EARN 2 CE CREDITS: Corneal Dystrophies Front to Back, *p. 80*

REVIEW® OF OPTOMETRY

September 15, 2020

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# 43rd Annual Technology Report

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# 43rd Annual Technology Report

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Not an actual patient.

*In some patients with continued daily use. One drop in each eye, twice daily (approximately 12 hours apart).[3]

†Xiidra is an LFA-1 antagonist for the treatment of dry eye disease. Pivotal trial data: The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. Use of artificial tears was not allowed during the studies. The study end points included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported Eye Dryness Score [EDS] on a visual analogue scale of 0 to 100).[3] A larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials. Effects on signs of dry eye disease ICSS (on a scale from 0-4; 0=no staining; 4=coalescent) was recorded at each study visit. At day 84, a larger reduction in inferior corneal staining favoring Xiidra was observed in 3 of the 4 studies.[3]

## Indication

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

## Important Safety Information

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.

NOVARTIS

**Novartis Pharmaceuticals Corporation**
East Hanover, New Jersey 07936-1080


## Important Safety Information (cont)

- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.
- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

**For additional safety information about XIIDRA®, please refer to the brief summary of Full Prescribing Information on adjacent page.**

**References: 1.** US Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). Accessed April 17, 2020. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349&showFR=1 **2.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf.* 2017;15(3):575-628. **3.** Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2020.

**XIIDRA® (lifitegrast ophthalmic solution), for topical ophthalmic use**
**Initial U.S. Approval: 2016**

**BRIEF SUMMARY: Please see package insert for full prescribing information.**

**1 INDICATIONS AND USAGE**
Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

**4 CONTRAINDICATIONS**
Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation *[see Adverse Reactions (6.2)]*.

**6 ADVERSE REACTIONS**
The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4)]*

**6.1 Clinical Trials Experience**
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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.

In five clinical trials of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had less than or equal to 3 months of treatment exposure. One hundred-seventy patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5%-25% of patients were instillation-site irritation, dysgeusia, and reduced visual acuity.

Other adverse reactions reported in 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

**6.2 Postmarketing Experience**
The following adverse reactions have been identified during post-approval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare serious cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, urticaria, allergic conjunctivitis, dyspnea, angioedema, and allergic dermatitis have been reported. Eye swelling and rash have also been reported *[see Contraindications (4)]*.

**8 USE IN SPECIFIC POPULATIONS**
**8.1 Pregnancy**
Risk Summary
There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from premating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Data
*Animal Data*
Lifitegrast administered daily by IV injection to rats, from premating through gestation day 17, caused an increase in mean pre-implantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal no observed adverse effect level (NOAEL) was not identified in the rabbit.

**8.2 Lactation**
Risk Summary
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low *[see Clinical Pharmacology (12.3) in the full prescribing information]*. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

**8.4 Pediatric Use**
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

**8.5 Geriatric Use**
No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

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## IN THE NEWS

Researchers have found that using **keratopigmentation**, or corneal tattooing, to change the color of the eyes for purely cosmetic reasons **can be a safe surgical option with positive feedback**. The researchers found that the follow-up evaluation (from one to six years post-op) was excellent in 90% of cases, and patients' satisfaction was excellent in 92.5% of cases. The researchers did note that one patient with a history of LASIK developed corneal ectasia.

D'Oria F, Alio JL, Rodriguez AE, et al. Cosmetic keratopigmentation in sighted eyes medium- and long-term clinical evaluation. Cornea. July 29, 2020. [Epub ahead of print].

While both accelerated transepithelial (epi-on) corneal collagen crosslinking (CXL) and standard CXL (epi-off) halted keratoconus progression in children, **epi-off CXL was safer and more effective**, a recent study reported. Researchers compared 32 eyes that had accelerated epi-on CXL and 46 that had epi-off. The keratoconus progression rate was 9.37% (3/32) in the epi-on group, and **no progression was seen in the epi-off group at the five-year follow-up**.

Henriquez MA, Hernandez-Sahagun G, Camargo J, et al. Accelerated epi-on versus standard epi-off corneal collagen cross-linking for progressive keratoconus in pediatric patients. Cornea. August 11, 2020. [Epub ahead of print].

Researchers recently identified a **new sign of AMD progression** that will be a useful endpoint for monitoring treatment effects, beyond relying on geographic atrophy (GA) lesion size progression. **Progressive photoreceptor degeneration** was both evident and quantifiable in a cohort study of 93 patients with GA secondary to AMD. The researchers noted that **the ellipsoid zone loss-to-GA boundary distance and outer segment thickness were prognostic for future progression rates**.

Pfau M, von der Emde L, de Sisternes L, et al. Progression of photoreceptor degeneration in geographic atrophy secondary to age-related macular degeneration. JAMA Ophthalmology. August 13, 2020. [Epub ahead of print].

# Trifocal IOLs Good for Some Astigmats

Bifocals suited for post-op astigmatism between 0.75D and 1.00D. **By Jane Cole, Contributing Editor**

Visual acuity (VA) impairment due to postoperative astigmatism—and particularly distance VA—may be more prominent in eyes implanted with a trifocal IOL than in bifocal IOL eyes, a new study reports.

The team of researchers from Japan also found trifocal IOLs allowed for good VA at all distances when the refractive astigmatism was 0.75D or less. However, bifocal IOLs might be a better choice for eyes with postoperative astigmatism within 0.75D and 1.00D.

The study enrolled 50 eyes with trifocal IOLs and 50 eyes with bifocal IOLs. The researchers measured corrected logMAR VA after simulating astigmatism by adding cylindrical lenses of zero, 0.50D, 0.75D, 1.00D and 1.50D.

The researchers reported VA at most distances significantly worsened in proportion to the added astigmatism with no significant difference in near VA at 0.3m in the trifocal group or in intermediate VA at 0.7m in the bifocal group. The investigators noted the intermediate VA at 0.5m was better in the trifocal group than in the bifocal group when the astigmatism was 0.75D or less, but distance VA and at 5m was worse in the trifocal group when the astigmatism was 0.50D or more. Useful mean logMAR VA of 0.20 at all distances was achieved when the astigmatism was 0.75D or less in the trifocal group and 1.00D or less in the bifocal group.

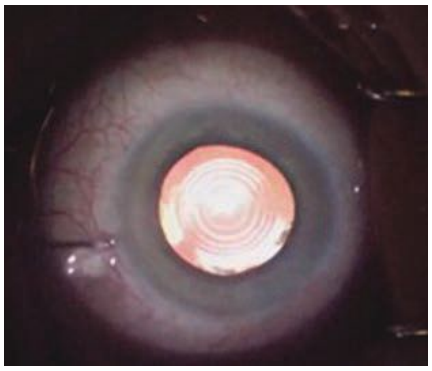

Photo: Katherine Rachon, OD

**Trifocal IOLs allowed for good VA when the refractive astigmatism was 0.75D or less.**

When the residual astigmatism is assumed to be greater than 0.75D, surgeons should perform astigmatism correction procedures, such as using an IOL with a toric component and a corneal relaxing incision. Otherwise, bifocal IOLs might be a better selection for eyes that are assumed to have a postoperative astigmatism within 0.75 and 1.00D, they added.

Because the present study was a simulation, the effect of residual refractive astigmatism should be confirmed in actual postoperative eyes implanted with the trifocal IOL, the researchers said.

Hernandez-Llamas S, Paz-Ramos AK, Marcos-Gonzalez P, et al. Symptoms of ocular surface disease in construction workers: comparative study with office workers. BMC Ophthalmology. July 20, 2020. [Epub ahead of print].

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# New Tool May Boost Compliance

*More than 40% of glaucoma patients reported difficulty using eye drops.*

Medication adherence is often a hurdle for glaucoma patients. To help combat this problem, a new study created a tool that identified several behavior factors associated with poor compliance. The researchers suggest the new tool could be used for personalized interventions and to optimize glaucoma drug adherence.

The study enrolled patients with poor self-reported glaucoma medication compliance and electronically monitored them for three months. At enrollment, a coordinator administered the Glaucoma Treatment Compliance Assessment Tool (GTCAT), a questionnaire based on the Health Belief Model that gathers data about cues-to-action, barriers, susceptibility, benefits, severity, patient-physician relationship, health status, depression and self-reported adherence.

The participants were from the Support, Educate, Empower (SEE) personalized glaucoma coaching program pilot study at the University of Michigan Kellogg Eye Center. All subjects had a diagnosis of either glaucoma, glaucoma suspect or ocular hypertension.

The researchers also considered socioeconomic factors, health insurance status and best-corrected visual acuity.

Of the total study participants, 51 (54.3%) were Caucasian, 33 (35.1%) were Black, eight (8.5%) were Asian and two (2.1%) were unknown or other.

The GTCAT identified multiple statements with low scores. For example, only 54% of participants answered the first question, "My personal knowledge of the symptoms of glaucoma is excellent," suggesting patients would benefit from better glaucoma education, the researchers noted.

While more than 88% of study subjects agreed with the GTCAT statement, "Sometimes I forget to use my eye drops," less than 32% agreed with the statement, "I use reminders to take my eye drop medications." In the latter group, the investigators suggest it might be useful to problem solve with the patient and encourage reminders.

Additionally, only 50% of the respondents agreed with the statement, "My eye drops cause me no pain or discomfort," side effects could be better addressed by the care team, the researchers say. Similarly, more than 20% of subjects agreed with the statement, "My eye drops are difficult to use." Overall, GTCAT found more than 68% of participants did not use medication reminders, and more than 40% reported difficulty using eye drops.

The overall adherence rate was 73.8%. The tool also showed that better adherence was linked with increased knowledge, increased cues-to-action, decreased barriers, less depression and increased self-efficacy.

The researchers noted their analysis tool identified more than 50% of patients who wanted more education about glaucoma.

Clinicians and researchers could use this tool to identify specific barriers to adherence and develop potential interventions to improve adherence, the researchers noted.

Sanchez FG, Mansberger SL, Newman-Casey PA. Predicting adherence with the glaucoma treatment compliance assessment tool. J Glaucoma. July 29, 2020. [Epub ahead of print].

# Napping in Ortho-K Lenses Improves Vision

Researchers recently found that overnight orthokeratology (ortho-K) patients may benefit, at least visually, from wearing their contact lenses during an afternoon nap. They didn't find any significant changes in corneal curvature or elevation, however.

The study instructed 12 patients with a history of ortho-K wear to either wear their lenses or remove them during a 30-minute nap. A team assessed anterior corneal curvature, elevation and corneal pachymetry before eye closure (baseline), immediately after eye opening/lens removal and 30 minutes after the nap.

The investigators did not observe statistically significant differences in anterior corneal curvature or elevation between any of the time points, with or without contact lenses. They noted that corneal swelling immediately after the 30-minutes of eye closure was greater without contact lenses than with contact lenses. The researchers added that recovery 30 minutes later was slower when lenses were worn.

The study authors concluded that only a statistically significant improvement in objective quality of vision and visual acuity was achieved when patients napped with their lenses.

Pérez-Corral J, Cardona G, Piñero D, et al. Should overnight orthokeratology patients wear their lenses during their afternoon nap? Eye Cont Lens. July 20, 2020. [Epub ahead of print].

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# RNFL in Glaucoma Stable at 10 Years

Considering the effect of age and glaucoma progression on the thickness of the circumpapillary retinal nerve fiber layer (cpRNFL) over a 10-year period, a team of researchers from Sweden found no significant differences in the change of cpRNFL thickness in glaucoma patients compared with healthy subjects between visits.

The investigation, published online in *Acta Ophthalmologica*, used OCT to re-examine a group of healthy individuals and a group of glaucoma patients 10 years after they were first evaluated in 2008, to analyze the effect of aging on cpRNFL thickness with a long-time follow-up interval and to compare the results with the changes observed in glaucoma patients. The study also evaluated the performance of a set of OCT progression analyses in the same subjects.

The results showed a small effect of age on the cpRNFL and a higher rate of thinning in glaucoma patients with mild to moderate disease defined by their visual fields, but it was still limited and statistically non-significant. The findings also suggested a thickening of the cpRNFL in eyes with severe glaucoma.

The researchers found OCT progression analyses generated a substantial number of false positives and, considering the current literature, the investigators said using OCT for glaucoma follow-up "may not be straightforward."

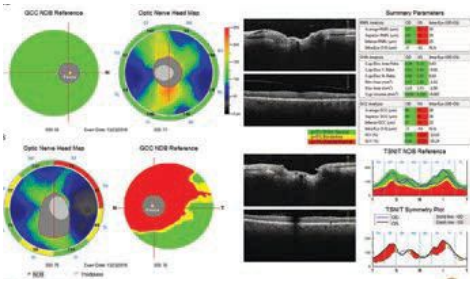

Photo: Michael Cymbor, OD, and Jenae Stiles, OD

**Using OCT for glaucoma follow-up might not be straightforward.**

The study included 69 healthy individuals and 49 glaucoma patients. The researchers measured the cpRNFL in both groups twice with OCT at each of the two visits made 10 years apart. Both visits also included 24-2 visual field testing.

The study reported an average cpRNFL thickness deterioration of approximately -0.16µm/year in the healthy cohort, an increase of 0.03µm/year in the glaucoma cohort and a deterioration of -0.24µm/year in eyes with less severe glaucoma.

The researchers found no statistically significant differences between the groups. For 17 (30%) of 56 healthy individuals, at least one of the three different OCT progression analyses incorrectly indicated progression.

Li S, Tang G, Fan SJ, et al. Blindness short after treatment of acute primary angle closure in China. Br J Ophthalmol. August 7, 2020. [Epub ahead of print].

# Immediate Endophthalmitis Care is a Must

Endophthalmitis is always a race against time. Researchers conducted a study to see just how much each delayed day may count against visual outcomes and found significantly different outcomes based on the timing of care.

The retrospective study, published online in *Ophthalmology Retina*, included 130 patients with endophthalmitis who were seen at the Duke Eye Center between 2009 and 2018. Patients were grouped by those presenting to medical care early (within two days) or later (delayed, three days or more) from the time of symptom onset.

Patients who presented later had significantly worse visual acuity on initial exam (delayed 20/2941 vs. early 20/1124) and at six months follow-up (delayed 20/547 vs. early 20/173). The researchers found that pre-endophthalmitis visual acuity was significantly correlated with visual acuity at six months, regardless of time to presentation.

Though rare, endophthalmitis sometimes occurs after intraocular surgery. Patients with glaucoma drainage device-related endophthalmitis were more likely to have a delayed presentation, and eyes with a delayed presentation were more likely to have conjunctival injection on initial exam (delayed 73% vs. early 52%). The researchers noted that pre-endophthalmitis visual acuity, pain and patient-reported blurred vision weren't associated with early or delayed presentation.

As suspected, any delay in seeking medical care for endophthalmitis was associated with worse visual acuity on both the initial exam and at six months follow-up. The researchers note that further investigation may help to improve anticipatory guidelines for at-risk patients. ■

Mirzania D, Fleming TL, Robbins CB, et al. Time to presentation after symptom onset in endophthalmitis: Clinical features and visual outcomes. Ophthalmology Retina. August 1, 2020. [Epub ahead of print].

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# Contents

Review of Optometry
September 15, 2020

43rd ANNUAL
TECHNOLOGY REPORT

# Practical Opportunities in AMD Management

*Inside...*



Four years ago, only a select group of early adopters and key opinion leaders had real world experience using dark adaptation in AMD patients and suspects. Although several peer reviewed studies strongly confirmed the benefits of this testing, clinical experience lagged behind the overwhelming body of evidence. Such was the case when MacuLogix partnered with optometric leaders and AdaptDx® users to publish its first annual report on AMD in 2017.

There's no denying that 2020 is a unique year in our nation and in our profession. But one thing is certain: with regard to AMD, we are no longer in uncharted territory, attempting to navigate uncertain terrain. On the contrary, this year's report celebrates yet another milestone in AMD diagnosis with the introduction of the wearable, artificial intelligence-driven AdaptDx Pro™ guided by Theia™.

Although AMD is a devastating disease, the report that follows is saturated with hope and backed by the promise of clear, published scientific evidence. Indeed, we have come a long way in four years. The path forward is bright, heavily traveled and undeniably in the best interests of our patients and our practices.


A Supplement to
REVIEW® OF OPTOMETRY
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# When Opportunity Knocks


## By Pamela A. Lowe, OD, FAAO, Dipl. ABO


For far too long, our profession has viewed age-related macular degeneration (AMD) as a disease that cannot be addressed in optometric settings. Conversely, I feel strongly that AMD is one of optometry's biggest opportunities to impact patient lives and build stronger, more profitable practices.

*Here's why:*

1. *There is an obvious demand. AMD is more prevalent than glaucoma and diabetic retinopathy combined.*
2. *There is an obvious need. AMD is easy to miss during a clinical exam.*
3. *With a limited budget and equipment, early AMD is easier to diagnose—especially now that a wearable artificial intelligence-driven device is available.*
4. *There are proven treatments that span the entire disease continuum.*
5. *High-quality AMD patient care in an optometric practice can be beneficial to optometrists' bottom lines.*

## 1. Data Demonstrates Massive Demand for Optometric AMD Care

Statistically, AMD is more prevalent than glaucoma and diabetic retinopathy combined. In fact, you should have three times as many AMD patients as you do glaucoma patients in your practice! Currently, 58,000 eye care professionals are licensed to perform comprehensive eye exams; 40,000 of these are optometrists, 18,000 are ophthalmologists.[1] Retinal specialists account for about 10% of all ophthalmologists. Imagine if all of these patients with AMD tried to make an appointment with a retinal specialist. Chances are, they would wait a very long time for an exam. More importantly, retina specialists generally see the more advanced cases of AMD—not the 85% or more who are in the early to intermediate stages of disease.

Optometrists are on the front line for AMD, and now is the time to embrace the responsibility. One study found that 69% of patients are unaware that they have AMD until they are diagnosed with late-stage disease,[2] with another study showing that up to 78% of patients when first diagnosed already have 20/50 or worse best corrected visual acuity, including 40% with 20/200 or worse.[3,4] These are our patients and we are in a position to change these outcomes. With improved practice protocols to proactively identify and monitor disease progression, we can potentially eliminate sending patients to the retina specialist with such poor vision.

## 2. Studies Show an Urgent Need for a More Proactive Response

Put simply, optometrists are not diagnosing AMD as often as we could and should be. Historically, this failure to diagnose was largely due to a lack of available diagnostic tools. After all, we are great clinicians, but research demonstrates that observing the macula with


### Jeffry Gerson, OD, FAAO
***Olathe, KS***


***AdaptDx Model:*** Tabletop & Headset
***Testing Protocol:*** All patients over age 60 as part of a comprehensive exam. If they pass, I generally test every other year. Those who fail return for the Extended Test. I also test any patient under age 60 with any night- or dark-related vision issues, as well as any patient who asks about AMD and/or has a family history.
***% Failed:*** Just under 40%
***ROI:*** Don't forget to look at the indirect benefits. For instance, patients who fail the Rapid Test come back for the Extended Test, an exam and an OCT.
***Advice:*** It's hard to understand what you are missing until you prove it to yourself. If you have patients over the age of 60, you have plenty of AMD patients to justify AdaptDx testing.

a 90D lens and evaluating fundus photos for small drusen and pigmentary changes isn't easy. For example, a study published in *JAMA Ophthalmology* showed just how often diagnoses are missed by optometrists and ophthalmologists alike—even when the doctors were aware that their findings would be double-checked by trained graders.[5] This cross-sectional study, which included 1,288 eyes (644 adults) from patients enrolled in the Alabama Study on Early Age-Related Macular Degeneration (ALSTAR),[6,7] revealed that doctors are missing AMD about 25% of the time. Also quite concerning is that 30% of the undiagnosed eyes in the study already had intermediate-stage disease with large drusen, a well-known risk factor for progression to advanced disease.[5]

When you consider the poor outcomes that often result from delayed diagnoses, there is no question that we need to take a more proactive approach and utilize tools that improve our diagnostic acumen. Use of dark adaptation testing in primary eye care practices would significantly increase the likelihood of diagnosing AMD in affected cases,[4] while also making diagnosis simple and fast. Imagine if you could refer at-risk CNV patients with BCVA of 20/20—in both eyes. With early detection, diagnosis, and close monitoring, you can. With dark adaptation (DA) testing, the number of AMD patients identified in our practices can more accurately reflect the true incidence of disease in this country.

***Use of dark adaptation testing in primary eye care practices would significantly increase the likelihood of diagnosing AMD in affected cases, while also making diagnosis simple and fast.***

## 3. AMD Can Be the Easiest Diagnosis of the Day

The past several years have been a time of tremendous innovation in AMD. As a result, we have a much more in-depth understanding of disease pathogenesis and access to affordable tools to help us make a definitive diagnosis very early in the disease process. We now know that, as with glaucoma, structural changes are present in AMD prior to even the earliest clinical indicators of the condition. However, unlike using an OCT in glaucoma to detect these optic nerve changes before vision loss occurs on a visual field, we are unable to detect the earliest retinal damage in AMD with any of our currently available imaging devices. Instead, we need to find the functional biomarker of AMD to detect it at its earliest stages. Specifically, functional changes presenting as impaired dark adaptation take place several years before clinically evident damage to the eye has occurred. Better still, interpreting these functional changes in AMD is often much simpler than identifying the structural changes seen with early glaucoma.

Impaired dark adaptation is the first clinical biomarker for AMD and precedes visible presentation of drusen. In fact, this functional test enables eye care professionals to detect subclinical AMD with 90% accuracy three years before it can be observed clinically.[4] When you couple this test with your own clinical findings and structural measurements, it's obvious how much more confidence you will have in managing patients. In fact, managing AMD is infinitely easier than managing glaucoma. Glaucoma is complex and it is often extremely difficult to determine who will progress and who won't. Even IOP can sometimes be a false indicator. Still we follow our glaucoma suspects closely, though it's very likely their disease will progress quite slowly.

To enhance our ability to stage and monitor progression of AMD by looking at it clinically, we must consider

***Glenn Corbin, OD***
***Wyomissing, PA***

***AdaptDx Model:*** Tabletop & Headset
***Testing Protocol:*** All patients with night vision complaints and/or drusen
***Tests per Week:*** >15
***ROI:*** Based on over 60/month at $60/patient reimbursement, the instrument can be paid off in less than 1 year.
***Advice:*** It has become our standard of care for confirming an AMD diagnosis in patients with drusen, especially when acuity is good or clinical findings are minimal. Dark adaptation testing should be considered a must-have for practices and would compare to diagnosing and treating glaucoma without a visual field.

other options—namely functional testing in the form of dark adaptation. Several peer-reviewed studies have shown that dark adaptation function is impaired from the earliest stages of AMD, with increasing impairment as the disease progresses.[8,9] Visual acuity loss is not a surrogate for dark adaptation testing because visual acuity is largely undisturbed during early disease,[10] whereas longitudinal data demonstrate that dark adaptation, as measured by Rod Intercept™ (RI™) time, exhibits significant change over four years among AMD eyes despite stable visual acuity.[11] Based on this and other research, as well as clinical observations and in accordance with the Preferred Practice Patterns of the American Academy of Ophthalmology,[12] it is clear that dark adaptation functional testing can overcome the practical challenges associated with diagnosing AMD using only traditional subjective clinical assessment.

## 4. There Are Effective Treatments for All Stages of AMD

Intravitreal injection (anti-VEGF) has become one of the most commonly performed procedures in the United States within any field of medicine.[13-15] But by the time a patient reaches this stage, significant damage and vision loss has likely already occurred. Just as we would never wait until late-stage disease to manage a glaucoma patient, we should not wait to treat AMD. Unfortunately, until recently, that was the trend. In fact, several studies have shown that doctors have been too passive when diagnosing and treating nonexudative AMD.[2,3,16] This mindset MUST change. Optometric care is significantly valuable in AMD, and it all begins with the earliest possible diagnosis. Knowing for sure that a patient has AMD makes all the difference in confident management and patient compliance.

For diagnosed patients, effective behavior modification, nutritional supplementation, and prompt anti-VEGF treatment reduce the incidence and progression of irreversible vision loss.[4] Although lifestyle changes, diet and exercise modification, systemic disease management, nutritional supplementation, retinal light protection, and more careful follow-up will not cure AMD, they have each been shown to slow or even halt the progression of the disease. This is extremely relevant to how we care for our patients. They want to know if they have a disease that we can do something about. Even if we can't make it go away, we can keep them safe by giving them the tools and attention they need to enjoy additional years of high-quality central vision, enhancing the odds of a better quality of life.

## 5. It Can Strengthen and Grow Your Practice

Performing dark adaptation is not only good for your patients, it has tremendous potential to grow your practice. Based on the disease prevalence, these patients are already in your practice. By using the right tools, you will start diagnosing a fair number of AMD patients. Once an AMD patient is diagnosed, your course of care and recommendations will be focused on slowing disease progression, which can lead to additional medical, nutraceutical and optical revenue for your practice. When we focus on what's best for our patients, we often realize it is also best for our practice.

Up to the point of advanced AMD, macular degeneration is well within the scope of primary optometric care. So, get passionate about improving visual outcomes and start managing AMD more proactively. It's a win-win for everyone.

### *Ryan Powell, OD*

***Kansas City, MO***

***AdaptDx Model:*** 2 Tabletops & 1 Headset
***Testing Protocol:*** All patients over the age of 60 and any patient under the age of 60 who has a family history or a night vision complaint
***Tests per Week:*** 12-15 tests
***% Failed:*** 15-20%
***ROI:*** The AdaptDx is essential to our priority to do the best we can for our patients. The ROI comes from the billing we do with the instrument directly, the supplements we start patients on to slow the rate of disease progression, the office visits we see for macular degeneration patients that we were missing before we had the AdaptDx, and the referral network our practice has built by being recognized by our patients as a practice that is leading the way in diagnosing macular degeneration at its earliest stages.
***Advice:*** Our AdaptDx instruments easily pay for themselves. However, I do not think that comes close to representing the full ROI that this technology has for optometric practice and for our patients.

# *Anatomy and Pathogenesis of AMD*

## *Understanding These Basics Will Make Disease Management Simple*

***By Julie Rodman, OD, MSc, FAAO***

As many of the other articles in this report explain, poor AMD outcomes are driven, in large part, by how difficult it is to detect and properly grade drusen. However, even our currently accepted grading systems are insufficient in fully describing the degree of damage our patients have from AMD.[17] The reality is that we simply cannot diagnose what we cannot see. The pathogenesis of AMD is such that disease destruction begins years before we can see it clinically, and detecting progression is made difficult by the subtlety of structural changes and the lack of reduction in Snellen acuity. Fortunately, functional testing can alert us to these sometimes undetectable physical changes, ensuring that we are vigilant in monitoring patients for change that can quickly result in vision loss.

***Functional testing can alert us to undetectable physical changes, ensuring that we are vigilant in monitoring patients for change that can quickly result in vision loss.***

### How AMD Starts

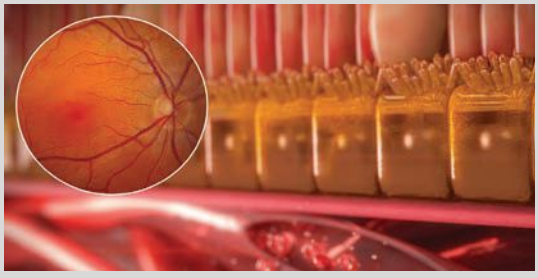
AMD represents a pathologic stage of an otherwise normally occurring deteriorative process.[18] As you know, drusen and subretinal drusenoid deposits become clinically visible at 30µm while changes in RPE cells are substantially smaller.[19] In AMD specifically, damage takes place before we can detect it using structural tests like optical coherence tomography (OCT) and fundus autofluorescence; and too often the harm it's caused comes as an alarming surprise during a regularly scheduled annual exam. That's because drusen are not the earliest-stage markers for AMD. They are visible structural evidence of a pathological process that has been underway for quite some time.

Cholesterol that is locally produced by the RPE and deposited in Bruch's membrane as layers of basal linear and basal laminar deposits is accumulating beneath the surface long before it becomes the drusen we see using current structure-based methods of detection such as OCT.[20] Yet all along the way as this process unfolds, the cholesterol buildup is causing inflammation, oxidative stress, and disruption of oxygen and nutrients such as Vitamin A to the outer retina and photoreceptors.[21] Rhodopsin is the pigment in rod photoreceptor cells that allows us to see dim light. As rhodopsin regeneration is diminished, patients will cite problems with night vision despite very good visual acuity in early disease.[10] As the disease progresses, the cholesterol layer continues to build, eventually thickening to a stage where the tell-tale drusen can be clinically visualized. Therefore, the drusen we finally see are just the proverbial tip of an iceberg of much larger cholesterol deposition.

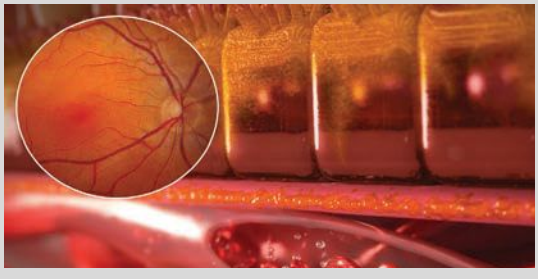
***Claudio Lagunas, OD***
***The Woodlands, TX***

***AdaptDx Model:*** Tabletop & Headset
***Testing Protocol:*** Patients 50 or older with a night vision complaint
***Tests per Week:*** 10-12
***% Failed:*** 25%
***ROI:*** At 10-12 tests per week, our AdaptDx Pro will be paid for in about 1 year
***Advice:*** Impaired dark adaptation is a biomarker for AMD. Therefore, it can tell you if a patient has or doesn't have the disease. Knowing up to 3 years before we can find it with OCT, retinal imaging or dilated fundus exams is critical in saving vision and having better outcomes. My patients deserve to know and deserve the best technology...do yours?

## The Functional and Structural Progression of AMD

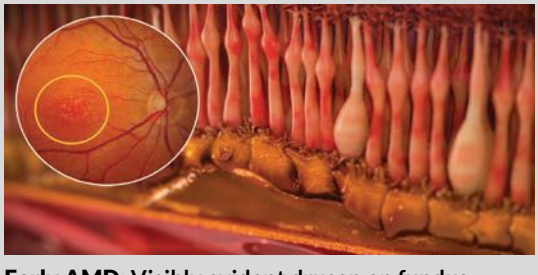


**No AMD:** Normal fundus appearance. Healthy choriocapillaris, Bruch's membrane, RPE, and photoreceptors.



**Subclinical AMD:** Normal fundus appearance. Invisible layers of cholesterol are forming along Bruch's membrane, blocking transport of vital nutrients and impairing dark adaptation function.

**Subclinical AMD:** Normal fundus appearance. Cholesterol continues to build, along with functional impairment.



**Early AMD:** Visibly evident drusen on fundus evaluation. Functional impairment continues to worsen.

## Making Sense of What We Can't See

Nothing can replace a comprehensive dilated exam. Likewise, fundus photography, OCT and other structural tests have a critical place in practice because they help us document and measure clinically detectable drusen. But just because we don't see it, doesn't mean it's not there. Rather, it means we need to consider other ways to detect it. This is where functional testing is most valuable.

Functional testing not only makes us aware of what we can't see—it measures the effects of clinically invisible damage by reliably measuring patients' ability to dark adapt. Remember, early cholesterol accumulation impairs normal transport of vitamin A across Bruch's membrane and creates a localized vitamin A deficiency which results in poor night vision. Unlike characterizing the risk associated with small drusen, a patient's ability to dark adapt can be easily measured in any office setting using an automated dark adaptometer like the AdaptDx or AdaptDx Pro.

The AdaptDx devices test retinal function that has been shown in clinical trials to aid in the identification of patients at all stages of AMD—even when they have no visible structural signs of disease. It does this by revealing impaired dark adaptation function that is 90% specific and 90% sensitive for the presence AMD, sometimes at least three years before it becomes clinically evident.[10] This is significant because it means we can actively take part in the patient journey and do everything possible to protect patients' vision before structural damage has occurred. Because functional impairment of the rod photoreceptors happens in the earliest stages of AMD, dark adaptation becomes affected before visual acuity declines,[10] which means we can be there every step of the way, ensuring that when and if aggressive injection therapy is needed, the referral can potentially be made before lines of vision are lost.

## Knowledge Is Power

When you know that a patient has AMD, you have a duty to treat that patient. Indeed, there is no magic bullet for patients with early-stage AMD, but the same can be said of almost any degenerative disease. We can't completely stop AMD in its tracks nor can we make it go away, but as with almost every other disease, we manage it. If we can get a head start, that's great news for our patients.

So how do we manage AMD when we detect it early using dark adaptation? The same way we would if we knew the patient had AMD based on structural findings. In other words, the treatment of AMD should be initiated at first detection. Why? Because based upon our current understanding of AMD pathogenesis, the stages of subclinical, early, and intermediate AMD all represent different clinical manifestations of the same underlying disease process. From a pathophysiological standpoint AMD is AMD—regardless of stage or how long the disease has progressed. Although the deposits may not become visible drusen for several years after their formation, damage is well underway. As such, the following treatments should be offered to patients—even at the earliest stages of AMD:

- **Prescribe smoking cessation programs.** Smoking is the largest modifiable risk factor for the progression of both CNV and GA,[22] yet in one study, 90% of patients with AMD were not advised to stop smoking.[23] Although most patients have been counseled on the ill effects of smoking, most don't realize that it affects their eyes and potentially their vision.
- **Prescribe nutritional supplementation.** Although there is extensive debate about which supplements are most appropriate, evidence strongly suggests prescribing them because, on average, treated patients have better outcomes than untreated patients.[24-26]
- **Discuss lifestyle modifications with respect to diet and exercise.** Following a healthy diet, exercising regularly and maintaining overall health are sound goals for all patients.[26] These lifestyle choices may act synergistically to prevent or delay onset or progression of AMD. One study found that women who followed a healthy diet, engaged in physical exercise, and avoided smoking had substantially lower risk of early AMD compared with women who did not follow these healthy lifestyles.[27,28]
- **Systemic disease management.** Several systemic conditions carry an increased risk of the development of AMD based on epidemiological studies—and it is our job to educate patients on how overall health can impact eye health. Cardiovascular disease, diabetes, hypercholesteremia, and obesity have all been associated with increased risk of AMD and/or progression of AMD.[29-32] Body mass index and abdominal obesity are independent risk factors for progression to advanced AMD. [29]
- **Prescribe retinal light protection.** Epidemiological evidence suggests that chronic sunlight exposure increases the risk of incident AMD and its progression.[33] Based on increased study in this area, you may also want to consider recommending HEVL-blocking eyeglass lenses.

Finally, for a patient with AMD, more frequent retinal examinations are recommended. Moving from a 12-month follow-up interval to a six-month (or even shorter in some cases) follow-up interval may be useful for monitoring disease progression.[12] More frequent visits provide the clinician increased opportunity to detect CNV before visual acuity loss.

## An Easy and Obvious Choice

As optometrists, we aren't faced with a lot of clear-cut decisions. We make tough calls all day long. For example, we try to fight contact lens over-wear using every trick in the book; we assess risk in patients with glaucoma and try to decide if they need to start or switch drops; we consider investments in new in-office treatments for patients with ocular surface disease. Making the call to treat AMD is easy. With every early diagnosis and timely intervention, we empower our patients to take control of their ocular health and potentially delay or prevent blindness from AMD.

***Jessica Marshall, OD***
***Holmdel, NJ***

***AdaptDx Model:*** Tabletop
***Testing Protocol:*** All patients with a complaint of difficulty with night vision over age 50
***Tests per Week:*** 15-20
***% Failed:*** 60%-70%
***ROI:*** Assuming we have 50 failed tests in a month, we are looking at an additional ~107K in revenue for the practice.
***Advice:*** The ROI has been great for us. More importantly, because we see patients more frequently, our doctor-patient relationships have become even stronger.

# *Dark Adaptation Testing is Proven to Find Treatable AMD*

***By Jeffry Gerson, OD, FAAO***

Earlier in my career, I was not fully confident in diagnosing AMD on the appearance of drusen alone. I knew that even the smallest druse was a harbinger of AMD, yet I was hesitant to give a patient a diagnosis of AMD. Instead, like many of my colleagues, I would say, "You might have some early signs of AMD." For the patient, that was neither definitive nor reassuring.

Then, a few years ago, I incorporated dark adaptation (DA) testing into my practice. Based on the science, it was clear that functional testing could change the way I diagnose and treat AMD. To be clear, impaired dark adaptation is not an indication of risk. Delayed rod-mediated dark adaptation in older adults with normal macular health is associated with incident early AMD three years later, and thus is a functional biomarker for early disease.[10] In fact, the Preferred Practice Patterns of the American Academy of Ophthalmology indicate that an initial patient history should consider difficulties in dark adaptation.[12] As this paper details, impaired dark adaptation has been found in numerous cross-sectional studies of AMD and may be used as an aid in the diagnosis and staging of AMD.[4]

To prove it to myself, I did a simple study with my own patients. I tested 100 patients over the age of 60 who had no visible indications of drusen. In the end, I was shocked to discover that 38 of them failed the dark adaptation test—which meant they had subclinical or early AMD that I would have otherwise missed. This drastically changed the way I thought about the disease and my approach to patient care. Today, I schedule every patient over 60 for an AdaptDx test, so I can find the functional biomarker of AMD as early as possible. This gives me the confidence to diagnose disease and have a deeper discussion around treatment, while providing my patients with vital information about their health.

Importantly, the definitive AMD diagnosis made possible by the AdaptDx dark adaptometer helps secure patient buy-in with critical lifestyle changes, such as smoking cessation, while also increasing the likelihood that patients will comply with a more frequent follow-up schedule. Offering a true AMD diagnosis, versus hypothetical conversations about risk, also helps inform supplementation recommendations and other interventions. *(See guidelines on page 11).*

***Several peer-reviewed studies have shown that dark adaptation function is impaired from the earliest stages of AMD, with increasing impairment as the disease progresses.***

## Rod Intercept: An Established Measurement of Disease Severity

The science proving that Rod Intercept™ (RI™) times correlate strongly with both the presence of AMD and disease severity has long been known. RI, as measured by the AdaptDx and AdaptDx Pro, is the number of minutes it takes for the eye to adapt from bright light to darkness at a standard threshold stimulus level. Indeed, several peer-reviewed studies have shown that dark adaptation function is impaired from the earliest stages of AMD, with increasing impairment as the disease progresses.[8,9]

RI is a simple and objective measurement of retinal function:

- An RI of less than 6.5 minutes indicates normal dark adaptation consistent with healthy photoreceptor function.
- An RI of 6.5 minutes or higher indicates impaired dark adaptation, most often due to AMD in patients over age 50, unless there is a pre-existing hereditary retinal degeneration or significant vitamin A deficiency, which is rare in the United States.[8,34,35]

When compared with older adults with normal macular health, patients with early-phase AMD have delayed dark adaptation.[7,8,10,35,36] Studies also indicate that the

higher the RI, the worse the AMD. In fact, a significant worsening of dark adaptation in eyes with early or intermediate AMD over a 12-month period can occur without a change in visual acuity or fundus appearance.[7,37] Further, in patients over age 50, declines in dark adaptation function correlated with patient-reported functional deficits and were accelerated in eyes with greater AMD severity.[11] Finally, dark adaptation has been identified as a suitable outcome measure in early-to-intermediate AMD.[38]

## High Sensitivity and Specificity

Prior to the release of the AdaptDx, methods for measuring dark adaptation were time intensive (> 30 minutes) and not very patient or technician friendly, making them unsuitable for everyday clinical use.[4] Conversely, the AdaptDx devices can help you identify patients with AMD in as little as 6.5 minutes using the Rapid Test protocol.

In 2014, researchers at Penn State College of Medicine, Massachusetts Eye and Ear Infirmary and the University of Tennessee published their findings in the peer-reviewed ARVO Journal, *Investigative Ophthalmology & Visual Science* and, since that time, numerous investigations have supported these findings.[4] To calculate the diagnostic sensitivity and specificity for the Rapid Test, dark adaptation was measured by using the AdaptDx dark adaptometer in two groups: subjects with normal retinal health and subjects with AMD. Subjects were assigned to their group by clinical examination and grading of fundus photographs. Sensitivity was defined as the percentage of AMD subjects who exhibited a Rod Intercept > 6.5 minutes. Specificity was defined as the percentage of normal subjects who exhibited a Rod Intercept ≤ 6.5 minutes. In the study results:

- Diagnostic test sensitivity was calculated to be 90.6% (115/127, P < 0.001). The 95% CI for diagnostic sensitivity had a lower bound of 85.1% and an upper bound of 100%.
- Diagnostic test specificity was calculated to be 90.5% (19/21, P = 0.0271). The 95% CI for diagnostic specificity had a lower bound of 72.9% and an upper bound of 100%.

In short, this study found that the AdaptDx Rapid Test protocol can be used to detect abnormal dark adaptation associated with AMD and that the diagnostic sensitivity and specificity with this Rapid Test were both greater than 90%, which is comparable with longer-duration research protocols studied earlier.[4,8,39]

***Gary Kirman, OD***
***Hummelstown, PA***

***AdaptDx Model:*** 1 Tabletop & 3 Headsets
***Testing Protocol:*** All patients 55 and older as well as those younger with night vision complaints or a strong family history of AMD
***Tests per Week:*** 30 tests per week
***% Failed:*** 45%
***ROI:*** 6 months
***Advice:*** Improve the quality of your examination, save sight and prolong patients' independence with earlier AMD detection and intervention plans.

***Beginning an AMD treatment for a patient with marked visual loss may result in a poorer visual outcome when compared to patients with better baseline visual acuity at time of first injection.***

## Earlier Detection and Intervention Can Make a Big Difference

We are fortunate to live in a time when there are several treatments for late-stage wet AMD. However, by the time injections commence, vision has most likely already been compromised. In fact, it has been clearly established that beginning an AMD treatment for a patient with marked visual loss may result in a poorer visual outcome when compared to patients with better baseline visual acuity at time of first injection.[16,40,41]

Because visual acuity is so closely correlated with treatment delay,[16,42] retinal specialists are increasingly interested in early detection. Likewise, every optometrist's goal should be to diagnose AMD in its earliest stages and monitor disease progression more closely to refer patients at the first sign of choroidal neovascularization (CNV)—before significant vision is lost. With proactive treatment and monitoring, our primary goal is to delay or avoid the onset of CNV. But with this approach, if CNV does occur, we are far more likely to achieve improved outcomes in partnership with our patients and retina specialists.

**Damon Dierker, OD**
***Indianapolis, IN***

***AdaptDx Model:*** Tabletop & Headset
***Testing Protocol:*** Symptomatic patients and patients with any fundus findings indicative of possible early AMD
***Tests per Week:*** 10
***% Failed:*** 70%
***ROI:*** With the AdaptDx Pro headset, our testing is up approximately 100%
***Advice:*** AMD is the leading cause of adult blindness in the United States. We should be doing everything we can to diagnose it and manage it early to reduce risk of bad outcomes.

As was reported in a 2014 natural history study published in *Optometry and Vision Science*, AMD patients can exhibit a significant change in DA speed in 12 months, which is a serious concern given the correlation between DA impairment and disease severity that's been well established for many years in multiple cross-sectional studies.[7,37] For example, a study of 325 patients age 60 and older found that those with normal macular health were approximately twice as likely to develop early AMD 3 years later if they had abnormal rod-mediated DA at baseline.[10] This is important on multiple levels. First, consider the danger that these patients face if they aren't seen for 12 months. Knowing that a patient has delayed dark adaptation alerts us to the importance of more frequent follow-up, so vision is not lost unnecessarily. Second, dark adaptation delays are associated with difficulty and emotional distress when performing visual activities under dim illumination and at night (driving, reading, detecting objects, ambulatory mobility.)[43,44] We should not sit idly, pretending a problem does not exist when we know that there is a very real problem. Vigilance is essential as early AMD patients age. For now, progression may be inevitable, but it is our duty to impress upon patients the need for follow-up, and to advise them on options, such as supplements and smoking cessation, that are intended to slow disease progression.

Second eye outcomes provide yet another example of the positive impact of earlier diagnoses. Research demonstrates second eye outcomes could be potentially better than the first eye with careful monitoring.[16] There are several reasons for this, the most obvious of which involves closer monitoring, which is spurred by our knowledge of the patient's much higher risk. When we know a patient has AMD, we proceed differently and we take steps to prevent disease progression in the fellow eye, a strategy that appears to work.[16] Dark adaptation makes this even easier because it tells us whether or not AMD exists in the other eye, even before vision declines. These patients are not ticking time bombs in the hands of doctors who utilize dark adaptation testing.

The great news is that major research utilizing dark adaptation continues on a global scale.[11,34,38,45] For example, these two multi-year studies are using the AdaptDx device as a clinical endpoint:

- ***MACUSTAR:*** The AdaptDx was selected as a key testing device in the MACUSTAR project, a five-year study aimed at reducing the disease burden of AMD worldwide. Currently funded with more than 16 million euros from the European Union and leading European pharmaceutical companies, the investigation expects to enroll 750 patients at 20 clinical study centers in seven countries across Europe.
- ***AMD Ryan Initiative Study (ARIS):*** Led by the National Eye Institute, this study is designed to follow 500 people over five years to learn more about the natural history of early AMD and identify biomarkers of disease progression well before it advances and causes vision loss. All ARIS participants will undergo routine spectral-domain optical coherence tomography (SD-OCT); and visual function will be measured by dark-adapted fundus perimetry and dark adaption with the AdaptDx.

## No Room for Doubt

AMD is a devastating disease, but the damage can be mitigated with early diagnosis, proactive treatment and regular monitoring. This wasn't possible a decade ago. We were often forced to somberly accept poor outcomes and significantly diminished quality of life in our patients. We can change these outcomes because we now can use dark adaptation in conjunction with the clinical exam and imaging technology to help us monitor for disease progression and identify those patients who are most at risk for developing advanced, vision threatening AMD.

# AMD Staging, Treatment and Management Guidelines

| | Subclinical AMD | Early AMD | Intermediate AMD | Advanced AMD |
|---|---|---|---|---|
| **Functional Testing (Average Rod Intercept*)** | **RI >** 6.5<br>The diagnostic specificity and sensitivity of the 6.5 minute cut-point for the presence of AMD is greater than 90% | **12.9** (+/- 6.1) | **16.6** (+/- 5.2) | **19.0** (+/- 4.5) |
| | **Dark adaptation speed is correlated with disease severity. The AdaptDx Pro Extended Test is a useful aid for staging AMD severity based on these average RI times.** | | | |
| **Structural Imaging** | • No drusen or small drusen ≤ 63 µm<br>• No pigmentary abnormalities | • Medium drusen > 63 µm and < 125 µm<br>• No pigmentary abnormalities | • 1 large druse > 125 µm and/or<br>• Pigmentary abnormalities | • Geographic atrophy (GA) or<br>• Choroidal neovascularization (CNV) |
| **Treatment Guidelines**** | • Prescribe smoking cessation program<br>• Prescribe nutritional supplementation<br>• Discuss lifestyle modifications with respect to diet and exercise<br>• Discuss systemic disease management<br>• Prescribe blue light protection<br>• Prescribe UVA and UVB protection | • Monitor smoking cessation compliance<br>• Monitor nutritional supplementation<br>• Review diet and exercise regimen<br>• Partner with primary care provider on systemic disease management<br>• Check blue light protection<br>• Reinforce UVA and UVB protection | • Monitor smoking cessation compliance<br>• Review vitamin and supplement recommendations<br>• Discuss diet and exercise regimen<br>• Manage systemic diseases with primary care provider<br>• Re-evaluate optical protection | • Low vision rehabilitation for GA<br>• Anti-VEGF injections for CNV |
| **Frequency of Exams** | **Every 6-12 months** to monitor for rapid progression with clinical exam, imaging and dark adaptation testing | **Every 6 months** to monitor for rapid progression with clinical exam, imaging and dark adaptation testing | **Every 3-6 months** to monitor for CNV with clinical exam, imaging and dark adaptation testing | Refer to retina specialist at first sign of CNV and continue to closely monitor the fellow eye |

* Jackson, G. R., Scott, I. U., Kim, I. K., Quillen, D. A., Iannaccone, A., & Edwards, J. G. (2014). Diagnostic Sensitivity and Specificity of Dark Adaptometry for detection of Age-Related Macular Degeneration. Investigative Ophthalmology & Visual Science, 55, 1427–1431.

** Practical Guidelines for the Treatment of AMD, published as a supplement to Review of Optometry in October, 2017

# AMD Practice Guidelines

**By Paul Karpecki, OD, FAAO**

I've been fortunate to be on the forefront of many advances, including the breakthrough in diagnosing and managing AMD with the 2014 release of the AdaptDx. As with any new technology, there are often a few early adopters who are the real-life testers and help us figure out the best way to implement testing in practice. The same goes for dark adaptation. With this in mind, MacuLogix brought 25 AdaptDx users together in January 2019. Our goal was to discuss and debate the real-life application of AdaptDx testing. After two days of discussion, this diverse group of optometrists came to a consensus on AMD standards of care in optometry.

1. **The goal of managing AMD is to preserve visual function—not to wait until vision has already been lost.** We often see patients with a few small drusen, but we rarely know for sure what those drusen will mean for the patient down the road. In the absence of a definitive AMD diagnosis, many of these patients would be seen only once per year. The result: CNV seems to develop without warning and the patient loses vision before being referred for injections. That was old world optometry. Now we can refer on time based on earlier detection and regular monitoring, prompted by AdaptDx tests.
2. **Dark adaptation testing can overcome the practical challenges associated with diagnosing AMD using only traditional subjective clinical assessment.** Subjective assessment of AMD prior to CNV is exceedingly complex. In fact, a study published in *JAMA Ophthalmology* revealed that optometrists and ophthalmologists miss AMD about 25% of the time.[5] In performing dark adaptation, we are obtaining the critical puzzle piece and eliminating the guesswork that used to make AMD diagnosis and management so difficult. Now, we simply use the AdaptDx to test patients over a certain age or who have drusen, difficulty seeing at night, or other risk factors.
3. **Optometrists must establish improved practice protocols to proactively identify early disease and monitor it on a regular basis to ensure that CNV is detected as soon as it occurs.** As many as 78 percent of AMD patients seek their first treatment after having already suffered irreversible vision loss in one eye, and nearly half of them have an acuity of 20/200 or worse.[2,3] This is an unacceptable statistic that doctors with access to dark adaptometry have the power and tools to change. Patients who are monitored with the AdaptDx potentially have a much better opportunity to have a timely referral to a retina specialist at the first signs of CNV because the doctors who use this technology are identifying the patients who require more frequent follow up.
4. **Optometrists can, and should, recommend treatments that make a meaningful difference.** As described above, knowledge is our most powerful tool and, for patients with AMD diagnoses confirmed by dark adaptation, the best thing we can do is watch them more closely. That said, a confirmed AMD diagnosis also gives us more confidence in suggesting supplements and blue blocking lenses for example. It also helps encourage better patient compliance with lifestyle changes such as smoking cessation and diet.
5. **The treatment of AMD should be initiated at first detection, regardless of the stage.** Without knowing whether a patient has AMD, we might not suggest any treatments. Conversely, when we are armed with the knowledge that a patient has AMD—no matter how early in the disease process—we definitely should intervene by prescribing lifestyle changes, such as diet and exercise modification, better systemic disease management, nutritional supplementation, retinal light protection, and more careful follow-up. While the current early- and intermediate-stage treatments will not cure AMD, they have each been shown to slow or even halt the progression of the disease, allowing patients to enjoy additional years of high-quality central vision.

***In the absence of a definitive AMD diagnosis, many patients would be seen only once per year. The result: CNV seems to develop without warning and the patient loses vision before being referred for injections. That was old world optometry.***

## Understanding Supplement Research

### By Steve Ferrucci, OD, FAAO

Based on AREDS2 research,[46] most doctors advocate supplementation in patients who have intermediate-stage or worse AMD. However, controversy abounds regarding the use of supplements in patients who have early or subclinical stage AMD. Currently, in patients with early disease, no definitive guidelines exist defining precisely which vitamins and nutrients doctors should recommend. Despite this unfortunate lack of consensus, one thing is certain: Evidence strongly suggests that patients with AMD should be prescribed some form of nutritional supplement.[24-26]

***AREDS2 authors never stated that supplements are useless in patients with early disease because that was outside the scope of the study and could not possibly be extrapolated from the data based on the study's inclusion criteria.***

Contrary to what you may have heard, the AREDS2 authors never stated that supplements are useless in patients with early disease because that was outside the scope of the study and could not possibly be extrapolated from the data based on the study's inclusion criteria. Patients with early disease were not included in AREDS2 to begin with. To directly quote the paper, "Enrollment was restricted to people between the ages of 50 and 85 years at high risk of progression to advanced AMD with either bilateral large drusen or large drusen in one eye and advanced AMD in the fellow eye."[46] That means both eyes had to be at the intermediate stage, or one eye at the intermediate stage and one eye at the advanced stage.

Conversely, the original AREDS research did investigate early disease and found no statistically significant benefit to supplementation with the original formula. But, as you know, the original AREDS formula, containing beta-carotene and devoid of lutein and zeaxanthin, is no longer recommended. Since publication in 2001, and following the many years of research that went into AREDS2, we have discovered so much more about AMD pathogenesis and about the role of carotenoids and antioxidants.

This leaves us with an important choice about what to do for our patients who present with early disease. Do we wait to prescribe supplements until the patient's AMD progresses to a worse disease state simply because AREDS1 supplements were not found to be of significant benefit? Or do we consider the risk-benefit ratio and prescribe a supplement that we know is inexpensive and safe at an earlier stage? Although practitioners favor certain formulas and brands, at the early stage, a carotenoid-based supplement seems to be an obvious choice.

The *Practical Guidelines for the Treatment of AMD* identify three primary options for appropriate nutritional supplementation.[47] The first option is to prescribe a macular pigment supplement (the carotenoids: lutein, zeaxanthin, meso-zeaxanthin). The second option is to prescribe a supplement containing both carotenoids and antioxidants, including zinc and vitamins C and E (e.g., an AREDS2 supplement). The third option is to prescribe a carotenoids supplement to patients with subclinical and early AMD, and a xanthophyll-antioxidant combination supplement to patients with intermediate AMD or patients that progress to intermediate AMD. It is beyond the scope of this report to dictate which of these is best for your patients. However, one fact is clear: Patients treated with supplements have better outcomes than those who are not.[24-26]

# *Wearable Technology Enables Modern AMD Care*

***By Claudio Lagunas, OD***

The original AdaptDx automated dark adaptometer was introduced in 2014 and has since been used by more than 1,000 eye care professionals worldwide to help identify and monitor AMD. In 2020, MacuLogix introduce a radically new and elegantly simple way to measure dark adaptation. As a self-contained wearable headset with an on-board technician named Theia powered by artificial intelligence, the AdaptDx Pro is a true game changer in eye care.

Although the original and more traditional tabletop form of the dark adaptometer is easy to administer, it required a dark room, a modest footprint, and a dedicated technician. The AdaptDx Pro guided by Theia was designed from the ground up to easily fit into any practice workflow, while providing a completely reimagined user experience for the technician and the patient.

Years of development went into creating this one-of-a-kind medical device to make modern AMD management practical in almost any eye care setting. In fact, it creates a comfortable, personal dark room so patients can take the test anywhere in the office, in any light. Additionally, the medical grade hardware withstands all necessary disinfection, and the hygienic barrier that makes contact with the patient's face is designed for single use, offering a greater level of patient confidence in this new era of point-of-care testing.

## Virtual Tech in a Portable Darkroom

Theia, the on-board technician, uses artificial intelligence to help ensure a consistent testing experience and reliable results. After your technician selects the testing protocol and places the device on the patient, Theia administers the test from start to finish. She gently and confidently guides the patient through the test using automated instructions and adaptive feedback.

The built-in cameras and pupil tracking software enable Theia to monitor the patient in real time, reminding the patient to stay focused on the fixation light, or open or close the eyes as needed. She also uses positive reinforcement to keep the patient engaged and on task. As Theia administers the test, your technician is free to work on other high-value tasks while easily monitoring testing progress by glancing at the interactive LCD screen on the device.

**AdaptDx Pro guided by Theia**

## The Future of AMD Care Starts Today

There is no question that earlier models of AMD care delivery are inadequate and not doing enough to save patients from avoidable vision loss. However, practical challenges sometimes stood in the way of best practices. The AdaptDx Pro guided by Theia removes those barriers, offering a truly revolutionary way to measure dark adaptation quickly and effectively in virtually any clinical setting, without requiring too much additional staff or doctor time.

A better future for your patients, your technicians and your practice can start right now. Are you ready to join your colleagues in embracing progress and improving AMD care by welcoming Theia and the AdaptDx Pro into your practice?

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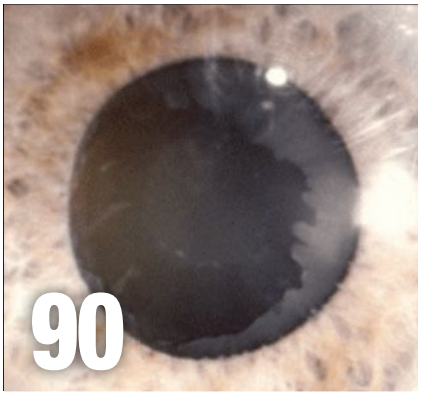


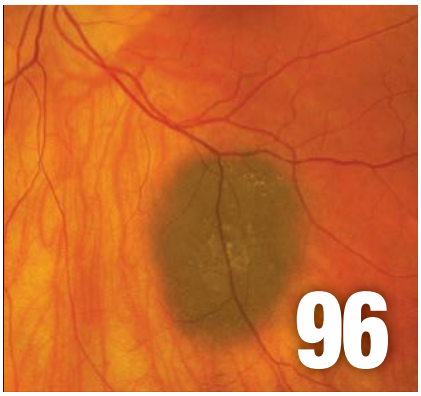




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# Outlook

**By Jack Persico, Editor-in-Chief**

# Abort, Retry, Fail?

Telehealth isn't exactly a rousing success yet in optometry. Will it ever be?

Our annual technology issue comes at a time when the tools and techniques of eye care are being rethought—sometimes radically—out of sheer necessity. Even before the pandemic, meeting the needs of an aging population was already an uphill climb. We've all seen projections of ever-increasing rates of AMD, diabetic retinopathy, glaucoma and cataracts. But a two-month shutdown of practices and a drastic reduction in capacity due to safety measures has upped the stakes.

Understandably, interest in telehealth among optometrists soared in the early days of the pandemic. It was a bit of a shotgun wedding—and has aged about as well as one.

In mid-March, just 22% of eye care practitioners surveyed by Jobson said they were thinking of offering telehealth services; one month later, it jumped to 54%. However, the percent of respondents who said they actually planned to integrate telehealth in practice on a regular basis started high and then dropped precipitously, from 90% in May to 58% in August. Billings for telehealth peaked at 70% in late April at the height of the shutdown but have since dropped to 39%.

But telehealth can succeed if done correctly; just look at the model created by the Dept. of Veterans Affairs. "The COVID era may have highlighted how useful and profitable this technique is under different circumstances," one VA optometrist told us, noting that the VA's Technology-based Eye Care Screening (TECS) program expanded this year. "There was, and still is, a lot of pushback from optometry, and I've personally been plenty resistant; however, now that COVID has set us back months, we're latching onto it to help us with the backlog of routine exams."

TECS has an infrastructure that most optometry practices can't replicate, including robust IT support, evidence-based protocols for provision of care and a widely dispersed network of primary care practices staffed and equipped to conduct remote screenings.

VA docs had a solid telehealth foundation to build on; the rest of the profession is largely winging it. Many have developed their own ad hoc exam techniques that rely on phones and laptops instead of medical-grade equipment. "We use telehealth for our soft contact lens follow-ups," one OD told us. "I have the patient send me pictures of their eyes closed and open: up, down, left, right and straight ahead." Is that good enough? Time will tell.

Others worry a rush to telehealth may degrade optometry. "In a backhanded way, we're validating some elements of the 1-800 model," one noted. Another cautioned, "We need to make sure optometry does not end up practicing like urgent care GPs—antibiotics for all red eyes."

Insurers, of course, will have the final word. If actuaries determine telehealth increases their costs, that'll be the end of that.

ODs are to be commended for improvising new methods in a time of need. Let's hope the lessons learned under battlefield conditions foster a discussion among policy-makers that yields long-term solutions. ■

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# Finding the Balance

When it comes to contact lenses, prizing convenience over health is a recipe for disaster. **By Paul M. Karpecki, OD, Chief Clinical Editor**

Finding the right combination of ocular health screening and patient convenience is the name of the game in contact lens fits—now more than ever with COVID-19 disrupting the traditional care model. But focusing too much on convenience at the expense of ocular and systemic health is not in the best interest of patients.[1]

Unfortunately, the recent Federal Trade Commission (FTC) ruling may have shifted the balance in the wrong direction, potentially preventing the timely diagnosis of ocular and systemic disease.

## The Ruling

The FTC's decision places a significant burden squarely on a law-abiding profession. Now, optometrists must document every contact lens prescription by obtaining signed acknowledgment forms, whether it's a separate confirmation statement, a prescriber-retained copy of the prescription or a prescriber-retained copy of the sales receipt for the exam that contains a statement confirming the patient received the prescription. Clinicians must maintain these records for three years. If a patient or their designated agent requests an additional copy of the prescription, optometrists must comply within 40 business hours.

Hundreds of members of Congress have expressed concerns over this red tape, and the American Optometric Association (AOA), led by Bill Reynolds, OD, is doing all it can to encourage the FTC to reconsider and reverse the ruling.

Ultimately, this update—designed to facilitate contact lens shopping by "requiring prescribers to automatically provide a copy of a patient's prescription to the patient and to verify or provide prescriptions to third-party sellers,"—harms the American citizens the FTC is designed to protect.[2]

## Online Sales

We know that the business models for certain online contact lens sellers are based solely on convenience. These new burdensome FTC rules that punish optometry can only push these companies' agendas of patient convenience with little to no regard for ocular health. (To be fair, Hubble has recently expressed sincere interest in working with optometry to better serve patients by promoting yearly exams. The company is working to educate patients on the importance of the yearly eye exam to ensure ocular and systemic health, and it has plans to push 10,000 to 25,000 patients that visit their site daily into optometric offices.)

If patients are foregoing their annual eye exams because they can get their contact lenses online, optometrists lose the opportunity to ensure each patient's ocular health and catch any early signs of disease—especially asymptomatic blinding conditions such as glaucoma.

Not only that, contact lens wearers require more frequent monitoring of their corneal health to help avoid infectious and inflammatory events; and we've all seen examples of patients who eventually require corneal transplants due to poorly fit contact lenses and lens wear and care non-compliance, resulting in microbial keratitis.

We also know the eye is the window to the body. Each year thousands of patients see their eye doctor and their ocular findings lead to a diagnosis of diabetes, hypertension, brain tumors or even choroidal malignancies, to name a few. Although convenience is a necessity in the COVID era, the increase in morbidity, blindness and undiagnosed systemic diseases is the last thing we need at this time.

The balance of ocular health and convenience has tipped in a troublesome direction. While providing convenience is important, especially today, but balance is necessary. The most recent FTC ruling appears to have tipped that balance in a direction where the ramifications on ocular and systemic health are serious. The AOA has done a great job of immediately acting on the need to protect the public and the eye care professions, but each of us must step up and contact our representatives. Our patients' health and our livelihood depend on it. ■

*Note: Dr. Karpecki consults for companies with products and services relevant to this topic.*

1. The interchange of health and convenience. Personal communication with Thomas Swinnen, North American President of Johnson & Johnson.
2. FTC Announces Final Amendments to the Agency's Contact Lens Rule. www.ftc.gov/news-events/press-releases/2020/06/ftc-announces-final-amendments-agencys-contact-lens-rule. Federal Trade Commission. June 23, 2020.

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# Whatever Floats Your Goat

I've seen a lot in 41 years of practice. This week, I added one more to my misadventures in optometry. **By Montgomery Vickers, OD**

You would think I've seen and heard just about everything that could possibly come along. I found a dead bug embedded in the conjunctiva of a patient whose chief complaint was that his eye was "bugging" him. His words.

I sparred with a patient who kept repeating, while reading letters on the Snellen chart, "It's awful" no matter what lens I tried. It took me a couple of minutes to realize the letters were *O-F-L*… ooh, "awful." He cracked up at his prank.

I've practiced a full day with two different shoes on, with my fly unzipped and with all manner of food in my mustache. I once asked a patient if his eyes were always that red and he told me, "No, just since I smelled your breath." At least the pizza I had was phenomenal.

I adjusted glasses on an embalmed patient at the visitation service. I was asked to be the minister at a wedding. I once assumed the initials CP at the top of a patient's chart represented a nickname and not a reference to her cerebral palsy.

I had a prim 60-year-old lady ask me if I knew anything about "alternative medicine." When I stuttered some generic answer, she pulled her dress up to her waist. As I shoved it back down, I exclaimed, "I've been married for over 20 years and I still don't know anything about that!"

I have diagnosed Peyronie's disease for a hapless soul who got optometry confused with urology. The two pairs of new glasses did not help! (That's a joke, by the way. I mean, they may have helped, who knows?) I recommended a colonoscopy for a patient based on his retinal findings and he did indeed have early-stage colorectal cancer.

I got so mad at an elderly patient's no-good son that I challenged him to meet me out back for a fight (Don't be impressed. The police station was also out back. But, for the record, he didn't show, the chicken!).

## Lessons From a Goat

But, I never really spent time in my office with a goat. Until this week.

In the Dallas area of Texas where I now practice, you can be driving through the city and see some bison, longhorn cattle or horses grazing beside a law office. Turns out if you own an empty lot, you have to pay heavy taxes. If you throw a sheep or something on there, it's taxed like farm acreage at a much lower rate.

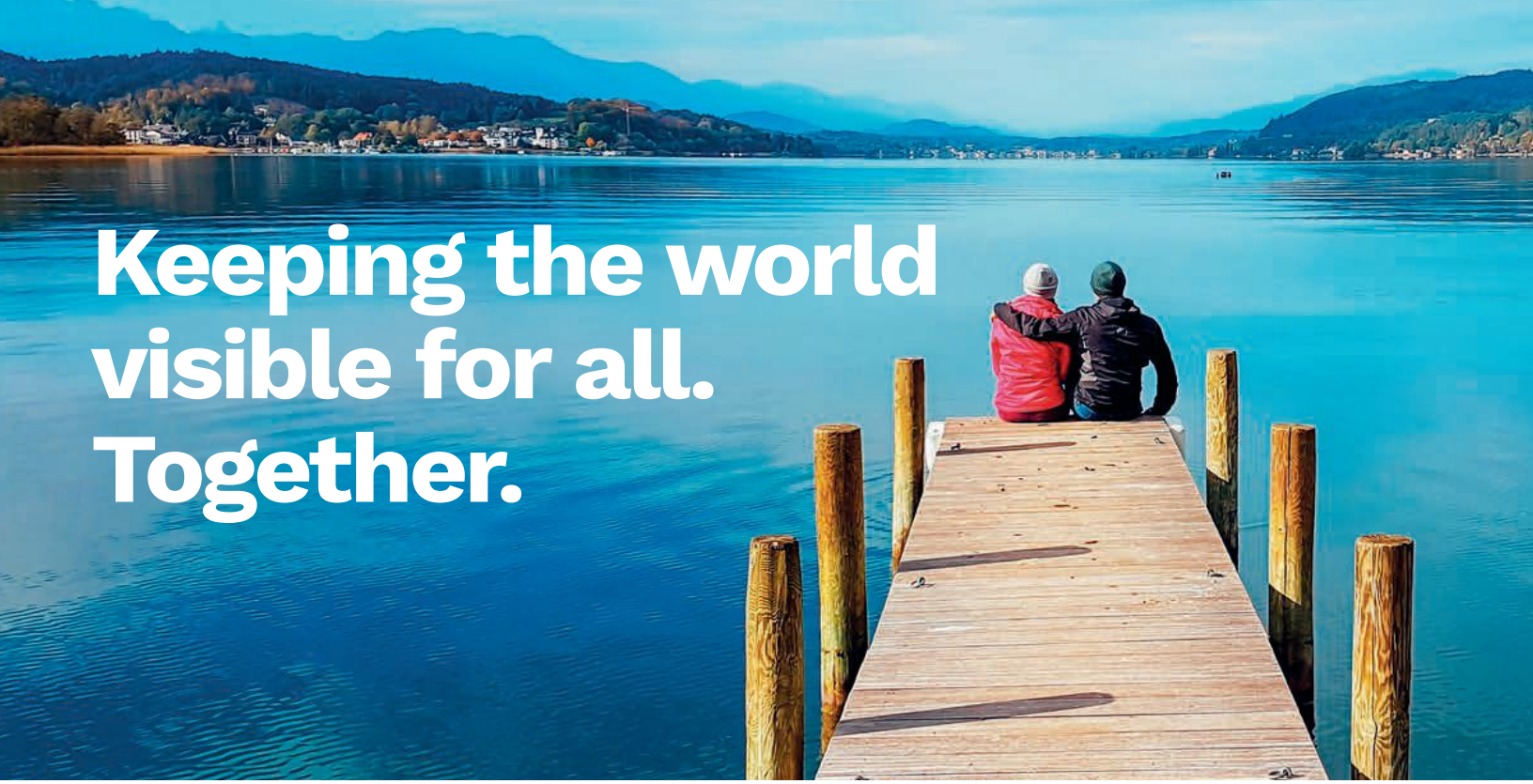
So, owning some farm animals is a good idea here in Texas. One of my wonderful technicians showed up this week with a little newborn goat. He was born a runt and the mom, instinctively only saving the strong for the benefit of the herd, decided she would just not take care of him.

I guess nature has a plan so, unfortunately, the little fellow didn't make it. We were all sad but understood it simply wasn't his time. Maybe he was just meant to give us all a smile for a day.

His short but seemingly stress-free life made us all appreciate the days we have, even with the strange and unusual events that punctuate the practice. And, I can now add to my list that, unlike any other optometrist in the world, I have stated, right in my office and during the care of patients that, "The goat died."

To me, this puts the misplaced progressive right back in its place.

So, no matter what weird stuff is going on in your practice, something weirder will appear. And, as the goat taught us, time is short. Enjoy even the strange and unusual moments that you have had and that you will certainly have in the future. ■



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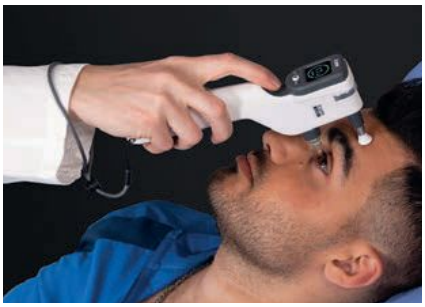

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# Put It on Ice

Single out a myasthenia gravis diagnosis with this quick and easy test.

**Edited by Paul C. Ajamian, OD**

**Q My 56-year-old patient presented with a "droopy" eyelid and double vision that could only be relieved by squinting. How should I proceed with my differential?**

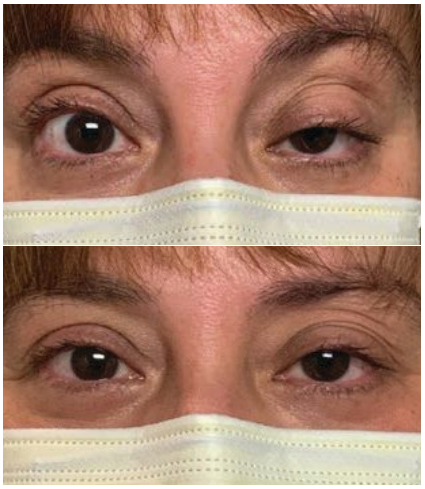
**A** David J. Baptiste, OD, of El Paso, Texas, recently saw a patient who was at home under quarantine because she is a healthcare worker and was exposed to the coronavirus. On day eight, she contacted Dr. Baptiste after noting ptosis of her left upper lid and was concerned that it was related to COVID-19. Dr. Baptiste had just seen the patient for her annual eye exam three weeks prior and only noted s/p monovision LASIK with 20/20 vision OD distance and J1 OS for near. Interestingly, she had just reduced the dosage of her Plaquenil (hydroxychloroquine, Sanofi-Aventis) that she was taking for rheumatoid arthritis.

"Following our COVID-19 protocols, we saw her as an emergency patient in-office in order to assess her concerns," Dr. Baptiste notes.

## The Three Amigos

According to Dr. Baptiste, there are three conditions that the optometrist should initially consider: Bell's palsy or facial nerve palsy, cranial nerve (CN) involvement or myasthenia gravis (MG).

Bell's palsy, sometimes referred to as idiopathic facial palsy, is a form of temporary facial weakness or paralysis, usually on one side. "It results from CN VII (facial nerve) dysfunction and the etiology is usually unknown," Dr. Baptiste notes.



**Figs. 1 and 2. The ice pack test can help diagnose MG associated with lid ptosis.**

Bell's palsy has recently been reported as one of the growing number of neurological complications from COVID-19.[1]

The patient's diplopia complaints caused Dr. Baptiste to consider the involvement of the cranial nerves III, IV and VI, leading to a check of extraocular muscle (EOM) function. Other than the ptosis, there was no facial asymmetry. Dr. Baptiste ruled out motility restrictions and anisocoria, and there were no confrontation field defects and no afferent pupillary defect.

## Conduct an Ice Pack Test

Dr. Baptiste's final consideration, since it can mimic many EOM palsies, was MG. With the significant onset of ptosis, performing the ice pack test was an easy way to gather evidence to support a diagnosis.

"Place an ice-filled bag over the affected eyelid for two to three minutes," Dr. Baptiste says. The transient resolution of the ptosis occurs because the cold temperature decreases the breakdown of acetylcholine at the neuromuscular junction. The patient's lid droop improved to almost equal the opening of the palpebral fissure of the fellow eye (*Figures 1 and 2*).

## What's Next?

Dr. Baptiste then referred the patient to a neurologist to rule out MG. Blood work was drawn and an MRI with contrast was performed. The MRI was normal, and all ordered labs were myasthenia gravis seronegative. The test for COVID-19 was also negative.

Despite the results, the neurologist felt strongly that it was ocular myasthenia, supported by the ice pack test.

The patient was started on a course of Mestinon (pyridostigmine, Bausch + Lomb), after which the ptosis intermittently improved. Oral prednisone was eventually added to her regimen, resulting in further resolution. The neurologist told the patient he could not predict if the ocular myasthenia would progress to generalized MG.

The patient has joined a Facebook MG support group where many said that it took them years to be diagnosed. "Thanks to you, I discovered the diagnosis quickly, and for that I am grateful," the patient wrote to Dr. Baptiste. ■

1. Elkhouly A, Kaplan A C Noteworthy neurological manifestations associated With COVID-19 infection. Cureus 12(7): e8992.

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### INDICATIONS AND USAGE

ZERVIATE™ (cetirizine ophthalmic solution) 0.24% is a histamine-1 (H1) receptor antagonist indicated for treatment of ocular itching associated with allergic conjunctivitis.

### DOSAGE AND ADMINISTRATION

Instill one drop in each affected eye twice daily (approximately 8 hours apart).

### IMPORTANT SAFETY INFORMATION

### WARNINGS AND PRECAUTIONS

**Contamination of Tip and Solution:** As with any eye drop, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle or tip of the single-use container in order to avoid injury to the eye and to prevent contaminating the tip and solution. Keep the multi-dose bottle closed when not in use. Discard the single-use container after using in each eye.

**Contact Lens Wear:** Patients should be advised not to wear a contact lens if their eye is red. ZERVIATE should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of ZERVIATE. The preservative in ZERVIATE, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted 10 minutes following administration of ZERVIATE.

### ADVERSE REACTIONS

The most commonly reported adverse reactions occurred in approximately 1–7% of patients treated with either ZERVIATE or vehicle. These reactions were ocular hyperemia, instillation site pain, and visual acuity reduced.

**Please see brief summary of Full Prescribing Information on the adjacent page.**

HPMC=hydroxypropyl methylcellulose.

[a]Based on a U.S. News report on data from the 2019 Pharmacy Times Survey of Pharmacists' OTC Recommendations.

**References: 1.** ZERVIATE [package insert]. Fort Worth, Texas: Eyevance Pharmaceuticals LLC; 2020. **2.** *U.S. News & World Report.* Antihistamines for allergies. https://health.usnews.com/health-products/top-rec-antihistamines-oral-8. Accessed October 7, 2019. **3.** Meier EJ, Torkildsen GL, Gomes PJ, et al.Phase III trials examining the efficacy of cetirizine ophthalmic solution 0.24% compared to vehicle for the treatment of allergic conjunctivitis in the conjunctival allergen challenge model. *Clin Ophthalmol.* 2018;12:2617-2628. **4.** Malhotra RP, Meier E, Torkildsen G, et al. Safety of cetirizine ophthalmic solution 0.24% for the treatment of allergic conjunctivitis in adult and pediatric subjects. *Clin Ophthalmol.* 2019;13:403-413.

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**ZERVIATE™ (cetirizine ophthalmic solution) 0.24%**

**Brief Summary**

## INDICATIONS AND USAGE

ZERVIATE (cetirizine ophthalmic solution) 0.24% is a histamine-1 (H1) receptor antagonist indicated for treatment of ocular itching associated with allergic conjunctivitis.

## DOSAGE AND ADMINISTRATION

**Recommended Dosing:** Instill one drop of ZERVIATE in each affected eye twice daily (approximately 8 hours apart). The single-use containers are to be used immediately after opening and can be used to dose both eyes. Discard the single-use container and any remaining contents after administration. The single-use containers should be stored in the original foil pouch until ready to use.

## CONTRAINDICATIONS

None.

## WARNINGS AND PRECAUTIONS

**Contamination of Tip and Solution:** As with any eye drop, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle or tip of the single-use container to avoid injury to the eye and to prevent contaminating the tip and solution. Keep the multi-dose bottle closed when not in use. Discard the single-use container after using in each eye.

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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 trial 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.

In 7 clinical trials, patients with allergic conjunctivitis or those at risk of developing allergic conjunctivitis received one drop of either cetirizine (N=511) or vehicle (N=329) in one or both eyes. The most commonly reported adverse reactions occurred in approximately 1%–7% of patients treated with either ZERVIATE or vehicle. These reactions were ocular hyperemia, instillation site pain, and visual acuity reduced.

## USE IN SPECIFIC POPULATIONS

### Pregnancy

*Risk Summary*

There were no adequate or well-controlled studies with ZERVIATE in pregnant women. Cetirizine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Data*

Animal Data

Cetirizine was not teratogenic in mice, rats, or rabbits at oral doses up to 96, 225, and 135 mg/kg, respectively (approximately 1300, 4930, and 7400 times the maximum recommended human ophthalmic dose (MRHOD), on a $mg/m^2$ basis).

### Lactation

*Risk Summary*

Cetirizine has been reported to be excreted in human breast milk following oral administration. Multiple doses of oral dose cetirizine (10 mg tablets once daily for 10 days) resulted in systemic levels (Mean $C_{max}$ = 311 ng/mL) that were 100 times higher than the observed human exposure (Mean $C_{max}$ = 3.1 ng/mL) following twice daily administration of cetirizine ophthalmic solution 0.24% to both eyes for 1 week. Comparable bioavailability has been found between the tablet and syrup dosage forms. However, it is not known whether the systemic absorption resulting from topical ocular administration of ZERVIATE could produce detectable quantities in human breast milk.

There is no adequate information regarding the effects of cetirizine on breastfed infants, or the effects on milk production to inform risk of ZERVIATE to an infant during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZERVIATE and any potential adverse effects on the breastfed child from ZERVIATE.

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**Geriatric Use:** No overall differences in safety or effectiveness have been observed between elderly and younger patients.

## NONCLINICAL TOXICOLOGY

### Carcinogenesis, Mutagenesis, Impairment of Fertility

*Carcinogenicity*

In a 2-year carcinogenicity study in rats, orally administered cetirizine was not carcinogenic at dietary doses up to 20 mg/kg (approximately 550 times the MRHOD, on a $mg/m^2$ basis). In a 2-year carcinogenicity study in mice, cetirizine caused an increased incidence of benign liver tumors in males at a dietary dose of 16 mg/kg (approximately 220 times the MRHOD, on a $mg/m^2$ basis). No increase in the incidence of liver tumors was observed in mice at a dietary dose of 4 mg/kg (approximately 55 times the MRHOD, on a $mg/m^2$ basis). The clinical significance of these findings during long-term use of cetirizine is not known.

*Mutagenesis*

Cetirizine was not mutagenic in the Ames test or in an *in vivo* micronucleus test in rats. Cetirizine was not clastogenic in the human lymphocyte assay or the mouse lymphoma assay.

*Impairment of Fertility*

In a fertility and general reproductive performance study in mice, cetirizine did not impair fertility at an oral dose of 64 mg/kg (approximately 875 times the MRHOD, on a $mg/m^2$ basis).

## PATIENT COUNSELING INFORMATION

**Risk of Contamination:** Advise patients not to touch dropper tip to eyelids or surrounding areas, as this may contaminate the dropper tip and ophthalmic solution. Advise patients to keep the bottle closed when not in use. Advise patients to discard single-use containers after each use.

**Concomitant Use of Contact Lenses:** Advise patients not to wear contact lenses if their eyes are red. Advise patients that ZERVIATE should not be used to treat contact lens–related irritation. Advise patients to remove contact lenses prior to instillation of ZERVIATE. The preservative in ZERVIATE solution, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted 10 minutes following administration of ZERVIATE.

**Administration:** Advise patients that the solution from one single-use container is to be used immediately after opening. Advise patients that the single-use container can be used to dose both eyes. Discard the single-use container and remaining contents immediately after administration.

**Storage of Single-use Containers:**
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# The Gang's (Not) All Here

RGC death is the hallmark of glaucomatous damage—and it can now be captured with OCT. **By Bisant A. Labib, OD**

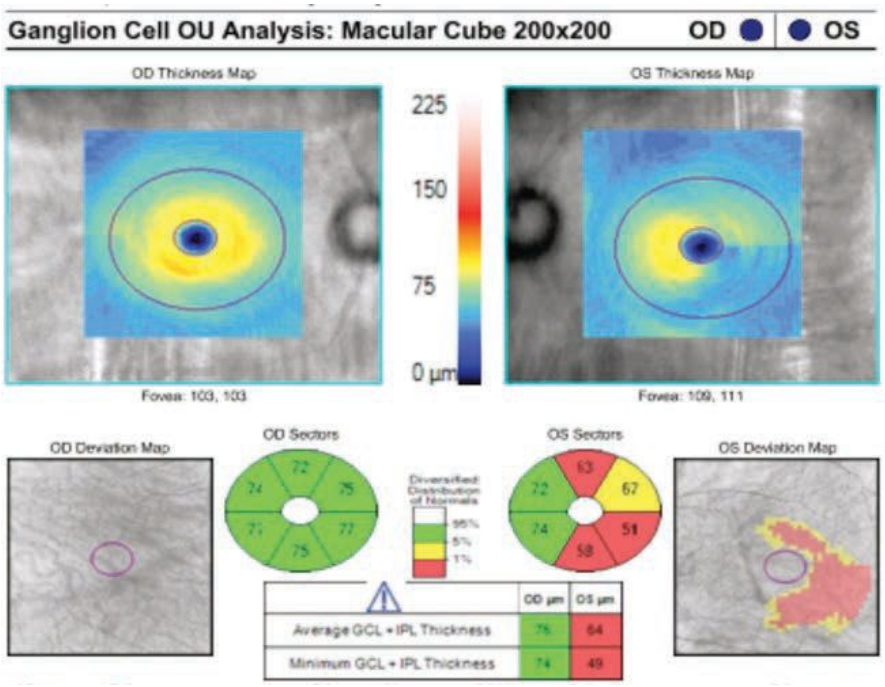
Glaucomatous optic neuropathy is a disease we all encounter in our daily practices, with an estimated 64 million people affected.[1-3] As one of the leading causes of vision loss worldwide, early detection is vital in establishing a treatment plan to reduce the risk of progression. Damage from glaucoma can be traced back to one essential retinal neuron: the ganglion cell.[1-6]

## Follow the Light

When light enters the eye, it passes through the cornea, aqueous, pupil and vitreous to land on the neural retina. The group of neurons that constitutes the retina includes photoreceptors and bipolar, horizontal amacrine and ganglion cells. One of the larger neurons is the retinal ganglion cell (RGC), which resides within the inner retinal layers.[3]

The RGCs are the sole efferent fibers within the retina—their intricate network of dendrites receives input and ultimately transmits the signal to the necessary areas of the brain. Thousands of RGC axons travel towards the center of the retina, converging at the optic nerve head. They then exit the lamina cribrosa and pass their information to the lateral geniculate nuclei within the thalamus for visual stimulation.[3]

There are two main groups of RGCs: (1) midget cells, which are responsible for the P visual pathway and (2) parasol cells, which are responsible for the M pathway.




**This patient's macular GCC OCT indicates reduced GCL and IPL thickness in their left glaucomatous eye.**

They differ in their receptive field size, luminance, contrast and spectral sensitivities (*Table 1*).[4]

RGCs can be further classified based on their response to light with respect to the receptive fields. ON cells are excited by increments of light while OFF cells are excited by excrements of light. ON-OFF RGCs are a mixture of both.[2]

Studies determining susceptibility of specific RGCs and glaucoma have found that larger parasol cells are more prone to IOP-induced injury.[4] No distinction was found regarding the difference between ON/OFF cell susceptibility to glaucomatous damage.[2]

## Tracing Cell Death

RGC destruction is the hallmark of glaucoma and other optic neuropathies, such as Leber's hereditary optic neuropathy, optic neuritis and ischemic optic neuropathy, to name a few.[3] With glaucoma, research shows RGCs are the most susceptible neurons to stressors such as intraocular pressure (IOP).[4] Increases in IOP lead to a reduction in retrograde axonal flow, causing death.[5] Due to the RGC pathway, cell death leads to optic nerve degeneration and subsequent visual field loss.

Research estimates that 25% to 40% of RGCs are lost before a

| Table 1. Retinal Ganglion Cells by Type | |
|---|---|
| **Midget Cell** | **Parasol Cell** |
| P visual pathway | M visual pathway |
| Small receptive fields | Large receptive fields |
| Decreased luminance sensitivity | Increased luminance and contrast sensitivity |
| Spectral sensitivity | No spectral sensitivity |

visual field defect is evident, emphasizing the importance of careful examination of the innermost retinal layers.[5,6]

Traditional optical coherence tomography (OCT) of the circumpapillary optic nerve has become essential in quantifying structural loss of RGCs within the retinal nerve fiber layer (RNFL), as it is the first detectable sign of glaucoma. However, the RNFL contains only the axonal portion of the RGC.[6] The remaining portions of the RGC—the cell body and dendrite—are located within the ganglion cell layer (GCL) and the inner plexiform layer (IPL), respectively.

RGC death dynamics suggest that mitochondrial changes that harm the dendrites within the IPL layer occur first, followed by the GCL and RNFL. These findings have given rise to the utility of the OCT macular ganglion cell complex (GCC) map, which analyzes all three layers of the retina and, ultimately, the entire structure of the RGCs. The GCL+IPL measurements incorporate the cell body and dendrite as well; whereas, the standard RNFL map only measures RGC axons.[5]

The GCC also provides clinicians the capability to measure macular thickness, which may be reduced in glaucoma due to the high distribution of RGCs within the macular complex. Studies demonstrate that this specific type of OCT is quite useful when attempting to distinguish glaucomatous damage in a patient with high myopia. This is because myopic optic discs are difficult to distinguish in RNFL measurements alone due to the presence of peripapillary atrophy, staphylomas or tilted insertions.[6]

RGCs are vital to the visual pathway, and their destruction is a key mechanism of glaucomatous optic neuropathy. With a better understanding of the complex structure of RGCs and their role in glaucoma, researchers have been able to improve our imaging modalities to help us detect glaucomatous changes earlier, even preceding vision loss.

The early and subtle degenerations to RGCs must be identified to initiate IOP-lowering treatment in glaucoma patients and preserve visual function. ■

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## The Nerve of These Cells

While glaucoma is the most common disorder, RGCs are affected in many other optic nerve diseases as well. Neuro-ophthalmic disorders, such as dominant optic atrophy, affect the RGCs because they originate primarily from the diencephalon of the central nervous system. Clinically, this optic atrophy appears as gradual, bilateral significant vision loss that manifests early in life and is characterized by optic nerve pallor.[1]

Leber's hereditary optic neuropathy (LHON) is another example. It's a genetic disorder primarily affecting males that causes painless and acute monocular vision loss. LHON pathology is confined to the RNFL, affecting the RGCs. The GCC OCT is useful in diagnosing these patients and monitoring for progression, with typical patterns reflecting early thinning within the inner ring of the nasal sector, progressing to a centrifugal and spiral pattern of RNFL and IPL thinning.[2]

The GCC is also helpful in distinguishing between optic neuritis and non-arteritic ischemic optic neuropathy (NAION), as both conditions present initially with optic nerve swelling. In the GCC of NAION patients, the ganglion cell loss generally follows an altitudinal pattern, consistent with the subsequent visual field defect; whereas, ganglion cell damage in optic neuritis is more diffuse.[3]

Even in compressive optic neuropathies, where a mass in the brain is the cause such as in a pituitary adenoma, the lesion may inhibit nerve impulses of RGC axons. Often, following decompression, GCC thinning may remain although vision is restored. This can be attributed to the temporary, physiological block in nerve conduction without the death of RGC axons.[4]

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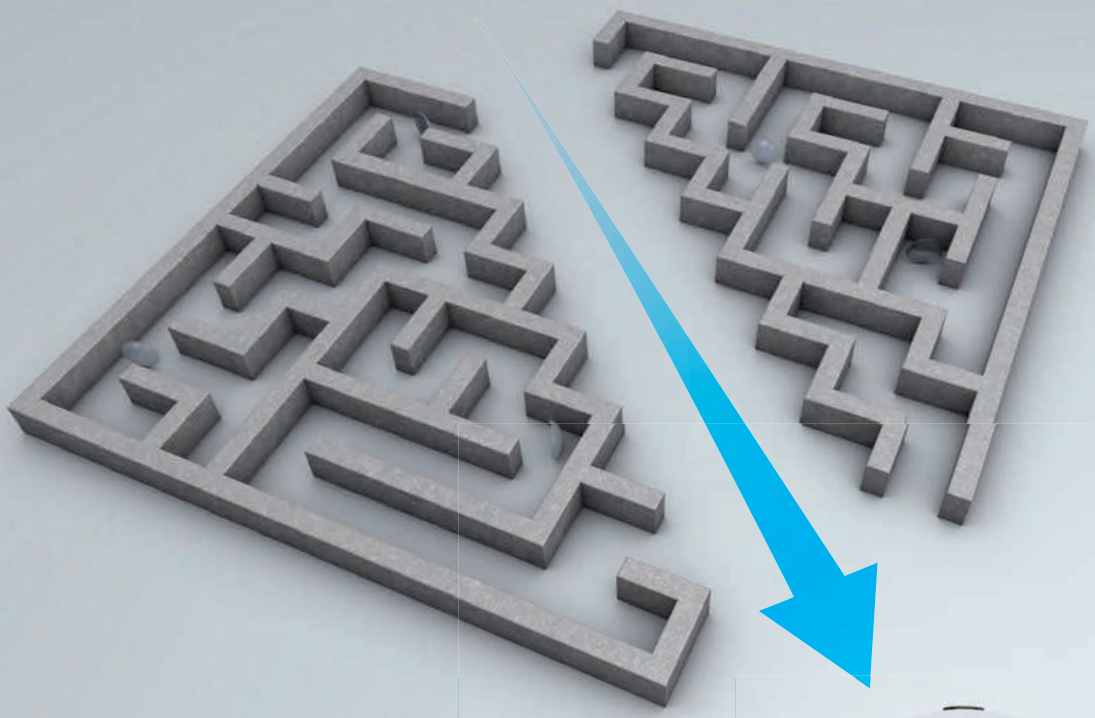

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# A Rare Case of Nevus of Ota

This Caucasian patient with primary choroidal melanoma presented with a surprising finding. By Paul G. Krabill, OD, and Chung T. To, OD

*In April 2016, optometry lost a giant when the author of the seminal work* Primary Care of the Posterior Segment, *Larry Alexander, OD, died. In addition to being an optometric physician, author and educator at the University of Alabama Birmingham School of Optometry, Dr. Alexander was a past president of the Optometric Retina Society (ORS). That group has chosen to honor his legacy by accepting case reports from optometric residents across the country relating to vitreoretinal disease. The contest is sponsored by Optovue, Zeiss, Heidelberg and Optos.*

*As selected by the board of the ORS, this case was a co-winner of the fourth annual Larry Alexander Resident Case Report Contest.*

Nevus of ota is a hyperpigmentation of the ocular adnexa and globe. Patients with this condition are usually of Asian descent, and it rarely occurs in Caucasians. This report features a 71-year-old Caucasian male with nevus of ota who presented with a choroidal mass in his left eye. Clinical features of the mass include a dome-shaped elevation with indistinct borders and orange pigment spots overlying the surface. Evaluation with B-scan and optical coherence tomography (OCT) confirmed the elevation and underlying subretinal fluid.

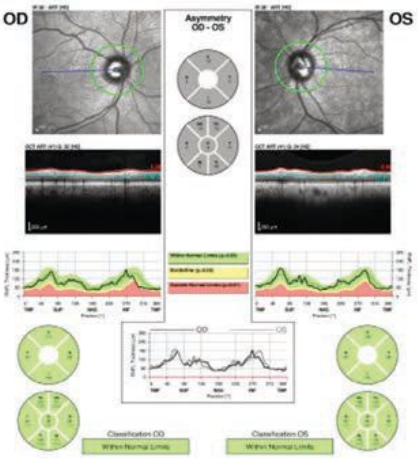



**Fig.1. The patient's retinal nerve fiber layer analysis at presentation shows no glaucomatous thinning for both eyes.**

This is a rare case of a Caucasian patient with nevus of ota that progressed to primary choroidal melanoma. Here we discuss the advanced management and treatment.

## Background

Nevus of ota, also known as oculodermal melanocytosis, was first reported by Hulke in 1860. Later in 1939, Ota and Tanino described the findings as a unilateral, patchy, grey and irregular discoloration of the skin supplied by the ophthalmic and maxillary divisions of the trigeminal nerve.[1] Nevus of ota affects 0.014% to 0.034% of the Asian population, with incidence highest in individuals of Japanese descent affecting 0.2% to 1%.[2,3] Explanation for this higher incidence in the Japanese population is unknown. Nevus of ota rarely occurs in Caucasians, affects women more than men and is typically present at birth but can appear during puberty or pregnancy.[2] Nevus of ota occurs unilaterally in 90% of the cases, with incidence of bilateral involvement as low as 1.4%.[4,5]

Ophthalmic complications associated with nevus of ota include open-angle glaucoma (10%), cataracts and development of a primary choroidal melanoma (4%) that is usually ipsilateral to the side of the nevus of ota.[1,4,6]

The diagnosis of nevus of ota

is usually made clinically. Physical exam reveals a unilateral, patchy, hyper-pigmented lesion following the ophthalmic and maxillary divisions of the trigeminal nerve, especially within the periorbital region.[1] Differential diagnosis for nevus of ota includes café au lait patch, spilus nevus and acquired bilateral nevus of ota-like macules.[2] Acquired bilateral nevus of ota, also known as Hori's nevus, appears later in life in the third to fourth decade and has no known associated ophthalmic associations.[7] Systemic conditions associated with nevus of ota include Sturge-Weber syndrome, Klippel-Trenaunay syndrome, neurofibromatosis, multiple hemangiomas, spinocerebellar degeneration and ipsilateral deafness.[1]

## Case Report

A 71-year-old white male presented to our clinic for his annual eye exam with no complaints. The patient's past medical history was positive for coronary artery disease, benign prostatic hyperplasia, hypertension, hyperlipidemia and Crohn's Disease. His past ocular history included suspicion for glaucoma due to a moderate cup-to-disc ratio in both eyes with previously normal retinal nerve fiber layer using OCT and full 24-2 visual fields (*Figures 1 and 2*).

Systemic medications included aspirin 81mg daily, terazosin 2mg daily, atorvastatin 10mg daily, omeprazole 20mg twice daily, finasteride 5mg daily and tramadol 50mg twice daily. His ocular medications included preservative-free artificial tears twice daily in both eyes. The patient has no known drug allergies and was oriented to time, place and person. He denied smoking, illegal drug use and alcohol consumption.

His best-corrected visual acuity was 20/20 at distance and near in both eyes. Pupils were equally round and reactive to light without an afferent pupillary defect. Confrontation visual fields were full to finger counting in both eyes. Extraocular muscles were unrestricted in all gazes and cover test demonstrated orthophoria at distance and near. Intraocular pressures were 17mm Hg in the right eye and 16mm Hg in the left eye at 10:47am.

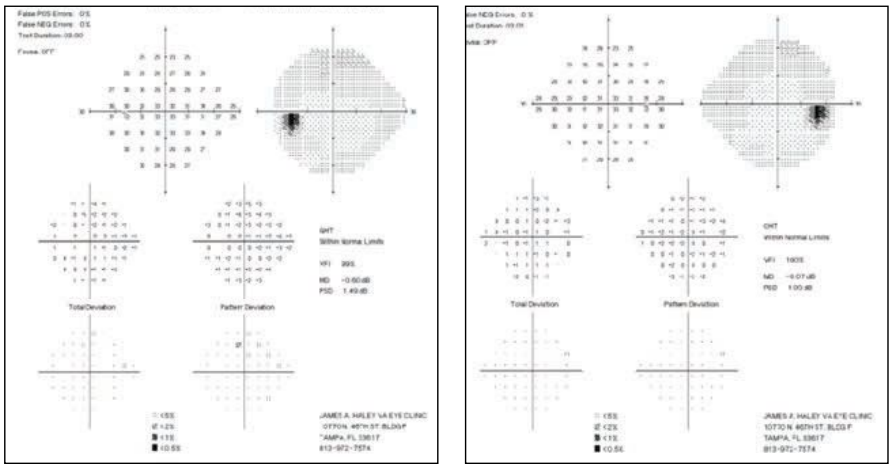


**Fig. 2. His 24-2 visual fields from the year prior show no glaucomatous defects.**

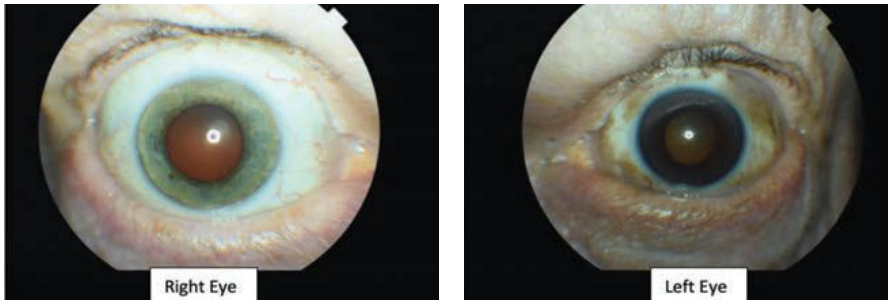



**Fig. 3. The patient's left upper and lower eyelids show visible areas of dermal pigmentation. The left temporal, nasal, superior and inferior bulbar conjunctiva also shows similar areas of pigmentation. The iris color was noted to be blue in the right eye and brown in the left eye (iris heterochromia).**

The slit lamp examination revealed bilateral upper eyelid dermatochalasis. The left upper and lower eyelids showed visible areas of dermal pigmentation. The left temporal, nasal, superior and inferior bulbar conjunctiva also showed similar areas of pigmentation (*Figure 3*). The right eyelid and right bulbar conjunctiva lacked similar pigmentation and appeared normal.

Both corneas were clear. The iris color was noted to be blue in the right eye and brown in the left eye. The anterior chamber appeared clear without cells or flare and the estimate of the anterior chamber angles

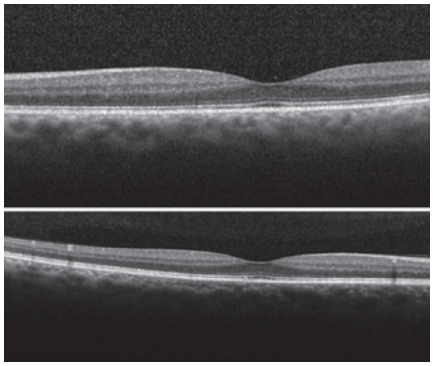


**Fig. 4. The right top and left bottom macular scans show normal foveal contour without evidence of fluids.**

Help your patients with DIABETIC RETINOPATHY (DR), and

# HELP DRIVE PATIENT OUTCOMES

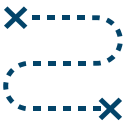
Through early detection, monitoring, and timely referral, you can play a pivotal role in managing your DR patients' vision[1-3]

## IF YOU SEE OR SUSPECT DR:

**Educate your patients** about living with DR and potential treatment options[2,3]

**Refer** DR patients for timely intervention

- According to the AOA, you should refer patients with[2,3]
  - Severe nonproliferative DR (NPDR) within 2 to 4 weeks
  - Proliferative DR (PDR) within 1 week



**Follow up** to ensure they have visited a retina specialist

## INDICATIONS AND IMPORTANT SAFETY INFORMATION

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

## CONTRAINDICATIONS

- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

## WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.

**References: 1.** Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. *Ophthalmology*. 1991;98(5 suppl):823-833. **2.** Care of the Patient With Diabetes Mellitus: Quick Reference Guide. American Optometric Association website. http://bit.ly/2M22OUJ. Accessed August 7, 2019. **3.** Ferrucci S, Yeh B. Diabetic retinopathy by the numbers. *Rev Optom*. June 15, 2016. http://bit.ly/2KNNJ4E. Accessed August 7, 2019.



REGENERON


777 Old Saw Mill River Road, Tarrytown, NY 10591

# EYLEA®
## (aflibercept) Injection
## For Intravitreal Injection

*Brought to you by* ***REGENERON***

Visit **diabeticretinaldisease.com** for additional information and useful patient resources

**Continue to monitor** your patients with DR[2,3]

- The AOA recommends frequent monitoring of patients[2]
  - At least every 6 to 8 months in patients with moderate NPDR and more frequently for patients with greater disease severity[2]

**The more you know** about emerging clinical science about anti-VEGF and other potential therapies for DR, the better you can help inform your patients about how treatment may be able to help

**Refer patients to a retina specialist** who can treat DR[2,3]

## WARNINGS AND PRECAUTIONS (cont'd)

- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

## ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

***Please see Brief Summary of Prescribing Information on the following pages.***

anti-VEGF = anti–vascular endothelial growth factor; AOA = American Optometric Association.

03/2020
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EYLEA®
(aflibercept) Injection
For Intravitreal Injection

**BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.**

**1 INDICATIONS AND USAGE**
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:

**Neovascular (Wet) Age-Related Macular Degeneration (AMD); Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR).**

**4 CONTRAINDICATIONS**

**4.1 Ocular or Periocular Infections**
EYLEA is contraindicated in patients with ocular or periocular infections.

**4.2 Active Intraocular Inflammation**
EYLEA is contraindicated in patients with active intraocular inflammation.

**4.3 Hypersensitivity**
EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

**5 WARNINGS AND PRECAUTIONS**

**5.1 Endophthalmitis and Retinal Detachments.**
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Patient Counseling Information (17)*].

**5.2 Increase in Intraocular Pressure.**
Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

**5.3 Thromboembolic Events.**
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

**6 ADVERSE REACTIONS**
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

**6.1 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 other clinical trials of the same or another drug and may not reflect the rates observed in practice.
A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

**Neovascular (Wet) Age-Related Macular Degeneration (AMD).** The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

**Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies**

| | Baseline to Week 52 | | Baseline to Week 96 | |
|---|---|---|---|---|
| **Adverse Reactions** | **EYLEA (N=1824)** | **Active Control (ranibizumab) (N=595)** | **EYLEA (N=1824)** | **Control (ranibizumab) (N=595)** |
| Conjunctival hemorrhage | 25% | 28% | 27% | 30% |
| Eye pain | 9% | 9% | 10% | 10% |
| Cataract | 7% | 7% | 13% | 10% |
| Vitreous detachment | 6% | 6% | 8% | 8% |
| Vitreous floaters | 6% | 7% | 8% | 10% |
| Intraocular pressure increased | 5% | 7% | 7% | 11% |
| Ocular hyperemia | 4% | 8% | 5% | 10% |
| Corneal epithelium defect | 4% | 5% | 5% | 6% |
| Detachment of the retinal pigment epithelium | 3% | 3% | 5% | 5% |
| Injection site pain | 3% | 3% | 3% | 4% |
| Foreign body sensation in eyes | 3% | 4% | 4% | 4% |
| Lacrimation increased | 3% | 1% | 4% | 2% |
| Vision blurred | 2% | 2% | 4% | 3% |
| Intraocular inflammation | 2% | 3% | 3% | 4% |
| Retinal pigment epithelium tear | 2% | 1% | 2% | 2% |
| Injection site hemorrhage | 1% | 2% | 2% | 2% |
| Eyelid edema | 1% | 2% | 2% | 3% |
| Corneal edema | 1% | 1% | 1% | 1% |
| Retinal detachment | <1% | <1% | 1% | 1% |

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

**Macular Edema Following Retinal Vein Occlusion (RVO).** The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

**Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies**

| | CRVO | | BRVO | |
|---|---|---|---|---|
| **Adverse Reactions** | **EYLEA (N=218)** | **Control (N=142)** | **EYLEA (N=91)** | **Control (N=92)** |
| Eye pain | 13% | 5% | 4% | 5% |
| Conjunctival hemorrhage | 12% | 11% | 20% | 4% |
| Intraocular pressure increased | 8% | 6% | 2% | 0% |
| Corneal epithelium defect | 5% | 4% | 2% | 0% |
| Vitreous floaters | 5% | 1% | 1% | 0% |
| Ocular hyperemia | 5% | 3% | 2% | 2% |
| Foreign body sensation in eyes | 3% | 5% | 3% | 0% |
| Vitreous detachment | 3% | 4% | 2% | 0% |
| Lacrimation increased | 3% | 4% | 3% | 0% |
| Injection site pain | 3% | 1% | 1% | 0% |
| Vision blurred | 1% | <1% | 1% | 1% |
| Intraocular inflammation | 1% | 1% | 0% | 0% |
| Cataract | <1% | 1% | 5% | 0% |
| Eyelid edema | <1% | 1% | 1% | 0% |

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

**Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR).** The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

**Table 3: Most Common Adverse Reactions (≥1%) in DME Studies**

| | Baseline to Week 52 | | Baseline to Week 100 | |
|---|---|---|---|---|
| **Adverse Reactions** | **EYLEA (N=578)** | **Control (N=287)** | **EYLEA (N=578)** | **Control (N=287)** |
| Conjunctival hemorrhage | 28% | 17% | 31% | 21% |
| Eye pain | 9% | 6% | 11% | 9% |
| Cataract | 8% | 9% | 19% | 17% |
| Vitreous floaters | 6% | 3% | 8% | 6% |
| Corneal epithelium defect | 5% | 3% | 7% | 5% |
| Intraocular pressure increased | 5% | 3% | 9% | 5% |
| Ocular hyperemia | 5% | 6% | 5% | 6% |
| Vitreous detachment | 3% | 3% | 8% | 6% |
| Foreign body sensation in eyes | 3% | 3% | 3% | 3% |
| Lacrimation increased | 3% | 2% | 4% | 2% |
| Vision blurred | 2% | 2% | 3% | 4% |
| Intraocular inflammation | 2% | <1% | 3% | 1% |
| Injection site pain | 2% | <1% | 2% | <1% |
| Eyelid edema | <1% | 1% | 2% | 1% |

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

**6.2 Immunogenicity.**
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

**8 USE IN SPECIFIC POPULATIONS.**

**8.1 Pregnancy**
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
*Animal Data*
In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.
Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

**8.2 Lactation**
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

**8.3 Females and Males of Reproductive Potential**
Contraception
Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility
There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

**8.4 Pediatric Use.**
The safety and effectiveness of EYLEA in pediatric patients have not been established.

**8.5 Geriatric Use.**
In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

**17 PATIENT COUNSELING INFORMATION**
In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].
Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:
**Regeneron Pharmaceuticals, Inc.**
777 Old Saw Mill River Road
Tarrytown, NY 10591



Issue Date: 08/2019
Initial U.S. Approval: 2011

Based on the August 2019
EYLEA® (aflibercept) Injection full Prescribing Information.

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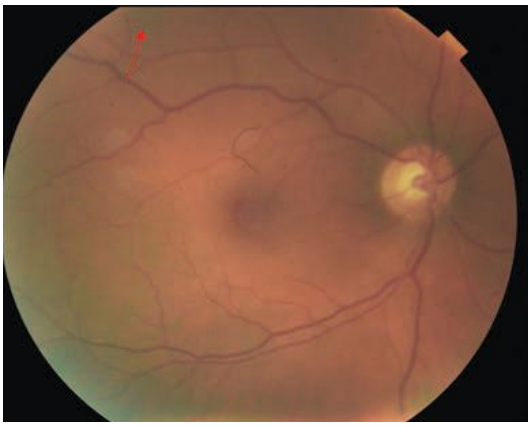

**Fig. 5. The fundus photo of the right eye reveals a 0.75-disc diameter flat choroidal nevus in the superior-temporal arcade region (red arrow). The pigment appearance temporally and inferiorly is an artifact from the fundus camera.**

were open nasally and temporally by Von Herick technique.

The dilated exam by slit lamp with a 90D lens and by binocular indirect ophthalmoscope with a 20D lens revealed trace nuclear cataracts in both eyes with clear vitreous media bilaterally. Fundus assessment revealed large optic nerves with a cup-to-disc ratio of 0.5v/0.5h right eye and 0.7v/0.7h left eye. The neuroretinal rims were healthy and intact. Retinal vessels appeared normal with an arterial-venous ratio of 2/3 noted bilaterally. Both eyes presented with trace macular drusen without evidence of hemorrhages or thickening (*Figure 4*).

The posterior pole of the right eye had a 0.75-disc diameter flat choroidal nevus in the superior-temporal arcade region (*Figure 5*). The left eye had a 5- to 6-disc diameter dome-shaped lesion in the mid-peripheral arcade temporal to the macula (*Figures 6 and 7*). This dome-shaped lesion in the left eye appeared to have orange pigment spots on the surface with an absence of drusen and halo, as well as overlying subretinal fluid (*Figure 8*). When compared with the fundus photos taken nine years prior, there are clear changes in the progression of the lesion.

Both peripheral retinas were flat and intact with no evidence of tears or breaks. Additional testing was done to further investigate the lesion in the left eye.

Using the multicolor image feature of the Heidelberg OCT, the orange pigment spots as well as the irregular borders on the dome-shaped lesion in the left eye became more apparent (*Figures 9 and 10*).[8]

The patient was diagnosed with nevus of ota, even though the condition is exceedingly rare in Caucasian patients. The patient had developed a highly suspicious choroidal mass in the left eye, presumably a primary intraocular melanoma, given the abnormal clinical characteristics. An immediate consult to the retinal oncologist was placed to discuss treatment and management options.

## Follow-up One

The patient returned two days later for an initial evaluation with a retinal oncologist. His visual acuity, entrance testing and ocular health remained stable. B-scan ultrasonography revealed the following measurements: high internal reflectivity, transverse = 6.76mm; longitudinal = 5.92mm; horizontal (thickness) = 1.11mm (*Figure 11*). Retinal oncology confirmed and agreed with the initial findings and plans to follow up with the patient within two months for repeat testing.

## Follow-up Two

The patient returned two months later and denied any changes since the last visit. An updated OCT and B-scan through the lesion in left eye

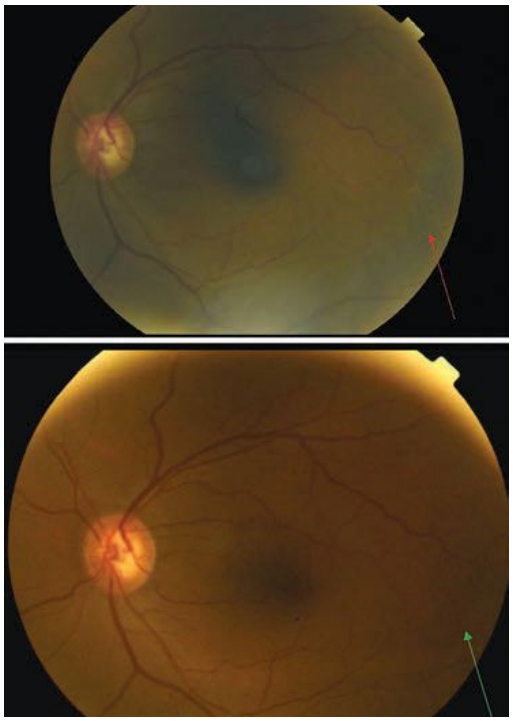

**Fig. 6. Fundus photo of the left eye taken at presentation, top, reveals pigmentary changes temporal to the macula (red arrow). When compared with the fundus photo of the same eye taken nine years earlier, bottom, one can see the progression of pigmentary changes over the years (green arrow).**

revealed stable findings. A thorough discussion of different treatments, including risks and benefits, were explained to the patient. Ultimately, the decision for plaque brachytherapy was recommended, but the patient requested more time before initiating treatment. The patient was scheduled in another two months for repeat testing and further discussion of the treatment options.

## Follow-up Three

The patient returned almost three months later and again denied any changes since the last visit. His visual acuity, entrance testing and ocular health remained stable. Plaque brachytherapy was again discussed with the patient, but he declined the recommended treatment against medical advice. Retinal oncology planned to continue two-month interval follow-ups with the patient to monitor for changes over time.

## Discussion

The differential diagnoses in this case included intraocular melanoma (primary and secondary), choroidal nevus and congenital hypertrophy of the retinal pigment epithelium (CHRPE). Choroidal nevi are common, benign melanocytic lesions that are typically flat and slate gray in color, whereas congenital hypertrophy of the retinal pigment epithelium are typically flat with well-defined scalloped edges and central depigmented lacunae.[9]

In this case, the growth and change in size over time with the presence of thickness, subretinal fluid, irregular borders and orange pigment spots led to the diagnosis of an intraocular choroidal melanoma.

Melanomas of the choroid, ciliary body and iris of the eye are known as uveal melanomas with nearly 80% affecting the choroid.[7,10] The incidence is six cases per one million with about 7,000 new cases diagnosed per year worldwide.[7,11] Primary intraocular melanomas are the most common malignant tumor in adults.[7] Up to 4% of patients with nevus of ota will go on to develop a uveal melanoma in the affected eye.[6]

Women tend to be diagnosed more than men, although research does not support any sex predilection.[7,10] Recent research shows a possible hereditary component with presence of the *BAP1* gene having the poorest survival rate.[11]

## Risk Factors

General risk factors for developing a uveal melanoma include cutaneous freckles/nevi, history of welding, individuals with fair skin color, light iris color and individuals who have a propensity to sunburn.[12] The risk of progression from a choroidal nevus to a malignant melanoma is relatively rare and is estimated to be one in 8,845.[13] Researchers developed a mnemonic to aid the clinician for determining the risk factors of ocular melanoma: "To Find Small Ocular Melanoma Using Helpful Hints Daily" (TFSOM-UHHD).[14] This mnemonic helps clinicians remember: thickness that is more than 2mm, presence of subretinal fluid, symptoms, overlying orange pigment, margins within 3mm of the optic disc, ultrasonographic hollowness, absence of halo and absence of drusen. Studies using TFSOM-UHHD found that patients with no risk factors had a 4% risk factor for growth, and patients with three or

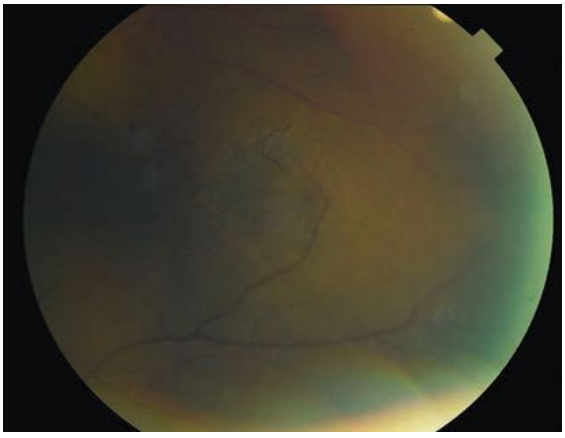

**Fig. 7. A magnified fundus photo shows the dome-shaped lesion in the left eye temporal to the macula measuring 5- to 6-disc diameters. The presence of orange pigment spots, indistinct boarders, absence of drusen and halo can also be appreciated.**

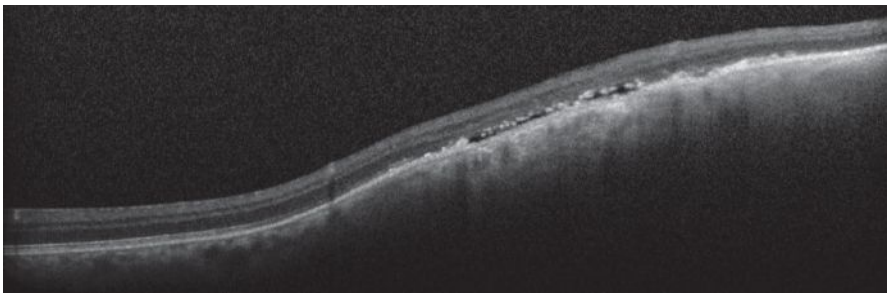

**Fig. 8. The patient's macula OCT shows underlying subretinal fluid with elevation within the lesion.**

more risk factors had a more than 50% chance of tumor growth.[15]

Unfortunately, about 50% of all choroidal melanomas will develop metastatic disease.[16] The size of the tumor is the single most important predictor of metastasis.[17] The five-year mortality rate for a small uveal melanoma (less than 3mm in thickness) was 13%, medium sized (3mm to 10mm) is 23% and large (more than 10mm) is 43%.[18]

The thickness of the presumed choroidal melanoma of our patient is 1.11mm, which is considered a small choroidal melanoma; however, growth over a short period of time increases the risk of metastasis by eight times.[12] Additionally, the presence of subretinal fluid, orange pigment spots, absence of drusen, absence of halo on B-scan and progression from previous examinations significantly increases the patient's risk of metastasis and mortality.

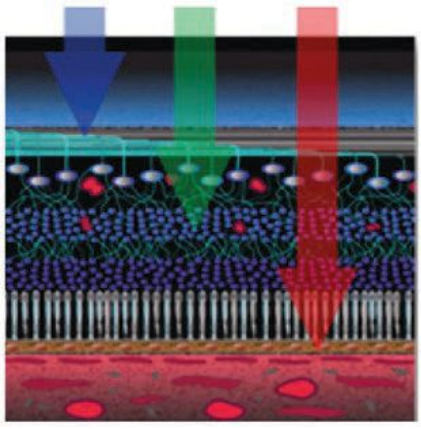

**Fig. 9. Multicolor images help visualize separate layers of the retina by using different wavelengths.**

A systemic workup should be performed prior to any ocular treatment to rule out metastasis.[10] Staging workup to rule out metastases of a choroidal, or uveal, melanoma should include a minimum of complete blood count, liver function tests and diagnostic imaging using at least one of following: computed tomography (CT) of chest and abdomen, whole body positron emission-CT or liver magnetic resonance imaging (MRI) and chest CT.[19]

The patient chose to have his medical care provided outside of our hospital, and any update on a systemic oncology workup is unknown at this time.

## Treatment Options

There are numerous treatments for ocular tumors, including laser, radiation and surgical therapies.[7] For this patient, the ocular oncologist recommended plaque brachytherapy, which is a type of radiation therapy. Plaque brachytherapy is the most common globe-sparing therapy.[20] The procedure generally includes sewing an individualized plaque made of gold with embedded radioactive iodine-125 seeds to the outside of the eye behind the tumor. Gold plaques block the soft radiation emanating from the iodine seeds.[21] The ophthalmic oncologist

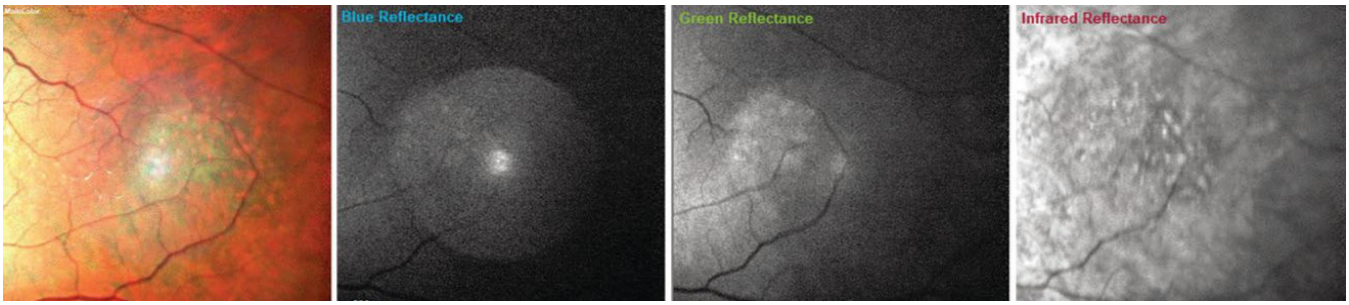


**Fig. 10. With multicolor images, the orange pigment spots, far left, as well as the irregular borders, far left and far right, on the dome-shaped lesion in the left eye become more apparent. Blue wavelengths isolate the inner retinal structures, middle left; green wavelengths isolate the intraretinal structures, middle right; and the infrared wavelengths visualize the outer retinal structures, choroid and retinal pigment epithelium, far right.[8]**

then delivers a highly concentrated dose of radiation to the tumor.[22] The plaque typically remains in place for one to seven days.[23]

Potential radiation side effects are highly variable and depend on many parameters, including tumor size and location, but may also be related to procedure planning and surgical techniques.[24] The most common side effects include strabismus, cataracts, glaucoma, vitreous hemorrhage, retinal detachment, radiation retinopathy, radiation maculopathy and scleral necrosis.[25] Anterior segment pathology has been reported in 4% to 23% of treated patients.[24]

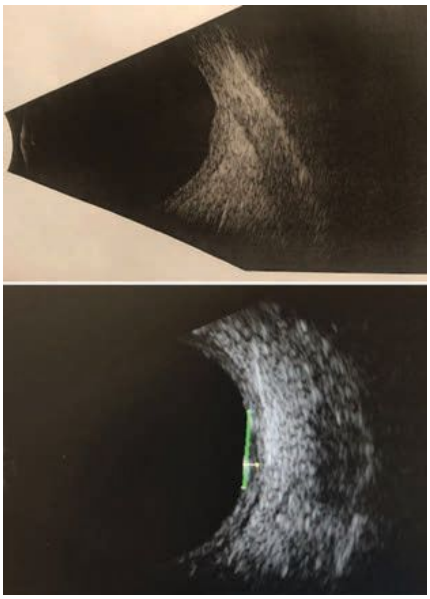

**Fig. 11. B-scan ultrasonography through the suspicious lesion in the left eye without measurements (A) and with measurements (B): High internal reflectivity; transverse = 6.76mm; longitudinal = 5.92mm; horizontal (thickness) = 1.11mm.**

This is an extremely rare case of a Caucasian patient with nevus of ota that progressed into a primary choroidal melanoma. Any ocular melanoma is a serious malignancy with a poor prognosis when metastasis occurs.[26] When evaluating a patient with a suspected choroidal melanoma, documentation of growth and imaging, including fundus photos, OCT and B-scan, are critical.

Management of these patients warrants a prompt consult to a retinal ophthalmologist with clinical expertise in ocular tumors and oncology, and radiation oncology when appropriate.[10,26] ■

*Drs. Krabill and To are optometrists at the James A. Haley Veterans' Hospital Eye Clinic in Tampa, FL.*

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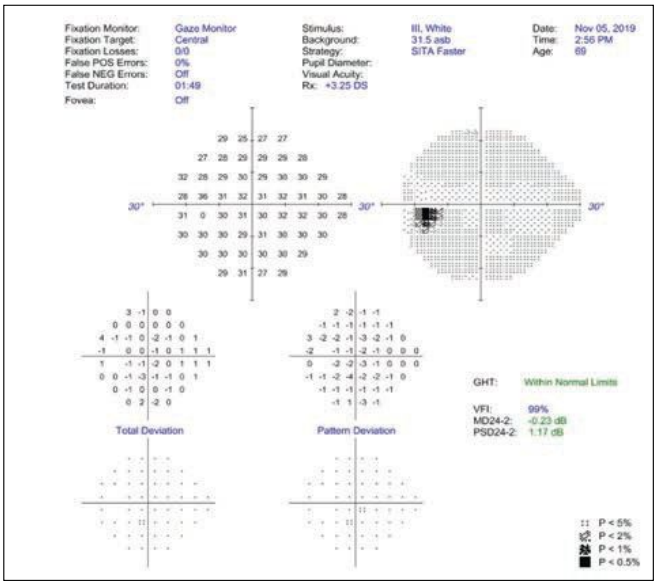
43rd Annual Technology Report

# Glaucoma: How to Build a Better Baseline

With these tips, tricks and tests in mind, you'll be providing more comprehensive patient care in no time. By Jennifer Sanderson, OD, and Andrew Rixon, OD

All optometrists know what we're up against in glaucoma: retinal ganglion cell (RGC) death, retinal nerve fiber layer (RNFL) thinning and neuroretinal rim loss conspire to produce visual field (VF) defects—and our only means of intervention does nothing to turn back the tide. Intraocular pressure (IOP) reduction merely slows down the process; adding insult to injury, the weapons at our disposal to do so are difficult to wield with any precision.

Because glaucoma care is a years- or decades-long endeavor, it's critical for us to have a thorough sense of each patient's starting point so that we can carefully monitor for progression. Historically, the battery of tests in a baseline assessment has included funduscopy, fundus photography, tonometry, gonioscopy and perimetry. With the advent of newer technologies—chief among them optical coherence tomography (OCT)—requirements now include tests that provide more objective and quantitative information about both structure and function. Here, we review the necessary steps of every baseline glaucoma exam.




**False positives and gaze tracking are the best ways to assess VF reliability.**

## Funduscopy

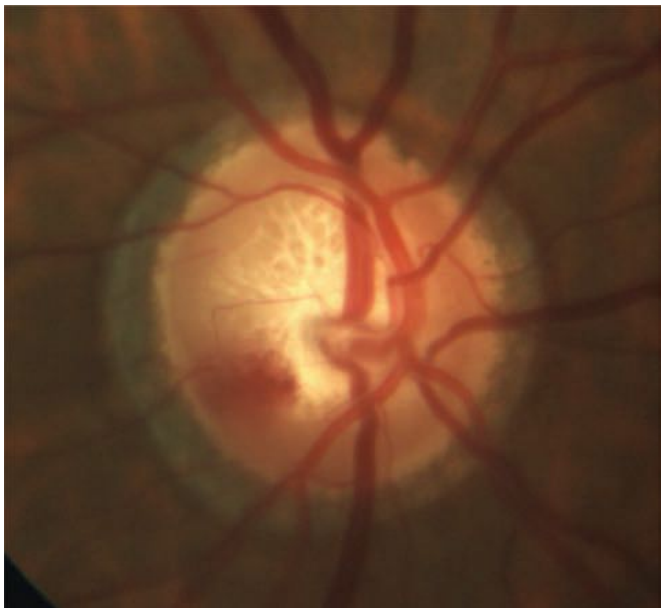
Foundationally, the designation of glaucoma suspect or the diagnosis of glaucomatous optic neuropathy comes from conducting a detailed analysis of the optic nerve head (ONH) by assessing it stereoscopically behind the slit lamp. A systematic approach to evaluating the ONH is compulsory, and attention to the structure's morphological aspects and surrounding tissues outweighs simply judging a cup-to-disc (C/D) ratio.[1]

There are several templates that emphasize comprehensive evaluation of the optic nerve head. Three popular ones are:

- Focusing Ophthalmology on Reframing Glaucoma Evaluation (FORGE)
- Glaucomatous Optic Neuropathy Evaluation (GONE)
- Disc Damage Likelihood Scale (DDLS)

All are reproducible systems that can improve practitioner accuracy during baseline funduscopy. Specifically, FORGE employs five rules by evaluating neuroretinal rim size and shape, RNFL thickness and the scleral ring to determine disc size and monitoring for the presence of parapapillary atrophy and optic disc hemorrhages.[2] GONE is a standardized, internet-based system that underlines the importance of focusing on more than C/D ratios when determining glaucoma likelihood to improve risk assessment.[3] DDLS emphasizes the clinical evaluation of the narrowest width of the rim (called the rim/disc ratio) and incorporates disc size into its assessment of damage.[4]

Other resources include instructional videos that help both trainees and experienced clinicians visualize ONH assessment. A particularly helpful video by Peter Lalle, OD, can be accessed at https://vimeo.com/373647096.



**Quality ONH photography can supplement slit lamp assessment and provides a permanent historical record for future comparison.**

## Fundus Photography

Imaging of the ONH and surrounding RNFL is a valuable tool in capturing a patient's baseline. Photos provide documentation of the nerve at any given point, the ability to scrutinize the qualitative details of the tissue that can be affected by glaucoma without time constraints or limited field-of-view and a historical record to assess change.[5] They complement funduscopy and other imaging techniques to provide a comprehensive overview of each patient's case.

The Ocular Hypertension Treatment Study (OHTS), published in 2002, highlighted the disconnect between clinical examination and photography, finding that 84% of disc hemorrhages that were missed clinically were detected on photographs.[6]

Stereoscopic photography of the disc, consisting of photographic pairs of an optic disc separated slightly so they can be fused binocularly to provide the appearance of a three-dimensional image, is considered most appropriate. Also, red-free photography can enhance the detail of the RNFL and highlight its brightness and texture, facilitating the identification of RNFL defects.[7] While photographs are imperfect and require an astute review, they aren't biased, replaceable or confounded.

## Gonioscopy

Although primary open-angle glaucoma (POAG) is the most common form, numerous others exist under the disease's umbrella, many of which are more aggressive and potentially more vision-threatening.[8,9] Failure to determine the appropriate form of glaucoma can lead to a lack of understanding on the practitioner's part and subsequently increase the risk of mismanagement.

Gonioscopy is, in spite of newer technologies that assess the anterior chamber angle, the only technique available that provides comprehensive, dynamic and qualitative information about the angle *in vivo*.[10] Despite its importance in accurate classification of glaucoma, studies indicate that gonioscopy is not performed, or at least not documented, by the majority of frontline eye care providers, regardless of their degree or practice modality.[11-15] Optometry and ophthalmology have been shown to employ gonioscopy just 50% of the time.[11-15]

Gonioscopy has been considered the standard of care in baseline and chronic glaucoma care in both optometry and ophthalmology for more than 30 years.[16,17] Knowing this, all practitioners should make an effort to incorporate gonioscopy into their glaucoma baseline screening. Many resources are available to help practitioners enhance their skillset and become more proficient with gonioscopy for the best chance of success, most notably those at gonioscopy.org.

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**REFERENCES: 1.** Results of an online survey with patients who completed an evaluation program for Biotrue® ONEday for Astigmatism contact lenses and wore their trial lenses for ≥4 days (n=1001). **2.** Results from a 7-investigator, multi-site study of Biotrue® ONEday for Astigmatism contact lenses on 123 current non-daily disposable toric soft contact lens wearers. Lenses were worn on a daily wear basis for 1 week.



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## Tonometry

One of the most frequently expressed and wholly accurate statements in the world of glaucoma is that IOP is currently the only modifiable risk factor. This renders IOP as arguably the most important factor in glaucoma management. The literature supports the widely held belief that patients with higher IOP levels are, on average, at a higher risk of both developing glaucoma and experiencing disease progression.[18-21]

Minimally, the primary objective of current medical and surgical treatment is to reduce IOP. From baseline IOP values, we're able to establish an initial target IOP and assess treatment efficacy. The difficulty lies in both the physiological characteristics of IOP and the accuracy of the instrumentation used to capture it and the time at which it is captured, as IOP is a dynamic parameter. To further complicate matters, past research has implicated IOP fluctuation as an independent risk factor for disease progression; whereas, more recently, peak IOP has been reported as the most problematic. It is likely that diurnal mean IOP, peak IOP and fluctuation in IOP all influence the disease process, suggesting that a comprehensive understanding of each patient's IOP is essential in our risk assessment.[22,23]

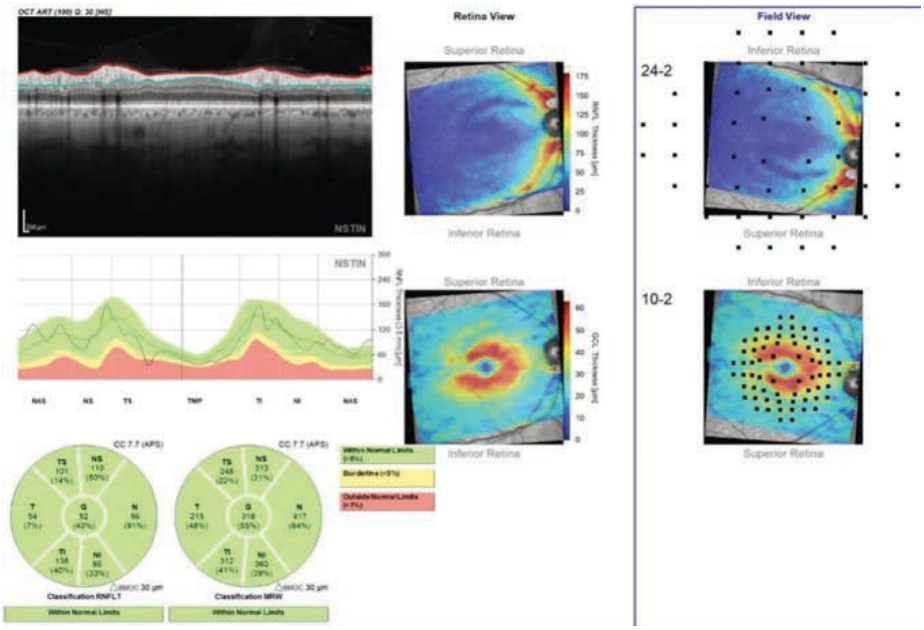
Often, practitioners only take one IOP measurement during office hours once every three to four months. By doing so, they have at least a 75% chance of missing the peak of the diurnal curve.[24] Additionally, 24-hour sleep studies show, on average, a peak in IOP occurring nocturnally as patients shift from an upright awake position to a nocturnal, supine sleep position.[25] In early glaucoma, supine IOP tends to increase around the time that patients wake up, which does not occur in healthy patients.[26] This means that clinicians are missing both nocturnal and waking IOP.

The ability to conveniently capture IOP over 24 hours would be ideal and potentially capture greater peaks and wider fluctuations. Currently, there are two devices that are FDA-approved for at-home IOP monitoring, Triggerfish (Sensimed) and iCare Home (iCare). However, only iCare Home is commercially available in the United States. Unfortunately, a low percentage of ODs are currently using these devices, and most still have insufficient knowledge of their patients' IOP behavior, and treatment decisions are often made based on incomplete data.[27]

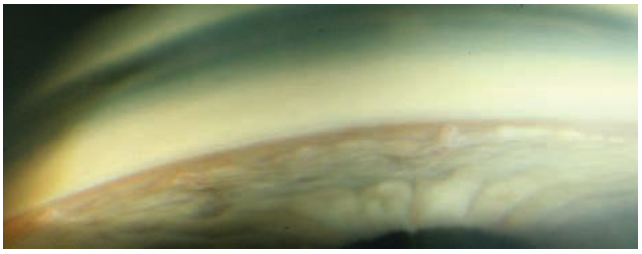
Acquiring IOP over a 24-hour period may not be feasible or realistic in some cases. A practical, but admittedly imperfect, option is to capture four to five IOP readings every two hours in-office over the course of a day from 8am to 4pm.[28] One of these readings should be taken in the supine position, as an in-office supine reading is a good estimate of peak nocturnal IOP.[29] This creates a modified diurnal tension curve (mDTC), which may improve risk assessment compared with a single IOP reading. Studies on the reproducibility of mDTC from day-to-day are, however, conflicting, so one day of mDTC may not reflect true diurnal IOP characteristics.[30]

An additional option is to use the average of the in-office mDTC to estimate peak nocturnal IOP. A recent study found a correlation between average mDTC and peak nocturnal IOP acquired during 24-hour IOP testing. This correlation was more significant than it was with a single IOP reading.[31] Notably, although studies on correlation between 24-hour peak and in-office IOP are conflicting, this finding was stronger in untreated patients, indicating that taking IOP in-office at the very least does have value.[31]

Given that the capture of IOP is integral to the baseline




**This Hood Report of a patient with a superior arcuate RNFL defect provides a comprehensive baseline that integrates RNFL, minimum rim width, GC-IPL and projected 10-2 and 24-2 VFs.**



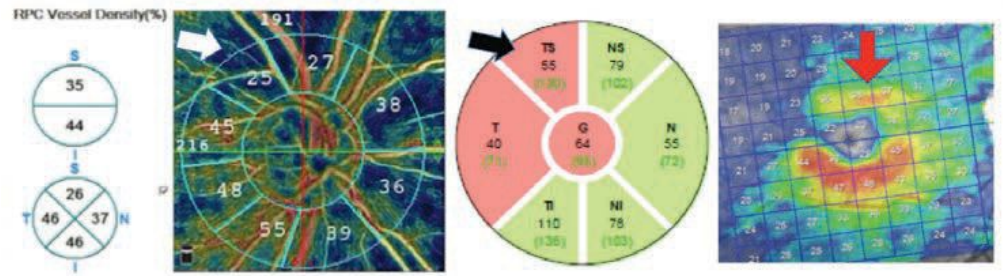
**Gonioscopy shows an unremarkable anterior chamber angle.**

process, the technology we use to measure IOP is equally important and must be as accurate as possible. Although multiple forms of tonometry exist, including applanation, indentation and rebound, Goldmann applanation tonometry (GAT) remains the standard of care.[32,33] This was recently reinforced in a survey showing that 89% of responding optometrists and 82% of responding glaucoma specialists consider GAT to be the most accurate form of tonometry.[34] Although GAT is useful for monitoring IOP changes, it is not an accurate representation of the pressure within the eye; rather, it reflects the pressure difference across the cornea, known as transcorneal pressure difference, and inherently does so with multiple sources of error, most significantly error created by the biomechanics of the cornea.[35,36]

True IOP is measured intracamerally using a pressure transducer. Studies comparing GAT to intracameral applications consistently show that GAT underestimates true IOP in both living and cadaver eyes.[37] Dynamic contour tonometry (DCT), the Corvis ST (Oculus) and, most recently, a modified Goldmann prism with a correcting applanation tonometry surface (CATS) can more closely approximate true IOP.[38,39] The CATS device is arguably the most convenient of the three, as it is placed in a standard Goldmann tonometry mount, simply replacing the older-generation prism. DCT requires a switch in tonometry mounts and the Corvis ST is a stand-alone instrument. All three are promising but have not influenced a paradigm shift away from GAT.

## Pachymetry

Central corneal thickness (CCT) is an independent risk factor for the conversion from ocular hypertension (OHTN) to POAG.[20] Further study also shows that CCT is inversely related to both the progression and severity of glaucoma.[40] The OHTS divided participants by CCT into thick, intermediate and thin subgroups.[20] The thin subgroup (average 530.8µm) was more than three times more likely to develop




**This open-angle glaucoma patient has substantial reduction in vessel density (white arrow), which correlates with a superior temporal RNFL (black arrow) and GC-IPL thinning (red arrow). Note that hotter colors indicate greater vessel density than cooler colors.**

glaucoma over five years than the thick subgroup (average 613.5µm).[20] When OHTS data was pooled with data from the European Glaucoma Prevention Study (EGPS), every 40µm decrease in CCT from the thickest subgroup was associated with at least a twofold risk of developing glaucoma over five years.[41]

Pachymetry has long been considered a routine part of baseline testing in glaucoma suspects and patients with OHTN.[40] Many technologies measure pachymetry (i.e., OCT, optical biometry, confocal microscopy, corneal topography and specular microscopy), but the standard for evaluating risk in glaucoma patients is ultrasound pachymetry, which was the technique used in OHTS, EGPS and the Early Manifest Glaucoma Treatment Study.[40,42] Studies show that these technologies are not directly interchangeable, so clinicians should rely on ultrasound pachymetry for the sake of consistency and accuracy.[40]

Recent studies show that the relationship between the cornea and glaucoma involves more than just corneal thickness, which is merely a dimension, not a biomechanical property, and is therefore unlikely to indicate how the eye adapts to the forces to which it is exposed.[40,43] Corneal hysteresis (CH), however, reflects the cornea's ability to absorb and release energy created by applanation forces during measurement. Research suggests that CH could actually be a surrogate measure for the globe's ability to resist deformation from various confounding pressures.[44-46]

CH is now known to have a more significant association with both the presence and rate of glaucoma progression than previously thought.[47] Essentially, high CH may confer a protective effect, whereas low CH increases the eye's susceptibility to glaucomatous damage.[43] To highlight this point, a study comparing patients with glaucoma with their non-glaucoma counterparts reported an average CH of 8.95±1.27mm Hg in the disease group and an average CH of 10.97±1.59mm Hg in the control group.[48]

CH is directly influenced by CCT and inversely influenced by IOP.[49] Thus, both relationships should be considered when interpreting CH. Ultimately, assessing CCT and CH in combination, rather than isolation, improves the sensitivity of diagnosis.[49]

## OCT

The evolution of OCT has given us the ability to consistently gauge the structure of neural tissue damaged by glaucoma. Early in the disease state, OCT is often favored over visual fields, and multiple studies support its superiority over standard automated perimetry (SAP).[50] OCT is, in fact, able to detect glaucomatous change on RNFL scans up to eight years prior to detection by VFs.[51]

With reference to glaucoma, OCT measures the ganglion cell–inner plexiform layer (GC-IPL), which houses RGC bodies and their dendrites, the RNFL filled with ganglion cell axons before they enter the optic nerve and neuroretinal rim.[52] Tissue thickness indicates glaucomatous damage, with the assumption that thinner tissue equates to a worse disease state and thicker tissue is indicative of good tissue health. The various commercially available OCT devices each employ their own capture algorithms, scanning protocols and reference databases.[53] However, all capture tissue thickness and display it as normal, borderline or abnormal.

**Testing Indicated For Glaucoma Suspects and Early-stage Patients**

| Test | Initial Visit | One-month Visit | Six-month Visit | Annual Visit |
|---|---|---|---|---|
| Funduscopy | x | | suspect: no, patient: yes | x |
| Fundus Photography* | x | | | x |
| Gonioscopy* | x | | | x |
| Tonometry | x | x | x | x |
| Pachymetry* | x | | | |
| OCT* | x | | x | x |
| Perimetry* | x | x | x | x |

*Practitioner must decide on a case-by-case basis whether to conduct at initial or one-month visit.

Maximal scan quality and reflectivity is critical in diagnostic and management decisions. The World Glaucoma Association (WGA) recommends that the managing physician vet each image prior to proceeding any further. They must be aware of possible patient, operator and machine errors.[54,55]

Clinicians should capture multiple high quality OCT images of the GC-IPL, RNFL and neuroretinal rim at regular intervals following baseline screening to confirm accuracy and gauge progression.[56] Although studies found that, in isolation, the sensitivities of macular, RNFL and optic disc parameters are comparable in their diagnostic abilities, evaluating all tissues affected by glaucoma is recommended at baseline and maximizes outcomes.[57] The combined analysis of the GC-IPL and circumpapillary RNFL performs better diagnostically than each individual parameter in early glaucoma cases.[58]

Available OCT analyses include the Cirrus PanoMap Analysis (Zeiss), which combines RNFL, GC-IPL and ONH data, and the Hood Report (Heidelberg and Topcon), which integrates RNFL, RGC and rim width data and relates it to function by overlying test points from both 24-2 and 10-2 VFs. In classifying an eye as glaucomatous, the Hood Report can perform as good as or better than glaucoma specialists with fundus photos, 24-2 VFs and RNFL imaging on OCT, reinforcing the necessity of capturing all tissues and streamlining their analysis at baseline.[59]

## OCT Angiography (OCT-A)

Impaired retinal blood flow has been implicated as a factor contributing to glaucoma. Until recently, there was no noninvasive technology available to explore the microcirculation of the ONH *in vivo*.[60] OCT-A employs motion contrast (the comparison of sequential B-scans of the same static retinal or ONH area) and uses differences in the intensities of the cross sections as a surrogate for red blood cell movement.

Studies evaluating the optic nerve head and peripapillary and macular regions using OCT-A show altered vasculatures and found that OCT-A is able to discriminate between patients with glaucoma and those without it.[60,61] Additionally, OCT-A has adequate reproducibility and reliability, meaning that it can be useful in the longitudinal care of glaucoma.[60,61] Although it is not presently considered part of the standard of care for glaucoma, OCT-A has potential and should be considered, if available, when screening suspects.

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## INDICATIONS AND USAGE

CEQUA™ (cyclosporine ophthalmic solution) 0.09% is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye).

## IMPORTANT SAFETY INFORMATION

### WARNINGS AND PRECAUTIONS

**Potential for Eye Injury and Contamination:** To avoid the potential for eye injury and contamination, advise patients not to touch the vial tip to the eye or other surfaces.

**Use with Contact Lenses:** CEQUA should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution.

## ADVERSE REACTIONS

The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection.

**Please see brief summary of Full Prescribing Information on the adjacent page.**

**References: 1.** CEQUA [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2018. **2.** Data on file. Cranbury, NJ: Sun Pharmaceutical Industries, Inc. **3.** US Patent 9,937,225 B2. **4.** Tauber J, Schechter BA, Bacharach J, et al. A Phase II/III, randomized, double-masked, vehicle-controlled, dose-ranging study of the safety and efficacy of OTX-101 in the treatment of dry eye disease. *Clin Ophthalmol*. 2018;12:1921-1929.


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## CONTRAINDICATIONS

None.

## WARNINGS AND PRECAUTIONS

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To avoid the potential for eye injury and contamination, advise patients not to touch the vial tip to the eye or other surfaces.

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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.

In clinical trials, 769 patients received at least 1 dose of cyclosporine ophthalmic solution. The majority of the treated patients were female (83%).

The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection.

## USE IN SPECIFIC POPULATIONS

### Pregnancy

Risk Summary

There are no adequate and well-controlled studies of CEQUA administration in pregnant women to inform a drug-associated risk. Oral administration of cyclosporine to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses.

Data

*Animal Data*

Oral administration of cyclosporine oral solution (USP) to pregnant rats or rabbits was teratogenic at maternally toxic doses of 30 mg/kg/day in rats and 100 mg/kg/day in rabbits, as indicated by increased pre- and postnatal mortality, reduced fetal weight, and skeletal retardations. These doses (normalized to body weight) were approximately 3200 and 21,000 times higher than the maximum recommended human ophthalmic dose (MRHOD) of 1.5 mcg/kg/day, respectively. No adverse embryofetal effects were observed in rats or rabbits receiving cyclosporine during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively (approximately 1800 and 6400 times higher than the MRHOD, respectively). An oral dose of 45 mg/kg/day cyclosporine (approximately 4800 times higher than MRHOD) administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. No adverse effects in dams or offspring were observed at oral doses up to 15 mg/kg/day (approximately 1600 times greater than the MRHOD).

### Lactation

Risk Summary

Cyclosporine blood concentrations are low following topical ocular administration of CEQUA. There is no information regarding the presence of cyclosporine in human milk following topical administration or on the effects of CEQUA on breastfed infants and milk production. Administration of oral cyclosporine to rats during lactation did not produce adverse effects in offspring at clinically relevant doses. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CEQUA and any potential adverse effects on the breastfed child from cyclosporine.

### Pediatric Use

The safety and efficacy of CEQUA ophthalmic solution have not been established in pediatric patients below the age of 18.

### Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

## PATIENT COUNSELING INFORMATION

### Handling the Vial

Advise patients to not allow the tip of the vial to touch the eye or any surface, as this may contaminate the solution. Advise patients also not to touch the vial tip to their eye to avoid the potential for injury to the eye.

### Use with Contact Lenses

CEQUA should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. Advise patients that if contact lenses are worn, they should be removed prior to the administration of the solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution.

### Administration

Advise patients that the solution from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

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## Perimetry

Ultimately, the objective of glaucoma care is to prevent patients from losing functional vision, which is why perimetry remains an essential part of baseline exam and longitudinal management.[62] Perimetry quantitatively assesses the function of RGCs at various retinal locations that are susceptible to damage. VF defects should therefore manifest as RGC function diminishes. Diagnostically, perimetry is used to find patterns of loss consistent with glaucoma, while concurrently ruling out non-glaucomatous patterns. The alignment of clinical observation with glaucomatous data on perimetry helps to ensure diagnostic accuracy.

SAP is the most commonly used method of assessing the VF.[63] Multiple instruments offer SAP and all aim to capture as much RGC function as possible, while minimizing testing error. In deciding which testing algorithm to run, keep in mind that both structural and functional damage to the macular region occur across the spectrum of glaucoma, including early disease, as approximately 50% of RGCs are concentrated within the parafoveal area.[64-66] It is generally accepted that a traditional 24-2 strategy (which uses a grid of 54 loci separated by 6° across the central 24° of the retina) may miss early disease that is detectable with a denser sampling through the use of a 10-2 strategy (which uses a grid of 68 loci separated by 2° across the central 10° of the retina).[67-69]

Given the potential lack of coverage with traditional testing, there is confusion around the best baseline approach to perimetry. Some suggest performing a 10-2 for any patient who already had a 24-2. As the clinic flow logistics of this suggestion are not ideal, researchers suggest commercial integration of alternative test patterns to better and more efficiently test the macular and perimacular regions.[66,70] The Octopus G-Program (Haag-Streit) can be modified to accomplish this, and Zeiss recently developed the SITA Faster 24-2c test pattern.[66] A recent study comparing the SITA Fast 24-2 and the 24-2c grids in glaucoma suspects and patients showed the 24-2c identified more clusters of central defects.[71] Denser testing of the macular region with perimetry should improve alignment with OCT testing of the GC-IPL. The authors did find improved structure-function alignment with the 24-2c but noted that half of the VF test locations did not correspond with commonly used OCT macular thickness scans.[71]

Despite its importance as the only direct method of measuring function, perimetry is often not performed as frequently as recommended by current guidelines for newly diagnosed patients or suspects.[72] A team published practical recommendations for measuring rates of VF change in glaucoma patients based on empirical data and statistical modeling. They concluded that three exams per year are required to identify an overall change in mean deviation of 4dB over two years in a patient with average VF variability.[73]

The WGA recommends conducting at least two reliable baseline VFs in the first six months of management and at least two additional fields over the next 18 months.[56] More frequent VFs may be necessary in advanced disease to detect fast progressors (-2dB per year or faster). Accordingly, the WGA suggests taking six reliable VFs in the first two years in patients at risk for visual disability.[56]

Reliability is key in baseline VF capture. Developers of the Humphrey Field Analyzer (Zeiss) noted that fixation loss is more indicative of technician inattention than patient gaze instability and that they prefer to turn off fixation loss catch trials in favor of gaze tracking. They have also eliminated false negative catch trials in the 24-2c, as studies show that false negatives are more indicative of glaucomatous damage than poor reliability.[74,75] Gaze tracking parameters are closely related to reproducibility results and are likely—in combination with false positives—the most useful way to assess reliability.[76-78] A recent study found gaze tracking to be predictive of field variability, while traditional reliability indices were not.[77]

## Electrodiagnostics

Electroretinography, in particular the pattern-reversal electroretinogram and the full-field electroretinogram, provides an additional minimally invasive, objective tool for assessing baseline RGC function. These techniques glean functional data through full-field, focal or multifocal visual stimulation of the macula. They are sensitive to detecting RGC damage in glaucoma suspects and OHTN patients prior to detection by standard perimetry and have a significant correlation with optic disc morphology. Electroretinography may be able to detect RGC dysfunction prior to their death, making it possible to potentially reverse the disease process through early medical or surgical intervention.[79-81]

A recent systematic review of the literature on electrophysiology in glaucoma concluded that no current definitive indications for these tests have been established at baseline or follow-up.[82] Better protocols and correspondence with conventional glaucoma testing are warranted prior to routine use.[82]

Glaucoma is an insidious disease that requires accurate diagnosis and vigilant monitoring to avoid loss of function and reduced quality of life for patients. Combining the proper tools for testing and interpretation with astute clinical assessment should give practitioners the foundation they need to build a stepwise approach to care. ■

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43rd Annual Technology Report

# Is OCT-A Right For My Practice?

This new imaging device may be a part of your diagnostic toolkit in the near future. Here's why. By Julie Rodman, OD, MSc

Optical coherence tomography angiography (OCT-A) is a noninvasive, dyeless imaging modality that has emerged as an important tool in eye care. It provides three-dimensional, volumetric images of the retinal and choroidal vasculature, which are ideal for evaluating any number of ocular conditions such as diabetic retinopathy (DR), age-related macular degeneration (AMD) and glaucoma.

This imaging technology has widespread clinical utility as a noninvasive alternative to traditional fluorescein angiography (FA) for viewing retinal and choroidal microvasculature in detail.

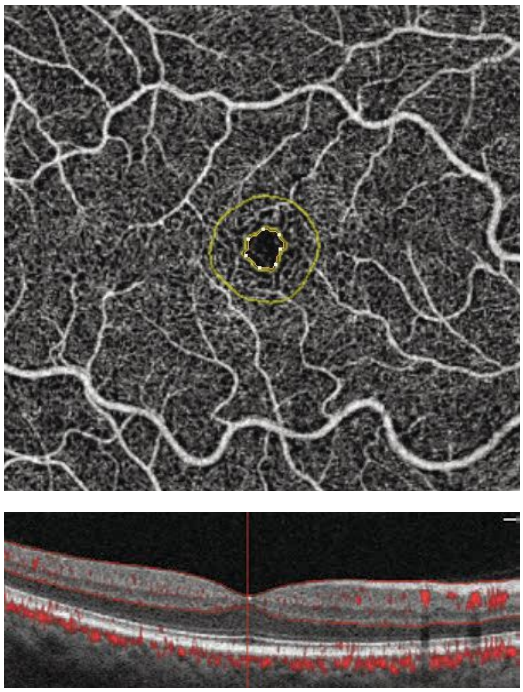
OCT-A was developed as a special application of standard spectral-domain OCT (SD-OCT) B-scans. By analyzing both standard OCT and OCT-A scans, clinicians have a comprehensive look at the retina, optic nerve and choroid, with information about the structure, vascular perfusion and the dynamic changes in blood flow.

## Scan Anatomy

Each OCT-A angiogram is based on predefined segmentation slabs that provide precise visualization of the vascular supply to the specified area. Automated slabs or preset maps vary by device but often include: vitreoretinal interface map, superficial capillary plexus (SCP) map, deep capillary plexus (DCP) map, outer retinal or avascular map, choriocapillaris map and choroidal map.

## OCT-A in Practice

As with any new device, OCT-A's adoption in clinical practice has been slow. Many clinicians remain unsure of its utility within their practice, as it depends largely on each practice's existing patient base and future plans. For instance, if the patient base is generally young and healthy, OCT-A is not essential.

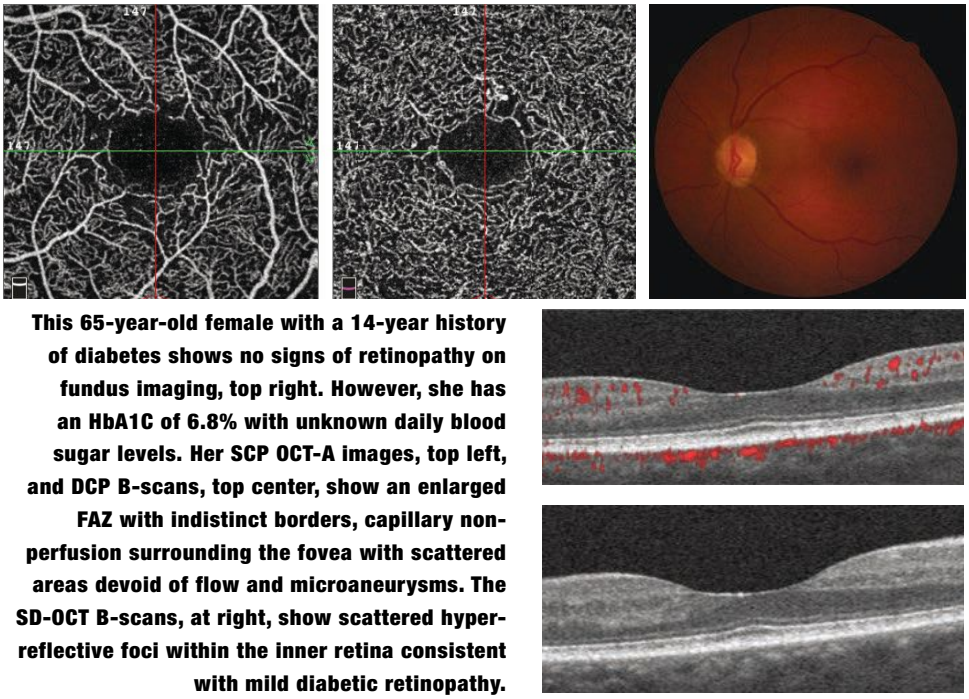


**These are the FAZ metrics in a normal patient. Software analytics allow for an objective means of quantifying the FAZ and the surrounding area. The FAZ's perimeter is outlined in yellow. Simultaneous visualization of the OCT angiogram alongside the structural B-scan provides optimal image interpretation.**

OCT-A also has a few limitations that make some doctors wary. For example, because the technology uses a motion decorrelation algorithm, any motion—including blinks and saccades—may result in image artifacts. This can make image interpretation challenging for novice users. In addition, OCT-A does not image leakage, which limits its usefulness in some respects.

OCT-A is also more expensive than a standard SD-OCT device. However, if a practice has a patient base that includes a steady flow of people over the age of 50 at risk for AMD, glaucoma and diabetes, then the practice could justify the upgrade to OCT-A. For practices looking to focus on posterior segment disease management, OCT-A could be a true game-changer for both the practice and patients.

Clinicians who answer "Yes" to any of these three questions could benefit from an OCT-A device in their practice:



**This 65-year-old female with a 14-year history of diabetes shows no signs of retinopathy on fundus imaging, top right. However, she has an HbA1C of 6.8% with unknown daily blood sugar levels. Her SCP OCT-A images, top left, and DCP B-scans, top center, show an enlarged FAZ with indistinct borders, capillary non-perfusion surrounding the fovea with scattered areas devoid of flow and microaneurysms. The SD-OCT B-scans, at right, show scattered hyper-reflective foci within the inner retina consistent with mild diabetic retinopathy.**

**1** ***Do you see a lot of patients with diabetes?*** This condition has become a worldwide epidemic and the leading cause of vision loss among working-age adults in the developed world.[1] Optometrists are at the forefront of providing eye care for these patients. Despite better medication and therapeutic options, diabetic retinopathy is a mounting healthcare concern.

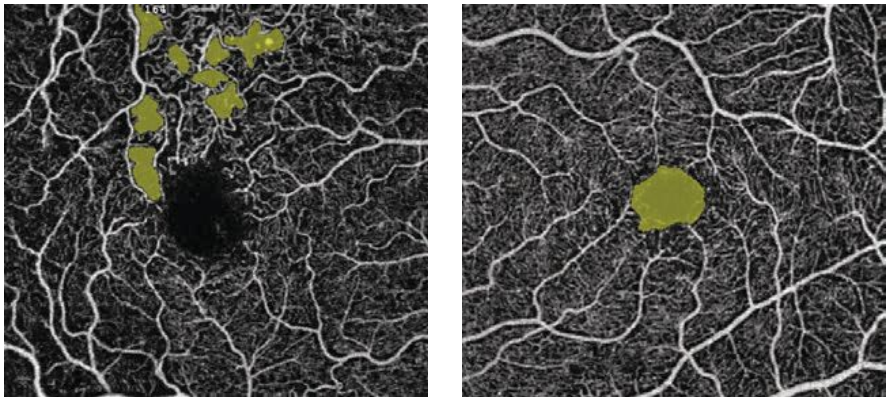
Before the advent of OCT-A, patients with mild or no diabetic retinopathy were considered well controlled and seen annually. Research now shows that OCT-A can provide early, pre-clinical identification of microvascular abnormalities such as microaneurysms, enlarged foveal avascular zone (FAZ), capillary non-perfusion, vascular remodeling, capillary tortuosity and dilatation and impairment of choriocapillaris flow.[2-4] In addition, OCT-A parameters may also assist in the detection of diabetic macular ischemia.

Familiarity with these morphological changes common in diabetes can assist in early identification of disease. For example, the FAZ is defined as a round, "capillary-free" zone within the central macula with a homogenous, dense capillary network.[5] Its size, contour and border characteristics on OCT-A have been studied extensively with regards to diabetic retinopathy, and research shows FAZ perfusion and architecture is directly correlated with a patient's visual function.[2]

In diabetic retinopathy, the borders of the FAZ may become irregular and patchy due to the loss of integral vascular capillary networks. This results in an overall enlargement of the area of the FAZ within the SCP and DCP, which may be present even before ophthalmoscopic evidence of retinopathy develops.[4,6]

Research suggests assessing the size and characteristics of the FAZ can provide insight into both the disease severity and visual prognosis.[7,8] FAZ assessment can also help to determine efficacy of various treatment modalities.[9-11] Similarly, fewer microaneurysms within the SCP and DCP on OCT-A correlates with a better outcome for patients with diabetic macular edema treated with anti-vascular endothelial growth factor injections.[12]

Another quantitative measure of particular use in assessing diabetic retinopathy is vessel density. Vessel density is defined as the proportion of blood vessel area over the total measured area.[13] Patients with diabetic retinopathy will typically have less vessel density in their SCP and DCP, indicating a state of altered vascular perfusion. Even in patients with diabetes not manifesting retinopathy, the vessel density within the DCP is reduced compared with normal eyes, suggesting that the initial source of parafoveal capillary



**The "no-flow" tool measurement for a patient with diabetes allows for quantification of flow voids in pre-selected areas. The left panel shows scattered areas of non-perfusion highlighted in yellow; the right panel highlights the FAZ.**

non-perfusion may be at the level of the deep plexus.[14-16]

Getting a close look at these microvascular changes before they are visible ophthalmoscopically can have a huge impact on how clinicians manage patients with diabetes—it may even alter the course of the disease and help to eradicate sight-threatening sequelae.[17] Quantifying the FAZ and non-perfused areas using OCT-A can help clinicians stage non-proliferative DR and can be an accurate means of predicting possible disease progression.[18-20]

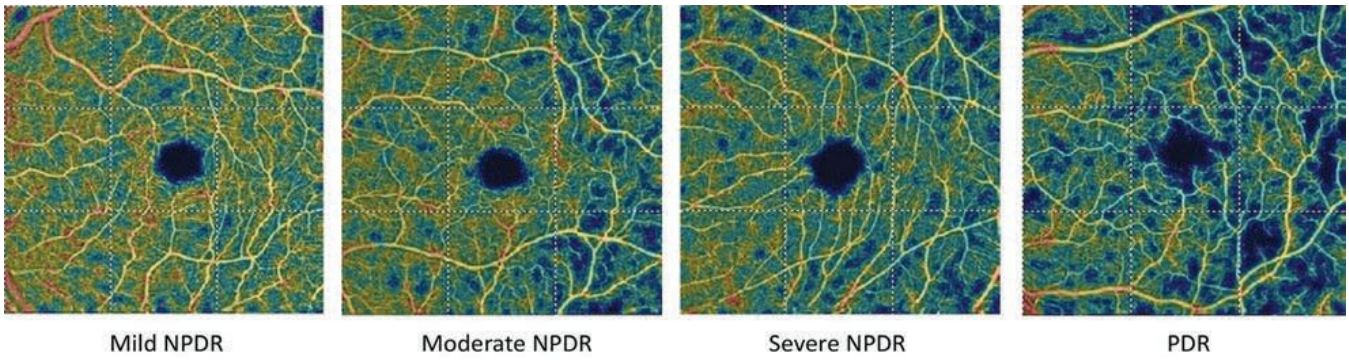
Visualizing early signs of disease will ultimately allow for more timely communication with the patient's internist and optimize the overall outcome. Clinicians can repeat OCT-A imaging after modulation of glycemic control, and reassess perfusion values to help determine efficacy of treatment.

**2 *Do you want to avoid unnecessary AMD referrals?*** Clinicians often encounter SD-OCT B-scans on which it's difficult to discern evidence of neovascular activity. Perhaps a patient has a history of dry AMD but their fundus exam looks suspicious for conversion. The SD-OCT B-scans show soft, confluent drusen, extensive pigment epithelial detachments of variable hyper-reflectivity and serous fluid that may be suggestive of underlying vascular activity; yet, the clinical picture leaves a measure of doubt. Without OCT-A, clinicians must obtain FA or indocyanine green angiography (ICGA), which usually involves consulting with a retina specialist.

Historically, AMD has been classified as non-exudative, or dry, and exudative, or wet. Exudative AMD is characterized by the presence of fluid, lipid exudate or blood.[21] The membrane extends from the choriocapillaris anteriorly towards the retinal pigment epithelium (RPE); classic membranes course over the RPE while occult membranes reside under the RPE.

FA and ICGA capture the source of leakage through dye visualization of the anomalous vasculature.[21] Occult membranes are best visualized with ICGA, and patients should be referred to a retinal specialist that uses this technology. Proper identification and classification of the lesion can streamline the referral process and guide the management.

While beneficial diagnostic tools, these technologies involve the use of intravenous dyes that can cause adverse effects for certain patients and are even contraindicated in high-risk populations.[22] Reported side effects range from mild, including nausea, vomiting, itching/hives and fainting, to more severe concerns such as heart attack, bronchospasm, laryngeal edema and anaphylaxis. Dye-based procedures should be avoided in pregnant women and patients with a history of renal failure or allergy to dye/iodine or shellfish.[22] In addition, the retinal consult can be costly for




**These OCT-A vessel density analysis images depict the decreased blood flow with increasing diabetic retinopathy severity.**

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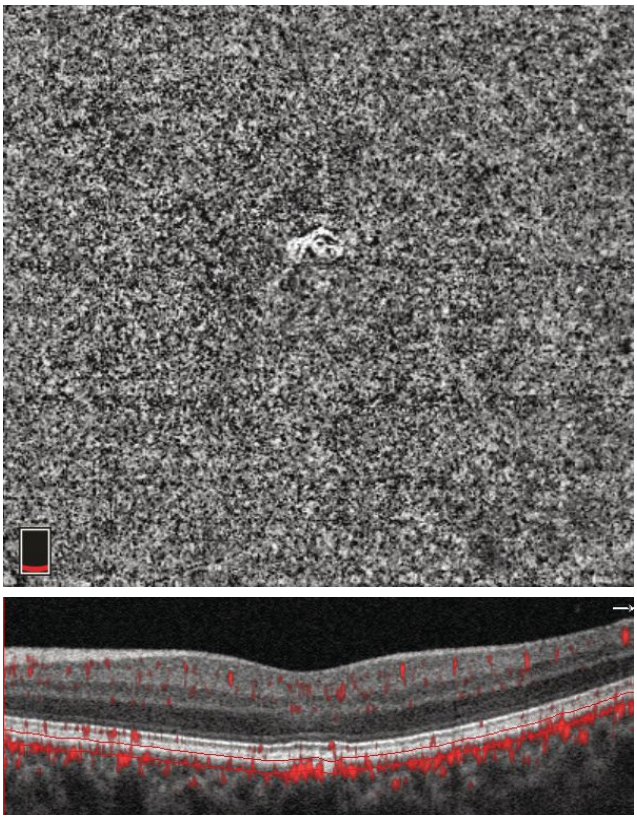


**This 63-year-old African American male is a glaucoma suspect with no visible abnormality noted in the macula on fundus examination. However, the choriocapillaris slab and the B-scan with segmentation lines set at the choriocapillaris depict a non-exudative occult choroidal neovascular membrane. In this case, OCT-A identified a naïve macular lesion that was not visible clinically, allowing for timely referral and comanagement.**

patients and requires additional time out of work.

In cases of suspected wet AMD or other conditions that cause choroidal neovascularization (CNV), OCT-A now allows for visualization of potential abnormal blood vessels in-office—reserving referrals for necessary cases.

OCT-A can provide detailed visualization of CNV secondary to AMD and other maculopathies, and the automated angiogram segmentation maps of the outer retina and choriocapillaris allow for precise identification of lesion location and characteristics. Such evaluation of CNV structure can assist in the classification and differentiation of the lesion and can drive management and referral decisions.

In 2015, researchers introduced a novel form of CNV called non-exudative, occult choroidal neovascular membranes. As the term implies, these membranes manifest with anomalous flow within the choriocapillaris angiogram but no signs of exudation on SD-OCT or leakage on FA and ICGA.[23] Data suggests the presence of these lesions increases the risk of future exudation compared with unaffected eyes.[24] Now, more frequent follow-up with OCT and OCT-A is recommended in this subset of patients.[24]

In AMD, research shows OCT-A metrics provide qualitative and quantitative analysis of choroidal neovascular membranes. Measurements of CNV flow area (area of abnormal vascular activity within the lesion) and flow index can be used to assess treatment efficacy, including response or relapse.[25]

## 3 *Do you manage glaucoma?*

There is growing evidence suggesting that vascular dysfunction plays a role in the pathogenesis of glaucoma. By monitoring blood flow within the retina, OCT-A provides a way to assess the health of the ganglion cells that are affected in glaucoma. Vessel density measurements provide a means of measuring vascular function and are highly repeatable and reproducible.

Vessel density assessment of the peripapillary retina and macular region are strong diagnostic indicators and may be negatively impacted in glaucoma.[26,27] Glaucoma affects the superficial vascular complex, comprised of the nerve fiber layer (NFL) plexus and the ganglion cell layer (GCL) plexus. Evaluation of the vessel density within the peripapillary NFL and macular GCL is a new and informative way of identifying focal, glaucomatous defects.

Studies show that OCT-A can detect early, pre-perimetric glaucoma better than structural OCT.[28,29] In addition, OCT-A

## When to Consider Upgrading Your OCT

*By Jane Cole, Contributing Editor*

Since OCT came on the market nearly two decades ago, this ever-evolving technology has become a staple for diagnosing and monitoring myriad ocular conditions, from detecting retinal nerve fiber layer (RNFL) loss in glaucoma patients to tracking corneal epithelial thickness following refractive surgery.

As new OCT applications hit the market, optometrists who already have an OCT may wonder when to upgrade and whether switching platforms is worth the headaches.

"You need to consider upgrading your OCT device when it is no longer able to measure with the precision and resolution required to diagnose and treat conditions that are commonly managed by doctors of optometry," says Jeannette Wong-Powell, OD, clinical assistant professor at the Rosenberg School of Optometry in San Antonio.

Ten years ago, clinicians marveled at OCT's ability to measure retinal thickness and used it extensively to detect diabetic macular edema and RNFL thinning in glaucomatous eyes, she adds. But the OCTs of today are far more advanced in their capabilities. These five considerations can help you make the right decision when pondering whether or not to upgrade your OCT:

***1. Get the facts.*** It's important to research and check peer-reviewed studies that offer evidence that prove these new technologies offer superior diagnostic and progression analysis, says Lee Vien, an optometrist at the Veterans Affairs Palo Alto Healthcare System.

New technology is constantly being developed, but as a clinician, you have to consider if these new platforms are clinically applicable and supported by the literature, he says.

***2. Weigh the cost.*** A doctor's biggest consideration is likely the cost association with upgrading to a newer model OCT, Dr. Vien says. With this in mind, you must consider an instrument that is advanced in hardware but also supports software upgrades in the future, he adds.

"Many OCT instruments release new software upgrades that allow new scans and analysis without the need for new hardware," Dr. Vien says. "You want an instrument that will be supported by the manufacturer for many years.

In addition, it's best not to seek out an equivalent level of technology but instead take the next step despite the increased price, says optometrist Mile Brujic of Bowling Green, Ohio. In 2006, Dr. Brujic bought his first spectral-domain OCT after debating whether to opt for a time-domain system that was significantly less expensive. "We realized if we bought time-domain, literally in a few years it would've been obsolete. So you always want to incorporate the newest technology," Dr. Brujic says.

***3. Count the clinical uses.*** Clinicians should consider whether the instrument allows scans and analysis of both anterior and posterior segment, including optic nerve/RNFL thickness, macula/retina thickness, angle assessment, corneal thickness/pachymetry and OCT-A, Dr. Vien suggests.

"This allows you to have an instrument that can be versatile," he says. "You can do a full glaucoma evaluation and get an optic nerve scan, a ganglion cell scan, angle assessment and corneal pachymetry all in one instrument."

One potential plus: you may not need to purchase all the licenses right away if cost is an issue, Dr. Vien says. As long as the hardware is built-in, you can always upgrade the software in the future.

***4. Look at patient care.*** Whatever instrument you have your eye on, it must provide a benefit to patient care. Newer anterior segment OCTs provide larger corneal scans, which gives the clinician even more information for diagnosis and management of the patient, Dr. Brujic explains. These advanced scans can also help determine whether a patient is qualified for a medically necessary lens, he adds.

As for posterior segment imaging, OCT-A may be the next step, Dr. Brujic says. He treats dozens of healthy diabetes patients who say their HbA1c levels are fine and their physicians are generally happy with their measurements. However, Dr. Brujic says these patients sometimes admit that they cheat on their diet. In these instances, Dr. Brujic uses OCT-A to measure the patient's FAZ. Even in the absence of traditional diabetic retinopathy, angiography's advanced measurements of the retina can show increased FAZ and capillary dropout outside of that macular region.

***5. Investigate other manufacturers.*** Switching between technology platforms may pose some challenges. For example, changing OCT manufacturers could create some difficulty in monitoring the optic nerve for subtle RNFL thinning/progression due to variability between machines.

"Since each instrument has its own proprietary technology for acquiring data and analysis, this will pose an issue when tracking disease progression between different instruments," Dr. Vien says. "This can even occur with instruments from the same manufacturer." In addition, the normative database used for each instrument is different, he says.

When Dr. Vien adds a new OCT instrument or upgraded software with a different normative data, he obtains a new baseline with the new instrument once the patient is stable on the older OCT platform, and the patient will then be followed with the new technology.

"These challenges are present but manageable, given the benefits offered by having multiple manufacturers and platforms to choose from," Dr. Wong-Powell says. "It's also worthwhile to remember that despite OCTs being very accurate, there is a constant need and responsibility by the doctor to integrate OCT information with other clinical findings to see the big picture."

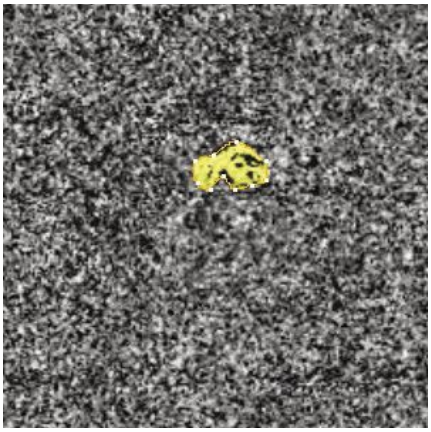
One final piece of advice from Dr. Brujic: "If you're thinking about upgrading your OCT, make sure you're using the most advanced technology because technology will change. If you don't get the most advanced technology now, you'll be left behind."

parameters correlate better with visual field parameters compared with structural OCT.[26,30] Research now shows that retinal vascular changes (specifically a reduction in vessel density) in the peripapillary retina and macula may develop in all stages of glaucoma, not just advanced disease states.

The latest research is focusing on the role of OCT-A perifoveal vessel density in assessing patients with advanced glaucoma. There does not appear to be a detectable measurement floor as is seen in SD-OCT; thus, OCT-A can be used to monitor the stability of patients at all stages of disease, including end-stage.[31]

Optometry is constantly evolving with new technologies and advanced imaging modalities. OCT-A has proven to be a true game-changer for many practices and can elevate the delivery of care clinicians provide. This technology will only grow in the next decade and will continue to advance optometrists' role as primary eye care providers. ■

*Dr. Rodman is a professor and chief of the Fort Lauderdale (Broward) Eye Care Institute at Nova Southeastern University in Florida. She is a consultant and speaker for Optovue.*



**OCT-A software analytics allow for quantification of the lesion size, which can be used to monitor a patient over time. The objective measurement correlates to the "flow" within the lesion.**

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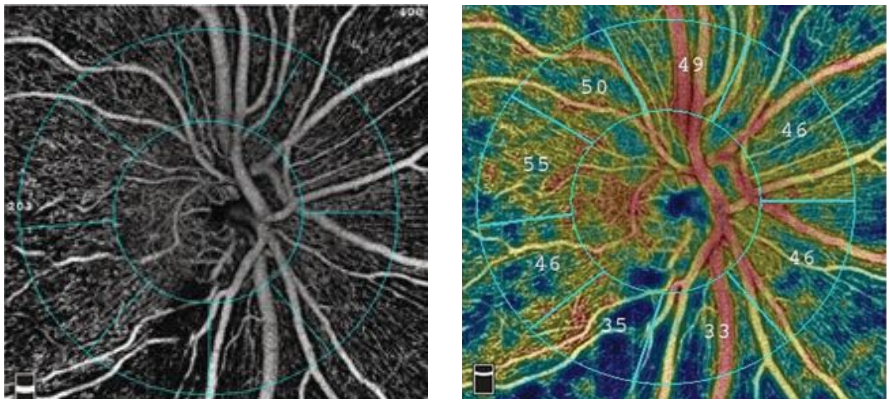


**The radial peripapillary capillary angiogram, at left, and vessel density map, at right, show an inferior temporal wedge defect with reduced vessel density in a patient with primary open-angle glaucoma.**

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# The Many Uses of Orbital Ultrasonography

This tried-and-true tool can help you evaluate far more than axial length. Here's what else it can do. By Jessica Steen, OD

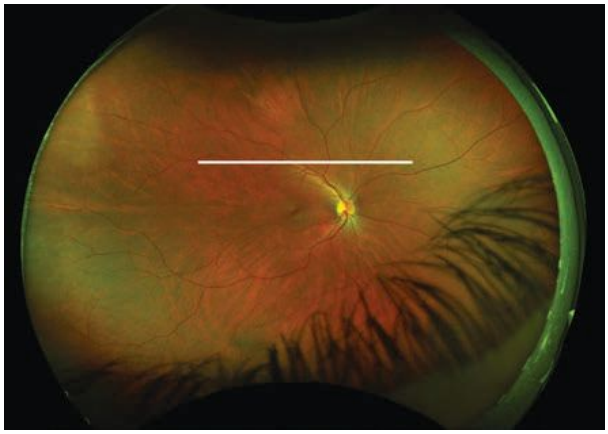
When we think about today's multimodal imaging, we tend to focus on the latest and greatest technology and procedures: optical coherence tomography (OCT), fundus autofluorescence, indocyanine green and fluorescein angiography and fundus imaging—whether traditional, widefield or multicolor. But ultrasonography rarely makes the cut. In a primary care setting, ultrasonography is often reserved as a 'last-resort' tool for the evaluation of a patient with opaque media when clinical examination and other light-based imaging techniques fall short.

However, the availability of portable and small-footprint devices—at better prices—have made ophthalmic ultrasound more accessible than ever to a wider group of practitioners.

As an ophthalmic imaging modality and therapeutic instrument, ultrasonography's history is mature, and its applications are wide-ranging.[1-8] The tool can be beneficial for evaluating any number of patients, including those undergoing myopia management and those with peripheral retinal/vitreoretinal interface issues, anterior segment concerns, optic disc drusen and choroidal lesions.


**B-scan probe position for transverse scan of 12 o'clock (T12). Note that the manufacturer's mark on the probe is directed nasally.**

Ultrasonography provides additional structural information beyond clinical evaluation and other ancillary testing and can enhance the clinician's ability to understand ocular pathology, improve referral patterns and comanage complex pathology.[1-8]



**This fundus image has an ultrasound plane overlay for a T12 scan of the right eye (white line).**

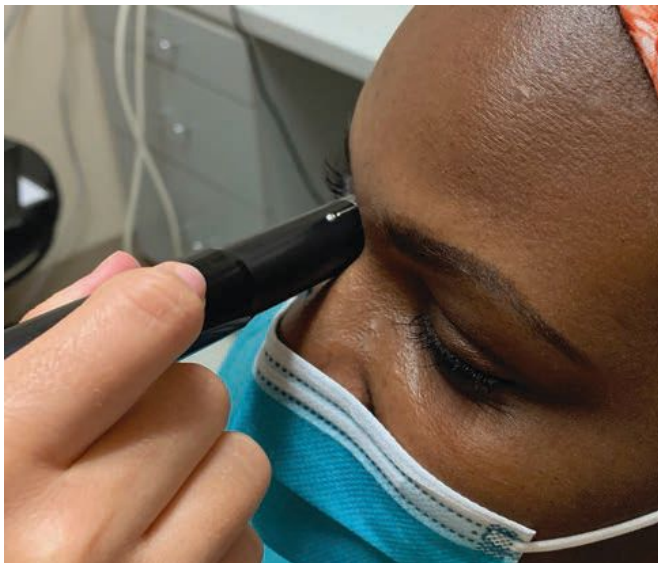
## Behind the Scenes

Echography (or 'echo'), the basic principle of ultrasonography, is analogous to OCT—right down to the nomenclature of A- and B-scans.[1,2,4] Instead of using optical interferometry and focused, collimated light sources, ultrasonography generates sound waves at frequencies much higher than the limit of human hearing through electrical stimulation of a thin crystal in the tip of an oscillating probe.[1,2]

These sound waves propagate through tissues and undergo partial reflection back to their starting point each time the wave passes through a material of different acoustic impedance.[1,2] When the wavefront returns to the transducer located in the ultrasound probe, it is converted back into electrical energy, where it is amplified and converted to a positive sine wave, which is displayed as an image.[1,2]

The images produced by ultrasonography are not based on density of a material but rather on the variation of density detected when sound waves pass from one medium to another.[1] When two materials are next to each other—water and air, for example—the reflectance of the sound waves at their interface is significant due to the large difference in density between water and air, producing a large acoustic echo.[1,4]

Ultrasonography is often broken down into discussion of A-scans and B-scans. A-scan is most commonly used for corneal pachymetry and ocular biometry, with implications for intraocular lens calculation and myopia management.[1,2,4,7] A-scan is a time-amplitude scan. The largest spikes on the graph are produced at the cornea, the front and back surfaces of the lens and the retina.[1,4]



**Here the clinician is capturing the transverse B-scan of 9 o'clock (T9). The probe is placed over the upper lid with the marker directed superiorly while the patient looks to the right.**

Axial length measurement is an important metric in myopia management and one many clinicians would consider as standard of care.[7] While the risk of vision-threatening complications of myopia, including myopic macular degeneration, retinal detachment, open-angle glaucoma and cataract, is often described in relation to refractive error, it is more accurately characterized by axial length.[7]

Axial length elongation precedes myopia development and is associated with myopic progression, which makes its measurement valuable information for determining candidacy for myopia control therapies and tracking treatment effectiveness.[7] While most of today's biometers are light or optical-based, they rely on the technology of A-scan biometers, which are still used for patients where media opacities, such as a dense cataract, exist and light-based technologies cannot be used.[7]

Ultrasound corneal pachymeters operate at significantly higher frequencies than most axial probes, between 20MHz and 50MHz, which provides the high resolution necessary to accurately determine corneal thickness.[1,4] The chief drawback of ultrasound pachymetry is the concern of overestimation of corneal thickness measurement if the probe is placed outside of the corneal center, or at any angle other than completely perpendicular to the corneal surface.[1]

For the most part, the use of diagnostic A-scan is limited to a small number of academic-based centers and ocular oncology practices.[1,4] For patients with choroidal tumors, the addition of diagnostic A-scan aids in evaluation of tumor features, including internal acoustic features, and evaluation of the extent of extrascleral extension.[8-10]

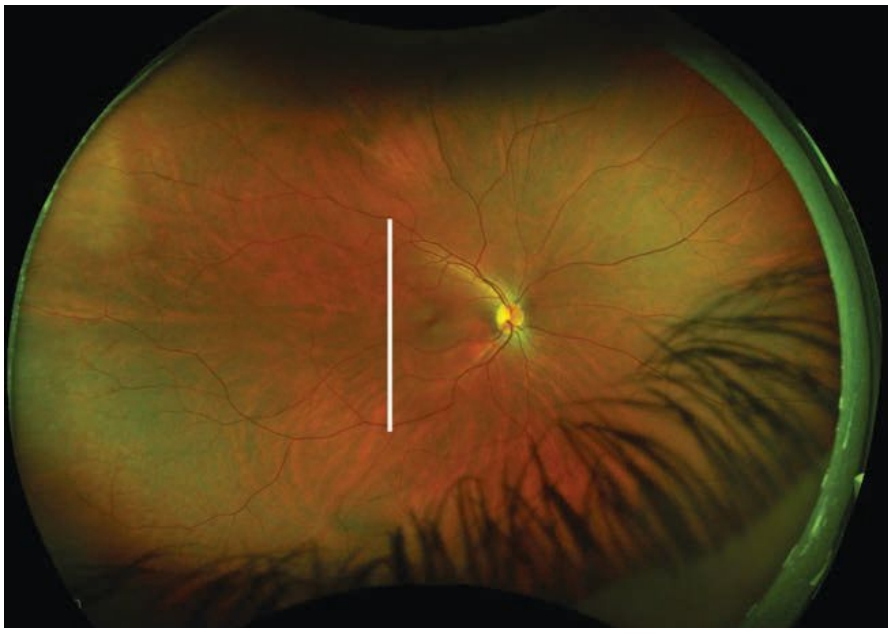
B-scan complements A-scan as it provides a two-dimensional map of orbital and intraocular tissue.[1,4] When we think of orbital ultrasonography, contact B-scan is typically the technique we have in mind.

Ultrasound has a wide range of clinical indications. For example, following examination of a patient with ocular discomfort or pain, clinicians can use ultrasonography to help confirm a diagnosis of scleritis, orbital myositis or dacryoadenitis.[1,3]

Clinicians can use ultrasonography to evaluate retrobulbar tissue, including the extraocular muscles, in a patient with exophthalmos and suspected soft tissue expansion secondary to Graves' disease.[1]

The device can help differentiate between vitreous membranes and retinal detachment because of the differences in reflectivity and inherent variations in patterns of movement with eye motion.[1,3] The vitreous has low reflectivity and tends to be much more mobile compared with the retina, which is highly reflective and undulating when detached.[1] Overlaying an A-scan onto a B-scan can help to highlight the differences in internal reflectivity of the area of interest from surrounding tissue.[1]

Clinicians can use ultrasonography to evaluate eyes with vitreous opacity, including hemorrhage, inflammation and phthisis, for retinal integrity and to identify the presence of intraocular mass lesion and foreign body. Ultrasonography features have important diagnostic and prognostic significance for retinal and choroidal lesions such as retinal or choroidal hemangioma, choroidal nevi, melanoma, osteoma and sclerochoroidal calcification.[1,3,8-10]



**This fundus image includes an ultrasound plane overlay for a T9 scan of the right eye (white line).**

## How to Use

The goal of contact B-scan ultrasonography is to reconstruct the globe into a three-dimensional image using multiple two-dimensional B-scans. While there are many approaches and individual methods to the examination, the key is to ensure a methodical, repeatable approach to evaluating the entire posterior segment and globe.

As a kinetic test, the clinician is evaluating the patient in real-time, which allows visualization of vitreoretinal traction and helps to differentiate between vitreous, retinal and choroidal membranes due to inherent differences in movement of the tissue as the patient changes their gaze.[1] By having a clear understanding of the exam technique and the spatial awareness that comes with it, clinicians can successfully identify subtle pathology.[1]

One of the most common methods for evaluation uses a series of five B-scans referring to clock hours. Four dynamic transverse scans and one static longitudinal scan are used to reconstruct the posterior segment and orbit.[1]

The advantage of using transverse and longitudinal scans compared with an axial scan is that the scans bypass the lens. Just as the lens refracts and reflects incoming light, it also reflects sound waves. By not aiming the probe through the center of the lens, clinicians can image orbital structures with the highest resolution and best image quality possible.[1,12]

Typically, contact B-scan images are acquired through the patient's eyelid; however, to avoid the slight attenuation of signal as the wavefront passes through the lid, the probe may be placed directly onto the conjunctiva following instillation of topical anesthesia.[1,4] Rather than asking the patient to close their eyes,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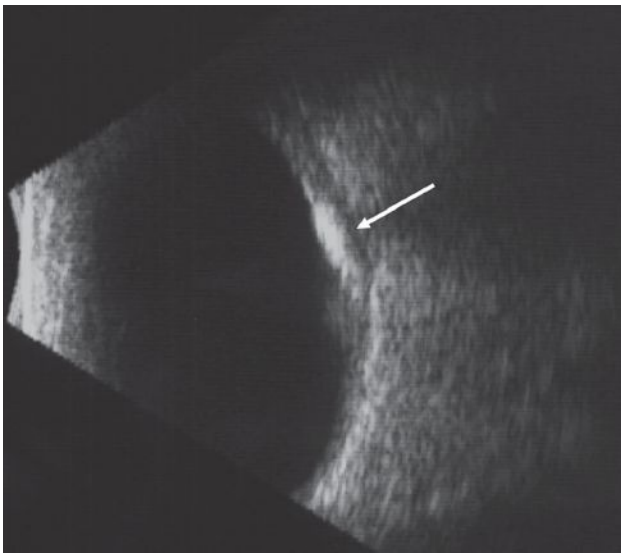
which can make it difficult for a patient to maintain fixation and for the clinician to know exactly where the probe is placed in relation to the limbus, the scan can be performed over the upper or lower eyelid, with the patient's eyes open.[1]

It's helpful to begin with the device's gain at its maximum level to allow for evaluation of lesions producing a weak signal, such as posterior vitreous detachment or vitreous opacities. By lowering the gain, the details of more overt lesions, such as intraocular mass lesions, will be more apparent. Adjust the gain, either higher or lower, to maximize the quality of the image of the lesion.[1]



**This B-scan image of choroidal osteoma highlights the high internal reflectivity of the lesion and the acoustic shadowing posterior to the lesion.**

To orient yourself, think of the globe and orbit with clock hours superimposed: for the right eye, 12 o'clock refers to the superior globe and orbit, 3 o'clock to the nasal quadrant, 6 o'clock to the inferior quadrant and 9 o'clock to the temporal quadrant. To perform a transverse scan, the manufacturer's marking on the probe should be placed perpendicular to the quadrant being imaged: nasally for evaluation of the superior (T12) and inferior (T6) quadrant and superiorly for nasal (T3) and temporal (T9) quadrants. For evaluation through the macula and optic nerve using a longitudinal scan (L9), direct the marker toward the center of the pupil. The marking denotes what is displayed at the top of the display screen.[1]

To evaluate the superior globe (T12, transverse superior), prepare the probe by applying a methylcellulose-based or oil-based coupling solution. Have the patient look up and then place the probe, marker nasally, on the inferior aspect of the conjunctiva near the limbus (over the lower eyelid). This will give you a cross-sectional image of the globe at approximately the level of the optic nerve head. Then, sweep the probe toward the inferior fornix for examination of the anterior globe.

This technique provides evaluation through many clock hours of the superior globe, as well as anterior and posterior to the equator, from superior nasal at the top of the image to superior temporal at the bottom of the image, with the area of interest (the 12 o'clock position) located at the center of the image.[1]

To evaluate the nasal aspect of the right eye (T3, transverse nasal), have the patient look to their left and place the probe over the top lid on the temporal aspect of the conjunctiva with the manufacturer's mark directed superiorly. This captures an image straight across the globe. Again, sweep the probe towards the fornix to evaluate structures anterior to the equator. The top of the image corresponds to superior nasal and the bottom of the image corresponds to inferior nasal.[1]

After evaluation of the superior, inferior, nasal and temporal quadrants, the final scan of the five-scan approach, L9, is a longitudinal scan through the macula and optic disc performed with the mark directed towards the center of the pupil.

For evaluation of the right eye, the patient looks to their right with the probe placed on the upper lid over the nasal conjunctiva, with the marking on the probe directed temporally. Remember that the optic disc is approximately 5° higher than the fovea anatomically, and as the fovea will only be identifiable by ultrasonography if it is edematous, the optic nerve is a more reliable reference point.[1]

It can be challenging to understand what each image represents when piecing the two-dimensional B-scan images together to reconstruct the globe and orbit in three dimensions. Clinicians should first practice on eyes with clear media and no pathology to develop the spatial awareness of reconstructing the globe using ultrasonography.

## Optic Disc Dilemmas

For patients with optic disc elevation on clinical examination, differentiation between papilledema and other causes of optic disc elevation, such as optic disc drusen and anomalous optic disc, is crucial to ensure appropriate and timely intervention when needed. It also avoids unnecessary, invasive and costly testing in healthy patients.[12,13]

Ultrasonography is the standard in the diagnosis of optic disc drusen, which are identified by

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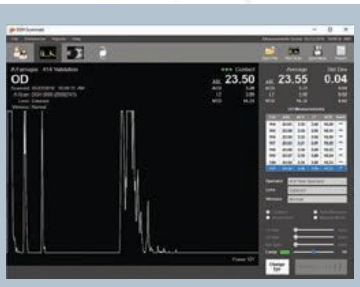
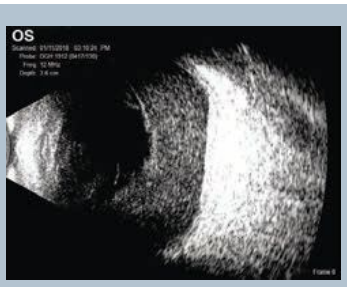
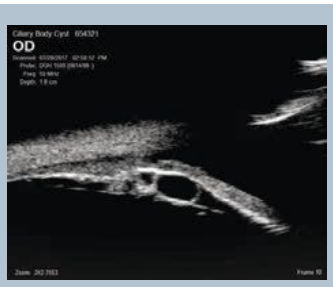



Scanmate Flex A-scan, showing the Flex user interface. The basic interface is the same for all three probe types.




Visualizing vitreous hemorrhaging with the Scanmate Flex B-Scan probe.




Visualizing ciliary cysts with the Scanmate Flex UBM probe.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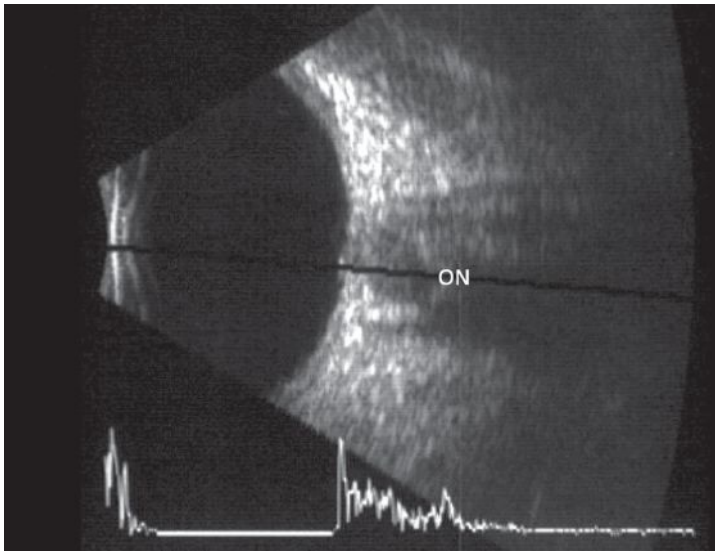
the presence of hyperreflective material at the level of the optic nerve head when the gain is reduced.[12] On ultrasonography, the calcific drusen represent a significant change in acoustic impedance from surrounding tissue, producing a significant hyperechoic signal.[12,13]

In patients with elevated intracranial pressure causing bilateral optic disc elevation, evaluation of retrobulbar structures can help guide the need, and timeliness, for further evaluation.[13] Optic nerve sheath diameter varies with cerebral spinal fluid (CSF) pressure: as CSF pressure increases, optic nerve sheath diameter increases.[14]

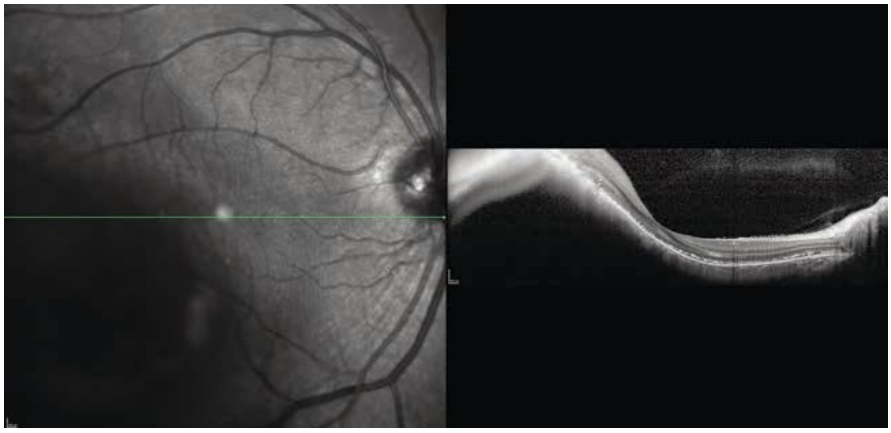
Rapid and noninvasive evaluation of optic nerve sheath diameter using ultrasonography is highly sensitive for identification of elevated intracranial pressure.[14] Measuring 3mm behind the optic nerve, an optic nerve sheath diameter of 5.9mm or greater is highly suspicious for elevated intracranial pressure.[14]




**This B-scan image of a longitudinal scan includes an overlaid A-scan. The optic nerve is located in the center of the scan.**

In addition, the presence of the 30° sign—a reduction of retrobulbar optic nerve sheath diameter on ultrasonography when the patient changes gaze from primary to 30° eccentric gaze—is highly sensitive (90%) in the diagnosis of elevated intracranial pressure in a cohort of patients evaluated for optic disc edema; lumbar puncture has a similar sensitivity.[15] While the presence of the 30° sign is highly sensitive, due to its modest positive predictive value and low specificity, individuals with a positive result require further diagnostic testing.[15]

Because the image quality and interpretation often depend on the echographer, diagnostic sensitivities presented in the literature for specific conditions and diagnoses vary significantly. Diagnostic sensitivity is especially high in large trials performed in academic centers or ocular oncology practices that employ trained ultrasonographers. In clinical practice, clinicians can expect significantly lower diagnostic sensitivity that is highly dependent on training and experience.



**The inversion of the OCT B-scan image through a choroidal melanoma limits its utility in measuring lesion thickness.**

## Oncology Applications

There is no ophthalmic specialty more reliant on the art and science of ultrasonography than ocular oncology. The Collaborative Ocular Melanoma Study, a long-term, multicenter group of randomized, controlled clinical trials, established ultrasonography as a standard of care in evaluation of ocular melanoma and nevi.[8] More recently, researchers have used ultrasonography to identify lesion-based risk factors for prognosis and survival.[9,10]

Clinical risk factors of choroidal nevi, which increase the likelihood of progression to choroidal melanoma, are encompassed in the most recent mnemonic: "To Find Small Ocular Melanoma Doing IMaging (TFSOM-DIM)."[9] While OCT, fundus autofluorescence and fundus imaging parameters are used for identification of overlying subretinal fluid, lipofuscin or orange pigment and tumor diameter >5mm, ultrasonography is still a mainstay in the contemporary evaluation of choroidal lesions for the identification of

## Coding Connection

By John Rumpakis, OD, MBA, Clinical Coding Editor

# Ultrasound: Code with Purpose

Your testing intentions drive how you bill for this diagnostic procedure.

Ultrasonic procedures in eye care have been around for quite a while. Whether you are using them to visualize an intraocular foreign body, measure axial length for an intraocular lens (IOL) or even for pachymetry, they are an important part of an ophthalmic practice. If you're just getting started with ultrasonic procedures in your practice, here are some important reminders about the codes, reimbursements and rule sets.

An ultrasonic procedure uses high-frequency sound waves that are transmitted from a probe placed on the eye. As the sound waves strike intraocular structures, they reflect back to the probe and are converted into an electric signal. The signal is reconstructed as an image on a monitor, which can be used to make a dynamic evaluation of the eye or can be photographed to document pathology. Different types of ultrasonography scans provide different data for the evaluation, depending on the purpose of the procedure. These differences are crucial for determining medical necessity for the medical record.

## Scans By Purpose

A-scans provide data on the length of the eye, which is a major determinant in common vision disorders. The most common use of the A-scan is to determine eye length to calculate the necessary IOL power before cataract surgery.

B-scans are an important tool for the clinical assessment of various ocular and orbital diseases. It is most useful when direct visualization of intraocular structures is difficult or impossible. Situations that prevent normal examination include lid problems, dense cataracts, corneal scars and vitreous opacities or hemorrhages. In such cases, diagnostic B-scan ultrasound can accurately image intraocular structures and give valuable information on the internal structures of the eye. However, in many instances, ultrasound is used for diagnostic purposes even though pathology is clinically visible to better differentiate the pathology.

## Scans By Code

Here is a list of codes you need when billing for various ultrasonography scans. *Note: All of these require an interpretation and report and are subject to the Multiple Procedure Payment Reduction:*

- ***76519:*** ophthalmic biometry by ultrasound echography, A-scan; with IOL power calculation. This bilateral code pays 100% of first eye and 50% of second eye if performed on the same date of service. This code has a relative value unit (RVU) of 1.88.
- ***76516:*** ophthalmic biometry by ultrasound echography, A-scan. This code is the same as 76519 without the IOL power calculation. It is also a bilateral code and has an RVU value of 1.36.
- ***76511:*** ophthalmic ultrasound, diagnostic; quantitative A-scan only. This code is a unilateral code and has an RVU value of 1.75.
- ***76513:*** ophthalmic ultrasound, diagnostic; anterior segment ultrasound, immersion (water bath) B-scan or high-resolution biomicroscopy. This code is also a unilateral code and has an RVU value of 2.81.
- ***76512:*** ophthalmic ultrasound, diagnostic; B-scan (with or without superimposed non-quantitative A-scan). This is a unilateral code and has an RVU value of 1.49.
- ***76510:*** ophthalmic ultrasound, diagnostic; B-scan and quantitative A-scan performed during the same patient encounter. This is a unilateral code and has an RVU value of 2.56.
- ***76514:*** ophthalmic ultrasound, diagnostic; corneal pachymetry, unilateral or bilateral (determination of corneal thickness). This is a bilateral code and has an RVU value of 0.34.

## Choose Carefully

Based on the CPT, you must use the code that most closely describes the procedure performed on the patient. In doing so, it is also important to realize that you must choose the procedure that provides you with what you specifically need. Thus, you can't choose a procedure that pays more or is bundled with another procedure simply because you want confirmatory information for the patient record. Over-embellishing the medical record or upcoding the procedure over what the record would dictate is necessary is a common audit trigger.

Ultrasonography is often complimentary with other clinical procedures when additional diagnostic information is required. It can provide beneficial diagnostic data that allows you to properly refine your assessment of many clinical conditions. Learning which codes properly describe your clinical testing is crucial when billing for ultrasonography, just as it is elsewhere in diagnostic testing.

*Send your own coding questions and comments to rocodingconnection@gmail.com.*

thickness >2mm, lesion configuration (i.e., flat or dome-shaped) and hollow echogenicity of melanoma.[9]

For each 1mm increase in thickness of choroidal melanoma, as measured by ultrasonography, the risk of metastatic disease at 10 years increases by 5%.[11] Therefore, early diagnosis and detection of choroidal melanoma is crucial for prognosis and survival.[11]

Enhanced-depth imaging OCT (EDI-OCT) is designed to improve the detail of choroidal lesions, including choroidal nevi and melanoma.[9,11] While EDI-OCT provides a higher resolution image than ultrasonography and is commonly used as part of the choroidal nevus or melanoma evaluation, EDI-OCT thickness cannot be used in place of thickness measured by ultrasonography when discussing prognostic significance of lesion thickness as identified in the literature.[11]

Research shows small choroidal melanoma thickness was 55% less when measured by EDI-OCT compared with ultrasonography.[11] This has significant clinical implications because the 2mm thickness 'tipping point' for which a clinician should be suspicious of small choroidal melanoma or the risk of progression to choroidal melanoma is based on ultrasonography thickness measures, not EDI-OCT thickness measures.[8-10] The significant difference in these tumor thickness measurements may be due to the differences in resolution between the two devices, as ultrasonography may incorporate retinal or scleral tissue with imprecise identification of tumor margins.[11]

As tumor thickness increases, ultrasonography plays an even more critical role in lesion evaluation because EDI-OCT is unable to accurately measure thick choroidal melanoma due to image inversion.[11]

## Take It Higher

Ultrasound biomicroscopy (UBM) is a high frequency B-scan with frequency up to 100MHz is analogous to what corneal pachymetry is to the A-scan.[4,16] High frequency images provide increased resolution, but have an exponential increase in absorption, which limits evaluation to the anterior segment.[4,16] UBM is most frequently used to evaluate iris and ciliary body cysts and tumors and to evaluate plateau iris syndrome.[1,16] The transducer is submerged in a water-filled bubble tip which is placed directly in contact with the eye, following administration of topical anesthesia.[16]

## Looking Ahead

Advancements in ultrasound technology aim to expand its therapeutic role beyond ablative procedures, including cyclodestructive procedures.[4,6] Diagnostic ultrasonography uses very low energy to ensure no tissue alteration; however, by increasing the energy applied through an ultrasound probe, therapeutic effects can be reached.[5,6]

Ongoing research uses high frequency ultrasound to temporarily increase the permeability of ocular barriers to improve medication bioavailability; however, finding a balance between tissue alteration to improve topically applied medication penetration and tissue destruction is crucial.[5,6]

Challenges to employing ultrasonography are typically related to the clinician's familiarity with the technique and comfort level with image interpretation. While highly-trained, highly-skilled echographers are true experts in the art of acquiring and interpreting images, an understanding of the basic technique of performing the scan and interpreting its results are still quite useful in clinical practice.

In a time of profound technological advancement in optometry and ocular imaging, orbital ultrasonography has often been relegated to a niche/ancillary test. With improved affordability of available ultrasonography systems, now is the time to embrace the many applications of ultrasonography to best serve your patients. ■

*Dr. Steen is an attending optometrist and assistant professor of ocular pharmacology at Nova Southeastern University College of Optometry.*

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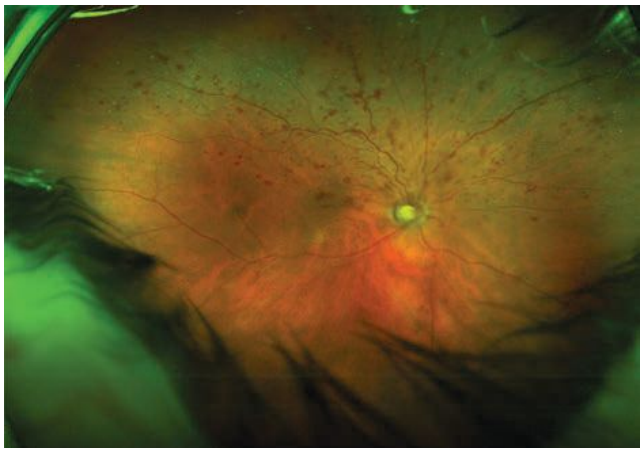
# Tighten Your Testing Protocols to Pass an Audit

Be scrupulous in your choices and make sure you document what's medically necessary.

**By Scott Moscow, OD**

Getting reimbursed by insurance doesn't guarantee you won't be audited—or that you'll pass if you are. The hard truth is, regardless of how you bill, an audit may be in your future.

Still, you can lower your chances of failing an audit by tightening up your diagnostic testing protocols, which includes knowing what tests are warranted, when they aren't necessary and how to document for them properly.



**Interpretation and report of widefield imaging taken in office:**
***Clinical findings/diagnosis:*** **H34.8310 tributary (branch) retinal vein occlusion, right eye, with macular edema.**
***Reliability of the test:*** **reliable OD.**
***Comparative data/change in condition:*** **baseline OD.**
***Clinical management:*** **referral to retinal surgeon tomorrow for evaluation and anti-VEGF intravitreal injection OD.**

## Be a Rule Follower

To pass an audit, you must comply with the rules set by each payer (i.e., insurance company), establish medical necessity and document appropriately.

Although some payers' rules are similar to Medicare, medical necessity rules vary. For each payer, you need to acquire a Local Coverage Determination (LCD) or provider agreement to know which diagnostic tests you can perform and which diagnosis codes are covered.

Diagnostic tests can be done on the same day as an exam/office visit (992XX or 920XX) if both the diagnostic test and exam/office visit are medically necessary.

For certain procedures, such as amniotic membranes, a prior authorization may be necessary from the insurance carrier.

## Ensure Necessity

Claims for diagnostic tests may be rejected if the insurance company determines the test was not medically necessary. A test is only medically necessary if it helps clinical decision-making and management. For example, some insurers may not consider retinal photography for a patient with diabetes without diabetic retinopathy to be useful for decision-making and management, and they may flag the imaging as not medically necessary. On the other hand, photographing diabetic retinopathy over an appropriate period of time to track changes noted after a physical retinal examination helps with clinical decision-making and management and would be considered medically necessary.

The medical necessity of any test must be crystal clear to an auditor. Thus, all documentation in the interpretation and report (I&R) of the patient's medical record needs to reflect to a potential auditor why the doctor ordered a diagnostic test and how it aided the clinical decision-making and patient management.

## Order First, Run Second

Before performing any test, the doctor must first order it. At the end of each exam in my office, we order all of the tests we know will be necessary at the next exam based on what is medically necessary for that case.

For initial exams, unscheduled exams or during the instances when additional testing is necessary the day-of, we will order tests to be performed on that day.

Regardless of the circumstances, you must order and enter tests into the record prior to performing the actual test. Further, you can only interpret the test after it's completed.

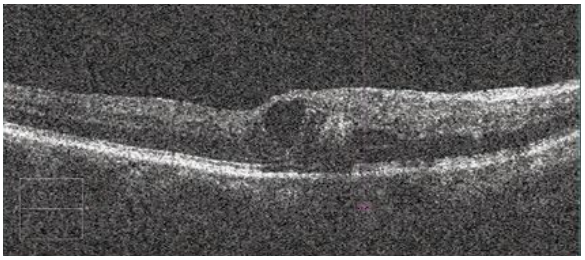
Another must for your records: always sign your test orders. If the test is ordered during an exam record, the doctor's signature at the end of the exam will suffice. If the test is ordered on a day when the exam is not performed, it's essential that the doctor still sign the order.

If a patient comes in with vision insurance and needs a diagnostic test billed to their medical insurance, you have three options:

***1. Ask the patient for permission to bill the exam and diagnostic test under their medical insurance.*** It is always the patient's choice if they want to use their vision insurance if one of their complaints is refractive in nature on a given day. If a patient has both a refractive and a medical complaint, you cannot force them to use their medical insurance for the exam if they have vision insurance.

***2. Bill the exam to vision insurance and the diagnostic test to medical insurance using coordination of benefit.*** With this option, you will have to collect both the vision insurance and medical insurance copays (if there are any) that day.

*3. Perform only the exam that day and bill it to vision insurance.* Have the patient return on another day to perform the diagnostic test (and maybe an office visit, if medically necessary) and bill it to medical insurance. You will collect the vision insurance copay (if applicable) at the first visit and medical insurance copay (if applicable) at the second visit.



**Interpretation and report of OCT performed at the surgeon's office the next day:**
***Clinical findings/diagnosis:*** **H34.8310 tributary (branch) retinal vein occlusion, right eye, with macular edema.**
***Reliability of the test:*** **reliable OD.**
***Comparative data/change in condition:*** **baseline OD.**
***Clinical management:*** **anti-VEGF intravitreal injection performed OD.**

## Don't Skimp on Paperwork

Most tests have a global fee that equals the sum of the technical and professional components. Simply put, the technical component covers the cost of equipment, maintenance and technician services. The professional component is the I&R document. This may be very similar to the assessment and plan of the exam and must contain the following:

- Clinical findings/diagnosis
- Reliability of the test
- Comparative data/change in condition
- Clinical management (i.e., how the test affected patient care and physician decision making going foward)

Without the I&R, the provider is not entitled to the full global fee for the test. Whenever a current procedural terminology (CPT) code states "with interpretation and report," this information must be included in the chart documentation. For example, optic nerve OCT, retinal OCT, visual field and fundus photography all require I&R. However, not all tests have this stipulation. Gonioscopy, for one, does not require an I&R. Also, if you perform more than one test that requires an I&R on a given day, each test will require its own I&R.

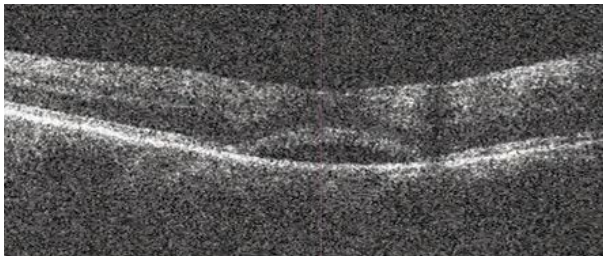
## Avoid Testing Taboos

Although clinicians order diagnostic tests numerous times on a typical day, misuse of tests and their documentation can be common, regardless of the best of intentions. Here are four red flags to avoid:

***1. Don't perform "screening" photography and then bill the photo to medical insurance if pathology is found.*** This is inappropriate for two reasons. One, a screening test must be completely different than the test billed to medical insurance (although it can be performed on the same piece of equipment). Two, a test must be ordered before the test is performed.

***2. It is only appropriate to bill a patient's symptom as a diagnosis if you can't find the cause of the symptom or if the cause of the symptom does not have an ICD-10 code.*** If the cause of the symptom does not provide reimbursement for

the test, it is not appropriate to bill the symptom just to get paid. For example, the diagnosis of external hordeolum (H00.01__) generally does not pay for an external ocular photo (92285). However, edema of the eyelid (H02.84__) generally does pay for an external ocular photo (92285). If your patient has an external hordeolum on their right upper eyelid (H00.011), you cannot use the diagnosis of edema of right upper eyelid (H02.841) to get paid for the external ocular photo. Because the eyelid edema is a symptom of the external hordeolum, it would be wrong to bill for eyelid edema.



**Interpretation and report of OCT performed in office two weeks after anti-VEGF injection:**
***Clinical findings/diagnosis:*** **H34.8310 tributary (branch) retinal vein occlusion, right eye, with macular edema.**
***Reliability of the test:*** **reliable OD.**
***Comparative data/change in condition:*** **improving OD.**
***Clinical management:*** **follow-up with retinal surgeon as scheduled in two weeks to consider repeating anti-VEGF intravitreal injection OD.**

***3. Don't enter an incorrect diagnosis into the patient's chart just to get paid for a test.*** Not only is that against insurance company rules, but that diagnosis will follow the patient for the rest of their life and can affect insurance coverage and/or premiums in the future.

***4. If it doesn't help with your clinical decision-making and management, don't repeat a test that was already done at another doctor's office just because you didn't get the chance to bill for it.***

In instances where you are comanaging a patient with another doctor, you should get a copy of the patient's records with all tests performed from the comanaging doctor. For example, if a glaucoma surgeon did optic nerve OCT imaging a week earlier and you have a copy of the test, in most cases, it would be inappropriate to repeat the OCT since you wouldn't normally perform a weekly optic nerve OCT on a glaucoma patient.

On the other hand, if a retina surgeon did a macular OCT two weeks prior on a patient with cystoid macular edema (CME) and then gave the patient an anti-VEGF injection, it may be appropriate for you to repeat the macular OCT two weeks later to confirm the CME has improved or resolved.

## Be Strict with Modifiers

If you perform a bilateral test on one eye only, you must use the -52 modifier and the RT or LT modifier, and payment will be reduced by 50%. The following are commonly performed bilateral tests:

- External photos (92285)
- Topography (92025)
- Gonioscopy (92020)
- Pachymetry (76514)
- Fundus photos (92250)
- OCT, optic nerve (92133)
- OCT, retina (92134)
- Visual fields (92083)

If a unilateral test is performed on both eyes, use the -50 modifier. In this case, you will receive 150% of the unilateral reimbursement.

## Structure Same-day Testing

If you are performing multiple diagnostics tests on the same day, you should bill the most expensive test first, since each subsequent test will have a decreased reimbursement.

Remember, certain CPT codes can't be billed together when performed by the same physician during the same visit on the same day; these are called mutually exclusive. For example, external ocular photography (92285), fundus photography (92250), retina OCT (92134) and optic nerve OCT (92133) will not be reimbursed if they are performed on the same day because they are mutually exclusive. If you want to be reimbursed for mutually exclusive tests, you must perform these tests on different days. In addition, some tests are components of another test, and they cannot be billed separately.

## When to use ABN/Waivers

If you have a specific reason you believe a test may be denied, you must use a waiver of liability that states that if the claim is denied, the patient will be fully and personally liable to pay you for the test.

*Note: clinicians should never use an advance beneficiary notice (ABN)/waiver to get paid for two or more mutually exclusive tests on the same day.*

A waiver of liability will not influence determination of coverage. Some insurance companies have their own waivers. For example, Medicare uses the ABN, while Tricare has its own waiver and will not honor any others.

When in doubt, have the patient sign a waiver. ■

*Dr. Scott Moscow is the clinical director of Roswell Eye Clinic in Roswell, GA, where he focuses on fitting specialty contact lenses and treating eye disease. In addition to lecturing, he consults on billing and coding, including for specialty contact lenses and vision therapy.*

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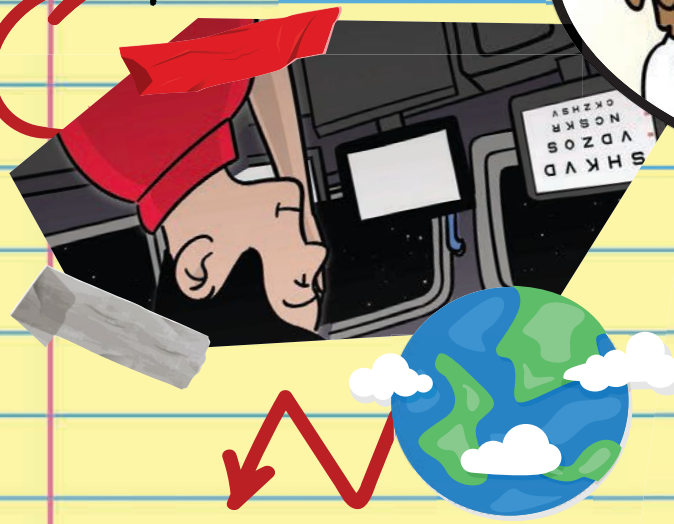


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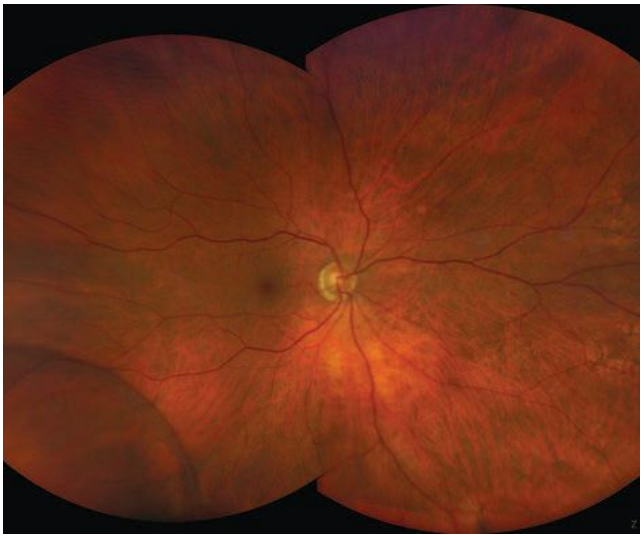
# Can We Pre-empt Damage from Retinal Detachment?

Learn to spot the warning signs and how to counsel at-risk patients to act quickly before their condition worsens. By Jay M. Haynie, OD

The frequency of retinal detachments (RD) is estimated to be approximately one per 10,000 people per year.[1] The most common risk factors include myopia (especially high myopia), aphakia, trauma, retinal detachment in the fellow eye and a family history of retinal detachment. In addition, a variety of peripheral retinal abnormalities are associated with an increased risk of a retinal detachment.

While you cannot lower a person's absolute risk of developing a retinal detachment, by prioritizing patient education on RD signs and symptoms, your patients will know to call your office as soon as symptoms present. Seeing these patients early is imperative, as early intervention has a better chance of limiting visual loss from RD.

Optometrists must manage and educate their patients who have asymptomatic retinal breaks or peripheral retinal lesions that are known to be associated with a higher risk of developing RD. They must also take care of referral recommendations for patients with symptomatic or otherwise high-risk horseshoe retinal tears.

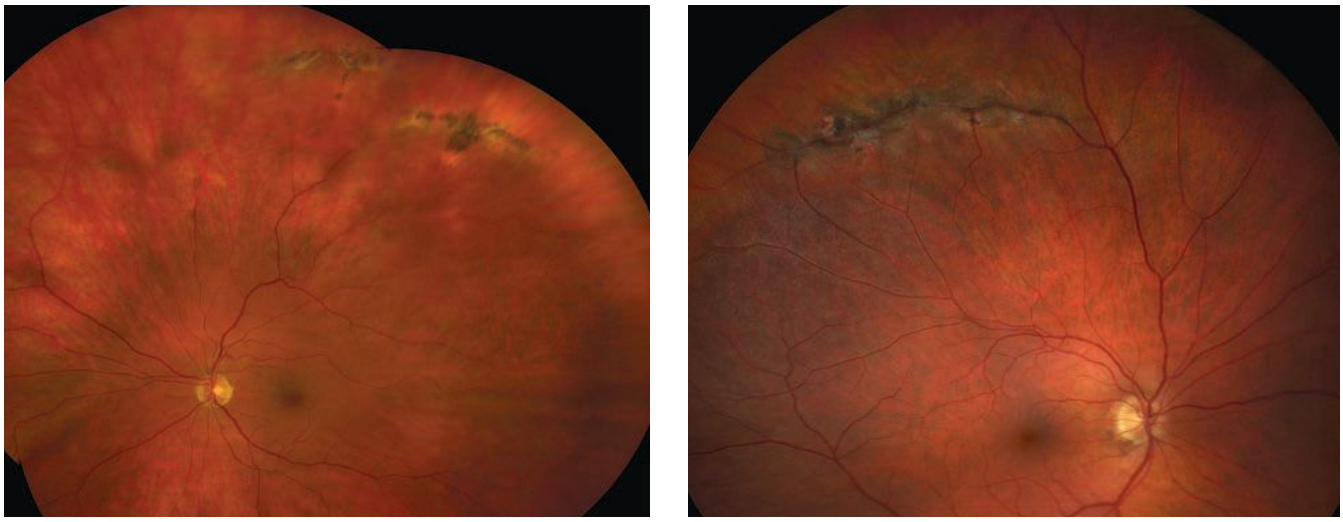


**In most cases, a retinoschsis will neither impact vision nor carry any symptoms. However, on rare occasions, it can evolve into a retinal detachment.**

## Posterior Vitreous Detachment

A posterior vitreous detachment (PVD), which can lead to a full-thickness retinal break, is the most common event that precedes RD development. A PVD occurs when the vitreous separates from the surface of the retina and collapses anteriorly toward the vitreous base. The vitreous base is a broad adherence of the vitreous to the peripheral retina near the ora serrata. The well-known symptoms of a PVD are flashes and floaters.

Vitreous traction on the peripheral retina causes these flashing lights, or photopsia, in the patient's vision. If RD is present, patients may also present with what they might describe as a curtain, shade or a shadow obscuring their side vision. Ask all patients at risk for RD whether they see these signs or if they feel like they have lost a portion of their peripheral vision.



**Lattice degeneration, as seen here, is associated with an increased risk of a retinal detachment.**

Patients who present with a symptomatic PVD without peripheral retinal breaks require no immediate treatment; however, it is pertinent to re-examine these patients within one to two weeks, as retinal breaks may develop days to weeks after the onset of symptoms.

When examining a patient with an acute PVD, carefully look at the vitreous cavity and note the presence or absence of pigment cells (a tobacco dust sign or Shafer's sign) or the presence of red blood cells consistent with a vitreous hemorrhage. In 10% to 15% of patients, a retinal tear is a sign of an acute PVD.[2,3] If the symptomatic patient has red blood cells or a vitreous cavity hemorrhage, there is a 70% likelihood of an associated retinal tear.[4]

Patients who present with asymptomatic PVD and have peripheral retinal degeneration at a higher risk of developing a retinal tear. Warn these patients of the signs and symptoms and to return immediately if these symptoms occur.

If a patient returns and is symptomatic, you should perform a dilated examination with scleral depression in addition to widefield photography, if available. Be sure to document what drops used to dilate the patient, the lens you used to examine the fundus (90D, 20D, 28D, etc.) and whether you performed scleral depression.

## Lattice Degeneration

This is present in 7% to 8% of the general population, and, of those cases, up to 45% are bilateral.[5] Patients with lattice lesions are at a 1% risk of developing RD in their lifetime.[1] Lattice degeneration is a lesion characterized by sharp demarcated margins, oval or round in appearance and may vary in pigmentation but have common white lines in the crossing retinal vessels.

Another characteristic of lattice degeneration is a pocket of liquefied vitreous anterior to the lesion as well as firm vitreoretinal attachments on the margins. These adherent vitreoretinal attachments are the reason that this lesion carries a risk of retinal tear and detachment following an acute PVD. In a large review of clinical cases, 30% of eyes who suffered an acute RD had lattice degeneration, and, in 83% of these cases, the associated retinal tear was within the bed of the lattice lesion.[6]

Prophylactic treatment of lattice degeneration is not indicated; however, patients with photopsia or increased floaters (symptomatic) should be followed closely or referred for a retinal evaluation.

## Cystic Retinal Tufts

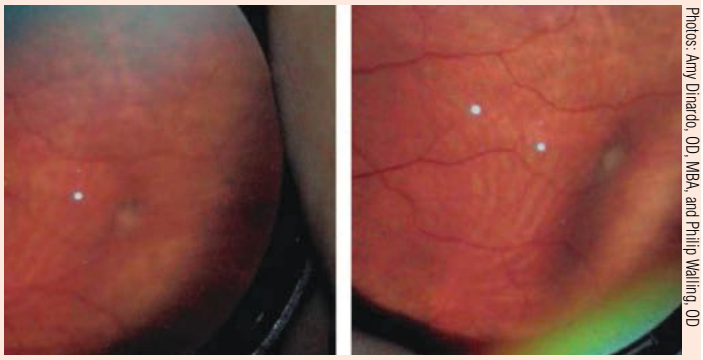
These are noted in approximately 5% of the population and are thought to be a congenital abnormality in the development of the peripheral retina.[7] Peripheral retinal degenerations are found during a dilated examination with indirect ophthalmoscopy or documented with widefield retinal imaging of the peripheral fundus. In appearance, a cystic retinal tuft is chalky white in color, round or oval in shape and primarily composed of glial tissue.

Vitreous condensations are attached to the surface and base of the cystic retinal tuft and may be associated with pigmentary changes secondary to the chronic vitreous adhesion. These small anomalies in the peripheral fundus may be hard to appreciate without use of scleral depression.

## How to Perform Scleral Depression

Scleral depression combined with binocular indirect ophthalmoscopy (BIO) lets you evaluate the retinal periphery, which may not be well viewed with slit-lamp biomicroscopy or BIO alone. Scleral depression indents the retinal periphery to bring it into better view with BIO. I typically perform scleral depression on areas that BIO indicates further evaluation, such as area suspicious for peripheral retinal pathology such as lattice degeneration, atrophic retinal holes, cystic retinal tufts or retinoschisis.

There are two techniques for performing scleral depression: transdermal (i.e., through the skin) and transconjunctival, in which you place the scleral depressor directly on the bulbar conjunctiva. I use the transdermal technique more often because it is more comfortable for the patient. A topical anesthetic is not necessary when the transdermal technique is performed correctly.



Photos: Amy Dinardo, OD, MBA, and Philip Walling, OD

**In this patient with a retinal traction tuft (left), applying scleral depression provided better detail of the lesion.**

The transconjunctival technique is necessary for examining the temporal and nasal aspects of the peripheral fundus or when you attempt to depress a posterior lesion. This technique requires a topical anesthetic such as tetracaine, and the scleral depressor should be placed posterior to the ciliary body. When performed correctly, transconjunctival scleral depression should cause only minimal discomfort for the patient. Whether with the transdermal or transconjunctival technique, be sure not to apply pressure on the lacrimal gland.

To examine the superior retina, ask the patient to look down, then place the scleral depressor at the base of the lashes. Next, instruct the patient to look superiorly as you concomitantly move the depressor along the contour of the globe.

The objective of scleral depression is to view the far retinal periphery and evaluate peripheral retinal lesions. By gently indenting the globe, you can also study the effects of motion and contrast on various lesions. Scleral depression also allows you to see whether a hole or tear is open or sealed by pigmentation, which can help you decide whether to refer a patient to a retina specialist for treatment.

Scleral depression is necessary for patients who have symptoms or a history of retinal disease because it enables you to see the entire retina, to the ora serrata, to observe or rule out a change in retinal pathology. Perform scleral depression in the opposite quadrant or location of patient symptoms, as superior pathologies produce inferior symptoms.

Do not perform scleral depression on patients who have had recent blunt ocular trauma, as it could exacerbate a penetrating injury, or on patients who have recently undergone surgery, including cataract and LASIK procedures, because you could open the eyeball or dislodge the flap. Also avoid scleral depression in patients who have angioid streaks unless it is necessary; it could induce perforation of the globe in such cases.

When documenting your findings of the peripheral retinal examination, note what techniques and lenses you used.

**When examining the patient in the supine position, scleral depression indents the retinal periphery to bring it into better view with BIO.**

Photos: Amy Dinardo, OD, MBA, and Philip Walling, OD

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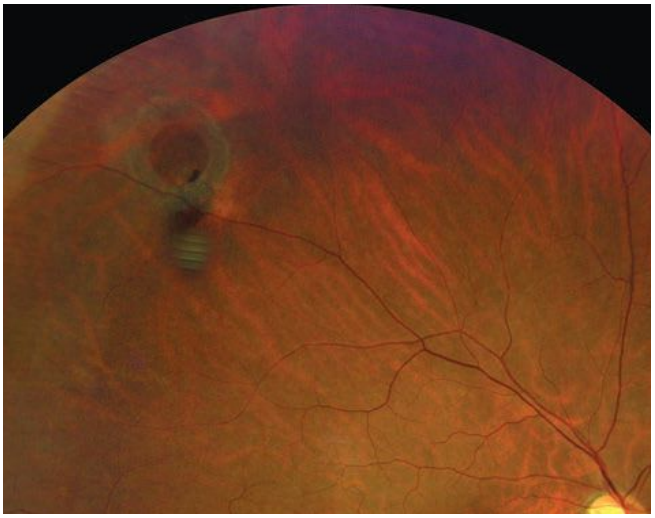
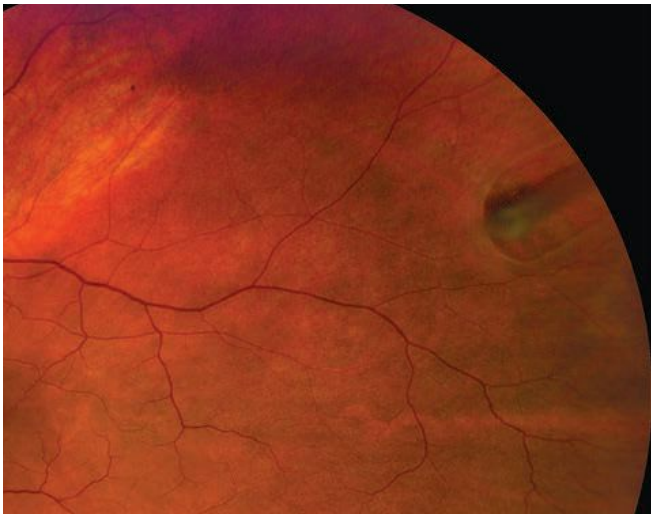


**Refer operculated retinal hole patients with symptoms associated with RD to a retina specialist.**



**Refer any horseshoe retinal tear case emergently for prophylactic treatment.**

The incidence of developing RD from a cystic retinal tuft is approximately 0.28%.[8] There is no recommendation for treatment of the cystic retinal tuft alone.

## Retinoschisis

Acquired degenerative retinoschisis is thought to be idiopathic and present in 1% of the population, with up to 82% of cases being bilateral.[9] Although retinoschisis is typically a benign peripheral lesion, vision-threatening complications may occur over time. Retinoschisis is most commonly seen in the inferotemporal quadrant, although it can occur in the superior temporal and superior nasal quadrants as well. The clinical features of a retinoschisis include a smooth, dome-like appearance that is transparent and allows visualization of the RPE and choroid. It is immobile, with an abrupt transition between the schisis cavity and normal posterior retinal anatomy.

The natural history of a retinoschisis reveals that it rarely progresses more posterior from where it first appeared, and the incidence of RD from a retinoschisis is less than 2.5%.[10] Although the incidence of RD arising from progression of a retinoschisis is low, the mechanism is associated with the formation of an inner wall hole and an outer wall break, which is defined as a full-thickness retinal defect.

The appearance of an inner wall hole is small and round, resembling an atrophic retinal hole, whereas outer wall retinal breaks are usually much larger and located more near the posterior margin of the retinoschisis. Outer wall breaks occur in approximately 17% of retinoschisis whereas inner wall holes are much less frequently at less than 4%.[10]

Although the incidence of RD secondary to retinoschisis is low, using optical coherence tomography can be very helpful to rule out RD if the schisis lesion appears to be migrating posterior.

Given the low incidence of an associated RD, there is no formal recommendation for prophylactic treatment. I tell these patients that in most cases a retinoschsis will not impact vision nor carry any symptoms, but, on rare occasions, it can evolve into RD. Discuss the signs and symptoms of RD with the patient and perform a dilated examination annually.

## Atrophic Retinal Holes

The underlying cause of these defects is a poorly functioning choriocapillaris that no longer gives adequate circulation to the retinal layers above the hole. This chronic thinning and decompensation of the chorioretinal blood supply has a domino-like effect on the overlying neurosensory retina, resulting in thinning.

Atrophic retinal holes are present in approximately 5% of the overall population and often identified on routine dilated examination with or without widefield imaging. When present in conjunction with lattice degeneration, the incidence of atrophic holes is higher. Atrophic holes may be found in isolation, within areas of lattice degeneration (18%) or adjacent to lattice degeneration (42%).[11]

The incidence of RD from an atrophic retinal hole is exceptionally low, as atrophic holes are not a result of vitreous traction. The

etiology of an atrophic retinal hole is secondary to a focal degeneration of the neurosensory retina from abnormal blood supply to the retinal pigment epithelium from the underlying choriocapillaris. It is vital to perform a careful examination with scleral depression and determine if there is any associated subretinal fluid surrounding the hole. Use annual dilated exams or serial widefield retinal imaging to observe asymptomatic atrophic retinal holes.

## Operculated Retinal Holes

Unlike atrophic retinal holes, operculated retinal holes originate secondary to vitreous traction and may carry a higher incidence of RD if they fail to seal spontaneously. The operculum signifies a release of vitreous traction, and, in most cases, the edges of the hole will flatten and seal spontaneously. If a patient presents with acute symptoms and an operculated retinal hole, evaluate with scleral depression and determine if there is any residual vitreous traction on the anterior surface of the retina or subretinal fluid.

One clinical pearl based on my clinical experience is, when the size of the operculum is five times smaller than the associated retinal hole, this lesion has reached end stage.

If the patient has operculated retinal holes as well as associated symptoms of flashing lights and floaters, then refer to a retinal specialist.

## Horseshoe Retinal Tears

Horseshoe retinal tears are the cause of most detachments. The estimated incidence of a horseshoe retinal tear in a patient with an acute PVD is 8%.[12] Acute PVD, in which there is a strong adhesion of the vitreous to the retinal surface, causes the horseshoe retinal tear. Although most vitreous will spontaneously separate from the retinal surface during a PVD, areas where there is a firm vitreoretinal adhesion traction can result in tearing the retina and cause a full thickness defect. These retinal breaks are associated with a higher incidence of RD, as liquefied vitreous will traverse through the retinal break and accumulate in the subretinal space separating the neurosensory retina from the retinal pigment epithelium.

Any horseshoe retinal tear, whether symptomatic or asymptomatic, should be referred emergently for prophylactic treatment to prevent progression to RD.

## Prophylactic Treatment

Consider prophylactic retinopexy for symptomatic peripheral retinal lesions as well as horseshoe retinal tears, even for those without symptoms of flashing lights or floaters, given the high risk for progression to a retinal detachment. Prophylactic treatment can include laser photocoagulation or cryotherapy. The decision on which method to use is typically based on the location of the pathology, as more anterior lesions require cryotherapy. The end result of prophylactic treatment is a chorioretinal reaction around the lesion that prevents the accumulation or spread of subretinal fluid.

The optometrist's role in post-treatment care depends on the treating retina specialist. The optometrist's responsibilities may include widefield retinal imaging of the treated lesion, dilated examination with scleral depression as well as ongoing education of symptoms of RD.

For any patient with peripheral retinal pathology associated with a risk of RD, it is important to educate them on the signs and symptoms and follow-up accordingly. When patients present with symptoms of RD, dilate them and perform BIO with scleral depression to rule out a retinal tear or detachment. If you are not comfortable managing symptomatic patients, make a referral to a specialist for a second opinion.

Evaluating these retinal defects is not enough, as the complications may escalate and cause significant vision loss. Preventing the effects of retinal detachment requires proper management and decisive action to implement effective management strategies. More importantly, clinicians must communicate with their patients about the risk of retinal detachment associated with peripheral retinal pathology. ■

*Dr. Haynie is an adjunct clinical profressor at Pacific University College of Optometry and practices at Sound Retina in Tacoma, WA. He is a fellow of the American Academy of Optometry and a member of the Optometric Retina Society.*

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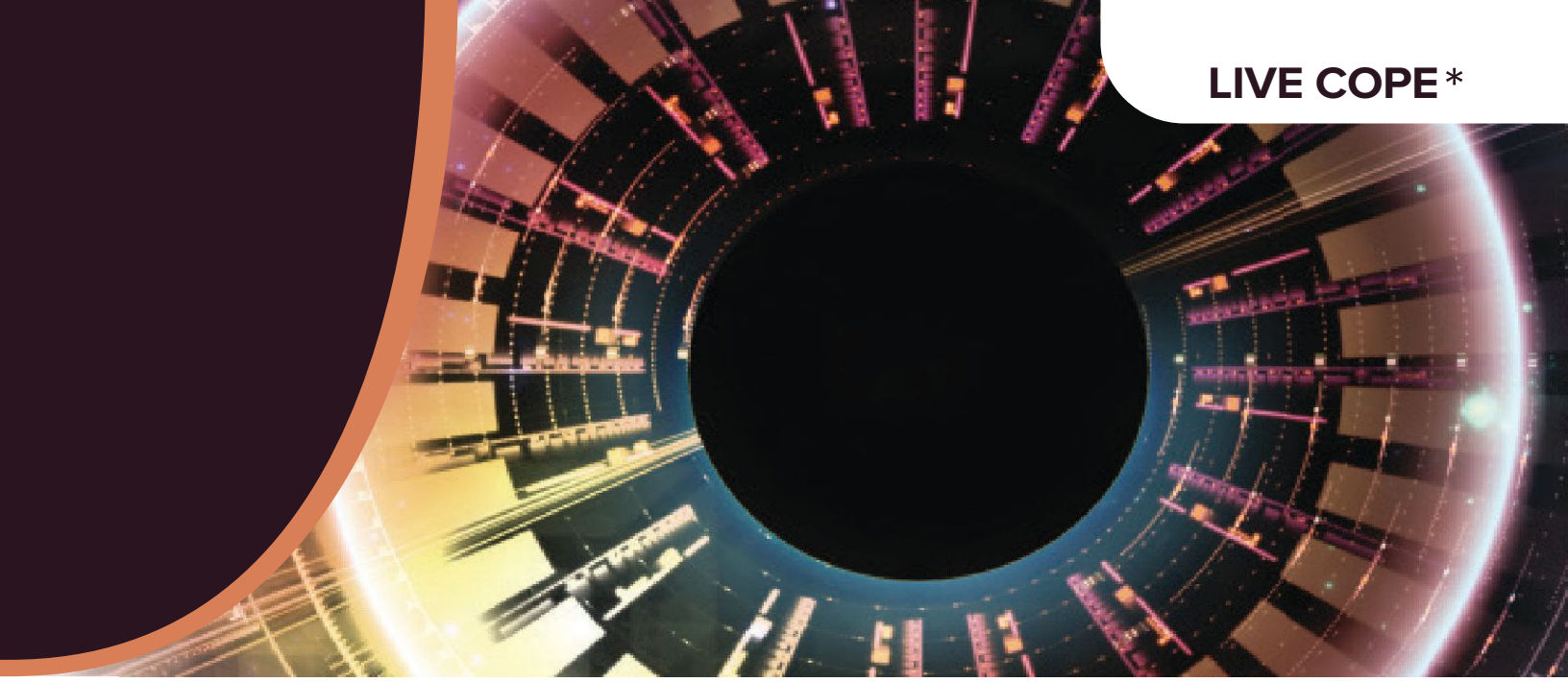

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# CORNEAL DYSTROPHIES FRONT TO BACK

This stepwise approach can help you diagnose and manage these conditions.

By Stephanie Fromstein, OD

Corneal dystrophies are some of the most fascinating—and frustrating—corneal findings eye care providers encounter. Along with anomalies, degenerations, inflammations and infections, it can be challenging to navigate appropriate history and clinical findings to narrow down an accurate diagnosis.

Dystrophies do, however, have several distinguishing features that can help in their identification. Owing to their genetic basis, dystrophies are most often bilateral and relatively symmetric.[1-3] They are usually noted in patients younger than age 20 and tend to progress slowly over time; generally, there is no acute change in vision or symptoms, but rather a gentle decline into relative dysfunction.[1-3] The vast majority of corneal dystrophies are not only hereditary but also autosomal dominant, meaning that immediate family members will share clinical findings, which may aid in diagnosis.

On clinical exam, associated corneal findings tend to present with no other related ocular or systemic disease. Perhaps most importantly for diagnosis, these conditions are located in a single layer of the cornea; thus, accurate determination of location can go a long way toward narrowing the field of potential diagnostic contenders.[1-3]

Corneal degenerations, on the other hand, represent a slow and steady deterioration of corneal tissue with wear and tear. Degenerations usually present as unilateral/asymmetric changes in older patients, often with no underlying genetic etiology. Corneal changes tend to present predominantly peripherally and may impact several corneal layers. These differences from dystrophic changes can be essential in helping to differentiate the two types of corneal changes.

## Epithelial Dystrophies

Moving front to back, we start with dystrophies localized to the corneal epithelium, a five-layer thick structure bound on the southern border

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**Educational Objectives:** After completing this activity, the participant should be better able to:

- Describe the commonly confused corneal dystrophies.
- Use the clinical exam and diagnostic technology to distinguish different corneal dystrophies.
- Review the prevalence and genetic patterns of corneal dystrophies.
- Comprehend the implications for patients and their families.
- Discuss the various treatment options.

**Target Audience:** This activity is intended for optometrists engaged in the care of patients with corneal dystrophies.

**Accreditation Statement:** In support of improving patient care, this activity has been planned and implemented by the Postgraduate Institute for Medicine and Review Education Group. Postgraduate Institute for Medicine is jointly accredited by the Accreditation Council for Continuing Medical Education, the Accreditation Council for Pharmacy Education, and the American Nurses Credentialing Center, to provide continuing education for the healthcare team. Postgraduate Institute for Medicine is accredited by COPE to provide continuing education to optometrists.

**Faculty/Editorial Board:** Stephanie Fromstein, OD, Illinois College of Optometry.

**Credit Statement:** This course is COPE approved for 2 hours of CE credit. Course ID is **69300-AS**. Check with your local state licensing board to see if this counts toward your CE requirement for relicensure.

**Disclosure Statements:**

*Dr. Fromstein* has nothing to disclose.

*Managers and Editorial Staff:* The PIM planners and managers have nothing to disclose. The Review Education Group planners, managers and editorial staff have nothing to disclose.

by a basement membrane. There are only two epithelial dystrophies, significantly narrowing the field for an accurate diagnosis. Moreover, one of the epithelial dystrophies is strikingly common, while the other is exceedingly rare.

***Epithelial basement membrane dystrophy (EBMD).*** When discussing prevalence, EBMD is the most common dystrophy, with a prevalence of more than 40% in the general population. In fact, this condition is so prevalent—jumping to 70% in those over 50 years old—that there is debate within the eye care community as to whether it may instead represent a corneal degeneration. A lack of clear inheritance pattern also speaks to this suspicion.[4]

This condition—by any definition and any other name (anterior basement membrane dystrophy, map-dot dystrophy, microcystic epithelial dystrophy and Cogan's microcystic dystrophy)—represents a pathognomonic set of superficial corneal findings due to a faulty epithelial basement membrane.[1] The overzealous basement membrane extends abnormally into the epithelium, heaping up the epithelial tissue and forming large well-demarcated areas of opacification known as maps (*Figure 1*). Migrating cellular material becomes trapped and manifests as corneal dots and other unnamed cystic changes. Adjacent rows of thickened and elevated epithelium appear as fingerprints (*Figure 2*).[1-3]

The clinical presentation of these findings can range from evident to elusive; where the etiology of symptoms is opaque, sodium fluorescein (NaFl) can be an invaluable diagnostic aid, as the heaped-up epithelial tissue—devoid of fluorescein—appears black, highlighted by the pooling of green around it, in a configuration known as negative staining.[5] (As a side note, it is due to this very finding that I stress to my students to record "clear to NaFl" on healthy corneal evaluations rather than "(-)NaFl," as this insinuates that the patient has been, or should be, evaluated for EBMD).

**Fig. 1. Large "maps" of redundant epithelium in EBMD.**

When accurately identified, EBMD is noted more often in female patients and increasingly with advancing age.[4] Cases are largely asymptomatic or mild, with the most common symptoms relating to visual changes—usually blur (worse in the morning) or diplopia. Nonspecific symptoms such as foreign body sensation and dry eye may also be present. Most often these cases subsist with simple monitoring until complications arise in the form of recurrent corneal erosion (RCE).[6]

The thickened and redundant basement membrane means that epithelial hemidesmosomes are not able to do their job of anchoring the epithelium into the anterior stroma. This inability of the epithelium to "anchor down" explains the high association of EBMD with RCE. It is estimated that about 33% of EBMD patients will experience RCE at some point in their lives, making it the second most common underlying cause behind trauma.[7]

As a clinical note, the vast majority of EBMD-mediated RCE is found in the inferior one-third of the cornea, so be sure to direct special attention to this area during your slit-lamp evaluation.[8]

If the patient is symptomatic for visual changes, foreign body sensation or dry eye, firstline treatment is lubrication. For RCE prevention, hypertonic salt solutions are a mainstay of therapy to decrease corneal swelling and keep the epithelial tissue anchored to the underlying stroma.[9] Topical therapy, such as steroids, and oral therapy, such as doxycycline (by way of metalloproteinase-9 suppression), are also effective therapies for preventing RCE.[10]

Moderate to severe cases—most commonly those with a positive history of RCE—may require surgical intervention to remove the irregular epithelium. This debridement can be performed with a round blade, spatula, diamond burr or excimer laser. Excimer-laser mediated phototherapeutic keratectomy (photorefractive keratectomy, but for the purpose of minimizing the irregular epithelium and scarring) is preferred by many surgeons for this indication.

Stromal micropuncture has also been used with good success to induce scar tissue to anchor the epithelium to the underlying tissue. Long-term management may additionally include soft or gas-permeable contact lenses to protect the cornea from further erosion and mask any residual irregularity. Lamellar keratoplasty is generally not indicated.[9]

***Meesman corneal dystrophy.*** This epithelial dystrophy is a rare condition despite its autosomal dominant inheritance pattern. Also known as juvenile hereditary epithelial dystrophy, the condition manifests early in life with intraepithelial cysts and vesicles due to localized keratin dysfunction. These cysts are generally small and filled with granular, filamentary material known as "peculiar substance." While they may extend limbus-to-limbus, they tend

to be more concentrated centrally and interpalpebrally, and are best viewed via retroillumination.

The condition is largely asymptomatic other than mild visual changes (blur, glare, light sensitivity) and discomfort if and when the cysts rupture onto the epithelial surface.[1-3] If symptomatic, lubricants and debridement may be considered as well as lamellar keratoplasty in rare cases where significant opacification has led to decreased acuity.[11]

## Bowman's/Anterior Stromal Dystrophies

As we move deeper into the cornea, we arrive at Bowman's layer, which is notable because it is much more likely to scar than its epithelial counterpart.[12] Much like with the epithelial dystrophies, there are only a handful of dystrophies to consider, once accurately localized.

While it is nearly impossible to identify changes specific to Bowman's layer on slit-lamp examination, a few clinical pearls can aid in differentiation. Anteriorly, the appearance of the dystrophic changes in Bowman's layer do not resemble those of the epithelium; thus, these are not easily conflated.

Posteriorly, when compared with dystrophies of the anterior stroma, it is helpful to recall corneal anatomy; Bowman's layer dystrophies will appear subepithelial and deposition will appear to be in a very thin layer just below the epithelium. Anterior stromal dystrophies present deeper than Bowman's layer dystrophies, and the deposits are dispersed more diffusely throughout a thicker slice of the corneal landscape.

As such, Bowman's layer dystrophies are not quite epithelial while not quite stromal, which can be diagnostic unto itself. Anterior segment OCT can also be helpful in isolating the deposits, should this technology be available in-office.

Until recently, these dystrophies were considered one and the same, and even since being distinguished (based on electron microscopy and not on clinical findings), they remain variations rather than completely distinct entities. Given their similitude, the three Bowman's layer dystrophies (Reis-Buckler's, Thiel-Behnke and Grayson-Willbrandt/Stocker-Holt) can be considered as a single clinical entity.[13]

All Bowman's layer dystrophies are bilateral, symmetric and autosomal dominant. Clinical examination reveals central ring-shaped subepithelial opacities that generally appear in early childhood. Compared with epithelial dystrophies, these patients are more likely to be symptomatic, complaining of visual changes (blur, photophobia, diplopia) as well as foreign body sensation and pain, often due to RCE.[1-3]

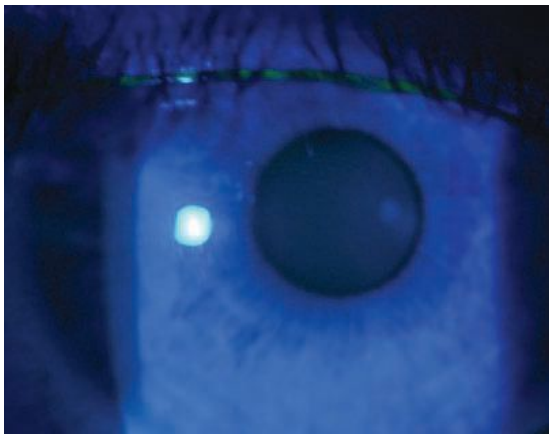

**Fig. 2. Adjacent rows of thickened and elevated epithelium ("fingerprints") viewed with NaFl in a patient with EBMD.**

If symptoms are mild, they can often be managed with lubrication. More severe cases may require debridement and/or keratoplasty for those with significant scarring impacting acuity. RCE should be managed as indicated.[1-3]

## Stromal Dystrophies

The stroma takes up the bulk of corneal real estate (90%) and, accordingly, many of the dystrophies demonstrate clinical changes in this layer.[14] There are a larger number of stromal dystrophies compared with any other layer, though frequent recategorization means that the actual number varies slightly as more advanced technology allows us to more accurately localize our findings. While there is massive variation among the stromal dystrophies, they can broadly be narrowed based on prevalence, type of deposition and location within the layer (anterior or posterior).

***Lattice dystrophy.*** This is the most prevalent stromal dystrophy, displaying autosomal dominant inheritance and an early onset of symptoms (usually within the first decade). The condition is characterized by fine, branching irregular amyloid deposits arranged in fine lines in the anterior stroma.[1-3] These deposits may initially be surrounded by haze that fibroses over time, causing the refractile deposits to become opacified.

There were formerly two types of lattice dystrophy, distinguished mainly by the presence of systemic manifestations of amyloid accumulation (Type I has no systemic associations, while Type II has been associated with connective tissue disorders and ataxia). However, Type II is now considered a systemic disorder with ocular findings, not a separate corneal dystrophy.[1-3,15]

Decreased acuity is likely a result of the deposition and attendant haze. Reduced corneal sensitivity is common.[1-3,15] RCE may also occur as a result of disruption of the hemidesmosomes anchoring the epithelium to the stroma, though this time the interruption comes from below.

***Granular dystrophy.*** This condition is next in line in prevalence, with two distinct iterations each

demonstrating autosomal dominant inheritance and an onset in the first or second decade of life. Granular dystrophy Type I (classic type) is characterized by small, discrete white granules composed of hyaline in the anterior stroma (*Figure 3*).[1-3] These demarcated deposits are initially separated by clear spaces, but as the condition progresses, the breadcrumb/snowflake-like deposits become more confluent.

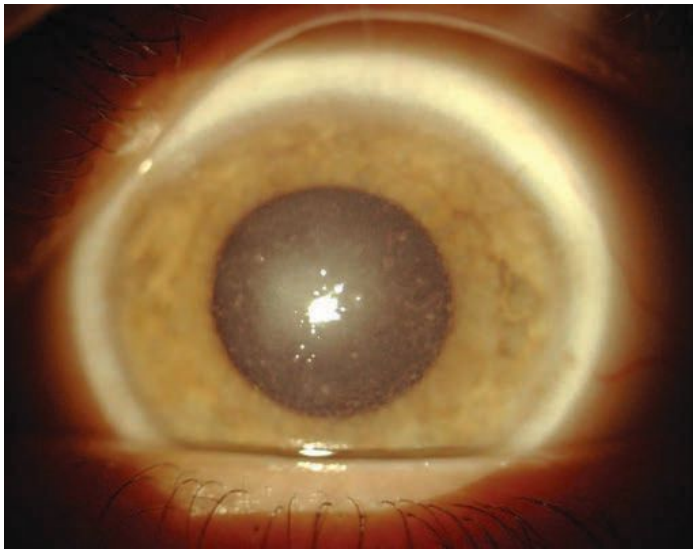

**Fig. 3. Stromal hyaline deposits seen in a patient with granular dystrophy.**

Symptoms are initially mild but progressive, and patients are likely to suffer from consequent decreased acuity requiring treatment.[1-3] This dystrophy may cause decreased acuity, decreased corneal sensitivity and RCE. In contrast to other corneal dystrophies, lattice dystrophy is more likely to be unilateral or largely asymmetric.[1-3]

The second form of granular dystrophy (Type II)—also known as granular-lattice or Avellino dystrophy—combines features of both granular and lattice dystrophy. Anterior stromal, discrete gray-white opacities and lattice lesions in the mid- and posterior stroma are pathognomonic for the condition.[16]

In contrast to classic lattice dystrophy, the branches do not cross and form the classic "lattice" pattern for which the dystrophy is named, in addition to other more subtle differentiating features.[15] The condition tends to have more severe symptoms with an earlier onset compared with its classic counterpart, owing in part to its autosomal dominant nature with high penetrance.[1-3]

***Macular dystrophy.*** Rounding out the top three stromal dystrophies is macular dystrophy, which is unique in several ways. First, it is the only autosomal recessive stromal dystrophy, meaning that the patient may not have the marked family history that will be noted in previous conditions. Despite this, it still shows a relatively high prevalence, even greater than lattice and granular in some studies. It also has a tendency to extend limbus-to-limbus (not sparing the periphery) and anterior-to-posterior stroma.[1-3]

Clinical examination reveals gray-white, ill-defined focal opacities composed of glycosaminoglycan. Diffuse cloudiness results from changes in the collagen fibril arrangement. Interestingly, as the regular collagen tissue is replaced by fibrotic tissue, the condition may be associated with corneal thinning.[17] Given that it breaks so many of the rules of corneal dystrophies as well as its similar appearance to a host of other corneal findings (including inflammatory corneal signs seen as a result of infection or other corneal insult), this can be a challenging identification. However, symptoms of visual changes, decreased corneal sensitivity and the potential for RCE remain consistent with other stromal dystrophies.

***Fleck dystrophy.*** Beyond these 'big three,' there are several increasingly rare stromal dystrophies that bear mentioning for completeness. Fleck or speckled dystrophy is autosomal dominant with onset in the first decade. It may be unilateral or relatively asymmetric. The condition is most often mild, with patients reporting no symptoms or occasional photophobia.

On clinical examination, very small gray-white opacities can be seen scattered in the stroma, giving the appearance of dandruff. While not entirely clear why, there is an association with other ocular findings, including keratoconus, ocular dermoids, cataracts and papillitis, which may speak to a defect of collagen metabolism, which has not yet been fully elucidated.[1-3]

***Central crystalline dystrophy of Schnyder.*** This autosomal dominant condition presents in the first decade of life with central disciform opacities often surrounded by a finding of dense arcus (related but distinct). This combination of central and peripheral findings is distinct and pathognomonic for this dystrophy.

Deposits consist of polychromatic needle-shaped crystals composed of cholesterol, reflecting a localized disorder of cholesterol metabolism. This localized dysfunction can be, and often is, exacerbated by systemically elevated serum cholesterol. Given that 50% have elevated levels of cholesterol, every patient presenting with Schnyder dystrophy warrants a hyperlipidemia workup.[1-3]

***Central cloudy dystrophy of Francois.*** This rare, autosomal dominant dystrophy is minimally symptomatic. Like Schnyder, it is also thought to be a result of cholesterol deposition,

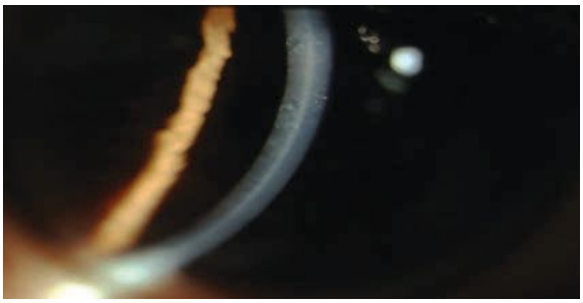

**Fig. 4. Endothelial vesicles in a patient with PPMD.**

but with far less visual complication. The polygonal, cloudy gray opacities are thought to be an inherited form of Crocodile Shagreen, giving a leather-like appearance to the posterior stroma.[1-3]

***Gelatinous drop-like dystrophy.*** This is one of the least common but most visually devastating corneal dystrophies. It is the result of a localized dysfunction of amyloid in the cornea that deposits subepithelially and stromally, leading to significant signs and symptoms. For this reason, it is sometimes classified alongside the more anterior dystrophies. Patients complain of severe redness, irritation, photophobia and tearing.

A clinical examination may reveal decreased acuity as well as centrally raised mounds of amyloid. The late-stage appearance of the condition is referred to as a "nubbly mulberry" surface, which almost invariably requires intervention.[1-3]

***Therapeutic options.*** Treatment for stromal dystrophies depends on the severity of signs and symptoms. Mild forms may be monitored or may encourage use of lubrication for any discomfort or foreign body sensation. More severe cases may require phototherapeutic keratectomy or other forms of debridement, which can be effective in delaying the need for corneal transplantation by up to two years.[17]

If acuity and erosion continue to be problematic, keratoplasty (lamellar or otherwise) may be required for management. While penetrating keratoplasty (PKP) was formerly a mainstay of treatment, studies suggest deep anterior lamellar keratoplasty (DALK) may also be considered with similar acuity outcomes and a lower risk of complication.[17]

Keep in mind, the genetic coding of this information is not eliminated along with the dysfunctional tissue in the case of debridement and transplantation. Thus, recurrence (even in the donor tissue) ranges from possible to probable depending on the individual dystrophy and is more likely to occur with stromal dystrophies (most especially with lattice corneal dystrophy).[18] The patient should be made aware of this likelihood before proceeding with surgery.

## Endothelial Dystrophies

There are three endothelial dystrophies of note, two of which are significantly more common and much more likely to be diagnosed in your chair. Given the endothelium's principal enterprise as the corneal dehumidifier, any disfunction of the endothelium can lead to areas of localized or diffuse corneal edema as well as the attendant complications of decreased acuity and epithelial microcysts.

***Posterior polymorphous dystrophy (PPMD).*** This autosomal dominant dystrophy can impact both Descemet's membrane as well as the endothelium. PPMD can have a wide variety of presentations from linear, parallel, bandlike configurations to vesicles to irregular configurations with scalloped edges, mimicking a break in Descemet's membrane (*Figures 4 and 5*).[1-3] While the presentation varies widely, it tends to be consistent among families, so examination of an immediate family member can give an indication of what type of findings you are likely to see in your own patient.[19]

PPMD is, in a sense, the EBMD of the endothelium, with an abnormal proliferation of cells leading to a wide variety of clinical findings. Essentially, the endothelial cells begin to act as epithelial cells and proliferate, causing the accumulation of an abnormal basement membrane and the thickening of Descemet's membrane.[19] This abnormal proliferation can have a significant impact on endothelial function and may cause abnormalities in adjacent structures (most commonly the iris and angle structures), leading to increased incidence of secondary glaucoma.[1-3,19]

If PPMD is suspected, gonioscopy should be performed to evaluate the angle structures.[19] Iridocorneal endothelial and mesodermal dysgenesis syndromes may present similarly and should be considered as differential diagnoses; a strong family history can help you make an accurate diagnosis.

***Fuchs' endothelial dystrophy.*** This common endothelial dystrophy is marked by bilateral, accelerated endothelial cell loss. It is autosomal dominant and more common in women, usually with a symptomatic onset later in life (60s and 70s).[1-3,20] It is slowly progressive over time but may be acutely accelerated by cataract surgery, given the demographics of affected individuals. Early on, patients may complain of photosensitivity or decreased acuity. Early clinical signs are dominated by corneal guttata—seen as tiny dark spots on specular reflection. Pigment may also be noted on the dysfunctional endothelium.[1-3]

While seemingly a void, these dark spots represent not an absence of tissue but rather a function of the tissue being pushed out of the plane of focus. This happens due to a buildup of basal lamina (collagen),

causing Descemet's membrane and the endothelium to bulge posteriorly in tandem into the anterior chamber (and out of the plane of focus).[1-3]

To avoid total corneal decompensation, the endothelium remodels to help preserve whatever functionality it can. It undergoes a decrease in the number of endothelial cells, causing the remaining cells to both change shape (pleomorphism) and increase in size (polymegathism) as the functional endothelial cells try to cover the workload of the dysfunctional ones. These can both be monitored with specular microscopy, where available.[1-3,20]

As the condition progresses, patients are likely to experience decreased acuity secondary to profound corneal edema. This can and should be monitored by serial pachymetry. Depending on the level of swelling, stromal edema or epithelial microcysts and/or bullae may also be noted.[20]

***Congenital hereditary endothelial dystrophy (CHED).*** This endothelial dystrophy is quite rare and most often diagnosed at birth. The patient will present with bilateral, limbus-to-limbus diffuse corneal edema secondary to the dysfunctional endothelium. This is referred to as a "ground glass" appearance.

There are both autosomal dominant and autosomal recessive iterations, with varying degrees of associated systemic findings including nystagmus and hearing loss. The condition may be stationary or slowly progressive.[1-3]

***Management techniques.*** Treatment for endothelial dystrophies is mainly targeted at minimizing the secondary corneal edema. Mild cases may be monitored, often with serial pachymetry. Moderate conditions may be treated with hypertonic agents or even a hairdryer to minimize corneal hydration. Global decompensation often requires some form of corneal transplantation.

Fuchs' dystrophy was once the chief reason for a full thickness corneal transplant; as our ability to transplant more selectively has improved, these patients can now be treated with a lamellar transplant such as Descemet's membrane endothelial keratoplasty, Descemet's stripping endothelial keratoplasty and Descemet's stripping automated endothelial keratoplasty.[20] This has been a revelation for patients in terms of recovery time and outcomes, and has anecdotally impacted the number of patients willing to pursue treatment for the condition.

There are a wide variety of clinical findings associated with corneal dystrophies. This variety—along with an accurate localization of the findings—makes diagnosis of these conditions relatively straightforward. In any given corneal layer, there are no more than three common contenders, and in no case do the various conditions within a layer resemble each other closely.

This means that armed with an entry-level understanding of the prevalence, clinical features and associated findings, diagnosing these conditions should be relatively effortless. Features shared within a given lamella, such as probable signs, symptoms and complications, further simplify and streamline management. While dystrophies on the aggregate can and often do seem intimidating, as with most things, a stepwise approach yields dividends in terms of diagnosis and treatment. ■

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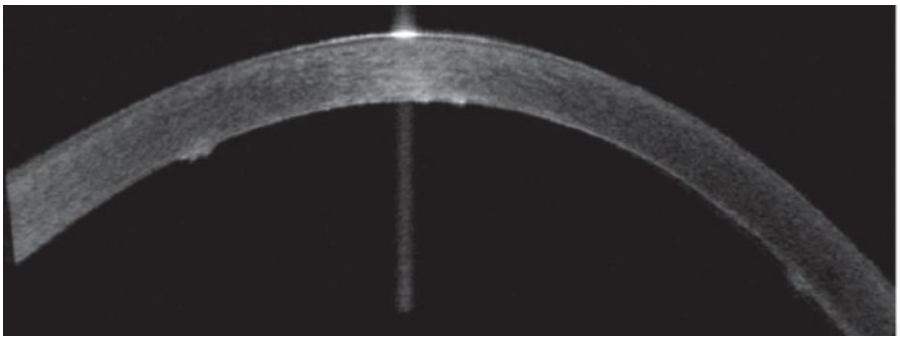

**Fig. 5. Endothelial vesicles as viewed with anterior segment OCT on a patient with PPMD.**

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## OSC QUIZ

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Please check with your state licensing board to see if this approval counts toward your CE requirement for relicensure.

1. Which of the following is not a defining feature of a corneal dystrophy?
a. Bilateral.
b. Symmetric.
c. Multiple corneal layers impacted.
d. Slowly progressive.

2. Which of the following is the most common corneal dystrophy?
a. Granular corneal dystrophy.
b. Epithelial basement membrane dystrophy.
c. Fuchs' corneal dystrophy.
d. Posterior polymorphous dystrophy.

3. Which of the following is not generally an indicated therapy for EBMD?
a. Hypertonic solutions.
b. Steroids.
c. Phototherapeutic keratectomy.
d. Penetrating keratoplasty.

4. All of these are classified as a Bowman's/anterior stromal dystrophy, *except:*
a. Cogan-Reese.
b. Reis-Buckler's.
c. Thiel-Behnke.
d. Grayson-Willbrandt.

5. Which of the following represents localized amyloid deposition of the corneal stroma?
a. Granular dystrophy.
b. Lattice dystrophy.
c. Macular dystrophy.
d. Fleck dystrophy.

6. Which of these represents the only recessive dystrophy of the corneal stroma?
a. Granular dystrophy.
b. Lattice dystrophy.
c. Macular dystrophy.
d. Fleck dystrophy.

7. Which of the following dystrophies should include a hyperlipidemia workup as part of your management?
a. Fleck dystrophy.
b. Central crystalline dystrophy of Schnyder.
c. Gelatinous drop-like dystrophy.
d. None of the above.

8. Avellino dystrophy shares features of which of the following corneal dystrophies?
a. Macular dystrophy.
b. Granular dystrophy.
c. Fleck dystrophy.
d. Crystalline dystrophy.

9. Deposition, corneal clouding and decreased acuity are likely to recur after which of the following procedures?
a. Phototherapeutic keratectomy.
b. Deep anterior lamellar keratoplasty.
c. Penetrating keratoplasty.
d. All of the above.

10. Which of the following dystrophies may be treated with Descemet's stripping endothelial keratoplasty?
a. Map-dot dystrophy.
b. Fuchs' dystrophy.
c. Granular dystrophy.
d. Lattice dystrophy.

11. Which of these should include gonioscopy as part of your management?
a. Fleck dystrophy.
b. Fuchs' dystrophy.
c. Posterior polymorphous dystrophy.
d. Gelatinous drop-like dystrophy.

12. Which of these should include specular microscopy as part of your management?
a. Fleck dystrophy.
b. Fuchs' dystrophy.
c. Lattice dystrophy.
d. Gelatinous drop-like dystrophy.

13. Which of the following dystrophies shows a pathognomonic negative-staining pattern?
a. Map-dot dystrophy.
b. Posterior polymorphous dystrophy.
c. Lattice dystrophy.
d. Gelatinous drop-like dystrophy.

14. Which of these is most likely to be associated with recurrent corneal erosion?
a. Map-dot dystrophy.
b. Fuchs' dystrophy.
c. Posterior polymorphous dystrophy.
d. Lattice dystrophy.

15. Which of these dystrophies is most likely to be associated with corneal edema?
a. Map-dot dystrophy.
b. Fuchs' dystrophy.
c. Lattice dystrophy.
d. Gelatinous drop-like dystrophy.

16. Which of these dystrophies are you more likely to note in a patient with keratoconus?
a. Avellino dystrophy.
b. Fleck dystrophy.
c. Crystalline dystrophy.
d. Cloudy dystrophy.

17. What is the etiology of pain often noted in conjunction with Bowman's layer dystrophies?
a. Dry eye.
b. Epithelial bullae.
c. Recurrent corneal erosion.
d. Disruption of stromal nerve plexus.

18. Which of the following dystrophies is most likely to cause changes to adjacent structures, including the iris?
a. Fuchs' dystrophy.
b. Posterior polymorphous dystrophy.
c. Lattice dystrophy.
d. Gelatinous drop-like dystrophy.

19. Which of the following dystrophies shows deposition of both amyloid and hyaline?
a. Lattice dystrophy.
b. Granular dystrophy Type I.
c. Granular dystrophy Type II.
d. Gelatinous drop-like dystrophy.

20. Which of the following dystrophies shows deposition of cholesterol?
a. Lattice dystrophy.
b. Granular dystrophy Type I.
c. Schnyder's dystrophy.
d. Gelatinous drop-like dystrophy.

# Examination Answer Sheet

Corneal Dystrophies Front to Back

*Valid for credit through September 15, 2023*

**Online:** This exam can be taken online at revieweducationgroup.com. Upon passing the exam, you can view your results immediately and download a real-time CE certificate. You can also view your test history at any time from the website.

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**Processing:** There is a four-week processing time for this exam.

**Answers to CE exam:**

1. Ⓐ Ⓑ Ⓒ Ⓓ
2. Ⓐ Ⓑ Ⓒ Ⓓ
3. Ⓐ Ⓑ Ⓒ Ⓓ
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19. Ⓐ Ⓑ Ⓒ Ⓓ
20. Ⓐ Ⓑ Ⓒ Ⓓ

**Post-activity evaluation questions:**

*Rate how well the activity supported your achievement of these learning objectives:*
*1=Poor, 2=Fair, 3=Neutral, 4=Good, 5=Excellent*

21. Describe the commonly confused corneal dystrophies. ① ② ③ ④ ⑤
22. Use the clinical exam and diagnostic technology to distinguish different corneal dystrophies. ① ② ③ ④ ⑤
23. Review the prevalence and genetic patterns of corneal dystrophies. ① ② ③ ④ ⑤
24. Comprehend the implications for patients and their families. ① ② ③ ④ ⑤
25. Discuss the various treatment options. ① ② ③ ④ ⑤

26. Based upon your participation in this activity, do you intend to change your practice behavior? (choose only one of the following options)
Ⓐ I do plan to implement changes in my practice based on the information presented.
Ⓑ My current practice has been reinforced by the information presented.
Ⓒ I need more information before I will change my practice.

27. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit? (please use a number): ☐

28. If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

ⓐ Apply latest guidelines ⓑ Change in pharmaceutical therapy ⓒ Choice of treatment/management approach ⓓ Change in current practice for referral ⓔ Change in non-pharmaceutical therapy ⓕ Change in differential diagnosis ⓖ Change in diagnostic testing ⓗ Other, please specify: _____

29. How confident are you that you will be able to make your intended changes?

ⓐ Very confident ⓑ Somewhat confident ⓒ Unsure ⓓ Not confident

30. Which of the following do you anticipate will be the primary barrier to implementing these changes?
ⓐ Formulary restrictions
ⓑ Time constraints
ⓒ System constraints
ⓓ Insurance/financial issues
ⓔ Lack of interprofessional team support
ⓕ Treatment related adverse events
ⓖ Patient adherence/compliance
ⓗ Other, please specify:

31. Additional comments on this course:

Please retain a copy for your records. Please print clearly.

First Name
Last Name
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The following is your: ☐ Home Address ☐ Business Address
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*Rate the quality of the material provided:*
*1=Strongly disagree, 2=Somewhat disagree, 3=Neutral, 4=Somewhat agree, 5=Strongly agree*

32. The content was evidence-based. ① ② ③ ④ ⑤
33. The content was balanced and free of bias. ① ② ③ ④ ⑤
34. The presentation was clear and effective. ① ② ③ ④ ⑤

By submitting this answer sheet, I certify that I have read the lesson in its entirety and completed the self-assessment exam personally based on the material presented. I have not obtained the answers to this exam by any fraudulent or improper means.

Signature _____ Date _____

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FALL AND WINTER 2020

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# More Than Meets the Eye

Even though there are no upfront contraindications, proceed with caution when transplanting from tissues with pseudoexfoliation syndrome. **Edited by Joseph P. Shovlin, OD**

**Q Can a donor cornea from a patient with pseudoexfoliation syndrome (PEX) be used for grafting?**

A "Technically, yes," says Christopher Luft, OD, of Woodstock, GA. "Though this multifactorial, systemic microfibrillopathy affects more than meets the eye."

As technology advances and our understanding of healthy corneal tissue improves, the number of corneas suitable for grafting and transplantation has significantly increased, according to Dr. Luft. While criteria is in place to prevent serious complications for the host, a successful transplant is largely dependent on the donor's systemic health profile, time-from-death to graft procurement and properly functioning tissue with a focus on the corneal endothelium.[1]

## Weighing Your Options

A recovery technician first completes an aseptic full body exam to rule out any signs of high-risk behavior, gross pathology and scars or identifiable marks.[1] The technician must pay close attention to any medical issues that occurred within the last week of the donor's life.[1]

A post-mortem blood draw is then performed and used to identify systemic disease. Infectious diseases, such as hepatitis, HIV, rabies and syphilis, malignancy around the anterior segment of the eye and other infections are contraindications for corneal grafting.[1] Neurodegenerative disease, drug use, travel history and acute infections may prohibit donation completely.[1]

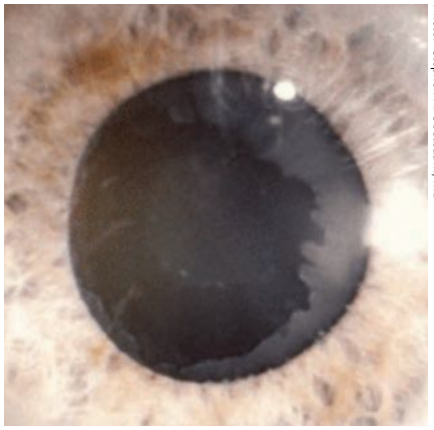

Photo: Stephen A. Obstbaum, MD

**The peripupillary and lenticular fibrillar material in this PEX patient can affect dilation and cause corneal and zonule decompensation and pressure spikes.**

Once a potential donor is determined to be a candidate, the graft is extracted and the corneal tissue is stored.[1] Grafts are suitable for transplantation for up to 14 days.[1]

## Assessing PEX

Specular microscopy is an objective way of analyzing the structure of the endothelial cells of the host cornea to determine underlying pathology.[1,2] Endothelial cell density must fall within a certain range (around 2000 cells per mm$^2$).[1,2] Endothelial cell shape and orientation in the setting of polymegethism and pleomorphism, along with other endotheliopathies, are contraindications, as they affect quality of vision and may lead to graft failure.[1]

When it comes to PEX, no immediately disqualifiable contraindications exist.[2,3] PEX is a systemic, age-related condition characterized by the production and deposition of extracellular, granular material, most notably in the anterior segment of the eye.[2-4] If this material is transplanted from the cornea to the host, PEX may cause corneal endothelial cell decompensation by breaking down the hexagonal connections of the endothelium and promoting apoptosis, which can lead to bullous keratopathy and, ultimately, graft failure.[2-4] Pre-op cytokine levels and fibrogenic growth factors associated with PEX may also be transferred to the host, causing a pro-inflammatory cascade and progressive damage to corneal tissue.[4]

With that being said, Dr. Luft notes that it is unknown whether these particles, if transplanted, will multiply and transfer the condition to a healthy cornea and anterior chamber. He adds that his colleagues believe they are an incidental part of the process and wash away with circulating aqueous over time with no visual significance.

Implantation success is directly related to graft health. While there are no upfront contraindications, proceed with caution when transplanting from tissues with PEX to a healthy host. While PEX particles entering a host may not cause lasting adverse effects to the grafted cornea or anterior chamber, the threat of potential complications should not be taken lightly. ■

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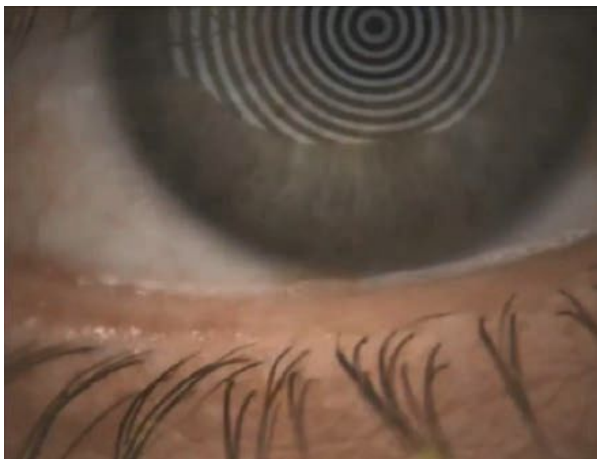
# Dry Eye: The Nose Knows

Neurostimulation is becoming a viable treatment option for patients who have exhausted their options. **By Paul M. Karpecki, OD**

Neurostimulation has become the new frontier in dry eye therapy, now that scientists know the trigeminal nerve is a critical factor in ocular surface health and symptomatology. In fact, the nerve plays a multifactorial role: it can become fatigued (often due to misalignment), causing dry eye symptoms, headaches and neck pain; it maintains the trophic supply to the cornea, preventing epithelial breakdown; and, when stimulated, it can also promote tear production. New products are taking advantage of the latter function to help dry eye patients produce natural, lubricating tears instantly.



**This patient exhibits significant meibum secretion after using the iTear100 neurostimulator.**

## A Novel Pathway

The parasympathetic nervous system (PNS), via the trigeminal parasympathetic pathway, controls tear film homeostasis by innervating the lacrimal functional unit (LFU), which includes the cornea, conjunctiva, lacrimal glands, meibomian glands and goblet cells.[1-3] The PNS is easily accessed through the nose, and research shows 34% of basal tear production is due to sensory stimulation from inhaled air through the nasal passage.[4]

Studies show that nasal neurostimulation affects all parts of the LFU and increases basal tears that have the same composition as the patients' naturally occurring basal tears.[5,6,8] This includes stimulation of the lacrimal glands, resulting in aqueous production and the goblet cells that secrete gel-forming mucins, such as mucin MUC5AC. The goblet cells mainly use apocrine methods; when they receive neural stimulation, they release all of the contents of their secretory granules at once. Intranasal neurostimulation also can change meibomian gland activity and lipid layer thickness with eight minutes of use.[5-7]

## Devices and Drops

Two therapies will soon make neurostimulation a viable treatment option for dry eye patients: the iTear100 (Olympic Ophthalmics) and verenecline (Oyster Point Pharma).

The iTear100 was FDA approved on May 1, 2020—just as Allergan discontinued its TrueTear neurostimulation device. Unlike TrueTear, which was an intranasal device that delivered small electrical currents to sensory neurons of the nasal cavity—the iTear100 is an electromechanical nerve stimulator applied externally. It is indicated for temporary use (up to 30 days) to increase acute tear production via vibratory stimulation of the external nasal nerve in adults. As with TrueTear, it also requires a prescription by an eye care provider.

Patient's apply the handheld, noninvasive device to the soft tissue fold on the *outside* of the nose for up to 30 seconds per side to activate the trigeminal parasympathetic pathway via a sonic frequency.

Patients can use it as needed throughout the day and after one month the device requires reactivation. Currently, the patient can exchange the device through the company or their doctor's office; in the near future, the patient will receive a reactivation code electronically or via an app, at the discretion of the eye care practitioner.

In the clinical studies, Schirmer's scores, fluorescein staining, tear break-up time and meibomian gland scores all improved statistically—and immediately—over the intermediateterm and long-term (180 days). Furthermore, Ocular Surface Disease Index scores showed statistical improvement at every study visit. Safety and patient comfort scores showed a favorable risk-benefit ratio with only 3% of the study population reporting adverse events such as

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sneezing, tickling or headaches, and 1% noted nasal pain.

This technology is a wonderful new option to add to your armamentarium, because our natural tear secretion is far more complex and potent, containing nerve growth factors, hundreds—if not thousands—of proteins, mucins and lipids. Patients who state they frequently rely on artificial tear use may be able to use neurostimulation to decrease their reliance on artificial tears (44.2% of patients in the study) or eliminate them (23.3%) altogether.

It's good to see a new neurostimulation device on the market, as many patients who had success with TrueTear are looking for an alternative. The external application of the iTear100 makes it an easy treatment option for doctors, staff and patients. Training is straightforward, and patients quickly learn how to use the device by watching an online video.

Anecdotally, I have found that providing patients the ability to boost their own tear production instantly, affecting all three components (aqueous, mucin and lipids), leads to a high patient satisfaction rate. It's an essential tool for mild dry eye patients who do not want to instill artificial tears; it's also useful for severe dry eye patients who still require significant artificial tear application while on other therapies.

During the clinical trials, I personally included patients with severe dry eye and those who were recalcitrant to other therapy and observed remarkable improvements in signs and symptoms in the patients using the iTear100.

## Pharma Pipeline

An intranasal spray may soon bolster your neurostimulation options, now that Oyster Point Pharma has reported its first phase III FDA clinical trial results for verenecline intranasal spray. This preservative-free spray contains a nicotinic acetylcholine receptor (nAChR) agonist designed to stimulate the trigeminal parasympathetic pathway.

The ONSET 2 study for Oyster Point's OC-01 drug candidate, verenecline, enrolled 758 subjects diagnosed with dry eye disease; the trial included an array of patients, including those with minimal symptoms. The subjects were randomized into three equal treatment groups: placebo (vehicle control) and two concentrations of verenecline intranasal spray, 1.2mg/ml and 0.6mg/ml). Patients were treated twice a day for four weeks.[9]

At four weeks, both active doses produced a statistically significant improvement in dry eye signs (Schirmer's score) compared with placebo, with a mean change from baseline of 11.0mm for the 0.6mg/ml and 11.2mm for the 1.2mg/ml group (the placebo group also experienced a mean change of 5.9mm).[9]

Both concentrations also met the secondary endpoint of symptom improvement, measured with the Eye Dryness Score, as soon as two weeks post-treatment.

Adverse events were mild and transient and, given the nasal route of delivery, there were no ocular related tolerability issues. The most common adverse events included sneezing after instillation (99% of patients, all of whom listed it as mild), cough after instillation, throat irritation and instillation site irritation.

Neurostimulation is giving us a whole new way to approach dry eye therapy. For patients who have exhausted traditional therapies, it might provide the relief they have been looking for, and for those who rely only on artificial tears, it can provide a better quality tear. Even for those with mild symptoms, the novel pathway could help relieve those symptoms when they crop up. Keep an eye out for the new device and the nasal spray on the way. ■

*Note: Dr. Karpecki consults for companies with products and services relevant to this topic.*

### TrueTear Off the Market

The first neurostimulation device approved for dry eye, TrueTear (Allergan), was recently discontinued. Allergan is offering a full refund to patients who purchased the device in the last three years. Here's how it works: Patients must submit proof of purchase with a consumer refund request form to Truetear@allergan.com. They will then information necessary to return the device. One Allergan receives the device, it will issue a full refund within two to three weeks. Patients can get started at www.truetear.com.

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# Check for Elevation

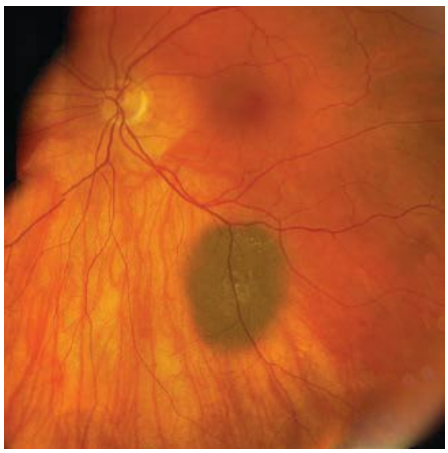
Imaging technology can help determine whether a lesion is benign or malignant.

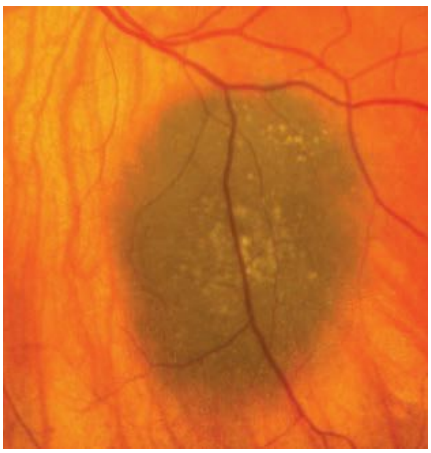
By Mark Dunbar, OD

A 71-year-old Caucasian female presented for a diabetic eye screening. She was diagnosed with type 2 diabetes about one year ago, and her endocrinologist told her that she needed to get an eye exam. She was on metformin 500mg per day and reported good blood sugar control. Her previous eye exam was one year earlier in a retail setting where she was told that she needed to be seen by a specialist.

On examination, the patient's entering distance acuities measured 20/20 OD and 20/20 OS. Her extraocular motility testing was normal. Confrontation visual fields were full to careful finger counting OU. The pupils were equally round and strongly reactive; there was no afferent pupillary defect. The anterior segment examination was unremarkable.

Dilated fundus exam of the right eye was normal, while the left eye showed changes (*Figures 1 and 2*). An OCT was obtained and is also available for review (*Figure 3*).





**Figs. 1 and 2. These are the fundus photographs of the left eye of our patient. What do they represent?"**

## Take the Retina Quiz

1. What is the most likely diagnosis for this patient?
a. Choroidal nevus
b. Choroidal melanoma
c. Melanocytoma
d. Metastatic carcinoma

2. What additional testing would be helpful in this patient?
a. Fluorescein angiogram
b. Ultrasound
c. Liver function testing
d. Chest X-ray

3. How should this patient be managed?
a. Observation
b. Enucleation
c. Plaque radiotherapy
d. Chemotherapy

4. What is your estimate of the likelihood the lesion will grow over the next five years?
a. Very low
b. Mild chance–about 25%
c. Significant chance–50%
d. Very high

5. What is the overall prognosis for this patient?
a. Very poor
b. Moderate
c. Excellent
d. Uncertain to determine

*For answers, see page 106.*

## Discussion

The slate gray-pigmented lesion along the inferior arcade in the left eye is suspicious. However, on stereoscopic evaluation, you could tell that it is flat. What's more, there are drusen overlying it that indicates the lesion has been present for a while. It's also important to note there is no orange pigment or lipofiscin present, which is not a good prognostic indicator and is often seen with choroidal melanoma. Given this presentation, our patient has a choroidal nevus.

Choroidal nevi are developmental tumors that are usually found as an incidental finding during a routine eye examination. In appearance, 95% of choroidal nevi are flat, slate gray and less than three disc-diameters in size. Choroidal nevi are made up of benign spindle cells and branched melanocytes.

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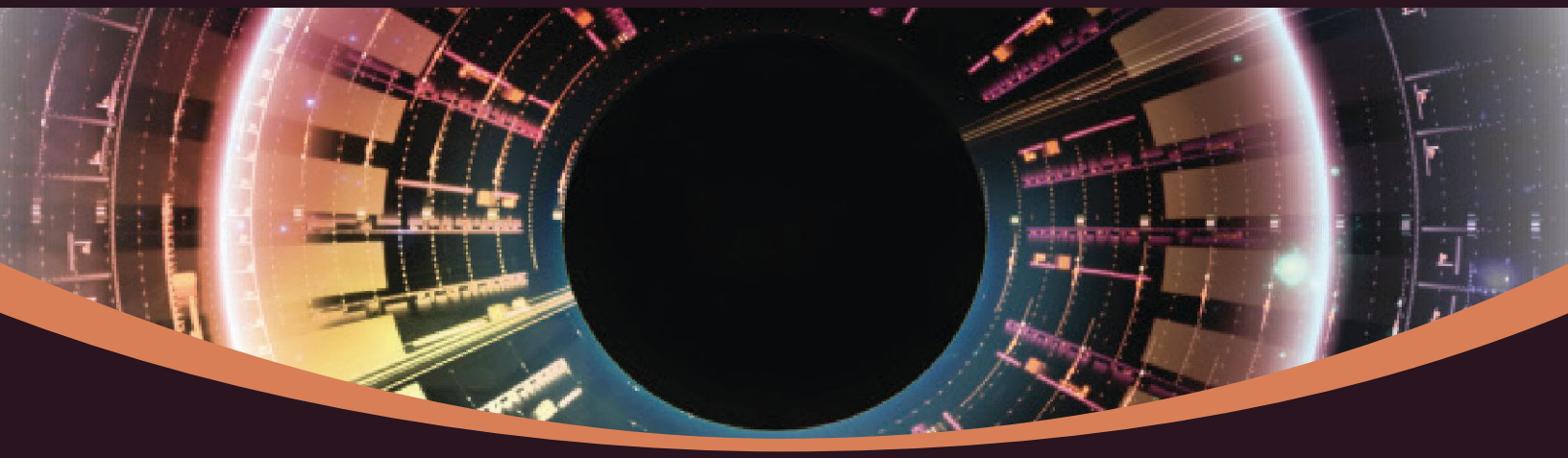

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## A Closer Look

In most instances, the diagnosis of a choroidal nevus is straightforward, and there is little or no concern that the lesion is a choroidal melanoma. However, that's not always the case, especially as choroidal nevi can have features that make it more difficult to distinguish between a benign nevus and a small malignant melanoma.

On clinical exam, it's not always easy to determine if the lesion is flat or minimally thickened. Fortunately, OCT can often help. Though not designed for tissue differentiation (like the standardized A-scan), the OCT can help determine if there is elevation, or if fluid is present.

Indeed, in our patient, we can see the nevus is flat but, interestingly, we can also see the posterior contours of the lesion within the choroid. This is a more dense or a homogenous localized area posterior to the retinal pigmented epithelium (RPE) within the choroid. Standardized A- and B-scans would be great additional tests for this patient, but they're not critical, as the OCT and clinical exam provide the necessary information to make the right diagnosis.

In addition to the presence of overlying drusen, other clues that may be helpful in differentiating a suspicious nevus from a small melanoma include the presence of RPE hyperplasia or atrophy, bony pigment spicules and even choroidal neovascularization. Any of those findings are signs of chronicity and suggest that the lesion has been present for some time. An actively growing melanoma does not have time to develop these more chronic changes.

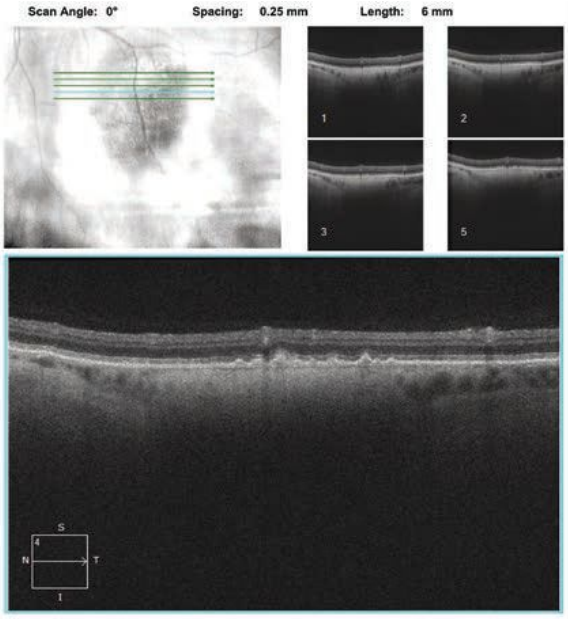


**Fig. 3. Note the changes in the choroid on the OCT through the lesion. What do they represent?**

In contrast, most melanomas are usually over 3.0mm in thickness, can be variably pigmented and may have lipofuscin present, which, as discussed earlier, suggests greater malignant potential. Ultimately the best way to determine if a suspicious lesion is a melanoma or a nevi is to take a photograph and document growth of the lesion over time. Choroidal nevi will rarely show any significant growth.

## Risk Factor Features

A question that often gets raised: do melanomas develop from transformation of preexisting nevi, or are they in fact separate entities? Most experts agree that the vast majority develops as separate entities. Malignant transformation from preexisting nevi is exceedingly rare, occurring between one in 4,800 to one in 8,800 individuals.[1] In one retrospective analysis of approximately 1,300 patients with small melanocytic lesions less than 3.0mm in thickness, the authors identified five factors associated with risk for growth: (1) tumor thickness greater than 2.0 mm; (2) subretinal fluid; (3) visual symptoms; (4) orange pigment; (5) posterior tumor margin touching the disc.[2]

In patients who had no risk factors, lesion growth was observed in only 4%.[2] Growth occurred in 36% of patients who had at least one risk factor, and in 50% of those with three or more risk factors.[2] These features may be remembered more easily using the mnemonic "To Find a Small Ocular Melanoma".[2] Clinical factors associated with an increased risk of metastasis included: (1) posterior margin touching the disc; (2) documented growth; and (3) increased tumor thickness (at least 1.1mm).[3]

In our patient, we were able to determine that her nevus was discovered over 10 years ago. Though we didn't have any old fundus photos to compare with, the fact that it was noted that long ago is further confirmation that this is just a nevus and will likely not change over time. She did not have diabetic retinopathy, but we did explain the importance of good blood sugar control and the importance of annual follow-up exams, given that she has a choroidal nevus as well as the long-term risk of developing diabetic retinopathy. ■

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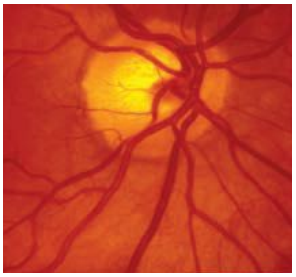

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# It Might Be a Giant

Recognizing these signs and symptoms immediately is critical to getting your patients the help they need. **By Jason Duncan, OD, Haley Baldridge, OD, and Richard Mangan, OD**

A 70-year-old Caucasian male presented on a Monday morning, reporting that he had lost his vision in his right eye the Friday prior and ended up in the emergency room with a blood pressure of 65/42. He had undergone a CT, MRI, carotid Doppler and EKG, all of which were normal. He was released and told his vision would likely recover. He had no such luck over the weekend.

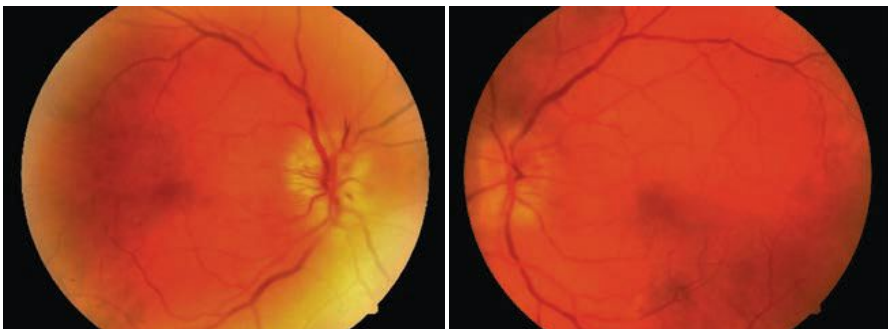
The patient said he has had a significant headache and scalp tenderness on the right side of his head for approximately one week. He had lost about 30 pounds recently and has had a fever of unknown etiology. Medical history was positive for controlled diabetes (HbA1c was 6.4), high cholesterol and a recent bout of shingles on the left side. He is currently finishing his Valtrex (valacyclovir, GlaxoSmithKline) and a low-dose oral steroid regimen.

The patient's entrance acuities were hand motion OD and 20/30 OS. His anterior segment was within normal limits OU, as were his intraocular pressures. The labs we ordered included CBC, ESR and CRP. The ESR, using the Wintrobe method, was 38mm/hr, with a reference range of 0mm/hr to 9mm/hr. The CRP was 11.78, with a reference range of 0 to 0.9.

## Diagnosis

Based on these findings, our first diagnosis was anterior ischemic optic neuropathy (AION).

The patient's inflammatory markers were atypical with regard to a varicella zoster virus (VZV) infection-associated neuritis, though VZV may have a potential association with giant cell arteritis (GCA), our second diagnosis.



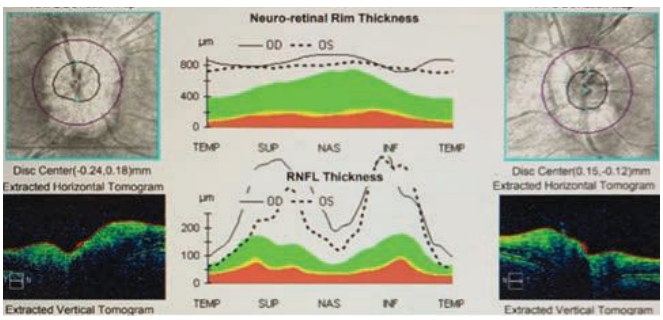
**Here are the findings from the patient's dilated fundus examination, OD on the left.**

GCA, named because of the giant cells found on vessel histology slides, is a granulomatous inflammation of the large- and medium-sized arteries, particularly in the external carotid branches, vertebral artery, subclavian artery, axillary artery and thoracic aorta. GCA is the most common form of vasculitis that occurs in adults.[1]

GCA and temporal arteritis have not always been synonymous. Traditionally, GCA was separated into Takayasu arteritis and temporal arteritis (Horton's disease). However, the Chapel Hill Consensus Conference (CHCC) has since provided an accepted convention to categorize vasculitides so that now, GCA is the accepted nomenclature for what is oftentimes still referred to as temporal arteritis.

Takayasu arteritis and GCA both affect more women than men.[2] While GCA has an average onset age of 72 years and is almost always found in patients over the age of 50, Takayasu arteritis is typically a disease seen in younger Asian women.[2]

GCA often presents with the following symptoms: headache, fever, scalp tenderness, dry cough, weight loss, depression, mononeuritis multiplex (which may manifest as numbness and/or tingling), glossitis, polymyalgia rheumatica and/or jaw claudication. Abrupt onset of a significant headache is the most frequent symptom of GCA and is seen in approximately 75% of cases.[3]




**OCT shows the relative swelling of the optic nerves, OD>OS.**

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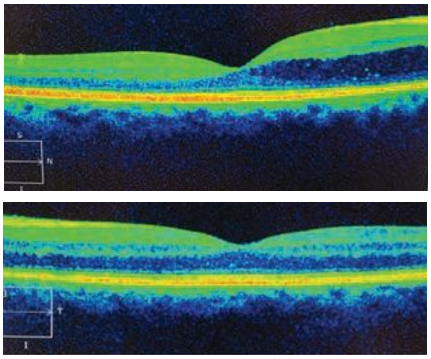
Vision loss due to AION is an early manifestation of GCA and can be a presenting symptom. AION occurs in 20% to 50% of people with untreated GCA.[4] Up to 10% of patients lose their vision in the second eye despite treatment.[5] This can happen within one week. Other possible ocular sequelae include cilioretinal artery occlusion, central retinal artery occlusion and transient ischemic attacks.

## Treatment

We diagnosed our patient with AION secondary to GCA based on age and associated signs and symptoms. In these cases, it is imperative to begin systemic steroidal treatment as soon as possible, so long as the patient can take systemic steroids. Because our patient was already suffering from more advanced effects of suspected GCA, starting prednisone superseded the need for a confirmatory temporal artery biopsy.

The general starting dose for prednisone in GCA is between 60mg/day and 80mg/day. Symptoms usually begin to rapidly resolve within one to three days. GCA is known to require a very long, slow taper. It is common for patients to remain on steroids for more than a year. For steroid regimens of this dose and duration, the doctor must educate the patient on possible side effects, such as blood glucose increase, gastric reflux (proton pump inhibitors are prescribed), weight gain, mood change and bone density reduction (biophosphonates are almost always prescribed concurrently with the steroids). The patient should have their electrolytes and liver enzymes monitored during treatment and be followed with imaging studies, as aortic aneurysms and/or dissections are possible with GCA. GCA patients are now routinely prescribed tocilizumab, an IL-6 inhibitor, as a steroid-sparing agent to increase steroid-free remission times.[6]



**There was fluid egression into the macula OD, top, not OS.**

Our patient's ESR returned to near-normal within a month, and his CRP returned to an acceptable value within a couple of weeks. Unfortunately, his diabetes worsened secondary to steroid treatment and required more extensive management, with his blood glucose levels rising to 263 and his HbA1c, to 11.3. His visual acuity remained at hand motion OD and improved to 20/20 OS. His florid optic nerve head edema OD and mild optic nerve head edema OS both resolved. Internal medicine took over management of his GCA-associated anemia.

This patient's case demonstrates one of the various ways GCA may present, as well as the effects that delays in diagnosis and treatment can have on any comorbidities, including vision. As we recognize the appropriate signs and symptoms, we can taper our laboratory and imaging studies to a tentative GCA diagnosis and get our patients on the road to recovery. ■

*Dr. Duncan is the founding coordinator of the Optometric Surgical Procedures program at the Southern College of Optometry.*

*Dr. Baldridge practices at Insight Eyecare in Tulsa, OK. She graduated from the Southern College of Optometry and completed an ocular disease residency at the Oklahoma Medical Eye Group.*

### Vasculitis Classifications

According to the CHCC, the known vasculitides are categorized as follows:

- Large-vessel vasculitis: Takayasu arteritis, GCA
- Medium-vessel vasculitis: Polyarteritis nodosa, Kawasaki disease
- Immune complex small-vessel vasculitis: Cryoglobulinemic vasculitis, IgA vasculitis (Henoch-Schönlein), hypocomplementemic urticarial vasculitis
- Antineutrophil cytoplasmic antibody (ANCA)-associated small-vessel vasculitis: Microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss granulomatosis
- Variable-vessel vasculitis: Bechect's disease, Cogan's syndrome
- Single-organ vasculitis: Cutaneous leukocytoclastic angiitis, cutaneous arteritis, primary central nervous system vasculitis aortitis
- Vasculitis associated with systemic disease: Lupus vasculitis, rheumatoid vasculitis, sarcoid vasculitis
- Vasculitis associated with probable etiology: Hepatitis C virus-associated cryoglobulinemic vasculitis, hepatitis B virus-associated vasculitis, syphilis-associated aortitis, drug-associated immune complex vasculitis, drug-associated ANCA-associated vasculitis, cancer-associated vasculitis

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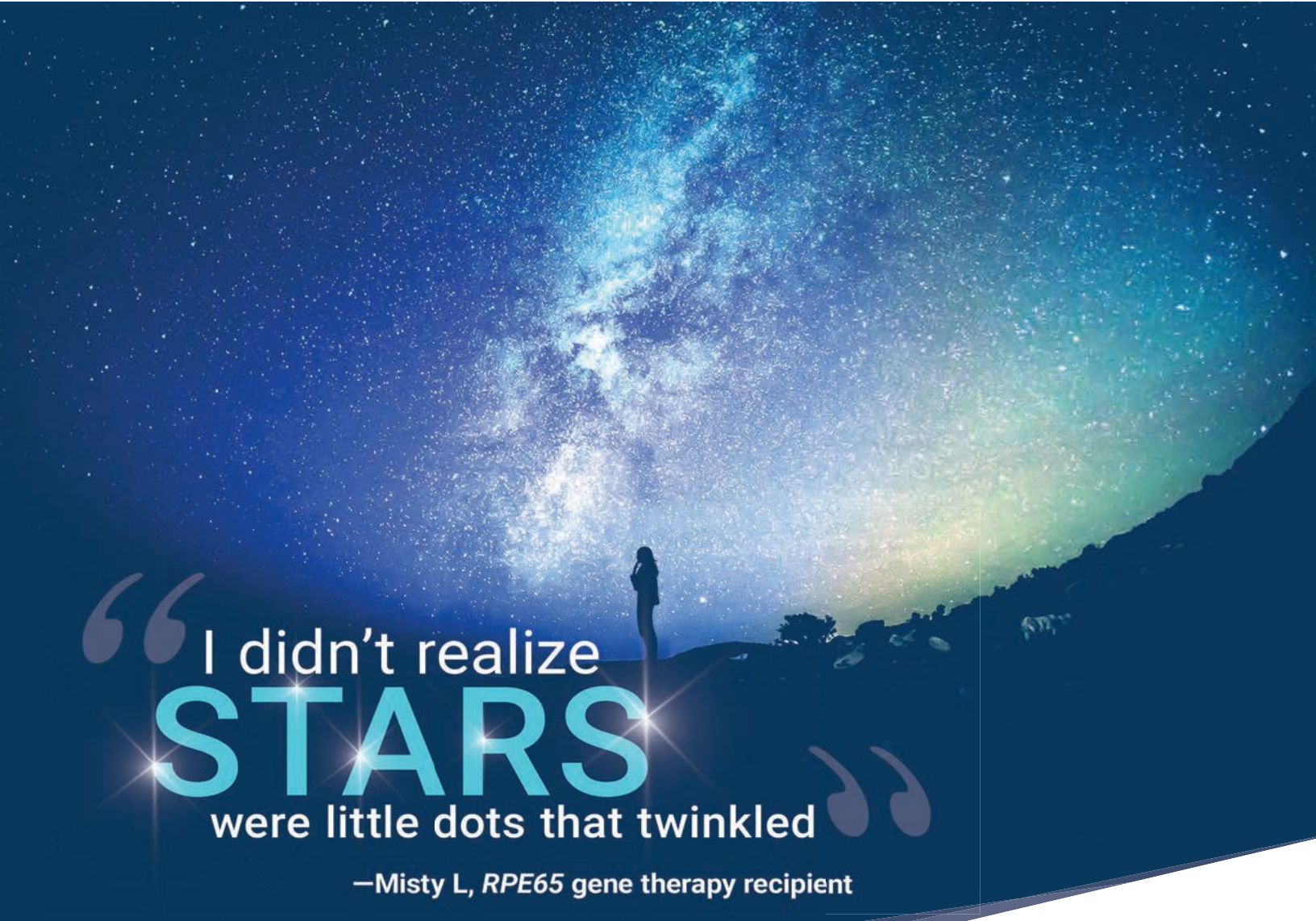


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Diagnostic **Quiz**

# A Tough Break

A physical altercation left this patient with internal injuries requiring urgent attention.

**By Andrew S. Gurwood, OD**

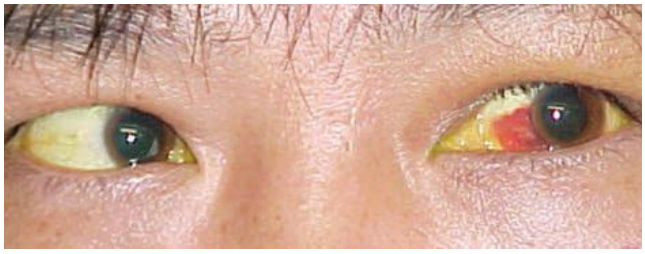
## History

A 38-year-old Asian male presented emergently following blunt trauma from a fist. While there was pain to the touch, the eye didn't ache and vision was not compromised. He did explain that he saw double when he looked to his left. The patient was otherwise free of systemic disease, previous history of trauma or ocular surgery. He denied having any allergies to medications or the environment.

## Diagnostic Data

His best-corrected entering visual acuity was 20/20 OU. His external exam was unremarkable, with no evidence of afferent pupillary defect. Biomicroscopic evaluation of the anterior segment showed mild ecchymosis adjacent to the area of impact and a small subconjunctival hemorrhage, OS. The pertinent exam finding is demonstrated in the photograph. Goldmann applanation tonometry measured 17mm Hg OU.

Additional testing included forced duction motilities to expose the limits of range of motion and magnetic resonance imaging of the face and head.



**The patient's left eye demonstrated subconjunctival hemorrhage and he reported double vision.**

## Your Diagnosis

Does the case presented here require any additional tests, history or information? What would be your diagnosis? What is the patient's likely prognosis? To find out, please visit www.reviewofoptometry.com. ■

**Retina Quiz Answers** *(from page 96)*—1) a; 2) b; 3) a; 4) a; 5) c.

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