

**CME**



# MANAGING GLAUCOMA: Beyond Intraocular Pressure

Enduring Material

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**Description/Goal:** The diagnosis and detection of glaucoma progression remains challenging, despite important technology developments in our field. Clinicians often want to know whether it is better to follow glaucoma patients by measuring function (via standard automated perimetry visual field testing) or structure, using any one of a number of imaging devices. In fact, neither method is sufficient on its own. The ability of structural and functional methods to detect change and accurately estimate the rate of change depends on the stage of the disease. Glaucoma is an optic neuropathy characterized by the progressive loss of retinal ganglion cells and their axons, but the pathophysiology resulting in RGC death is unknown and likely multifactorial. Identifying the extent of RGC loss may be a better method for monitoring glaucoma progression. The process of glaucoma-associated RGC death is by apoptosis, and prevention of apoptosis—and subsequent survival of RGCs—remains a highly desirable therapeutic target.

The expert faculty for this educational activity will review the cellular signaling mechanisms that promote RGC health and direct-programmed cell death by apoptosis. The promise of genetic testing for glaucoma is that it may help us identify early-stage glaucoma patients before they have lost so many RGCs that their vision is impaired. IOP reduction is currently the only established treatment for glaucoma, but does not appear to be effective in all patients. This activity will review the clinical settings in which IOP reduction—or further IOP reduction—may not be of benefit to the patient with glaucoma. In the absence of elevated IOP, the diagnosis of normal-tension glaucoma depends largely on clinical suspicion arising from careful inspection of the optic nerve and is often overlooked. The work-up of the NTG patient (or suspect) will also be reviewed, including a discussion of medical and surgical therapy options. Although clinicians vary in their choice of when to initiate glaucoma treatment, it is important to begin before significant visual field loss occurs, and this educational activity will discuss different approaches to treatment.

**Target Audience:** This educational activity is intended for general ophthalmologists who manage patients with

suspected or established glaucoma.

**Learning Objectives:** On completion of this educational activity, participants should be able to:

1. Effectively describe current thinking surrounding the diagnosis and management of glaucoma.
2. Identify factors that increase the risk of glaucoma or glaucoma progression, independent of IOP.
3. Devise alternative treatment approaches for glaucoma that progresses despite maximal medical therapy and/or low IOP.
4. Recognize when lowering IOP will fail to stop the progression of glaucoma.
5. Cite recent relevant studies and trials, and describe their implications for glaucoma therapy beyond IOP reduction.
6. Review the latest research on sources of optic nerve damage.

**Physicians Accreditation Statement:** This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Institute for the Advancement of Human Behavior (IAHB) and Postgraduate Healthcare Education LLC (PHE). IAHB is accredited by the ACCME to provide continuing medical education for physicians.

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**Medium or Combination of Media Used:** Monograph/print supplement and Internet. Internet site best viewed using Internet Explorer 7 and higher, or Firefox 3.0 and higher. An Internet connection with a minimum 56Kps modem is suggested.

**How to Receive CME Credit:** There are no fees for participating and receiving CME credit for this activity. During the period of October 15, 2014 and October 14,

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A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed post-test with a score of 80 percent or better. Your statement of credit will be mailed to you within 4 weeks; online test takers will be issued a printer-friendly, real-time certificate.

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# MANAGING GLAUCOMA: BEYOND INTRAOCULAR PRESSURE

## I. DIAGNOSIS

### PERSONALIZING THE MEASUREMENT OF IOP

*Twenty-four-hour measurement of IOP will provide new information for clinical practice.*

ROBERT N. WEINREB, MD

In clinical practice, we capture intraocular pressure a few times per year for most glaucoma and ocular hypertension patients. This presents several problems for clinicians.

### The Problem With Current Collected IOP Measurements

First, it is possible that peak IOP is measured during a routine visit—that would be helpful for clinical decision-making—but it is equally plausible that we are capturing a moderate or low IOP for the patient (i.e., the peak IOP may actually be higher than what is measured in the office).

Second, IOP is not conserved from day to day. This means that one cannot expect IOP to be the same on different days at the same time. Scheduling visits for the same time of day with every visit does not ensure a consistent IOP reading. This is particularly relevant to clinical practice, as the one eye therapeutic trial (in which eye drop efficacy is tested by comparing the change in IOP between two visits in a treated eye and untreated eye) depends on conservation of IOP, a characteristic that is not observed.

Moreover, we know that IOP is typically highest at a time (night) and in a position (supine) that is rarely reflected in glaucoma exams. Many have wondered whether patients' sleeping positions might influence glaucoma progression or perhaps contribute to asymmetry in progression between the two eyes.

These issues, and others, are a co-

nundrum. How do we assess a disease in which the only proven therapy is IOP lowering when our methods for measuring IOP are crude and often inaccurate or misleading? Of course, we also examine the visual fields and the optic disc, but clinicians often decide on whether the pressure is too high and treat based on the limited snapshot of IOP.

### Study Findings to Consider

Sit and colleagues have recently reported that the nocturnal decrease in aqueous humor flow rate in older, healthy subjects is compensated by a small decrease in outflow facility and a large decrease in uveoscleral outflow to maintain a stable IOP.<sup>1</sup> This may have important implications for how we treat glaucoma. Each of the different medication classes we use to lower IOP has differential effects on inflow and outflow. And because of that, you would expect that they might have differential effects on the ability to lower pressure over 24 hours. While a beta-blocker effectively lowers IOP during the day, it has no effect on pressure during the nighttime.<sup>2</sup> This is in contrast to a prostaglandin analogue, which lowers IOP throughout the 24-hour day.

### Routine Measurement Is Key

During the next several years, I expect that we will have the capability in clinical practice to routinely measure 24-hour IOP or some surrogate for IOP. There are two basic methods for accomplishing this.

Temporary continuous measurement typically employs a contact lens-based sensor to monitor IOP. Such a device is available commercially in many countries outside the United States. By measuring the change in corneal curvature, it obtains an estimate of IOP in eyes with healthy corneas. Testing

with this device has confirmed the 24-hour patterns that have been recorded in sleep lab tests in which IOP is maximal during the night for more than two-thirds of patients.

Another approach for 24-hour IOP measurement employs an implantable sensor. In clinical trials in Europe, one such sensor is placed at the time of cataract or glaucoma surgery to continuously record IOP.

### Change Is on the Horizon

In the future, it is likely that our treatment will be designed based on multiple IOP measurements throughout the entire day, rather than one IOP measurement at one time of the day every few months, as is done in current clinical practice. I suspect we also will integrate our ability to detect these changes in IOP with drug delivery or surgical devices. New technologies for 24-hour IOP monitoring offer the potential for personalizing IOP to improve our glaucoma management.

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### THE RGC INDEX

*Combining structure and function is a better measure than either alone.*

FELIPE A. MEDEIROS, MD, PHD

Disagreement in the assessment of progression and rates of change in glaucoma can be very confusing for clinicians and may lead to inadequate management. This is due in part to differences in scale in the structural and functional measures we use to follow glaucoma. Mean deviation loss in functional visual field testing is measured in a logarithmic decibel scale, while structure is measured on a linear scale of microns of retinal nerve fiber layer thickness.

### Knowing What to Expect

Early in the disease, small neural changes correspond to large changes in standard automated perimetry visual fields, while later in the disease, large neural losses correspond to small changes in SAP. Additionally, optical coherence tomography measurement of the RNFL performs poorly in discriminating moderate from advanced stages of disease.<sup>1</sup>

Experimental and clinical evidence has shown that, in many patients, significant retinal ganglion cell losses are required before a statistically significant change in the visual field can be detected. Although the amount of RGC loss associated with early development of a field defect will depend on the location and characteristics of the defect, on average, one would typically first detect field loss at a mean deviation of around -2 dB to -3 dB. That would correspond to an RGC population of approximately 600,000 to 700,000 cells, representing an approximately 30 percent loss from the average RGC number in healthy eyes.

### An Tool to Rely On

The RGC Index is an attempt to combine measures of structure and function to improve risk assessment and the diagnosis, staging and detection of glaucoma progression.<sup>2</sup> For this index, the RGC counts predicted by OCT and by SAP are weighted by disease severity.

The index has been shown to successfully discriminate pre perimetric glaucoma (progressive disc photos) from normals (ROC=0.88) and to successfully discriminate among early vs. moderate (ROC=0.94) and moderate vs. advanced (ROC=0.96) stages of damage.<sup>2</sup>

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### PARACENTRAL VISUAL FIELD LOSS IN GLAUCOMA

*Early diagnosis and treatment of glaucoma become increasingly important as the population ages.*

JEFFREY M. LIEBMANN, MD

Paracentral visual field loss, within 10° of fixation, significantly affects patient quality of life. This well-described feature of glaucoma can lead to difficulty reading, decreased contrast sensitivity, impaired driving, increased risk of falls and injury, blindness and even death.

Paracentral VF loss represents an increasingly important clinical concern as the U.S. population ages. That is because, as life expectancy increases, so too does the period of time those with glaucoma will have to live with its debilitating effects.

In a recent study, the cumulative incidence of bilateral blindness from glaucoma was 5.5 percent after 10 years and 13.5 percent after 20 years with the disease (see *Figure 1*).<sup>1</sup> In this study, the median age when developing bilateral blindness was 86 years, and median duration of bilateral blindness prior to death was just two years, but it is not difficult to imagine much worse scenarios. Recall, for example, that the average age in the Collaborative Initial Glaucoma Treatment Study (CIGTS) was 57. I don't think we are willing to accept bilateral blindness in 13.5 percent of our patients at age 77—particularly if those patients have a reasonable chance of living into their 80s and 90s and might therefore need to endure many years with blindness.

One way to deal with this is to do a better job of identifying early VF loss and understanding its progression in order to better protect our patients' vision over a longer period of time.

### Paracentral Loss and Progression

The scotomas that cause VF loss paracentrally may occur early in

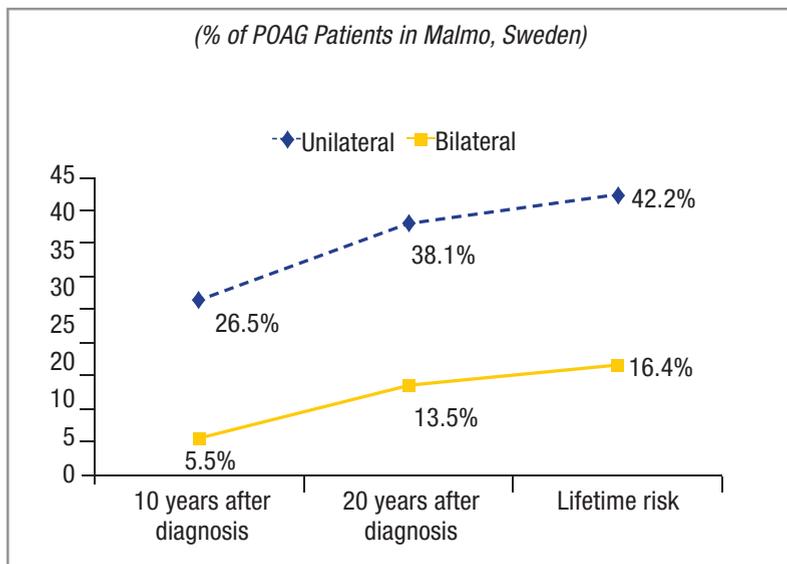


Figure 1. Risk of unilateral and bilateral blindness in patients with primary open-angle glaucoma.<sup>1</sup>

the disease course of glaucoma, at the time of initial VF defect.<sup>2,3</sup> On VF testing, initial parafoveal scotomas in the superior hemifield usually have an arcuate pattern and slowly deepen and expand toward the physiologic blind spot and nasal periphery.<sup>4</sup> IPFS in the inferior hemifield have a similar pattern, but are slightly farther from fixation. A denser test grid increases scotoma detection in the central 10°;

using a program designed for this purpose (such as the Humphrey Field Analyzer 10-2 program) allows for increased detection of progression.<sup>5,6</sup>

In general, frequency domain optical coherence tomography can be used to assess paracentral damage by measuring the thickness of the retinal nerve fiber layer and retinal ganglion cell plus inner plexiform (RGC+) layer. In glaucoma patients and suspects, the

average RGC+ layer typically shows greater thinning in the inferior retina (superior VF, see Figure 2). However, the central test points of the 24-2 visual field test (6° separate each point on the VF grid) miss the corresponding region of greatest RGC+ thinning.<sup>7</sup>

In individual patients, RGC+ loss is associated with VF sensitivity loss as long as the displacement of RGCs from the foveal center is taken into consideration and that macular damage is arcuate in nature, which is often associated with RNFL thinning in a narrow region of the disc.<sup>7</sup> As described by Dr. Don Hood, most of the inferior region of the macula projects to a “macular vulnerability zone,” which is located largely in the inferior quadrant of the disc, a region that is particularly susceptible to glaucomatous damage.<sup>7</sup>

The progressive nature of glaucomatous damage, over a long period of time, represents a challenge for clinicians, since patients have an increasingly long exposure time to the disease. Glaucoma progression begins with the death of individual retinal ganglion cells through apoptosis, which leads to RGC damage and

Image courtesy, Jeffrey M. Liebmann, MD

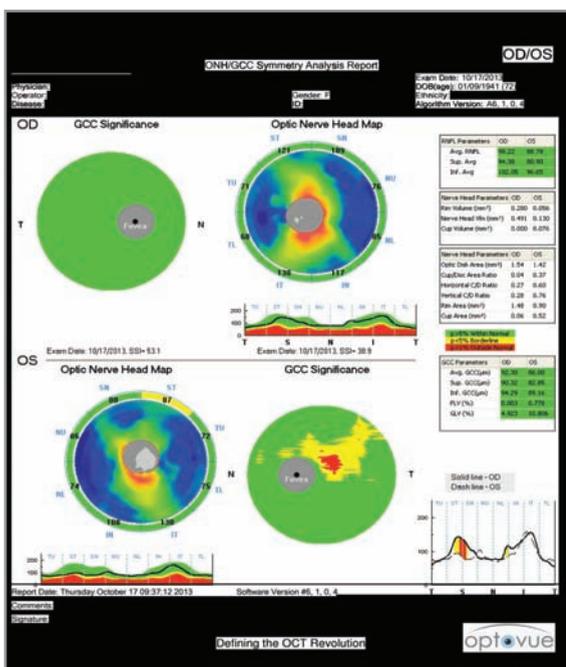


Figure 2. False color, spectral-domain optical coherence tomography image in the left eye indicating possible paracentral RGC loss in early glaucoma. Both the superior and inferior ganglion cell complex thicknesses are lower in the left eye than the right (arrow).

GCC Parameters	OD	OS
Avg. GCC(μm)	92.30	86.00
Sup. GCC(μm)	90.32	82.85
Inf. GCC(μm)	94.29	89.16
FLV (%)	0.003	0.778
GLV (%)	4.923	10.806

RNFL change that causes VF loss and, eventually, blindness. Historically, most of our patients did not live long enough to experience this functional disability. However, this is no longer the case. A person born today has a median life expectancy approaching 100 years; those diagnosed with glaucoma, then, will likely move further along the disease continuum before they die.

### Other Management Considerations

As a result of increasing life expectancy, there are other factors in the management of patients' overall health that may influence glaucoma progression—most notably, blood pressure regulation. Most blood pressure medications also lower ocular perfusion pressure, and multiple population studies have identified a link between OPP and progression of glaucoma, with lower OPP significantly increasing the risk for developing POAG significantly. In the Low-pressure Glaucoma Treatment Study (LoGTS), older age was a risk factor for VF loss, as was being treated for OPP and/or systemic hypertension.<sup>8,9</sup>

### If You Can't Cure It, Keep It in Check

Increasing life expectancy increases the risk for not only disability, but for blindness from glaucoma. The United States is, therefore, faced with a potential glaucoma epidemic, given the increasing life expectancy and overall aging of the population. Ophthalmologists, then, need to focus on earlier diagnosis and treatment of diseases such as POAG, with an emphasis on preventing VF loss, as there is significant morbidity associated with even small amounts of visual function decline.

Treatments that are designed to protect against RGC loss and/or RNFL thinning as well as counteract the OPP-lowering properties of hypertension medications may be key in slowing patients' progression along the glaucoma continuum.

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## THE ROLE OF ESTROGEN IN THE PATHOGENESIS OF POAG

*Given the gender differences in glaucoma, estrogen may be protective, suggesting new therapeutic targets and preventive strategies.*

LOUIS R. PASQUALE, MD, FARVO

Recently, a 61-year-old white female presented to our clinic. Her husband is an ophthalmologist, and he had been monitoring his wife for primary open-angle glaucoma since 2000, due to an enlarged cup-to-disc ratio in her optic nerve. This patient also has a history of pre-eclampsia, and she underwent a hysterectomy in 2007. Upon examination, a marked change in the superior portion of her visual field was observed; IOP was 21 mmHg. Treatment with timolol/dorzolamide (Cosopt, Merck), brimonidine tartrate (Alphagan P, Allergan) and latanoprost (Xalatan, Pfizer) was initiated.

This regimen reduced her IOP to 15 mmHg OD and 14 mmHg OS. But is that enough to reduce the risk of progression in this patient? Given that she

has a superior paracentral scotoma in the right eye and nasal step in the left eye, with significant cupping in both eyes (*see Figure 1*), it may not be.

This case illustrates the potential role for new therapeutic targets in both the prevention and treatment of POAG. Indeed, rather than focus treatment solely on IOP reduction, recent research indicates that we may be able to preserve visual function in cases like this one using novel strategies to prevent structural and functional vision loss.

### The Role of Estrogen

POAG is an age-related disease. It is well known that declining levels of sex hormones—including estrogen—are also part of the aging process. Given the lower incidence of POAG among women compared to men of the same age until about age 80 (*see Table 1*), it has been suggested that estrogen or other sex hormones may influence the development of POAG.

Estrogen may have a protective effect on retinal ganglion cells, which have estrogen receptors, and other mechanisms that reduce IOP.<sup>2,3</sup>

Several studies have noted that postmenopausal hormone therapy, including oral estrogen plus progesterone or estrogen plus androgen, is associated with modest reductions (approximately 2 mmHg) in IOP.<sup>4</sup> Early age at menopause has been associated with increased risk of POAG.<sup>5</sup> But estrogen and/or progesterone hormone therapy can reduce the risk for the development of POAG among postmenopausal women.<sup>6,7</sup>

Both environmental and genetic factors related to estrogen levels are associated with POAG. For example, in the 1980s, research showed that IOP drops during pregnancy despite an increase in corneal thickness. Sex hormone fluctuations occurring during a normal menstrual cycle in healthy women can significantly alter neuroretinal rim area and cup variables of the optic nerve head, and

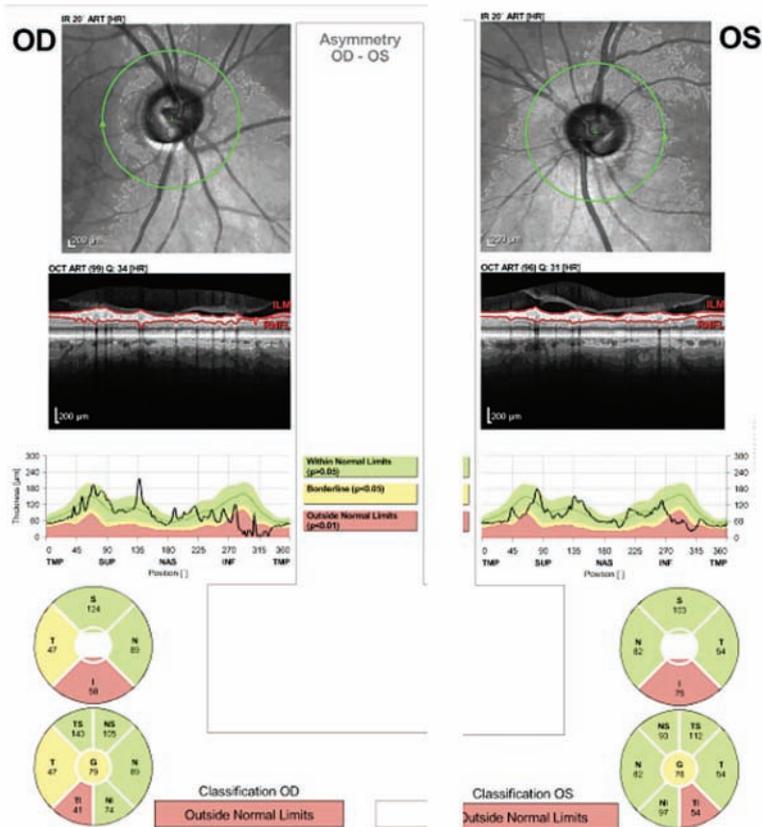


Figure 1. OCT of postmenopausal female patient at risk for primary open-angle glaucoma.

influence performance on visual field tests.<sup>8</sup> Women who use oral contraceptives for five or more years have an increased risk for developing POAG.<sup>9</sup>

Genetic epidemiology research has identified several potential targets for POAG including estrogen itself. In the NEIGHBOR Study, for example, we assessed the collection of estrogen metabolizing genetic polymorphisms in relation to POAG (see Table 2).<sup>10</sup> We found that this collection of polymorphisms was associated with POAG in women but not in men. One gene in the estrogen metabolic pathway that is intriguing is catechol-O-methyltransferase. Gene-based analysis indicated that polymorphisms in this gene is associated with high tension and normal tension glaucoma in women.<sup>10</sup>

Another potential target identified by gender biology and genetic epidemiology research is endothelial nitric oxide synthase (eNOS). Estrogen modulates eNOS activity and when estrogen levels decline, NO synthase activity also declines. In a mouse model with defective NO signaling, IOP increases modestly (2 mmHg) and the optic nerve degenerates.<sup>11</sup> In humans, the relation between eNOS common polymorphisms and POAG is significantly modified by postmenopausal hormone use.<sup>12</sup>

These findings suggest some novel therapeutic targets for future glaucoma therapy. In animal models, daily treatment with 17 $\beta$ -estradiol (E2)-containing eye drops in rats resulted in a significant increase in E2 concentration in the retina with concomitant profound neuroprotective therapeutic

### Incidence of POAG by Gender

Age (years)	5-Year Incidence: Men	5-Year Incidence: Women
40-49	0.0%	0.0%
50-59	0.3%	0.0%
60-69	1.0%	0.3%
70-79	2.0%	0.7%
80+	4.0%	4.1%

Table 1. The incidence of primary open-angle glaucoma in women begins to rise after the age of typical menopause, but does not match that of men until age 80.<sup>1</sup>

### Significance of the Estrogen Pathway in POAG: NEIGHBOR Study

	N		Mean Age (years)		Estrogen pathway permuted p-value
	Cases	Controls	Cases	Controls	
Overall	3108	3430	65.7	67.7	0.72
Males	1426	1493	65.6	68.4	>0.99
Females	1682	1937	65.7	67.3	0.006

Table 2. The estrogen pathway is associated with primary open-angle glaucoma in women (permuted p=0.006) but not in men.<sup>10</sup>

benefits, even in the presence of continually elevated IOP. The number of apoptotic cells in the RGC layer was significantly decreased in the E2-treated group, when compared to the vehicle-treated controls. Deterioration in visual acuity in these animals was also markedly prevented.<sup>13</sup>

### Time to Put the Spotlight on Estrogen

Gender biology research has already identified several potential therapeutic targets, including estrogen and NO signaling, that may lead to preventative strategies for patients at risk for POAG, such as the patient in our earlier case example. Although more research is needed, future prophylaxis in glaucoma management in women may include extended-release estrogen therapy, or the use of hormone therapy in post-hysterectomy patients at risk for POAG. Research has clearly highlighted the protective effect of estrogen in glaucoma, and future approaches should exploit this as a therapeutic target.

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## II. GLAUCOMA: A NEURO-DEGENERATIVE DISEASE

### MANAGEMENT OF DISC HEMORRHAGE

*Disc hemorrhage is one of the most important predictors of visual field loss and disease progression.*

JEFFREY M. LIEBMANN, MD

Disc hemorrhage is a clinical feature of glaucoma that is present in as many as 13 percent of patients with primary open-angle glaucoma and up to 20 percent of patients with normal-tension glaucoma.<sup>1,2</sup> Despite being relatively common, disc hemorrhages are missed in up to 84 percent of cases, even by well-trained clinicians.<sup>3</sup>

This is significant because virtually all research assessing disc hemorrhage identifies it as an independent risk factor for visual field loss in POAG and other forms of glaucoma.<sup>4</sup> Clinicians, therefore, need to be hypervigilant for disc hemorrhage in patients who have already been diagnosed with glaucoma or who are glaucoma suspects.<sup>5</sup>

### Disc Hemorrhages and VF Loss

The role of disc hemorrhage as a predictor of VF loss in glaucoma has been well-documented. The risk of developing POAG increases six-fold if disc hemorrhages are present.<sup>2</sup> Studies in Japan, where disc hemorrhage is more common than it is in the United States, have shown that patients with two disc hemorrhages have been reported to have up to a 100 percent chance of experiencing progressive VF loss and those with one hemorrhage have an 81

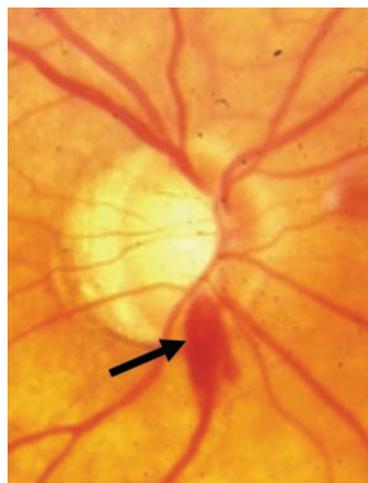
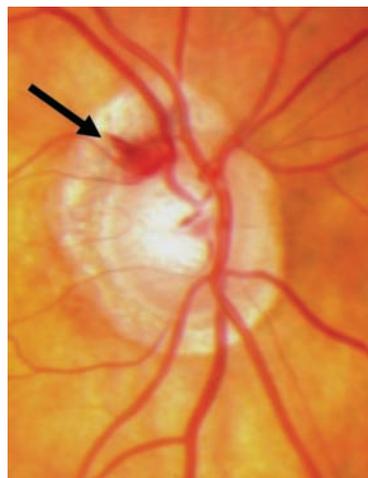


Figure 1. The clinical presentation of optic nerve disc hemorrhage.

percent chance of developing progressive disease, compared to a 45 percent chance in those with no disc hemorrhage.<sup>4</sup> And, an analysis of risk factors for VF progression in glaucoma revealed that the odds ratios for disc hemorrhage were 2.31 in a univariable model and 2.58 in a multivariable model. In comparison, the odds ratios for peak IOP are 1.10 and 1.13, respectively.<sup>6</sup>

Glaucoma patients with disc hemorrhage can suffer VF loss more rapidly and more severely than those without. Following hemorrhage, sustained, rapid VF progression occurs at an accelerated rate, even in patients on IOP-reducing therapy.<sup>7</sup>

Because recognition of a disc hemorrhage may be a key factor in the diagnosis of glaucoma and the

Images courtesy Jeffrey M. Liebmann, MD

management of VF loss over the course of the disease, an understanding of its clinical presentation is important. Typically, disc hemorrhage presents as an area of bleeding adjacent to, or in contact with, the disc rim and adjacent to, or within, the retinal nerve fiber layer.<sup>8,9</sup> Additionally, it occurs more frequently in eyes with parapapillary atrophy (PPA), and more frequently in eyes with worse PPA; in cases where disc hemorrhage and PPA are found together, the disc hemorrhage can typically be found at the location in the disc that corresponds to the area with the widest PPA.<sup>10</sup>

### How to Recognize Disc Hemorrhage

There are several known strategies for improved recognition of disc hemorrhage in patients with glaucoma and/or in glaucoma suspects. Stereophotographic imaging remains the best way to detect disc hemorrhage, as there is no computerized imaging technology that can automatically detect them. The larger the hemorrhage, the easier it is to see on stereophotographic images of the optic nerve (see *Figure 1*); however, a disc hemorrhage can be more difficult to spot as it progresses (see *Figure 2*).<sup>8,9</sup> Stereophotographic images are best kept with the patient's electronic health record for comparison; images captured previously can serve as a baseline and can assist clinicians in recognizing hemorrhages as they develop.

In addition, monitoring of the RFNL can also be useful in assessing for disc hemorrhage. RNFL loss is often seen at the edge of the hemorrhage, and often RNFL thickness decreases prior to disc hemorrhage onset.<sup>8,9</sup> From a VF perspective, this can be assessed by inspection of the field for progressive localized loss using algorithms designed for this purpose or following global VF indices such as mean deviation.

Finally, localized neuroretinal rim loss can predict the location of disc hemorrhage. Garway-Heath et al developed a clinically useful map that relates VF test points to regions of the optic nerve

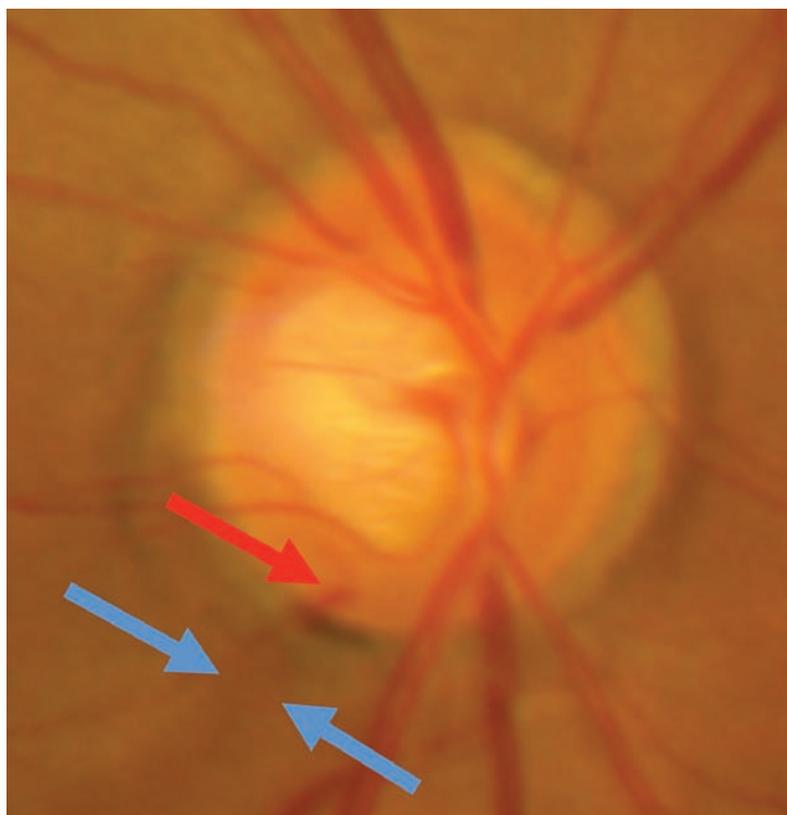


Figure 2. Optic nerve disc hemorrhages can be difficult to spot as they progress.

head. The map is designed to aid clinical evaluation of glaucoma patients and suspects, as well as form the basis for investigations of the relationship between retinal light sensitivity and ONH structure.<sup>11</sup> Using this method, De Moraes et al identified 168 disc hemorrhages in 122 patients; the VF sector with the fastest progression rate predicted the location of the future disc hemorrhage in 85 percent of cases, and after the detection of disc hemorrhage, the same VF sector maintained the fastest progression rate in almost all eyes (92 percent).<sup>7</sup>

### Future Implications

To conclude, the role of disc hemorrhage in glaucoma has a number of implications for future research and potential management approaches. We now know that VF progression occurs in the corresponding disc hemorrhage location before and after its onset; as evidence of past progression, disc hemorrhage could

be considered a glaucoma progression endpoint in clinical trials.

In clinical practice, because of its importance, the optic disc in glaucoma patients and suspects should be examined for a disc hemorrhage at the time of every visit, even when the pupil has not been dilated. For all eyes, disease surveillance should be modified to include earlier reassessment for disc hemorrhage, with additional structural and functional testing to quantify the rate of VF loss. If a disc hemorrhage is detected, it should be photographed or annotated by location in the patient chart. The clinician should assume that VF loss has occurred or is occurring until proven otherwise, and prior structural and functional tests should be re-evaluated to determine if spatially consistent optic nerve or VF injury has occurred.

For glaucoma suspects, including ocular hypertensives, those with disc hemorrhage should have their diagnosis changed to glaucoma and con-

sideration should be given to initiating treatment. For established glaucoma, consideration should be given to further IOP reduction, based upon the individual patient risk-benefit analysis and discussion with the patient.

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### III. TREATMENT AND THE FUTURE

#### NEW BIOMARKERS AND REGENERATIVE THERAPIES IN GLAUCOMA

*Promising gene and stem cell developments begin to lead to new technologies that can be translated into human clinical trials.*

JEFFREY L. GOLDBERG, MD, PHD

Currently, we measure loss of function in glaucoma with visual field testing and loss of structure with fundus photography and optical coherence tomography or other measures of the retinal nerve

fiber layer or retinal ganglion cell complex. But these measures are insufficient, leaving clinicians always struggling with whether the patient in the chair is adequately treated or not. We know that vision loss in glaucoma is due to the dysfunction or death of RGCs. But how do we measure RGCs? Is it possible to distinguish between dysfunction and death? These are open questions.

#### A Need for New Biomarkers

New biomarkers are needed for initial diagnosis, detecting impending progression and for guiding therapy. New biomarkers could also help us discover new treatments and cures. Currently, a major challenge in studying potential neuroprotective agents or regenerative therapies, for example, is that it takes a really long time to demonstrate neuroprotection in this slow-moving disease.

There are a few candidates for new biomarkers that draw on what is already known about the pathophysiology of glaucoma—namely axon injury, synapse loss, glial activation of other retinal cells and vascular compromise. There is some evidence in humans—and a lot of evidence in animals—that axon loss occurs prior to RGC death. It makes sense, therefore, to look at things such as axon transport failure and axon damage to see whether these might become appropriate biomarkers of the disease in humans. Ideally, we want to be able to quantify not just the presence of RGCs and axon, but whether they are fully functioning, stable and healthy.

One of my colleagues at the University of California—San Diego, Andrew Huberman, has been monitoring different retinal ganglion cell subtypes using fluorescent markers in an animal model of glaucoma. It turns out that some of the RGC subtypes, when they are healthy, have widely spread dendritic arbors. When they become unhealthy, the dendrites of these RGCs seem to retract. It is possible that these shrinking dendritic arbors could serve as an earlier marker of disease progression—a sort of “canary in the coal mine”?

The challenge, of course, is in imaging RGCs and their axons in the living retina, but we’ve seen exciting progress in the area of adaptive optics that may solve this problem. An adaptive optics scanning light ophthalmoscope (AOSLO) has been used by Dr. Alfredo Dubra at the Medical College of Wisconsin to visualize the retinal vascular structure and retinal vascular perfusion.<sup>1</sup> And new types of OCT, such as one under development by Dr. Vivek Srinivasan at the University of California—Davis, are also making it possible to image and potentially measure blood flow and oxygen metabolism *in vivo*.<sup>2</sup> Researchers are just starting to use these technologies to measure RGC metabolism. We may even be able to visualize oxygen consumption in the optic nerve. The expectation is that vascular imaging and metabolic imaging together will prove to be much more informative than either alone.

#### Regenerative Therapies

Typically, RGCs cannot regenerate after optic nerve injury. Once the RGC is significantly injured or dead, the optic nerve damage is permanent. But as we learn more about the genes that regulate regeneration, it’s possible that we could actually promote regeneration of the nerve cells. For example, turning off a gene called *kruppel-like factor 9* (KLF9) can actually increase long-distance regeneration. In rodent optic nerves, anti-KLF9 therapy has been able to get axons to regenerate all the way down the optic nerve to the optic chiasm. This is very exciting, although it of course must still be translated into human clinical applications.

We are also beginning to make progress on plausible applications for stem cell therapy in glaucoma. First, stem cells could create neuroprotective factors to protect remaining RGCs in patients with glaucoma to slow down the course of the disease. Secondly—and even better—would be the ability to actually replace dead or dying RGCs. To get stem cells to become RGC-like cells, they have to grow dendrites into the

retina and form connections with their neighbors. And they've got to grow that axon all the way down the optic nerve to connect to visual system targets in the brain. A stem-cell derived RGC that can't do both of those things isn't really doing the patient any good.

### Spotlight on Stem Cells

There are a lot of different types of stem cells, but no clear winner yet in terms of the ability to differentiate into RGCs. Once we have a way to do this, they must also be transplanted into the eye. Already, some very encouraging work in our laboratory has been done in animal models showing that transplanted RGCs can grow dendrites and get at least a few axons to progress down the optic nerve to the chiasm. In these preliminary experiments, transplanted RGCs can also respond to light in the retina after transplantation. This research is still in early stages, but it is exciting to think about the potential for restoring vision in patients with glaucoma.

One of the things that stem cells do that has been shown to be really good for RGCs is that they make a protein called ciliary neurotrophic factor (CNTF). An implant filled with cells

from a cell line genetically engineered to transmit CNTF has been developed by a company called Neurotech. The implant goes in through the sclera and pars plana and sits in the vitreous, right behind the crystalline or implanted intraocular lens.

I participated in a single-center, unmasked trial where 11 patients with significant visual field loss due to glaucoma were implanted in one eye with this CNTF implant, primarily to evaluate safety. In our initial analyses, there were no significant decreases in central visual acuity over 18 months of follow-up, no change in intraocular pressure, and no serious adverse events related to the implant. There were patients in whom the fellow eye got worse over the study period but the implanted eye remained stable. Even more interestingly, the nerve fiber layer, when measured either by OCT or by scanning laser polarimetry, actually got thicker rather than thinner, as the typical course would be. We know that thinning of the nerve fiber layer is associated with loss of visual field, but since we have no drugs that increase RNFL thickness, we don't know if this would protect against visual field progression. Certainly, no

efficacy claims can be made from this small study, but these are interesting preliminary observations that suggest a more extensive trial may be worthwhile.

### Great Things to Come

The next decade is going to be an exciting time for glaucoma specialists and for our patients, as I think we are on the cusp of developing a number of treatments that go beyond IOP lowering to directly target RGCs and their axons.

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### GENETIC RISK FACTORS INFLUENCING IOP

*A better understanding of the molecular processes underlying glaucoma could lead to novel therapeutic approaches.*

JANEY L. WIGGS, MD, PHD

To date, elevated intraocular pressure is the only known modifiable risk factor for glaucoma. Our current therapeutic options, therefore, are

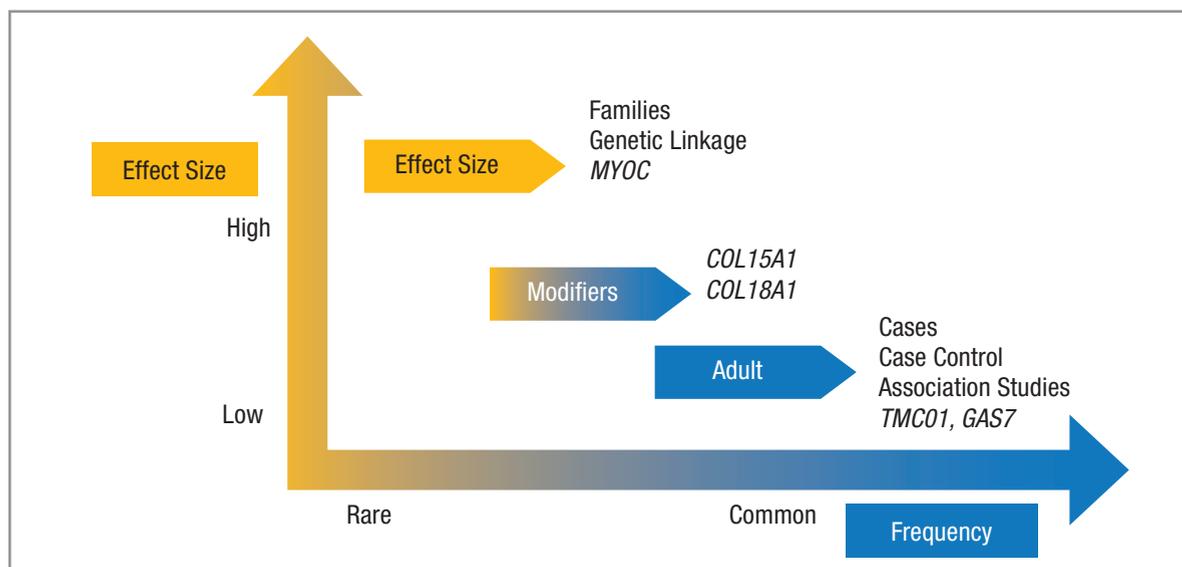


Figure 1. Genes contributing to elevated intraocular pressure in glaucoma. Glaucoma gene mutations causing elevated IOP in families with mendelian inheritance (autosomal dominant or recessive) are rare and have large biological effects. Mutations in the *MYOC* gene fall into this category and cause early-onset primary open angle glaucoma. Alternatively, glaucoma gene variants contributing to adult-onset glaucoma are common and have small effect sizes. DNA variants in the *TMC01* and *GAS7* contribute to adult-onset IOP. *TMC01* also contributes to adult-onset POAG. DNA variants in genes that can modify the severity of disease in both early-onset and adult-onset glaucoma (*COL15A1* and *COL18A1*) have a range of allele frequencies and also vary in terms of their biological effect sizes.

designed to modify the processes that regulate IOP, such as aqueous production and trabecular outflow.

However, for glaucoma treatment to advance, we need to develop therapies that modify or regulate the molecular events that lead to trabecular dysfunction and IOP elevation in the first place. Finding and characterizing genes that cause or contribute to IOP elevation (see Figure 1 on page 11) can help us define the responsible underlying molecular events and suggest novel therapies targeting the molecular pathophysiology. The ultimate goal would be to use each patient's genetic and other risk factors, as well as their structural and functional changes, to better predict progression and develop truly personalized treatments for glaucoma.

### Genes Linked to Disease Onset

To identify the genes implicated in glaucoma, two different approaches have been taken, based on when the disease manifests. In early-onset glaucoma, there is a large biological or hereditary effect. This condition runs in families and is typically inherited in the form of autosomal dominant or recessive traits. In the more common adult- or late-onset glaucoma, the disease is inherited as a complex trait due to multiple genetic and environmental risk factors. For complex traits, genetic variants do not directly cause elevated IOP or glaucoma, but they do contribute to the conditions and influence overall susceptibility.

**Early-onset glaucoma.** An important gene causing IOP elevation in early-onset POAG is myocilin (*MYOC*). In up to five percent of cases with POAG onset before age 50, *MYOC* mutations are responsible for the elevated IOP, and affected patients can have severely elevated IOP.<sup>1</sup> *MYOC* mutations are inherited as a dominant trait. There is a 50 percent chance that first-degree family members of patients with a *MYOC* mutation also have this mutation and are also at risk for glaucoma.

Recent research suggests that *MYOC*

mutations cause protein misfolding and endoplasmic reticulum (ER) stress. Zode et al. have shown that the chemical chaperone sodium 4-phenylbutyrate (PBA) can reduce the ER stress response and lower IOP.<sup>2</sup> In subsequent experiments they found that topical PBA lowers IOP in *MYOC* transgenic mice.<sup>3</sup> This is one of the first examples of using a personalized, gene-based approach to treat glaucoma.

*COL15A1* was identified as a gene involved in early-onset POAG in a study performed in our lab.<sup>4</sup> We found *COL15A1* variants in the youngest affected (i.e., earliest onset) members of seven of 15 families with variable disease onset. In addition, the most common *COL15A1* variant, R163H, influenced the age of onset in adult-onset POAG cases.<sup>4</sup>

Previous research showed that *COL15A1* is expressed in Schlemm's canal. We found that the gene is also expressed in several other intraocular tissues and structures related to glaucoma, including the ciliary body, trabecular outflow pathways, astrocytes of the optic nerve, and the retinal ganglion cell layer.

Taken together, these findings suggest that *COL15A1* variants could modify the trabecular outflow pathways or Schlemm's canal to reduce fluid outflow and elevate IOP. This type of genetic defect may lend itself to gene-based therapy, or it may be that patients who have *COL15A1* variants might benefit from a particular type of treatment. This is another example of how genetic information can be used to guide therapy, both existing and novel, for patients with elevated IOP.

**Adult-onset glaucoma.** At least six genes are known to contribute to adult-onset glaucoma—most notably, transmembrane and coiled-coiled domain 1 (*TMC01*) and growth arrest protein 7 (*GAS7*).

*TMC01* functions in the nucleolus of the cell and may be related to cell division and cell aging. Two studies have shown that variants in the gene are associated with elevated IOP.<sup>5,6</sup>

Additionally, in several genome-wide

association studies, researchers have found associations between *TMC01* variants and POAG. Investigators using samples from the Ocular Hypertension Study (OHTS) also found that *TMC01* variants contribute to the risk of developing glaucoma in non-Hispanic whites, the largest OHTS subgroup.<sup>7</sup> Finally, Sharma et al. reported that individuals homozygous for one *TMC01* risk allele are four to five years younger at POAG diagnosis than noncarriers of this allele, suggesting that it may lower age of disease onset.<sup>8</sup> Their research also demonstrates expression of the *TMC01* protein in most tissues in the human eye, including the trabecular meshwork and retina.

The *GAS7* protein likely participates in cell remodeling and also promotes the formation of neurons. Alleles of *GAS7* are also significantly associated with IOP, a finding that was recently replicated in the National Eye Institute's Glaucoma Human genetics collaBORation (NEIGHBOR) study.<sup>6</sup> To date, *GAS7* variants have not been associated with POAG in a case control study.

### Just the Beginning

The International Glaucoma Genetics Consortium recently completed a population-based multi-ethnic, genome-wide association study of 35,296 individuals and found four new genes associated with IOP.<sup>9</sup> It is likely that future genomic studies will yield more genes contributing to IOP, and this information could lead to a better understanding of the molecular events responsible for IOP elevation and the development of novel therapies targeting these processes.

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## PREVENTING EXFOLIATION SYNDROME

*Protecting the eyes from ultraviolet light exposure may hold the key to controlling this ocular disease that is closely associated with glaucoma.*

LOUIS R. PASQUALE, MD, FARVO

Exfoliation syndrome is an age-related disease that initially manifests in the anterior segment of the eye. Mounting evidence suggests that XFS should be included as a solar ophthalmopathy, along with pterygium, climatic keratopathy and cataract. Glaucoma occurs more commonly in eyes with XFS than in those without it; in fact, XFS has recently been recognized as the most common identifiable cause of secondary open-angle glaucoma, and glaucoma in XFS has a more serious clinical course and worse prognosis than in primary open-angle glaucoma.<sup>1</sup>

In seeking alternative therapeutic targets beyond IOP control, protection from ultraviolet light exposure might be a good place to start.

### UV Exposure

Recent research indicates that UV radiation is a major factor contributing to the development of XFS, but the sources of this harmful light may be surprising for some clinicians. Multiple studies, for example, have demonstrated that there is a "latitude effect" in terms of the risk for UV light exposure, with those in the northern tier of the United States (above 42° north latitude) at increased risk for

developing XFS compared to those living in the southern and middle tiers.<sup>2</sup>

It is a bit counterintuitive that those living farther away from the equator (where UV radiation is presumed to be lowest) would be at increased risk for a UV-related disease. However, solar UV is actually very strong closer to the North and South Poles. We know, for example, that arctic seals appear to sustain significant UV damage, in the form of lesions commonly associated with acute sun damage.

### The Dark Side of Light

An understanding of how damaging UV rays are more likely to penetrate the earth closer to the North and South Pole starts with an appreciation of a phenomenon called "sprites." Sprites can be described as large-scale, luminous lights that typically appear above storm clouds. They initiate near the base of the ionosphere, develop very rapidly, and assume many different geometrical forms (see Figure 1). Sprites are most commonly visible from the air, when flying at high altitudes, and appear like flashes of lightning that strike upward.

Sprites discharge straight up into the stratosphere and contribute to the solar shield that protects the earth from the solar wind, but there are natural weaknesses in this solar shield at the North and South Poles.

Gaps in the solar shield at the poles allow higher energy solar rays to mix with the upper atmosphere at the North Pole to create the phenomenon known as the Northern Lights. These beautiful lights may have a darker side: they have been implicated in the incidence of XFS, and thus POAG, in countries such as Sweden.<sup>3</sup>

Another factor that has to be considered is reflected light. Most people don't routinely engage in "sun gazing" or activities that would create acute UV exposure. Rather, eyes are more often exposed to UV radiation from incident light reflecting off surfaces, something that is likely key in the development of XFS. As we move away from the equator the sun is more angulated with respect to the horizon, creating more chances for reflectance into the eye (see Figure 2).<sup>4</sup>

In 1986, Sliney measured ocular UV-B radiation exposure levels at nine locations in the United States, near 40° north latitude and at elevations from sea level to 8,000 feet. His study showed that terrain reflectance is much more important than terrain elevation in dictating possible ocular exposure; cloud cover and haze may actually increase ocular exposure; and the value of wearing brimmed hats and sunglasses varies with the environment. Snow was the most

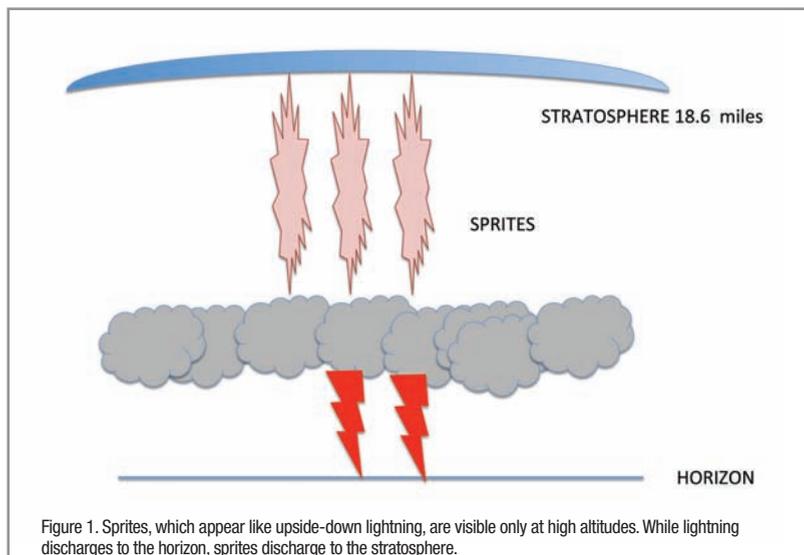


Figure 1. Sprites, which appear like upside-down lightning, are visible only at high altitudes. While lightning discharges to the horizon, sprites discharge to the stratosphere.

powerful reflecting surface in the Sliney study.<sup>4</sup>

### Impact of UV

An epidemiological study on the island of Rab, located in the North Adriatic Sea, which has a high level of solar radiation, identified a correlation between the incidence of age-related macular degeneration and exposure to sunlight.<sup>5</sup> Farmers and fisherman had an 18 percent incidence of AMD and 28 percent had XFS. Urban dwellers had only a 2.5 percent incidence of AMD and no cases of XFS at all.

Among U.S. adults, work over snow or water is associated with a 3.9-fold increased risk of XFS, and every additional hour per week spent outdoors increases the risk of XFS later in life by about four percent.<sup>6</sup> In particular, more time spent outdoors in young adulthood is associated with higher risk of exfoliation glaucoma, supporting an etiologic role of early exposures to climatic factors.<sup>7</sup>

One factor in this process may be the interaction between early UV exposure and genetic variants. UV exposure induces up-regulation of lysyl oxidase-like 1 and elastin-related genes, which have been linked to the development of XFS.<sup>8</sup>

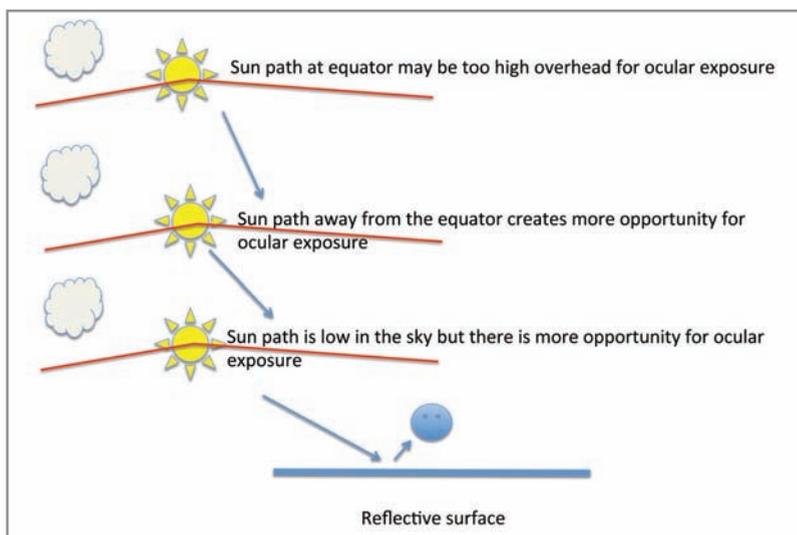


Figure 2. The Earth's 23° tilt creates more angular reflection as a function of the seasons. At high noon at the equator, the sun is directly overhead (top panel) throughout the year. Thus, there is little opportunity for sun to reflect off surfaces and into the eye. As one moves away from the equator (lower panels), the sun reaches varying positions in the sky that create more opportunity for it to reflect off the horizon and into the eye. Furthermore, at higher latitudes away from the equator, it is more likely the horizon has snow pack, which is an effective reflector of solar radiation.

### Improving Available Prevention Strategies

More research remains to be done, but the evidence to date certainly suggests that ocular UV protection, especially early in life, may be beneficial in the prevention of XFS and XFS-related glaucoma.

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## Crystal Ball: The Future of Glaucoma Management

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The future of glaucoma management will take us well beyond current practices and control of IOP. We'll be measuring IOP over 24 hours, which may transform how we practice clinically. A better understanding of genetic risk factors that affect intraocular pressure will be incorporated into our decision making. We'll be using more robust risk calculators to determine which of our glaucoma suspects are going to develop glaucoma and which of our glaucoma patients are going to progress. Paracentral visual field change and disc hemorrhages will factor into our risk calculation more than they currently do.

The field of glaucoma as a whole will increasingly come to appreciate that glaucoma is truly a neurodegenerative disease. We may one day be able to prevent or delay some types of glaucoma. Treatment options in the future may include stem cell therapy and treatments that can rescue or regenerate the retinal ganglion cells. It's certainly an exciting time in glaucoma, with much on the horizon to look forward to.

This enduring activity may contain discussion of published and/or investigational uses of agents and/or devices that are not indicated by the FDA. Off-label use of a medication or a biological is defined as use for an indication, or in a manner for which FDA approval has not yet been obtained and which is therefore not included on the FDA-approved label or product packaging. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. Practitioners should critically assess the information herein and are encouraged to consult appropriate resources for any product or device mentioned in this program.

The educational content of this activity has been peer reviewed and validated to ensure that it is a fair and balanced representation of the topic based on the best available evidence.

## Self-Assessment Questions

Online, real-time testing is available at:  
[www.revophth.com/BeyondIOP2014](http://www.revophth.com/BeyondIOP2014).

**1. In older, healthy subjects, IOP is kept stable at night despite a decrease in aqueous humor flow rate by:**

- a. A large decrease in outflow facility.
- b. A large increase in outflow facility.
- c. A large decrease in uveoscleral outflow.
- d. A large increase in uveoscleral outflow.

**2. Temporary continuous IOP measurement involves:**

- a. Contact lens measurement of IOP many times daily.
- b. An implanted 24-hour pressure monitor.
- c. 24-hour IOP monitoring in a sleep lab.
- d. A lacrimal gland insert that measures pressure.

**3. In early glaucoma, large changes in visual fields are associated with:**

- a. Lower IOP at night.
- b. Widely fluctuating IOP.
- c. Large neural loss.
- d. Small neural loss.

**4. Which of the following can discriminate early glaucoma vs. moderate and moderate vs. advanced stages of glaucomatous damage:**

- a. Confocal scanning laser ophthalmoscopy.
- b. Retinal ganglion cell index.
- c. Optical coherence tomography.
- d. Scanning laser polarimetry.

**5. The “macular vulnerability zone” is located largely in which quadrant of the optic disc that is particularly susceptible to glaucomatous damage:**

- a. Inferior.
- b. Superior.
- c. Nasal.
- d. Temporal.

**6. Blindness from glaucoma is of increasing concern due to:**

- a. Growing incidence of disc hemorrhage.
- b. Rising UV exposure.
- c. Lower access to health care.
- d. Longer life spans increasing chance of disease progression before death.

**7. Until about age 80, the incidence of POAG is:**

- a. About the same in men and women.
- b. Higher among men.
- c. Higher among women.
- d. Very low overall.

**8. In animal models, daily treatment with 17 $\beta$ -estradiol (E2)-containing eye drops resulted in:**

- a. Profound neuroprotective benefits.
- b. Some neuroprotective benefit, except in the presence of continually elevated IOP.
- c. An increase in the number of apoptotic cells in the RGC layer.
- d. Deterioration in visual acuity.

**9. Researchers in Japan have reported that patients with two disc hemorrhages have approximately what chance of experiencing progressive visual field loss?**

- a. 15 percent.
- b. 25 percent.
- c. 85 percent.
- d. 100 percent.

**10. Where do disc hemorrhages typically occur?**

- a. Far from the disc rim.
- b. Away from areas with parapapillary atrophy.
- c. Adjacent to or within the RNFL.
- d. There is no clear pattern.

**11. According to Dr. Liebmann, what is the best way to detect disc hemorrhages?**

- a. Use a structure-function index.
- b. OCT imaging of the RNFL.
- c. Stereophotographic imaging.
- d. Standard automated perimetry.

**12. Which of the following is not among the potential glaucoma biomarker candidates mentioned by Dr. Goldberg:**

- a. Stem cell failure.
- b. Axon transport failure.
- c. RGC metabolic changes.
- d. Shrinking dendritic arbors in certain RGC subtypes.

**13. In a recent study, one eye of subjects with glaucoma was implanted with a device filled with cells that transmit ciliary neurotrophic factor. What happened?**

- a. The study was cancelled due to a high rate of adverse events.
- b. Both the study eyes and the fellow eyes worsened over the course of the study but there was a statistically significant difference between the two.
- c. The nerve fiber layer in the study eyes got thicker.
- d. The nerve fiber layer in the study eyes got thinner.

**14. Myocilin (MYOC) mutations are responsible for the elevated IOP in approximately what percentage of patients with POAG onset before age 50?**

- a. One percent.
- b. Five percent.
- c. 15 percent.
- d. 50 percent.

**15. What is the chance that first-degree family members of patients with a MYOC mutation will also have this mutation that increases their risk for glaucoma?**

- a. One percent.
- b. Five percent.
- c. 15 percent.
- d. 50 percent.

**16. At least how many different genes are known to contribute to adult-onset glaucoma?**

- a. Two.
- b. Six.
- c. 12.
- d. 16.

**17. The finding that alleles of the gene GAS7 are significantly associated with IOP was recently confirmed in which study:**

- a. OHTS.
- b. LoGTS.
- c. NEIGHBOR.
- d. MARINA.

**18. In which geographic sector of the United States do people have the highest risk of developing exfoliation syndrome?**

- a. Northern tier.
- b. Southern tier.
- c. Middle tier.
- d. Western tier.

**19. Which of the following is not a true statement about sprites:**

- a. They initiate near the base of the ionosphere.
- b. They develop very rapidly.
- c. They typically appear above storm clouds.
- d. They are easy to see from the ground in the Northern hemisphere.

**20. Which of these is the most important factor in ocular exposure to UV:**

- a. Eye color.
- b. Terrain reflectance.
- c. Terrain elevation.
- d. Cloud cover.

