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Retina Today

JULY/AUGUST 2026 VOL. 21, NO. 5
RETINATODAY.COM

20TH ANNIVERSARY

Rare and Inherited RETINAL DISEASE

A look at novel therapies, trial endpoints, and clinical care.

eyetube

GENETIC TESTING IN THE RETINA PRACTICE | MOVING BEYOND SINGLE-GENE SOLUTIONS | RARE DISEASE MYSTERY CASES

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The **first and only** FDA-approved treatment for adults with idiopathic macular telangiectasia type 2 (MacTel)

ENCELTO™

(revakinagene taroretcel-lwey)

implant, for intravitreal use

Harness the tech with the survival effect ON PHOTORECEPTORS[1]

See the data behind ENCELTO

Scan the QR code or visit ENCELTO.com/ecp

INDICATIONS AND USAGE

ENCELTO is an allogeneic encapsulated cell-based gene therapy indicated for the treatment of adults with idiopathic macular telangiectasia type 2 (MacTel).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

ENCELTO is contraindicated in patients with active or suspected ocular or periocular infections, and in patients with known hypersensitivity to Endothelial Serum Free Media (Endo-SFM).

WARNINGS AND PRECAUTIONS

ENCELTO implantation surgery and/or implantation related procedures have been associated with the following:

Severe Vision Loss

Severe vision loss defined as three or more lines of visual acuity loss [≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters] has occurred following ENCELTO implantation. Monitor patients for signs and symptoms of vision loss and manage as clinically indicated.

Infectious Endophthalmitis

Infectious endophthalmitis may occur following ENCELTO implantation. Signs and symptoms of infectious endophthalmitis include progressively worsening eye pain, vision loss, or scleral and conjunctival injection. To mitigate the risk of endophthalmitis, use proper aseptic surgical technique for ENCELTO implantation. Monitor patients for signs or symptoms of infectious endophthalmitis. Remove ENCELTO implant if infectious endophthalmitis occurs and manage symptoms according to clinical practice.

Retinal Tear and Detachment

Retinal tears and retinal detachment may occur following ENCELTO implantation. Signs and symptoms of retinal tears include acute onset of flashing lights, floaters, and/or loss of visual acuity. Signs and symptoms of retinal detachment may include progressive visual field loss and/or loss of visual acuity. Use standard vitreoretinal surgical techniques during ENCELTO implantation to minimize the risk of retinal tears and retinal detachment. Monitor for any signs or symptoms of retinal tear and/or retinal detachment. Treat rhegmatogenous retinal detachment and retinal tears promptly. Remove ENCELTO implant, if vitrectomy with a complete gas fill or silicone oil fill is required.

Vitreous Hemorrhage

Vitreous hemorrhage, which may result in temporary vision loss, has occurred following ENCELTO implantation. Patients receiving antithrombotic medication (e.g., oral anticoagulants, aspirin, nonsteroidal anti-inflammatory drugs) may be at increased risk of vitreous hemorrhage. To reduce the risk of vitreous hemorrhage, interrupt antithrombotic medications prior to the ENCELTO implantation. Vitrectomy surgery may be necessary to clear severe, recurrent, or non-clearing vitreous hemorrhage. If the patient has a late onset vitreous hemorrhage (greater than one year following ENCELTO implantation surgery), examine the ENCELTO implantation site for possible implant extrusion. If implant extrusion has occurred, surgically reposition ENCELTO.

Implant Extrusion

Implant extrusion through the initial scleral wound has occurred following ENCELTO implantation. Signs and symptoms of implant extrusion include recurrent uveitis, vitreous hemorrhage, eye pain more than one year after implantation, or visibility of titanium fixation loop under the conjunctiva. To reduce the risk of implant extrusion, carefully follow the specific surgical steps for ENCELTO implantation.

Evaluate patients after 6 months to confirm proper positioning of ENCELTO and then annually. If ENCELTO begins to extrude, surgically reposition ENCELTO to a proper scleral wound depth either in the same site or in the opposing inferior quadrant of the vitreous cavity.

Cataract Formation

Cataract formation, including cataract cortical, cataract nuclear, cataract subcapsular, cataract traumatic, and lenticular opacities, has occurred following ENCELTO implantation. To reduce the risk of ENCELTO-related cataract formation or progression, carefully follow the specific surgical steps for ENCELTO implantation.

Suture Related Complications

Suture related complications, including conjunctival erosions due to suture tips and suture knots, have occurred following ENCELTO implantation.

To mitigate the risk of suture related complications, carefully follow the specific surgical steps for ENCELTO implantation and manage suture-related complications as clinically indicated.

Delayed Dark Adaptation

Delayed Dark Adaptation, a delay in the ability to adjust vision from a bright lighting condition to a dim lighting, has occurred following ENCELTO administration which remained unchanged for the duration of study follow up. Advise patients to take caution while driving and navigating in the dark.

ADVERSE REACTIONS

The most common adverse reactions (≥2%) reported with ENCELTO were conjunctival hemorrhage, delayed dark adaptation, foreign body sensation, eye pain, suture related complications, miosis, conjunctival hyperemia, eye pruritus, ocular discomfort, vitreous hemorrhage, blurred vision, headache, dry eye, eye irritation, cataract progression or formation, vitreous floaters, severe vision loss, eye discharge, anterior chamber cell, iridocyclitis.

Please see Brief Summary of full Prescribing Information on following pages.

Reference: ENCELTO [prescribing information]. Cumberland, RI. Neurotech Pharmaceuticals, Inc.

neurotech

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all of the information needed to use ENCELTO™ safely and effectively.

See full Prescribing Information for ENCELTO.

ENCELTO (revakinagene taroretcel-lwey) implant, for intravitreal use

Initial U.S. Approval: 2025

INDICATIONS AND USAGE

ENCELTO is indicated for the treatment of adults with idiopathic macular telangiectasia type 2 (MacTel).

DOSAGE AND ADMINISTRATION

Recommended Dose

For intravitreal implantation only

- ENCELTO is administered by a single surgical intravitreal procedure performed by a qualified ophthalmologist.
- The recommended dose is one ENCELTO implant per affected eye. Each ENCELTO implant contains 200,000 to 440,000 allogeneic retinal pigment epithelial cells expressing recombinant human ciliary neurotrophic factor (rhCNTF) (NTC-201-6A cell line), a neurotrophic factor.

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- Active or suspected ocular or periocular infections.
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ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

ADVERSE REACTIONS (cont'd)

Clinical Trials Experience (cont'd)

The safety data described in this section reflects exposure to ENCELTO in two clinical trials, Study 1 (NTMT-03-A) and Study 2 (NTMT-03-B) and are pooled for analysis. A total of 117 patients received ENCELTO, and 111 patients underwent a sham procedure and were followed for a duration of 24 months.

Serious adverse reactions occurred in six patients (5%) including suture related complications (n=5) and implant extrusion (n=1).

Table 1 lists the most common adverse reactions that occurred in ≥2% patients and with higher frequency in ENCELTO group compared to Sham group in Study 1 and Study 2.

Table 1. Adverse Reactions occurring in ≥2% of Patients and with higher frequency in ENCELTO group compared to Sham group in ENCELTO studies*

Adverse Reactions	ENCELTO (N=117) n (%)	Sham (N=111) n (%)
Conjunctival hemorrhage	36 (31)	29 (26)
Delayed dark adaptation	27 (23.1)	1 (1)
Foreign body sensation in eyes	18 (15)	15 (13.5)
Eye pain	18 (15)	10 (9)
Suture related complication**	18 (15.4)	3 (2.7)
Miosis	18 (15.4)	0 (0.0)
Conjunctival hyperemia	13 (11)	9 (8)
Eye pruritus	10 (9)	4 (3.6)
Ocular discomfort	10 (9)	1 (1)
Vitreous hemorrhage	10 (8.5)	0 (0.0)
Vision blurred	8 (7)	4 (4)
Headache	8 (7)	1 (1)
Dry eye	7 (6)	2 (2)
Eye irritation	6 (5.1)	2 (2)
Cumulative cataract incidence	6 (5)	0 (0)
Vitreous floaters	6 (5)	0 (0.0)
Severe visual loss>15 letters***	4 (3)	0 (0)
Eye discharge	4 (3.4)	1 (0.9)
Anterior chamber cell	4 (3.4)	0 (0.0)
Iridocyclitis	3 (2.6)	0 (0)

*Pooled data from Study 1 and Study 2; Adverse reaction rates were comparable between the two studies

**Suture related complications include exposed suture, foreign body sensation, conjunctival wound dehiscence, painful sutures, suture irritation, suture granuloma, scleral wound opening, and itchy suture

***Includes one case of visual loss due to cataract formation which remained unresolved at the end of the study

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no data on the use of ENCELTO in pregnant women. Endogenous CNTF is naturally found in maternal plasma, placental cells, and umbilical cord blood. It is not known if the use of ENCELTO increases CNTF above naturally occurring levels in these tissues.

In animal reproduction studies, subcutaneous administration of rhCNTF to pregnant rats and rabbits demonstrated no evidence of teratogenic effects on the fetus. However, when administered to rabbits at a dose level of 10ug/kg/day, a decrease in implantations and live fetuses was observed. When administered to rats at a dose level of 100ug/kg/day a decrease in corpora lutea was observed.

The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

See *Risk Summary* for details on data.

Lactation

Risk Summary

There is no data on the presence of ENCELTO in human milk, its effects on the breastfed infant, or its impact on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENCELTO and any potential adverse effects on the breastfed infant from rhCNTF or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of ENCELTO have not been established in pediatric patients.

Geriatric Use

There were 38 patients (32%) 65 years of age and older and two patients (1%) 75 years of age and older in Study 1 and Study 2 who received ENCELTO. Clinical studies of ENCELTO did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

Manufactured for:
Neurotech Pharmaceuticals, Inc.
Cumberland, RI 02864

ENCELTO™
(revakinagene taroretcel-lwey)
implant, for intravitreal use

neurotech

US-EO-PM-250200024 04/2025

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By Yannet Daniel, BS; Xiru Lyu, MS; Cagri Besirli, MD, PhD; and Emily Eton, MD

KEEP UP WITH THE IRD PATIENT STANDARD OF CARE

BY CHRISTINE KAY, MD; VINIT B. MAHAJAN, MD, PHD; AND JOSE PULIDO, MD, MS, MBA, MPH, GUEST MEDICAL EDITORS

With many gene therapies under evaluation in clinical trials for rare retinal conditions and one FDA-approved retinal gene therapy, genetic testing for inherited retinal disease (IRD) has become increasingly important for us in the clinic. In fact, our editors (along with the AAO) would argue that offering or facilitating genetic testing for monogenetic IRD patients is now a part of the standard of care. Hower, genetic testing for IRDs remains a complex and nuanced process that requires significant time and expertise to execute properly.

It also takes time and training to review and synthesize the clinical trial data for retinitis pigmentosa, Stargardt, Usher syndrome, choroideremia, Leber congenital amaurosis, and any number of other rare retinal conditions—whether it's natural history studies or investigations of novel therapies.

All this effort on the clinician's part is necessary to ensure they can properly advise patients with an IRD on potential clinical trials, which differs widely depending on the patient's genetic diagnosis and stage of disease.

Now, recently released FDA guidance adds further nuance to the field. The draft guidance is designed to help developers use existing scientific and regulatory knowledge to more efficiently bring promising gene therapies to patients. The document acknowledges, "The ability to leverage prior knowledge to expedite product development may be particularly helpful in the context of GE [genome editing] products intended to treat rare diseases, many of which may be serious and life threatening."[1]

Needless to say, IRD is not an easy field, and it's not for everyone. However, all retina specialists see patients with suspected or diagnosed IRD at some point or another, and knowing how to care for these patients is imperative.

To that end, this issue is designed to help bolster your clinical acumen regarding the management of IRDs, including genetic testing, the challenges of specific patient populations, diagnosing rare IRDs, and clinical trials for patients with IRDs. Sidney A. Schechet, MD, and his team provide a high-level look at genetic testing in the clinic, noting that it can take up to 15 years for some patients to receive a correct diagnosis.[2]

Other articles touch on managing IRDs in children (by Ramiro Maldonado, MD, and his colleagues at Duke) and the promise of gene-agnostic therapies (by an international team of researchers from Turkey and New York, led by Stephen H. Tsang, MD, PhD). Breaking from the clinical side of things, Melissa Yuan, MD, and Ahmad Al Moujahed, MD, PhD, discuss the challenge of IRD clinical trial endpoints, including the search for endpoints that better assess visual changes in patients with low vision. Lastly, several teams came together to provide a challenging mystery case article that will test your diagnostic acumen.

Whether genetic testing, clinical characterization of disease progression, and clinical trial candidacy is part of your practice or not, it's certainly something you must have a general understanding of to deliver a positive message and facilitate the best referral to an IRD specialist. We hope this issue boosts your confidence in understanding some of the complexities in caring for patients with an IRD and adds to the armamentarium of your clinical practice. ■

1. Leveraging prior knowledge in the development of human gene therapy products incorporating genome editing. FDA. June 2026. Accessed June 10, 2026. tinyurl.com/decww9f7
2. Shah AH, Park E, Luke T, Xu Q, Jewell A, Couser NL. The role of genetic testing in avoiding diagnostic delays in inherited retinal disease. [published online ahead of print April 27, 2024]. *Retin Cases Brief Rep.*

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RT NEWS

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STUDY IDENTIFIES OCTA BIOMARKERS OF ALZHEIMER DISEASE

A study published in *JAMA Ophthalmology* found that various OCT angiography (OCTA) biomarkers in the retina, choroid, and choriocapillaris are associated with cognitive degeneration and Alzheimer disease (AD). In particular, retinal vessel skeleton density (VSD) and choriocapillaris flow deficit (CCFD) were identified as potential indicators of cognitive status.[1]

The cross-sectional study enrolled 103 total patients, including 49 cognitively normal participants, 29 with mild cognitive impairment (MCI), and 25 with AD dementia, all of whom underwent swept-source OCTA. The results showed that, among 103 patients, the adjusted mean for CCFD was lower in those with MCI (8.12%) than AD dementia (9.07%, $P = .01$) but higher in those with AD dementia than control patients (8.33%, $P = .04$). In multivariate models, VSD ($P < .001$) and CCFD ($P < .001$) were both significantly associated with cognitive status, with an area under the curve of 0.72 to 0.87 in a test set of 21 participants (10 controls, six MCI, five AD dementia).[1]

These quantitative microvascular changes on OCTA may serve as accessible, noninvasive biomarkers of cognitive neurodegeneration in AD; as such, longitudinal validation in large clinical trials is warranted, the study authors concluded in their paper.[1]

1. Zhang Y, Jiang Y, Edalati K, et al. Quantitative swept-source optical coherence tomography angiography indicators of neurovascular dysfunction in Alzheimer disease. *JAMA Ophthalmol*. 2026:e261986.

FDA ISSUES DRAFT GUIDANCE TO ACCELERATE DEVELOPMENT OF GENE THERAPY PROGRAMS

Draft guidance issued in June by the FDA aims to help gene therapies progress more efficiently by allowing developers to leverage existing scientific and regulatory knowledge throughout the development process.[1] This new guidance could significantly affect the development of gene therapy candidates for inherited retinal diseases (IRDs), potentially leading to treatment options becoming available to patients sooner.[2]

When finalized, the draft guidance will provide recommendations for sponsors developing human gene therapy products and outline how companies can use publicly available information and established platform knowledge—including manufacturing and controls data, nonclinical study results, and clinical evidence—to streamline regulatory submissions and reduce development burdens. Sponsors seeking to rely on existing data must demonstrate how the information applies to their specific product and development program, the FDA clarified in the guidance.[1]

"For years, one of the biggest barriers to getting gene therapies approved has been the regulatory pathway. Proving efficacy in rare diseases is difficult when patient populations are small and traditional trial designs simply don't fit," said Jason Menzo, CEO of the Foundation Fighting Blindness. "The FDA's new draft guidance is a meaningful step toward addressing that."[2] The draft guidance is currently available for public comment on the Federal Register until September 1, 2026, after which the FDA will review all feedback prior to issuing a final version of the guidance.[2]

1. US Food & Drug Administration. Guidance document: leveraging prior knowledge in the development of human gene therapy products incorporating genome editing. June 2026. Accessed June 30, 2026. www.fda.gov/regulatory-information/search-fda-guidance-documents/leveraging-prior-knowledge-development-human-gene-therapy-products-incorporating-genome-editing
2. FDA issues draft guidance to accelerate development of gene therapies using existing scientific knowledge. Eyewire+. June 8, 2026. Accessed June 30, 2026. eyewire.news/news/fda-issues-draft-guidance-to-accelerate-development-of-gene-therapies-using-existing-scientific-knowledge

SEMAGLUTIDE USE DOES NOT AFFECT RISK FOR WET AMD

A large international study published in *Ophthalmology* found no difference in the risk for developing wet AMD associated with semaglutide use in adults with type 2 diabetes compared with other glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and non-GLP-1 RAs.[1]

The study included 227,971 new users of semaglutide and found that the risk of wet AMD among these patients was

not significantly different from those taking other medications for diabetes management, including dulaglutide, empagliflozin, sitagliptin, and glipizide. Furthermore, there was no evidence of either increased or decreased risk for wet AMD associated with semaglutide exposure (P = .92), nor with any of the other GLP-1 RA and non-GLP-1 RA drugs evaluated.[1]

1. Cai CX, Toy B, Martin B, et al. Semaglutide and neovascular age-related macular degeneration among adults with type 2 diabetes: an OHDSI Network Study [published online ahead of print June 1, 2026]. *Ophthalmology*.

OCULAR THERAPEUTIX TO SUBMIT NDA FOR WET AMD THERAPY

Ocular Therapeutix announced it has aligned with the FDA on plans to submit a new drug application (NDA) for OTX-TKI (Axpaxli) for the treatment of wet AMD in the fourth quarter of 2026. The planned NDA submission is based on positive efficacy and safety data from the phase 3 SOL-1 trial, as well as interim safety data from the ongoing SOL-R trial.[1]

The company reported that SOL-1 met its primary endpoint of superior vision maintenance at week 36 (P = .0006) compared with aflibercept (Eylea, Regeneron). Data also showed that the treatment effect strengthened over time and was supported by anatomic outcomes and statistically significant sensitivity analyses. The study was conducted under a Special Protocol Assessment agreement with the FDA.[1]

Ocular Therapeutix plans to submit the NDA through the FDA's 505(b)(2) pathway, which may allow for a more streamlined review process available for modified versions of previously approved therapies.[1]

1. Ocular Therapeutix aligns with FDA on planned Axpaxli NDA submission for wet AMD. Eyewire+. June 18, 2026. Accessed June 30, 2026. eyewire.news/news/ocular-therapeutix-aligns-with-fda-on-planned-axpaxli-nda-submission-for-wet-amd

CAN AI EYEGLASSES HELP PATIENTS WITH LOW VISION?

AI smart eyeglasses may be able to help patients with low to no vision, but limitations remain, according to Carol Shields, MD, and her team of researchers at the Ocular Oncology Service of Wills Eye Hospital.[1]

To investigate the utility of AI smart glasses, six study authors used Meta's Ray-Ban second-generation AI eyeglasses to read standard text and children's books and identify and describe objects and money. Their findings, published in *JAMA Ophthalmology*, showed that the eyeglasses identified common objects with 99% accuracy. When tasked with describing objects, the eyeglasses had a color discrimination and counting accuracy of 64% and 50%, respectively, while the accuracy for object directionality was 83%. When using the eyeglasses for reading medication labels, food labels, handwriting, and children's books, the tool performed best with children's book with a mean accuracy of 93%; accuracy was worse for handwriting (88%) and standard label text (59%). The tool was able to identify paper money with 91% accuracy but only had a 2% accuracy for coins.[1]

"AI smart eyeglasses may offer a unique intervention for patients with low to no vision, performing best for identifying common objects, identifying neutral colors, and reading children's books," the authors concluded in their paper.[1]

However, clinicians should warn patients with low vision to be wary of the limitations of these tools until technology evolves in this field to address them, they said.[1] ■

1. Medina RJ, Botros S, Gandhi P, et al. Artificial intelligence smart eyeglasses for the detection and description of stationary objects [published online ahead of print June 25, 2026]. *JAMA Ophthalmol*.

Eyewire+ Pharma Update

- **Atsena Therapeutics** dosed the first patient in the phase 3 LIGHTHOUSE trial evaluating ATSN-201, an investigational gene therapy for X-linked retinoschisis.
- **Lumibird Medical** launched Integre LIO, a fully wireless integrated laser indirect ophthalmoscope for panretinal photocoagulation. The FDA-cleared device includes a cordless headset, wireless foot pedal, 532-nm diode-pumped solid-state laser, heads-up display, and smart footswitch.
- **Ollin Biosciences** secured $330 million in Series B financing to support phase 3 development of OLN324, a VEGF/Ang2 bispecific antibody for the treatment of diabetic macular edema and wet AMD, and to advance OLN102, a TSHR/IGF-1R bispecific antibody for thyroid eye disease (TED) and Graves disease.
- **Samsung Bioepis** announced plans to relaunch its biosimilar product, ranibizumab-nuna (Byooviz), in the United States in partnership with Harrow.
- **Shenzhen Oculgen Biomedical Technology** enrolled the first US patient in the phase 2/3 STAT trial evaluating OCUL101, an investigational therapy for wet AMD that uses a dual-target mechanism to address both angiogenic and complement-mediated pathways.
- **Viridian Therapeutics** received FDA approval for veligrotug-vvze (Lumvoa), an insulin-like growth factor-1 receptor antagonist, for the treatment of TED.

Want more retina news from ***Eyewire+***?

RETINA: THEN AND NOW

As part of our 20th anniversary, *Retina Today* is digging into the archives to reflect on how much the profession has changed.

JULY/AUGUST SPOTLIGHT: MANAGING SUBRETINAL MEMBRANE

In 2006, Gregg T. Kokame, MD, MMM, FASRS, contributed an article to *Retina Today* on peripapillary subretinal neovascular membranes (SRNVM) entitled *An Indication for Surgery in the Antiangiogenic Era*. The article detailed the need for surgery in certain patients, even with the advent of anti-VEGF therapy. Here, Dr. Kokame shares how the treatment paradigm for various AMD subtypes has changed and what new therapies are in the pipeline.

– Rebecca Hepp, MA, Editor-in-Chief

RETINA TODAY (RT): How were you treating SRNVM in 2006?

Gregg T. Kokame, MD, MMM, FASRS: In 2006, the subretinal surgery for wet AMD trials had recently shown a negative result, as the retinal pigment epithelium and photoreceptors did not recover after removal of the SRNVM.[1] However, in a specific subset of patients with wet AMD, peripapillary SRNVM that spared the fovea could be removed with maintenance of good vision and limited need for supplemental therapy.[2]

RT: How has the treatment of SRNVM changed over the past 20 years?

Dr. Kokame: Since then, anti-VEGF therapy has proven very efficacious, and intravitreal anti-VEGF injections are now the treatment of choice for wet AMD. Subretinal surgery is now rarely used for peripapillary SRNVM. In addition, our diagnosis of AMD has become more advanced, further affecting the treatment approach.

For example, I recently saw a 79-year-old patient with a peripapillary SRNVM in the right eye. Although VA remained 20/20, there was peripapillary macular edema, nasal exudates depositing into the edge of the fovea, and serous detachment. ICG angiography showed that this was a specific subtype of wet AMD, polypoidal choroidal vasculopathy (PCV), which was rarely reported back in 2006.

PCV is a type of SRNVM in which there are polypoidal dilations, often at the tips of the SRNVM.[3] The EVEREST II study showed that combination photodynamic therapy (PDT) and anti-VEGF therapy had a superior response than anti-VEGF alone for PCV[4]; thus, this patient underwent combined therapy and did not require supplemental treatment for 3.5 years with maintenance of good vision. There was then a recurrence of the peripapillary SRNVM, which required frequent anti-VEGF injections, as PDT was no longer available.

RT: What are the biggest unmet needs in the treatment of wet AMD?

Dr. Kokame: PCV is known to be relatively resistant to anti-VEGF injections,[5] leading to the need for chronic treatment and significant treatment burden. This may be addressed by many of the newer therapies for wet AMD. For example, gene therapy creating an ocular biofactory for anti-VEGF is showing promising results. In addition, supplemental treatment with tyrosine kinase inhibitors may also decrease the treatment burden. Medications with combination targets or targets other than anti-VEGF may also decrease treatment burden, as well as possibly allowing improved vision results. ■

1. Bressler NM, Bressler SB, Hawkins BS, Marsh MJ, Sternberg P Jr, Thomas MA; Submacular Surgery Trials Pilot Study Investigators. Submacular surgery trials randomized pilot trial of laser photocoagulation versus surgery for recurrent choroidal neovascularization secondary to age-related macular degeneration: I. Ophthalmic outcomes submacular surgery trials pilot study report number 1. *Am J Ophthalmol*. 2000;130(4):387-407.
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FURTHER READING

READ NOW

An Indication for Surgery in the Antiangiogenic Era
December 2006
By Gregg T. Kokame, MD, MMM, FASRS

ONE TO WATCH

RT Retina Today

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Maura Di Nicola, MD

Dr. Di Nicola's advice: Let your decisions be guided by the kind of physician and person you want to become. Seek environments that stimulate your curiosity, challenge and support you, and allow you to care for patients in a way that feels authentic.

WHERE IT ALL BEGAN

I was born and raised in central Italy. My parents are both physicians and, growing up, I was sure I would never follow in their footsteps. In high school, I dreamt of a career as a journalist or in theater. Somehow, something changed during my last year of high school, and I decided to give medicine a chance. I applied and was accepted to medical school in Milan, where I later completed my ophthalmology residency.

MY PATH TO RETINA

During medical school, I worked with Giulio Modorati, MD, an ocular oncologist and uveitis specialist, and fell in love with the patient interaction, challenges of diagnosis, and the intricacies of treatment. I rotated as an observer at Wills Eye Hospital on the ocular oncology service with Carol Shields, MD, which solidified my passion. During residency, I became even more fascinated by the complexity and variety of retinal diseases.

After residency, I completed two ocular oncology fellowships at Wills Eye Hospital and the University of Cincinnati, and I then pursued an additional fellowship in medical retina and uveitis at the University of Illinois in Chicago.

SUPPORT ALONG THE WAY

Francesco Bandello, MD, facilitated my rotation as a student and fellowship with Dr. Shields. He continues to support my career from abroad, and I cherish the moments when we can catch up at various conferences. Dr. Shields taught me about ocular oncology and the importance of staying organized, paying meticulous attention to detail, and developing a systematic process in research.

I owe a lot to my uveitis mentors, Ann-Marie Lobo-Chan, MD, and Pooja Bhat, MD, who created my foundation for how to think through uveitis cases. Just as importantly, they showed me how vital it is to communicate with compassion and humility.

I am forever grateful to all the retina attendings at the University of Illinois in Chicago, especially R.V. Paul Chan, MD, MSc, MBA, who was an excellent teacher in clinic and is the essence of a true leader. He created, and continues to create, opportunities for my professional growth.

Finally, my husband, who is also a retina specialist and ocular oncologist, has been a constant source of support, offering endless encouragement and perspective to continue to grow professionally.

AN EXPERIENCE TO REMEMBER

As a new faculty member at Bascom Palmer Eye Institute, I cared for a patient in her early 20s who was visiting family in Miami when she noticed acute onset blurred vision. She presented to our emergency department with a melanoma too large to avoid enucleation. She had oculodermal melanocytosis but had never been told she was at risk for developing uveal melanoma. Delivering this diagnosis to such a young patient was emotionally challenging. Years later, she shared that this was the scariest time of her life, yet the way she was cared for helped her feel calm and supported. Hearing that reinforced for me how much our presence and approach matter, and the importance of the human side of our work, especially in moments of great vulnerability. ■

Maura Di Nicola, MD, is an assistant professor of Clinical Ophthalmology at Bascom Palmer Eye Institute in Miami. She is a consultant for Abbvie and SpringWorks Therapeutics. You can reach Dr. Di Nicola at mauradinicola@gmail.com.

HIGHLIGHTS FROM THE 2026 DUKE FAVS COURSE

Retina fellows gathered to learn from the experts and gain hands-on wet lab experience.

BY EMILY H. JUNG, MD; NAVEEN KARTHIK, MD; HALEY S. D'SOUZA, MD, MS; OMAR A. HALAWA, MD; AND RYAN SAMEEN MESHKIN, MD

The 2026 Duke Fellows Advanced Vitreous Surgery (fAVS) Course, held March 27-28, 2026, in Durham, North Carolina, brought together leaders in vitreoretinal surgery, medical retina, uveitis, inherited retinal disease (IRD), and ocular oncology for high-yield education, hands-on training, and collaborative discussion. The program was directed by Lejla Vajzovic, MD, with co-directors Dilraj Grewal, MD; Xi Chen, MD, PhD; and Durga S. Borkar, MD, MMCi. The course brought together expert faculty and fellows for a dynamic educational experience featuring didactic lectures, interactive panel discussions, fellows' surgical video presentations, and an extensive wet lab showcasing the latest innovations and technologies in vitreoretinal surgery.

MEDICAL RETINA EDUCATION

The meeting opened with a retinal pharmacotherapy session on advances in AMD, diabetic retinopathy, retinal vein occlusion, IRD, and uveitis. Margaret A. Chang, MD, MS, discussed tips for implanting the port delivery system with ranibizumab (Susvimo, Genentech/Roche). Mathew W. MacCumber, MD, PhD, highlighted the need for individualized care based on the DRCR Retina Network's recommendations. Nieraj Jain, MD, then reviewed optogenetics, gene editing, and AI-enabled low vision technologies in IRD.

The next session focused on pediatric retina and ocular oncology. Safa Rahmani, MD, stressed that success in pediatric retina often depends on rapport, dilation, and flexibility. When possible, try to make the examination a game with your youngest patients, she advised. Basil K. Williams Jr, MD, gave a case-based talk on ocular tumors, emphasizing the importance of obtaining a history and thinking carefully before taking patients to the OR who have unexplained or unusual findings. Michael I. Seider, MD, noted that recognizing pseudomelanomas can be equally as important as identifying melanoma itself; careful assessment can prevent both overdiagnosis and unnecessary treatment.

Figure. The 2025 Robert Machemer/IRRF Fellowship awardee, Dr. Mohammed, gave a talk on the biomechanics of the vitreous in vivo with the use of brillouin spectroscopy.

Image courtesy of Kevin Caldwell Photography

The Robert Machemer, MD/International Retinal Research Foundation (IRRF) Fellowship was introduced by Cynthia A. Toth, MD. In the spirit of Dr. Machemer's belief that "progress comes from doing the unconventional," the fellowship supports surgical fellows in their transition to independent research early in their careers. The 2025 Robert Machemer/IRRF Fellowship awardee, Taariq Mohammed, MD, shared

pearls on investing in strong mentorship relationships, developing research plans, and finding the right niche in academic ophthalmology (Figure). He then discussed his own research endeavors, which have pioneered imaging of the vitreous using brillouin spectroscopy.

SURGICAL EDUCATION

The surgical curriculum emphasized practical approaches to complex conditions and OR issues such as ergonomics (by Dr. Williams), patients without a posterior vitreous detachment (by Dr. Chen), the costs of retinal detachment (RD) repair (by Jason Fan, MD, PhD), risk factors for proliferative vitreoretinopathy (by Dr. MacCumber), and core principles of surgery for diabetic tractional RD (by Yannek I. Leiderman, MD, PhD). Alice Zhang, MD, took to the podium to review her own surgical tips for managing lens subluxation and reviewed approaches to scleral buckle surgeries.

The next session focused on the practical aspects of building a career in retina, including coding and billing (by Dr. Chang), collaboration between academia and industry (by Dr. Toth), and the transition from fellowship to independent practice (by Dr. Rahmani).

The day concluded with the fellows' surgical video session. Featured cases included combined tractional and rhegmatogenous RDs (by Mitchell Allphin, MD), submacular hemorrhage (by Beatriz Deud, MD), complex tractional RD with subretinal fibrotic bands and retained subretinal perfluorocarbon/oil (by Irmak Karaca, MD), biopsies (by Joseph Luvisi, MD), and an atypical intraoperative event in which subretinal fluid disappeared following perfluoro-octane injection due to a scleral rupture (by Linus Shen, MD).

MORE MEDICAL RETINA UPDATES

Day two began with discussions on treating wet AMD by Prithu S. Mettu, MD, and real-world data on pegcetacoplan (Syfovre, Apellis/Biogen) and avacincaptad pegol (Izervay, Astellas) by Eleonora G. Lad, MD, PhD. Majda Hadziahmetovic, MD, explored the role of AI in diabetic retinopathy screening, noting that it can identify changes before symptoms develop. She then highlighted the Duke Remote Retinal Imaging Program and other initiatives. Amol A. Sura, MD, presented a stepladder approach to immunotherapy in uveitis based on the ADVISE trial, and Oleg Alekseev, MD, PhD, reviewed cases in which genetic testing for IRD influenced patient counseling and management.

In the next session, Ramiro S. Maldonado, MD, gave an overview of the evolving strategies and current ongoing trials for treating Stargardt disease, including oral therapies, cell replacement, optogenetics, and the PRIMA implant (Science Corporation). Miguel A. Materin, MD, led a case-based discussion on differentiating benign versus malignant lesions in the eye. The session concluded with a case panel, including a discussion of retina pigment epithelium tears after intravitreal injections, building a list of differentials for hereditary maculopathies, recognizing salient features of toxic maculopathies (particularly from pentosan polysulfate), and managing delayed onset endophthalmitis after cataract surgery.

WET LAB AND EMERGING TECHNOLOGIES

The wet lab experience, a cornerstone of the course, offered fellows the opportunity to refine surgical skills and explore emerging technologies. Stations included subretinal delivery, membrane peeling, scleral fixation techniques, port delivery system implantation, and various intravitreal and suprachoroidal implants/injections. Attendees also engaged with next-generation surgical systems such as the Bausch + Lomb's SeeLuma 3D heads-up digital visualization platform, Alcon's Unity Vitreoretinal Cataract System, DORC's EVA Nexus machine, and Zeiss' Rescan iOCT and Artevo 800.

The course concluded with the well-loved annual, "Great Job Search Panel," moderated by Sharon Fekrat, MD, FASRS, during which panelists shared their pearls for job contract negotiations and starting a position as a new attending. The experts explored various practice setting considerations, the importance of clinic schedules, and how to find research opportunities. They all agreed that who you work with is the most important factor when searching for the right job. ■

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SAVE THE DATE:
13th annual Fellows Advanced Vitreous Surgery (AVS) Course and 24th Duke AVS Course
March 18-20, 2027

EMBRACING TRAINEES AT VBS 2026


This year's trainee-focused day featured pearls on succeeding at work and home, advocacy, early career challenges, billing, and more.

BY OGUL E. UNER, MD, AND BRIAN T. CHENG, MD

The 14th annual Vit-Buckle Society (VBS) meeting, held April 9-11, 2026, in Las Vegas, included a trainee program packed with clinical pearls and friendly competition. Here, we highlight the educational panels, Fellows track, Fostering Careers for Upcoming Stars (FOCUS) program, and the Fellows' Foray video competition.

AN EDUCATIONAL MORNING

The day began with a panel on professional societies, business, and personal aspirations, which included a candid discussion on what it means to succeed in retina. R.V. Paul Chan, MD, MSc, MBA, FACS, reflected on his own personal and professional challenges, including changes in his family dynamic and the pressure of raising children, especially for women in the profession (Figure 1).

Camille Palma, MD, discussed the myth of a perfect work-life balance, instead framing fulfillment as meaningful patient care, teaching, and community. She also mentioned imposter syndrome, describing it as a "humble confidence" that can be turned into a positive force that encourages introspection and lifelong learning.

Christina Y. Weng, MD, MBA, encouraged trainees to get involved with professional societies early in their careers, while Frank L. Brodie, MD, MBA, shared insights from collaborating with start-ups, stressing the importance of negotiating flexibility in a job rather than focusing only on compensation. Panelists returned to themes of mentorship, authenticity, community, and learning when to say "no" to build sustainable and fulfilling careers.

During the Advocacy 101 panel, moderated by Mrinali Gupta, MD, experts touched on Medicare payment reform, prior authorizations, and step therapy. The panelists discussed the need to educate patients on the source of rising prices (ie, insurance, hospitals, and broader health care economics, not physicians). The panel also addressed Medicare Part B drug pricing, buy and bill strategies, a new proposed model to tie drug costs to an international index, OR access issues, and scope of practice.

Image courtesy of Kevin Caldwell Photography

Figure 1. The Retina and Beyond panel discussion, moderated by Dr. Warren, included (left to right) Drs. Brodie, Wang, Palma, and Chan.

Aleksandra Rachitskaya, MD, noted that these advocacy issues affect everyone, saying "If you are not at the table, you're on the menu." AAO Advocacy Ambassadors Lauren Kiryakoza, MD, and Sean Berkowitz, MD, MBA, discussed their work on Capitol Hill and how powerful trainee testimonies can be, with a call to action for all trainees to join state societies and attend the AAO's Mid-Year Forum.

FELLOWS PROGRAM

The first Fellows program panel, moderated by Dr. Gupta, focused on navigating the transition into practice, emphasizing the importance of aligning career decisions with personal priorities, location, family considerations, and long-term quality of life. Phoebe Mellen, MD, shared that fellows should understand a practice's ownership structure, financial decision-making, compensation models, and referral culture before signing with a practice. Rebecca Soares, MD, MPH, encouraged fellows to review the practice's profit-and-loss statements, while Nikisha Kothari, MD, recommended fellows discuss the position with former employees and negotiate items often omitted from contracts, such as family leave. Jay Sridhar, MD, recommended fellows reach out to

Image courtesy of Kevin Caldwell Photography

Figure 2. The Fellows' Foray competition concluded with Dr. Virgolino (center) being crowned the winner.

mentors and industry representatives in the area to learn more about a practice's work culture.

The final session, moderated by Royce Chen, MD, and Grant Justin, MD, focused on advances in the field. Aliaa Abdelhakim, MD, PhD, spoke about gene-agnostic approaches, such as optogenetics and ultra-personalized medicine with anti-sense oligonucleotides or CRISPR. Tedi Begaj, MD, discussed emerging diagnostics and therapeutics in uveitis, including immune cell profiling and the promise of vamikibart (Genentech/Roche) as a potential interleukin-6 inhibitor for the treatment of uveitic macular edema. Steven Yeh, MD, discussed the positive results of suprachoroidal drug delivery platforms, with suprachoroidal triamcinolone acetonide (Xipere, Bausch + Lomb) injections showing no significant adverse events over the 3-year study period. Eliot Dow, MD, PhD, shared exciting AI platforms for retina, emphasizing the need to standardize real-world imaging data and expand electronic health record-based AI platforms. Finally, Durga Borkar, MD, MMCi, discussed the use of big data in retina, particularly it's utility in trial data analysis.

FELLOWS' FORAY

During the Fellows' Foray, eight retina fellows competed for the audience's votes with surgical cases, each more curious than the last. Here's a roundup of the lively discussion among the presenters, moderators, and audience.

Caroline Awh, MD, from Massachusetts Eye and Ear, presented the case of a 17-year-old patient with von Hippel-Lindau disease complicated by hemangioblastoma-associated tractional retinal detachment (RD) and a large macular hole. Management included a scleral buckle, removal of the fibrous sheets, and diathermy to feeder vessels, ultimately reattaching the retina and closing the macular hole. The moderators highlighted the value of support from the scleral buckle, given the possible incomplete removal of traction.

Viet Chau, MD, from Associated Retinal Consultants of Beaumont, shared a case initially diagnosed as a rhegmatogenous RD (RRD) and horseshoe tear; however, the team discovered a serous RD intraoperatively. An external scleral cutdown was used to drain the subretinal fluid without making an iatrogenic break. The panel agreed that this case was an excellent example to encourage open discussion about diagnostic errors and surgical flexibility.

Christopher Chung, MD, MS, from Illinois Eye and Ear Infirmary, presented an RRD in an aphakic eye after an open globe injury and dense corneal scarring. Given the poor corneal view and dense posterior synechiae, a temporary keratoprosthesis was placed, followed by PFO to localize the breaks. After the retina was flattened, silicone oil was placed, and a penetrating keratoplasty was performed. The moderators agreed that close collaboration with the anterior segment surgeons is necessary in these complex cases.

Joseph Giacalone, MD, PhD, from Mayo Clinic, introduced his technique for a nylon suture snare to remove large intraocular foreign bodies not amenable to removal with forceps. In this case, a glass fragment was safely removed using a 5-0 nylon suture looped through a 23-gauge cannula. Drs. Capone and Gupta shared their own strategies for removing large or smooth foreign bodies and praised this approach for using materials readily available in the OR.

(Continued on page 18)

SMILEY-SHAPED POSTERIOR RETINOTOMY FOR LARGE SMH

This surgical alternative is useful for thick and organized hemorrhages.

BY MANISH NAGPAL, MS, FRCS, FASRS; ANJANA MIRAJKAR, MS, FVRS; AND MALVIKA SINGH, MS, DNB, FICO

A large, submacular hemorrhage (SMH) is a vision-threatening condition commonly associated with wet AMD, although it may also arise from polypoidal choroidal vasculopathy, myopic choroidal neovascularization, retinal arterial macroaneurysm, trauma, inflammatory choroidal neovascular membranes, or idiopathic causes (Figures 1-4). Experimental studies have demonstrated that rapid photoreceptor injury can occur from subretinal blood due to iron toxicity, mechanical disruption, and impaired metabolic exchange.[1,2]

Although pneumatic displacement with intravitreal tissue plasminogen activator (tPA) and expansile gas is the most widely used treatment, with select cases also benefiting from subretinal tPA administration to facilitate more direct clot lysis and displacement, outcomes may be suboptimal for large, thick, and/or organized hemorrhages.[3-7]

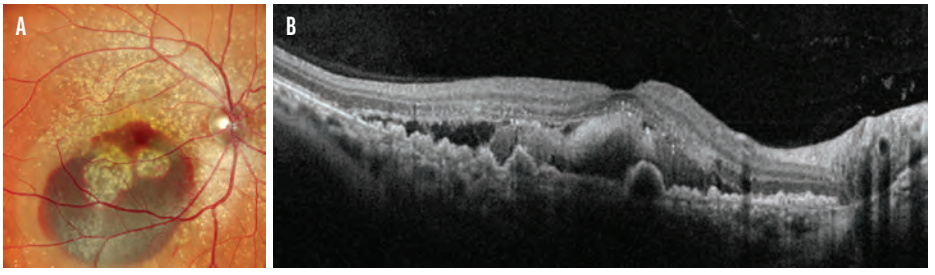

Figure 1. Preoperative fundus photography showed confluent drusen at the posterior pole consistent with Doyne honeycomb dystrophy and a medium-sized subretinal hemorrhage due to active macular neovascularization (A). OCT imaging showed drusenoid pigment epithelial detachments with subretinal fluid and subretinal hyperreflective material, consistent with hemorrhage (B).

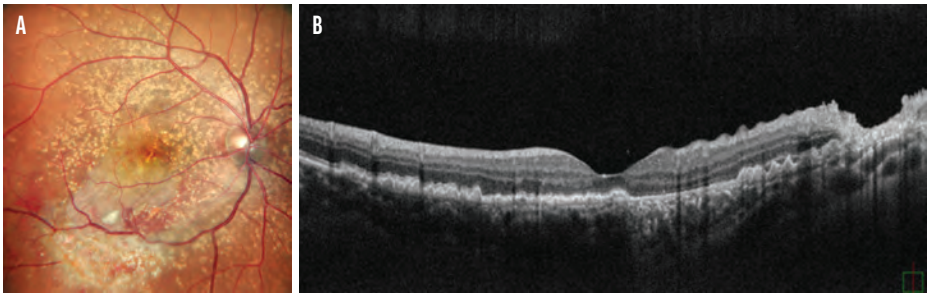

Figure 2. Postoperative fundus photography demonstrated a smiley-shaped posterior retinotomy placed at the area of maximal clot thickness and away from the fovea, with associated subretinal fibrosis (A). OCT imaging demonstrated complete resolution of subretinal fluid with restoration of foveal contour and focal nasal disruption of the ellipsoid zone (B).

We describe a modified curved ("smiley-shaped") posterior retinotomy technique for direct clot evacuation and report 6-month anatomical and functional outcomes in a consecutive case series of 11 eyes with large SMH (Table).

SURGICAL TECHNIQUE

All eyes underwent standard pars plana vitrectomy. Triamcinolone acetonide was used to facilitate and confirm posterior vitreous detachment. Following core and peripheral vitrectomy, a curved posterior retinotomy was fashioned adjacent to the hemorrhage in an area of maximal clot thickness and away from the fovea, allowing controlled access to the subretinal space without direct foveal manipulation.

The vitrectomy cutter was gently introduced through the retinotomy, and the submacular clot was engaged under high vacuum and carefully aspirated. Infusion pressure was transiently elevated to 60 mm Hg during clot evacuation to

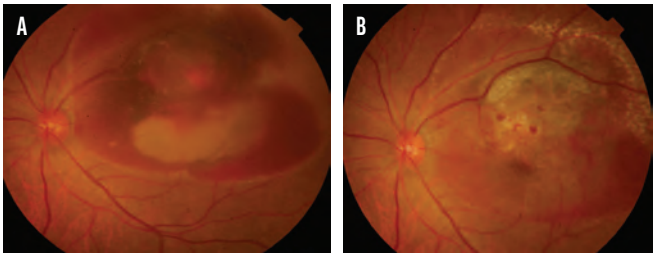

Figure 3. Preoperative fundus photography demonstrated a large subretinal hemorrhage consistent with idiopathic polypoidal choroidal vasculopathy (A). The postoperative fundus photograph demonstrated complete evacuation of the subretinal hemorrhage via smiley-shaped retinotomy with surrounding laser photocoagulation marks and adjacent fibrosis (B).

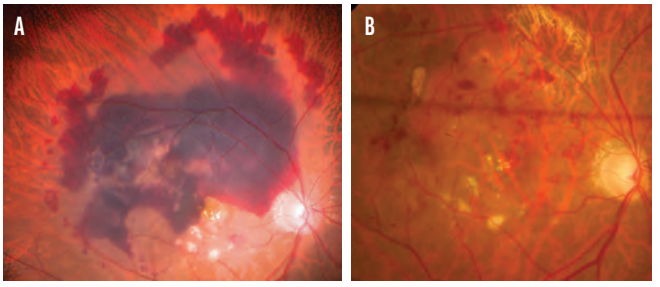

Figure 4. Preoperative fundus photography demonstrated a large subretinal hemorrhage secondary to active choroidal neovascular membrane in wet AMD (A). Postoperative fundus photography demonstrated the site of the smiley-shaped retinotomy with evacuation of the subretinal hemorrhage and minimal residual subretinal fibrosis (B).

reduce intraoperative bleeding and subsequently lowered to address any active bleeding.

Perfluorocarbon liquid was then injected to stabilize and flatten the posterior pole, followed by focal laser photocoagulation at the retinotomy site, fluid-air exchange, and C_3F_8 gas tamponade. This approach is based on principles previously described for surgical drainage of SMH and the use of subretinal tPA and perfluorocarbon liquids.[8-11]

RESULTS

Thirteen consecutive eyes with fovea-involving SMH (symptom duration of 2 to 12 days) were included. Four eyes had received prior intravitreal tPA 24 hours before surgery. Preoperatively, the mean BCVA was 1.78 ± 0.28 logMAR (approximately 20/1,200; range 20/660 to 20/90). The mean central macular thickness (CMT) was 589 ± 147 µm, and OCT imaging showed dense, hyperreflective subfoveal hemorrhage with foveal elevation in each eye.

At 6 months postoperative, mean BCVA improved to 0.52 ± 0.31 logMAR (approximately 20/66; mean gain 1.26 logMAR units; range 20/200 to 20/30), and mean CMT decreased to 232 ± 51 µm. OCT demonstrated complete hemorrhage clearance with restored foveal contour in seven eyes, restored contour with residual thinning in two eyes, and residual subretinal fibrosis in three eyes.

Eyes with complete anatomical restoration achieved superior visual outcomes. No cases of retinal detachment, recurrent hemorrhage, or persistent submacular blood were observed.

A GOOD OPTION IN SELECT CASES

Pneumatic displacement with intravitreal tPA and gas remains the preferred first-line approach for many cases of SMH.[3-5] However, in large, thick, and/or organized hemorrhages, incomplete clot liquefaction and displacement may limit visual recovery.[6,7]

TABLE. VISUAL, ANATOMICAL, AND OCT OUTCOMES OF SMILEY-SHAPED POSTERIOR RETINOTOMY

Case	Preoperative BCVA	Postoperative BCVA	Preoperative CMT (µm)	Postoperative CMT (µm)	Postoperative OCT Outcomes
1	Counting fingers at 2 m	20/50	612	300	Normal foveal contour restored
2	20/90	20/20	560	212	Complete SMH clearance
3	Counting fingers at 3 m	20/200	830	321	Subretinal fibrosis, pigmentary changes
4	Counting fingers, hand motion	20/50	432	194	Foveal contour restored with thinning
5	20/90	20/30	480	290	Complete SMH clearance
6	Counting fingers at 2 m	20/70	934	190	Foveal contour restored with thinning
7	Counting fingers at 4 m	20/90	425	241	Subretinal fibrosis, pigmentary changes
8	Counting fingers at 1 m	20/30	549	211	Normal foveal contour restored
9	Counting fingers at 3 m	20/200	642	160	Subretinal fibrosis, pigmentary changes
10	Counting fingers at 2 m	20/20	450	240	Complete SMH clearance
11	20/200	20/70	634	205	Complete SMH clearance

Abbreviations: CMT, central macular thickness; SMH, submacular hemorrhage

Direct surgical evacuation through a posterior retinotomy offers immediate clot removal, avoids dependence on postoperative positioning, and facilitates rapid anatomic restoration.[8-10] The curved or "smiley-shaped" retinotomy described in this series enables controlled access to the subretinal space while minimizing retinal trauma and preserving foveal integrity.

The significant reduction in CMT and restoration of foveal contour on OCT closely paralleled visual improvement, reinforcing a strong structure-function correlation. Residual subretinal fibrosis was associated with comparatively poorer outcomes, underscoring the importance of early intervention before irreversible photoreceptor damage occurs.

Although limited by its retrospective design and modest sample size, the study showed consistent anatomical and functional improvements, suggesting that this technique represents a valuable alternative approach in selected cases of large SMH. ■

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VIT-BUCKLE SOCIETY

(Continued from page 15)

Tulio Loyola, MD, from Sao Paulo Federal University, presented the case of a 41-year-old patient with bilateral RDs from acute retinal necrosis. Despite a guarded visual prognosis, a bilateral scleral buckle, vitrectomy, and retinectomy led to better-than-expected vision outcomes. He supported early intervention to prevent extensive retinal necrosis that would necessitate a more extensive retinectomy.

Ravin Punamia, MD, from Nethradhama Eye Hospital, discussed a young patient with bilateral funnel RDs due to a tennis ball injury. Repair involved PFO to flatten the retina, retinectomy, and peeling of preretinal and subretinal proliferative vitreoretinopathy. The panel discussed the timing of PVR maturity and the optimal timing of repeat surgery.

Ciro Virgolino, MD, from Fundacao Altino Ventura, presented a case of accidental injection of blue dye into the anterior and posterior chamber during conjunctival tattooing, leading to severe intraocular inflammation and fibrin membrane formation within hours. Management required anterior chamber washout of pigment, gonioscopy-assisted peeling of membranes from the trabecular meshwork, vitrectomy to clear the vitreous dye, and removal of blue dye membranes from the posterior retina. The discussion centered on the risk of secondary glaucoma in these patients, many of whom ultimately require filtering surgery.

Charles Zhang, MD, from Bascom Palmer Eye Institute, closed with a case of optic pit maculopathy in a 14-year-old patient. Because the peripapillary hyaloid could not be lifted using standard techniques, he used a flex loop with radial perifoveal motions to induce a fovea-sparing posterior vitreous detachment, followed by internal limiting membrane flap inversion to close the optic pit. The panelists praised the technique for difficult pediatric cases with strong vitreoretinal adhesion to avoid further iatrogenic damage.

The audience cast their votes to crown a winner: Dr. Virgolino's case of intraocular dye injection (Figure 2). ■

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SAVE THE DATE:
15th annual Vit-Buckle Society Meeting
April 1-3, 2027, Miami

PVRL: WHEN "UVEITIS" IS NOT UVEITIS

A steroid-responsive, uveitis-presenting phenotype was ultimately diagnosed as primary vitreoretinal lymphoma.

BY ANDREAS THEOCHARIS, MD; ROMY BEJJANI, MD; AND ERIN E. FLYNN, MD

A 58-year-old man presented with severe bilateral vision loss and flashes. His VA was counting fingers at 3 ft OU. There was no relative afferent pupillary defect, and his IOPs were 18 mm Hg OD and 16 mm Hg OS. His medical history was notable for human immunodeficiency virus, and he was on antiretroviral therapy with a reported undetectable viral load. He also had abdominal diffuse large B-cell lymphoma treated with a regimen of etoposide, prednisone, vincristine, cyclophosphamide, and hydroxydaunorubicin, which had been in remission since 2017, as well as prior cryptococcal meningitis and prostate cancer, also in remission. His ocular history included glaucoma suspect, dry eye disease, and mild cataract in each eye.

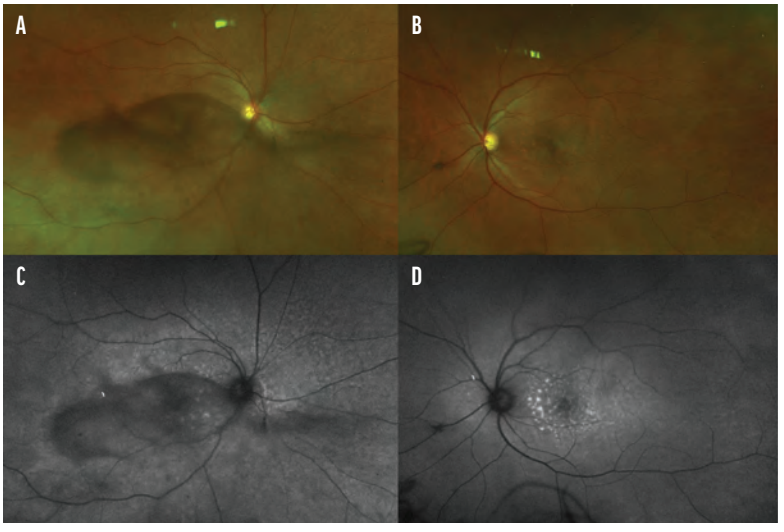

Figure 1. Widefield pseudocolor images of the right (A) and left (B) eye showed speckled yellow-white posterior pole lesions. Corresponding fundus autofluorescence images of the right (C) and left (D) eye demonstrated hyperautofluorescent abnormalities in the same regions.

IMAGING AND WORKUP

The anterior segment examination showed 2+ anterior chamber cells in each eye. There were also 3+ anterior vitreous cells with haze bilaterally, creating a panuveitis-like picture. Widefield fundus imaging demonstrated speckled, distinct, yellow-white posterior pole lesions (Figure 1A and B) with corresponding hyperautofluorescent abnormalities on fundus autofluorescence (Figure 1C and D). OCT revealed structural disruption, with subretinal and retinal pigment epithelium (RPE)-level hyperreflective material in each eye (Figure 2). Fluorescein angiography showed no evidence of vasculitis or other angiographic signs of active uveitic inflammation. The macular and subretinal lesions showed blockage, while patchy, granular staining in the midperiphery of each eye suggested RPE injury, possibly secondary to inflammation (Figure 3).

The differential diagnosis for bilateral vitritis with posterior pole lesions in an immunocompromised patient is broad, including infectious uveitis, inflammatory disease, and neoplastic masquerade syndromes, such as vitreoretinal lymphoma, choroidal metastasis, and bilateral diffuse uveal melanocytic proliferation.[1] Initial laboratory workup and chest radiography were unrevealing.

In the days following his initial examination, the patient presented to the emergency department with word-finding difficulty and blurry vision. A brain MRI demonstrated a 2.5-cm left frontal lobe lesion with surrounding edema, and a CT scan of his chest, abdomen, and pelvis showed no evidence of systemic metastatic disease. A stereotactic

brain biopsy was concerning for central nervous system (CNS) lymphoma, and a lumbar puncture was performed, which revealed large, atypical B cells positive for CD20, PAX5, and Ki-67. Immunostains were negative for CD30, CD34, CD117, and p53.

These findings were consistent with a diagnosis of diffuse large B-cell lymphoma. Hematology and oncology teams initiated treatment with intravenous methotrexate, rituximab, and dexamethasone. Given the absence of active systemic disease outside the eye and CNS, this presentation was most consistent with primary vitreoretinal lymphoma (PVRL) with concurrent CNS involvement rather than secondary ocular spread from systemic lymphoma.[2,3]

Because of persistent concern for PVRL, pars plana vitrectomy with vitreous biopsy was performed in his right eye. Cytology was nondiagnostic, showing predominantly macrophages and scattered lymphocytes without definitive evidence of lymphoma. Infectious evaluation was negative. The specimen also contained cohesive groups of bland-appearing cells of uncertain origin. There were too few B cells and insufficient remaining specimen for flow cytometry, interleukin (IL)-6 and -10 analysis, and immunohistochemistry. *MYD88* polymerase chain reaction testing was not available at the laboratory. However, given the biopsy-confirmed CNS diffuse large B-cell lymphoma, the ocular findings were presumed to represent PVRL.

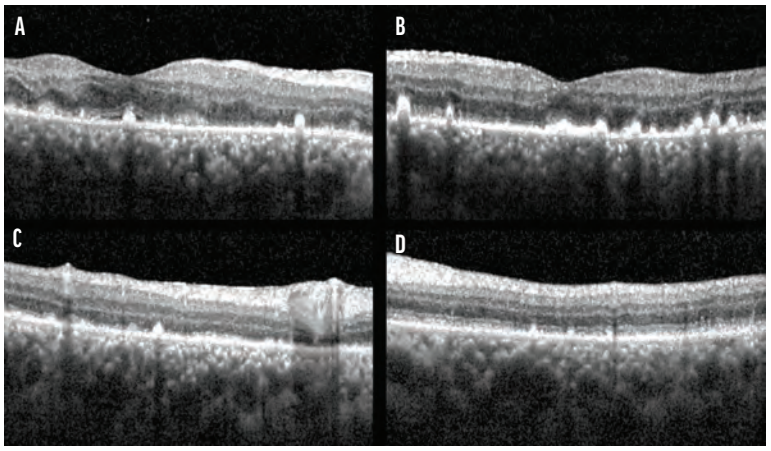

Figure 2. OCT images of the right (A, C) and left eye (B, D) showed subretinal and RPE-level hyperreflective material with associated outer retinal structural disruption. Panels A and B were centered on the fovea, whereas panels C and D highlighted additional macular involvement.

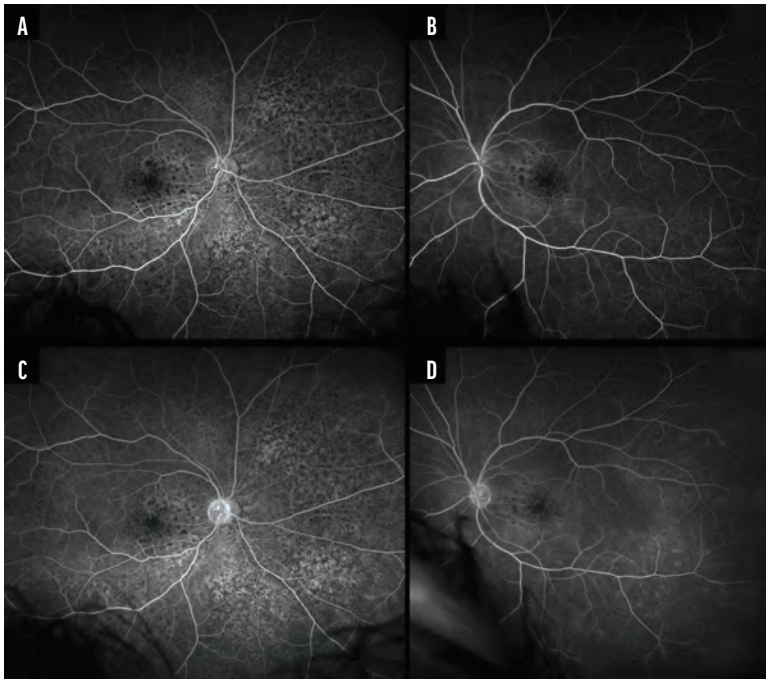

Figure 3. Fluorescein angiography of the right (A) and left (B) eye at 1 min and the right (C) and left (D) eye at 5 min demonstrated bilateral posterior pole abnormalities with blockage corresponding to the macular and subretinal lesions, without evidence of vasculitis or other angiographic signs of active uveitic inflammation.

REFRESHER ON PVRL

PVRL is a rare intraocular lymphoma within the spectrum of primary CNS lymphoma and is known for masquerading as chronic uveitis.[2,4,5] It often presents with vitritis and subretinal or sub-RPE infiltrates, and more than half of patients ultimately develop CNS involvement.[3,4] Ocular findings may be temporarily steroid responsive.[4]

A nondiagnostic vitreous biopsy does not exclude PVRL.[2] Diagnostic yield is limited by the fragility of lymphoma cells, low cellularity, prior corticosteroid exposure, and technical challenges of specimen processing.[2] Reported positive rates for vitreous cytology are variable, and current reviews recommend integrating cytology with adjunctive methods rather than relying on a single test.[3,5]

Adjunctive testing can substantially strengthen the diagnosis. Elevated IL-10 and increased IL-10/IL-6 ratio in aqueous or vitreous fluid support the diagnosis of PVRL over inflammatory uveitis, and *MYD88* mutation testing has emerged as a useful molecular adjunct, including in some aqueous humor samples.[5-8]

The case presented here highlights several practical points. First, the combination of bilateral vitritis, subretinal infiltrative-appearing lesions, and a CNS lesion should immediately raise suspicion for PVRL, even in a patient whose presentation may initially seem inflammatory.[4] Second, a negative or equivocal vitreous biopsy should not prematurely end the workup when the pretest probability for PVRL is high.[2] Finally, the diagnosis, staging, and treatment planning for PVRL require multidisciplinary coordination among ophthalmology, pathology/cytology, and oncology.[2,9]

Treatment strategies for PVRL vary, depending on whether disease is limited to the eye or accompanied

(Continued on page 29)

ONE TO WATCH

RT Retina Today

Editorially independent supported by abbvie REGENXBIO

Thomas Lazzarini, MD

Dr. Lazzarini's advice: Life is long, and things are always evolving. Listen to your mentors, never stop learning, and believe in yourself.

WHERE IT ALL BEGAN

My family moved to Southern California when I was 6, after my father got a position at the California Institute of Technology. He served as the Deputy Director of the Laser Interferometer Gravitational-Wave Observatory (LIGO) project, which won a Nobel Prize in Physics in 2017. Watching the LIGO collaboration was inspiring and showed me the incredible power of science, technology, and hard work from an early age. I attended Yale College, where I studied Biochemistry and Biophysics. After college, I spent a year in rural Borneo, Indonesia, leading a community-based project with non-profit Health in Harmony, which confirmed my desire to pursue medicine.

MY PATH TO RETINA

In my third year at Yale School of Medicine, I was considering internal medicine or psychiatry until I witnessed my first cataract surgery at the assistant's scope and never looked back. I matched for residency at the Bascom Palmer Eye Institute (BPEI) and joined an incredible class of co-residents who made residency some of the best years of my life. The BPEI emergency department was my first exposure to retina; the diversity and complexity of pathology was a tremendous motivator to continue to learn.

SUPPORT ALONG THE WAY

My first retina cases were with my chief residents, Jonathan F. Russell, MD, PhD, and Nathan L. Scott, MD. I can still hear their pearls in my head as I place scleral buckles and perform vitrectomy. Many of the principles that form the core of my anatomical understanding and surgical philosophy were crystalized in the late evening hours reattaching retinas and removing intraocular foreign bodies with my chiefs.

Throughout my time at BPEI, I leaned on and learned from Harry W. Flynn Jr, MD, and Audina M. Berrocal, MD. Rarely in my adult life have I felt as exposed as I often did during retinopathy of prematurity rounds with Dr. Berrocal—trading examinations with a world expert in pediatric retina was humbling and profoundly instructional. I remain grateful for her guidance and belief in me as a trainee.

I will never forget the first time I met Dr. Flynn. He told me, "Retina surgery can feel like flying a plane between buildings downtown," before adding "retina specialists don't have time to wait." He then bounded up the stairs, leaving me standing at the elevator landing. To this day, there are times that I wish I could lead my patient by the hand to see Dr. Flynn for a sage, same-day second opinion.

AN EXPERIENCE TO REMEMBER

Serving as chief resident at BPEI remains the most defining experience of my career. The demands of the role—directing the ocular trauma service, running a busy retina service, and teaching incredibly talented residents and fellows—forced a kind of growth that I could not have engineered any other way. The skills and instincts forged in that year are gifts I will carry for the rest of my professional life. My co-chief, Hasenin Al-khersan, MD, was the consummate partner, sounding board, and, too rarely, co-surgeon. ■

Thomas Lazzarini, MD, is a vitreoretinal surgeon at Retina Consultants San Diego. He is a consultant for Abbvie and can be reached at lazzarini@rcsd.com.

Scan the QR code to read about our other Ones to Watch.

RARE DISEASE MYSTERY CASES

Can you diagnose these unusual cases based on the examination and imaging?

By Kenneth C. Fan, MD, MBA; Caroline C. Awh, MD; Nimesh A. Patel, MD; Marta Stevanovic, MD, MSc; Maria Emfietzoglou, MD; Demetrios Vavvas, MD, PhD; Mary V. Lang; Lisa A. Schimmenti, MD; and Brittni A. Scruggs, MD, PhD

Patients are referred to retina specialists for myriad reasons, many of which are easy to diagnose. However, when a patient's symptoms, examination, and/or imaging don't add up, it's the retina specialist's job to unravel the mystery, regardless of the winding path to diagnosis. These challenging cases are designed to test your diagnostic skills and help improve your rare and inherited disease (IRD) know-how.

- Rebecca Hepp, MA, Editor-in-Chief

Visit retinatoday.com to see the diagnoses and discussion.

MYSTERY CASE NO. 1

By Kenneth C. Fan, MD, MBA

A 47-year-old woman presented with a history of central vision loss that began in her 30s. She described central vision distortion that had gradually worsened, now coalescing into blind spots. Her vision was 20/40 OU with normal IOP OU. Family history revealed that her mother had been diagnosed with AMD in her 50s. Her sister and two children have no visual symptoms. There was no evidence of consanguinity. The physical examination did not reveal any other syndromic findings.

Fundus imaging showed symmetric subtle flecks in the macula and posterior pole and a beaten-bronze appearance of central atrophy in each eye (Figure 1). Fundus autofluorescence (FAF) revealed severe central decreased autofluorescence with macular and midperipheral flecks (Figure 2). OCT imaging demonstrated patchy multifocal atrophy of the ellipsoid zone (EZ) and retinal pigment epithelium (RPE) in each eye (Figure 3).

Visit retinatoday.com to see the diagnosis and discussion.

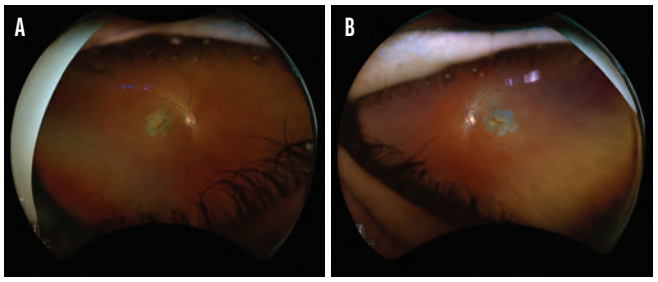

Figure 1. Fundus photography of the right (A) and left (B) eye demonstrates subtle flecks in the macula and posterior pole and a beaten-bronze appearance of central atrophy.

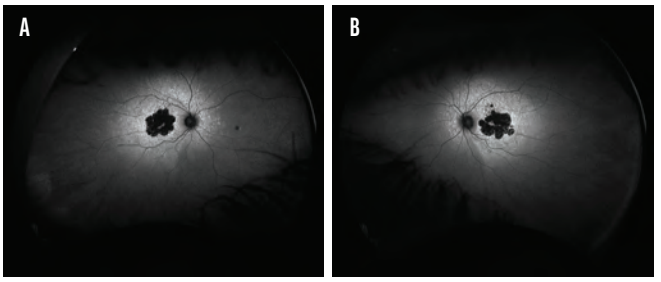

Figure 2. FAF of the right (A) and left (B) eye demonstrates severely decreased central autofluorescence with macular and midperipheral flecks.

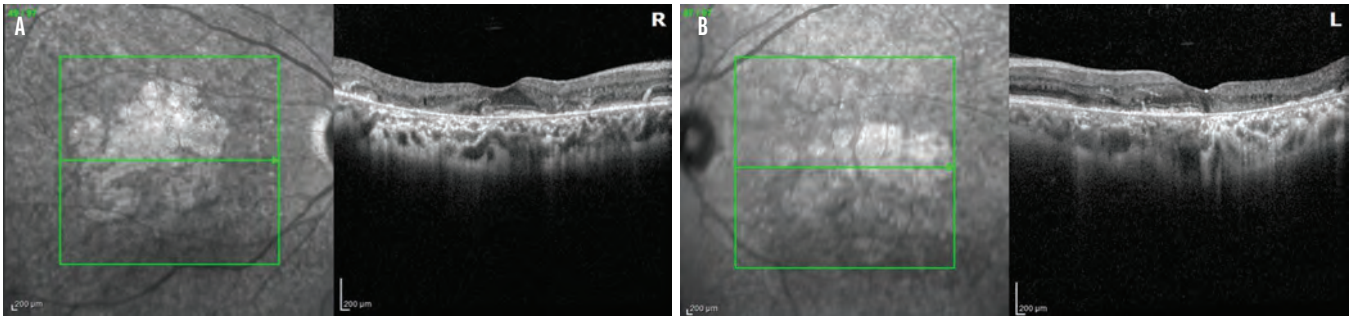

Figure 3. OCT imaging of the right (A) and left (B) eye demonstrates patchy multifocal atrophy of the EZ and RPE.

MYSTERY CASE NO. 2

By Caroline C. Awh, MD, and Nimesh A. Patel, MD

A 6-year-old healthy girl was referred for bilateral retinal pigmentary changes. She was asymptomatic with a VA of 20/25 OU. The dilated fundus examination demonstrated 360° peripheral retinal hyperpigmentation (Figure 4) with normal FAF imaging (Figure 5). OCT imaging revealed subtle outer plexiform deposits in the macula (Figure 6).

The referring ophthalmologist had ordered an autoimmune workup, an infectious and inflammatory workup, and a retinal dystrophy panel, all of which were negative. Her review of systems and family history for IRD were negative.

Visit retinatoday.com to see the diagnosis and discussion.

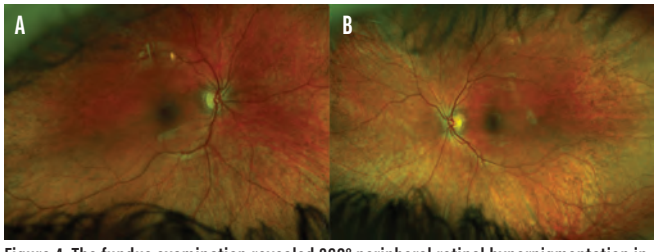

Figure 4. The fundus examination revealed 360° peripheral retinal hyperpigmentation in the right (A) and left (B) eye.

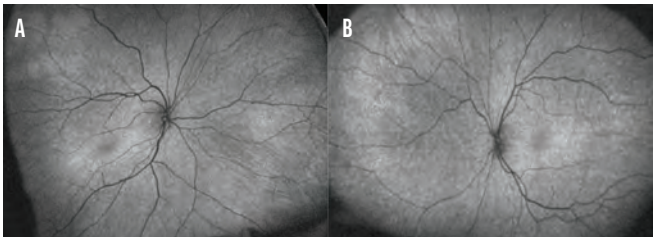

Figure 5. FAF showed a normal fluorescence pattern in the right (A) and left (B) eye.

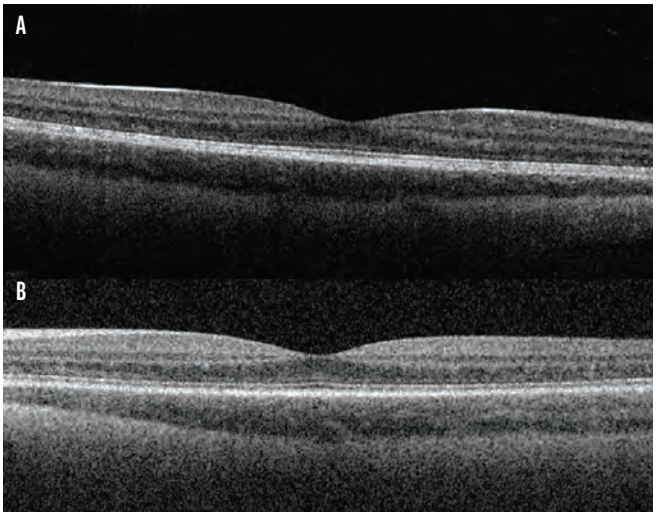

Figure 6. OCT imaging was remarkable for subtle outer plexiform deposits in the macula of the right (A) and left (B) eye.

Rare and Inherited Retinal Disease

MYSTERY CASE NO. 3

By Marta Stevanovic, MD, MSc; Maria Emfietzoglou, MD; and Demetrios Vavvas, MD, PhD

A 63-year-old man presented with a VA of counting fingers OU (Figure 7). He reported no personal medical history, and family history included an uncle and cousin (in his 40s) who also had decreased visual acuity. Dilated fundus examination revealed large areas of central atrophy with surrounding drusen. FAF showed central areas of hypoautofluorescence, and OCT demonstrated significant retinal thinning and EZ loss.

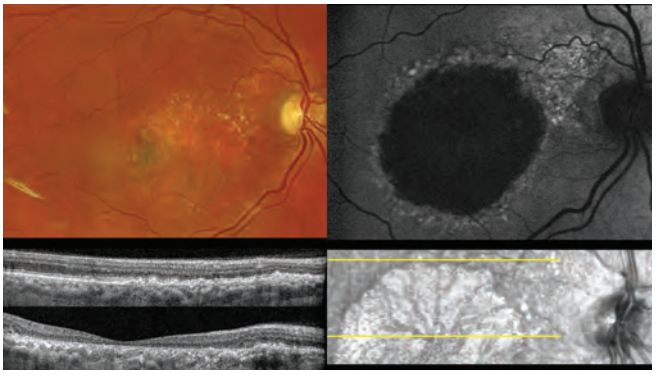

Figure 7. Fundus photography shows central retinal atrophy with surrounding drusen. There is a corresponding area of hypoautofluorescence. OCT shows significant central retinal atrophy and drusen surrounding the atrophic region.

Visit retinatoday.com to see the diagnosis and discussion.

MYSTERY CASE NO. 4

By Mary V. Lang; Lisa A. Schimmenti, MD; and Brittni A. Scruggs, MD, PhD

A 78-year-old man presented for a second opinion regarding progressive geographic atrophy (GA). He had a 7-year diagnosis of wet AMD managed with aflibercept (Eylea, Regeneron) every 6 weeks due to recurrent subretinal fluid accumulation with injection spacing. A review of systems revealed long-standing leg claudication. BCVA was 20/200 OD and 20/125 OS, and Ishihara color plates were 3/14 in each eye. Fundus examination and FAF were remarkable for profound GA, peripapillary atrophy, and subtle angioid streaks (Figure 8). ■

Visit retinatoday.com to see the diagnosis and discussion.

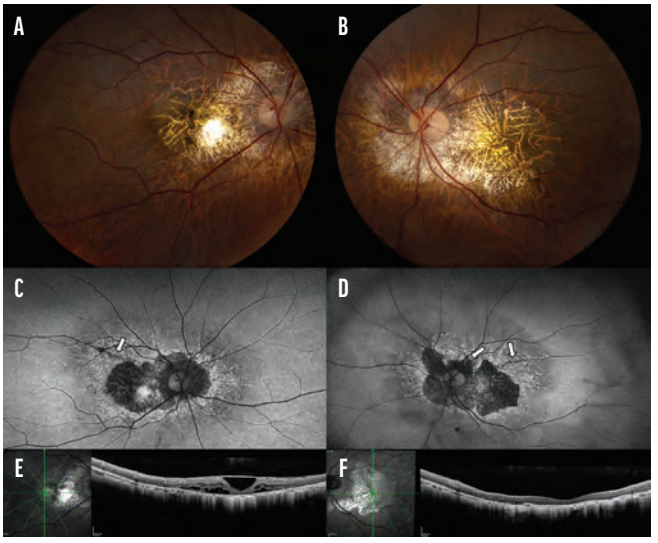

Figure 8. Fundus photography shows bilateral parafoveal and peripapillary atrophy (A, B). FAF imaging demonstrates angioid streaks (arrows) with peripapillary and parafoveal atrophy surrounded by perifoveal hyperautofluorescence (C, D). OCT demonstrates bilateral GA with a diffuse epiretinal membrane in the right eye (E) and disorganization of the inner retinal layers in the left eye (F).

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MYSTERY CASE MASQUERADE

By Yicheng Bao, MD, and Hossein Ameri, MD, PhD, FRCSI, MRCOphth

A 35-year-old man presented with a 2-year history of progressive nyctalopia. He reported difficulty adjusting from bright light to dark environments but noted no significant deficits in central or color vision. The patient lacked a family history of vision loss, and review of systems was negative.

BCVA was 20/40 OD and 20/25 OS. IOP was 9 mm Hg OD and 12 mm Hg OS. Dilated fundus examination revealed bilateral, symmetric fine granular pigmentary changes across the midperiphery (Figure 1), supported by fundus autofluorescence imaging (Figure 2). Spectral-domain OCT showed parafoveal inner retinal atrophy. Functional testing provided evidence of severe photoreceptor dysfunction. Electroretinography demonstrated a profound loss of rod function and significantly reduced cone responses (Figure 3). The clinical picture was complicated by a significant systemic history, including ANCA-positive vasculitis, focal segmental glomerulosclerosis, and chronic pancreatitis.

Visit retinatoday.com to see the diagnosis and discussion.

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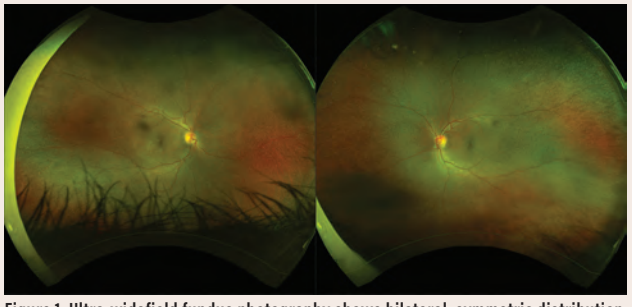

Figure 1. Ultra-widefield fundus photography shows bilateral, symmetric distribution of fine granular pigmentary changes across the midperiphery.

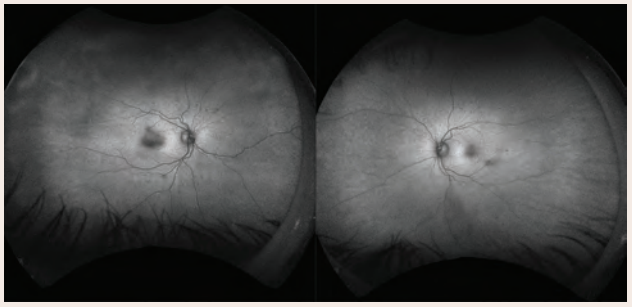

Figure 2. Fundus autofluorescence shows bilateral stippled hypoautofluorescence in the midperiphery.

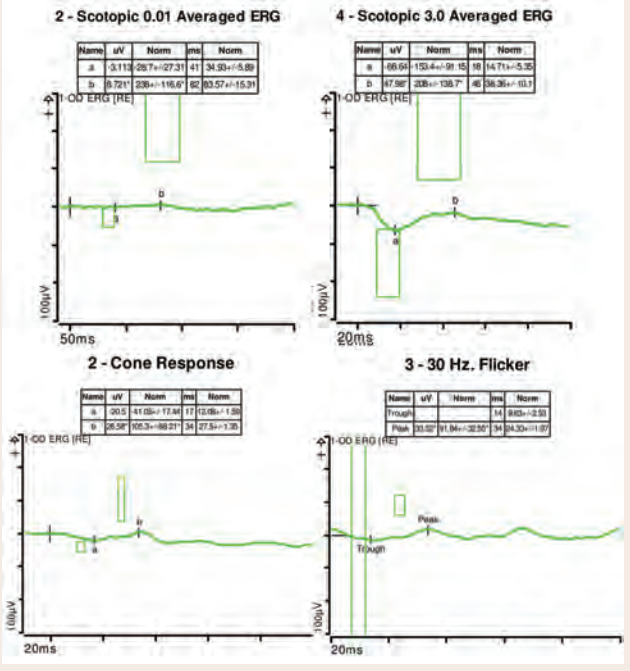

Figure 3. Electroretinography demonstrates severely reduced rod and cone function in each eye.

THE CHALLENGE OF IRD IN CHILDREN

Researchers are investigating ways to tackle delayed diagnosis, imaging complications, and unreliable access to genetic testing in pediatric care.

By Angela S. Li, MD; Cesar Estrada-Puente, MD; Paula C. Morales, MD; and Ramiro Maldonado, MD

The standard diagnostic and management framework for adults with inherited retinal diseases (IRDs) is well established, with symptom-driven referral, multimodal imaging, genetic testing, and, for a small subset, enrollment in clinical trials. However, children with an IRD represent a different clinical challenge, with distinct diagnostic pathways, phenotypic expression, and barriers to trial access (Table). A key limitation is the lack of imaging and functional technologies for children, making early and reliable disease characterization difficult. Here, we examine the differences in diagnostic delays, phenotypes, and management in children with IRDs compared with adults.

DIAGNOSIS AND CLINICAL PRESENTATION

Children with IRDs face significant diagnostic delays. For example, in our study of 87 patients with molecularly confirmed Stargardt disease at Duke University, the mean time from symptom onset to first IRD specialist evaluation was 9 years for early-onset patients (presenting in early childhood) and 14.4 years for intermediate-onset patients (presenting in adolescence) compared with 6.4 years for late-onset patients (presenting after age 45). The mean time from symptom onset to molecular diagnosis was even longer at 10.9 and 14 years for early- and intermediate-onset, respectively, compared with 6.7 years for late-onset.[1] In another study of 1,096 adult patients with an IRD across the United Kingdom and Latin America, the mean time from symptom onset to molecular diagnosis was 6.4 ± 9.1 years, with 57% waiting more than 1 year. Notably, children were 2.1 times more likely to wait more than 1 year for a diagnosis compared with adults.[2]

The reasons for this delay are multifactorial. Young

children cannot articulate visual symptoms, and the presenting complaint is often parental concern about a child's visual behavior, not a self-report of central scotoma or photophobia, as is more typical for adults. In children, nystagmus (76%) and abnormal visual behavior (28%) often lead to initial evaluation by a pediatric ophthalmologist and pediatric neurologist rather than a retina specialist.[3]

In addition, the nonspecific visual symptoms can be accompanied by a normal fundus examination, making diagnosis based on clinical examination more challenging. Early-onset Stargardt disease frequently presents with vision loss and cone-rod dysfunction on electroretinogram (ERG) that precedes any visible fundus abnormality.[4,5] In a series of 31 patients with early-onset Stargardt disease without fundus findings, 87% experienced delayed diagnosis (median 3 years), and 94% had visited more than two hospitals misdiagnosed as amblyopia, functional vision loss, or optic neuropathy.[4] Even in Leber congenital amaurosis, profound vision loss, nystagmus, and an undetectable ERG appear in the first 6 months of life, yet the fundus can appear normal at initial examination.[3]

Meanwhile, intermediate- and late-onset Stargardt disease show characteristic fundus autofluorescence (FAF) changes, while retinitis pigmentosa in adults shows ellipsoid zone (EZ) loss correlating with night blindness and peripheral visual field constriction.[6,7] Patients with late-onset Stargardt disease were misdiagnosed with AMD in 22% of cases, but the clinical presentation (macular atrophy, presence of flecks) tends to be interpretable enough to eventually prompt appropriate workup.[1]

Furthermore, IRD progression can be faster in children compared with adults. For instance, annual EZ area loss in childhood-onset Stargardt disease averaged 1.20 ± .29 mm^2/year, approximately three times the adult progression rate, and FAF showed that decreased definitive autofluorescence lesion growth in childhood-onset patients progresses roughly twice as fast as in adult-onset cohorts.[8-10] In our study, nearly 90% of early-onset patients lost subfoveal EZ integrity before reaching the IRD clinic, compared with 30% of adults with late-onset Stargardt disease.[1]

KEY TAKEAWAYS

- Children with inherited retinal diseases (IRDs) tend to experience faster disease progression and significant diagnostic delays due to a mismatch between patient/caregiver complaints and clinical examination.
- Handheld imaging, such as swept-source OCT and portable full-field electroretinography, are under investigation as tools to improve diagnosis and disease monitoring in the pediatric IRD population.
- The field needs additional studies to validate functional endpoints that are feasible in a pediatric population, or structural endpoints that are more objective and do not rely on patient cooperation.

Image courtesy of RML lab (Retina Machine Laboratory)

Figure. Portable full-field ERG performed in a pediatric patient using periocular skin electrodes and handheld flash stimulation, demonstrating a child-friendly, non-mydriatic approach with minimal dark adaptation.

THE ROLE OF IMAGING

Because most diagnostic tests are optimized for adults and difficult to perform in children, OCT imaging has become crucial to detect photoreceptor degenerative changes across different genotypes. Currently, there is only one commercially available handheld spectral-domain OCT (Envisu C2300, Leica), which was approved by the FDA in 2007.[11] However, its acquisition speed is suboptimal for children with IRDs, particularly those with nystagmus. To address this limitation, Duke has developed an investigational noncontact, 1,064 nm wavelength, high speed (400 kHz) handheld swept-source OCT (SS-OCT). Our group evaluated the feasibility of the Duke handheld SS-OCT and showed that successful imaging was achieved in 81.1% of awake children with IRDs, providing a unique opportunity to evaluate early retinal changes without the need for examination under anesthesia.[12] Other investigational ultra-widefield handheld SS-OCTs (eg, Theia T1-W, Theia Imaging) are currently being developed and have been shown to successfully image infants and children, both in clinic and under anesthesia.[13]

To bridge the gap between the International Society for Clinical Electrophysiology of Vision (ISCEV) standard protocol and the Great Ormond Street Hospital (GOSH) approach, we are integrating portable full-field ERG into

Rare and Inherited Retinal Disease

TABLE. ADULTS VERSUS CHILDREN WITH INHERITED RETINAL DISEASE: KEY DIFFERENCES

	ADULTS	CHILDREN
Average delay in diagnosis	6-8 years from symptom onset[1,2]	10-14 years from symptom onset[1,2]
Fundus at presentation	Often abnormal (flecks, atrophy)	Frequently normal; symptoms precede findings[3,4]
Primary presenting symptoms	Decreased central vision, photophobia	Nystagmus, poor visual behavior, school difficulty[5]
Electroretinography feasibility	Standard; cooperative patient	Sedation required < 3-4 years of age; non-adult norms[15,16]
Visual field reliability	Reliable	Unreliable < 8 years of age; maturation mimics improvement[17]
Preferred structural endpoint	Fundus autofluorescence-decreased definitive autofluorescence, BCVA, spectral-domain OCT	Fundus autofluorescence-decreased definitive autofluorescence, spectral-domain OCT ellipsoid zone area (validated ≥ 6 years of age)[7,8]

our pediatric retinal evaluation. ISCEV-ERG remains the standard but requires prolonged dark adaptation, corneal electrodes, and sustained cooperation, often necessitating examination under anesthesia in young children. In contrast, the GOSH-ERG enables rapid, awake testing using skin electrodes, minimal dark adaptation, and handheld stimulation, while maintaining strong concordance with ISCEV responses (Figure). This approach reduces reliance on anesthesia and expands access to functional retinal assessment in pediatric IRD.

GENETIC TESTING AND COUNSELING

Genetic testing is key to diagnosing IRD, but access remains limited, particularly for children. While commercial IRD gene panels (200 to 350 genes) and sponsored programs have expanded availability, children are less likely to go undergo testing due to referral gaps and logistical barriers. In a nationwide survey of pediatric retina and IRD specialists, children on Medicaid were perceived to have greater difficulty obtaining genetic testing despite state-level analysis indicating coverage in approximately two-thirds of states (68.6%); most providers were uncertain about this coverage, highlighting variability and poor transparency across policies. Cost concerns exceeded uncertainty in result interpretation or management as well.[14]

CLINICAL TRIALS AND MANAGEMENT

Gene therapies, antisense oligonucleotides, and small molecules are in active clinical trials for Stargardt disease, X-linked retinitis pigmentosa, Usher syndrome 2A, and *CNGB3*/*CNGA3* achromatopsia. Most trials were designed for adults: Eligibility typically requires BCVA between approximately 20/32 and 20/400 in the study eye, cooperative full-field ERG and Goldmann visual field testing, and a minimum of 18 years of age. For adults who reach an IRD specialist with moderate vision loss and preserved photoreceptor structure, these windows are generally accessible.

Children face a paradoxical exclusion from clinical trials in Stargardt disease: Their disease progression is often too advanced based on OCT imaging but too early based on FAF. In our Stargardt cohort, nearly 90% of early-onset patients had lost subfoveal EZ integrity at presentation, while FAF frequently showed questionable decreased autofluorescence.[1] Because many Stargardt trials require a minimum area of decreased definitive autofluorescence, these children do not meet enrollment criteria despite established photoreceptor damage.[2] Functional tests are also more challenging to perform on children. ERG requires sedation in young children and produces results not directly comparable with adult normative data (ie, smaller amplitudes, delayed implicit times).[15,16] Goldmann visual field testing is similarly unreliable before 7 to 8 years of age.[17] Currently, full-field stimulus testing requiring no fixation is the validated endpoint for severe pediatric vision loss. It was accepted as a clinical trial endpoint by the FDA for voretigene neparvovec (Luxturna, Spark) and is feasible in school-age children; the multiluminance mobility test is feasible from 4 years of age.[18-21] The use of EZ width measurements remains exploratory. Overall, this highlights the need for additional studies to validate other functional endpoints that are feasible in a pediatric population, or ideally structural endpoints that are more objective and do not rely on patient cooperation.

TAKE THE PICTURE

Children with IRDs face unique challenges, such as diagnostic delays, potential faster IRD progression, and difficulty with functional testing for trial endpoints. Some solutions for addressing these challenges include educating all pediatric eye providers on the importance of obtaining multimodal imaging, such as OCT and FAF, in children with visual impairment, even in the presence of a normal fundus examination. This can streamline referrals to IRD specialists and genetic testing, and further development of structural endpoints for clinical trials in IRDs. ■

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(Continued from page 20)

by CNS involvement.[2,3,10] Intravitreal methotrexate and rituximab are effective local treatments, whereas systemic methotrexate is commonly used when there is concurrent CNS disease.[2,3,10] In this case, the patient had difficulty with transport and expressed a preference to forgo intravitreal injections. Systemic rituximab and methotrexate were continued under the direction of hematology and oncology, along with topical prednisolone acetate for his anterior segment inflammation. His intraocular inflammation responded well to intravenous rituximab and methotrexate, and his vision improved to near baseline approximately a month after initiation of systemic therapy.

LOOK A LITTLE CLOSER

For retina specialists, the message is straightforward: Not all bilateral "uveitis" is inflammatory. In the right clinical setting, especially with subretinal infiltrates, atypical imaging, or concurrent neurologic findings, PVRL must remain high on the list.[3,4] Early suspicion and coordinated workup may reduce diagnostic delay in a disease where ocular and CNS involvement are often linked.[4,9] ■

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GENETIC TESTING IN THE RETINA PRACTICE

What's changing and why it matters.

By Timothy S. Lee, MD; Eric W. Lai, MD; and Sidney A. Schechet, MD

Retina specialists play a critical role in the early detection of inherited retinal diseases (IRDs). While individually rare, they collectively affect approximately 1 in 1,000 people worldwide.[1,2] The latest diagnostic yield of genetic testing in suspected IRD cases ranges from 65% to 70%, with 51% of cases initially misdiagnosed. On average, it takes 15 years for these patients to receive a correct diagnosis,[3] although ophthalmologists can identify IRDs more efficiently than general medical genetics clinics by approximately 16 months.[4] Thus, a detailed eye examination can raise clinical suspicion and help guide the decision to pursue genetic testing (Figure).[5-7]

ADVANCES IN GENETIC TESTING

Genetic testing for IRDs primarily relies on next-generation sequencing (NGS), using targeted panels of known IRD-associated genes to provide a relatively fast and accurate diagnosis. If NGS does not identify a causative mutation, particularly in those without a clear clinical diagnosis, broader approaches such as whole-exome sequencing (WES) or whole-genome sequencing (WGS) can be considered.[8,9]

WES enables comparison with all exons, including genes not found in a targeted gene panel sequencing,[10] while WGS tests the entire genome and has a wider scope than WES. When comparing the type of sequencing, NGS can be used to detect smaller genetic variants and has higher throughput; NGS has a poorer ability to detect larger genetic variants, including structural variants. In comparison, long-read sequencing, which involves reading several kilobases, has a better ability to detect larger, complex genetic variants, including structural variants and insertion-deletion errors, but can be more expensive and have a lower throughput.

There are several ways to obtain specimens for genetic testing. The least invasive and most cost-effective methods are through saliva and buccal swabs, which can be self-collected by patients at home, that are mailed directly to the testing company for processing. Sometimes, whole blood is

TABLE. AVAILABLE INHERITED RETINAL DISEASE PANELS

Company	Number of Genes Tested	Specimen Collection	Cost	Time to Results
My Retina Tracker	110; does not include mitochondrial genes	Whole blood specimen	Free through Foundation Fighting Blindness	Approximately 21 to 28 days
Invitae	330; does not include mitochondrial genes	Whole blood (preferred) or saliva specimen	Insurance, sponsorship through Invitae Unlock, or out-of-pocket	Approximately 10 to 21 days
Blueprint Genetics	351; includes mitochondrial genes	Whole blood or saliva specimen	Insurance or out-of-pocket	Approximately 28 days

the preferred specimen for genetic testing, as it has a higher DNA yield and can provide more information. However, blood samples must be taken in an outpatient laboratory and are more expensive. All the genetic testing companies collect saliva and whole blood samples (Table).

Despite these advances, genetic testing can yield inconclusive results. A common challenge is the identification of variants of uncertain significance (VUS)—genetic changes for which the effect on disease risk is unclear (see, "VUS: A Guide for Retina Specialists"). In one laboratory's experience, approximately 17% of unsolved IRD cases included at least one VUS.[11] These variants can potentially be reclassified through further investigations such as functional studies and segregation analyses. Classification categories include "benign," "likely benign," "uncertain significance," "likely pathogenic," and "pathogenic." However, even with reclassification, ambiguity can persist, necessitating careful clinical judgment when making management decisions.

To help improve access to genetic testing, several companies offer in-clinic or at-home testing kits, along with genetic testing analysis and, in some cases, genetic counseling.

Still, genetic testing for IRDs and other conditions has potential drawbacks. Patients can have significant psychological and familial distress that can lead to grief, anxiety, and uncertainty about their diagnosis. If genetic diseases are identified, insurance companies may impose higher premiums or even denials. Privacy and data security issues are also of concern, especially with the storage and use of this information for research and other databases. Furthermore, genetic testing may be inconclusive. Even when a pathogenic variant is identified, there may not be effective treatments available, limiting the effect on clinical management.

KEY TAKEAWAYS

- The latest diagnostic yield of genetic testing in suspected inherited retinal disease (IRD) cases ranges from 65% to 70%; 51% are initially misdiagnosed.
- To help improve access to genetic testing, several companies offer in-clinic or at-home testing kits, along with genetic testing analysis and, in some cases, genetic counseling.
- Genetic testing and referral to an IRD specialist can facilitate accurate diagnoses, provide insight into overall prognosis, guide family planning, and enable more personalized treatment strategies.

GENETIC TESTING OPTIONS

My Retina Tracker is a national IRD registry provided by the Foundation Fighting Blindness.[12] The genetic testing is provided by Prevention Genetics with an all-inclusive testing kit to be used in clinic or at home. The targeted gene panel consists of 110 genes and does not contain mitochondrial genes. Although a smaller gene panel than other testing options, this registry is typically free for eligible patients and useful for common IRD presentations. The turnaround time for results is estimated to be about 3 to 4 weeks. A third-party service called InformedDNA also provides optional genetic counseling for the patient.

Invitae offers an IRD panel that consists of 330 genes associated with various IRDs, including retinitis pigmentosa (RP), cone-rod dystrophy, Leber congenital amaurosis, and more.[13] However, this larger testing panel does not include mitochondrial genes. The Invitae panel can be subsidized through insurance if testing is indicated. Of note, Invitae also offers the Invitae Unlock sponsored program that allows patients to undergo testing for free if they meet the program eligibility criteria, with free counseling available as well. The turnaround time for this gene panel ranges between 10 and 21 days, with an average of 14 days.

Formerly the provider of the genetic panel for My Retina Tracker, Blueprint Genetics offers its own retinal dystrophy panel that consists of 351 genes, which *does* include those of mitochondrial origin.[14] Although it may carry a higher fiscal burden, the Blueprint Genetics panel can be subsidized through insurance if testing is indicated. The turnaround time for this testing panel is approximately 4 weeks.

Johnson & Johnson recently announced its own IRD registry, the EYERD Registry.[15] The company is recruiting patients, intending to use the registry as a database for

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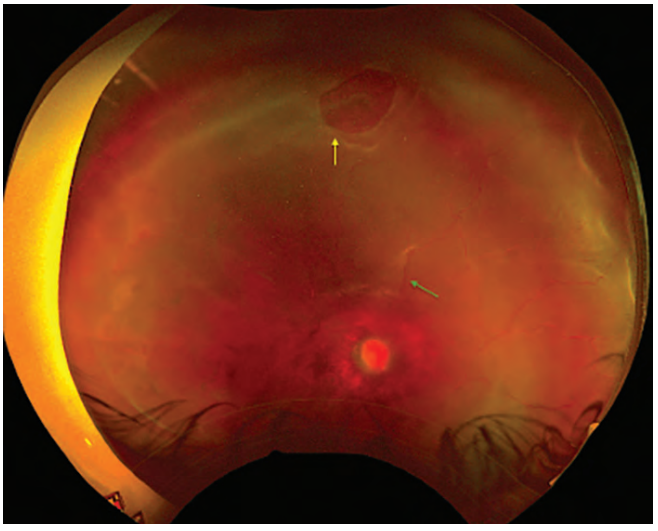

Figure. This patient with high myopia presented with a retinal break (yellow arrow), vitreous veils (green arrow), and a rhegmatogenous RD. Genetic testing revealing a diagnosis of Stickler syndrome type IV.

research on treatment options and to emphasize earlier diagnosis of IRDs, with an emphasis on X-linked RP and achromatopsia. In some instances, genetic testing may be available at an academic institution's genetics clinic.

If genetic variants are identified, phase testing can provide risk-stratification of these variants. Phase testing involves determining whether genetic variants within the same gene are located on the same or opposite chromosome, in cis or in trans, respectively. Phase testing is especially important in patients with identified recessive genetic conditions or for determining compound heterozygosity. The information gathered from phase testing can be used to counsel patients and allow for further management decisions.

CASE OVERVIEW

A 32-year-old man with a history of high myopia (-15 D OU) was referred to the retina clinic for suspicion of a retinal detachment (RD) after sustaining a traumatic head injury. The patient had a BCVA of 20/70 OD and 20/40 OS. On examination, the patient had macular subretinal fluid and a chronic, macula-off RD, along with multiple retinal breaks in the right eye (Figure). Both eyes had a posterior staphyloma. The patient had no apparent systemic syndromic features and no relevant positive family history. Due to the patient's severe myopia, chronic and severe RDs, and bilateral vitreous syneresis/veils, there was suspicion that he may have an underlying genetic disorder.

After RD repair, the patient underwent Invitae panel testing and was found to have a homozygous mutation in the *COL9A1* gene, confirming an autosomal recessive inheritance pattern and supporting the diagnosis of Stickler syndrome type IV. Based on these genetic findings, together with the clinical features, the diagnosis was ultimately established. In comparison to the autosomal dominant (AD) variant, autosomal recessive (AR) Stickler syndrome is much rarer. The proportion of *COL2A1* AD variants causing Stickler syndrome is about 80%, with *COL9A1* AR variants responsible for less than 1% of Stickler syndrome cases.[16]

AD Stickler syndrome has the typical findings of high myopia, vitreoretinal degeneration, and syndromic features including midface hypoplasia and cleft palates; AR Stickler presents with similar ocular findings but with heterogeneous expression of syndromic features. Even without a reported family history, genetic diseases can still occur de novo, and testing within the family should be pursued. Therefore, the patient was encouraged to have his family members undergo testing and ophthalmologic examinations, and he was referred to genetics for further evaluation and counseling.

IRDS IN CLINICAL PRACTICE

The evolving landscape of IRD diagnosis and management underscores the critical role of genetic testing as a diagnostic tool when clinical suspicion is high. Approximately half of the patients referred with clinical suspicion of an IRD receive a different diagnosis at the end of testing, with the potential of a delayed diagnosis of about 15 years.

Referral to an IRD specialist should be highly considered for patients with a strong family history of vision loss or known IRDs, any progressive, rapid vision loss unexplained on examination, any notable systemic/external findings that suggest an IRD, unusual examination findings, and when considering any IRD testing. Once testing is performed, the IRD specialist can analyze and interpret genetic tests along with the patient's history and examination findings to pursue a diagnosis and potential management.

Furthermore, counseling and education are important aspects of IRD care. Physicians should fully discuss the purpose and possible outcomes of testing. The effects of genetic testing go beyond the medical scope and can affect many aspects of the patient's life. It is especially important to counsel patients about these effects and suggest they pursue resources that are available to them if necessary.

Timely genetic testing is crucial when there is clinical suspicion of an inherited or syndromic retinal disorder. Available testing panels can facilitate accurate genetic diagnoses, providing insight into overall prognosis, guiding family planning, and enabling more personalized treatment strategies, including potential clinical trial opportunities. ■

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VUS: A GUIDE FOR RETINA SPECIALISTS

By Vinit B. Mahajan, MD, PhD

A variant of unknown significance (VUS) is a statistically rare genetic change found in a patient's DNA. However, rare does not equate to disease-causing; in fact, most VUS are benign variants that haven't been studied enough to know for certain.

INTERPRETING GENETIC TEST RESULTS

Genetic testing results typically come with a classification. If a variant is labeled pathogenic, there is strong evidence that this variant causes disease, which is useful information for diagnosis and counseling. When results show likely pathogenic, there is probable disease association but some uncertainty; with the appropriate caveats, this finding can be used for diagnosis and counseling. When the results list a VUS, there is insufficient evidence to classify the variant either way—this should not be used for clinical decisions. Variants classified as likely benign or benign are probably or definitely not disease-causing and can generally be ignored.

WHY ARE VUS COMMON IN RETINAL GENES?

Some genes are particularly prone to generating VUS reports, such as *ABCA4* (associated with Stargardt disease), *USH2A* (Usher syndrome and retinitis pigmentosa), and other Stargardt-associated genes. These genes are large, providing more locations where rare variants can occur. In addition, there is high natural variation in these genes across the normal population, and limited functional studies exist on most variants that have been identified. Finally, many variants have never been seen before in medical literature or databases, making it impossible to know their significance.

WHAT NOT TO DO WITH A VUS

Clinicians should never tell patients they have the gene for a particular disease based on a gene classified as VUS, as a VUS cannot be used for a definitive diagnosis. A VUS alone should never dictate treatment decisions. In addition, clinicians should not assume that a VUS will eventually be reclassified as pathogenic because many remain uncertain indefinitely, and some are eventually reclassified as benign.

WHEN CAN A VUS BE CLARIFIED?

A VUS may be resolved and reclassified, often when there is a strong multi-generational pedigree showing clear segregation of the variant with disease. Having multiple affected family members available for testing can be extremely helpful.

Additionally, functional studies that demonstrate biological effect of the variant can provide clarification. However, these approaches require genetics expertise to properly execute and interpret.

KEY TAKEAWAY FOR BEST PRACTICE

When genetic testing reveals a VUS, clinicians should explain to the patient and their family that unknown significance truly means we don't know if this variant is related to their condition, and refer them to a genetic counselor or geneticist for expert interpretation. Clinical findings, imaging results, and family history should dictate the diagnosis. ■

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THERAPIES FOR IRDS:

Moving Beyond Single-Gene Solutions

Emerging gene-agnostic strategies target shared pathways and offer options for IRD patients without mutation-specific therapies.

By Aykut Demirkol, MD; Rajvir Solanky; Jayvin Hernandez-Reyes; İlay Demirkol; and Kuzey Soydas. Reviewed by Stephen H. Tsang, MD, PhD

Inherited retinal diseases (IRDs) are a genetically and clinically heterogeneous group of disorders caused by pathogenic variants in more than 250 genes.[1,2] Mutation-specific gene augmentation and gene editing have transformed care for a small subset of patients, yet the sheer genetic diversity and cost of developing "one therapy per gene" mean that most individuals with an IRD still lack an approved treatment.[1,2] As a result, gene-agnostic strategies may broaden treatment options by targeting shared downstream pathways rather than individual mutations.[3-5] These broader therapeutic approaches aimed at preserving or restoring vision are gaining increasing attention.[1,6] For retina specialists, understanding these modalities is increasingly important when counseling patients about trial opportunities and realistic expectations.[1]

WHAT GENE-AGNOSTIC MEANS IN PRACTICE

Gene-agnostic therapies are designed to benefit patients regardless of the specific mutation, offering a unified approach across diverse IRD genotypes.[1] Rather than correcting a single faulty gene, they either preserve the viability of remaining cells, replace cells that have been lost, or rewire surviving retinal circuitry to regain light sensitivity.[1,6] A recent review grouped these strategies into

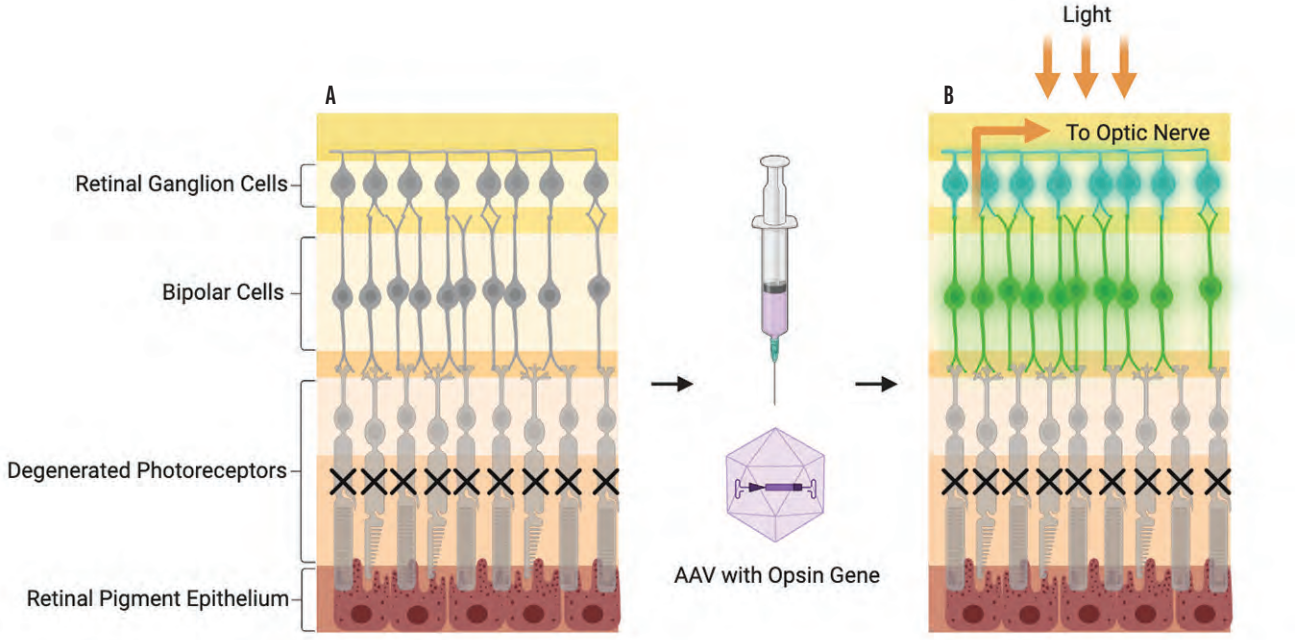

Figure 1. A simplified diagram of optogenetic therapy shows an untreated retina (A) and the AAV-mediated delivery of opsin to bipolar or ganglion cells, leading to the restoration of light-driven output (B). Created in BioRender. Solanky R. 2026. BioRender.com/ukztdxr

several categories: neurotrophic and metabolic support, immune modulation, retinal cell replacement or reprogramming, and optogenetics.[1] Because these interventions target common final pathways of degeneration, they can be applied across broad phenotypes such as rod-cone dystrophy or macular dystrophy, even when the underlying genetics are unknown or complex.[1,2]

Optogenetics: Restoring Light to a Silent Retina

Optogenetic approaches are attractive for patients with end-stage disease in whom photoreceptors are severely depleted but inner retinal neurons remain relatively intact.[7] Adeno-associated viral (AAV) vectors deliver microbial or engineered opsin genes into bipolar or ganglion cells, conferring de novo light sensitivity to the surviving neurons (Figure 1).[7] These strategies have generated visually evoked responses in preclinical models and early human studies, even when traditional photoreceptor-based vision is no longer possible.[7]

Clinical trial data from several candidates suggest optogenetic treatment can improve mobility, object recognition, and functional vision tasks in select patients with advanced retinitis pigmentosa (RP), although sample sizes remain small and visual acuity gains are modest.[8] Practical challenges include optimizing light delivery (often via light-enhancing goggles), balancing sensitivity and temporal resolution, and determining the ideal disease stage at which enough inner retinal architecture persists to benefit from treatment.[7,8]

Leading optogenetic candidates in this space include the following therapies:

- **MCO-010 (Nanoscope Therapeutics):** phase 2b/3 RESTORE trial (NCT04945772) in RP, rolling biologics licensing agreement underway[9]
- **RTx-015 (Ray Therapeutics):** phase 1 ENVISION dose-escalation study in RP/choroideremia (NCT06460844)
- **BS01 (Bionic Sight):** phase 1/2 open-label dose-escalation trial in advanced RP (NCT04278131)
- **GS030 (GenSight Biologics):** phase 1/2 PIONEER first-in-human optogenetic trial in late-stage RP (NCT03326336)

KEY TAKEAWAYS

- Gene-agnostic therapies aim to treat inherited retinal diseases by targeting shared downstream pathways such as photoreceptor loss, metabolic stress, inflammation, and circuit dysfunction.
- Optogenetics, cell replacement, and modifier gene or metabolic reprogramming approaches are progressing through clinical trials.
- Treatment selection is increasingly stage-dependent: Neuroprotective approaches are best suited for early disease, cell-based therapies for intermediate stages, and optogenetics for advanced disease.

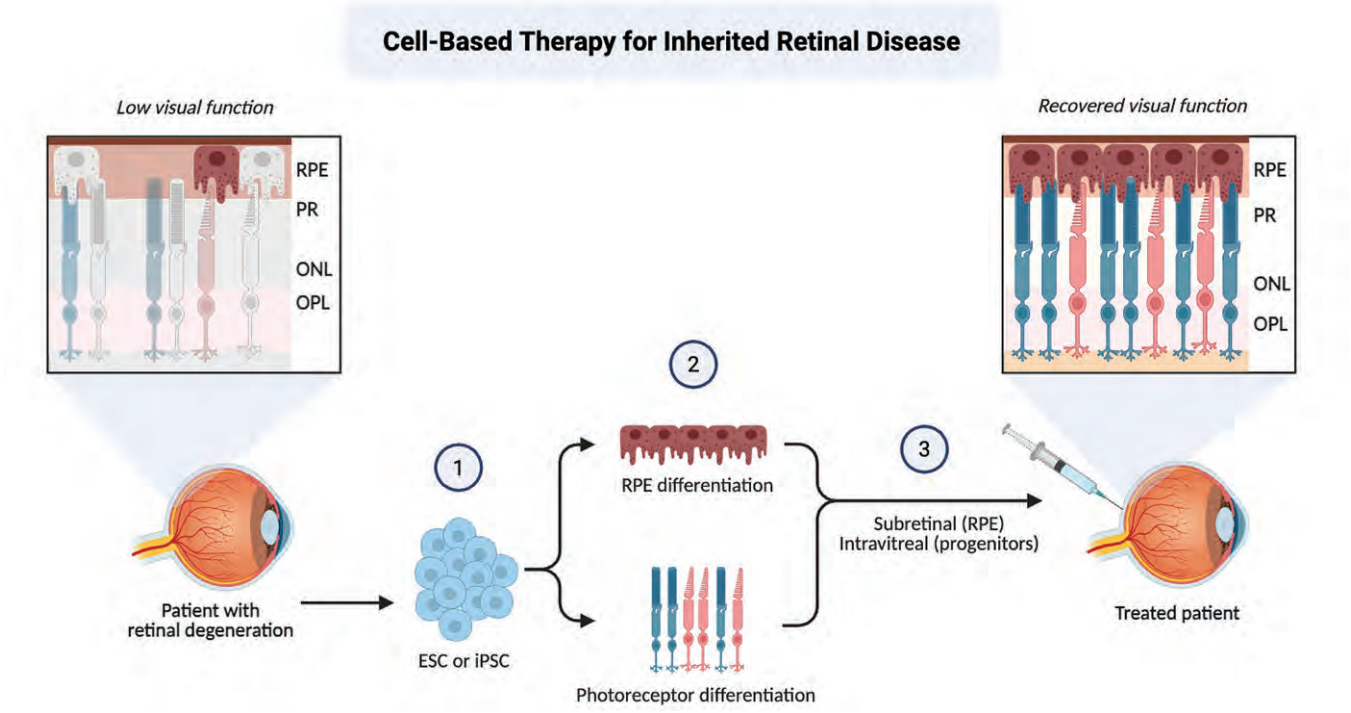

Figure 2. This diagram shows the steps of RPE monolayer transplantation and photoreceptor/progenitor cell delivery. Created in BioRender. Solanky R. 2026. BioRender.com/enz30p9

Cell Replacement: RPE and Photoreceptor Transplantation

Cell-based therapies aim to replace dysfunctional retinal pigment epithelium (RPE) and photoreceptors or provide trophic support through transplanted progenitor cells and organoids (Figure 2).[1,6] RPE transplantation has progressed from experimental macular relocation procedures to trials using human embryonic stem cell-derived or induced pluripotent stem cell-derived RPE monolayers for conditions such as AMD and Stargardt disease.[10,11] Early-phase studies of embryonic stem cell-derived RPE injected subretinally in patients with AMD or Stargardt disease reported that most participants experienced stabilized or modestly improved visual acuity with acceptable safety profiles.[10,11]

Photoreceptor replacement has developed in parallel, leveraging advances in retinal organoids and donor photoreceptor enrichment.[5,12] Recent reviews describe how transplanted photoreceptor precursors can integrate into host outer nuclear layers in animal models or at least transfer cytoplasmic material that partially restores function, although achieving robust synaptic integration and long-term survival remains challenging.[12,13]

Intravitreal or subretinal delivery of allogeneic retinal progenitor cells has entered early human trials for IRDs such as RP, with data showing dose-related mean BCVA improvements with patient-reported gains in light sensitivity and reading ability.[14]

Leading cell-based, gene-agnostic candidates include the following therapies:

- **Famzeretcel (jCell, jCyte):** phase 2 JC02-88 trial in RP (NCT06912633)
- **hRPC (ReNeuron):** phase 1/2 trial in RP (NCT02464436)
- **RG6501 (OpRegen, Lineage/Genentech/Roche):** phase 1/2 trial for geographic atrophy secondary to dry AMD (NCT02286089)
- **CNS10-NPC (Cedars-Sinai):** phase 1 trial in RP (NCT04284293)

Modifier Gene Therapy and Metabolic Reprogramming

Modifier gene therapy occupies an interesting middle ground between classic gene replacement and fully gene-agnostic neuroprotection.[1,2] Rather than correcting a single mutated gene, modifier therapies introduce a gene—often a transcription factor or regulator—that can rebalance dysfunctional networks across multiple IRD genotypes.[1,2] For example, OCU400 (Ocugen) is an AAV-based modifier gene therapy delivering NR2E3, a nuclear hormone receptor involved in photoreceptor development, metabolism, and survival.[15] The phase 3 liMeliGhT trial, which completed enrollment, is a broad, gene-agnostic trial enrolling patients with RP due to a diverse array of gene mutations.[15]

In parallel, several groups (including our own) have focused on gene-agnostic metabolic reprogramming in preclinical models of RP.[16-18] CRISPR editing of the prolyl hydroxylase domain protein 2 (PHD2/EGLN1), initially an anti-anemia drug target, was shown to reprogram the aerobic glycolysis node in rod photoreceptors. It was able

to rescue both rod and cone survival across divergent autosomal recessive and dominant RP models, independent of the underlying rod-specific gene mutation.[17,19]

Separately, ablation of von Hippel-Lindau in rod photoreceptors elevated hypoxia-inducible factor activity, enhanced glycolysis, and slowed degeneration of both rods and cones in RP models, while inducing reciprocal changes in RPE glycolytic flux, underscoring the importance of metabolic crosstalk between photoreceptors and the RPE.[18,20]

Targeting microRNA-mediated pathways offers another gene-agnostic strategy: Modulation of miR-181a/b in the RPE was recently shown to improve RPE morphology, reduce aerobic glycolysis, and slow photoreceptor degeneration in a mouse RP model, highlighting microRNAs as tunable regulators of retinal metabolism.[18,21]

Together, these studies support the broader concept that metabolic and transcriptional reprogramming can act as gene-agnostic interventions to prolong photoreceptor survival across multiple IRD genotypes.[1,16-18,22]

In addition to OCU400, other gene-agnostic or mutation-independent candidates include the following:

- **SPVN06 (SparingVision):** phase 1/2 PRODYGY trial in rod-cone dystrophy (NCT05748873)
- **KIO-301 (Kiora Pharmaceuticals):** phase 2 ABACUS-2 trial in late-stage RP (NCT06628947)
- **ACDN-01 (Ascidian Therapeutics):** phase 1/2 STELLAR trial for *ABCA4*-related Stargardt disease and other *ABCA4* retinopathies (NCT06467344)
- **Sepofarsen (Sepul Bio):** phase 3 HYPERION trial in *CEP290*-associated Leber congenital amaurosis type 10 (NCT06891443)
- **Ultevursen (Sepul Bio):** phase 2b LUNA trial for *USH2A* exon 13-related RP and Usher syndrome (NCT06627179)

ENABLING TOOLS AND CLINICAL ENDPOINTS

As gene-agnostic approaches move toward the clinic, sensitive structural, functional, and metabolic endpoints are essential for detecting treatment effects.[2,23] Stable isotope-resolved metabolomic protocols have been developed to quantify retinal and RPE glucose metabolism, providing a framework to evaluate how candidate therapies alter glycolytic and tricarboxylic acid-cycle flux in preclinical models.[22]

On the clinical side, chromatic full-field stimulus testing (FST) has emerged as a practical psychophysical endpoint to quantify residual rod- and cone-mediated sensitivity in IRD cohorts.[24] In a recent study comparing patients with rod-cone versus cone dystrophies, standardized chromatic FST using white, red, and blue stimuli showed high feasibility and moderate discriminative accuracy; blue-red threshold differences helped differentiate patterns of dysfunction but required interpretation alongside genetic testing and multimodal imaging.[24]

Such tools complement established outcome measures such as BCVA, microperimetry, ellipsoid zone integrity on OCT, and patient-reported outcomes, and they will be increasingly important in trials evaluating optogenetic therapies, cell-based interventions, and metabolic modifiers.[2,20,21]

PRACTICAL CONSIDERATIONS FOR THE RETINA SPECIALIST

Several themes are relevant when counseling patients about gene-agnostic therapies.[1,2] First, these approaches do not eliminate the value of precise molecular diagnosis; knowing the genotype remains important for eligibility in mutation-specific trials, prognosis, and family counseling, even if the therapy itself is gene-independent.[1,2]

Second, timing is critical; neuroprotective or cone-preserving strategies such as cone-viability factor–based therapies and certain cell therapies are likely to be most effective when sufficient photoreceptor structure remains. Optogenetic interventions may be reserved for advanced disease with minimal residual outer retina but preserved inner retinal circuitry.[6-8,14] This therapeutic window paradigm highlights the critical need to align the chosen therapeutic approach with the patient's specific clinical stage.

Third, patients should understand that most of these interventions are currently in early-phase trials, with primary goals of establishing safety and appropriate dosing; functional benefits, while promising in some reports, are still being defined and may be modest or variable.[6-8,14,15]

Regulatory designations such as orphan status and expedited pathways may accelerate the development of gene-agnostic treatments, but widespread clinical availability is still several years away.[15] In the interim, retina specialists must stay current with active trials, referring eligible patients, and setting balanced expectations that emphasize both the hope and the uncertainties inherent to first-in-class therapies.[1,23] ■

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IRD CLINICAL TRIAL ENDPOINTS: Lessons Learned

Choosing the right outcome measures for inherited retinal disease trials requires matching endpoints to disease biology, therapeutic mechanism, and patient experience.

By Melissa Yuan, MD, and Ahmad Al Moujahed, MD, PhD

Conventional ophthalmic endpoints using BCVA were developed for conditions such as cataract surgery, AMD, and diabetic retinopathy, for which large sample sizes and central BCVA changes are readily captured. Inherited retinal diseases (IRDs) challenge these conventional endpoints because patients with conditions such as retinitis pigmentosa (RP) may retain a VA of 20/20 for years while losing peripheral and night vision—changes that BCVA cannot detect. At the same time, patients with end-stage disease may already be at the measurement threshold, leaving no room to capture further visual decline.[1,2] Phenotypic heterogeneity, slow progression, and small patient populations compound these difficulties.[3]

The expanding diversity of potential therapeutic strategies means endpoints must be matched to both disease phenotype and mechanism of intervention.[4] With numerous candidates advancing through clinical development, endpoint selection has emerged as a critical determinant of trial success or failure. For example, the phase 3 STAR trial of timrepigene emparvovec (BIIB111, Biogen) for choroideremia investigated a primary endpoint of a gain of 15 ETDRS letters or more, which was borrowed from wet AMD trials where anti-VEGF therapy routinely produces such gains. Although a meaningful proportion of treated patients showed 10-letter gains versus controls, the rigid primary endpoint did not capture this signal, given the disease's slow progression.[5] Borrowing endpoints from other retinal diseases without adapting them to the natural history of the specific IRD risks masking a genuine treatment effect.[6]

ESTABLISHED CLINICAL ENDPOINTS

BCVA, a component of almost all IRD trials, offers regulatory familiarity but alone may be insufficient.[1,4,7] In the

pivotal trial for voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) for *RPE65*-associated retinal dystrophy, BCVA did not reach statistical significance between arms; efficacy was instead demonstrated through the multi-luminance mobility test (MLMT), which measured navigation ability through a maze and past obstacles in dim light—a clinically meaningful endpoint.

Electronic alternatives such as the Freiburg Visual Acuity Test extend measurement into the hand-motions range, serving as the primary endpoint in the phase 2b RESTORE trial of MCO-010 (Nanoscope) for advanced RP, in which patients' vision was so poor, it was "off chart."[8]

BCVA is most responsive when the disease disrupts central function early (as in achromatopsia or Leber congenital amaurosis [LCA] genotypes, including *GUCY2D*, *CEP290*, and *RPE65*), but it tells little about progression in rod-cone dystrophies where patients may continue to read 20/25 while their peripheral fields collapse.[4]

Contrast sensitivity remains underused in IRD trials. The standard Pelli-Robson chart samples a limited range and bottoms out quickly. Newer automated platforms such as the quick contrast sensitivity function have shown stronger correlation with patient-reported quality of life than BCVA.[9]

The MLMT is the only patient-focused outcome that has been approved as a primary endpoint for an IRD gene therapy trial. Its strength lies in directly measuring the patient's ability to move safely through an environment. However, the MLMT is labor-intensive, requires dedicated physical space and personnel, and is rarely used outside trial settings, complicating long-term monitoring.[1] Newer alternatives such as virtual reality mobility assessments may address these limitations.[10] Researchers have also expanded on standardized performance-based tests, including physical and virtual reality-based paradigms developed at the StreetLab (now at UPMC Vision Institute) that track gaze, gait, and head motion during navigation tasks across multiple lighting levels; these tests have been adopted for the RUSH2A follow-up studies (NCT03146078).[11]

Visual field testing is conceptually appealing for rod-cone dystrophies in which peripheral vision is lost, but standard automated perimetry has high test-retest variability in scotomatous regions.[12] Microperimetry, with real-time fundus tracking, partly addresses this and is designated as an efficacy endpoint in the phase 2/3 VISTA trial of laru-zova (AGTC-501, Beacon Therapeutics) for *RPGR*-related X-linked RP (XLRP).[3] A key statistical challenge is multiplicity: When sensitivity is tested at dozens of loci, the probability of false-positive improvements increases sharply.[13] The FDA has required a mean improvement of at least 7 dB in at least five prespecified loci, but this conservative approach contributed to the XIRIUS phase 2/3 study of cotoretigene toliparvovec (BIIB112, Biogen) for XLRP failing its primary endpoint despite apparent treatment signals.[14] An alternative binomial distribution approach requiring at least seven unspecified loci with at least 7 dB improvement across a 68-locus grid, as applied to the phase 2 SKYLINE trial data of laru-zova in XLRP, may offer a more balanced approach while maintaining the false-positive rate near 5% without the need for prespecification.[13]

For trials targeting rod-specific rescue, scotopic microperimetry and two-color dark-adapted perimetry can isolate rod-mediated versus cone contributions, although both add time and complexity.[4] Two-year data from the RUSH2A study demonstrated that quantitative static perimetry measures declined significantly in eyes with *USH2A*-related retinal degeneration while central measures declined more slowly.[15] Four-year results found that testing at functional transition points, which are loci at the boundary of the ellipsoid zone (EZ), was particularly sensitive and that rates of change were substantially more efficient than threshold-based proportions, often requiring half the sample size for equivalent statistical power.[16]

KEY TAKEAWAYS

- BCVA as a trial endpoint is most responsive when the disease disrupts central function early but tells little about progression in rod-cone dystrophies.
- The multi-luminance mobility test, Freiburg Visual Acuity Test, low-luminance visual acuity, full-field stimulus threshold testing, fundus autofluorescence, OCT-derived metrics, composite endpoints, and patient-reported outcome measures may all serve as more accurate endpoints in specific inherited retinal disease trials.
- With more than two dozen gene therapy trials in phase 2 or 3, endpoint strategy is integral to whether an effective therapy succeeds or fails on paper.

EMERGING ENDPOINTS

Low-luminance visual acuity (LLVA) adds a neutral density filter to simulate dim conditions, revealing functional deficits that are invisible under standard lighting. Many patients with choroideremia or *RPGR*-related RP report difficulty in dim environments before their standard acuity begins to decline.[17] LLVA has been approved by the FDA as an efficacy endpoint in the VISTA trial for *RPGR*-related XLRP.[18]

Full-field stimulus threshold testing (FST) is feasible in patients with nystagmus or eccentric fixation who cannot perform standard perimetry. Using chromatic stimuli can isolate rod versus cone contributions.[19] Japanese regulators accepted FST as the primary endpoint for voretigene

TABLE. OVERVIEW OF SELECT CLINICAL TRIAL ENDPOINTS FOR INHERITED RETINAL DISEASE

Endpoint	Principal Strengths	Principal Limitations	Regulatory Precedent
CENTRAL VISUAL FUNCTION			
BCVA	• Widely validated • Standardized charts	• Insensitive to peripheral/low-light deficits • Ceiling/floor effects	Accepted primary endpoint across multiple inherited retinal disease programs
Contrast sensitivity	• Detects contrast-based functional losses that BCVA misses (eg, difficulty in dim light or low-contrast environments) • Covers range of spatial frequencies	• Moderate inter-rater variability • Not standardized across devices	Secondary measure in select trials
LIGHT SENSITIVITY AND VISUAL FIELDS			
Static and kinetic perimetry	• Semi-automated • Standard statistical analysis • Established in glaucoma	• Insensitive at severely reduced baseline • Limited ability to detect small changes	Secondary endpoint in *RPGR* and *RPE65* trials
Microperimetry (mesopic and scotopic)	• Dark-adapted protocols assess rod function • Targeted stimulus on retinal loci	• Substantial learning curve • High test-retest and inter-rater variability	Secondary/exploratory in select gene therapy programs
Full-field stimulus threshold	• Practical post-treatment measure • Adaptable across disease stages	• Needs further validation as standalone primary • Overall sensitivity only	Primary in Japan (*RPE65*); secondary elsewhere
REAL-WORLD FUNCTIONAL PERFORMANCE			
Multi-luminance mobility test	• Reflects real-world visual performance holistically • Accepted as pivotal primary endpoint	• Labor-intensive • Observer-dependent • Not suited for routine clinical use	Primary endpoint in voretigene neparvovec-rzyl (Luxturna, Spark) pivotal trial
STRUCTURAL/ANATOMICAL IMAGING			
Ellipsoid zone and fundus autofluorescence imaging	• Objective • Correlates with phenotypic progression • High measurement precision	• Indirect link to visual function • Specialized equipment and expertise needed	Primary anatomical outcome in geographic atrophy and Stargardt trials

neparvovec-rzyl approval, supported by data showing concordance between FST thresholds and mobility performance.[19] In the RUSH2A study, FST showed worsening throughout the wide range of baseline values, with 47% of eyes exceeding the coefficient of repeatability at 4 years, making FST one of the most sensitive tests for detecting change.[16] However, the clinical effect of FST changes in patients with good central vision remains to be established.[16] Furthermore, a multi-stakeholder consensus concluded that FST is not yet ready as a primary endpoint, requiring further standardization and stronger linkage to patient-centered measures.[11]

Structural imaging has long played a supporting role in IRD trials, but regulatory acceptance of fundus autofluorescence (FAF)-measured atrophy as a primary endpoint in geographic atrophy trials has opened the door for imaging-based outcomes.[20] For IRDs, the most promising OCT-derived metrics are the EZ width and area, serving as surrogates for surviving photoreceptor territory. EZ measurements track disease progression with reasonable sensitivity.[21] However, the RUSH2A study found that only 33% of eyes had sufficient baseline EZ area (≥ 3 mm^2) to detect measurable change, and among those eyes, the standardized rate of change was lower than for most functional measures. These findings led to the recommendation that clinical trials for *USH2A* should require a minimum EZ area of at least 3 mm^2 at enrollment to ensure the endpoint can capture progression.[16] FAF provides complementary data, with loss of signal indicating retinal pigment epithelium loss and preserved autofluorescence area tracking progression in choroideremia and RP.[22]

Composite endpoints combining structural and functional measures may increase statistical sensitivity. In *ABCA4*-associated Stargardt disease, the most sensitive composite performed best without BCVA, which contributed more noise than signal.[23] Machine learning tools are also being applied to combine imaging and functional datasets, with early work in LCA suggesting that algorithmic

approaches can identify localized treatment potential that no single clinical test would.[24]

Patient-reported outcome measures have been limited to secondary endpoints in IRD trials due to concerns about subjectivity and variability. Newer IRD-specific instruments such as the Michigan Retinal Degeneration Questionnaire and the ViSIO-PRO tools may provide validated, disease-specific assessments.[25,26] While objective assessments detect biological treatment effects, changes in these measures may not necessarily translate into improvements patients perceive as meaningful, underscoring the importance of incorporating patient perspectives.

PRACTICAL CONSIDERATIONS

For investigators designing IRD trials, several principles emerge. Endpoint selection should be driven by the pathophysiology of the genetic condition: A rod-cone dystrophy preserving central vision requires different outcome measures than a macular dystrophy. The therapeutic mechanism should also play a role. Gene augmentation aiming to halt photoreceptor loss may be best served by a structural endpoint or functional mobility assessments for rod-mediated function in rod-cone dystrophies. An optogenetic therapy restoring light sensitivity to surviving inner retinal neurons may require a functional mobility assessment to capture the qualitative shift in visual capability. Small patient populations may necessitate surrogate endpoints offering greater sensitivity.

Across the trial landscape, endpoint choices have been tailored to individual genotypes (Table). In *RPE65*-associated LCA, the approved therapy validated the complementary use of both mobility and psychophysical endpoints. For choroideremia, multiple completed phase 1/2 trials relying on microperimetry, FAF, and BCVA have not demonstrated statistically significant treatment effects, fueling debate about whether these endpoints are sufficiently sensitive for slowly progressive diseases.[27,28] For achromatopsia, the stationary nature and the primacy of photophobia have led investigators to incorporate light sensitivity measures as functional outcomes, including palpebral aperture quantification and visual photosensitivity thresholds.[4]

ALIGNING ENDPOINTS WITH LIVED EXPERIENCE

With more than two dozen gene therapy trials in phase 2 or 3, endpoint strategy is integral to whether an effective therapy succeeds or fails on paper. The retina specialist's role in this process is becoming more important, as familiarity with the clinical nuances, the practical realities of administering and interpreting these tests, and the lived experience of patients all inform which measurements will matter. As the regulatory landscape evolves, the goal is not simply more endpoints but better alignment between what we measure and what patients gain from treatment. ■

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BE WARY OF MACULAR HOLE AFTER ANTI-VEGF INJECTION

This complication, although rare, is still possible.

BY CARLOS MARIO RANGEL, MD; KAROL QUINTERO LIZCANO, MD; MARIA ISABEL CORRALES, MD; MARIA A. PIEDRAHITA, MD; AND VIRGILIO GALVIS, MD

Intravitreal anti-VEGF injections are a mainstay of treatment for many retinal conditions, including wet AMD, macular edema following retinal vein occlusion (RVO), diabetic macular edema, diabetic retinopathy, and myopic choroidal neovascularization.[1,2] Despite their overall excellent safety profile, anti-VEGF injections can, rarely, lead to serious adverse effects, including endophthalmitis, rhegmatogenous retinal detachment, RVO, and others.[2] Development of a full-thickness macular hole (FTMH) has also been described, which is likely secondary to the severe contraction of the neovascular membrane and focal vitreoretinal traction forces induced by the anti-VEGF agent.[3-9]

Here, we present our case of a patient who developed a FTMH following a course of anti-VEGF intravitreal injections for macular edema secondary to combined central retinal artery and vein occlusion (CCRAVO).

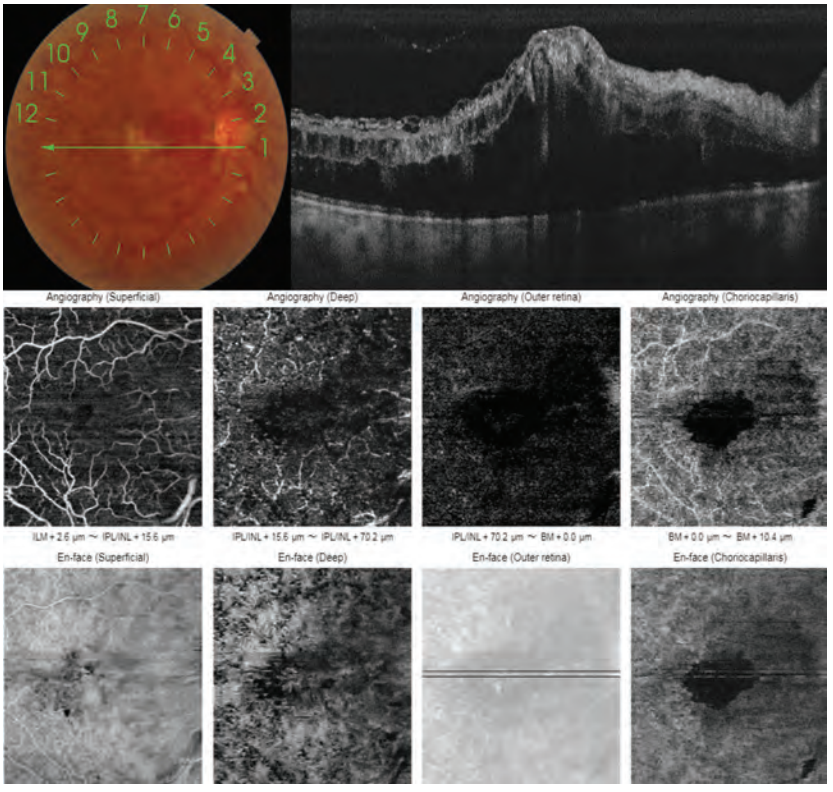

Figure 1. OCT and OCTA at baseline showing hyperreflective inner layers, subretinal fluid, and macular edema, with reduced vascular density in both the superficial and deep plexuses.

CASE EXAMPLE

A 54-year-old man presented with a 1-month history of vision loss in his right eye. His corrected distance VA (CDVA) was counting fingers at 2 m OD and 20/25 OS, and his IOP was 14 mm Hg OU. No abnormalities were observed in the anterior segment of either eye. Fundus examination of his left eye was normal, while his right eye revealed intraretinal hemorrhages and venous engorgement in all four quadrants demonstrating macular whitening (ischemic retinal edema) consistent with central retinal artery occlusion, as well as a "cherry-red spot" or foveal-sparing and peripheral intraretinal hemorrhages typical of central RVO (Figure 1). These findings were consistent with a diagnosis of CCRAVO.[10]

OCT angiography (OCTA) of the patient's right eye showed macular edema, hyperreflective inner layers, and subretinal fluid, likely secondary to CCRAVO. He was treated with three monthly intravitreal injections of ranibizumab (Lucentis, Genentech/Roche).

One month after the third injection, the patient's CDVA was counting fingers at 50 cm in his right eye. OCTA showed a FTMH, macular edema at its border, atrophy of the inner retinal layers, and signs of retinal ischemia (Figure 2).

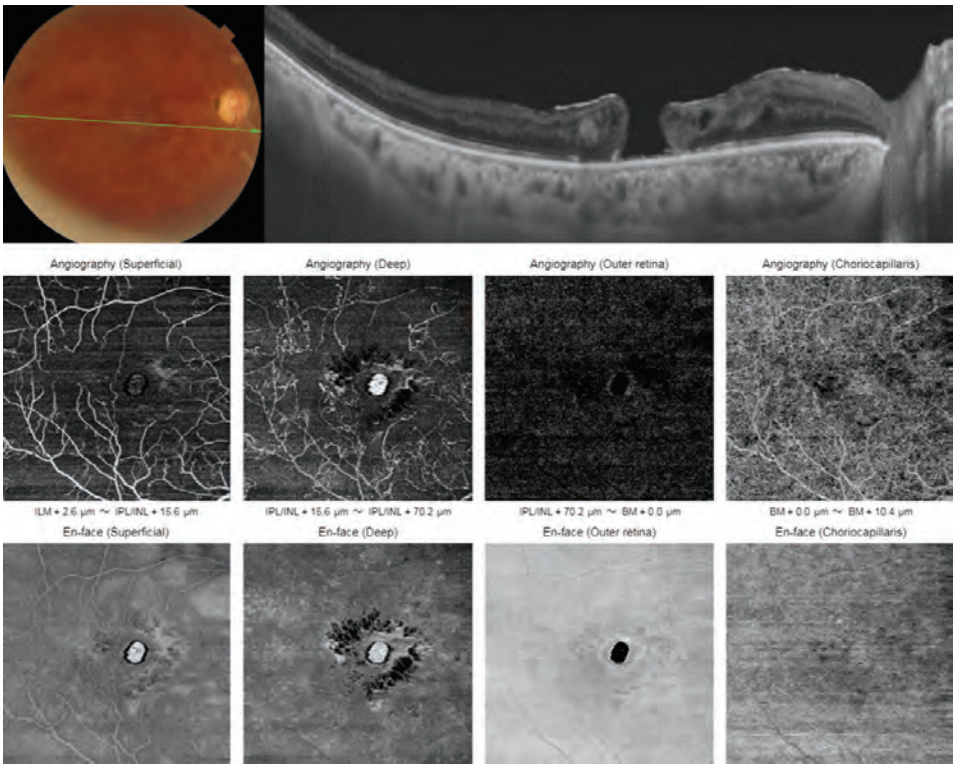

Figure 2. One month after the third intravitreal ranibizumab injection, OCT demonstrated an FTMH with persistent edema and inner retinal atrophy, while OCTA revealed vascular rarefaction and ischemic changes in the superficial and deep plexuses.

MANAGEMENT

Surgical repair via pars plana vitrectomy and internal limiting membrane peeling was deferred due to poor visual potential, extensive inner retinal atrophy, and profound macular ischemia as evidenced by OCTA. The presence of significant inner retinal atrophy, persistent macular edema, and signs of extensive ischemia further reduced the likelihood of functional visual recovery following vitrectomy.

Considering the widespread retinal ischemia observed on OCTA, the patient underwent panretinal laser photocoagulation in his right eye as a prophylactic measure to reduce the risk of complications, particularly neovascular glaucoma. He continues to be monitored regularly with multimodal imaging.

ABOUT CCRAVO

CCRAVO is a rare entity associated with multiple systemic diseases such as diabetes, lupus erythematosus, homocysteinemia, and dyslipidemia; therefore, management should involve a multidisciplinary approach.[10] Despite treatment, visual prognosis remains poor.

VEGF has been found to be elevated in RVO, leading to persistent vascular leakage and macular edema. Encouraging results have been published regarding the efficacy of intravitreal anti-VEGF therapy on diminishing macular edema, halting neovascularization, and improving final visual acuity; complications, albeit rare, can occur, including infectious endophthalmitis, uveitis, rhegmatogenous retinal detachment, temporal IOP elevation, ocular hemorrhage, and very uncommonly, FTMH.[2-4]

Several mechanisms have been proposed to explain the presentation of FTMH after intravitreal anti-VEGF injection. Some authors have suggested the globe deformation and potential induction of vitreous incarceration in the injection site following the procedure could enhance vitreomacular traction (VMT), especially with an overlying pigment epithelial detachment (PED), subsequently leading to FTMH development.[3,4] In addition, the chemical compounds introduced with the anti-VEGF therapy and the structural changes it induces could lead to VMT.[5]

In the available published cases of FTMH after intravitreal anti-VEGF injection,[3-9] most FTMHs developed in patients whose indication for the procedure was wet AMD, with or without VMT or PED. In almost all cases, the FTMH diagnosis was confirmed by OCT and fluorescein angiography, apart from one study, in which only OCT was used.[6] Surgical intervention led to improved visual outcomes but, unlike the case presented here, none of these reported cases had subjacent arterial occlusive compromise.

UNDERSTAND EVEN THE RAREST OF ADVERSE EVENTS

Intravitreal anti-VEGF injection plays an important role in the treatment of multiple retinal conditions. Although their most common adverse events are well known, FTMH has been reported in rare cases. It is important to acknowledge that development of a FTMH is a known risk in patients with chronic macular edema, such as the one

in this case; thus, it is prudent to maintain a high degree of suspicion of this complication, particularly in eyes with severe ischemic compromise. Adequate follow-up with OCT can facilitate a prompt diagnosis and treatment, if indicated, to improve final visual acuity. ■

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Rare and Inherited Retinal Disease

(Continued from page 37)

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The ZEISS Retina Workflow: Integrating Advanced Imaging and Surgical Technology in Retina Care

This is an adaptation of a conversation between Jorge Fortun, MD, and Katherine Talcott, MD, during a recent episode of New Retina Radio in which they discussed the role ZEISS Diagnostics plays in their clinics and ORs. To listen to the podcast, scan the QR code:

THE ZEISS RETINA WORKFLOW IN THE CLINIC | BY KATHERINE TALCOTT, MD

For me, OCT is the diagnostic backbone behind nearly every clinical decision. In particular, multimodal imaging that is available on integrated platforms like the ZEISS Retina Workplace has reshaped how we practitioners identify, monitor, and explain disease to patients. The ability to combine high-resolution structural OCT, fundus autofluorescence, infrared imaging, and composite B-scans within a single workflow has made it possible to assess and treat pathology with much greater clarity and efficiency.

FOLLOWING GEOGRAPHIC ATROPHY

A particular case of geographic atrophy (GA) illustrates how I use these tools in my practice. I've been following a 76-year-old woman who has had stable 20/25 UCVA OD for the past 3 years. Her fellow eye has count-fingers vision from a longstanding choroidal hemangioma. At her most recent visit, she reported increasing difficulty with reading, one of her favorite activities.

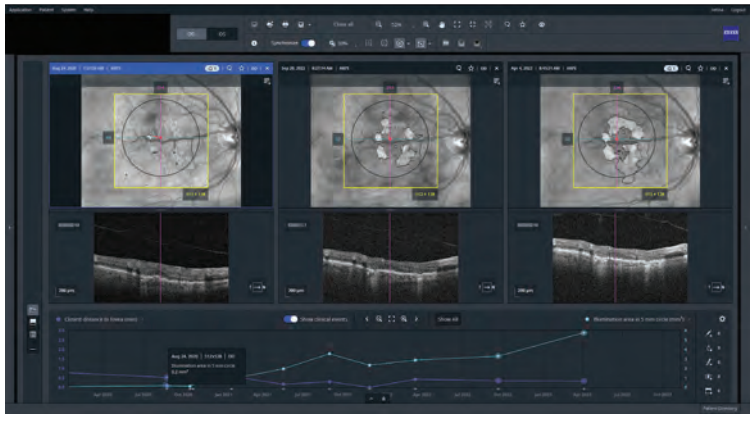

Figure 1. A patient with GA in the right eye as seen with infrared and OCT images showing progression over a 3-year period.

Structural OCT of her right eye showed no exudation, but multimodal imaging revealed the broader picture. On fundus autofluorescence, I saw areas of retinal pigment epithelium (RPE) loss surrounding the fovea, and with infrared imaging I noted the atrophic areas. Composite B-scans gave me additional confirmation that the atrophy in the right eye had expanded toward the fovea. In the left eye, unfortunately, the diffuse atrophy already involved the fovea.

It is very helpful to be able to compare earlier scans from all these modalities on the ZEISS Retina Workplace software. Scans of this patient's right eye from 2 years prior showed almost no atrophy, but scans from her last 3 visits revealed its progression (Figure 1). The composite B scan images, in particular, I find ideal not only for identifying GA and loss of RPE, but for educating patients so we can discuss the appropriate treatment options.

ANTI-VEGF EVALUATIONS

The ZEISS Retina Workplace is also great for evaluating patients who receive anti-VEGF injections. One of my patients with neovascular age-related macular degeneration had undergone 37 injections of aflibercept (Eyelea, Regeneron) in his left eye. We had not been able to extend the injections beyond 5 weeks before the fluid returned. At one point, he was interested in trying a newer anti-VEGF agent, which allowed us to extend to a 6-week interval. The following scan showed a reduction in fluid, and his vision was fine. When we tried an 8-week interval, however, the subretinal fluid returned, even more so than when he was on aflibercept, and I also found a hemorrhage (Figure 2). Ultimately, he decided to switch back to aflibercept at a 6-week interval. This case underscores the degree to which I rely on multimodal imaging to follow these types of patients and decide on the most effective treatment intervals.

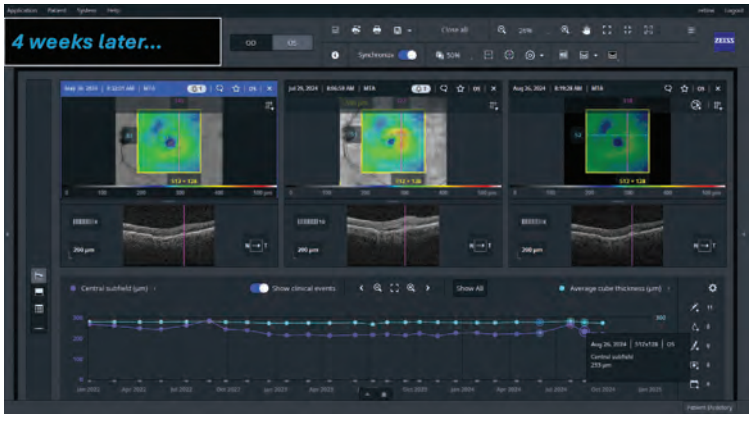

Figure 2. Patient with nAMD on anti-VEGF injections who had worsening subretinal fluid and hemorrhage at 8 weeks (middle panel) that improved 4 weeks later (right panel) after another injection.

OCT-A

I find myself relying on OCT-angiography (OCT-A) over fluorescein angiography for some diagnoses, especially choroidal neovascular membranes. For example, a 45-year-old patient with chronic central serous chorioretinopathy experienced a sudden decline in vision to 20/60 after years of stability. Structural OCT showed subretinal fluid and subretinal hyperreflective material, which made me suspect secondary choroidal neovascularization. Yet, on OCT-A, I used segmentation to find flow signals beneath the RPE that revealed the presence of a neovascular membrane (Figure 3). We initiated anti-VEGF therapy, which resolved the fluid and preserved the patient's vision.

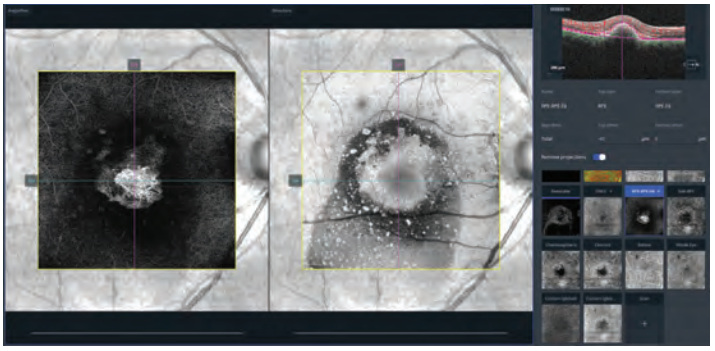

Figure 3. OCT angiography showing choroidal neovascular membrane in patient with subretinal fluid.

ZEISS FORUM

FORUM is ZEISS' data management software that enriches my understanding of a patient's imaging and how to manage their retinal disease. Its advanced review tools allow me to quickly synthesize changes in their imaging, including in response to treatment. For example, it tracks and applies time points to central subfield imaging, so that I can quickly compare scans from different dates and identify blips when more fluid was present. This is invaluable when a patient asks to extend the intervals between their injections. I can show them on their imaging history exactly the intervals at which the fluid recurred, and also how far they've progressed since starting treatment.

I appreciate having a platform that unifies imaging and diagnostic tools and that is accessible across the clinic and OR. ■

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THE ZEISS RETINA WORKFLOW IN THE OR | BY JORGE FORTUN, MD

In the OR, the ZEISS Retina Workflow is my workhorse. This integrated system includes the EVA NEXUS vitreoretinal and cataract surgical system by DORC (a ZEISS company) and the ARTEVO 850 3D digital microscope by ZEISS. Together, they enable me to perform more advanced surgery, reflective of the shift in our field away from purely traditional vacuum-based vitrectomy consoles and toward a true hybrid model of surgery with improvements in fluidics control, pressure management, visualization, and, ultimately, a more deliberate way to operate.

ULTRA-WIDEFIELD IMAGING AND INTRAOPERATIVE OCT

I have operated with heads-up displays for years, and ZEISS ARTEVO 850 has become my go-to system because it gives me ultra-widefield imaging and intraoperative OCT combined. Having a shared surgical view for everyone in the room, especially when I'm teaching, has been a real advantage. Instead of trying to describe subtle tissue planes through a teaching scope or a secondary monitor, I can walk people through the case as it is happening.

Intraoperative OCT allows me to be that much more responsive during surgery. It gives me real-time diagnostic feedback at the moment when I'm deciding whether to stop, whether to keep peeling, or whether the tissue is behaving the way I think it is. In macular surgery, it helps confirm whether a peel is complete or whether something unexpected has happened. In posterior proliferative vitreoretinopathy, it can show residual tissue that may not be obvious through the microscope alone. In an optic pit case, intraoperative OCT can show in real time how much improvement we have achieved after vitrectomy and hyaloid elevation, which may spare the patient unnecessary additional maneuvers like internal limiting membrane (ILM) peeling.

Also, I think that intraoperative OCT is going to become increasingly important as we move further into subretinal therapies and revisit submacular surgery. The more our maneuvers depend on exact tissue-plane information, the more valuable it is to have OCT integrated directly into the surgical workflow rather than relying on inference alone.

One case that captures this well was a surgery for an optic pit my partner Luis Haddock, MD, performed. These eyes always raise the question of how much intervention is needed, because every additional step carries risk. In that case, intraoperative OCT showed meaningful improvement after vitrectomy and hyaloid elevation alone. That real-time feedback helped guide the case and made it clear that more intervention, including ILM peeling, was not necessarily required. To me, that is exactly where this technology proves its value: in helping us make better intraoperative decisions.

ZEISS RESIGHT

The ZEISS RESIGHT 500/700 fundus viewing system is another place where the practical value shows up every day. The Single-use noncontact Lenses for ZEISS RESIGHT, including the ULTRA WIDE-ANGLE Lens, provide practical flexibility and excellent optics. The wider peripheral view can reduce the need for scleral depression in selected cases, which is particularly helpful early in practice or in settings without highly experienced assistance. For surgeons building an ambulatory surgery center, disposability also offers real-world advantages in cost structure, turnover, and optical consistency.

CONCLUSION

The ZEISS Retina Workflow offers a true value proposition: ZEISS ARTEVO 850 for a better heads-up surgical view, intraoperative OCT for real-time decision-making, and the ZEISS RESIGHT fundus viewing system for efficient, flexible visualization from the macula to the far periphery. These tools fit naturally into the way we already operate, but they let us do it with more information and, I would argue, with more confidence. ■

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BILATERAL SUBRETINAL FLUID IN A 66-YEAR-OLD WOMAN

Findings on multimodal imaging led to a diagnosis of autosomal recessive bestrophinopathy.

BY TIMOTHY T. XU, MD; JUSTIN C. MUSTE, MD; AND SIDRA ZAFAR, MD

A 66-year-old Asian woman was referred to our clinic for evaluation of bilateral subretinal fluid. The referring physician had raised concern for chronic central serous chorioretinopathy (CSCR). The patient reported chronic bilateral progressive vision loss since early adulthood but denied acute visual changes and nyctalopia. Her ocular history was notable for hyperopia and mild cataract, and her medical history included diet-controlled type 2 diabetes and hyperlipidemia. She denied all pertinent medications associated with retinal toxicity and had no known family history of vision loss.

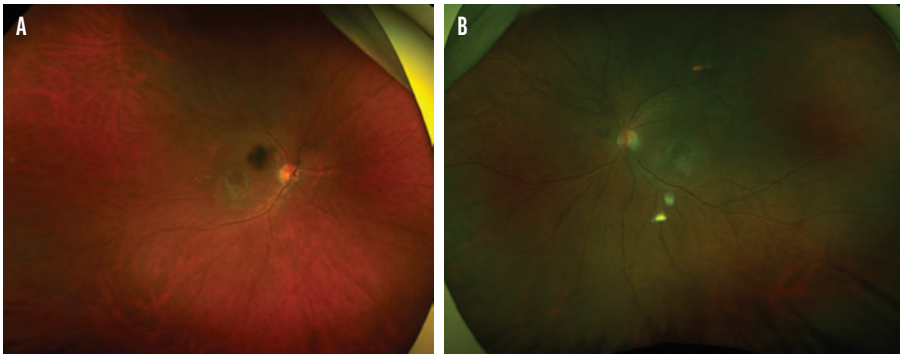

Figure 1. Ultra-widefield fundus photography of the right (A) and left (B) eye demonstrated bilateral perifoveal circular hypopigmentation with temporal vitelliform punctate lesions in the temporal macula.

On examination, her VA was 20/200 OU, and manifest refraction revealed mild hyperopia (+0.75 spherical equivalent OU). Examination of the anterior segment was unremarkable, other than 1+ nuclear sclerosis cataract in each eye. Vitreous cell and vitreous haze were not present. Dilated fundus examination demonstrated bilateral perifoveal circular hypopigmentation with temporal vitelliform punctate lesions in the temporal macula (Figure 1).

IMAGING AND WORKUP

Autofluorescence demonstrated corresponding hypoautofluorescent foveal changes with a surrounding hyperautofluorescent rim (Figure 2). OCT showed bilateral subretinal fluid and disruption of the outer retinal layers (ie, interdigitation zone, ellipsoid zone) with notable pachyvessels. Fluorescein angiography showed corresponding late macular hyperfluorescence without smokestack appearance or expansile dot (Figures 3 and 4). The combination of subretinal fluid, temporal vitelliform punctate lesions, and foveal outer retinal abnormalities prompted consideration of a broad differential diagnosis, including pachychoroid spectrum disease, infectious/inflammatory etiologies (eg, syphilis, tuberculosis, sarcoidosis, Vogt-Koyanagi-Harada disease, posterior scleritis), drug-induced retinopathies (eg, hydroxychloroquine, pentosan polysulfate sodium, tamoxifen), and inherited retinal disease (IRD; eg, Stargardt disease, *PRPH2*-associated pattern dystrophy, bestrophinopathies, cone-rod dystrophy, Sorsby macular dystrophy).

Complete blood count, comprehensive metabolic panel, syphilis serologies, QuantiFERON-TB Gold, angiotensin-converting enzyme level, and chest radiography were each unrevealing. Genetic testing was obtained, which demonstrated two compound heterozygous pathogenic variants in the *BEST1* gene in trans configuration (eg, located on opposite alleles), confirming a diagnosis of autosomal recessive bestrophinopathy (ARB).

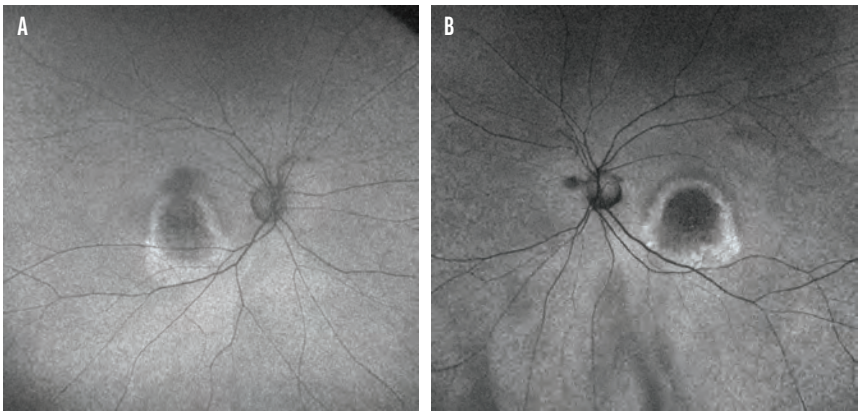

Figure 2. Fundus autofluorescence of the right (A) and left (B) eye demonstrated corresponding hypoautofluorescent foveal changes with a surrounding hyperautofluorescent rim.

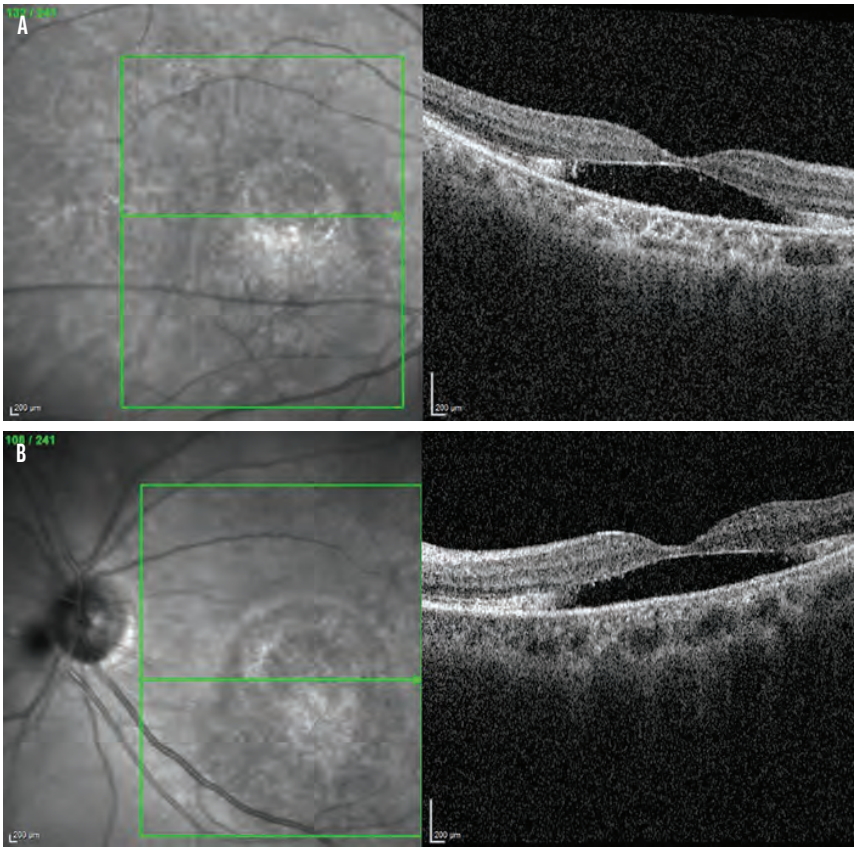

Figure 3. OCT of the right (A) and left (B) eye demonstrated bilateral subretinal fluid and disruption of the outer retinal layers.

ABOUT ARB

The *BEST1* gene encodes bestrophin-1, a calcium-sensitive chloride channel expressed in the retinal pigment epithelium.[1] Pathogenic variants in *BEST1* give rise to a spectrum of IRDs collectively known as bestrophinopathies. These disorders demonstrate substantial phenotypic variability including Best vitelliform macular dystrophy, adult-onset foveomacular vitelliform dystrophy, autosomal dominant vitreoretinochoroidopathy, and ARB. Electrooculogram abnormalities are a classic feature of bestrophinopathies.

ARB is a rare phenotype associated with biallelic *BEST1* pathogenic variants.[2] It often presents with multifocal vitelliform deposits, diffuse retinal pigment epithelium abnormalities, intraretinal and subretinal fluid, and widespread retinal dysfunction.[3,4] The phenotype can be highly variable. Reported findings include punctate subretinal fleck deposits extending beyond the vascular arcades, confluent yellow lesions extending into the midperiphery, macular atrophy or fibrosis, vitelliruptive lesions, and exudative retinal detachments. Our patient demonstrated several ARB features, including bilateral subretinal fluid, diffuse fleck-like subretinal deposits, chronic visual decline, and outer retinal abnormalities.

There is currently no definitive treatment for ARB. Management focuses on accurate diagnosis, avoiding unnecessary interventions (eg, intravitreal injections, lasers), low vision support, genetic counseling, and monitoring for complications. At the 1-year follow-up, our patient demonstrated no significant change in symptoms, visual acuity, or OCT findings.

As gene therapy advances, establishing an accurate molecular diagnosis may become increasingly important for future clinical trial eligibility and targeted therapies.

DIAGNOSTIC CHALLENGES WITH IRDS

Accurately diagnosing ARB and other IRDs presents several challenges. First, ARB can masquerade as more common retinal conditions, particularly chronic CSCR or inflammatory disease. Bilateral subretinal fluid frequently prompts evaluation for pachychoroid spectrum disease.

Second, IRDs may present later in life than expected. Although the patient described decreased vision since early

(Continued on page 52)

RISING STARS IN RETINA

Retina Today
YoungMD>Connect

Get to know outstanding retina fellows from the class of 2026.

Charlie Zhang, MD

***Retina Today (RT):* When did you first know you wanted to be a retina specialist?**

My residency program director, Andrew Reynolds, MD, is a pediatric ophthalmologist who performs just about every type of surgery. He used complex surgical cases as opportunities to teach us how to stay level-headed in the OR and how novel surgical challenges could be approached with creative problem-solving. I knew I wanted to pursue a specialty that embraced this mindset. Retina is unique in that it draws on techniques from nearly every other specialty while introducing its own distinct set of surgical principles, making it a natural fit for this approach.

***RT:* Who do you look to as mentors?**

I have been fortunate to have mentors such as Thomas Albini, MD; Audina Berrocal, MD; Harry Flynn Jr, MD; Basil K. Williams Jr, MD; and Nicolas Yannuzzi, MD. They helped shape my career by providing guidance and constantly pushing me to grow academically. They have also provided opportunities to present at conferences, contribute to leading retina journals, and refine my critical approach to scientific writing.

I'm also grateful for Jorge Fortun, MD; Luis Haddock, MD; Hong-Uyen Hua, MD; Ninel Gregori, MD; William Smiddy, MD; and Justin Townsend, MD, who have shaped my development as a retina specialist. Through their example, I learned the importance of delivering compassionate care, taking ownership of my patients, and approaching complex cases and complications with humility and composure. Their mentorship has fostered my commitment to continued growth as a surgeon and clinician.

FIRST CAREER MILESTONE

Dr. Zhang is joining Retinal Consultants of Texas in Houston.

***RT:* What was one of the most memorable experiences of your fellowship?**

One afternoon Dr. Williams and I saw two patients who underscored the importance of being a physician first. The first was a referral for a suspicious choroidal nevus. Dr. Williams identified it as benign and reassured the patient, immediately dissolving all concerns and anxiety. Within minutes, the tension gave way to laughter. Next, we saw a patient with metastatic cancer who was losing vision from her immunotherapy. She was terrified she might have to choose between her life-saving treatment and her sight. Dr. Williams adjusted his approach; he listened with empathy, acknowledged her fears, and offered assurance that we would do everything possible to preserve her vision while she continued treatment. He is one of the most knowledgeable physicians I know, but those encounters reminded me that knowledge isn't everything. Being the doctor each patient needs is what matters most.

***RT:* What advice can you offer to residents who are considering retina?**

Embrace a craftsman's mentality toward your training. Continuously push yourself out of your comfort zone, because that's where real growth happens. Work diligently to refine your skills until you become, as Steve Martin said, "so good they can't ignore you." A commitment to constant improvement, combined with humility, will serve you well in retina. ■

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- Financial disclosure: None

SPONTANEOUS LENS ABSORPTION FOLLOWING PPV

Two unusual cases of postoperative lens absorption, explained.

BY HIND SAFI, MD; SARAH BELGHMAIDI, MD, PHD; IBTISSAM HAJJI, MD, PHD; AND ABDELJALIL MOUTAOUAKIL, MD, PHD

Spontaneous lens absorption is a rare complication that can occur in association with various conditions, including hypermature or traumatic cataract, as well as in the late stages of uveitis or other infectious diseases.[1-3] Lens absorption following pars plana vitrectomy (PPV) is an unusual finding that has rarely been reported in the literature, with one case describing spontaneous cataract absorption diagnosed 7 years after the initial vitrectomy and silicone oil tamponade.[4]

We report here two similar cases of spontaneous lens absorption following PPV with gas tamponade to repair rhegmatogenous retinal detachment, which were subsequently treated with IOL implantation.

CLINICAL FEATURES

Case No. 1

A 54-year-old man with a history of systemic hypertension presented to our clinic with a sudden decrease in vision in his left eye. His VA was 20/25 OD and counting fingers at 1 m OS at presentation. On examination, the anterior segment was unremarkable with a transparent crystalline lens in each eye. Fundus photography revealed a superior macula-off retinal detachment in his left eye, extending from the 10 to 2 clock hours with multiple peripheral tears; the right fundus was normal.

The patient underwent 23-gauge transconjunctival PPV with C_2F_6 gas tamponade. No lens manipulation occurred during the surgery. On postoperative day 1, his VA was counting fingers at near OS, with mild corneal edema, a desiccation cataract and gas filling the entire vitreous cavity. At the follow-up appointment 1 week later, his VA improved to counting fingers at 3 m OS; the cornea was clear, and there was still a desiccation cataract, gas filling four-fifths of the vitreous cavity, and a flat retina. However, at the next visit 1 month postoperatively, VA declined to counting fingers at 1 m OS; on examination, the cornea was clear with a progression of the cataract, residual gas in the vitreous cavity, and a flat retina. At the 3-month follow-up, VA had further decreased to hand motion OS. The cornea remained clear, but the cataract had become total, obscuring the fundus. Ocular ultrasound showed a flat retina.

The patient was scheduled for cataract surgery in his left eye but was lost to follow up (LTFU). However, he was found and reexamined more than a year later, at which point his VA had spontaneously improved from hand motion to counting fingers at 1 m OS. His refractive error was not measurable, as the visual axis was obstructed by residual capsular opacities. The anterior segment showed a clear cornea, a deepened and quiet anterior chamber, iridodonesis, synechiae at the 4 and 5 clock hours, and aphakia with a ripped posterior lens capsule (Figure 1). The retina was flat. No trace of the lens was noted either on the ophthalmoscopic examination or echographically, and a thorough questioning ruled out any intervention during the period of LTFU.

The patient's aphakia was corrected via IOL implantation in the sulcus and surgical clearing of the visual axis with good functional vision recovery.

Case No. 2

A 49-year-old woman with an amblyopic left eye, likely due to a traum during childhood, presented with a retinal detachment in her better-seeing right eye. Her BCVA was 20/40 OD and counting fingers at 2 m OS. The crystalline lens was transparent in each eye. Her right eye showed a macula-on retinal detachment, extending from the 2 to 7 clock hours with multiple peripheral retinal tears. Fundus examination of her left eye was normal.

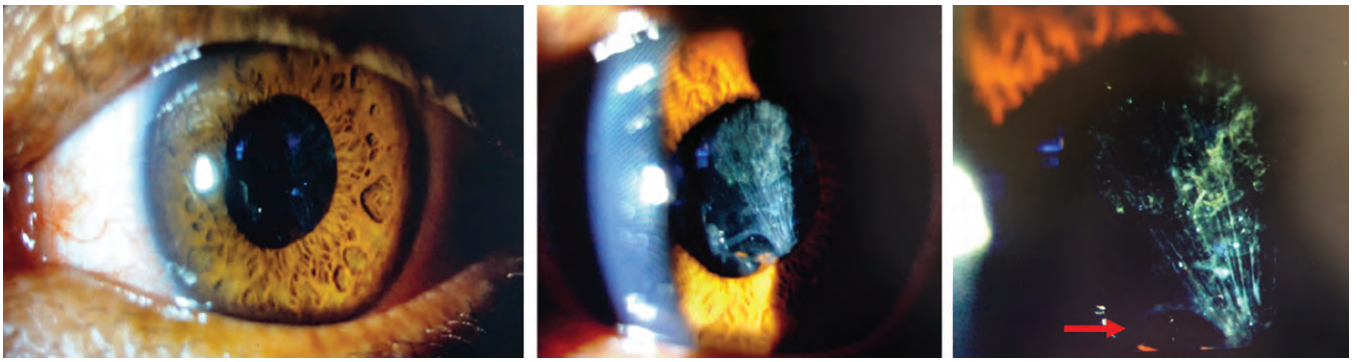

Figure 1. Anterior segment examination of the first patient's left eye shows an empty capsular bag with opacification of the capsular remnant. Note the small breach in the inferonasal region (arrow).

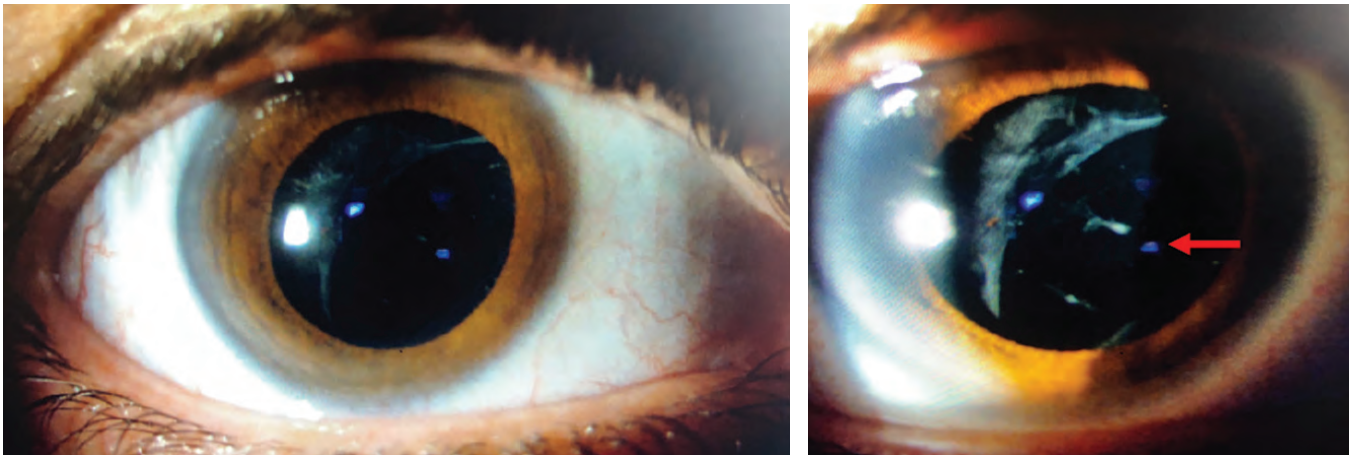

Figure 2. Anterior segment examination of the second patient's right eye shows an empty capsular bag with a large posterior lens capsule tear (arrow).

The patient underwent 23-gauge transconjunctival PPV with C_2F_6 gas tamponade. No lens manipulation occurred during the surgery. On postoperative day 1, her VA was counting fingers at 0.3 m OD, with mild corneal edema and a desiccation cataract, a complete gas fill, and a flat retina. At the 1-month follow-up, her VA was counting fingers at 0.5 m OD, with a clear cornea, a denser desiccation cataract, residual gas in the vitreous cavity, and a flat retina. At the 2-month follow-up, her VA declined to hand motion OD. The cornea remained clear, but the cataract had become total, with no fundus visibility. The ocular echography showed a flat retina. The ocular findings remained stable during the next two follow-up visits at 5 and 7 months postoperative.

The patient was scheduled for cataract surgery for her right eye but was LTFU. She was found and reexamined about 1 year later, at which time her uncorrected VA improved from hand motion OD to counting fingers at 0.5 m OD. Her BCVA after correction of the measured refractive error of +9.75 (-2 at 18°) was 20/63 OD. The anterior segment examination revealed a clear cornea, a deepened and quiet anterior chamber, iridodonesis, and aphakia associated with a large tear in the posterior capsule of the lens (Figure 2). The retina was flat. No trace of the lens was found either on the ophthalmoscopic examination or echographically. A thorough patient history ruled out any eye surgery or manipulation during the period of LTFU. The patient's aphakia was corrected by IOL implantation in the sulcus with good functional vision recovery.

PROPOSED MECHANISMS OF LENS ABSORPTION

In each of the cases reported here, a desiccation cataract was present during the postoperative period following 23-gauge PPV with gas tamponade. The cataract became progressively denser, and VA decreased to hand motion within 3 months for each patient. However, VA improved without any external intervention to counting fingers at 1 m for the first patient and counting fingers at 0.5 m for the second, which was corrected to 20/63. This improvement coincided with the transition from the cataractous lens state to the aphakic state, observed approximately 1 year after the initial surgical intervention, as both patients had a period of LTFU. This led us to conclude that spontaneous absorption of the cataractous lens occurred following PPV, as no external intervention occurred during this period.

The mechanism underlying spontaneous lens absorption has not been fully elucidated, but it has been theorized that structural, chemical/osmotic, and immunological events

likely facilitate this process.[2]

Spontaneous lens absorption is thought to be unlikely in the presence of an intact lens capsule; conversely, absorption may be facilitated following damage to the lens capsule as in traumatic cases and late, hypermature cataract.[2] In systemic infectious cases, such as leptospirosis and rubella, it is thought to be a response to either the bacteria or antibodies.[5,6] These pathophysiological mechanisms could allow for a macroscopic or microscopic leakage of crystalline lens material through a breached or abnormally permeable lens capsule, thus leading to its absorption.

The most likely explanation in our patients who underwent PPV is a breach in the posterior lens capsule that went unnoticed during surgery, thus facilitating lens absorption and bringing these cases closer to post-traumatic ones. This is further corroborated by the evidence of a tear in the posterior lens capsule in both patients observed after the period of LTFU.

CAREFULLY RULE OUT OTHER POSSIBILITIES

As lens damage is not uncommon during PPV in phakic patients, these cases draw attention to the possibility of spontaneous lens absorption in the postoperative period following PPV. ■

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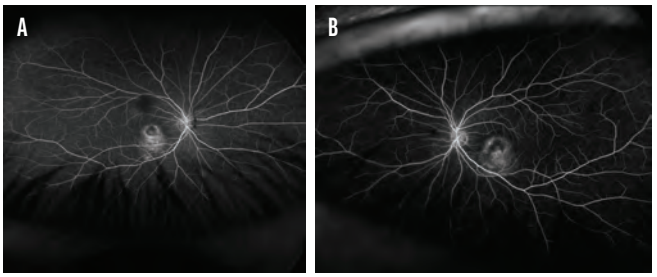

Figure 4. Ultra-widefield fluorescein angiography of the right (A) and left (B) eye demonstrated corresponding late-phase macular hyperfluorescence.

adulthood, she did not receive a definitive diagnosis until her sixth decade of life. Slowly progressive IRDs may remain unrecognized for decades, especially when patients present without a known family history. Lastly, the vitelliform deposits and/or flecked appearance of ARB can overlap with various retinal dystrophies and toxic retinopathies.

Careful attention to the distribution of lesions, presence of subretinal fluid, angiographic findings, and clinical history is critical.

MAINTAIN SUSPICION FOR IRD REGARDLESS OF PATIENT AGE

ARB is a rare IRD that can mimic chronic CSCR, inflammatory disease, and other retinal degenerations. Bilateral, chronic, refractory subretinal fluid accompanied by diffuse vitelliform or fleck-like deposits should prompt consideration of a bestrophinopathy. Multimodal imaging and genetic testing can help differentiate ARB. This case demonstrates the importance of a broad differential diagnosis and how IRD can remain undiagnosed well into adulthood. ■

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THE ROLE OF MULTIMODAL IMAGING IN GEOGRAPHIC ATROPHY

How imaging modalities support diagnosis, monitoring, treatment discussions, and patient education.

By Durga S. Borkar, MD, MMCi

Multimodal imaging is central to managing patients with geographic atrophy (GA) because each method used in the clinic contributes distinct information for diagnosis, risk stratification, treatment discussions, longitudinal monitoring, and education. Together, the various modalities provide a more complete understanding of GA than any single imaging method alone.

What Each Imaging Modality Adds

Each imaging modality offers a different perspective on GA and contributes unique information to the treatment conversation.

- Structural OCT serves as a foundational imaging modality for identifying early disease changes and monitoring progression over time. OCT helps to identify features such as nascent GA, incomplete retinal pigment epithelium and outer retina atrophy (iRORA), hyperreflective wedge-shaped bands, changes in the outer plexiform layer (OPL) and inner nuclear layer, and foveal involvement.
- Fundus autofluorescence (FAF) helps visualize lesion characteristics and supports both diagnosis and patient education. This modality is often used to distinguish AMD-related GA from lookalikes and help patients understand disease progression visually. For example, FAF may reveal lesion size and configuration, multifocal lesions, perilesional hyperautofluorescence, and features suggestive of inherited retinal disease mimickers of GA.
- OCT angiography provides noninvasive vascular assessment and adds vascular information that complements structural imaging. This imaging is used to evaluate for choroidal neovascularization, which can occur with increased frequency in patients with GA, and assess vascular changes without fluorescein dye.
- Color fundus photography remains useful for documenting visible pathology and facilitating patient communication. However, it is limited in its ability to detect early GA, identify subtle lesions, visualize non-exudative neovascularization, and detect high-risk findings such as reticular pseudodrusen/subretinal drusenoid deposits. Therefore, fundus photography alone is not sufficient for a comprehensive GA evaluation.

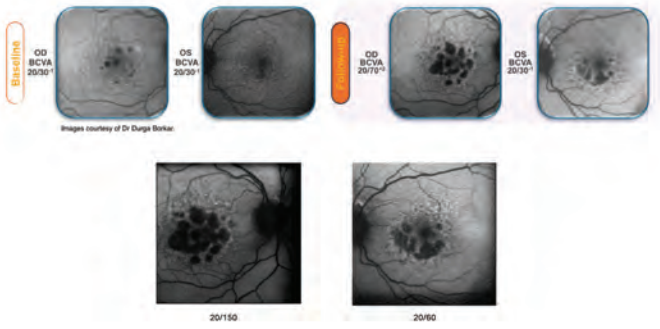

Figure. FAF of a 74-year-old woman with progressive extrafoveal multifocal GA OD > OS. FAF shows continued progression over time prior to initiating complement inhibition when available.

Imaging Frequency and Monitoring Approach

Imaging frequency varies according to disease severity, progression risk, and treatment status. In my experience, I collect images at the following intervals and disease progression points:

- OCT and FAF every 6 months for patients being followed with GA without treatment
- Imaging every 3 to 4 months for higher-risk patients or those considering therapy
- OCT at each injection visit during complement inhibitor treatment
- FAF approximately every 6 months during treatment during a dilated exam to facilitate improved image capture

These imaging intervals provide additional data points over time, which can help monitor disease progression, identify concerning changes, and support ongoing treatment discussions (Figure).

How Biomarkers Inform Treatment Discussions

When collecting patient images, I look out for several biomarkers that can suggest increased risk for GA progression. These include reticular pseudodrusen, hyperreflective foci, perilesional hyperautofluorescence, multifocal and extrafoveal lesions, and larger baseline lesion size.

Closing Takeaway

Multimodal imaging forms the basis of modern GA management. Structural, autofluorescence, vascular, and photographic imaging each contribute important, complementary information that supports a multitude of aspects including diagnosis, prognosis, and treatment planning. ■

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VERIFY THEN TRUST: USING AI IN RETINA CODING

This framework can help ensure accuracy and consistency when integrating AI into retina coding and billing workflows.

BY MATTHEW BAUGH, MHA, COT, OCS, OCSR

AI use is rapidly becoming common in retina practices, including to support documentation, coding, and claim review. While AI tools can offer meaningful efficiency gains, retina coding remains complex and dependent on precise clinical interpretation, payer policy, and documentation standards. When AI-generated output is used without verification, it can lead to inaccurate coding decisions. Thus, the safest approach is simple: Verify first, then trust.

Retina procedures are complex, frequently bundled, and closely scrutinized by payers. Errors in Current Procedural Terminology (CPT) selection, modifier use, or diagnosis linkage can trigger denials, repayment, or audit exposure.

In this article, I outline a framework for using AI in retina billing and coding that aims to mitigate errors, while still enjoying efficiency gains.

AI IN RETINA CODING: USEFUL, BUT IMPERFECT

AI tools can quickly generate coding suggestions, summarize documentation, and propose CPT and International Classification of Diseases, Tenth Revision (ICD-10) codes. However, these outputs may be incomplete, outdated, or incorrect, as retina procedures often involve multiple surgical steps, global period considerations, and diagnosis-specific coverage rules—details AI may miss.

Accurate retina coding requires a structured process: Review the documentation, confirm CPT descriptors, check National Correct Coding Initiative (NCCI) edits, apply modifiers, and validate diagnosis linkage. AI can support this workflow, but it cannot replace it.

The quality of AI output depends on the quality of input. In coding and billing, vague or incomplete questions often produce incomplete or even misleading answers. This is especially important in retina, where coding decisions depend on payer rules, diagnosis specificity, and clinical context.

When more specific questions are posed to AI tools, such as ChatGPT (Open AI), Copilot (Microsoft), or Google's AI overview, they produce more useful answers. Consider the following versions of asking a question about billing for OCT imaging:

Basic question (limited value): How often can you bill for OCT imaging?

- Lacks test specificity, diagnosis, and payer context.
- May produce generic or outdated guidance.

Better question (more useful): How often can you bill for retina OCT for AMD?

- Adds subspecialty and diagnosis.
- Narrows the scope but still lacks payer specificity.

Best question (actionable): How often can you bill for retina OCT (CPT 92134) for a patient with Medicare Part B insurance with exudative AMD with choroidal neovascularization to monitor active intravitreal injection treatments under a specific Medicare Administrative Contractor (eg, Novitas) policy?

CASE EXAMPLE NO. 1: PPV WITH IOL EXCHANGE

Scenario: A patient undergoes pars plana vitrectomy (PPV) for a dislocated IOL, followed by IOL exchange and sutured IOL due to floppy iris syndrome.

AI Input	AI Suggestion	Four-Step Framework
What CPT codes are used for a vitrectomy with IOL exchange and sutured IOL, left eye?	- CPT 67036 – H43.392 - CPT 66985 – T85.22XA *Issue:* Incorrect CPT selection.	1. Confirm CPT descriptors: CPT 66986 is correct for IOL exchange and CPT 66682 for suture IOL 2. Review NCCI edits: all three codes are allowed together 3. Validate diagnosis linkage: unique to each procedure 4. Review payer policy: confirms coverage

Final Coding

CPT	Description	ICD-10
66986	IOL exchange	*T85.22XA - Displacement of intraocular lens, initial encounter
67036	PPV	H43.392 - Other vitreous opacities, left eye, T85.22XA
66682	Suture IOL	H21.81 - Floppy iris syndrome

*T85.22XA cannot be listed as primary due to the Medicare National Coverage Determination (NCD) for vitrectomy.

CASE EXAMPLE NO. 2: REPEAT IMAGING ANDMEDICAL NECESSITY

Scenario: A patient with type 2 diabetes, mild nonproliferative diabetic retinopathy (NPDR), and diabetic macular edema (DME) undergoes OCT imaging at a follow-up visit 5 weeks after prior imaging.

AI Input	AI Suggestion	Four-Step Framework
Can you bill OCT again at a follow-up visit for DME in both eyes?	- CPT 92134 (posterior segment OCT) and E11.311 *Issue:* Overgeneralized guidance without timing, clinical context, staging, and treatment or documentation requirements. Also, unspecified DR with DME is not as specific as possible	1. Confirm CPT descriptors: CPT 92134 is appropriate for posterior segment OCT 2. Review NCCI edits: no bundling concerns with other services provided the same day 3. Validate diagnosis linkage: mild NPDR with DME supports OCT use but repeat testing must be clinically justified per payer guidelines, and ICD-10 must be highest level of specificity 4. Review payer policy: documentation must support medical necessity and confirm within frequency limitations *Additional step for this case:* Confirm the current treatment plan, as there are different answers for disease monitoring versus active treatment. For example, Novitas local coverage determination L35038 and local coverage article (LCA) A57600 state: "for retinal disease not undergoing active treatment, no more than one examination every 2 months is considered medically reasonable and necessary. For retinal conditions undergoing active treatment or suggestive of rapid deterioration (eg, wet AMD, choroidal neovascularization, macular edema, diabetic retinopathy, branch retinal vein occlusion/central retinal vein occlusion, cystoid macular edema), no more than one examination per month is considered medically reasonable and necessary." Monthly is defined as every 28 days by the LCA.

Final Coding

CPT	Description	ICD-10
92134	Posterior segment OCT	E11.3213 - Type 2 diabetes mellitus with mild NPDR with macular edema, bilateral

CASE EXAMPLE NO. 3: INJECTION DURING THE GLOBAL PERIOD Scenario: Intravitreal injection is performed postoperatively for an eye with proliferative DR (PDR) with DME.		
AI Input	**AI Suggestion**	**Four-Step Framework**
Can you bill an anti-VEGF injection during the postoperative period in the left eye for PDR with DME in the right eye?	- 67028 (no modifiers) – E11.3511 *Issue:* Missing modifiers	1. Confirm CPT descriptors: CPT confirmed 2. Review NCCI edits: not applicable 3. Validate diagnosis linkage: diagnosis supports necessity 4. Review payer policy: a modifier is required (-79, indicating an unrelated procedure that was performed by the same physician or other qualified health care professional during the postoperative period) and anatomical modifier
Final Coding		
CPT	**Description**	**ICD-10**
67028 with (-79) -RT	Injection	E11.3511

- Includes CPT code, diagnosis specificity, staging, treatment, payer, and jurisdiction.
- Produces an answer that can be verified against policy.

THE ABCS OF AI IN RETINA CODING

A structured approach is needed to evaluate whether an AI output can be trusted. The ABCs—accuracy, bias, and context—explain why AI output must be verified.

Accuracy: AI may generate outdated or incorrect guidance, as coding rules and payer policies change frequently. Confirm AI-generated information using current, trusted resources.

Bias: AI models are trained on broad datasets and may not reflect retina-specific nuances. This can lead to incorrect assumptions about procedure combinations or modifier use.

Context: AI lacks full context. Retina coding depends on encounter-specific details, including prior procedures and documentation. Thus, AI may produce technically correct, but clinically and surgically irrelevant, answers.

FOUR-STEP FRAMEWORK TO VERIFY AI OUTPUT

A dedicated framework can provide a practical method to apply these principles and ensure accurate, compliant coding.

The process begins with reviewing the documentation itself. Accurate coding depends on what is documented in the medical record, and each step of the framework builds upon confirming that the coding reflects the services performed.

Here are the four steps to the framework:

1. Review the full CPT descriptor to ensure the code accurately reflects the procedure performed.
2. Determine whether codes can be billed together and identify bundling restrictions.
3. Ensure each CPT code is linked to the most appropriate ICD-10 diagnosis.
4. Review payer policies and confirm guidance using current, trusted sources. Confirm coding aligns with payer-specific rules, including coverage and documentation requirements.

The three examples shared throughout this article demonstrate how this process can be used in common retina scenarios to identify and correct AI-driven coding errors.

AVOID COMMON AI PITFALLS

AI-generated coding suggestions can introduce errors that affect both reimbursement and compliance. The common pitfalls highlighted in this article demonsrate the importance of verifying all AI-generated coding before claim submission. ■

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- AI disclosure: This article was written by the author and reviewed and edited with the assistance of a large language model. All substantive content, analysis, and conclusions originated with the author.

FURTHER READING

10 Essential Steps for Accurate Retina Surgery Coding

By Joy Woodke, COE, OCS, OCSR, and Matthew Baugh, MHA, COT, OCS, OCS

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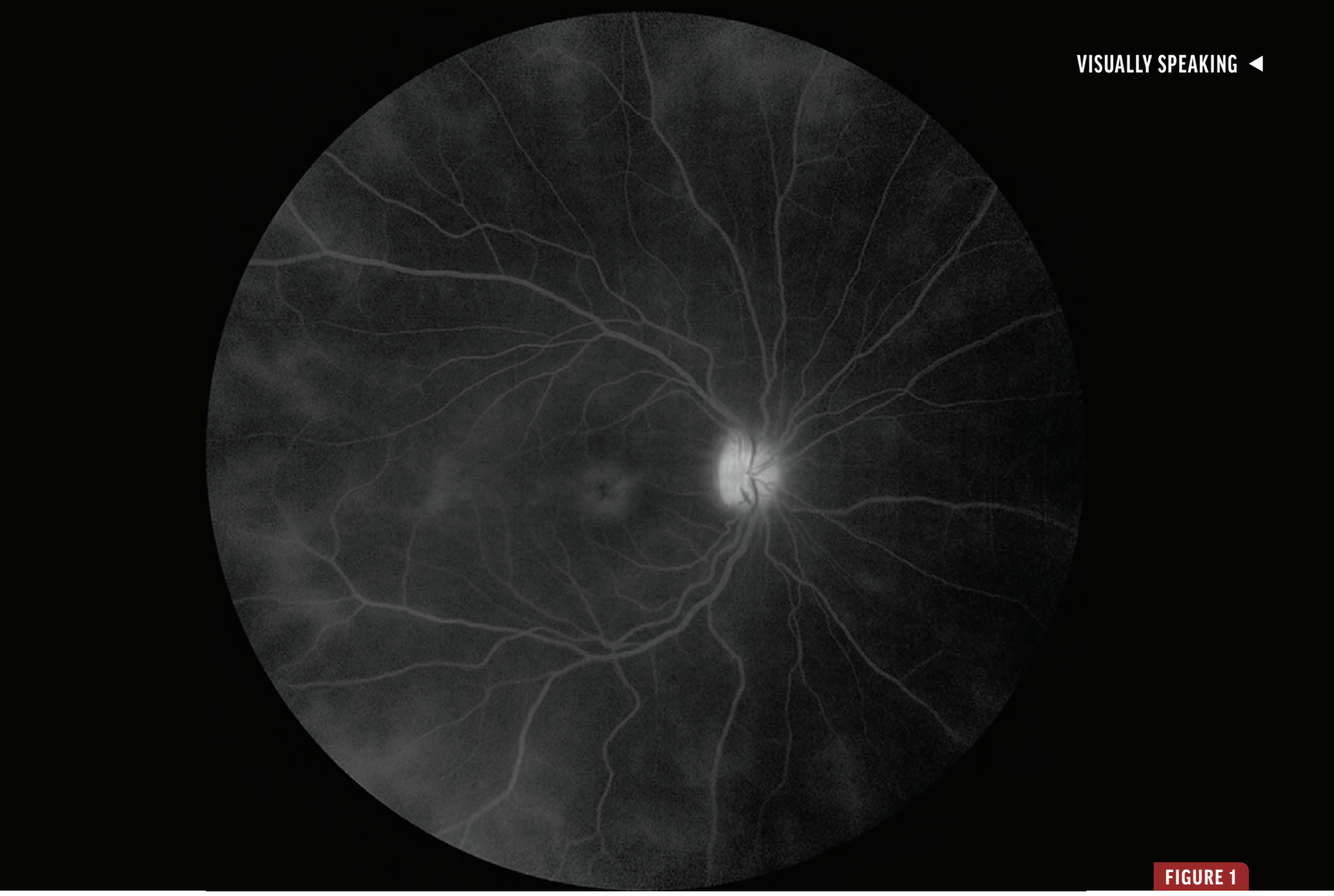

FIGURE 1

FA IMAGING IN BEHÇET DISEASE

Imaging is essential for diagnosis, disease staging, and prognostication.

BY KANWALJEET HARJOT MADAN, MS(OPHTH), FAICO

An 11-year-old girl presented with a sudden decrease in vision in her left eye for a week. She reported no history of trauma or positive family history. Her medical history included oral ulcers.

On examination, her BCVA was 20/80 OD and hand motion at 20 cm OS. The anterior segment examination revealed the presence of 2+ cellular reaction in each eye.

The fundus examination revealed the presence of vitreous hemorrhage in her left eye. Her right eye showed cystoid macular edema (CME) with active vasculitis. Fluorescein angiography in her right eye revealed the presence of hyper fluorescence of the disc, CME, and perivenular leakage in a fern-like pattern (Figure 1). Based on these findings and fundus and OCT imaging (Figures 2 and 3), she was diagnosed with Behçet disease.

The patient was started on systemic corticosteroids, received an intravitreal anti-VEGF injection in each eye, and was scheduled to receive panretinal photocoagulation in each eye before being lost to follow-up.

DISCUSSION

Behçet disease is an autoinflammatory disorder that predominantly affects the mucocutaneous, ocular, urogenital, vascular, and gastrointestinal systems. Ocular involvement occurs in nearly 70% of patients and often presents as recurrent bilateral nongranulomatous panuveitis

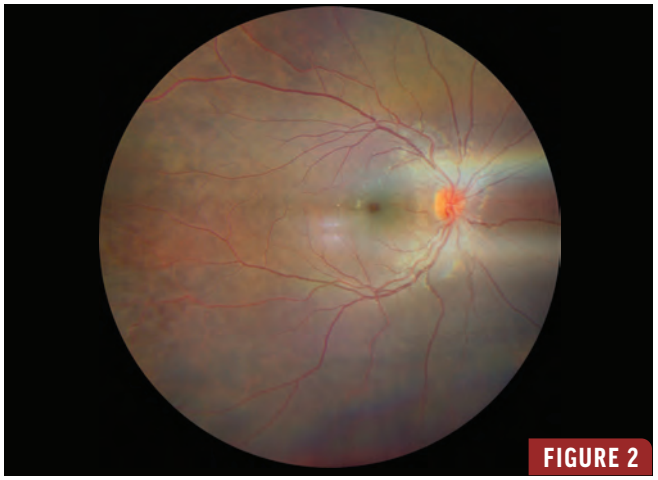

FIGURE 2

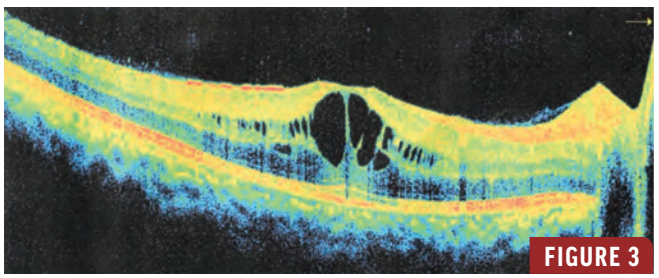

FIGURE 3

and retinal vasculitis. It typically manifests between 20 and 40 years of age. Fluorescein angiography commonly reveals hyperfluorescence of the optic disc, vascular dye leakage from retinal capillaries, and staining of retinal vessels due to retinal perivasculitis. Diffuse vascular leakage in a fern-like pattern is the characteristic finding and is commonly observed during the chronic phases of inflammation.[1-3]

The main goal of treatment includes resolving the intraocular inflammation, preventing recurrent flare-ups, and achieving complete remission while preserving vision. Systemic corticosteroids, immunosuppressive drugs, and biologics are used.[4] Panretinal photocoagulation along with anti-VEGF agents may be necessary to manage neovascularization secondary to chronic ischemic retinal vasculitis. The prompt and effective treatment of uveitis flare-ups, ensuring rapid resolution of intraocular inflammation, is essential to prevent vision loss. ■

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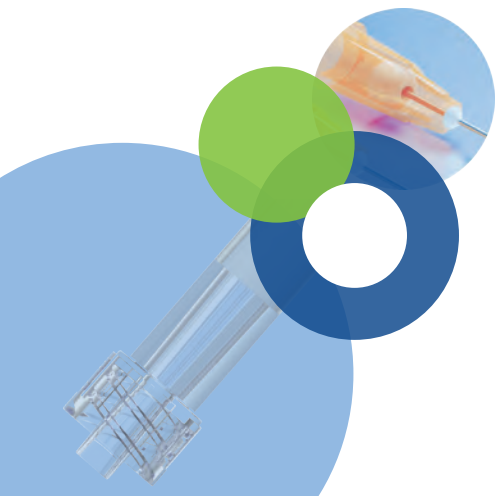

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