or frequency deemed appropriate for the job and the individuals involved.

Equipment

ARA will compile a list of equipment used by the employee in the course of carrying out work at the home-based worksite. The employee will exclusively use equipment belonging to ARA at the home-based worksite, and use it solely for the purposes of ARA work. All equipment owned or leased by ARA will remain ARA property, and the employee agrees that ARA may have access to the home-based worksite during hours of work.

Employee agrees to notify ARA of any problems or difficulties that arise with the operation of ARA equipment and allow access as required to replace, service, or repair the equipment.

An employee who experiences an outage should contact IT immediately. Once IT assesses the situation, they can set expectations and a time frame of when the employee will be back up and running. If for any reason, IT cannot get the employee's system back up and running in less than 30 minutes, the employee has the following options:

1. If the employee works in or around one of the 3 ARA locations, he or she should inform the direct supervisor and report immediately to the closest location to return to work.
2. If the fix is estimated to take less than 2 hours, the employee can communicate with his or her direct supervisor and discuss punching out for the time period, and returning to work later in the day to complete the employee's work and time.

Figure 1. Sample work-from-home policy. Many considerations are involved in successfully managing remote employees. Austin Retina Associates' Stephanie Collins Mangham has developed this policy for her practice to delineate the responsibilities of the employer and the telecommuting employee.

encrypted ARA equipment only—laptop computers, internet setup, and internal phone setup if the employee takes frequent patient calls," she explains.

Which retina employees can work from home?

Of course, some positions in a retina practice are not suitable for remote work, such as office greeter or workup technician staff. But some practices are using technology to remotely work with scribes, as presented at the 2019 ASRS Business of Retina Meeting.[6]

Chief Executive Officer Andrew Laverghetta at Southeastern Retina Associates (SERA) in Knoxville, Tennessee, is considering remote workers for several positions—primarily billing and coding/charge entry. "These positions would be amenable to remote work, as long as the employees are in production-based roles where tracking an individual's work is straightforward and where benchmarks, quotas, and expectations can be easily set," he notes.

At ARA, Stephanie Collins Mangham has employees in multiple positions who work remotely, either part-time or full-time. "I have 2 chart auditors, 1 surgery/hospital consult poster, 3 surgery schedulers, 3 physician liaisons (patient triage calls, disability paperwork, prescription refills), 1 insurance check poster (electronic funds transfer only, not live checks), 1 Medicare/Medicaid accounts receivable (AR) person, 1 accounting assistant, and 1 claims processor," she notes, adding that she telecommutes part-time as well. "My financial director, my payroll person, and I work from home 1 day a week."

Telecommuting opportunities enhance recruitment

Today's burgeoning telecommuting trend can give a retina practice an edge in employee recruitment. With the national unemployment rate at a near-historic low of 3.6% as of October 2019,[7] finding talented employees qualified to work in a retina practice for traditional wages can be challenging.

AUSTIN RETINA ASSOCIATES

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3. If the employee works outside the main locations and is informed that he or she will be unable to be reconnected for most of the workday, the employee can choose to work later in the day to make up the lost time and hours, if approved by the supervisor (ie, if the employee's job doesn't require duties to be completed during normal business hours) or if able, connect to the employee's phone as a hotspot, and ARA will reimburse the employee for data overages should they occur. This option must be approved by IT and the employee's direct supervisor.

ARA will supply the employee with appropriate office supplies (pens, paper, etc) as deemed necessary. ARA will reimburse the employee for business-related expenses, such as shipping and internet costs reasonably incurred in carrying out the employee's job, or reasonable portion thereof. The employee is responsible for understanding the amount of any eligible reimbursements before beginning to work from home.

The employee will establish an appropriate work environment within his or her home for work purposes. ARA will not be responsible for costs associated with the setup of the employee's home office, such as remodeling, furniture, or lighting, nor for repairs or modifications to the home office space.

Upon termination of employment, all company property will be returned to ARA, unless other arrangements have been made.

Communication

The employee agrees to be contactable and available for communication with ARA during the periods in which home-based work is carried out.

Security

Consistent with ARA's expectations of information security for employees working at the office, employees working from home will be expected to ensure the protection of proprietary company and patient information accessible from their home office. Steps include locked file cabinets and desks, regular password maintenance, and any other measures appropriate for the job and the environment.

An employee working from home is also not allowed to work in a public WiFi area or location (eg, Starbucks), as the free WiFi provided at these locations is not secure. The only exception would be if the employee has an ARA hotspot or connects his or her computer to the employee's phone's personal hotspot, since these are password protected. If the employee chooses to work from a public location, ARA will not be responsible for any excess data usage on his or her data plan, unless previously authorized by IT and/or direct supervisor.

Safety

Employees are expected to maintain their home work space in a safe manner, free from hazards. Injuries sustained by the employee in a home office location and in conjunction with his or her regular work duties are normally covered by the company's Workers' Compensation policy. Employees who work from home are responsible for notifying their supervisor of such injuries immediately. The employee is liable for any injuries sustained by visitors to his or her home work site.

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Time Worked

Employees who work from home and are not exempt from the overtime requirements of the Fair Labor Standards Act (FLSA) will be required to accurately record all hours worked using ARA's time-keeping system. Hours worked in excess of those scheduled per day and per workweek require the advance approval of the employee's supervisor. As is the case for employees working on site, work-from-home employees must not be engaged in any non-work activity during the course of their paid work-from-home time.

Ad Hoc Arrangements

Temporary work-from-home arrangements may be approved for circumstances such as inclement weather, special projects, or business travel. These arrangements are approved on an as-needed basis only, with no expectation of ongoing continuance.

Other informal, short-term arrangements may be made for employees on family or medical leave to the extent practical for the employee and the organization, and with the consent of the employee's health care provider, if appropriate. Failure to comply with this requirement may result in the immediate termination of the work-from-home agreement.

I have read and understand the conditions set out in this work-from-home policy. I indicate my acceptance of the terms of this policy by signing below:

Employee Name	Signature	Date

Reviewed and Approved By:

Supervisor _____ **(write name and date)**

HR _____ **(write name and date)**

IT _____ **(write name and date)**

Payroll _____ **(write name and date)**

RT ONLINE> For a downloadable version of Austin Retina Associates' work-from-home policy, including 2 forms not shown here, **visit www.asrs.org/work-from-home.**

Workers are looking for positions with added benefits that fit their lifestyle and provide a competitive income. Research shows that 68% of millennials would consider a prospective job more attractive if it included the opportunity to work from home.[8]

There are multiple benefits to the remote worker, including a more flexible schedule, a less stressful work environment, and less time and money spent on commuting. Some estimates have shown that the at-home worker can save over $4,000 a year in commuting costs, and up to 11 days a year in commuting time.[8]

Remote work reduces employee turnover

In addition to strengthening employee recruitment, offering remote work can improve employee retention. In one study, 34% of employees said they would take a 5% pay cut to be allowed to work from home.[3]

Stephanie Collins Mangham has found telecommuting helpful primarily for employee retention at ARA. Working from home is "not something we offer when posting jobs," she notes, "but it has helped us not lose any employees due to moving or commuting issues." A study by Stanford Graduate School of Business Professor Nicholas Bloom found that offering a remote work option reduced employee turnover by 50%.[9]

Because offering a work-from-home option allows a practice to retain experienced workers, it lessens the time managers need to spend recruiting new employees. Andrew Laverghetta believes that retention will improve if SERA implements a work-from-home policy. "We have lost 2 coders this year to large companies that are paying more per hour and allowing these individuals to work from home," he explains.

In addition to saving the practice time and money on recruitment and retention, remote work offers potential financial benefits. According to virtual teleconferencing company PGI, the average real estate cost savings of telecommuting is $10,000 per employee per year. PGI also cites a 63% reduction in unscheduled absences, a potential savings of over $1,000 per employee per year.[10]

Monitoring remote workers' performance

While there are benefits to allowing employees to telecommute, one immediate concern about remote workers is their productivity. Andrew Laverghetta describes how a bad experience with several employees in the distant past has made telecommuting more difficult to implement at SERA. "There were individuals who 'worked from home' occasionally, but took advantage of the situation," he recalls, "so understandably, several of our partners are strongly against allowing anyone to work from home."

While the recent Stanford study showed that productivity actually increased when working from home,[11] there can be a big difference between generalized studies and specific people and practices. Most offices that offer remote employment have productivity measures that they monitor, and even probationary periods where production levels have to meet a predefined level.

> 'We would expect higher production from those who work from home because they are not subject to the same interruptions as those in the office ...'
>
> —Andrew M. Laverghetta, MBA

> 'Of those who currently work remotely, 99% indicate that they prefer to continue to do so.'

Some employers require their telecommuting workers to provide pictures of their home work space, so they can ensure a clean and private environment without distractions.[5] At ARA, Stephanie Collins Mangham requires employees who work from home to self-report weekly, using metrics based on the job position:

- Chart auditors: the number of charts reviewed and messages sent to physician/scribe per week
- Check posters: the dollar amount posted per week
- Accounts receivable: number of claims worked per week, and number of corrections made
- Surgery schedulers: number of surgery cases scheduled per week
- Surgery charge poster: number of surgeries posted per week and time frame from date of service
- Claims runner: number of claims run, number of corrections made, and how many times a day claims are sent out
- Chart auditors, surgery poster, scribe supervisor, and billing manager: the service-to-billed number provided by the practice management system. "This number shows me the average number of days between the date of service and when the claim goes out," Stephanie Collins Mangham explains. "Their current metric is less than 2 days."

Andrew Laverghetta says he anticipates increased efficiency from his remote workers. "We would expect higher production from those who work from home because they are not subject to the same interruptions as those in the office, and because being allowed to work from home is a privilege based on the trust the individual has earned."

Preparing your practice for telecommuting

A common question is, how can we prepare our practice for remote workers? First, identify which positions may be available for remote work. Second, gain acceptance from the stakeholders, including physicians, on whether telecommuting is an option for the practice.

Creating a policy to outline remote work is also critical. Stephanie Collins Mangham has developed a policy for her practice in Austin (Figure 1, pages 24-25). By preparing for this possibility, your practice can be ready for the time when an established employee may have to move, and may ask to work remotely.

Despite some challenges, remote working is a trend that is not going away. Of those who currently work remotely, 99% indicate that they prefer to continue to do so.[12] As technology progresses to allow more secure communication, and companies grow more comfortable with the telecommuting process, there will be increasing expectations of this opportunity in upcoming years.[4]

Stephanie Collins Mangham agrees that the trend will continue "because of society norms and expectations, or for the reasons we did

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PRACTICE PEARLS

Lisa J. Faia, MD
Section Editor

Phoebe Lin, MD, PhD
Section Editor

Uveitis or Not? These Pearls Could Save a Patient's Sight—or Life

Uveitis and retina specialists are often faced with managing patients who have a mystery diagnosis. These patients may *appear* to have intraocular inflammation due to uveitis, but, in fact, they might have something more, such as noninflammatory conditions that can have devastating consequences if left undiagnosed.

The key to uncovering these diagnoses and avoiding the trap of bias by the referring diagnosis—or misdiagnosis of a masquerade syndrome—is to evaluate every new patient with objectivity.

Pay attention to all the details—the review of systems, the medical and medication history—and integrate and corroborate the details with the examination findings. Take the time to generate a broad-list differential diagnosis based on the compilation of findings, and hone in on a lead diagnosis with the additional facts discovered through focused imaging or laboratory testing.

Taking the time to do a thorough review of systems and obtain a good medical history can make a life-saving difference for your patients. The 5 cases below were referred for uveitis, but instead were found to have other diagnoses.

Case 1. A head banger

A 36-year-old Caucasian man with a history of unilateral open-angle glaucoma was referred for anterior uveitis on the ipsilateral side. A fundus examination from the referring doctor was noted to be normal except for an asymmetric cup-to-disc ratio. He had a maximum intraocular pressure (IOP) of 39 mmHg in the left eye (OS), which was treated with timolol-brimonidine combination drops. The patient had a medical history of severe seasonal allergies and football-related head injuries in high school in the 1990s without known direct eye trauma. He was otherwise healthy on no systemic medications.

On examination, his visual acuities were 20/20 in the right eye (OD) and 20/25 OS. His IOPs were 13 mmHg OD and 15 mmHg OS on IOP-lowering medications OS. Slit-lamp examination revealed 2+ anterior chamber glistening tan-colored cells without Krukenberg's spindle. Dilated fundus examination of the left eye revealed a chronic superonasal rhegmatogenous retinal detachment with superonasal retinal dialysis and a large mid-peripheral retinal cyst (Figure 1). The right eye was normal.

The differential diagnosis included viral anterior uveitis, Schwartz-Matsuo syndrome, pigmentary dispersion glaucoma, and traumatic iritis with glaucoma. The lead diagnosis was Schwartz-Matsuo syndrome due to chronic release of photoreceptor outer segments into the aqueous humor, resulting in elevated IOP. After repair of the retinal detachment, his IOP normalized and he no longer required IOP-lowering medications. The anterior chamber cells resolved after retinal detachment repair.

PRACTICE PEARL

In a patient with unilaterally elevated IOP and pigmented or tan cells in the anterior chamber, dilate the eye to investigate for chronic retinal detachment and inquire about a history of head trauma, even without direct ocular trauma.

Case 2. Blue and red balls

A 48-year-old Caucasian woman was referred for posterior uveitis. She had noted seeing "blue and red balls" acutely starting 3 months prior to referral. She was started on oral prednisone by her referring doctor after infectious causes had been ruled out and the patient felt her vision was still getting worse.

She had an ocular history of LASIK, previously being a +3 D hyperope. Her commercial genetic testing revealed a small percentage of Native American ancestry. The patient reported being completely healthy on no medications. She did not note any viral prodrome and her review of systems was completely negative. On examination, her visual acuity was 20/50 OD and 20/40 OS, without anterior chamber cell, nor vitreous cells in either eye.

Her dilated fundus examination revealed yellowish, subretinal, exudative pseudohypopyons along the inferotemporal arcades in the maculas in both eyes (OU) and yellow, multifocal, subretinal lesions in the peripapillary region and along the superotemporal arcades OU (Figure 2). Lesions were hyperautofluorescent on fundus autofluorescence imaging and hyperreflective on optical coherence tomography (Figure 2).

The differential diagnosis included serpiginous choroidopathy, acute posterior multifocal placoid pigment epitheliopathy, central serous retinopathy, uveal effusion syndrome, Vogt-Koyanagi-Harada syndrome, sarcoidosis, tuberculosis, syphilis, early-onset exudative age-related macular degeneration, and acute exudative polymorphous vitelliform maculopathy. Upon further questioning, she revealed a remote history of cutaneous

melanoma and basal cell cancer that was completely excised.

Our lead diagnosis was acute exudative polymorphous vitelliform maculopathy. Imaging was pursued with a positron emission tomography-computed tomography (PET-CT) scan that discovered lymph nodes positive for metastatic melanoma in the absence of current cutaneous involvement. She was started on check-point inhibitor immunotherapy for her metastatic melanoma and her vision eventually improved to 20/30 OU.

PRACTICE PEARL

When a patient's ocular disease is not responding as expected, rethink the diagnosis, pursue further testing, and consider a paraneoplastic disorder.

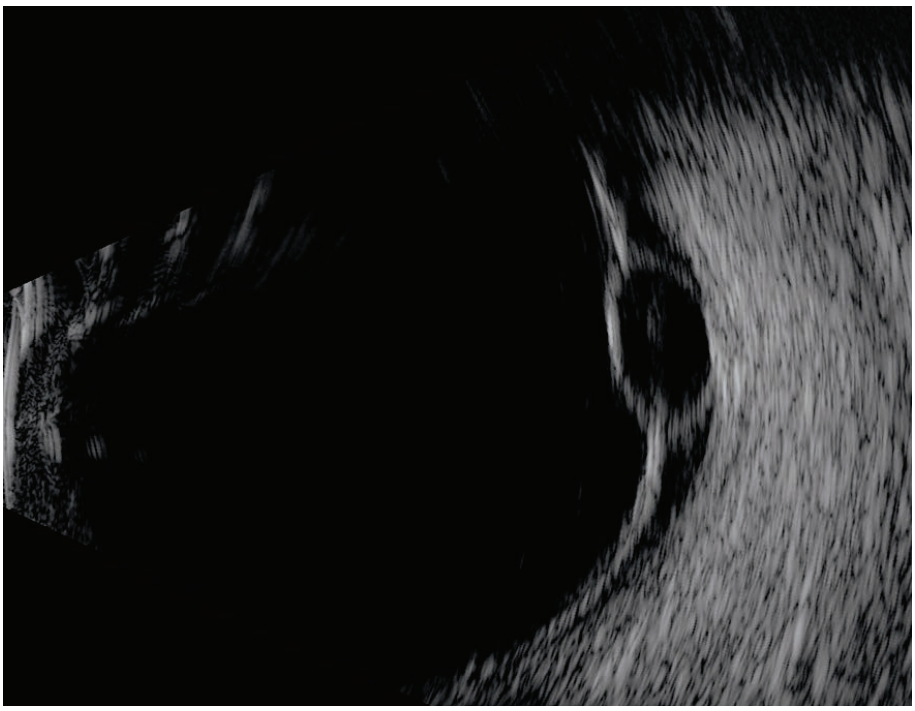

Figure 1. B-scan ultrasonography of chronic retinal detachment with large intraretinal cyst in a patient with Schwartz-Matsuo syndrome thought to have hypertensive anterior uveitis. *Images courtesy of Phoebe Lin, MD, PhD.*

Case 3. Hypopyon uveitis or not?

A 31-year-old Caucasian man was referred as a potential study subject for a steroid iontophoresis clinical trial for noninfectious anterior uveitis. He had a history of pre-B-cell acute lymphoblastic leukemia with leukemic retinopathy about 5 years previously that had been in remission since receiving a sibling allogeneic bone marrow transplant 6 months earlier. The patient had recently suffered from graft-vs-host disease affecting the bowel.

Upon presentation, he was 20/20 OD and 20/40 OS, and IOPs were normal bilaterally. Slit-lamp examination and fundoscopy revealed 4+ cell OS with hypopyon, a large inferior choroidal and ciliary body mass, as well as a serous retinal detachment (Figure 3, page 30) without vitreous cell. The differential diagnosis included intraocular leukemia, HLA-B27-associated uveitis, Behçet's uveitis, graft-vs-host disease-associated uveitis, sarcoidosis, syphilis, tuberculosis, and infectious endogenous endophthalmitis.

A diagnostic anterior chamber washout revealed leukemic cells on cytology and flow cytometry. The patient was later diagnosed with systemic recurrence of leukemia and underwent experimental therapy for severe refractory pre-B acute lymphoblastic leukemia (ALL) as well as orbital radiation for the

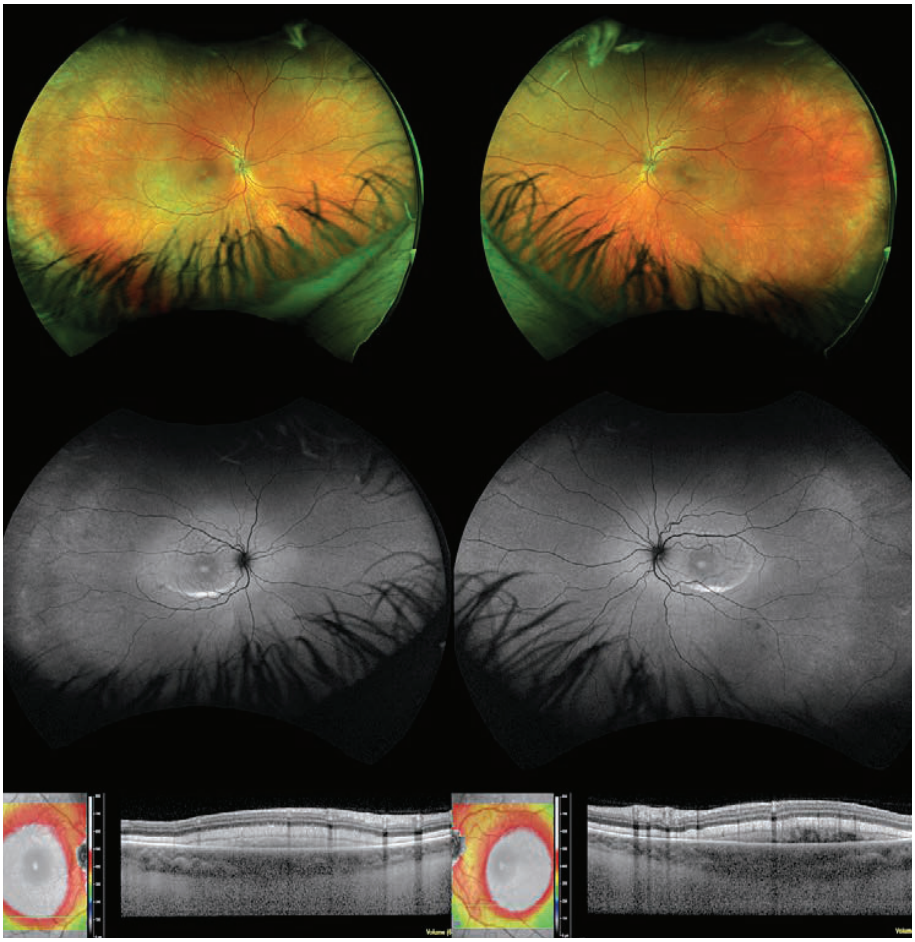

Figure 2. A 48-year-old woman with acute exudative polymorphous vitelliform maculopathy masquerading as posterior uveitis in a patient with occult metastatic melanoma. *Images courtesy of Phoebe Lin, MD, PhD.*

intraocular involvement. He had complete resolution of the intraocular mass, hypopyon, and retinal detachment. The patient was not enrolled in the noninfectious-uveitis trial.

PRACTICE PEARL

In patients with a previous neoplastic diagnosis, remission does not equal cure; intraocular recurrences can be a harbinger of systemic recurrence.

Case 4. When the stars align

A 48-year-old Caucasian female was referred for posterior uveitis. Though her doctor had found lesions in her posterior pole, the patient denied any visual complaints: no flashes, no floaters, and no metamorphopsia. She denied any viral prodrome and her review of systems was completely negative. On examination, her vision was 20/20 OU with a refraction of -7.00 + 0.50 x 013 OD and -4.75 +0.25 x 004 OS. The patient's external examination was normal, and her anterior segment revealed only the start of mild nuclear sclerotic cataracts.

Posterior examination revealed pisciform, pigmented, scattered yellow lesions in the posterior pole, worse OD than OS. The lesions appeared to be in different stages of development. There were no signs of hemorrhage. No vitritis was noted OU. The differential diagnosis included punctate inner choroidopathy, acute posterior multifocal placoid pigment epitheliopathy, macular serpiginous, syphilis, and tuberculosis.

She proceeded to have a workup and saw a rheumatologist to check for any systemic involvement. All results were negative. We entertained the possibility of an atypical age-related macular degeneration, though she had no family history and no true drusen or typical pigment changes were seen. As we followed her, her lesions appeared to evolve but she continued to deny visual complaints. We discussed initiating therapy, mainly oral steroids, which she vehemently would not allow.

Due to good vision, she chose no treatment but allowed us to follow her closely. The patient continued to have progression of her lesions on her next visit, but denied vision changes (Figure 4). Her only new complaint was increased difficulty driving at night, which her general ophthalmologist attributed to her cataracts. This prompted us to get an electroretinogram and genetic testing, which revealed the *ABCA4* mutation, consistent with Stargardt disease. Three years later, though her lesions continue to progress, her vision remained 20/20 OU without any signs of choroidal neovascularization.

PRACTICE PEARL

Do not forget inherited retinal diseases, even in the face of atypical disease features and age presentation, in the differential diagnosis of a posterior "uveitic" patient.

Case 5. A quiet, white eye

An 11-year-old African American female was seen in clinic for new onset of anterior uveitis and decrease in vision OD for 1 month. Her father noted a white pupil OD for 1 week. She denied any pain, photophobia, flashes, or floaters. The patient and her family denied recent travel, illness, fevers, arthralgias, shortness of breath, cough, trauma, contact with cats, outdoor activity, tick bites, or tuberculosis exposure. She had had contact with a 2-year-old dog at a friend's house about 1 month prior. Medical history was unremarkable, and her immunizations were up-to-date. Her examination was hand motion (HM) OD (20/20 OD one year prior) and 20/20 OS. There was a relative afferent pupillary defect OD and IOPs were normal.

The patient had no proptosis. Anterior segment examination revealed no injection OD with 1+ anterior chamber cells OD with clear lens OU (Figure 5). The posterior OD view was limited by numerous white clumps in the vitreous and an inferior mass (Figure 5). B-scan ultrasonography did not reveal any calcifications.

Despite her good health and lack of family history of neoplasms and autoimmune disease, our differential diagnosis included retinoblastoma, leukemia, medullo-epithelioma, tuberculosis, toxocariasis, and juvenile sarcoidosis. Due to the suspicion for retinoblastoma, an MRI was obtained, which revealed a pineal mass (Figure 5).

The patient was sent for retinoblastoma evaluation and treatment. Her eye was enucleated and histopathology revealed poorly differentiated retinoblastoma with microscopic retrolaminar invasion of the optic nerve and small foci of choroidal invasion. She received systemic chemotherapy and continues to do well.

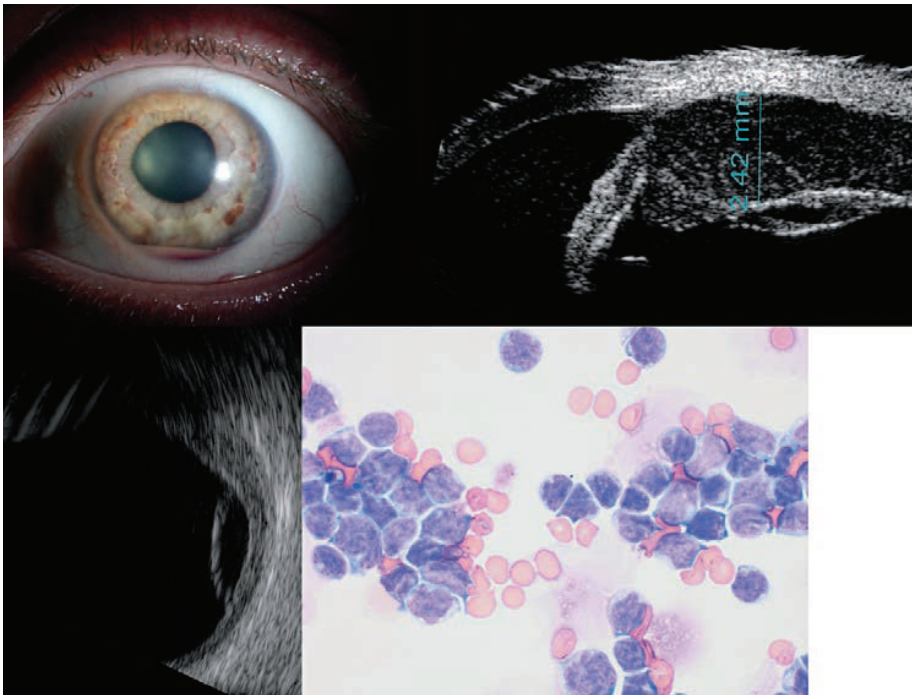

Figure 3. A 31-year-old man with pre-B acute lymphoblastic leukemia presenting with candy-cane hypopyon, ciliary body and choroidal mass, and serous retinal detachment thought to be due to graft-vs-host disease. Cytology and flow cytometry from an anterior chamber washout revealed intraocular leukemia. *Images courtesy of Phoebe Lin, MD, PhD.*

PRACTICE PEARL

When ocular signs and symptoms are not consistent with the presenting diagnosis, think again. Do not let age interfere with your differential diagnosis.

Although retinoblastoma is mostly associated with a much younger cohort, the patient's clinical picture was very suspicious for retinoblastoma from the beginning.

In summary, consider nonuveitic diagnoses such as traumatic, neoplastic, and hereditary diseases, in the differential diagnosis when a patient presents with atypical signs, symptoms, treatment responses, and clinical pictures. One can be easily misled (when all you have is a hammer, everything looks like a nail) and biased by the referring diagnosis. A broad approach and broad differential diagnosis are key to *not* missing the true diagnosis.

Financial Disclosures
Dr. Faia – None.
Dr. Lin – None.

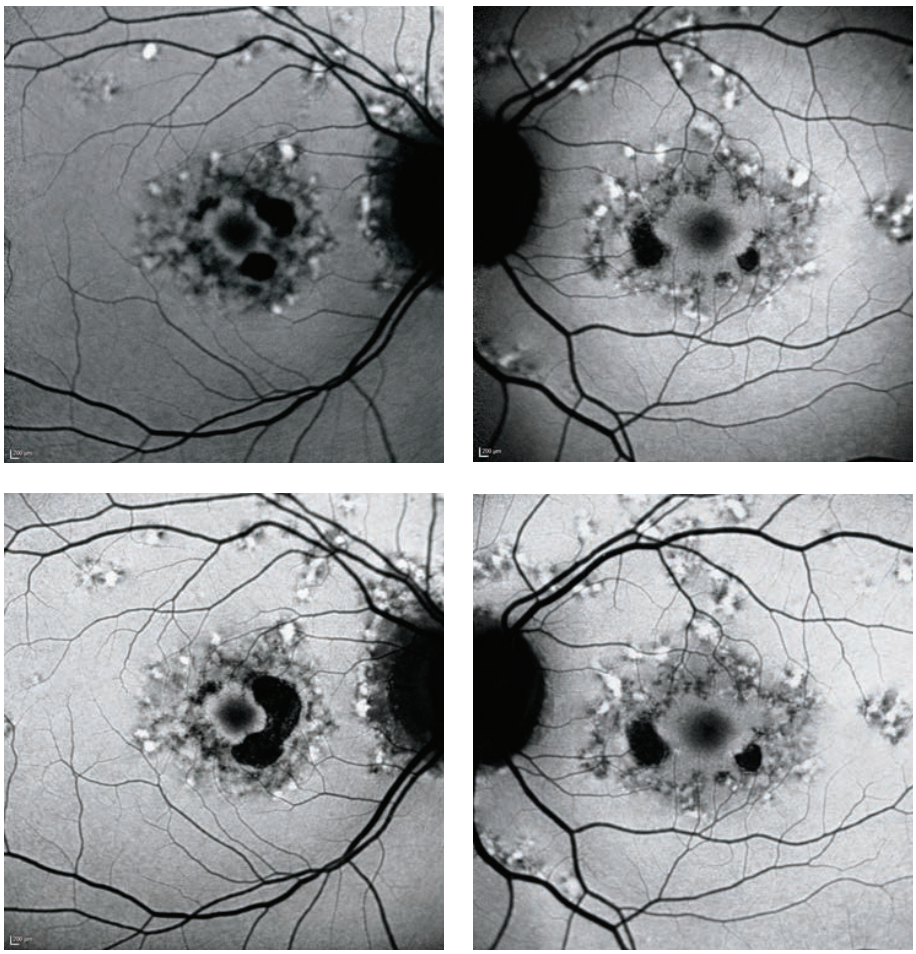

Figure 4. A 48-year-old myopic Caucasian woman with macular lesions suspicious for punctate inner choroidopathy without visual complaints. The top panel reveals her initial presentation; imaging from the follow-up visit is shown in the bottom panel. Despite progression seen on autofluorescence, she remained asymptomatic. This prompted further testing, which ultimately revealed Stargardt disease. *Images courtesy of Lisa J. Faia, MD.*

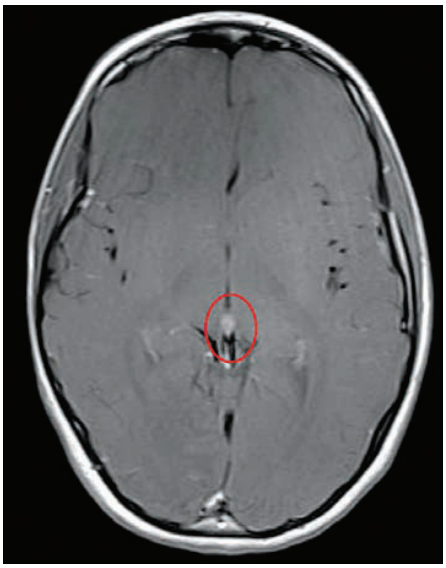

Figure 5. An 11-year-old African American female with new onset of blurred vision OD with a history of 20/20 vision OU. She had no complaints normally seen with noninfectious anterior uveitis, and examination revealed a relatively "quiet" eye. Further testing revealed an examination most consistent with retinoblastoma (including histopathology) with trilateral involvement. *Images courtesy of Lisa J. Faia, MD.*

SriniVas R. Sadda, MD
Section Editor

Sharon Fekrat, MD, FACS
Section Editor

Retina Surgeons Share Tips for Using a 3D Heads-Up Display

Retinal imaging technology is advancing rapidly—not only in our offices and clinics, but in our operating rooms (ORs). Whether it is heads-up display, digital viewing, augmented reality, or intraoperative real-time optical coherence tomography, these advanced tools are evolving at a fast and furious pace.

How do we make the best choices of which technologies to incorporate into our practices? Given the expense of these new systems and diminishing reimbursements, these are difficult decisions. To help us make sense of this, we have invited 4 seasoned retina specialists from 3 continents to share their experience and viewpoints on 3-dimensional heads-up display (3D HUD) systems.

Katherine E. Talcott, MD
Staff Physician
Cole Eye Institute
Cleveland Clinic
Cleveland, Ohio

Over the years, there have been many advances in vitreoretinal surgical technology, from small-gauge instrumentation, increased cut rates, and design enhancements to new visualization agents and novel surgical techniques. Until recently, however, the traditional operating microscope has remained relatively stagnant. With the rollout of the 3D HUD platform in the OR, we have been introduced to new technology in an effort to improve intraoperative resolution of vitreoretinal pathology that we can so elegantly image in our clinics.

The 3D HUD offers a step forward for the vitreoretinal surgeon; it provides a digital stereoscopic view of the surgical field on a high-definition monitor and frees the surgeon from the confines of the traditional microscope's eyepieces. The 3D HUD remains an evolving technology, yet offers multiple benefits.

The first use of 3D HUD technology for ophthalmology was reported by Eckardt and Paulo in 2016.[1] Further studies by Adam et al and prospective studies by Romano et al and our group when I was a fellow at Wills Eye Hospital further delineated some of these benefits,[2-4] such as improved ergonomics that limit back, neck, and shoulder discomfort from years of repetitive strain while operating seated at the operating microscope.

Visually, a 3D HUD offers enhanced stereopsis, an increased depth of field, and greater magnification with a larger field of view than a standard scope. It also allows for real-time digital manipulation of images by changing color profiles or camera gain. In terms of safety, 3D HUD can limit the risk of phototoxicity by reducing the required endoillumination intensity. The 3D HUD can offer significant benefits for surgical teaching of trainees, engaging support staff, and helping those in the OR to anticipate surgical needs through shared visualization.

I use a 3D HUD for a significant number of my macular surgical cases, including traction retinal detachments. These cases play well to the visual strengths of 3D HUD, as described above. Playing with various color profiles and settings can also help to highlight tissue and membrane planes, making the surgeon less reliant on adjuvant surgical stains. I find the 3D HUD particularly helpful in teaching during these cases.

While sitting in the assistant's chair, you can use the cursor on the device's remote to point out planes and traction as well as quietly and efficiently show where to grab tissue with forceps and the direction in which to pull the tissue. The 3D HUD can also offer improved ergonomics for these cases, which often involves more mental than physical work.

The improved posture makes a significant difference for a teaching surgical assistant who would otherwise be crouched over the side, viewing through microscope oculars next to the anesthesia cart or surgical table. The 3D HUD enables a more relaxed position without worrying about readjusting the scope to account for a trainee's accommodation.

Outside of macular work, I still prefer the standard microscope for anterior segment cases such as sutured and secondary intraocular lenses and cases requiring excellent peripheral retinal visualization. There is still some room for improvement in terms of lag as well as depth of field peripherally for 3D HUD. This can be more pronounced while doing certain cases such as anterior proliferative vitreoretinopathy, as well as for non-clearing vitreous hemorrhage where peripheral depth is important and significant peripheral panretinal photocoagulation is needed.

> 'A 3D HUD offers enhanced stereopsis, an increased depth of field, and greater magnification with a larger field of view than a standard scope.'
>
> —Katherine E. Talcott, MD

It is important to check the iris diaphragm at the beginning of each case, as this can be inadvertently moved and significantly change peripheral visualization—setting it to 67% can be helpful for the majority of cases.

Another potential benefit of a 3D HUD is the ability to integrate multiple forms of information onto the 3D monitor, including intraoperative optical coherence tomography (iOCT), which may be helpful for surgical decision making. At Cole Eye Institute, the prospective Determination of Feasibility of Intraoperative Spectral Domain Microscope Combined/Integrated OCT Visualization During En Face Retinal and Ophthalmic Surgery (DISCOVER) study, led by Justis P. Ehlers, MD, integrates iOCT during retinal surgery and includes a subset of patients imaged with 3D HUD.

Integration of iOCT into this surgical visualization system has been described as an "integrative surgical theater," which allows for unique static and real-time feedback on tissue manipulation during surgical cases and can assist in surgical decision-making.[5] The latest version of the Alcon 3D HUD (NGENUITY) allows for the projection of real-time vitrectomy settings using their Constellation Vision System (Alcon Laboratories, Inc) onto the 3D monitor. This enables an immersive experience where the surgeon can focus on one monitor and get real-time information about vitrectomy settings and macular tissue using the iOCT while observing the surgical field.

Several additional things can be done to optimize the benefits of using a 3D HUD, beginning with setup of the room. First is setting up the monitor in the OR. Every OR is unique in size and configuration. Attention should be given to the location of the 3D monitor before the case in order to maximize resolution and stereopsis while avoiding interference with other equipment in the OR.

It can be helpful to trial sitting in the surgeon's chair while looking at the monitor to ensure that you can see adequately and are comfortable. The OR staff can then coordinate the placement of their equipment. It is also important to perform a white balance before starting the cases for each day to ensure proper color hues and saturation. Also, make sure the necessary equipment (eg, keyboard, remote control) is accessible and covered with a sterile bag as needed for the case.

It can be helpful to make several adjustments during a case to better utilize the 3D HUD. Turning down the endoillumination intensity can reduce the risk of phototoxicity while allowing for better tissue contrast, especially for macular work. If you encounter difficulty with peripheral visualization, it can be helpful to minimize magnification. If you are teaching, note what stage the surgical trainees are in their training. If they are learning a new surgical skill or technique, changing the surgical visualization system can add another, yet-unfamiliar variable and may require a period of adjustment.

Adding a 3D HUD offers significant advancement in surgical visualization and improved ergonomics in addition to enhanced stereopsis, an increased depth of field, and greater magnification with a larger field of view compared with a standard operating microscope. Although this system still has room for improvement, it is important to continue to use and push this surgical technology forward so it grows and better meets our needs.

Michele Coppola, MD
Director
Ophthalmology Department
San Gerardo Hospital
Monza, MB, Italy

In the past several years, a variety of 3D visualization systems have been released for use in the OR; however, it has become clear that the 3D widescreen is not just an expensive toy for ophthalmic surgeons, but instead represents the future of intraoperative visualization during vitreoretinal surgery. In fact, the addition of a 3D imaging system to vitreoretinal surgery is one of the latest and most exciting advances in our field.

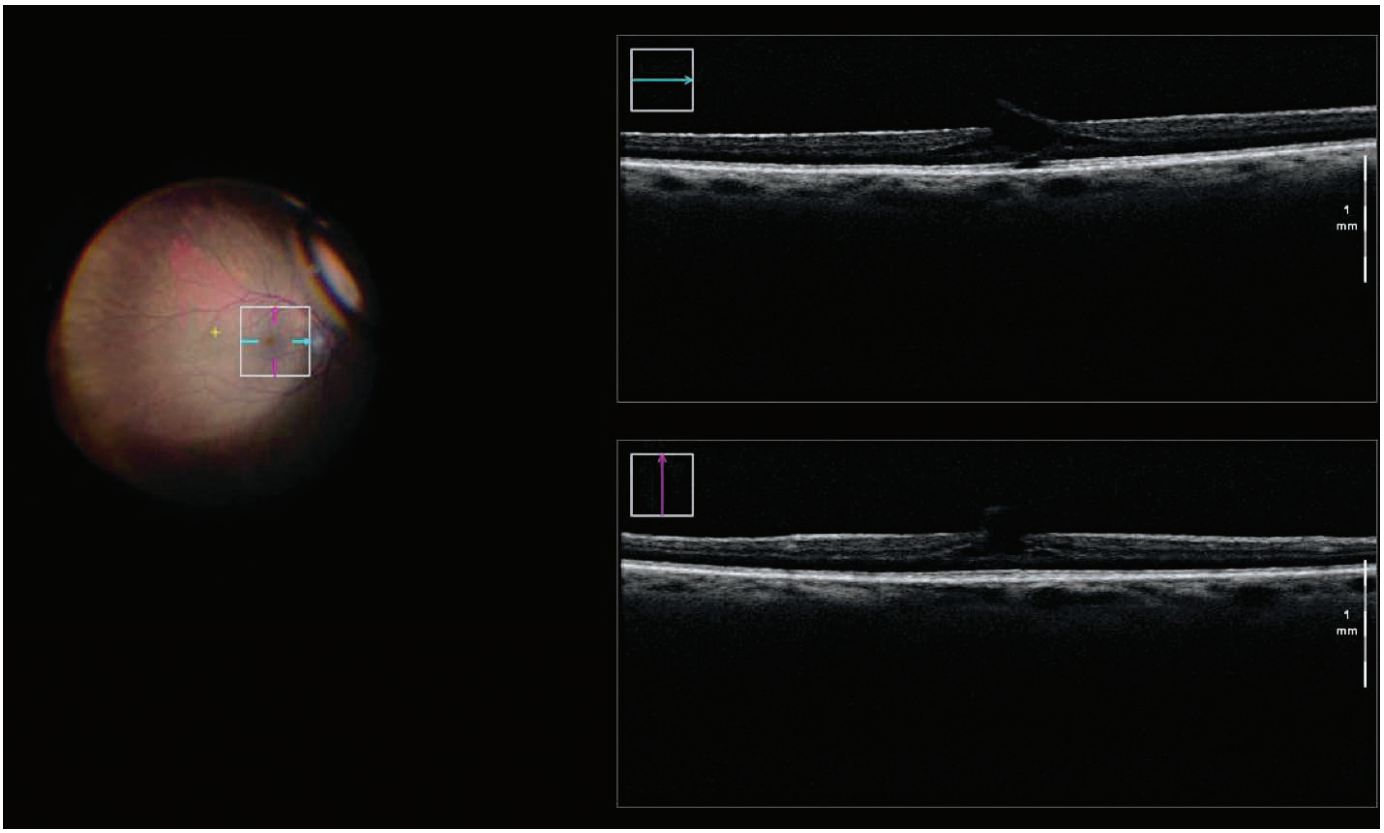

Figure 1. Integration of iOCT with 3-dimensional heads-up display during a vitrectomy for epiretinal membrane. *Image courtesy Katherine Talcott, MD.*

There are many benefits to incorporating a 3D HUD system in surgery, including the surgeon's ability to maintain a "heads-up" position. The possibility of working "heads up" might lead to significantly less lower-back and neck pain. Many reports confirm that surgeons finish a day in the OR less tired using 3D systems compared to being hunched over a traditional microscope. With 3D technology, some changes in the OR layout may be needed, such as where the monitor is placed in relation to the vitrectomy platform and the scrub table with the surgical instruments.

A 3D visualization system offers many benefits for the "audience" (ie, nurses, fellows, residents, students, and visiting observers) because they share the same view as the surgeon. This improves the learning curve for all involved.[3] From an educational point of view, mentors can easily "guide" fellows' movements while performing their own cases as primary surgeons. This is possible due to the higher resolution, definition, and magnification on the 3D HUD compared to the view through the traditional microscope. A recent study by Romano and colleagues using a satisfaction questionnaire showed that 3D HUD surgery scored significantly more points among younger vitreoretinal fellows than among experienced surgeons.[4]

> 'A 3D visualization system offers many benefits for the "audience" ... because they share the same view as the surgeon.'
>
> —Michele Coppola, MD

The real-time digital processing of the image comes along with automated brightness control. This means that endoillumination can be lowered as much as 40%,[6] thus reducing potential phototoxic effects on the retina. The 3D system makes it possible to computerize digital images and obtain filtered images without using potentially harmful dyes or light filters.

While performing macular procedures, it helps to open the iris aperture to 30%, ensure maximal magnification, and set the power output for the light source at 20%. During vitreoretinal surgery, a high level of contrast is often needed. A lower magnification is suggested when working in the periphery. Using the minimum iris diaphragm needed is also useful while performing cataract surgery and helps to highlight the red reflex.

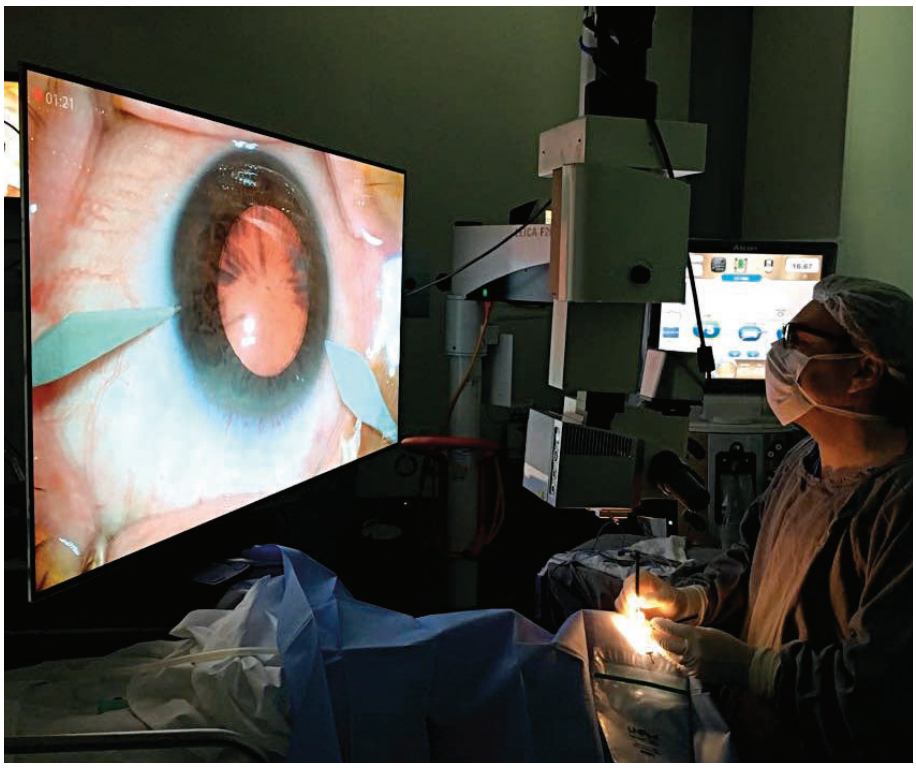

Figure 2. The distance between the screen and the surgeon should be around 3 to 6 feet (1 to 2 meters).[10] ***Image courtesy Rodrigo Antonio Brant Fernandes, MD, MBA.***

The 3D HUD also offers the possibility of maintaining high-definition visualization even at very high magnifications.[3] The technical feasibility has been explored in preclinical studies,[1,6] where the advantages of using this new imaging system were partially highlighted. The best definition is obtained when the monitor is at 3 to 6 feet (1 to 2 meters) from the surgeon. The assistant and the scrub table with instruments should be positioned so the 3D HUD screen is not obscured.

We recently published procedural and safety results from our initial experience using 3D heads-up during vitrectomy for retinal detachment. The comparison of our outcomes to the standard technique showed how the new 3D system is safe and effective.[7]

As all that glistens is not gold, some drawbacks of the 3D systems must be taken into account. Surgeons need some time to get accustomed to the new technique—for many, it takes about 10 to 15 cases to feel confident using this system. And there is a little delay between the surgeon's movements and visualization on the monitor (around 0.09 seconds) that is more noticeable during anterior segment maneuvers.

For vitreoretinal surgeons, 3D HUD represents the future of intraoperative visualization. It offers the same surgical performance as conventional surgery, once the learning curve has passed. The 3D system also gives some crucial advantages, such as the benefits of training novice surgeons and more comfortable operating conditions for the primary surgeon.

Michel Eid Farah, MD, PhD
Director, São Paulo Ophthalmology Center
Professor, São Paulo Federal University Paulista School of Medicine
São Paulo, Brazil

Rodrigo Antonio Brant Fernandes, MD, MBA
Director, Vitreoretinal Section Ophthal Hospital
Staff, Retina Section Federal University of São Paulo (UNIFESP)
São Paulo, Brazil

Since the introduction of pars plana vitrectomy by Machemer in the 1970s, surgical visualization of the operating field and ocular structures has been obtained by direct view through an analog surgical microscope.

Through its lenses, the surgeon could increase the image size of the eye structures

and perform very fine maneuvers needed to address the tiny and fragile intraocular and extraocular structures during the operation. This standard mode of viewing was unchanged until recent years, when the optics and technology of surgical microscopes improved to a very high level.

Manufacturers' and retinal surgeons' main concerns have always been focused on developing new equipment with lower costs, decreased instrument size (smaller gauges), finer and more reliable instruments, and more efficient fluidics. Only recently have manufacturers digitally addressed the issue of improving the surgeon's ability to visualize the operating field, providing a different real stereoscopic view with better ergonomics.

With the technological revolution in the last few years, video cameras, chipsets, and electronic components have reached a level of quality and performance—along with a corresponding decrease in cost—that has allowed the first digitally enhanced images to reach the OR. The pitfalls to be overcome by these new devices were to provide real-time (latency of < 100 ms) digital ultra-high-definition stereoscopic images of the retinal structures, with a high contrast ratio, and all the natural colors, along with great sharpness and depth of focus.

Use of a commercial 3D system for vitreoretinal surgery was pioneered by Claus Eckardt, with the former TrueVision system (TrueVision 3D Surgical).[1] The system then evolved into an accessible tool for vitreoretinal surgeons around the world, with varying acceptance rates from country to country.

We have had a 3D HUD NGENUITY system available in our private clinic for 2 years and for 6 months at the university. In both settings, the 3D system is available in only one operating room, while the other rooms have only analog microscopes. The acceptance of the 3D system was immediate for all vitreoretinal surgeons, including the fellows.

The most striking difference between the 2 systems is the depth of focus; the 3D system allows all of the eye structures to be simultaneously in focus at all times. A few experienced surgeons initially did not prefer the 3D HUD system due to this difference and the associated challenges in judging depth and instrument proximity to the retinal surface compared to the analog microscope. Over time, they adapted to this difference in focus.

Visualizing the retina during fluid-air exchange with 3D HUD is much improved over the analog microscope, so we began to see more and more fellows performing laser retinopexy under air—a maneuver traditionally performed under perfluorocarbon liquid. When using the 3D HUD during vitreous surgery, illumination levels—which traditionally were around 40% to 50%—can be decreased to around 10% to 15%.[3] Lower illumination may lead to less associated phototoxicity, an important point as the duration of surgery is often longer when training fellows.

When using the analog microscope in dislocated intraocular lens (IOL) or intraocular foreign body (IOFB) cases, visualization of the operating field can become poor when holding the IOL or IOFB with forceps while inverting the image and redirecting attention to the anterior segment. In these cases, the 3D system allows the surgeon to digitally invert the image back to the anterior segment while preserving visualization of the operating field.

Figure 3. The 3D HUD allows the surgical education of all trainees and staff in the OR. *Image courtesy Lejla Vajzovic, MD.*

> 'The most striking difference between the [traditional microscope and the 3D HUD] is the depth of focus; the 3D system allows all of the eye structures to be simultaneously in focus at all times.'
>
> —Michel Eid Farah, MD, PhD, and Rodrigo Antonio Brant Fernandes, MD

In Brazil, some of us use the 3D system in 100% of our cases, while others use it in around one-third, since some hospitals do not yet have the 3D system.

We performed a study to assess the initial experiences of experienced vitreoretinal surgeons and their adoption of the 3D system for different vitreoretinal surgical procedures. All surgeons favored the 3D heads-up viewing system compared to the traditional microscope; the magnitude of the benefit depended on the type of surgery. Peeling of the internal limiting membrane or epiretinal membrane benefited most from the system ($P < .001$), while the anterior segment surgeries showed the least benefit ($P < .001$).[8]

In another study, we compared the learning curves of experienced surgeons with those of 3 fellows, specifically looking at the procedure times of different maneuvers during 40 macular hole cases. The experienced surgeons had shorter operating times than the fellows, but there were no differences between the 2 systems regarding a given surgeon's duration of surgery or anatomical results.[9]

If we had access to additional 3D HUDs, we would likely perform all of our cases under 3D viewing, especially for recording and teaching purposes.

Cases combined with anterior segment procedures (eg, phacoemulsification) may require a longer learning curve, and some surgeons still prefer to use the traditional microscope.

However, after a few days of training, all cases are likely manageable with 3D viewing, including scleral buckling procedures. The magnification is higher with the 3D system, though, which sometimes makes suturing more challenging.

In cases where an assistant is needed or where the OR size is not adequate, the traditional operating microscope—especially when ceiling mounted—may be a better fit. [10,11]

A common challenge in the earlier versions of 3D systems was the latency being longer than 200 ms, which translated into a delay between the surgeon's movements and the image viewed on the screen, especially with anterior segment procedures. This has been addressed in newer versions of the 3D system.

	Advantages	Disadvantages
Alcon NGENUITY	1. Add-on system: functions with any microscope 2. High dynamic range (HDR) camera with large sensor 3. Broad depth of field, mechanically controlled 4. Digitally enhanced ("super 3D") stereopsis	1. Current software may not perform white balance perfectly 2. To change to the standard binocular analog microscope, you have to stop the surgical procedure to assemble the equipment
Zeiss ARTEVO 800	1. All-in-one system with assistance (alignment) function and integrated intraoperative OCT (for both anterior and posterior surgery) 2. HDR camera with low latency 3. Keeps the binoculars in position, so no need to assemble/disassemble the system when different surgeons use the device 4. Reproduces colors with high reliability	1. HDR has lower range values than NGENUITY and less depth of field 2. In macular surgery, everything may appear in 2D mode (in the same plane) 3. Requires purchase of a new microscope, even if you own a LUMERA 700

Table 1. Comparison of the Alcon and Zeiss 3D systems. *Courtesy of Michel Eid Farah, MD, PhD.*

"The Alcon NGENUITY system may be preferred for vitreoretinal surgery due to image features," notes Michel Eid Farah, MD, PhD. "However, the Zeiss ARTEVO 800 performs better in anterior segment procedures, such as cataract and glaucoma surgery, because those procedures use a lot of light and do not need 'super 3D.' Beyond that, ARTEVO 800 has alignment functions that assist with toric intraocular lens implantation.

"In 2022, Alcon's NGENUITY 2 will incorporate rotational movements in addition to the existing X, Y, and Z movements, making it possible to visualize the far periphery more easily."

The high cost of 3D systems, in addition to the already-purchased operating microscope and phacovitrectomy system, makes the financial outlay prohibitive in some settings.

Acceptance of 3D HUD may increase with cost-saving combinations in the future. Some surgeons also prefer having the option of using the binoculars in case they need to perform a maneuver in analog mode, and as such, a system that can offer the 2 capabilities may be more in demand.

The 2 main challenges to acquiring a 3D system are having a traditional operating microscope with poor image quality and having a smaller OR. The 3D system cannot compensate for poor images provided by an older microscope. Acquiring a better microscope would be advisable before adopting the 3D system, but that increases the overall financial outlay. In addition, the 3D system utilizes floor space in the OR, so it is more easily incorporated into the flow in bigger rooms.

Conclusion

The 3D HUD system appears to be here to stay. Our contributors have highlighted the many potential benefits and advantages of this technology. One needs to recognize, however, that this technology is still evolving and is only one element of the exciting OR of the future where imaging and real-time diagnostics are playing an increasingly prominent role. While we are all excited about these advances in imaging in the OR, the benefits of these new tools need to be weighed against their cost.

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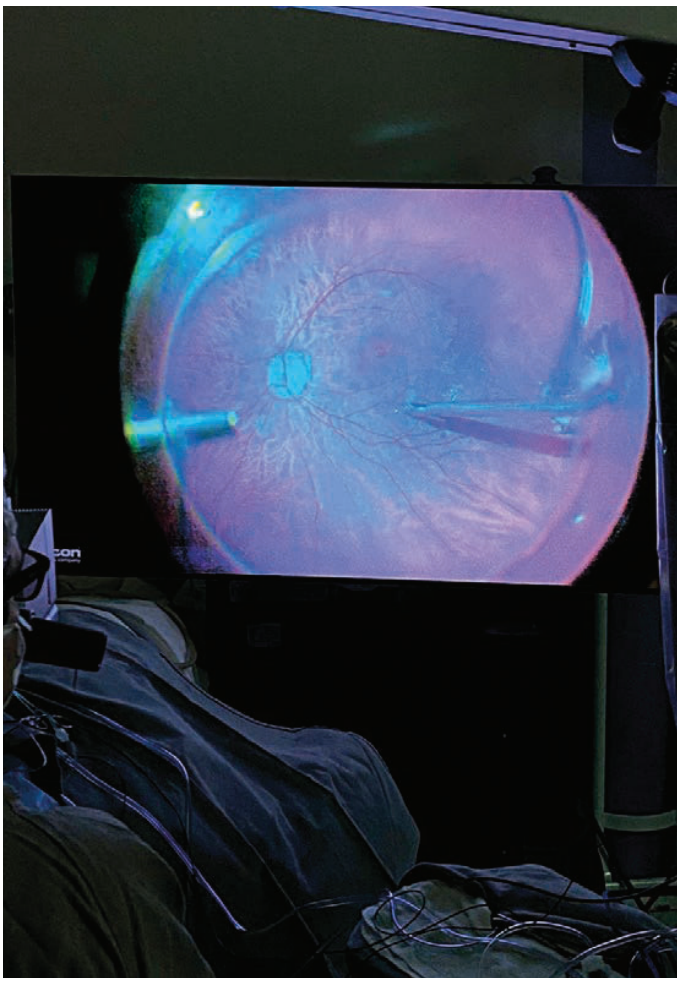

Figure 4. The surgeon's view with the 3D HUD system. ***Image courtesy Rodrigo Antonio Brant Fernandes, MD, MBA.***

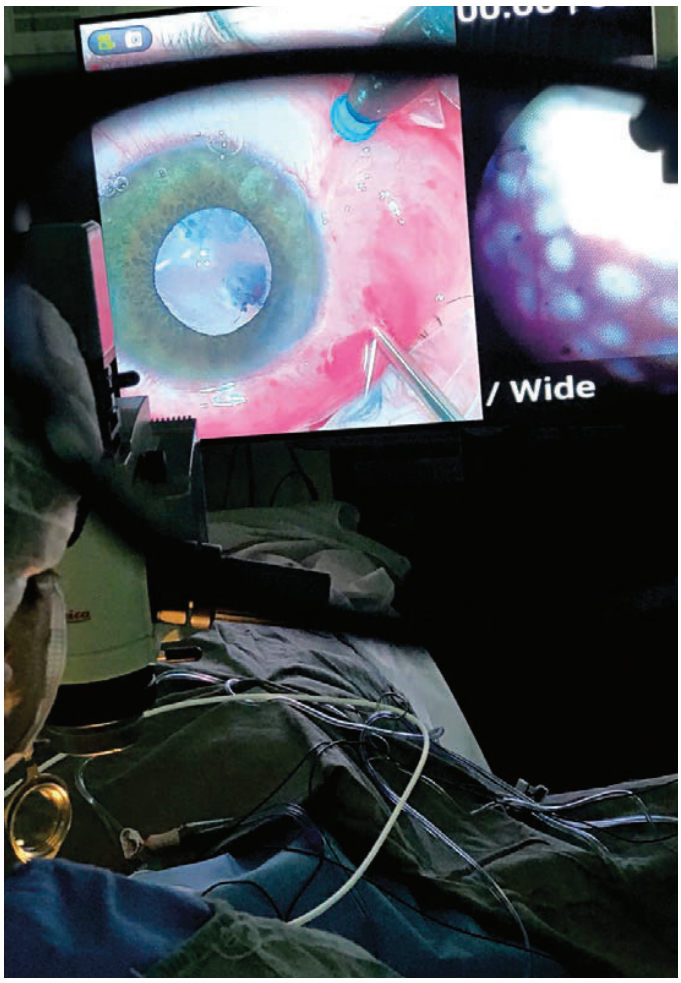

Figure 5. The fellows'/students'/OR staff's view with the 3D HUD system. ***Image courtesy Rodrigo Antonio Brant Fernandes, MD, MBA.***

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Financial Disclosures

Dr. Coppola – None.

Dr. Farah – None.

Dr. Fekrat – ALCON LABORATORIES, INC: Other, Royalty.

Dr. Fernandes – None.

Dr. Sadda – 4D MOLECULAR THERAPIES: Advisory Board, Honoraria; ALLERGAN, INC: Consultant, Investigator, Honoraria; AMGEN, INC: Consultant, Honoraria; BAYER HEALTHCARE PHARMACEUTICALS: Consultant, Honoraria; CARL ZEISS MEDITEC: Consultant, Investigator, Equipment (Department or Practice), Grants; CENTERVUE INC: Consultant, Other, Equipment (Department or Practice), Honoraria; GENENTECH, INC: Consultant, Investigator, Grants, Honoraria; HEIDELBERG ENGINEERING: Consultant, Other, Equipment (Department or Practice), Honoraria; NIDEK CO, LTD: Other, Equipment (Department or Practice); NOVARTIS PHARMACEUTICALS CORPORATION: Consultant, Honoraria; OPTOS PLC: Consultant, Investigator, Equipment (Department or Practice), Honoraria; THROMBOGENICS, INC: Consultant, Honoraria; TOPCON MEDICAL SYSTEMS: Other, Equipment (Department or Practice).

Dr. Talcott – None.

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www.cairoretinameeting.com

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48th Annual Aspen Retinal Detachment Society Meeting
The Viceroy Snowmass
Snowmass, Colorado
https://mcpi.cvent.com/ards2020

March 26-28, 2020
8th Annual Vit-Buckle Society Meeting
Fontainebleau Miami Beach
Miami Beach, Florida
https://vitbucklesociety.org/annual-meeting

PAT SURVEY: A DEEPER DIVE >> *Continued from page 17*

in Figure 4 (page 17), indicates a trend toward diminished interest in PE with fewer years out of practice—most notably seen in the third response, "No and we have no interest." If we combine the first and third response choices in the survey question (as "no interest") and combine the second and fourth (as "interest"), as shown in Figure 5 (page 17), we see a similar trend.

Conclusion

This inaugural PAT Survey Deeper Dive helps us better identify PE patterns on a more individual level. We hope you find the subanalysis interesting, and we welcome your feedback and ideas for additional questions to explore.

Of course, these data are only as strong as the number of responses; we encourage you to respond to the annual PAT Survey and examine how your practice compares to the broader retina community. Look for more PAT Survey Deeper Dive analyses in upcoming issues of *Retina Times*.

Financial Disclosures

Dr. Hahn – ALCON LABORATORIES, INC: Consultant, Honoraria; ALLERGAN, INC: Advisory Board, Consultant, Honoraria; CARL ZEISS MEDITEC: Advisory Board, Honoraria; GENENTECH, INC: Advisory Board, Speaker, Honoraria.

Dr. Schneiderman – None.

CLINICAL TRIALS: FUTURE PATHWAYS >> *Continued from page 23*

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Financial Disclosures

Dr. Chin – None.

Dr. Shah – ALCON LABORATORIES, INC: Investigator, Grants; ELLEX MEDICAL LASERS LTD: Speaker, Investigator, Grants, Honoraria; GENENTECH, INC: Investigator, Grants; NOVARTIS PHARMACEUTICALS CORPORATION: Investigator, Grants; REGENERON PHARMACEUTICALS, INC: Advisory Board, Investigator, Grants, Honoraria.

Dr. Witkin – None.

PRACTICE MANAGEMENT >> *Continued from page 26*

it—we didn't want to lose employees just because they were moving to another city, or we ran out of room at our main hub."

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Financial Disclosures

Mr. Laverghetta – REGENERON PHARMACEUTICALS, INC: Advisory Board, Honoraria.

Ms. Mangham – NOVARTIS PHARMACEUTICALS CORPORATION: Advisory Board, Honoraria; REGENERON PHARMACEUTICALS, INC: Advisory Board, Speaker, Honoraria; SAMACARE, INC: Advisory Board, Honoraria.

Dr. Stone – AERPIO THERAPEUTICS: Investigator, Grants; CLEARSIDE BIOMEDICAL, INC: Investigator, Grants; ELI LILLY AND COMPANY: Investigator, Grants; GENENTECH, INC: Consultant, Investigator, Grants, Honoraria; REGENERON PHARMACEUTICALS, INC: Investigator, Grants, Other Financial Benefit.

Ms. Yockus – GENENTECH, INC: Advisory Board, Speaker, Honoraria; NOVARTIS PHARMACEUTICALS CORPORATION: Advisory Board, Honoraria; REGENERON PHARMACEUTICALS, INC: Advisory Board, Speaker, Honoraria; SANTEN, INC: Advisory Board, Honoraria.

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Section Editor

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Section Editor

Diagnosing and Treating Retinal Detachments in Children

Retinal detachments (RDs) in children can occur for a variety of reasons. Unlike in adults, where retinal tears most commonly result from posterior vitreous detachments, in children there are myriad underlying reasons for RDs—eg, trauma, lattice with atrophic holes, and a multitude of inherited systemic and ocular diseases.

This Issue's Key Opinion Leaders

Audina M. Berrocal, MD
Professor of Clinical Ophthalmology
Medical Director, Pediatric Retina and Retinopathy of Prematurity
Bascom Palmer Eye Institute
University of Miami
Miller School of Medicine
Miami, Florida

Antonio Capone Jr, MD
Co-president/Partner
Associated Retinal Consultants
Royal Oak, Michigan

Yoshihiro Yonekawa, MD
Adult and Pediatric Vitreoretinal Surgery
Assistant Professor of Ophthalmology
Wills Eye Hospital
Mid Atlantic Retina
Philadelphia, Pennsylvania

> 'The vast majority of RRDs in young children should be repaired with a scleral buckle.'
>
> —Yoshihiro Yonekawa, MD

The patient's age and clinical presentation can help narrow down the underlying reason for the RD and guide the best surgical approach. While rhegmatogenous retinal detachments (RRDs) can occur in young children, they are more common in older ones. In young children, exudative and traction detachments should be strongly considered, which will likely affect the treatment type.

The KOL Corner presented several pediatric retina specialists with challenging (mostly rhegmatogenous) retinal detachment cases to see how they think about and manage these challenges.

An 8-year-old boy presents with a new-onset, macula-involving RRD. The other eye has extensive lattice but no holes. You suspect Stickler syndrome. The patient is difficult to examine in the office, so you plan an exam under anesthesia (EUA) prior to surgical repair.

How would you decide on your surgical repair technique?

Yoshihiro Yonekawa: Children this age often have difficulty realizing that they have lost vision in an eye, as they are functioning just fine with the fellow eye. Chances are likely that the "new" retinal detachment occurred some time ago, and this is an acute realization of a chronic issue.

Pediatric retinal detachment also tends to progress more slowly than that in adults because children have an intact posterior hyaloid. However, giant retinal tears (GRTs), as seen in eyes with vitreoretinopathies, progress faster. Chronicity is an important consideration for optimal surgical planning and guides discussion with parents regarding prognosis.

The vast majority of RRDs in young children should be repaired with a scleral buckle. The posterior hyaloid is almost always attached firmly to the retina (though it can be different for patients with Stickler syndrome), and surgeons will encounter difficulties separating the hyaloid from the retinal surface with vitrectomy techniques.

Even if the hyaloid can be lifted from the posterior pole, it is extremely difficult to release the hyaloid to the retinal break and to the periphery. If the hyaloid cannot be separated to the break, the retina will likely redetach from lack of optimal tamponade and from proliferative vitreoretinopathy (PVR) formation. An external approach is preferred to prevent the downward spiral of PVR that can be relentless in young eyes.

Even if eyes present with characteristics that would normally push one toward vitrectomy, such as relatively posterior breaks, imperfect views from heme, and even moderate PVR, I would roll up my sleeves and fix these eyes with primary buckling techniques.

Audina Berrocal: In pediatric cases, there are 2 major considerations: the patient's age and the pathology. A scleral buckle combined with a vitrectomy is the best option for this 8-year-old child. In children, you want to maximize the effectiveness of the treatment and minimize the number of procedures performed. By doing a buckle and a vitrectomy, we are maximizing the effectiveness of the treatment with one surgery.

I would tamponade with either silicone oil or a long-lasting gas tamponade. The choice of tamponade will depend on the ability to separate the hyaloid and remove all the traction. If there is an inability to elevate the hyaloid or if there are areas where it is still adherent, I would opt for silicone oil. If I am able to remove all the traction and the hyaloid, an expansile gas tamponade is ideal, even when they cannot position.

Antonio Capone: Stickler syndrome detachments often have atypical breaks—giant tears, posterior breaks, radial breaks, alone or in combination, etc. I would perform a scleral buckle for sure, and would often do a vitrectomy if the buckle didn't adequately support the breaks.

If I were performing vitrectomy, I would almost always use silicone oil. The failure rate due to PVR with recurrent detachment is high. With oil in place, one can optimize the chance that the macula will stay on under oil should PVR develop—optimizing prospects for visual outcome.

Would you treat the other eye, and if so, how?

Yoshihiro Yonekawa: My approach would depend on the level of suspicion for type 1 Stickler syndrome. I would examine the patient for typical facial features and ask for a detailed family history of retinal detachment.

Because the eye has extensive lattice, I would perform prophylactic retinopexy. If there were hard signs of type 1 Stickler syndrome or a strong family history, including young family members with blinding retinal detachment and ideally genetic confirmation, I also would consider prophylactic buckling. This, of course, would be after a careful informed-consent process.

While this patient has extensive lattice, many patients with Sticker syndrome can detach spontaneously without having any significant lattice-like lesions. That's an even more worrisome sign—that the retina slid off without grossly visible pathology. I think prophylactic treatment is critical in such eyes.

Audina Berrocal: I would definitely treat the other eye. Once the surgical eye is stabilized, my preferred method of prophylaxis for the other eye is a scleral buckle with laser.

Antonio Capone: I would always treat the other eye. It's not a question of *whether* to treat—the Cambridge prophylactic treatment study[1] clearly spoke to that—but *how*. Opinions vary as to the approach—prophylactic buckle, cryopexy, or laser. The only large-cohort data are for cryotherapy, and there have never been comparative studies addressing the relative efficacy of the other options. None of these approaches are a guarantee, as retinal dehiscence behind the "support" remains possible.

My preference is laser ablation—ora serrata to equator, 4 to 6 rows, 1.5 burn widths between grey burns with sparing of the long posterior ciliary nerve—as the best compromise between benefit, morbidity, and risk of the 3 options.

A 6-month-old female presents with bilateral bullous retinal detachments. There is no history of prematurity.

How would you determine the underlying cause of her detachments?

Yoshihiro Yonekawa: A 6-month-old should not have retinal detachments. Something bad is happening that needs to be diagnosed and treated, and there are strong possibilities of systemic conditions. The description indicates that the retinal detachments are bullous—so let's assume these are serous retinal detachments, and not rhegmatogenous or tractional.

The first step is to obtain a detailed medical and family history. The most important rule in pediatric retina is to rule out retinoblastoma. Ophthalmoscopy in a 6-month-old can be challenging so B-scan ultrasonography is a great way to supplement the exam, and in this case, is essential for identifying underlying tumors.

If my suspicion for retinoblastoma is very low, I would follow with a detailed EUA with funduscopy, more detailed ultrasonography, and widefield fluorescein angiography to look for subtle lesions, retinal vascular anomalies, vasculitis, and vitreoretinal causes for exudation.

Audina Berrocal: First, I would spend some time eliciting the pregnancy, birth, and family history. Due to this unusual presentation, I would perform an MRI of the head and orbits before this child is taken to the operating room (OR) for an EUA. Once I had the results of the MRI, which would be done expeditiously, an EUA would be performed.

> **'I would always treat the other eye. It's not a question of *whether* to treat … but *how*.'**
>
> —Antonio Capone Jr, MD

In the OR, the first thing would be to check intraocular pressures and then perform a good funduscopic examination with scleral depression. This would be followed by ultrasonography, axial length measurement, fluorescein angiography (FA), and possibly optical coherence tomography (OCT)/OCT angiography. If I were to suspect a genetic cause, I would recommend a broad genetic panel to the parents.

Antonio Capone: This is a very uncommon presentation for bullous RD. The fact that these detachments are bullous meaningfully removes retinopathy of prematurity from the differential diagnosis, whether the patient was premature or not. Bilateral congenital retinal detachment is, by far, more commonly tractional.

If bullae are seen, they're likely to represent bullous schisis, which one typically wouldn't encounter in an infant girl. Bilateral bullous RD can be seen in facioscapulohumeral dystrophy (very rare) as well. So, I would start with a thorough family history and EUA with imaging to include FA and OCT to confirm that they're truly bullous RDs as billed. I would follow up with genetic testing based on suspicions raised on the EUA.

Under what circumstances would you consider pars plana vitrectomy to try to repair the detachments?

Yoshihiro Yonekawa: If you determine that the retinal detachments are from active retinoblastoma, *do not* perform vitrectomy; violating the eye can cause orbital extension and systemic metastasis, which can be lethal. The tumors are the source of the exudation, so the tumors need to be treated, not the retinal detachment. I would immediately refer the patient to our ocular oncology service. In fact, if there is *any* suspicion from the exam in clinic, I would either refer to—or coordinate a joint EUA with—the oncology team, and obtain an MRI in the interim.

Vitrectomy in eyes with retinoblastoma is possible, but only after the tumor has been definitively treated. Serous retinal detachment should not be present, and if it is, there are chances that the tumor may still be active. There are 3 main indications for vitrectomy in eyes with controlled retinoblastoma: vitreous hemorrhage (often from radiation retinopathy), traction retinal detachment from hyaloidal contraction, and rhegmatogenous or traction/RRD.

Visual potential should be considered carefully, as this is a high-risk procedure. Tumor cells can theoretically dislodge from the turbulence in the setting of a penetrated eye with connection to the orbital and systemic circulation. Make sure the tumor is cleared by the oncology team, and that there is a reasonable chance for visual improvement.

Let's say that the bilateral serous retinal detachment is not from retinoblastoma. There are several other possibilities. Coats' disease can present with bullous serous retinal detachment in young patients, but this is more often unilateral and slightly more common in boys.

Bilateral Coats'-like retinopathies do exist, and these conditions usually do not discriminate between genders. They are often caused by systemic disorders, such as CTC1 mutations (Coats' plus disease, a telomere disorder), Parry Romberg syndrome (associated with hemifacial atrophy, more common in girls), Senior Loken syndrome (a ciliopathy), facioscapulohumeral muscular dystrophy, and other rare muscular dystrophies.

> **'The tumors are the source of the exudation, so the tumors need to be treated, not the retinal detachment.'**
>
> —Yoshihiro Yonekawa, MD

For Coats' or Coats'-like exudative retinal detachment, the goal is also to treat the source of the exudation. In this case, it's from incompetent retinal vasculature that needs to be ablated with laser. To aid the reattachment of severe detachments, the fluid can be externally drained (don't forget the anterior chamber infusion) and fluorescein-guided laser can be subsequently applied.

If the drainage is not sufficient, a careful vitrectomy (although the vitreous is collapsed in these bullous detachments) may be performed after confirming that the pars plana is actually available. The last thing you want to do is to create an iatrogenic retinal break from the trocar insertion, which creates a whole new set of problems.

The vitrectomy is not to remove the vitreous, though; it's to instill perfluoro-N-octane (PFO) to squeegee out the remaining subretinal fluid externally through the sclerotomy and to apply endolaser to the vascular lesions. The lens may need to be sacrificed if the retina is too bullous to enter through the pars plana, in which case limbal incisions will be needed.

Audina Berrocal: Bilateral bullous detachment in a child sounds like an exudative process. The most important thing is to understand the cause of the exudative bullous detachment and then treat appropriately.

In an unusual presentation like this, it is important to always think of the possibility of retinoblastoma and non-accidental trauma. If either is suspected, there are specific steps to take.

Antonio Capone: Whether I would consider pars plana vitrectomy would depend on the findings at the time of EUA, ie, the decision would be driven by the pathology. If a scleral buckle were used, I usually would hope to transect at 3 to 6 months post-placement.

> **'Bilateral bullous detachment in a child sounds like an exudative process.'**
>
> —Audina M. Berrocal, MD

A 15-year-old male presents with a GRT with associated macula-involving retinal detachment after being poked in the eye playing basketball. On exam, his other eye has extensive lattice degeneration.

How would you repair the eye with the GRT?

Yoshihiro Yonekawa: It depends. If the GRT is relatively confined and shallow, I would fix it with a buckle in this pediatric patient. (I would perform a vitrectomy in an adult.) If the GRT is bullous, flapped over, or extending too posteriorly, I would perform a vitrectomy, remove the anterior leaflet, flatten the retina with PFO, and tamponade with long-acting gas or silicone oil. Gas has higher surface tension, so it is preferred if the patient can position, but oil is commonly needed for children.

However, there are 2 issues. First, kids often cannot reliably position; and second, the hyaloid is sticky and cannot be reliably separated satisfactorily and may cause insufficient tamponade and PVR formation, leading to redetachment.

Concurrent buckles can mitigate these effects, but the downside, as we all know, is slippage. A low-lying buckle to accompany the vitrectomy is a nice compromise, especially if either end of the GRT is in the inferior quadrants.

Audina Berrocal: The eye with the GRT would be treated with a vitrectomy with gas vs oil. If the detachment was old and the edge of the tear stiff, I would do a direct perfluorocarbon-oil exchange. If it was a recent detachment, the retina was mobile, and the separation of the hyaloid was complete, I would use a long-lasting expansile gas tamponade.

Antonio Capone: For this eye, scleral buckle with vitrectomy and silicone oil is my go-to procedure. A simple GRT would not necessarily

require a buckle, but the trauma and likely increased risk of PVR are the decision drivers.

Would your choice of surgical repair be different if this were a giant dialysis rather than a GRT?

Yoshihiro Yonekawa: Primary scleral buckling is fantastic for dialysis-related retinal detachment. By definition, the hyaloid is attached, and the very anterior break is easily supported by most buckling elements. Even for "giant" dialysis breaks, my go-to technique is the scleral buckle.

Audina Berrocal: For a dialysis detachment, I would probably do a scleral buckle with external drainage and cryotherapy with or without indirect laser. My experience with dialysis detachments, whether fresh or old, is that a buckle is the best option. In many of these children, the vitreous is formed, and a buckle is all that is needed.

Antonio Capone: Dialyses are effectively managed with a scleral buckle, and doing a vitrectomy tips the case management in those eyes toward giant-tear territory, with slippage issues, etc. The more this case looked like a garden-variety dialysis—despite the traumatic etiology—the more likely a buckle. The more unusual, the more likely a combined buckle-vitrectomy with a good chance of silicone oil as well.

Would you prophylactically treat the other eye?

Yoshihiro Yonekawa: Prospective studies have not evaluated this question, but several high-quality retrospective studies[2,3] have shown that prophylactic treatment of fellow eyes of GRTs decreases the risk for detachment—and if they do occur, the possibility of macula-involving detachment is less likely.

The studies mostly examine spontaneous GRTs, but nevertheless, we have a physically active pediatric patient with extensive lattice degeneration asleep in front of us under general anesthesia—this is an opportune time to intervene to decrease the risk of future RD.

Audina Berrocal: This is when an honest, extensive discussion with the child and the parents is necessary. Many times, we are faced with families whose children have athletic dreams or children and parents who will not agree to stop playing contact sports. In these children, I would offer to do a prophylactic buckle with laser.

> **'My experience with dialysis detachments, whether fresh or old, is that a buckle is the best option.'**
>
> —Audina M. Berrocal, MD

Antonio Capone: You bet I would prophylactically treat the other eye. There are no guarantees that the right eye will behave properly postoperatively, ie, reattach in a single procedure with no PVR/redetachment. That alone is reason to protect the companion eye.

No details were provided on the severity of the trauma. If he detached with trivial trauma, he might have undiagnosed Stickler syndrome or Marfan syndrome. The downside to laser treatment is minimal.

A 10-year-old boy with suspected Marfan syndrome presents for a second opinion. His right eye underwent scleral buckling for a detachment 1 month ago. His left eye has extensive untreated lattice. On exam, his right eye has a segmental scleral buckle from 10 o'clock to 12 o'clock. There is persistent detachment with an open hole at 9 o'clock and an early starfold posteriorly.

How would you treat this patient's right eye, and what is your rationale?

Yoshihiro Yonekawa: Buckles can fail for various reasons, but here it appears that the buckle missed the pathologic break by a clock hour. There are 2 options in this case: buckle revision or vitrectomy.

Buckle revisions are challenging for many reasons, especially if you are not the surgeon who placed the original buckle. The buckle misplacement is the main reason for the persistent retinal detachment though, so my initial recommendation would be to revise the buckle and properly support the break. I would discuss this with the original surgeon and see if he or she would prefer to do the revision surgery. If not, I would do it myself.

For several reasons, vitrectomy is best avoided, if possible, in 10-year-olds with RRDs. Positioning will not be reliable and the hyaloid will be very difficult to completely remove, which creates a downward spiral of PVR formation, and subsequent surgeries will likely require retinectomies, oil, etc. It's best if you can fix the eye without entering it.

However, the patient has early PVR. (Unlike in this patient's case, pediatric detachments usually present with subretinal PVR, which tends to be less contractile.) That doesn't concern me very much, as the retina will still attach nicely in pediatric eyes with a properly placed buckle, despite early PVR.

Even if the buckle revision fails, you would not lose much with a failed buckle—but you would lose lots of ground in terms of the PVR life cycle with failed pediatric vitrectomies. A vitrectomy would be, without question, the choice here if he were an adult patient—but pediatric eyes do infinitely better with properly placed buckles.

Audina Berrocal: I would do a vitrectomy in the right eye, stain the vitreous, make sure the hyaloid was elevated, then peel around the area of the starfold, releasing as much traction as possible, hoping it would flatten. I would laser and use silicone oil due to the patient's age and pathology. I believe buckle revisions in eyes with thin sclerae are difficult and risky to perform.

Antonio Capone: I would treat the patient's right eye. The child's eye will continue growing—the knot of PVR obviously will not. So, as the eye grows, there will probably be additional traction on the retina and a likelihood that the detachment will progress. That aside, eyes with partial RDs are potentially unstable. Add that to the underlying syndromic status of the child, and there's no compelling reason *not* to treat the right eye.

But how to treat the right eye depends on how big the detachment is. As I would do in an adult, if it's a small, localized detachment and everything else looks good, I'd consider laser-barricading the detachment. The more extensive the collection of subretinal fluid, the more likely I'd be to take him back to the OR. Then the question would be whether to do a vitrectomy alone, or revise the scleral buckle to completely encircle the eye as well.

Continued on page 57

Pravin U. Dugel, MD
Section Editor

PART 2 IN A SERIES

How Will Cell Therapy Be Integrated With Other Treatment Technologies?

We are on the verge of a new dimension of complementary and complex therapeutics. Part 1 of our cell therapy series (available at asrs.org/retina-times-cell-1) discussed the basics of cell therapy. In part 2, we discuss where cell therapy may fit in retinal diseases—specifically how it may interact with other technologies, such as gene therapy. As Steven Schwartz, MD, observes below, what was science fiction is now simply science!

Panelists

Allen C. Ho, MD
Attending Surgeon and
Director of Retina Research
Wills Eye Hospital
Professor of Ophthalmology
Thomas Jefferson University
Mid Atlantic Retina
Philadelphia, Pennsylvania

Steven D. Schwartz, MD
Ahmanson Professor
of Ophthalmology
Retina Division Chief
Stein Eye Institute
Department of
Ophthalmology
David Geffen School
of Medicine at UCLA
Los Angeles, California

Mark S. Humayun, MD, PhD
Cornelius J. Pings Chair
in Biomedical Sciences
Professor of Ophthalmology,
Biomedical Engineering,
and Integrative
Anatomical Sciences
Director, USC Ginsburg
Institute for Biomedical
Therapeutics
Co-Director, USC Roski
Eye Institute
Keck School of Medicine
University of
Southern California
Los Angeles, California

Pravin Dugel: We've talked about the cell types and how they work. Allen, let me ask you about the diseases themselves. So far, the trials we have seen have been on geographic atrophy (GA) and retinitis pigmentosa (RP). Is that appropriate? If a cell therapy treatment works in one, can we assume it may work in the other? In what diseases may we be trying this? What are your thoughts about the target diseases for cell therapy?

Allen Ho: I'll take the easy aspect of your question first. Just because it a certain cell therapy treatment works in one disease—let's say a retinal degeneration—does not mean it's going to apply to a disease like atrophic age-related macular degeneration (AMD). We think about AMD and GA as one bucket of aging in the macula, when it's much more nuanced than that.

We can attempt to tackle this problem based on size of GA, by genetics, or by complement mutation. These very different strategies are a reflection of our rudimentary understanding of the disease process of an aging macula. We can think about GA in terms of size and what strategy may be suited to address this issue.

A larger area of macular GA may be more amenable to repair with Mark Humayun's subretinal human RPE cell monolayer on a biosynthetic patch graft. On the other hand, smaller areas of GA might be addressed by a simpler subretinal delivery of an RPE cell fluid suspension. In essence, we have become transplant surgeons because cell replacement strategies are pursued in clinical trials.

Perhaps progress in GA will begin in eyes with larger GA where the most technical surgical transplant maneuvers are required to place a subretinal RPE patch graft. Anatomically, the RPE patch graft recreates the subretinal environment more accurately than an RPE cell suspension in fluid. Transplanting RPE cell suspensions in fluid can be complicated by epiretinal membrane formation when performed via a retinotomy, so we have designed surgical techniques and new devices to limit these complications.

Choosing the appropriate RPE cell lines for safety, efficacy, and manufacturing considerations is important. Perhaps complement inhibition could act synergistically with cell therapy strategies. We are in an age of immunotherapy, and complement inhibition may be relevant as a monotherapy or combination therapy with cell strategies.

'In essence, we have become transplant surgeons ...'

—Allen C. Ho, MD

'Just because a certain cell therapy treatment works in one disease—let's say a retinal degeneration—does not mean it's going to apply to a disease like atrophic AMD.'

—Allen C. Ho, MD

We're talking about transplanting RPE cells in atrophic AMD. In retinal degenerations, a variety of genetic conditions affect neurosensory retinal cells and photoreceptors. Photoreceptor transplantation might be amenable to a patch graft-type procedure with subretinal insertion of monolayer photoreceptor elements.

Administering adjunctive growth factors may or may not be necessary to bridge neural connections with transplanted photoreceptors. Experience with autologous full-thickness retinal transplant grafts in eyes with large macular holes suggests that full-thickness retinal transplants may survive and develop connections to neighboring host retinal cells. This is the transplant (cell replacement approach) to a retinal degeneration, but there is also a cell trophic factor approach whereby cells therapies are hypothesized to benefit host cells by a paracrine effect or by cell-to-cell interactions. Positive cell-therapy trophic effects been observed in animal models of retinal degeneration but have yet to be proven for a human retinal degeneration.

Again, because one cell therapy treatment works for one condition doesn't mean it's going to work for another, and for complex problems, I see different solutions. As cell therapy strategies evolve for retinal disease, so will the retinal transplant surgeon.

Pravin Dugel: So, Steve, Allen sees this in a very sophisticated, nuanced way. Is that the way to see it, or is there a final common pathway and it doesn't matter what caused a patient's cells to be gone; we can replace them with good cells? Are we going to have a therapy where ultimately, it doesn't matter how you got to GA or RP—if the cells are gone, we've got great cells to replace them?

Steve Schwartz: It's interesting you asked about common pathways, Pravin. Allen makes great points, and I agree with him—especially on the point that we are becoming transplant surgeons. If you think about transplant surgeons, they are replacing organs that are pathophysiologically destroyed for a variety of reasons, and function can be surgically restored with new, transplanted tissue.

So, if your kidney function is gone for whatever reason, or heart function is lost, surgical replacement is possible, depending on organ availability. Are nuanced approaches to transplant protocols unique to variables such as underlying disease state, severity, and comorbidity? Absolutely. But I think Allen's point about retina potentially becoming a transplant subspecialty is exactly right, and that's what we're driving toward.

Proof of concept is here. The next step is refining approaches, techniques, and indications toward outcomes that make sense for society from a regulatory perspective, and for patients on an individual basis.

For our current project at the Stein Eye Institute, and the Broad Stem Cell Research Center at UCLA, we're looking at autologous induced pluripotential stem cell (AiPSC)-derived RPE to treat the final common pathway in a variety of maculopathies, including but not limited to age-related GA. But there are a whole host of other maculopathies in which the RPE is lost as the first insult, followed by loss of the photoreceptors and choriocapillaris.

We don't know the answers yet. It may well be that Allen's prediction is right, that each condition is going to require its own treatment. He may also be right that we're becoming transplant surgeons and will be replacing tissue with varying success rates across different conditions and stages of disease—each with its own approach and prognosis, or "dose" patients with autologous RPE, giving them an extra decade or 2 of macular function, regardless of the underlying condition. This may require a patch graft with a parylene membrane or only a micro subretinal injection of RPE suspension.

We foresee an age in which drug delivery through gene therapy—long-term protein delivery with steady-state pharmacokinetics—is going to change the world. If some smart person comes up with 1 or 2 proteins, whether complement inhibitors or something else, that treat dry AMD or GA, you can bet these proteins are going to get delivered through gene therapies, and those are going to come fast and furious if somebody proves the concept. We've all seen the subretinal and intravitreal gene therapy approaches to wet AMD demonstrate stunning results in early trials.

'We foresee an age in which drug delivery through gene therapy—long-term protein delivery with steady-state pharmacokinetics—is going to change the world.'

—Steven D. Schwartz, MD

Similarly, these proteins may be delivered very efficiently through the RPE that we are transplanting. If the RPE is treated ex vivo, or in the lab prior to transplant, the therapeutic RPE may both deliver a therapeutic protein or a naturally occurring protein at a therapeutic level, and provide enhanced RPE functionality.

Remember that compared to photoreceptors, RPE is the low-hanging fruit in the transplant world for the retina and the macula. RPE is the easier, first transplant target because it does not have integrated synaptic connections and because RPE can be grown at scale.

'RPE is the low-hanging fruit in the transplant world for the retina and the macula.'

—Steven D. Schwartz, MD

While RPE transplants do face challenges such as forming functional tight junctions, a polarized monolayer, and a host of other anatomic and functional criteria, they are still far less complex to grow and transplant than photoreceptors.

However, when we move up to the photoreceptors and we're asking the cells to not only do all of the above, but also to integrate synaptically, I believe the complexity and difficulty increase by an order of magnitude. With relatively delicate photoreceptor cells involved in complex, incompletely understood neural integration, photochemical signaling, sensing photons, and signaling with chemical connections, the probability of successful transplantation approaches seems more challenging.

So I would say we're in the early days. There are lots of potential outcomes. Gene therapy is going to play a role, whether it's in these regeneratively transplanted tissues or through viral vectors, and whether it's a final common pathway approach or creating a biofactory for therapeutic proteins.

We are becoming transplant surgeons, and most of us are going after the easiest transplant with the greatest impact and the highest probability of success, which is the RPE. We've

learned just how tough and complicated this approach has been over the last 7 or 8 years. Yet tangible progress is observed.

As a positive, from my perspective on the Audacious Goals Initiative Regenerative Medicine Advisory Board at the National Eye Institute (NEI), the projects funded by the NEI are absolutely gorgeous science and biology that are knock-your-socks-off promising, and the basic science coming down the road for translation is extremely exciting. It's beyond the scope of this discussion, but the groups working around the country and collaborating across interdisciplinary boundaries are just astounding. It makes me so optimistic.

Pravin Dugel: Thanks, Steve. So, Mark, we've talked a lot about how cell therapy may integrate with gene therapy. Describe how that may happen. How will cell therapy and specifically, what you potentially have with patch therapy— integrate with gene therapy? How would one work with the other?

Mark Humayun: This is a tough question. *Current gene therapy* is aimed at fixing a genetic defect or overexpressing a protein—it's not focused on trying to replace, for example, the RPE in geographic atrophy.

If I were to hypothesize and go out on a limb, I suppose you could genetically modify the RPE cells you are injecting, either in a suspension or in the sheet, to be more robust or potentially survive longer or secrete more beneficial growth factors. This is blue-sky thinking.

Another way to combine the 2 approaches is that one can fix a photoreceptor defect through gene therapy and then address the concomitant RPE problem through an RPE transplant and, in doing so, address both the photoreceptors and RPE pathologies. But the regulatory hurdle becomes quite challenging when you're combining gene therapy with cell-based therapy, whether you're doing it in one step with one product or you're doing it sequentially.

So it's very interesting to think about the various technologies we have in our toolbox such as gene therapy and cell therapy. Connecting these different technologies and approaches as I'm trying to do here is challenging. Let's see what Steve Schwartz and Allen Ho have to say.

Pravin Dugel: Blue-sky a little bit—and I do want to hear from Steve and Allen. From a simplistic point of view, gene therapy changes a pathway by suppression or by overexpression, whereas cell therapy replaces the cells. So, in my simplistic way of thinking, you can certainly change the pathway of a disease, and then you can replace whatever cells you need to replace with cell therapy. I've always thought of the two as complementary.

Allen, what do you think, in terms of the potential complementary roles of gene and cell therapy?

> 'The regulatory hurdle becomes quite challenging when you're combining gene therapy with cell-based therapy ...'
>
> —Mark S. Humayun, MD, PhD

Allen Ho: It is kind of playing connect the dots, and we look to innovation and sometimes chance for things to come together. Mark Humayun described genetically modifying cells that we will be transplanting for whatever condition as one way to fuse the technologies. I think this is an interesting concept.

Many think of gene therapy as a gene replacement for a disease that is caused by a genetic mutation. Gene therapy for an inherited retinal degeneration (IRD), Leber congenital amaurosis (*RPE65* mutation), is the best example. We can think about gene therapy as insertion of a gene that gets expressed in a diseased tissue to produce a therapeutic protein, as is the strategy for the gene therapy companies like Adverum Biotechnologies, Regenxbio, and others looking to attack wet AMD by creating the body's own biofactory with gene therapy.

But you alluded to another way gene therapy can work—it's a way to knock down a genetic problem that, for example, is causing a retinal degeneration. So, there are rhodopsin-based IRDs produced by toxic rhodopsin that people are producing natively on the basis of a genetic mutation. The toxic rhodopsin, the photo chromophore, then causes destruction of the cell producing it.

Let's say you wanted to try to restore sight in someone who had completely lost vision from an IRD caused by a toxic metabolite. You could use gene therapy to knock down that toxic protein and simultaneously or sequentially do a cell therapy replacement. If you replaced neurosensory retina, underlying RPE, or a combination of both, that might be attacked by the surrounding tissue producing toxic metabolites—but if you combined the 2 technologies, maybe you'd get a better chance of your transplant's survival. This thinking is way out there, but you can envision these kinds of strategies because these tools have such promise.

Pravin Dugel: They certainly do. Steve, what do you think?

Steven Schwartz: Mark Humayun makes a strong point—the regulatory pathway is long. You guys described gene therapy extremely well; it's really good for providing a protein, like RPE65, that's necessary but is either absent or not functional. Or gene therapy is potentially really good for creating a therapeutic biofactory inside the eye—for example, a VEGF inhibitor.

If you could produce aflibercept locally in the eye and keep it a steady-state level through an intravitreal injection or a subretinal surgery, that might be spectacular, right? And we'll see whether or not you need subretinal surgery or if an intravitreal injection might suffice.

> 'Gene therapy changes a pathway by suppression or by overexpression, whereas cell therapy replaces the cells.'
>
> —Pravin U. Dugel, MD

Another fascinating possibility is whether we can replace the chromophores, as Allen Ho mentioned. For example, there's been a lot of discussion—we talked about this years ago at Avalanche Biotechnologies (now Adverum Technologies), and I'm sure it's going to come up again—color vision and all the rhodopsin and other opsin mutations, whether they are in RP or color blindness or achromatopsia. Those are all going to come, so I predict we're going to see a wave of gene therapy plays, strategies, and tactics that go after all sorts of protein replacements and long-term deliveries.

How do we envision gene therapy and regenerative medicine coming together? Imagine, for example, that protein survival factors or regeneration factors, immune-cloaking factors are discovered to be potentially safe and effective. Discrete overexpression of such a factor might increase the safety and efficacy of transplanted tissue.

Achieving the goal of improving transplant survival, safety, and/or efficacy by pretreating transplant with a gene therapy that drives expression, production, or secretion of advantageous proteins might make sense. Similarly, using CRISPR-type genetic manipulation technology on autologous tissue before it is transplanted might improve outcomes. I predict these strategies will be brought forward and explored in the near future.

There is no question that this is really complex—from a scientific, business, and regulatory perspective. The Food and Drug Administration (FDA) has been great; the branch responsible for cell and gene therapy has been really supportive. They have good, helpful scientists, and I think these projects are possible from a regulatory perspective.

As is true with the rest of our lives, what was once science fiction is now science. The question is, can we manage the ethical, moral, and social issues that come with this type of biotechnology? As always, with scientific progress comes more questions than answers. It's coming.

Pravin Dugel: That's great. In the next part of our series, I'd like to go into the actual delivery of the system. I think we had a really nice discussion regarding the overall picture of what cells are, how they work, as well as what diseases and what other technology may complement cell therapy. It's a really complex topic, but you guys did a fantastic job describing it. Thank you so much.

'What was once science fiction is now science.'

—Steven D. Schwartz, MD

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Jason Hsu, MD
Section Editor

Mitchell S. Fineman, MD
Section Editor

Managing Diabetic Traction Retinal Detachments: The Inside Scoop

Staring at the dreaded wolf's-jaw configuration of an advanced diabetic traction retinal detachment (TRD) is a daunting experience at any career stage. TRDs are some of the most complicated surgical cases we face, testing our every skill. They can be time consuming and pose many challenging variables, from determining how to attack the case to managing patient expectations.

Despite these concerns, it is precisely these types of cases that led many of us to surgical retina. We were drawn to the creativity involved in planning a surgical approach and the opportunity to save vision in these desperate, often younger patients. While no 2 TRD cases are the same, there are many useful tips and tricks, as well as recent technological advances that have improved our ability to manage these cases successfully.

Preoperative considerations

1. **No matter how good a job we do in the operating room (OR), we must do an even better job of educating our patients.** Be sure they understand the importance of controlling their diabetes and associated comorbidities.
2. **A single antivascular endothelial growth factor (anti-VEGF) injection a few days prior to surgery is the one thing that can really improve the efficiency of a diabetic TRD case.** While many have suggested various time ranges, an injection given about 1 to 5 days prior to surgery works well. The timing often depends on how concerned one is about "crunch" or worsening the TRD via contraction of the neovascularization (NV).

   With the advent of anti-VEGF, the idea of delaying surgery in order to get panretinal photocoagulation (PRP) on board preoperatively to quiet down the neovascular vessels is less relevant. By regressing the NV, it is much easier to dissect the membranes and sometimes gently lift them off of the retinal surface with less associated hemorrhaging.
3. **Make sure the patient is medically cleared to proceed with vitrectomy surgery prior to proceeding with a preoperative anti-VEGF injection.** This is especially important if there are multiple broad, active, and less fibrotic neovascular fronds, as these are the ones at highest risk of "crunch." It is never a good situation to have the TRD dramatically worsen after an anti-VEGF injection and not be able to proceed with the surgery due to lack of medical clearance.
4. **Consider whether to perform surgery under local vs general anesthesia.** Particularly for younger patients, the thought of being awake during surgery can lead to severe anxiety. In addition, TRDs tend to be the longest cases we do. Trying to rush through a case like this due to a restless patient may lead to a poorer outcome. On the flip side, it's important to consider a patient's multiple comorbidities that could increase the risk of general anesthesia.
5. **Be cognizant of any anticoagulants or antiplatelet medications the patient is taking.** Consult with the patient's primary care physician or cardiologist to see whether it is safe to discontinue these medications temporarily prior to surgery. While these patients often have an underlying coagulopathy, anything that can be done to reduce risk of more hemorrhage is worthwhile.
6. **Managing expectations from the start is critical.** For most of these severe cases, the prognosis is very guarded and there is a long recovery period—sometimes months. Patients need to know this ahead of time so there are no postoperative surprises and unrealistic expectations.

27-gauge and hybrid vitrectomy offer new options

One of the most significant advances in TRD repair is 27-gauge vitrectomy—but it involves a learning curve. The small cutter allows the surgeon to wiggle the instrument between fairly tight adhesions to segment and delaminate the fibrotic membranes. With the decreased "sphere of influence," there is less risk of iatrogenic retinal breaks.

> 'A single anti-VEGF injection a few days prior to surgery is the one thing that can really improve the efficiency of a diabetic TRD case.'

Increased precision is necessary when using a 27-gauge cutter, as the vitreous gel will not come to the cutter as readily as it does with larger-gauge systems. The flexibility of the thinner instruments also requires an adjustment in surgical technique. Learning to pivot around the cannulas, almost like oars in an oar lock, is an effective strategy to avoid bent instruments and frustrated surgeons.

Hybrid vitrectomy gives us the best of all worlds (Figure 1). One option is to open a 27-gauge vitrectomy pack and 25- or 23-gauge valved

cannulas separately. (Alternatively, a 27-gauge cutter often can be opened separately and used with a 25- or 23-gauge vitrectomy pack.)

Place the 27-gauge cannula inferotemporally for the infusion and the 25- or 23-gauge cannulas superonasally and superotemporally. Note that the 27-gauge infusion will stay in a 25-gauge cannula, but tends to slip out of a 23-gauge cannula, so another option would be to use all 25-gauge cannulas, particularly if you plan to use 25-gauge instruments and wish to be able to place them into any port.

Position your superior cannulas more horizontally (3 o'clock and 9 o'clock); this improves your ability to approach the membranes along both the inferotemporal and superotemporal arcades. Don't hesitate to move the infusion line to the superotemporal port and use the inferotemporal cannula to get a better angle to dissect the membranes when needed.

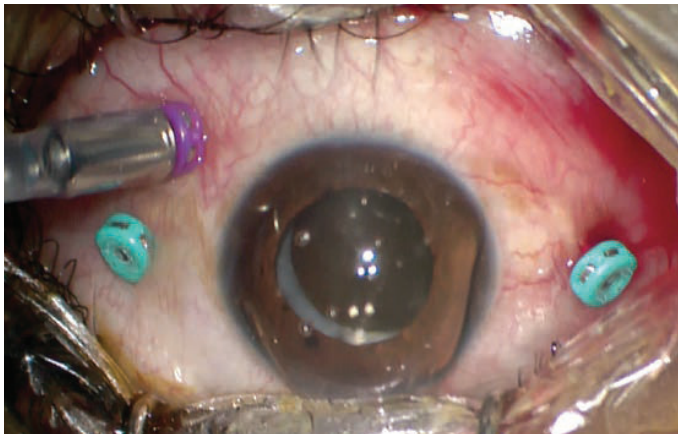


Figure 1. Hybrid vitrectomy. The purple 27-gauge cannula and infusion are placed inferotemporally (top left), whereas the blue 25-gauge cannulas are placed horizontally.

> 'Learning to pivot around the cannulas, almost like oars in an oar lock, is an effective strategy to avoid bent instruments and frustrated surgeons.'

With hybrid vitrectomy, you can use a whole host of larger, stiffer instruments that may not be available in 27-gauge, such as pneumatic scissors. Also, a larger extrusion cannula can be used to help wash out any hemorrhage more efficiently than the 27-gauge cutter. Silicone oil injection is also easier through a larger-diameter cannula.

Intraoperative considerations

How to tackle the actual TRD depends on multiple factors; no single approach is best for all cases. Here are some guidelines:

1. **If the peripheral hyaloid is already detached, consider relieving the anteroposterior traction first** by finding the plane of the hyaloid and cutting across it just anterior to the TRD for 360 degrees (Figure 2). You then have the option of moving from the outside of the TRD inward toward the disc, segmenting and delaminating along the way.

2. **If the peripheral hyaloid is still generally attached, take a deep breath**—this is likely going to be a trying case. Consider an inward-out approach, similar to how we induce a posterior vitreous detachment. We don't start cutting in the periphery until we lift the hyaloid.

   Often there is an opening in the premacular bursa that allows you to start segmenting around the disc and along the vascular arcades. Once these areas are released, you can often start lifting up the peripheral hyaloid and extending the dissection toward the periphery.

3. **Do not be overly aggressive when trying to use vacuum alone to elevate the hyaloid.** In these cases, neovascular tufts will often anchor the hyaloid to the retina and lead to retinal breaks if too much traction is applied. Using the cutter as a pick or probe may help to lift and delaminate more gently. By keeping your foot off the pedal (no vacuum or cutting), the cutter can be very effective in identifying the best openings in the membranes or around the tufts (Figure 3, page 50).

4. **When possible, consider cutting around any disc neovascularization rather than lifting it off the nerve (Figure 4, page 50).** Even with preoperative anti-VEGF, the base of the NV tends to ooze in these situations. Because of the location on the optic nerve, the usual applications of cautery or laser to stop the hemorrhaging are limited. If you segment around the disc and there is hemorrhage from the edge of the fibrovascular tissue, careful diathermy applied at a lower than normal intensity to these areas is often effective in stopping the bleeding.

   Always proceed with caution and try to avoid any spillover diathermy onto the nerve or peripapillary retina. Nevertheless, there will be times where the membranes are so adherent to the retina that the only place to start the dissection is to pull the fibrotic NV off the disc and expand outward.

5. **When using the 27-gauge cutter to segment, always make sure the port is visible as you are cutting through the membrane (Figure 5, page 51).** If the instrument is in the right

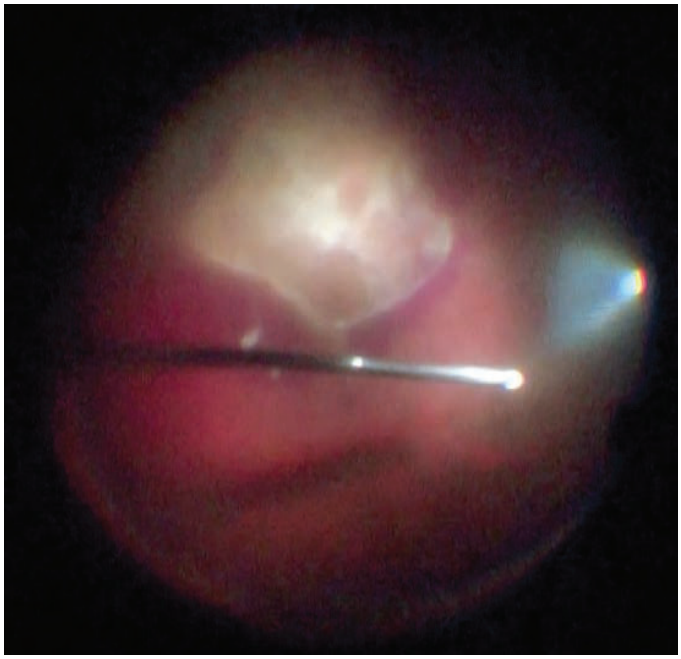


Figure 2. Releasing antero-posterior vitreous traction with the 27-gauge cutter. The cutter is staying in the plane of the posterior hyaloid. The edge of the hyaloid can be seen as a more opacified area adjacent to the light pipe. Note the broad fibrovascular tissue covering the macula and optic nerve as well as the subhyaloid hemorrhage peripherally.

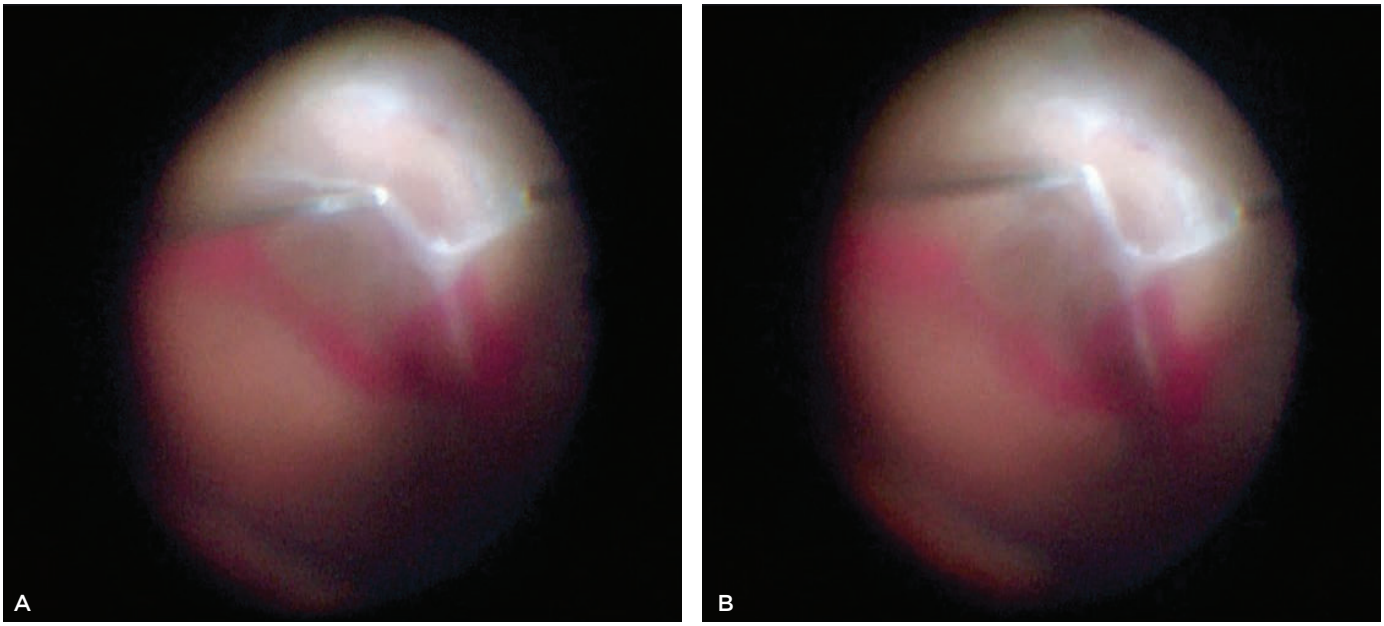


Figure 3. Using the cutter as a pick with the cutting and vacuum completely off. The cutter is (A) wiggled between the membrane and retina and (B) lifted to identify areas of firmer adhesion and gently lyse weaker adhesions.

plane, relatively low vacuum and even high cut speed will allow you to advance quite easily. A slight up-and-down motion can sometimes help facilitate the segmentation, as it keeps the cutter in the appropriate plane as the dissection proceeds.

Remember, don't push too deep, as you don't want to inadvertently enter the plane of the retina. If you run into an area of firm adhesion, try coming off the pedal and probing around the area with the cutter to find the best opening.

6. **If you have trouble getting across one side of a membrane, keep probing around the edges and even try the other side of the membrane.** Most times, once you find a good pathway through the membrane, the segmentation and eventual delamination proceeds well.

7. **It is also okay to leave stumps as long as you have relieved all traction.** Trying to remove every last piece of a membrane can spell trouble, as the neovascular fronds can then ooze and there is a higher risk of iatrogenic breaks. Remember the saying, "Perfect is the enemy of good."

8. **Placing a chandelier so you can use bimanual techniques is always a good option (Figure 6).** Why operate with one hand behind your back? With the advent of 27-gauge cutters, a bimanual technique may not be necessary as often. However, using a forceps and scissors is a tried-and-true combination that can successfully and efficiently delaminate and segment tissue, particularly when confronted with very broad, adherent membranes.

   Gently wiggling the tip of the closed scissors between the membrane and retina, then opening the scissors to create space generally works well. When delaminating with scissors, try to lift the membrane upward slightly from the retina before closing the scissors. The space created by performing this maneuver decreases the likelihood of iatrogenic retinal injury and hemorrhaging. If you have a chance, try pneumatic scissors, which provide a very stable platform.

9. **Controlling hemorrhage is important for visualization.** Use diathermy or laser to stop bleeds early when possible. When using laser as a means to control bleeding, adjust the laser settings to a lower power and longer duration than typically used for retinal laser treatment.

   Often, setting the laser duration to "continuous" can be effective in titrating the appropriate amount of treatment to achieve hemostasis. Lowering the intraocular pressure (IOP) at the end of the case can help spot any oozing. On the flip side, be careful about staying on tamponade pressure for extended periods of time; the

'Trying to remove every last piece of a membrane can spell trouble ...'

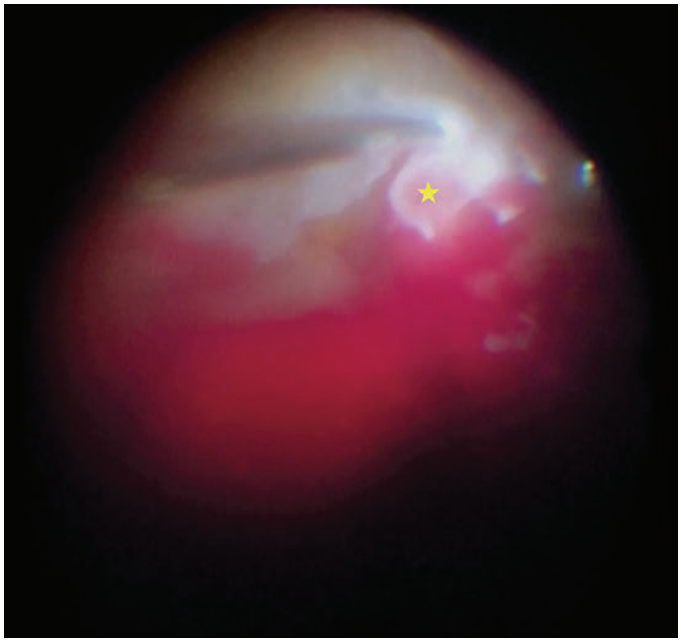


Figure 4. Segmenting around the optic disc (star) rather than lifting the membrane off the disc. In some cases, this can help decrease hemorrhaging which occurs when neovascularization of the disc (NVD) is avulsed from the nerve. If there is hemorrhaging from the edges of the residual NVD, it can often be stopped with cautious, gentle diathermy.

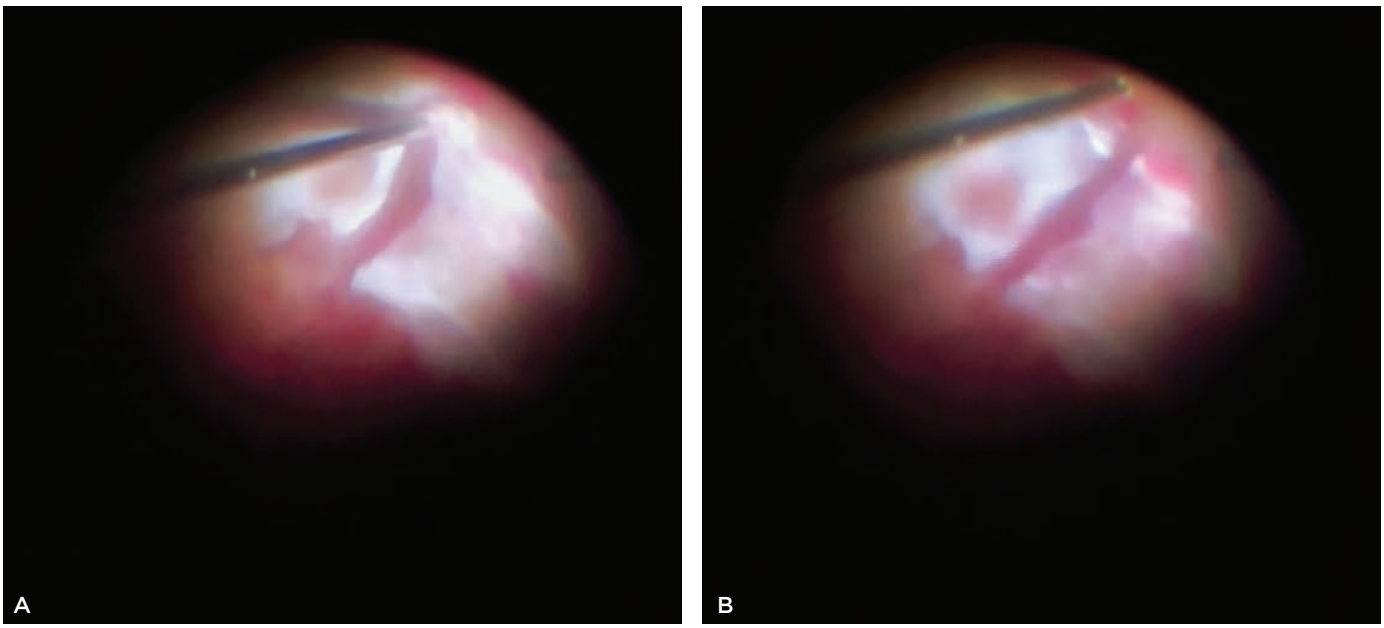


Figure 5. Segmenting fibrovascular membranes with a 27-gauge cutter. The port of the cutter is pointed away from the retina and engages the membrane with a gentle up (A) and down motion to keep the port in the plane of the membrane and create space to bisect the tissue (B).

high IOP can quickly lead to worsening ischemia as these eyes are, in general, already severely ischemic.

10. **Maintaining a clear cornea and lens is vital for an optimal surgical outcome.** For these long cases, we prefer using a hyperosmotic viscoelastic (eg, VISCOAT, Alcon Laboratories, Inc or OcuCoat, Bausch+Lomb) on the corneal surface to keep it clear the whole time. For phakic eyes, don't forget to tell your nurses to add dextrose to the balanced salt solution (BSS) bottle. If the intraocular lens (IOL) fogs under air, inject some viscoelastic onto the posterior surface of the IOL to improve visualization.

11. **Know when to stop operating.** The biggest question we often struggle with is, when have I done enough? Focus on all membranes around the macula first, as these are the most critical to segment and delaminate. Try to relieve all anteroposterior vitreous traction on the edges of any membranes.

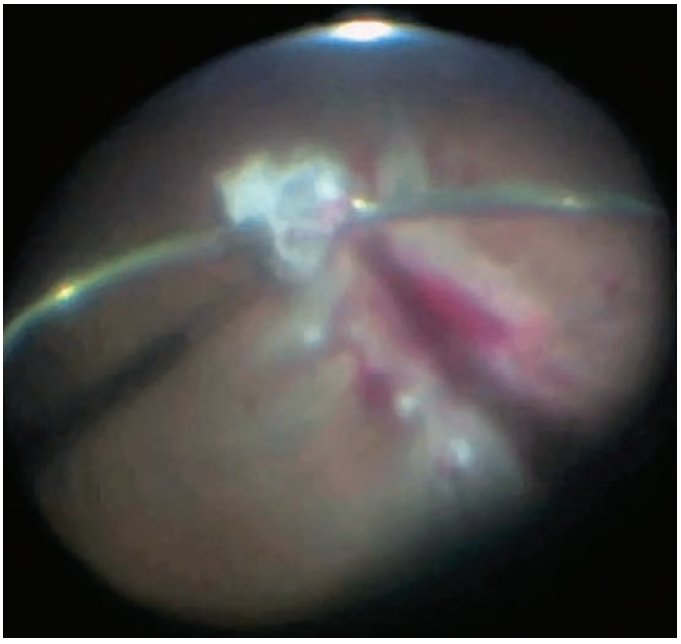


Figure 6. Pneumatic scissors (right hand) in combination with forceps (left hand) are being used to delaminate a thick fibrovascular membrane off the macula. The chandelier light, seen at the top of the image, enables bimanual manipulation.

> 'The biggest question we often struggle with is, when have I done enough?'

The best-case scenario is when the peripheral hyaloid is completely released up to the vitreous base for 360 degrees. If this is not possible, at least try to release it from the macular arcades. The downsides of leaving vitreous attached to fibrovascular proliferation are postoperative persistent TRD and recurrent vitreous hemorrhage.

12. **While silicone oil is often the go-to tamponade agent for these complex cases, consider the downsides.** If there is active hemorrhage postoperatively, the IOP can end up being very high due to the volume of the hemorrhage adding to that of the silicone oil, simulating an oil overfill. In addition, any hemorrhage trapped between oil and the retina may lead to formation of another membrane.

    On the flip side, this complication generally does not occur if gas tamponade is used. Often, it may be more advantageous to go back to the OR to wash out any nonclearing VH in an eye that had a gas tamponade, rather than going back to remove oil and deal with reproliferation of membranes that occurred under the oil. Still, in a monocular patient with a complex TRD, tamponade with oil may be preferable to perfluoropropane (C3F8) to permit some functional vision for the patient.

Postoperative considerations

1. **Dealing with postoperative vitreous hemorrhage is more an art than a science.** Frequently, patients will have some

Continued on page 63

Allen Z. Verne, MD
Section Editor
Co-founder, ASRS

Foreseeing the Future of Retina: What Will the Next 50 Years Bring?

What's past is prologue is a well-known Shakespearean phrase. Connecting the dots from the past and extrapolating them into the future is a difficult, and often inaccurate, pastime. However, we will now try to do the seemingly impossible.

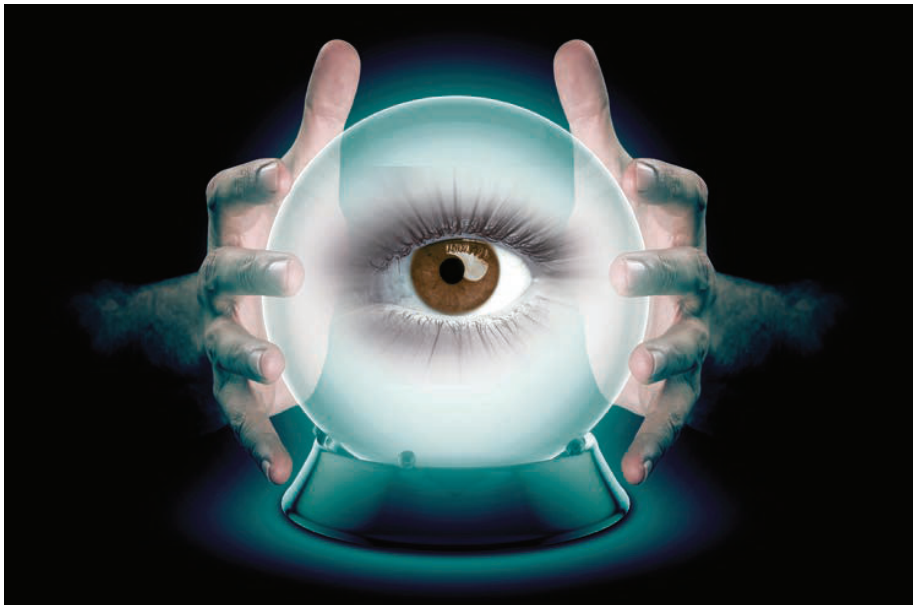
In my fall column (available at www.asrs.org/retina-times/game-changers), our 4 esteemed contributors outlined what they considered the most important changes in retina during the course of their careers.

Now these seers will consult their crystal balls, Ouija boards, and tarot cards and attempt to connect the dots from the past and forecast the exciting changes that will develop over the next 50 years.

We are already at the beginning of a major paradigm shift in how we approach our specialty. Surgery has become less important, with surgical treatments being usurped by pharmaceutical treatments. In the future, bio-cellular, computer-driven optical prostheses will connect directly to the occipital cortex, possibly eliminating the need for some of our current surgical and medical therapies.

Yes, we will still need to perform surgery for certain problems (eg, retinal detachment, trauma), but surgical treatments for many disease entities will fall away à la bloodletting, and will be replaced by medical therapies. Pharmaceuticals will become the mainstay of treatment for epiretinal membranes, age-related macular degeneration (AMD), tumors, vitreous hemorrhage, and diabetic retinopathy. Gene therapy and retinal pigment epithelium (RPE) transplantation will become commonplace. Training programs will evolve to meet these new paradigms.

Patients and doctors will spend less time in the operating room (OR). Today's typical OR procedures will be performed in the office—possibly at the slit lamp. New gases and vitreous replacements will expand the indications for pneumatic retinal reattachment to include inferior breaks as well as proliferative vitreoretinopathy (PVR) and traction detachments. More and more practitioners will become solely office based and will refer patients who need OR intervention to OR-based retina specialists.



The structure of our practices will also change. Much of eye care delivery will be performed by ophthalmic assistants, who will be able to do more (eg, injections). Telemedicine, computer management, and imaging will continue to play a bigger part in our practices.

> 'Today's typical OR procedures will be performed in the office—possibly at the slit lamp.'
>
> —Allen Z. Verne, MD

Of course, the government and insurance companies will be increasingly involved in how we deliver care. The "businessification" of medicine will continue to increase. The good news is that our specialty will be able to do more to treat our patients' previously untreatable problems.

Steve Charles, MD
Charles Retina Institute
Germantown, Tennessee

The last 50 years have brought the vitreoretinal community and our patients the incredible success of pars plana vitrectomy, anti-VEGF therapy, optical coherence tomography (OCT) imaging, laser photocoagulation, and angiography. Advances in surgical visualization and biotherapeutics will be the hallmarks of future breakthroughs.

Treating geographic atrophy secondary to dry AMD remains an extremely common—and growing—unmet clinical need. Hopefully, therapeutic targets in the alternative complement pathway will deliver a suppression therapy, albeit not curative nor able to reverse visual loss.

RPE replacement using induced pluripotent stem cell (iPSC)-derived RPE cells on a biodegradable scaffold will enable visual gains. It is likely that iPSC-derived photoreceptors and iPSC-derived 3-dimensional (3D) bioprinted choroid in a multilayer construct will be developed for highly functional outer-retinal replacement.

A more effective treatment for PVR remains an unmet clinical need; using wound-healing modulation instead of cytotoxic agents to treat PVR would be a great advance. Drug delivery in silicone oil-filled eyes is problematic. A nondegradable, biocompatible elastomeric retinal patch would obviate the need for retinopexy, gas, and silicone oil, and would facilitate drug delivery.

'Advances in surgical visualization and biotherapeutics will be the hallmarks of future breakthroughs.'

—Steve Charles, MD

Digital surgical visualization has been a recent and remarkable advance 75 years after the introduction of the operating microscope. Although the term *heads-up surgery* implies ergonomic benefit, the real benefit is better visualization—and we are seeing only the beginning. Artificial intelligence (AI), while crucial to improving refractive outcomes and data analytics, will not deliver major advances in visualization. The advances will come from photonics and optical systems design.

Harry W. Flynn Jr, MD
Professor of Ophthalmology
The J. Donald M. Gass Distinguished Chair in Ophthalmology
Bascom Palmer Eye Institute
UHealth—University of Miami Health System
Miami, Florida

Over the coming decades, innovations in technology will drive improvements in medical and surgical care of patients with vitreoretinal diseases. The improvements will be manifested through better prevention programs using novel imaging and population-screening techniques, and better treatment options through improved surgical approaches, newer drugs, and better medication-delivery systems.

In outpatient clinics, the combined use of telemedicine, AI, and machine learning will allow earlier and appropriate treatment of patients with vitreoretinal diseases. Telemedicine in eye care will be more established through cloud-based referral systems. Food and Drug Administration (FDA)-approved AI devices will allow early detection of diabetic retinopathy, resulting in earlier referrals to an ophthalmologist. In patients with AMD, AI and machine learning will predict disease progression and identify patients in need of early treatment.

In vitreoretinal surgery, wide-field OCT imaging techniques should provide real-time dynamic observation of vitreous and retinal pathology. Intraoperative OCT already has enabled surgeons to confidently achieve complete vitreous and ERM removal.

Even today, 3D viewing systems and heads-up displays offer improved depth perception and more precise membrane peeling. Robotic-assisted instrument control has proven its worth in other surgical fields, and future ophthalmic robotic surgery may allow more precision—potentially eliminating tremors and unwanted movements. Improved endoscopic technology may enable us to save vision for patients with the most-advanced diseases.

There is an unmet need for new vitreous substitutes. For decades, vitreoretinal surgeons have used silicone oil, long-acting gases, and perfluorocarbon liquids. Ongoing efforts to engineer biocompatible, biodegradable, optically clear vitreous substitutes are underway and, hopefully, will provide better postoperative retinal tamponade options. Various medications, such as intravitreal methotrexate, also may play an important role in reducing postoperative membrane proliferation.

'FDA-approved AI devices will allow early detection of diabetic retinopathy ...'

—Harry W. Flynn Jr, MD

The hot topic today is gene therapy for retinal diseases, and the future for this approach is promising.

The best example of a paradigm shift in vitreoretinal surgery is the story of macular hole surgery, which was once thought to be untreatable and incurable, and is now one of the most successful surgical procedures. Likewise, OCT at first was just an expensive laboratory toy; now OCT is an indispensable clinical tool. Let's keep an open mind to new procedures and new technologies as we move forward in the 21st century.

Kirk H. Packo, MD, FACS
Professor and Chairman
Department of Ophthalmology
Director, Retina Section
Rush University Medical Center
Illinois Retina Associates, SC
Chicago, Illinois

It is interesting how our specialty has evolved through various "eras," in both the office and the OR. Surgically, we have transitioned from the buckling era to the vitrectomy era. Instruments have evolved, getting smaller, faster, and more integrated. In the office, we've gone from the destructive-laser era to the pharmacologic.

Our mix of patients has changed, too, as those with diabetes and retinal detachments have become less frequent. On our surgical schedules, many medical conditions such as vein occlusions and neovascularization have been replaced by surface macular work such as membranes and holes.

During the past 50 years, so too has our world evolved from the analog era to the smart digital age. Consider what has happened to our phones and to our methods of accessing information. Books are being replaced by the internet. Using cell phones has become as critical as breathing air. All of medicine has gone digital, too, with the electronic health record and Digital Imaging and Communications in Medicine (DICOM) imaging revolution.

Digital imaging has now started in the OR. Our digital imaging systems will evolve just as have our smartphones. All surgeons will be using smart digital systems that not only elegantly integrate black ink and real-time imaging modalities, but also have many "smart app" additions that will enhance control of our instruments.

My feeling is that robotics will never become our standard, even 50 years from now. But robotic technology will spin off hybrid versions with "smart tools" that will control metrics such as depth, traction, cutting forces,

and tissue recognition. We drive cars now that give the driver vastly enhanced control and warnings; OR machines and imaging will do the same.

"Driverless cars" will, I'm sure, be common in the future. Will "surgeon-less surgeries" also be the norm? I think not. The main arguments against this will be the economy and the need for patient access to technology that is likely to dampen such expensive technologies. Still, the digital revolution in ophthalmology will continue to explode.

The 2 most evolutionary and revolutionary technologies that will define what we as retina specialists do are already here, but are still in their infancy: AI and gene therapy.

AI will have its quickest uptake in the office. It will not replace the human intelligence factor, but will enhance it enormously. The ability to interpret our family of imaging modalities with exquisite accuracy will be akin to the way flying aircraft has evolved. A pilot is always still needed, but changes in the acquisition, integration, and suggested plans of action now make flying much safer.

> 'The 2 most evolutionary and revolutionary technologies ... are already here, but are still in their infancy: AI and gene therapy.'
>
> —Kirk H. Packo, MD, FACS

Our ability to accurately diagnose and follow therapeutic responses will make the office not only more efficient, but infinitely more accurate. AI will have its place in the OR too, given its digital transformation. Instruments will see things a surgeon can't, keep instruments in the right position and plane, move them with the correct force, and actually learn how tissues change during the surgery.

Our instruments will learn how one surgeon's movements differ from another's and will adapt accordingly. It will be as if we were flying a Boeing 777 in the eye, with full control and safety—and it will be a thing of beauty.

Gene therapy is likely to be in full swing 50 years from now. So many retinal diseases, both rare and commonplace, have a definite genetic basis. The development of gene therapy for Leber congenital amaurosis with the *RPE65* mutation is akin to the invention of the printing press; it has opened up the floodgates for treating many other diseases. It is likely that most, if not all, of these therapies will need to be surgically delivered as well, radically altering our surgical diagnostic mix.

In the end, the ability to alter and correct genetic mistakes will be a defining technology for most of medicine. The greatest challenge 50 years from now will not be its scientific development, but rather how to pay for it. Luxturna (voretigene neparvovec-rzyl, Spark Therapeutics, Inc) costs over $800,000 for 2 eyes. If common diseases such as macular degeneration ultimately need such treatments, our out-of-control health care spending will jump logarithmically to an impossible-to-sustain level.

Pharmaceutical companies will finally have to balance better the high cost of these medications against the money in the payer bank. In the end, however, retina specialists will be making life-altering changes for millions of patients by altering the genetic blueprint.

What is likely to be gone in 50 years? The intravitreal injection bubble surely will have burst by then. Surgical implantation of various reservoirs and further development of longer-duration medications will be the bubble breaker. We will look back and laugh at how we lived through the circus of needles during the first part of the millennium. Although intravitreal injections will still be needed, their burdensome frequency is likely to plummet—and I can't wait.

Reflecting on my 35 years in practice as a retina specialist and surgeon, it is extraordinary to see how we have evolved. The next 50 years will be even more extraordinary. I envy the men and women just embarking on their retina careers who will be practicing in those future years. I wish I could be there to see it. Our patients will be doing the "seeing."

Paul E. Tornambe, MD, FACS
President
Retina Consultants, San Diego
San Diego, California

Mamas, don't let your children grow up to be ophthalmologists. Well, almost. In the years ahead, I think most retinal diseases will be treated pharmacologically and through gene manipulation. I'm sure robotic surgery will be used, a type of LASIK for the retina (and a complete waste of a medical education).

For eyes that cannot be manipulated with drugs or robotic surgery, which present in advanced, irreparable stages such as glaucoma, trauma requiring enucleation, advanced melanoma, etc, I believe surgeons will bypass the conventional anterior pathways of the visual system by getting the image directly to the visual cortex.

> 'In the years ahead, I think most retinal diseases will be treated pharmacologically and through gene manipulation.'
>
> —Paul E. Tornambe, MD

It is unlikely stem cells will be the answer —they are unlikely to hook up to the optic nerve or "growing" a new eye. (Even though a salamander can grow an eye, a eucalyptus tree can grow a new tree even if you cut it down to the base, but not an oak tree—or my mother's chicken soup, which could grow a limb.)

The answer will be up to the nanoengineers. They will develop very high-resolution cameras, perhaps as a contact lens, prosthetic conformer, or prosthetic globe attached to the eye muscles so they move and create a neural network to the visual cortex—possibly distal to the synapse of the lateral geniculate body to the optic radiation area, or directly to the visual cortex, completely bypassing the optic nerve, chiasm etc. Mark Humayun, MD, PhD, is working on this now. There's no reason why several cameras could not be inserted to increase depth perception and give a 360-degree view of the surroundings. It will be exciting!

Financial Disclosures

Dr. Charles – ALCON LABORATORIES, INC: Consultant, No Compensation Received, Royalty.

Dr. Flynn – None.

Dr. Packo – ALCON SURGICAL, INC: Advisory Board, Consultant, Speaker, Grants, Honoraria, Salary; ALLERGAN, INC: Investigator, Grants; COVALENT MEDICAL, LLC: Stockholder, Stock; GENENTECH, INC: Other, Grants; REGENERON PHARMACEUTICALS, INC: Other, Grants; USRETINA: Stockholder, Stock.

Dr. Tornambe – CLEARVIEW TECHNOLOGIES, INC: Consultant, Stock Options; OPTOS PLC: Consultant, Honoraria; OPTOVUE, INC: Consultant, Honoraria; POWAY RETINAL TECHNOLOGIES, LLC: Founder, Intellectual Property Rights; STEMEDICA CELL TECHNOLOGIES, INC: Consultant, Stock Options.

Dr. Verne – None.

Roy A. Levit, MD
Section Editor
ASRS Co-founder

It's Magic!

'We don't care about the active ingredient; what we care about is that the pill works.'

In 1980, my wife, Rachel and I traveled to the Himalayas to visit Bhutan, Nepal, and Tibet. Bhutan was an emerging nation that got its first paved roads in 1969, Nepal was not yet westernized and was right out of Hollywood's central casting, and traditional culture in Tibet remained vibrant.

After meeting our group of 10 in Bangkok, we boarded a Bhutan Airways plane that stopped in Kolkata (in those days, *Calcutta*) on the way to Paro, Bhutan. Indian Sikh pilots, dressed in all-black uniforms along with black turbans, were impressive. Just before landing in Paro, they informed us that access to the airport landing strip was through a narrow valley, and advised us not to be concerned that the wings were too close to the hillsides. Looking out the window, I felt I could reach out and touch the people working the fields below the airplane's wings.

Once on the ground, we entered the country through an airport terminal the size of a standard 2-car garage. Everything about Bhutan was fascinating, but after 2 days of travel, the group, one by one—including our guides—became quite ill with flu-like symptoms. For the next day, we were an incapacitated, sick group. We think the virus infected the plane on the Kolkata stop. The illness lasted for about 24 hours, after which we all got better, except for a severe, nonstop cough.

After everyone used up their cough medicine without any effect, the group leader and I went to a pharmacy. I use the term loosely, as it was a hole-in-the-wall space in a little village in which the locals had rarely heard English. We made ourselves understood with our coughs and were presented with a bottle with the label written in Hindi. There were around 15 ingredients, none of the names of which we could read. However, the concentration of each was so small, I thought it would be safe to try. We purchased the entire stock of the cough medicine, and within half a day, all of our coughs were gone, and stayed gone. Magic!

Roy Levit, MD, checks out the local office space in Thimphu, Bhutan.

Having multiple ingredients in oral preparations was typical of medicines in India, Bhutan, and Tibet—more about that later.

Tibetans have codified their medicines and illnesses for the past 2000 years, and about 400 years ago, they began to display them in written and illustrated pages called *tantras*. There are 72 medical tantras that illustrate medical conditions such as urinary tract infections, gastrointestinal problems, and childbirth. Tibetans have specific medicines for each condition, and a pharmacologic tantra that describes the herbal formulas for the pills.

Because of my interest in local traditional medicine, I encountered 3 Western-medicine-trained Italian physicians who had been working for the past 10 years in a traditional medicine clinic in Bhutan. They had a large garden outside of the clinic where they were growing herbs. Rather than harvesting herbs in various parts of Bhutan, the physicians established better control of the herbs' potency by growing them all in the same soil, under the same weather conditions.

The physicians used the formulas in the Tibetan tantras to make medicines for various illnesses. I asked them if they knew which of the ingredients were the active ones, and they said, "No, we don't care about the active ingredient; what we care about is that the pill works."

This is hardly the attitude of the Food and Drug Administration (FDA), nor of many of our colleagues who conscientiously work at identifying the proper dosage and appropriate anti-VEGF product to treat wet macular degeneration, diabetic macular edema, and other causes of cystoid changes of the macula.

However, many parts of the world use a different parameter to evaluate medical usefulness. It is always an interesting exercise for us in medicine to learn what works in other environments.

As a last note, I took the bottle of cough medicine to a pharmacist, or *chemist*, in India, to find out the ingredients. Petals of a daisy, roots of mint, and varied other plant parts made up the medicinal soup. I bought as many of these bottles as I could take back to the United States, and we have used them through the years. Magic!

Financial Disclosures
Dr. Levit – None.

Jerald A. Bovino, MD
Section Editor
ASRS Co-founder

Fly Me to the Moon

Fifty years ago, mankind sent a crew of astronauts to the moon and brought them home safely. So if you think retrieving a dislocated posterior-chamber intraocular lens (PCIOL) and suturing it back in place with one hand tied behind your back is complicated, you might want to think again. Repositioning and fixating the PCIOL is probably child's play compared with sending a man to the moon in 1969.

I chose the word *mankind* for 2 reasons. The first is that Apollo 11 astronaut Neil Armstrong used that word in his famous moon-walk statement about small steps and giant leaps. But more importantly, the entire world took pride in landing on the moon. The era of space exploration had begun. Every "citizen" of the Earth understood its importance.

On the day of the moon landing, I was a third-year medical student backpacking around Europe with a couple of hundred dollars in my pocket, which had to last me the entire summer. I slept on rooftops, in hostels, in caves, and even on beaches trying to stay warm and dry inside my worn-out sleeping bag.

But on that momentous day, July 20, 1969, I was in the south of France as Neil Armstrong stepped out of the Lunar Module Eagle after radioing NASA Mission Control, "Houston, Tranquility Base here—the Eagle has landed." I was with a group of about 100 people, huddled close to a tiny black-and-white TV placed in a storefront window facing the Promenade des Anglais—the famous boulevard in Nice. You could hear the crackling of the voices on TV, punctuated by excited murmurs in at least 15 different languages coming from the crowd pressing in around that storefront.

We all gasped in synchrony and held our breath collectively as Armstrong laboriously stepped down the ladder onto the moon's surface. It was like a Wimbledon crowd watching a Djokovic-Federer fifth-set championship point, but magnified 10,000 times.

The first major Apollo contract assigned for devising how to send a man to the moon and bring him back safely was awarded to the Massachusetts Institute of Technology (MIT).

Photo by NASA / Getty Images.

Everyone who was around in 1969 remembers where they were when Apollo 11 astronaut Neil Armstrong landed on the moon.

There was no competitive bidding. The MIT scientists, mathematicians, engineers, and physicists were tasked with designing the computer hardware and the software to make the computers functional. But it was definitely uncharted territory for the entire team.

"You can't get a degree in how to fly to the moon," said Dana Densmore, who joined the MIT lab in 1965 and became a control supervisor for lunar-lander software. "You had to get people who know how to think, who are creative and alert. It was all invented on the spot."

Do you remember the legend about the Staff of Ra in the 1981 Steven Spielberg movie, *Raiders of the Lost Ark*? As you may recall, the headpiece of the staff was discovered by archeologist Abner Ravenwood in 1926. His daughter, Marion, wore the medallion on a necklace. The original wooden staff was lost to the ages, but the headpiece contained instructions describing how to make a new staff of the correct height.

The headpiece had come into the momentary possession of a Nazi Gestapo agent during a fight at Ravenwood's bar, but it fell in the fire and ultimately burned an image of the instructions onto the Nazi's hand. This scorched image allowed the French archeologist René Belloq to create his own headpiece.

The headpiece contained instructions to make the staff 6 kadams high, but Belloq did not know that the obverse of the medallion said you must subtract 1 kadam out of respect for the Hebrew God. Because Indiana Jones had the real medallion and was able to read both sides, it was simple for him to build a staff of precisely the right height by subtracting 1 kadam according to the instructions.

> **'You can't get a degree in how to fly to the moon.'**
>
> —Dana Densmore
> Control Supervisor
> Apollo 11 Lunar Landing Software

Ultimately, Indy brought the properly sized Staff of Ra to the map room at Tanis, and as the sunrise hit the crystal in the headpiece, it precisely directed a shaft of light to the map room Well of Souls, where the Ark of the Covenant had remained hidden for thousands of years.

I recently was sleeping like a baby in my New York City apartment, which faces due west

over Central Park and the NYC skyline. One expression we have all heard is that you can always be confident that "the sun will rise in the east tomorrow." But here I was, at 6:12 AM, just after the summer solstice, with a beam of the brightest sunlight waking me out of the deepest slumber with drool dribbling out of the corner of my mouth onto my pillow.

The light was brilliant and spectacular—exactly like the shaft of light in the map room that revealed the location of the Ark. It couldn't have been car headlights or searchlights because our apartment is on the 18th floor, and the temperature and wavelength of the warm red light were consistent with the sun at dawn.

As I tried to shake the cobwebs out of my brain and get my bearings, I remember thinking that we were headed toward the proverbial end of time. It was like some doomsday scenario where the sun rises in the west, the earthquakes start, the meteors hit, and the animals run wild. However, I once learned that you can successfully predict the end of the world only once. Accordingly, I tried to think of other reasons that the "sun was rising in the west."

I wiped the drool off my cheek and deduced that the sun, on just this day at this magical hour and minute, was probably reflecting off a glass building on Central Park West, directing the sunlight like a laser into my bedroom window. And you can imagine my delight as I jumped up and looked out the window and confirmed my deduction. *Eureka!*

Interestingly, one theory about the current high rate of physician burnout relates to the effects of modern technology on our diagnostic paradigms. In the old days, physicians had to use all their knowledge and skill to make difficult diagnoses. It led to what the Alpha Omega Alpha journal, *The Pharos*, called "Eureka moments."

As individual docs, we were thrilled and energized by the prospect of figuring things out. Who didn't want to diagnose amyloidosis or sarcoidosis by examining a patient's fingernails, just like Sir William Osler? But modern technology, including high-tech x-rays, ultrasounds, and blood work, has decreased the relevance of our hard-earned clinical skills. Sadly, in many cases, physicians are evolving into highly educated technicians.

Retina surgery may not be rocket science, but we share something special with those original MIT engineers who sent a man to the moon. As Dana Densmore noted, they were not able to get a college degree in how to fly to the moon; they had to figure it out. Similarly, we get only a residency and fellowship to educate us in the existing body of knowledge up to the day we graduate. But after a few years, most of what we learned in training becomes obsolete.

'Retina surgery may not be rocket science, but we share something special with those original MIT engineers who sent a man to the moon.'

Medicine is changing so quickly these days that we regularly are forced to metaphorically figure out new ways to send our patients to the moon.

To foster great retina surgeons for the next 5 decades, it will not be enough to know the Krebs cycle, the phacomatoses, or a classification of macular holes. Like the moon-shot guys in the 1960s, we will need to choose doctors who know how to think and who are creative and alert. Since none of us learned how to do retinal transplants last week, we will just have figure it out and "make it up on the spot."

Financial Disclosures

Dr. Bovino – None.

THE KOL CORNER >> *Continued from page 39*

Would you prophylactically treat his left eye?

Yoshihiro Yonekawa: Yes.

Audina Berrocal: In this case, I would treat the left eye with laser photocoagulation and follow this child closely, watching for progression despite laser. In pediatric retina, we cannot overemphasize how important it is to manage the "good," "better," or "normal" eye.

Antonio Capone: Yes, for reasons similar to those mentioned above. This patient has an underlying predilection to detachment, and there is already one eye at risk of poor outcome.

The common theme running through all 4 of these cases is that often, the greatest value we offer such children is not repair of the "index" eye, with its poor visual potential and need for complicated vitreoretinal acrobatics to effect repair, but protection of the intrinsically at-risk, better-seeing companion eye.

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Financial Disclosures

Dr. Berrocal – ALCON LABORATORIES, INC: Speaker, Honoraria; ALLERGAN, INC: Advisory Board, Honoraria; BAYER HEALTHCARE: Consultant, Honoraria; CARL ZEISS MEDITEC: Consultant, Honoraria; DUTCH OPHTHALMIC USA: Consultant, Speaker, Honoraria; NOVARTIS PHARMACEUTICALS CORPORATION: Advisory Board, Honoraria; PHOENIX RESEARCH LABS: Advisory Board, No Compensation Received; VISUNEX MEDICAL SYSTEMS CO, LTD; Consultant, Honoraria.

Dr. Capone – ALCON LABORATORIES, INC: Investigator, Grants; AURA BIOSCIENCES, INC: Investigator, Grants; BROADSPOT IMAGING: Stockholder, Stock; GENENTECH/ROCHE, INC: Investigator, Grants; NOVARTIS PHARMACEUTICALS CORPORATION: Advisory Board, Salary; PHOENIX TECHNOLOGY GROUP: Stockholder, Stock; RETINAL SOLUTIONS, LLC: Stockholder, Intellectual Property Rights, Stock; SPARK THERAPEUTICS, INC: Consultant, Honoraria.

Dr. Regillo – AERPIO THERAPEUTICS: Investigator, Grants; ALCON LABORATORIES, INC: Consultant, Investigator, Grants, Honoraria; ALLERGAN, INC: Consultant, Investigator, Grants, Honoraria; ASTELLAS PHARMA US, INC: Investigator, Grants; GENENTECH, INC: Consultant, Investigator, Grants, Honoraria; ICONIC THERAPEUTICS, INC: Consultant, Investigator, Grants, Honoraria; NOTAL VISION: Consultant, Investigator, Grants, Honoraria; NOVARTIS PHARMACEUTICALS CORPORATION: Consultant, Investigator, Grants, Honoraria; OPHTHOTECH CORPORATION: Investigator, Grants; REGENERON PHARMACEUTICALS, INC: Investigator, Grants.

Dr. Spirn – None.

Dr. Yonekawa – ALCON LABORATORIES, INC: Advisory Board, Consultant, Honoraria

Derrick Wang, BA
UCLA Stein Eye Institute
Los Angeles, California

David Sarraf, MD
Section Editor

Case History

A 65-year-old male presented with a 5-day history of blurred vision as if "looking through wax paper" and diminished color vision in the right eye. Medical history was remarkable for hypertension, pulmonary emphysema, allergic rhinitis, and benign prostatic hyperplasia.

On examination, visual acuity was 20/40 in the right eye (OD) and 20/20 in the left eye (OS). Anterior segment examination was within normal limits except for mild nuclear sclerotic cataracts.

Dilated fundus examination was notable for geographic macular lesions, central OD and superior OS (Figure 1). Spectral-domain optical coherence tomography (SD-OCT) demonstrated hyperreflective areas of ellipsoid zone disruption with radial extension into Henle's fiber layer OD (Figure 2).

OCT angiography (OCTA) displayed geographic areas of inner choroidal flow deficit that progressively increased over a 3-week period in each eye consistent with progressive inner choroidal ischemia in both eyes (OU) (Figure 3).

Wide-field indocyanine green angiography (ICGA) showed widespread areas of choroidal ischemia in the posterior pole and periphery (Figure 4).

Systemic workup for underlying inflammatory and infectious disorders was unremarkable. Specifically, antinuclear antibody (ANA), rheumatoid factor (RF), and P- and C-antineutrophil cytoplasmic antibodies (ANCA) were negative and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were within normal limits. QuantiFERON tuberculosis (TB) and Lyme enzyme immunoassay were also negative and Treponema pallidum particle agglutination (TP-PA) was nonreactive.

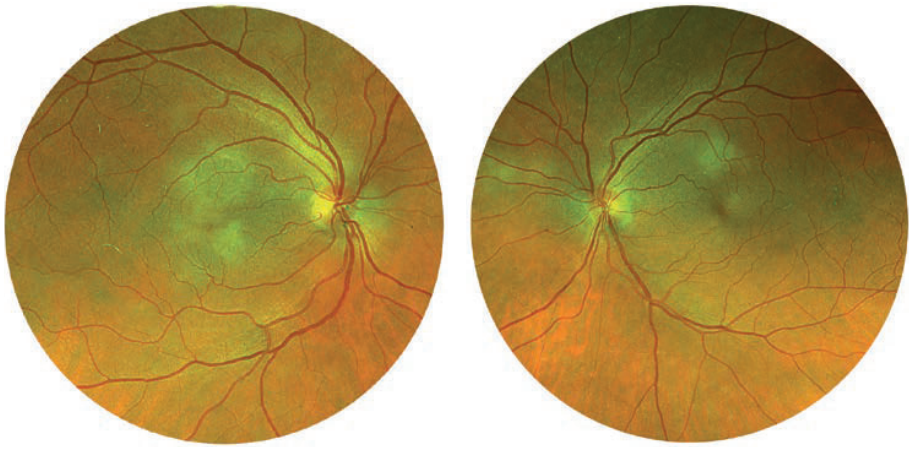

Figure 1. Fundus color images illustrate creamy white macular lesions central OD and superior OS.

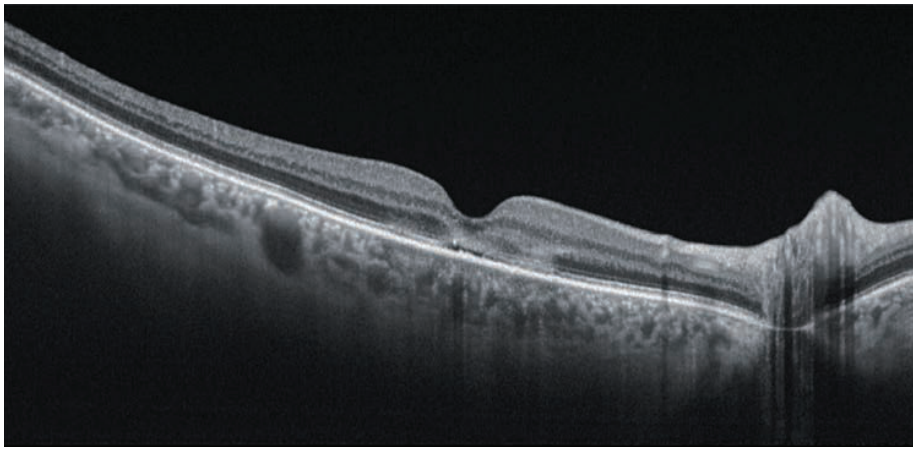

Figure 2. SD-OCT through the central lesion OD illustrates outer-retinal hyperreflective lesions with radial extension into Henle's fiber layer.

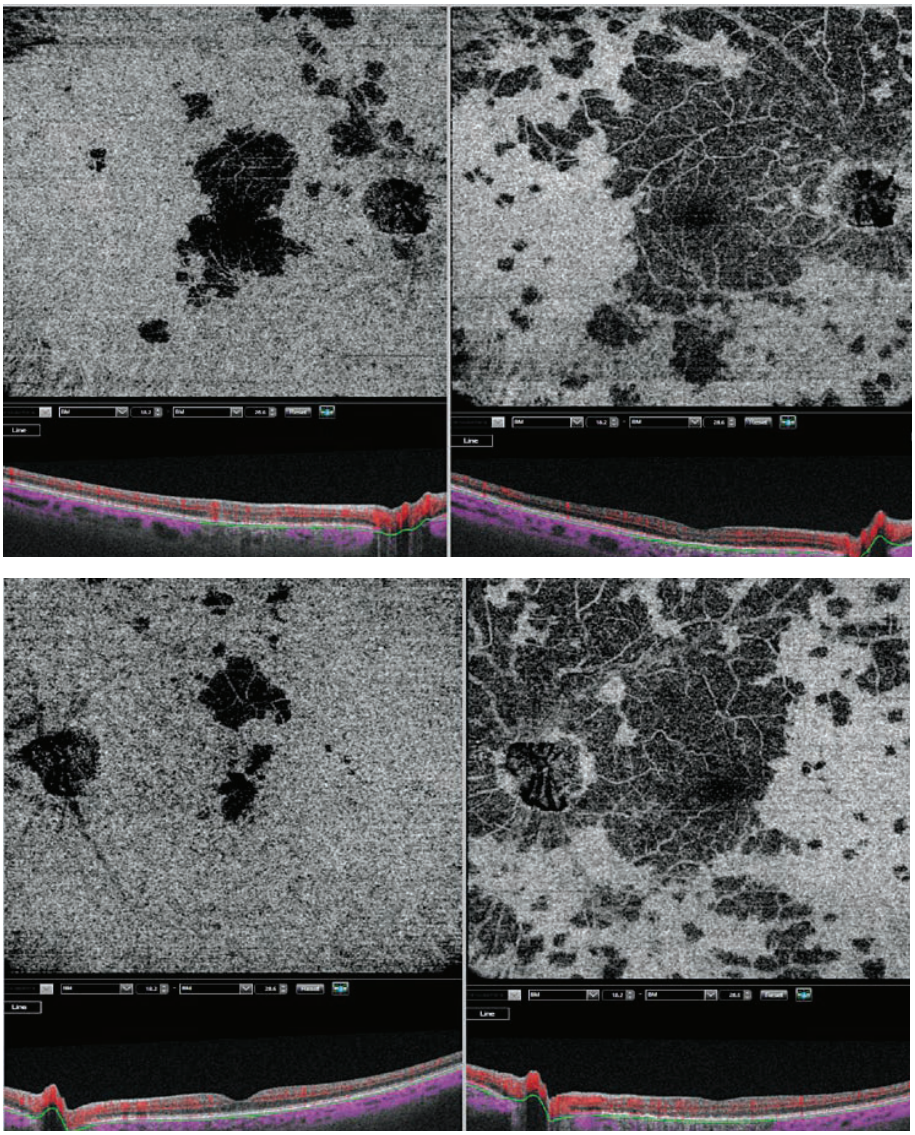

Figure 3. OCTA of the right (top) and left (bottom) eyes with segmentation at the level of the choriocapillaris illustrates inner choroidal flow deficit at baseline (left) with remarkable progression of the flow void at the 3-week visit (right).

What is your diagnosis?

See discussion on page 64

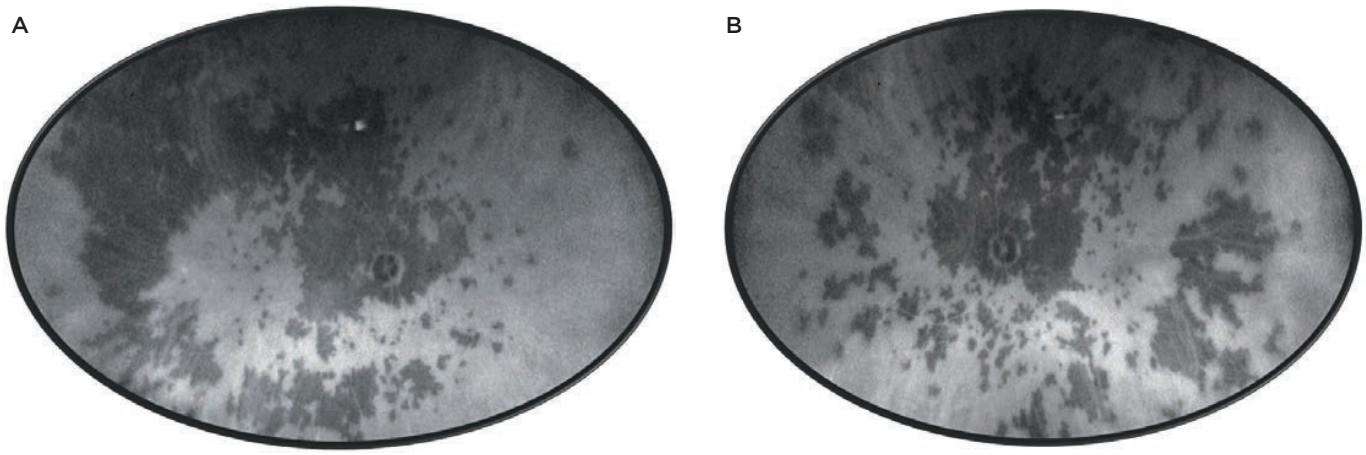

Figure 4. ICGA showing diffuse choroidal ischemia in the right (A) and left (B) eyes.

Joseph D. Boss, MD 

Joseph Raevis, MD 

Michael M. Altaweel, MD
Section Editor 

Asheesh Tewari, MD
Section Editor 

The Incidence of Retinal Breaks Induced by Posterior Hyaloid Separation During 27-Gauge Pars Plana Vitrectomy

[published online March 19, 2019]. Rahman R, Patil A, Stephenson J. *J VitreoRetinal Dis*. 2019;3(2):76-79. doi:10.1177/2474126419831908

During pars plana vitrectomy (PPV), iatrogenic retinal breaks increase the chances of postoperative rhegmatogenous retinal detachments and loss of vision. Prior studies have reported the incidence of iatrogenic retinal breaks with 20-gauge, 23-gauge, and 25-gauge vitrectomies to be 15.2%, 18.2%, and 15.7%-15.8%, respectively. This study is the first to characterize the risks associated with suction-induced posterior hyaloid face separation during 27-gauge vitrectomy.

Breaks that occur during PPV are thought to result from multiple mechanisms: insertion and withdrawal of instruments, posterior vitreous detachment (PVD) induction, or residual vitreous left after PPV. The insertion of instruments through the sclera may cause traction at the vitreous base; conversely, withdrawal of instruments may cause incarceration of vitreous within the sclerostomy wounds, resulting in traction and retinal tears.

Induction of a PVD may directly cause breaks from adherent vitreoretinal adhesions, while removal of the vitreous base may induce traction to the peripheral retina and cause tears. It is hypothesized that residual vitreous may undergo postoperative shrinking, which may lead to tears and subsequently a retinal detachment.

The authors performed a retrospective, consecutive, observational study of a single surgeon between 2015 and 2017 at Calderdale Royal Hospital in the United Kingdom. A total of 94 patients known preoperatively to have an attached posterior hyaloid face were included. All patients underwent 27-gauge PPV to treat either a macular hole (MH), epiretinal membrane (ERM), floaters, or vitreomacular traction (VMT). In 82 out of 94 patients, 27-gauge PPV was combined with 2.2 mm phacoemulsification.

An incidence rate of iatrogenic retinal tears was found to be 17% (95% CI 9.43%-24.6%). A multiple regression analysis did not find an association with the indication for surgery (MH, ERM, floaters, VMT), age, sex, or axial length. Even with a retinal break incidence of 17% (16/94 patients), no patient developed an immediate or late postoperative rhegmatogenous retinal detachment.

The authors hypothesized that the high detection rate of peripheral breaks without postoperative detachments may have been made possible by the surgeon's preference for combined phacoemulsification and vitrectomy. This combined approach allows for more complete removal of peripheral vitreous and improved visualization of the periphery.

Application to Practice: This study shows the relatively high incidence (17%) of iatrogenic retinal breaks that occur with suction-induced posterior hyaloid face separation. This fact highlights the importance of thorough, 360-degree, intraoperative examination and treatment of all iatrogenic breaks to prevent postoperative complications.

Association of Intravitreal Anti-Vascular Endothelial Growth Factor Therapy with Risk of Stroke, Myocardial Infarction, and Death in Patients with Exudative Age-Related Macular Degeneration

[published online January 31, 2019]. Dalvin L, Starr M, AbouChenhade J, Damento G, et al. *JAMA Ophthalmol*. 2019;137(5):483-490. doi:10.1001/jamaophthalmol.2018.6891

Antivascular endothelial growth factor (anti-VEGF) is the main treatment for age-related macular degeneration (AMD), used millions of times a year. Despite numerous studies, there is disagreement in the literature as to whether systemic risks are present with intravitreal anti-VEGF therapy.

When a significantly higher dose of bevacizumab is used systemically to treat colorectal cancer, it has been associated with an increased risk of stroke; thus, it is essential to understand the risks when used off-label as an intravitreal injection.

The authors report a population-based, retrospective cohort study looking at the risk of stroke, myocardial infarction (MI), and all-cause mortality after intravitreal anti-VEGF therapy for exudative AMD. They included 504 patients who received at least 1 intravitreal injection; the mean age was 76.5 years. The 3 control groups consisted of individuals with no prior anti-VEGF therapy who had either no AMD, dry AMD, or exudative AMD in the era prior to anti-VEGF (1990 to 2003).

A Kaplan-Meier analysis revealed a 5-year risk of stroke, MI, and all-cause death of 7.2%, 6.1%, and 30.0% respectively in the anti-VEGF cohort. No increased risk of stroke or MI was found when anti-VEGF was compared to any of the controls. Also, no increase in all-cause mortality was found between the anti-VEGF cohort and the no-AMD and dry-AMD cohorts.

Despite the lack of risks noted above, an increased risk of all-cause mortality was detected when anti-VEGF therapy was compared specifically to the cohort with exudative AMD in the era prior to anti-VEGF therapy (hazard ratio 1.63, 95% CI 1.30-2.04; $P < .001$). However, a similar result was not found when the anti-VEGF group was compared with patients receiving at least 3 injections within 1 year of death.

While another study supported these results and a meta-analysis noted increased risks of cerebrovascular events with intravitreal anti-VEGF, other studies and meta-analyses have not replicated the findings, which indicates that these results should be interpreted with caution. The increased risk of death in patients who received anti-VEGF therapy compared to the past-exudative-AMD cohort may have been due to chance alone, inability to completely match the 2 cohorts, or an actual increase in mortality.

Overall, intravitreal anti-VEGF therapy appears to be safe. The MARINA, ANCHOR, and SAILOR trials did not find increased risks for nonfatal stroke, MI, or vascular-related death, and the VISION trial found no increased risk for thromboembolic events or death.

Application to Practice: Use of anti-VEGF therapy for exudative AMD is not associated with a consistent finding of increased stroke, MI, or death and appears to be systemically safe.

HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration

[published online April 12, 2019]. Dugel P, Koh A, Ogura Y, Jaffe G, et al. *Ophthalmology*. doi:10.1016/j.ophtha.2019.04.017

The current model of treating patients with neovascular age-related macular degeneration (nAMD) involves frequent clinic and injection visits which is not ideal for patient satisfaction or outcomes. Brolucizumab is a single-chain antibody fragment that inhibits vascular endothelial growth factor-A.

This antibody fragment is the smallest functional subunit of an antibody, thus allowing for improved tissue penetration and a greater molar dose compared with larger molecules. Preclinical studies demonstrated that compared with ranibizumab, brolucizumab has a 2.2-fold higher exposure in the retina and is 1.7-fold higher in the retinal pigment epithelium/choroid.

HAWK and HARRIER were 2 similarly designed phase 3, randomized, double-masked, active-controlled trials that compared treatment of nAMD with brolucizumab to aflibercept. The primary outcome was to determine if brolucizumab was noninferior to aflibercept regarding best-corrected visual acuity (BCVA) from baseline to 48 weeks. Other main measures included the percentage of patients who maintained q12-week dosing through week 48 and anatomic outcomes.

A total of 1817 treatment-naive patients were enrolled. The HAWK trial randomized eyes 1:1:1 to brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg, while the HARRIER trial randomized eyes 1:1 to brolucizumab 6 mg or aflibercept 2 mg. Three monthly loading injections were performed in each arm. Brolucizumab participants then received injections every 12 weeks (q12), and the interval was adjusted to every 8 weeks (q8w) if disease activity was present. All aflibercept eyes received q8w dosing.

At week 48, each brolucizumab arm was noninferior to aflibercept regarding BCVA (+6.6 [6 mg] and +6.1 [3 mg] letters with brolucizumab vs +6.8 letters with 2 mg aflibercept [HAWK]; +6.9 letter with brolucizumab 6 mg vs +7.7 letters with aflibercept 2 mg [HARRIER]). Eyes treated with brolucizumab 6 mg were maintained on q12w dosing through week 48 in 56% of patients in HAWK and 51% in HARRIER.

Participants who were able to be maintained on q12w dosing had 2 fewer injections per year compared with q8w dosing. Also, time-to-event analyses showed that most patients with disease activity requiring q8w dosing were identified during the first q12w interval (weeks 16 and 20).

At week 16 (8 weeks after 3 loading doses), the arms had identical treatment exposure, yet the brolucizumab 6-mg-treated eyes had less disease activity when compared to aflibercept 2 mg in HAWK (24.0% vs 34.5%, $P = .001$) and HARRIER (22.7% vs 32.2%, $P = .0002$). This suggests that there is increased duration of effect with brolucizumab when compared to aflibercept.

Both studies demonstrated superiority of brolucizumab with regard to central subfield thickness and presence of intraretinal fluid and/or subretinal fluid. The improved anatomic outcomes support the hypothesis that the higher concentration of the lower molecular weight, single-chain antibody fragment brolucizumab allows for improved drug delivery at the target site. Adverse events were similar with brolucizumab and aflibercept.

Application to Practice: Brolucizumab was recently FDA approved for nAMD. It offers the potential to extend the interval of treatment to q12w after 3 monthly loading doses, which could decrease the treatment burden for patients.

Autologous Retinal Transplant for Refractory Macular Holes: Multicenter International Collaborative Study Group

[published online January 31, 2019]. Grewal DS, Charles S, Parolini B, Kadonosono K, Mahmoud TH. *Ophthalmology*. 2019;126(10):1399-1408. doi:10.1016/j.ophtha.2019.01.027

With current surgical techniques, the primary closure rate of full-thickness macular holes (MHs) is very favorable, with single-surgery closure reports exceeding 90%. However, refractory MHs following prior vitrectomy and internal limiting membrane peel are difficult to manage with limited surgical options, lacking a defined standardized technique. The current report describes the long-term visual and anatomic outcomes and complications of autologous neurosensory retinal free flaps for closure of refractive MHs.

This international multicenter, retrospective consecutive case series included a total of 41 eyes of 41 patients with refractory full-thickness MHs after at least 1 failed surgical attempt. All patients underwent 20-, 23-, or 25-gauge pars plana vitrectomy, autologous neurosensory retinal transplant with C3F8, silicone oil, or short-term perfluoro-n-octane (PFO) heavy-liquid tamponade. All patients had more than 6 months postoperative follow-up (mean 11.1 months).

The harvest site was the mid-periphery, typically superior to the superotemporal arcade, subject to surgeon preference. A 2-disc diameter area of the retina was harvested using endolaser barricade, endodiathermy to the blood vessels at the site edge, and curved or vertical scissors.

The diathermy marks at the harvest site edges were used to maintain the correct orientation of the retinal free flap. PFO was used over the free flap after it was placed to cover the MH. Alternatively, PFO was used over the harvest site and the free flap was extracted under PFO. When silicone oil was used, a direct PFO-silicone oil exchange was performed.

Patients were positioned face down for 1 week with gas or oil, and supine if PFO was used as the tamponade. PFO was removed within 2 weeks, and oil was removed within 1 to 3 months.

The main study outcome evaluated was MH closure, with secondary outcomes including visual acuity (VA) improvement, restoration of outer retinal layers using OCT, and surgical complications.

The mean number of prior surgeries was 1.5 (range 1-3), with a mean preoperative MH largest basal diameter of 1468 µm. Anatomic closure of MHs was achieved in 36 of 41 eyes (88%). The mean preoperative

VA was approximately 20/257 (logMAR 1.11) and the overall mean VA at the last postoperative visit improved to approximately 20/214 (logMAR 1.03; P = .03).

In this cohort, vision improved in 36.6% of eyes, was stable in 41.5% of eyes, and worsened in 21.9% of eyes. Of eyes with successful MH closure, VA improved in 52% and worsened in 14%. In eyes with failed closure, VA worsened in 40% and improved in none. Baseline MH size was smaller in those with visual improvement than in those without visual improvement.

Postoperative neurosensory retinal flap dislocation was seen in 2 procedures. Major postoperative complications were a retinal detachment in 1 eye and a vitreous hemorrhage in 1 eye. Of note, there were no cases of intraocular inflammation, proliferative vitreoretinopathy, PFO toxicity, endophthalmitis, suprachoroidal hemorrhage, or choroidal neovascularization.

Application to Practice: The outlined surgical technique using autologous neurosensory retinal transplants for refractory MHs resulted in an anatomical closure rate approaching 90%, with an overall marginally improved visual acuity and minimal surgical complications. This technique offers high safety and efficacy rates to close refractory MHs.

Effect of Corticosteroid-Sparing Treatment With Mycophenolate Mofetil vs Methotrexate on Inflammation in Patients With Uveitis: A Randomized Clinical Trial

Rathinam SR, Gonzales JA, Thundikandy R, Kanakath A, et al. *JAMA*. 2019;10;322(10):936-945. doi:10.1001/jama.2019.12618

Uveitis is a significant cause of vision loss worldwide, in both developed and developing countries. Numerous clinical manifestations and systemic associations exist, and treatment options include both regional and systemic short-term and long-term therapeutics. Both timely and chronic management of patients with uveitis often necessitate multidisciplinary collaboration given the need for corticosteroid-sparing immunosuppression following standard regional and systemic corticosteroid first-line treatments.

Of corticosteroid-sparing treatment options, antimetabolites including commonly used methotrexate and mycophenolate mofetil are often initially preferred due to the comparative interclass efficacy and safety profile. However, there is uncertainty regarding whether methotrexate or mycophenolate mofetil is more effective for treating noninfectious uveitis. Therefore, the First-line Antimetabolites as Steroid-sparing Treatment (FAST) uveitis trial's primary objective was to compare the relative effectiveness of methotrexate and mycophenolate mofetil for achieving corticosteroid-sparing control of noninfectious intermediate uveitis, posterior uveitis, and panuveitis.

This National Eye Institute (NEI)-funded international multicenter, randomized clinical trial included patients 16 years of age or older with active noninfectious intermediate uveitis, posterior uveitis, or panuveitis in at least 1 eye. Patients with a justification for starting corticosteroid-sparing therapy were randomized 1:1 to receive methotrexate (25 mg weekly) or mycophenolate mofetil (3 g daily). Patients were prescribed oral prednisone (1 mg/kg up to 60 mg daily, with a mean dose of 50 mg daily) at enrollment and tapered with a goal of holding at no more than 7.5 mg daily.

The primary outcome was treatment success at 6 months follow-up, defined as inflammation control in both eyes, no more than 7.5 mg prednisone daily, 2 or fewer drops of prednisolone acetate 1%, and no treatment failure due to safety or intolerability. Treatment and follow-up continued to 12 months, and allowed switching to the other antimetabolite at 6 months if treatment failure occurred.

Of patients randomized, 194 of 216 patients completed follow-up through 6 months. One-hundred and seven patients received methotrexate while 109 patients received mycophenolate mofetil. Treatment success occurred in 66.7% patients in the methotrexate group and 57.1% in the mycophenolate mofetil group ($P = .20$). In the subgroup analysis, patients with posterior uveitis or panuveitis had higher treatment success in the methotrexate group (74.4%) compared to the mycophenolate mofetil group (55.3%; $P = .02$). There was no difference in success rates between the groups for anterior or intermediate uveitis.

No differences were seen in vision and central subfield thickness between the groups at 6 months. Of the cohort with treatment success at 6 months, 80% of the methotrexate group and 74% of the mycophenolate mofetil group continued to be controlled at 12-month follow-up. Elevated liver enzymes were the most common lab-related adverse effect, occurring more commonly in the methotrexate group.

Application to Practice: This large and geographically diverse randomized study suggests there is little overall difference in inflammation control between mycophenolate mofetil and methotrexate for noninfectious uveitis. However, patients with posterior uveitis or panuveitis, the most severe and largest subgroup in this trial, had higher treatment success in the methotrexate group.

Persistent Avascular Retina in Infants With a History of Type 2 Retinopathy of Prematurity: To Treat or Not to Treat?

Al-Taie R, Simkin SK, Douçet E, Dai S. *J Pediatr Ophthalmol Strabismus*. 2019;56(4):222-228. doi:10.3928/01913913-20190501-01

Retinopathy of prematurity (ROP) is a vasoproliferative disorder affecting premature infants and is one of the leading causes of childhood blindness. Prior landmark studies have standardized screening and treatment guidelines. The CRYO-ROP and ETROP studies established therapeutic interventions for threshold disease (5 consecutive clock hours or 8 cumulative clock hours of stage 3 with plus disease in zone I or II) or type 1 ROP (zone II stage 2 or 3 ROP with plus disease, zone I any stage ROP with plus disease, or zone I stage 3 ROP without plus disease).

Infants with type 2 ROP (zone I stage 1 or 2 ROP without plus disease or zone II stage 3 ROP without plus disease) are recommended to be screened until complete vascularization, resolution of ROP, or post-menstrual age (PMA) of 45 weeks. Patients older than 45 weeks PMA with persistent avascular retina fall outside established management guidelines, with unknown long-term risks and treatment needs.

The present research by Al-Taie et al was a prospective observational study investigating persistent avascular retina in infants with type 2 ROP that persisted after the standardized 45-week PMA monitoring window. Retinal vascular features were evaluated using fundus fluorescein angiography (FFA) and widefield retinal imaging to collect useful data to translate toward evidence-based decision making in the treatment of this patient population.

Seventy-two eyes of 36 consecutive infants were studied with FFA, with a mean gestational age of 26.0 weeks and mean birth weight of 834.6 grams. Thirty-one infants had bilateral avascular retinas. All infants had a history of anemia and required respiratory support during their neonatal period.

The worst stage of ROP in all patients was type 2, and predominantly stage 2 disease in zone II or III. Other than avascular retina, no other retinal abnormities were observed. The mean age was 18.8 ± 10.3 months (range: 3 to 39 months) at the time of FFA. FFA showed abnormal terminal punctate leakage and aberrant retinal vessels in 3 eyes (5.5%) of 2 children (aged 11 and 32 months), who subsequently received laser photocoagulation. Additionally, hyperfluorescent spots or popcorn lesions were seen in some patients.

Application to Practice: When considering ROP screening cessation after 45 weeks PMA in patients with persistent type 2 ROP, fluorescein angiography is recommended. FFA aids in decision making for treatment and follow-up needs in these cases given a 5.5% rate of neovascular leakage that may portend future complications.

Financial Disclosures

Dr. Altaweel – ALCON LABORATORIES, INC: Investigator, Grants; NATIONAL EYE INSTITUTE: Investigator, Grants; NOVARTIS PHARMACEUTICALS CORPORATION: Investigator, Grants; OPSIS THERAPEUTICS: Advisory Board, Consultant, Honoraria.

Dr. Boss – None.

Dr. Raevis – None.

Dr. Tewari – BAUSCH+LOMB: Consultant, Honoraria; BEAVER-VISITEC INTERNATIONAL: Consultant, Honoraria; DUTCH OPHTHALMIC USA: Consultant, Honoraria.

BLOCK TIME >> *Continued from page 51*

postoperative vitreous hemorrhage, which may take weeks to clear. It can be difficult to know when to go back to the OR to wash out the blood. Regular monitoring with B-scan ultrasonography is important to detect worsening retinal detachment, which would be one indication to return to the OR urgently.

In general, if the hemorrhage seems to be clearing at each postoperative visit, observation makes sense. If you can make out even some hazy details of the posterior segment, it is usually a good sign the blood will clear spontaneously. Postoperative anti-VEGF injections can also promote regression of any residual NV and reduce the likelihood of additional vitreous hemorrhage. However, if it is not clearing within 2 to 3 months, consider washing out the hemorrhage with victrectomy, depending on the patient's needs and wishes.

2. **Watch out for elevated IOP.** Gas or oil overfills in these eyes can be a death knell, as they already have significant ischemia and can easily be tipped over to dramatic nonperfusion from high IOP. Medically manage these eyes with close monitoring, making sure the IOP is coming down on the same day in office. If needed, tap off gas quickly or go back to the OR urgently to remove some oil.

'If the hemorrhage seems to be clearing at each postoperative visit, observation makes sense.'

While our advice is by no means meant to be all inclusive, we hope you find some of these tips useful for your complex diabetic TRD cases. As challenging as these cases can be, they may also be some of the most rewarding—from both a surgical perspective that you have accomplished a great feat, and from a physician perspective that you have rescued someone's vision.

All images courtesy of Jason Hsu, MD.

Financial Disclosures

Dr. Fineman – PHYSICIAN RECOMMENDED NUTRICEUTICALS: Consultant, Honoraria; THROMBOGENICS, INC: Consultant, Investigator, Grants.

Dr. Hsu – GENENTECH, INC: Investigator, Grants; OPHTHOTECH CORPORATION: Investigator, Grants; SANTEN INC: Investigator, Grants.

Discussion

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) is an inflammatory condition first described by Gass in 1968,[1] characterized by bilateral creamy placoid lesions at the level of the retinal pigment epithelium (RPE) that subsequently progress to RPE atrophy and hyperpigmentation.[2] Patients can present with acute reductions in visual acuity with rapid recovery within weeks to months without treatment.[3]

Gass was unable to classify the disease as involving primarily the RPE, choroid, or both,[1] and coined the term *pigment epitheliopathy* because the RPE appeared to be most significantly affected. Deutman et al[2] proposed inflammation of the choriocapillaris as the underlying pathogenesis of APMPPE. Spaide[4] described the autofluorescent RPE alterations in APMPPE and implicated the choroidal vasculature as the primary level of involvement.

Howe et al[5] identified hypofluorescent areas on ICGA that did not co-localize with the clinically evident placoid lesions, showing that reduced inner choroidal flow rather than shadowing from the RPE was the primary etiology of APMPPE. Mrejen et al[6] captured hypofluorescent peripheral choroidal lesions with wide-field fluorescein angiography in the absence of RPE disruption, lending further support to choroidal ischemia as the mechanism explaining placoid disorders like APMPPE.

Using OCTA and en face structural OCT, Klufas et al precisely co-localized areas of inner choroidal flow deficit with the OCT outer retinal lesions in eyes with placoid diseases such as APMPPE and definitively proved that placoid outer retinal lesions were driven by inner choroidal ischemia.[7] OCTA provides a noninvasive, simple, and practical modality to diagnose inner choroidal ischemia and monitor the progression and response to treatment of placoid disorders.[7,8] OCTA also can be used to differentiate APMPPE from more-severe placoid presentations such as persistent placoid maculopathy.[7]

Given the dramatic progression of inner choroidal ischemia associated with vision loss, our patient was started on oral prednisone therapy (1 MG/KG) with improvement of the inner choroidal ischemia and commensurate recovery of visual acuity (Figure 5). The subsequent resolution of inner choroidal ischemia, without persistence beyond 3 months, distinguishes our case of APMPPE from a more severe variant such as persistent placoid maculopathy.[9]

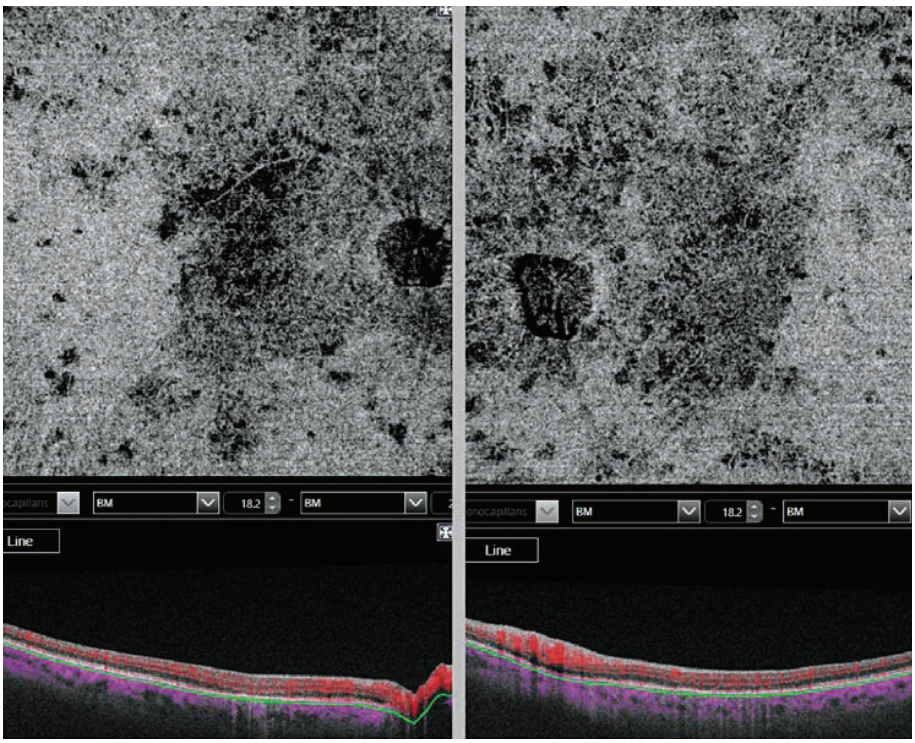

Figure 5. OCTA showing bilateral improvement of choriocapillaris flow at 6 weeks follow-up after initiation of immunosuppressive therapy.

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Financial Disclosures

Dr. Sarraf – AMGEN INC: Consultant, Honoraria; BAYER HEALTHCARE: Consultant, Speaker, Honoraria; GENENTECH, INC: Consultant, Investigator, Grants, Honoraria; HEIDELBERG ENGINEERING: Investigator, Equipment (Department or Practice), Grants; NOVARTIS PHARMACEUTICALS CORPORATION: Consultant, Speaker, Honoraria; OPTOVUE INC: Advisory Board, Consultant, Investigator, Speaker, Equipment (Department or Practice), Honoraria, Other Financial Benefit, Salary, Stock Options; REGENERON PHARMACEUTICALS, INC: Investigator, Grants.

Mr. Wang – None.

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