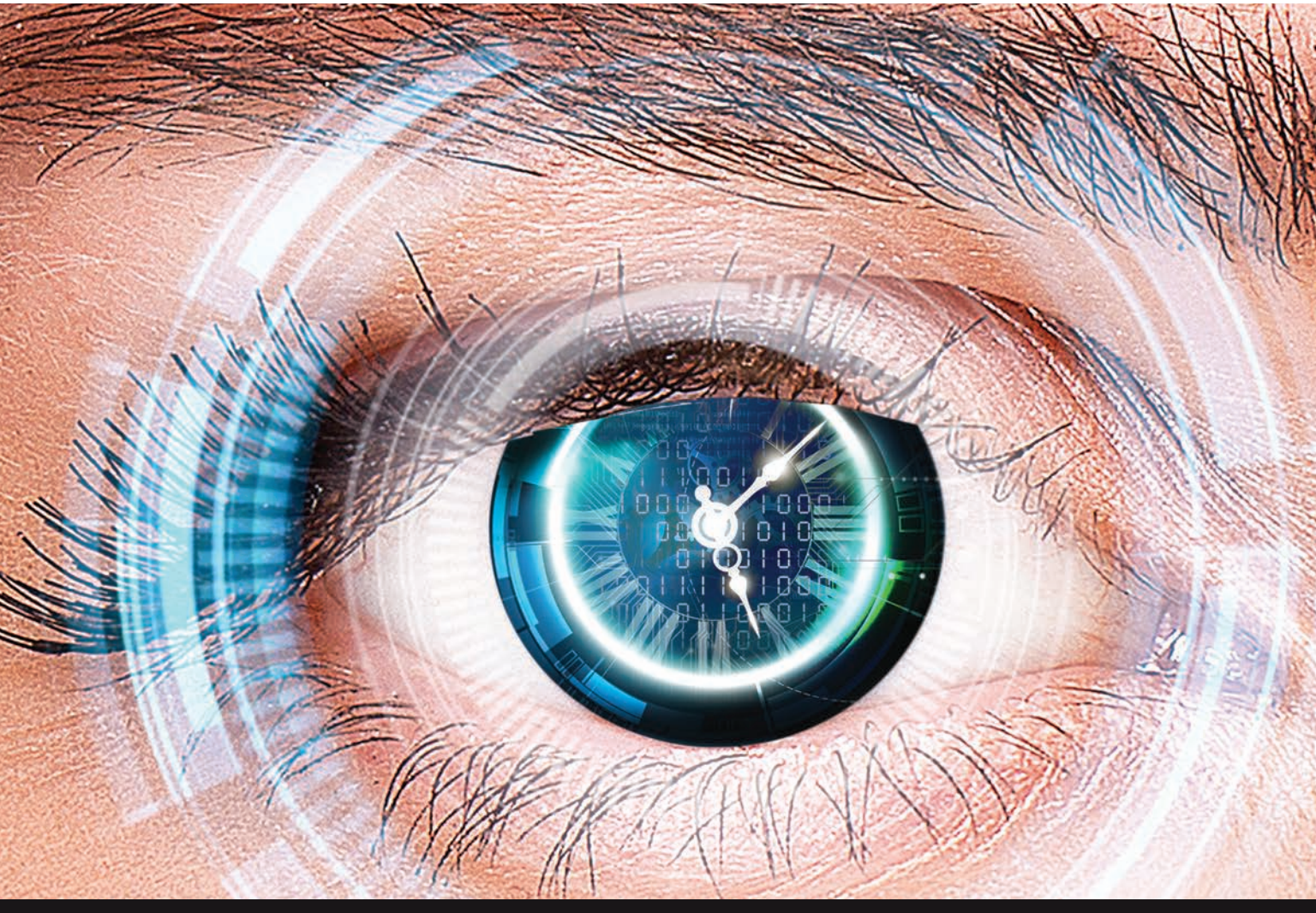
# Innovations in Glaucoma Care & Treatment

Proceedings of the 17th Annual Meeting of the Optometric Glaucoma Society



## INSIDE:

- Glaucoma Reversibility
- OCTA's Evolving Role in Glaucoma
- Primary Angle Closure Glaucoma
- Pressure Variability

Supplement to
REVIEW® OF OPTOMETRY
MARCH 2019

# Only VYZULTA Expands the Trabecular Meshwork with the Power of Nitric Oxide[1-5]

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## DUAL ACTION:

› VYZULTA increases aqueous humor outflow by targeting the **uveoscleral pathway** with latanoprost acid and the **trabecular meshwork** with nitric oxide[1,6]

## PROVEN EFFICACY:

› VYZULTA decreased mean IOP up to **9.1 mmHg** from baseline in clinical trials of up to 12 months[6]

## DEMONSTRATED SAFETY:

› **6%** of patients in pivotal trials reported **hyperemia**[6]

› **6 out of 811** patients on VYZULTA in pivotal trials **discontinued** treatment[1]

## INDICATION

VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

## IMPORTANT SAFETY INFORMATION

- Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent
- Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation
- Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA should generally not be used in patients with active intraocular inflammation
- Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema
- There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients

## IMPORTANT SAFETY INFORMATION (CONTINUED)

- Contact lenses should be removed prior to the administration of VYZULTA and may be reinserted 15 minutes after administration
- Most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%)

**For more information, please see Brief Summary of Prescribing Information on next page.**


**References:**

**1.** Cavet ME, DeCory HH. The role of nitric oxide in the intraocular pressure lowering efficacy of latanoprostene bunod: Review of nonclinical studies. *J Ocular Pharmacology and Therapeutics*. 2018;(34)1,2:52-60. DOI: 10.1089/jop.2016.0188. **2.** Wareham LK, Buys ES, Sappington RM. The nitric oxideguanylate cyclase pathway and glaucoma. *Nitric Oxide*. 2018;77:75-87. DOI/10.1016/j.niox.2018.04.010. **3.** Stamer DW, Ascott TS. Current understanding of conventional outflow dysfunction in glaucoma. *Curr Opin Ophthalmol*. 2012;23:135-143. DOI:10.1097/ICU.0b013e32834ff23e. **4.** Cavet ME, Vollmer TR, Harrington KL, VanDerMeid K, Richardson ME. Regulation of endothelin-1-induced trabecular meshwork cell contractility by latanoprostene bunod. *Invest Ophthalmol Vis Sci*. 2015;56(6):4108-4116. **5.** Kaufman PL. Enhancing trabecular outflow by disrupting the actin cytoskeleton, increasing uveoscleral outflow with prostaglandins, and understanding the pathophysiology of presbyopia: Interrogating Mother Nature: asking why, asking how, recognizing the signs, following the trail*. *Experimental Eye Research*. 2008;86:3-17. DOI:10.1016/j.exer.2007.10.007. **6.** VYZULTA Prescribing Information. Bausch & Lomb Incorporated. 2018.


**For more information about VYZULTA and how it works, visit VYZULTANOW.com**

IOP=intraocular pressure

BAUSCH + LOMB

VYZULTA®
(latanoprostene bunod ophthalmic solution), 0.024%

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

**This Brief Summary does not include all the information needed to use VYZULTA safely and effectively. See full Prescribing Information for VYZULTA.**

# VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024%, for topical ophthalmic use.

**Initial U.S. Approval: 2017**

## 1 INDICATIONS AND USAGE

VYZULTA™ (latanoprostene bunod ophthalmic solution) 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

## 4 CONTRAINDICATIONS

None

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Pigmentation

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% may cause changes to pigmented tissues. The most frequently reported changes with prostaglandin analogs have been increased pigmentation of the iris and periorbital tissue (eyelid).

Pigmentation is expected to increase as long as latanoprostene bunod ophthalmic solution is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes are likely to be reversible in most patients. Patients who receive prostaglandin analogs, including VYZULTA, should be informed of the possibility of increased pigmentation, including permanent changes. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17) in full Prescribing Information]*.

### 5.2 Eyelash Changes

VYZULTA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and the number of lashes or hairs. Eyelash changes are usually reversible upon discontinuation of treatment.

### 5.3 Intraocular Inflammation

VYZULTA should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation as it may exacerbate this condition.

### 5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. VYZULTA should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

### 5.5 Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

### 5.6 Use with Contact Lens

Contact lenses should be removed prior to the administration of VYZULTA because this product contains benzalkonium chloride. Lenses may be reinserted 15 minutes after administration.

## 6 ADVERSE REACTIONS

The following adverse reactions are described in the Warnings and Precautions section: pigmentation (5.1), eyelash changes (5.2), intraocular inflammation (5.3), macular edema (5.4), bacterial keratitis (5.5), use with contact lens (5.6).

### 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 the clinical trials of another drug and may not reflect the rates observed in practice.

VYZULTA was evaluated in 811 patients in 2 controlled clinical trials of up to 12 months duration. The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

Latanoprostene bunod has caused miscarriages, abortion, and fetal harm in rabbits. Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (IV) to pregnant rabbits at exposures ≥ 0.28 times the clinical dose. Doses ≥ 20 µg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat when administered IV at 150 mcg/kg/day (87 times the clinical dose) *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

*Animal Data*

Embryofetal studies were conducted in pregnant rabbits administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 19, to target the period of organogenesis. The doses administered ranged from 0.24 to 80 mcg/kg/day. Abortion occurred at doses ≥ 0.24 mcg/kg/day latanoprostene bunod (0.28 times the clinical dose, on a body surface area basis, assuming 100% absorption). Embryofetal lethality (resorption) was increased in latanoprostene bunod treatment groups, as evidenced by increases in early resorptions at doses ≥ 0.24 mcg/kg/day and late resorptions at doses ≥ 6 mcg/kg/day (approximately 7 times the clinical dose). No fetuses survived in any rabbit pregnancy at doses of 20 mcg/kg/day (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0.24 mcg/kg/day (0.28 times the clinical dose). Malformations included anomalies of sternum, coarctation of the aorta with pulmonary trunk dilation, retroesophageal subclavian artery with absent brachiocephalic artery, domed head, forepaw hyperextension and hindlimb malrotation, abdominal distention/edema, and missing/fused caudal vertebrae.

An embryofetal study was conducted in pregnant rats administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 17, to target the period of organogenesis. The doses administered ranged from 150 to 1500 mcg/kg/day. Maternal toxicity was produced at 1500 mcg/kg/day (870 times the clinical dose, on a body surface area basis, assuming 100% absorption), as evidenced by reduced maternal weight gain. Embryofetal lethality (resorption and fetal death) and structural anomalies were produced at doses ≥ 300 mcg/kg/day (174 times the clinical dose). Malformations included anomalies of the sternum, domed head, forepaw hyperextension and hindlimb malrotation, vertebral anomalies and delayed ossification of distal limb bones. A no observed adverse effect level (NOAEL) was established at 150 mcg/kg/day (87 times the clinical dose) in this study.

### 8.2 Lactation

Risk Summary

There are no data on the presence of VYZULTA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for VYZULTA, and any potential adverse effects on the breastfed infant from VYZULTA.

### 8.4 Pediatric Use

Use in pediatric patients aged 16 years and younger is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

### 8.5 Geriatric Use

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

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Latanoprostene bunod was not mutagenic in bacteria and did not induce micronuclei formation in the *in vivo* rat bone marrow micronucleus assay. Chromosomal aberrations were observed *in vitro* with human lymphocytes in the absence of metabolic activation.

Latanoprostene bunod has not been tested for carcinogenic activity in long-term animal studies. Latanoprost acid is a main metabolite of latanoprostene bunod. Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime rodent bioassays, was not carcinogenic.

Fertility studies have not been conducted with latanoprostene bunod. The potential to impact fertility can be partially characterized by exposure to latanoprost acid, a common metabolite of both latanoprostene bunod and latanoprost. Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

### 13.2 Animal Toxicology and/or Pharmacology

A 9-month toxicology study administered topical ocular doses of latanoprostene bunod to one eye of cynomolgus monkeys: control (vehicle only), one drop of 0.024% bid, one drop of 0.04% bid and two drops of 0.04% per dose, bid. The systemic exposures are equivalent to 4.2-fold, 7.9-fold, and 13.5-fold the clinical dose, respectively, on a body surface area basis (assuming 100% absorption). Microscopic evaluation of the lungs after 9 months observed pleural/subpleural chronic fibrosis/inflammation in the 0.04% dose male groups, with increasing incidence and severity compared to controls. Lung toxicity was not observed at the 0.024% dose.

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# INTRODUCTORY REMARKS

The 17th Annual Scientific Meeting of the Optometric Glaucoma Society (OGS), held Nov. 5-6, 2018, in San Antonio, assembled a group of esteemed researchers and practitioners in the field of glaucoma. These individuals shared groundbreaking information about the latest strategies, therapies and devices that are making their way into clinical practice.

The OGS Honoree Lecture was especially thought-provoking, as L. Jay Katz, MD, pushed us to question whether glaucoma is a reversible disease—contrary to prevailing wisdom. Spoiler alert: Yes, glaucoma reversibility is not only possible, but it has been documented for the last three decades. Dr. Katz shared research that was not only intriguing, but also offered clinicians a great deal of hope about the potential to reverse glaucoma damage.

Alex A. Huang, MD, PHD, brought us up to speed with the latest findings about the clinical usefulness of optical coherence tomography angiography. OCTA, in spite of some technical limitations, holds tremendous promise for clinical evaluation of a patient's glaucoma risk as well as possibly guiding treatment options.

Turning to primary angle-closure glaucoma in the President's Lecture, Robert M. Feldman, MD, opened our eyes to the staggering increase in the number of PACG cases worldwide. He highlighted a new marker—the band of extracanalicular lamina (BELL)—identified by his team to help pinpoint the scleral spur using swept-source anterior-segment optical coherence tomography, along with new measurements to assess for angle closure.

Arthur J. Sit, MD, shed light on how changes to circadian rhythms and body position can alter intraocular pressure, based on the results of research that he and other investigators have conducted. He outlined emerging strategies for 24-hour IOP control, given that IOP variation has been shown to be a risk factor for glaucoma pathogenesis and progression in susceptible populations.

This supplement, developed by *Review of Optometry*, was made possible with generous support from Bausch + Lomb.

Please visit the OGS website (www.optometricglaucomasociety.org) and consider signing up for our free, quarterly e-journal to keep up with the latest developments in glaucoma diagnosis, treatment and management.

**Murray Fingeret, OD**
*Founding Member and Past President, Optometric Glaucoma Society*
*President, Optometric Glaucoma Foundation*

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OGS Honoree Lecture

# Is Glaucoma a Reversible Disease?

*L. Jay Katz, MD*

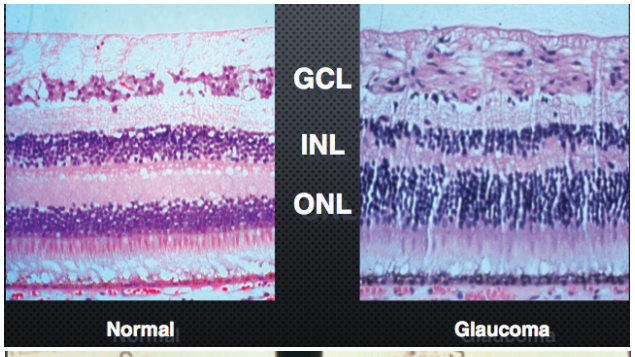
The field of glaucoma has made great strides in diagnosis, treatment and management, but in order to take the next quantum leap for our patients, we have to drop one preconceived notion that has been perpetuated over time: that glaucoma is irreversible. We have been telling our patients for years that the best we can offer them is to arrest the disease, and I think that's a bar we need to raise. Frankly, our patients deserve better from us.

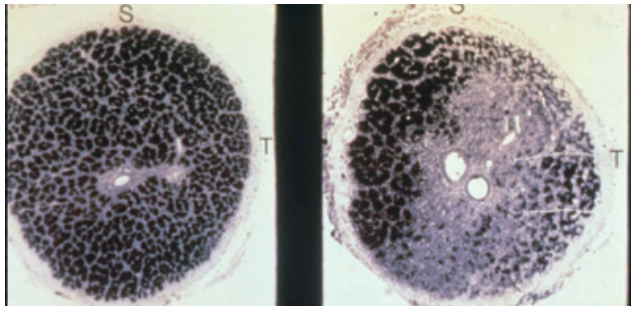
In order to suspend these deeply ingrained ideas, we first need to question many aspects of our conventional wisdom and practice.

Take, for example, the definition of primary open-angle glaucoma (POAG)—a multifactorial optic neuropathy leading to the development of optic nerve atrophy and loss of retinal ganglion cells (RGCs) in the presence of an open angle. This definition implies that the disease is unidirectional without the possibility of reversibility.

From a structural perspective, if we look at histologic slides of RGCs in glaucoma, cell losses are apparent. But is it possible that some cells still exist with dysfunction? Can we take glaucoma patients who have a great deal of functional vision loss as a result of RGC damage and reverse this trend?

Let's think about intraocular pressure (IOP). It's widely accepted that pressure is an important risk factor for the development and progression of glaucoma. Research has shown us that lowering IOP appears to slow or suspend the disease. As such, IOP has become our surrogate marker for conventional therapy. But could other systemic risk factors—whether they are circulatory, genetic, neurotrophic, or otherwise—become targets to improve glaucoma?




**FIGURES 1 AND 2. RGCS ON HISTOLOGY**
Histology slides depict the loss of retinal ganglion cells in glaucoma.
*Images: L. Jay Katz, MD*

The first step toward breaking out of our current disease paradigm is to understand that reversibility is not only possible, but it has been documented for the last three decades.

## Reversibility in the Literature

Starting in the 1980s, anecdotal reports of glaucoma improvements led us to question whether conventional therapy could do more than stabilize disease. Several giants in the field documented less cupping in the optic nerve and expansion of the visual field (VF) in patients who experienced marked IOL reductions while on various glaucoma therapies.[1,2]

Spurring these findings, George L. Spaeth, MD, a world-renown glaucoma researcher at Wills Eye Hospital, wrote an editorial in 1989 suggesting that the endpoint or target when treating a glaucoma patient should not be stability, but rather objective signs of improvement.[3] This led to subsequent decades of fellows training under George Spaeth looking at that particular issue.

As one of those fellows, I led a study using three masked glaucoma specialists to review optic disc stereophotographs and VFs taken before and after a clinical course of patients undergoing glaucoma treatments. My team found, among individuals with marked pressure lowering, that one in five showed less ocular disc cupping, and one in three showed better VFs, along with higher visual function.[4] The degree of optic disk and VF improvement was significantly ($p<.05$) associated with the amount of IOP reduction. Mark Lesk, another fellow at Wills Eye, used imaging technology to similarly reveal that 85% of subjects who experienced a 40% IOP reduction after glaucoma surgery also exhibited better optic nerve morphology, as measured by the Heidelberg Retina Tomograph.[5] The amount of change highly correlated with the percent reduction of IOP.

With the introduction of optical coherence tomography (OCT), Michael Waisbourd continued the pattern of finding a relationship between marked pressure reduction and improvement on OCT imaging of the nerve fiber layer along with better VFs.[6] In addition, Joe Caprioli led a study looking at post-trabeculectomy POAG patients who were followed with serial perimetry over several years. Not only did trabeculectomy slow the rate of perimetric decay, but investigators saw evidence of sustained, long-term enhancements in visual function in glaucoma.[7]

In a more objective study using electrophysiology and pattern electroretinograms (ERG) to assess RGC function, researchers once again found that pressure reductions led to glaucoma improvements on ERG recordings.[8] Laboratory studies on animals have revealed similar results.[9]

## Vascular Hypothesis

So we know glaucoma reversibility is possible. But in order to find ways to potentially undo glaucoma damage, it's necessary to understand why the disease occurs and how to positively or negatively affect it. Some papers point to the idea that vascular dysregulation might be occurring in certain glaucoma patients.

Costa and others have focused on the impact of blood pressure (BP) and diastolic BP on glaucoma. Costa et al. wrote that the balance between IOP and BP could be partly responsible for whether an individual develops optic nerve damage.[10] The team stressed the importance for the eye to maintain adequate ocular perfusion of the optic nerve head, and suggested that ocular perfusion pressure—mean

BP minus IOP—and its fluctuations might be important parameters to measure in glaucoma patients.[11]

In addition, several large population studies (Barbados Eye Study, Baltimore Eye Survey, Early Manifest Glaucoma Trial) have looked at BP as a risk factor for the development and progression of glaucoma. The studies are revealing that the prevalence of glaucoma spikes as diastolic perfusion pressure drops to a fairly low level. So we are learning that people with low diastolic BP are at greater risk for the disease. In addition, ocular hypertension and some forms of glaucoma might be influenced by factors outside of IOP such as insufficient blood supply or reduced ocular blood flow.[12,13]

Investigators who are looking at how BP circulation around the optic nerve affects glaucoma and whether the circulation could be altered are finding that certain actions might improve the pressure indirectly. Years ago, as a Wills Eye resident, Jack Trible evaluated on color Doppler imaging the posterior ciliary artery in patients who underwent filtering surgery.[14] It turned out that many of these subjects' diastolic and systolic BP pulse waves increased dramatically postoperatively. Likewise, other researchers have revealed with color Doppler imaging better ocular blood flow in post-trabeculectomy patients as a result of IOP reductions.[15]

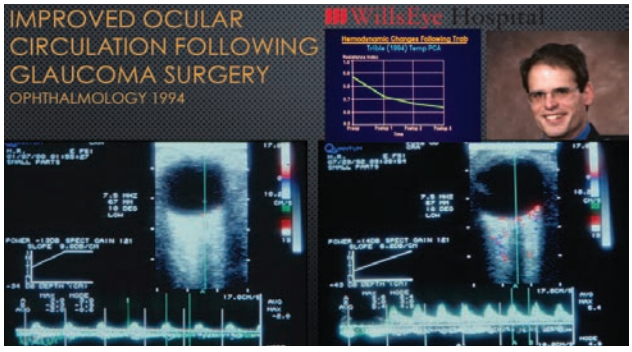



**FIGURE 3. IMPROVED OCULAR CIRCULATION POST-SURGERY**
While a resident at Wills Eye Hospital, Jack Trible evaluated the posterior ciliary artery patients who underwent filtering surgery on color Doppler imaging, and found that the diastolic and systolic pulse waves dramatically increased postoperatively.[14]

More recently, a team assessed via OCT angiography the posterior displacement of the lamina cribrosa (LC) in post-trabeculectomy POAG patients.[16] The group found that about two-thirds of eyes had less LC posterior bowing and improved vessel densities near the optic nerve related to IOP reductions.

Therapeutically, in addition to surgical procedures to lower IOP, glaucoma treatment often involves medications to lower pressure. One important question to ask about our glaucoma and other drug classes is if they are vasoactive in a good or a bad way for our patients.

Some positive findings have revealed that latanoprostene bunod, which has a nitric oxide-donating side chain, appears to improve trabecular meshwork (TM) outflow and offer an added pressure-lowering effect apart from latanoprost.[17] Since nitric oxide is a potent vasodilator, it might also offer posterior segment benefits. In addition, one team prospectively studied the effect of oral brovincamine, a relatively selective cerebral vasodilator, on further VF deterioration in patients with normal-tension glaucoma (NTG) and low-normal IOP, and found that oral brovincamine might be protective against VF progression in this Japanese population.[18]

On the other hand, some experimental evidence has shown that Endothelin-1, a vasoconstrictive agent expressed in many organs and tissues, could play a role in glaucoma pathogenesis. And one study looking at the effect of topical glaucoma medications on automated perimetry found that just one drop of the nonselective beta-blocker levobunolol impaired perimetry sensitivity.[19]

Other reports are more of a mixed bag. One study compared the effects of the prostaglandin analog bimatoprost and beta-blocker timolol on IOP and choroidal circulatory patterns of blood flow.[20] Bimatoprost was associated with increased pulsatile ocular blood flow and choroidal blood flow—providing an added benefit to patients along with IOP lowering—while timolol was linked to a reduction in pOBF. My Wills team, including Drs. Sergott and Dr. Harris, compared betaxolol and timolol in NTG patients and found that timolol lowered IOP more than betaxolol but didn't provide ocular circulation benefits on color Doppler imaging, while betaxolol boosted circulation.[21] Research is ongoing on these kinds of vascular implications for glaucoma progression and reversal.

## Neurotrophins: Mediators of RGC Survival

Another school of thought has sought to understand the mechanisms of RGC health to discover new ways to mitigate and reverse glaucoma damage. First, it's necessary to understand why cells die. There are two types of cell death: necrotic cell death, created by a hostile environment such as ischemic injury; and apoptosis, programmed cell death—a natural occurrence in the body. In the latter case, apoptosis promotes homeostasis by killing abnormal cells; however, with signal interruptions or overactive behavior, it can lead to diseases such as glaucoma.

In animal ischemic models, researchers have accelerated apoptosis by axotomies, or cutting the optic nerves and their associated blood circulation, to better understand glaucoma pathogenesis.[22,23] Quigley et al. found in an experimental glaucoma model that primates' dying RGCs exhibited morphologic features of apoptosis.[24] By mimicking what could be occurring in human glaucoma, the researchers showed an upswing in the number of apoptotic cells in the RGC layer. This process might be especially important to consider in glaucoma patients with seemingly reasonable eye pressures who are still progressing. Is it possible that excessive apoptosis might be part of that picture? If so, how do we promote homeostatic balance and RGC survival?

Research is showing us that neurotrophins are an essential factor for RGC health. We now know that cell bodies promote their own survival by maintaining a certain level of neurotrophic substances. In healthy eyes, neurotrophins appear to migrate toward the neuronal cell body by retrograde axonal transport. So it makes sense that acute experimental glaucoma in rats has revealed obstructions in retrograde transport to RGCs of a neurotrophin such as brain-derived neurotrophic factor (BDNF), a protein encoded by the BDNF gene.[25]

In an experimental model, when the alpha2-adrenergic agonist brimonidine tartrate, an IOP-lowering drug, was injected into the vitreous, it caused a marked endogenous increase of BDNF.[26] The late Dr. Krupin led a randomized glaucoma treatment trial to compare brimonidine tartrate 0.2% and timolol maleate 0.5% in preserving visual function in NTG subjects.[27] The mean IOP reduc-

tion in both groups was about 2 mmHg, but when looking at VF progression, the brimonidine group exhibited a 9% progression rate vs. a nearly 40% progression rate in the timolol-treated group. With such a staggering discrepancy, we could postulate that brimonidine might have offered neuroprotection apart from lowering eye pressure.

A group in Italy noted clinical evidence of neuroprotection using topical neurotrophic factor.[28] Significantly less RGC death by apoptosis was observed with nerve growth factor (NGF) treatments in laboratory studies, and patients treated with topical NGF demonstrated long-lasting improvements in visual fields, contrast sensitivity and visual acuity. Unfortunately, researchers based this study on three patients, so the analysis wasn't robust. Another study found similar results in a rodent population; NGF exerted a protective action on RGC degeneration occurring in rat glaucomatous retinas.[29]

Larger human trials are attempting to replicate such findings. Neurotech is using NT-501 encapsulated cell therapy (ECT), consisting of genetically modified encapsulated human cells that secrete therapeutic doses of ciliary neurotrophic factor into subject eyes with glaucoma. Jeff Goldberg at Stanford University has investigated the safety and efficacy of intravitreal implantation of NT-501 ECT to treat glaucoma, in a randomized clinical study.[30] In a pilot series Goldberg conducted with NT-501 on deteriorating glaucoma patients despite low IOPs, the majority of eyes seemed to improve on perimetry and contrast sensitivity, as he reported at the 2015 American Glaucoma Society annual meeting.

### Intracranial Pressure

Another area of exploration aiming to understand reversal of glaucoma damage is intracranial pressure (ICP) and its affect on the translaminar pressure gradient. This research was prompted by astronauts who have returned from extended space travel with temporary papilledema and reductions in vision. In zero gravity, cerebrospinal fluid pressure (CFP) tends to congregate around the brain as opposed to the spinal column, increasing the ICP that contributes to papilledema. Research has shown us that elevated CFP resolves when astronauts return to gravity on Earth.

John Berdahl of South Dakota has developed goggles that are vacuum-sealed around the eyes to reduce the eye pressure environment. So, with a low ICP, the goggles shift the pressure gradient toward the eye and away from the brain. Ongoing studies are evaluating whether such a strategy might be beneficial.

### Visual Pathway Stimulation

In the realm of more unconventional glaucoma therapy, investigators are using light and electrical stimulation to improve visual function and reverse damage in glaucoma patients. For example, researchers are directing light to stimulate shrinkage of scotomas.[31] Another team used repetitive transorbital alternating [electrical] current stimulation (rtACS) in partially blind patients to activate their residual vision.[32]

The rtACS-treated group had a mean VF improvement of 24%, which was significantly greater than sham stimulation (2.5%). Researchers concluded that rtACS treatment was a safe and effective means to partially restore vision after optic nerve damage, probably by modulating brain plasticity.


**FIGURE 4. ELECTRICAL STIMULATION IN GLAUCOMA**

Researchers compared transorbital alternating current stimulation therapy against sham stimulation in partially blind patients, and nearly one-quarter of eyes that had electrical stimulation had improvements on perimetry vs. 2% of the sham group.[32]

### Stem Cells

As stem cell research has exploded over the last several decades, the field of glaucoma is no stranger to these advancements. Potential roles for stem cells in glaucoma include neuroprotection, RGC replacement, and altering the "plumbing" in the eye.

Researchers have shown an upregulation of cell survival in an experimental model of glaucoma by injecting bone marrow-derived stem cells into rodent eyes.[33] The positive cell activity could be due to neuroprotection. And intravitreal mesenchymal stem cell transplantation, accompanied by decreased IOP, has resulted in statistically significant increases in RGC axon survival in laser-induced ocular hypertensive glaucoma. Other clinical trials are looking at improving macular function in animal retinas by injecting stem cells that differentiate into RGCs, and through growing in vitro human stem cells into RGCs.[34,35]

One group focusing on glaucoma patients is injecting bone marrow-derived stem cells into different locations in the eye.[36] The team reported on an optic neuritis patient who had tremendous improvement in VFs and visual function in both eyes after the placement of stem cells. However, the *New York Times* reported three patients were blinded following such stem cell placements. So ongoing challenges exist.

The cells also are helping to improve pressure. Dr Joel Schuman's group has reported that stem cells could differentiate the mature TM cells.[37] Repopulating the TM with functional endothelial cells might yield better visual function by lowering of IOP.

However, investigators are still grappling with where to get stem cells, where to place them, and how to ensure proper "hookups" to have good function in the eye and the brain. Stay tuned for further developments.

### Gene Therapy

Gene therapy continues to be the wild west of evolving therapies. Scientists, who have identified a number of gene mutations that can lead to glaucoma, are culturing stem cells with genetic defects to determine how to alter the genetic makeup to halt bad proteins and

produce more good proteins.

Outside of glaucoma, researchers have inserted a virus vector inside of a defective gene to promote visual function improvements in Leber's congenital amaurosis patients.[38] Other investigators have also injected modified DNA into the mitochondrial matrix of Leber's hereditary optic neuropathy subjects, leading to visual improvement in certain individuals.[39] And Dr. Paul Kaufman's group is supporting the eye's "plumbing system" by using virus vectors to genetically modify endothelial cells in the TB and adjust proteins.[40]

In summary, I think we live in exciting times right now. I am very optimistic for the future of our field and for glaucoma patients. Conventional pressure reduction therapies will continue to be critical for disease amelioration. But other possibilities are emerging; whether it's ocular perfusion, neurotrophin placement, visual pathway stimulation, stem cells, or gene therapy—these advances offer us evolving technologies to provide not just glaucoma stability, but real and tangible disease improvements.

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Glaucoma Imaging

## OCTA's Evolving Role in Glaucoma

*Alex A. Huang, MD, PHD*

Optical coherence tomography angiography (OCTA) is a noninvasive imaging technique that can rapidly generate cross-sectional, volumetric angiography images of the eye. It is a significant advancement over older angiographic imaging standards that suffer from the inability to depth resolve the images and the need for intravenous injection of contrast agents.

On a macro level, OCTA offers the ability to visualize and quantify ocular blood flow movement—an increasingly important aspect of glaucoma pathophysiology, given research indicating possible associations with vascular abnormalities. On a micro level, OCTA can produce high-resolution, three-dimensional angiograms

of the retinal and choroidal vascular networks. Importantly, the imaging modality can simultaneously depict structural and blood flow information to better delineate pathology. Clinicians are able to see, for example, optic disc perfusion, and changes in retinal and choroidal blood vessel flow in glaucomatous eyes.

However, OCTA is not a panacea. Limitations of the imaging technique include a relatively small field of view, inability to show leakage, and a tendency to produce artifacts due to patient movement and blinking.[1] Published studies have suggested that OCTA might be helpful in evaluating age-related macular degeneration, diabetic retinopathy, artery and vein occlusions, and glaucoma. Yet, Level 1 evidence of OCTA's clinical utility, particularly in glaucoma, is lacking, and researchers are striving to add more scientific findings to our knowledge base.[1]

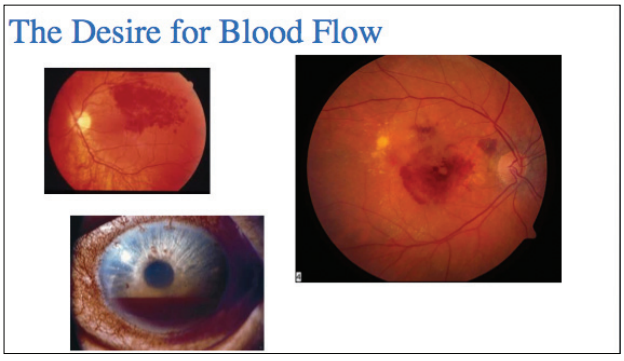


**FIGURE 1.**
A vein occlusion (top left), a choroidal neovascularization (top right) as well as an iris neovascularization (bottom left) can be seen in these OCTA images.
*Images: Alex A. Huang, MD, PHD*

## Getting Into the Flow

The desire to look at blood flow in glaucoma likely originates from the fact that the anterior and posterior eye are rife with blood flow issues. Why does retinal blood flow matter in glaucoma? Ganglion cells—types of neurons or nerve cells—are located in the retina, and retinal ganglion cells (RGCs) are damaged in glaucoma; in addition, the retina is vulnerable to ischemia.

To better understand blood flow in glaucoma, it's important to recall some basic ocular biology. Fundamentally, RGCs contain threadlike axons that conduct impulses to brain cells and form the optic nerve. A myelin sheath encapsulates these axons to accelerate this process. Gaps in the sheath known as Nodes of Ranvier are where action potential signals and saltatory conduction occur, and sodium and potassium ion channels are spaced out here, so signals can easily jump between nodes for further energy efficiency.

The retina, which is essentially brain tissue, is the largest Node of Ranvier in the body. And yet, the macula lacks myelinated nerve fiber. On one hand, the lack of myelin is essential to avoiding blind spots in our vision; on the other hand, it means the retina is energetically deprived, opening the door to blood flow problems that might impact RGC health.

The potential importance of blood flow in glaucoma is tied to the concept of the ocular perfusion pressure gradient. Arterial pressure brings blood into the eye, and intraocular pressure (IOP) can prevent blood from entering by pushing back. The difference between this arterial pressure and IOP is the ocular perfusion pressure gradient. As one could imagine, less blood flow into the eye could be deleterious, and elevated IOP (a known glaucomatous risk factor) lowers ocular perfusion pressure in the previously mentioned relationship.

Thankfully, imaging methods to assess blood flow imbalances that might contribute to these mismatches have evolved. Beginning in the 1960s, the rise of choroidal and retinal angiography meant practitioners could inject indocyanine green (IGC) and fluorescein (FA) dyes into veins and employ angiographic cameras to elucidate the choroidal and retinal vessels.[2-5] In the 1970s, researchers pulled the camera back to focus on the anterior segment with iris angiography.[6] And in the 1980s, scleral angiography was described by Peter Watson at Moorfields Eye Hospital in London.[7] Tracer injected into the veins provided a view of blood flow in the front and back of the eye, with the ability to see vessel leakage and take direct measurements, although the modality was still invasive, and had low resolution and a lack of depth resolution.

## Advent of OCTA

These imaging techniques paved the way for OCTA. This fast, noninvasive technology offered good contrast and resolution to reveal important details about vascular structure and blood flow; its biggest advantage was the ability to tease out and differentiate layers in a depth-resolved and noninvasive manner.

A metaphor I have for OCTA is a cartoon "flipbook." Consider images of a bird flapping its wings over a series of pages; the difference between those images is the motion of the bird's wings. In a similar manner, OCTA extracts microvascular circulation (i.e., movement) from OCT image data with specialized acquisition and processing techniques. In other words, motion is seen as the difference between separate individual images.

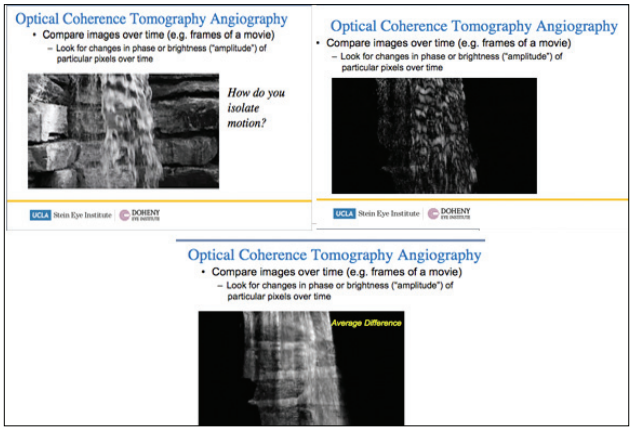


**FIGURE 2. OCTA SPECIALIZED ACQUISITION & PROCESSING**
In this series of OCTA images of a waterfall, the following is visible: (1) an image of a waterfall over rocks, (2) the water moving with the rocks subtracted out, and (3) a cleaned-up image to average the difference. Such an OCTA-processed image could help assess blood flow in the retina.

More specifically, the clinician can isolate RBC movement or blood flow from an otherwise motionless retina by analyzing differences in phases or amplitudes between scans. Taking multiple structural images of the retina at the same location, or repeated B scans—cross-sectional images in which amplitudes of reflections are represented in a gray- or false-color scale—enables the clinician to see differences, i.e., signals. The signals (appearing as yellow dots) can then be reconstructed to

reveal, for example, the vascular network in the retina.

Originally, clinicians relied on ImageJ, an open-source, image-processing program designed for multidimensional scientific images, to analyze OCTA scans. But new software offers the ability to quantitatively measure parameters that are more useful in the clinic. Currently, some technology platforms binarize (i.e., brighten or darken) images to assess perfusion density, while others also "skeletonize" the renderings to assess vessel density. In addition, axial profile analysis is another view that offers clinicians a different vascular perspective of the retina.

## Disease Assessment

The field of glaucoma has lagged behind other specialties in using OCTA to evaluate clinical disorders, but it is starting to pick up speed. In 2016, Yarmohammadi, et al. compared retinal nerve fiber layer (RNFL) thickness and OCTA retinal vasculature measurements in healthy individuals, glaucoma suspects, and open-angle glaucoma (OAG) eyes.[8] Researchers concluded that OCTA vessel density (VD) had similar diagnostic accuracy as RNFL thickness measurements to differentiate healthy and glaucoma eyes.

Our group at UCLA and Doheny Eye Institute, led by Dr. Vikas Chopra, evaluated optic nerve VD using swept-source (SS) OCTA in individuals with early primary OAG, pre-perimetric glaucoma and normal eyes.[9] Specifically we assessed vessel area ratios in the optic nerve head (ONH), a 3 mm papillary section around the optic disc and the peripapillary region.

We found a statistically significant difference between control and pre-perimetric glaucoma eyes for peripapillary, ONH, and papillary VD area values (p=0.001 to 0.007). The ONH VD, and superior and inferior papillary area VDs were highly correlated with the mean overall superior and inferior RNFL thickness in POAG eyes (p=0.04, p=0.02 and p=0.04 respectively). Multiple linear regression analyses of the POAG group showed that ONH VD had a greater association with RNFL thickness than other variables. The fact that the VDs were more diminished in POAG eyes than in the pre-parametric and control groups indicated that less VD was a characteristic of disease. We concluded that OCTA-derived retinal VD measurements were effective in helping us differentiate mild POAG from pre-perimetric glaucoma and normal eyes.

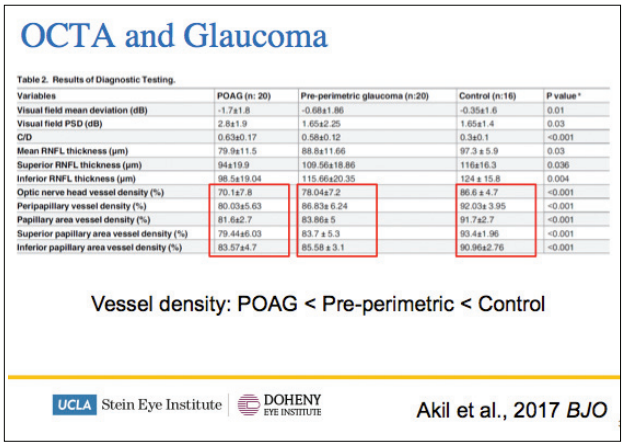


**FIGURE 3. VESSEL DENSITY ON OCTA**
Our group at the Doheny Eye Institute at UCLA found that vessel densities in POAG eyes were lower than those in pre-perimetric glaucoma and control eyes.[9]

We also used SS-OCTA to evaluate the macular capillary network density of superficial and deep retinal layers (SRL/DRL) in POAG patients, and compared the results with those of normal subjects.[10] Twenty-four eyes of 24 subjects with mild-to-moderate POAG, and 24 normal eyes underwent fovea-centered, 6×6 mm3 macular OCTA imaging by a SS-OCTA device. We quantitatively analyzed the retinal vasculature by VD measurements (i.e., ratio of the retinal area occupied by vessels in the SRL and DRL).

Our team found that the mean VDs in the SRL and DRL were statistically significantly lower in POAG patients (SRL: p<0.001; DRL: p<0.001). In the SRL, the mean ±SD VD ratio was 0.34±0.05 in POAG patients and 0.40±0.02 in normal eyes (p<0.001). In the DRL, the mean ±SD VD ratio was 0.37±0.05 in POAG patients and 0.43±0.02 in normal eyes (p<0.001). The mean VD in the SRL was significantly correlated with ganglion cell inner plexiform layer thickness (r=0.42, p=0.04), but not with VF mean deviation (r=0.4, p=0.06) and RNFL thickness (r=0.5, p=0.06). The mean VD in the DRL did not show significant correlation with any other glaucoma parameters (p>0.05). The study revealed that SS-OCTA-aided assessment of macular VD might offer additional clues to detect glaucoma as well.

In another recent study, OCTA offered improved structural/functional information to analyze factors associated with POAG eye dropout.[11] Forty-two eyes were identified as having microvasculature dropout in the optic disc, 37 with pseudo-microvasculature dropout and 44 with no dropout. Eyes with dropout were shown on OCTA to have significantly lower IOP, worse VF mean deviation, larger cup-to-disc ratio, thinner circumpapillary RNFL, and lower circumpapillary VD in the RNFL compared with eyes with pseudo-microvasculature or no dropout.

## Clinical Usefulness

The question of how to use OCTA information in glaucoma persists. Part of the problem is a 'chicken-or-egg' dilemma: Did glaucoma's loss of nerve tissue lead to deteriorating blood vessels? Or did blood flow problems and a downgraded vascularity yield glaucoma? The answer requires more longitudinal data than we currently have. As such, I don't get OCTA on every glaucoma patient because I don't know what to do with all of the information I can obtain.

That said, I have my own views on OCTA's evolving clinical purpose while waiting for science to catch up. Starting out with diagnosis, I believe that for OCTA to be useful diagnostically, the field has to first re-consider the definition of glaucoma. Currently the disease definition is optic neuropathy with a VF defect; nowhere does it mention blood flow. How can you use a test to reliably diagnose a pathology with a parameter that isn't mentioned in the disease definition? In addition, many factors can change blood flow—diabetes, high blood pressure, and sickle-cell anemia, for example. So, by that argument, OCTA is non-specific to glaucoma.

However, OCTA likely has a role in glaucoma risk assessment and treatment guidance. Think of the primary surrogate marker now used to guide glaucoma therapy that isn't part of disease diagnosis: IOP. We heavily rely on IOP to manage patients, even with IOP's primary limitation—the lack of a standard target for lowering. Some patients need 20% or 30% reductions, while other individuals require greater-than-40% reductions that ultimately can only be achieved by surgery.[12,13] Thus,

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

**This Brief Summary does not include all the information needed to use VYZULTA safely and effectively. See full Prescribing Information for VYZULTA.**

# VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024%, for topical ophthalmic use.

**Initial U.S. Approval: 2017**

## 1 INDICATIONS AND USAGE

VYZULTA™ (latanoprostene bunod ophthalmic solution) 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

## 4 CONTRAINDICATIONS

None

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Pigmentation

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% may cause changes to pigmented tissues. The most frequently reported changes with prostaglandin analogs have been increased pigmentation of the iris and periorbital tissue (eyelid).

Pigmentation is expected to increase as long as latanoprostene bunod ophthalmic solution is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes are likely to be reversible in most patients. Patients who receive prostaglandin analogs, including VYZULTA, should be informed of the possibility of increased pigmentation, including permanent changes. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17) in full Prescribing Information]*.

### 5.2 Eyelash Changes

VYZULTA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and the number of lashes or hairs. Eyelash changes are usually reversible upon discontinuation of treatment.

### 5.3 Intraocular Inflammation

VYZULTA should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation as it may exacerbate this condition.

### 5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. VYZULTA should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

### 5.5 Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

### 5.6 Use with Contact Lens

Contact lenses should be removed prior to the administration of VYZULTA because this product contains benzalkonium chloride. Lenses may be reinserted 15 minutes after administration.

## 6 ADVERSE REACTIONS

The following adverse reactions are described in the Warnings and Precautions section: pigmentation (5.1), eyelash changes (5.2), intraocular inflammation (5.3), macular edema (5.4), bacterial keratitis (5.5), use with contact lens (5.6).

### 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 the clinical trials of another drug and may not reflect the rates observed in practice.

VYZULTA was evaluated in 811 patients in 2 controlled clinical trials of up to 12 months duration. The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

Latanoprostene bunod has caused miscarriages, abortion, and fetal harm in rabbits. Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (IV) to pregnant rabbits at exposures ≥ 0.28 times the clinical dose. Doses ≥ 20 µg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat when administered IV at 150 mcg/kg/day (87 times the clinical dose) *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

*Animal Data*

Embryofetal studies were conducted in pregnant rabbits administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 19, to target the period of organogenesis. The doses administered ranged from 0.24 to 80 mcg/kg/day. Abortion occurred at doses ≥ 0.24 mcg/kg/day latanoprostene bunod (0.28 times the clinical dose, on a body surface area basis, assuming 100% absorption). Embryofetal lethality (resorption) was increased in latanoprostene bunod treatment groups, as evidenced by increases in early resorptions at doses ≥ 0.24 mcg/kg/day and late resorptions at doses ≥ 6 mcg/kg/day (approximately 7 times the clinical dose). No fetuses survived in any rabbit pregnancy at doses of 20 mcg/kg/day (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0.24 mcg/kg/day (0.28 times the clinical dose). Malformations included anomalies of sternum, coarctation of the aorta with pulmonary trunk dilation, retroesophageal subclavian artery with absent brachiocephalic artery, domed head, forepaw hyperextension and hindlimb malrotation, abdominal distention/edema, and missing/fused caudal vertebrae.

An embryofetal study was conducted in pregnant rats administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 17, to target the period of organogenesis. The doses administered ranged from 150 to 1500 mcg/kg/day. Maternal toxicity was produced at 1500 mcg/kg/day (870 times the clinical dose, on a body surface area basis, assuming 100% absorption), as evidenced by reduced maternal weight gain. Embryofetal lethality (resorption and fetal death) and structural anomalies were produced at doses ≥ 300 mcg/kg/day (174 times the clinical dose). Malformations included anomalies of the sternum, domed head, forepaw hyperextension and hindlimb malrotation, vertebral anomalies and delayed ossification of distal limb bones. A no observed adverse effect level (NOAEL) was established at 150 mcg/kg/day (87 times the clinical dose) in this study.

### 8.2 Lactation

Risk Summary

There are no data on the presence of VYZULTA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for VYZULTA, and any potential adverse effects on the breastfed infant from VYZULTA.

### 8.4 Pediatric Use

Use in pediatric patients aged 16 years and younger is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

### 8.5 Geriatric Use

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

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Latanoprostene bunod was not mutagenic in bacteria and did not induce micronuclei formation in the *in vivo* rat bone marrow micronucleus assay. Chromosomal aberrations were observed *in vitro* with human lymphocytes in the absence of metabolic activation.

Latanoprostene bunod has not been tested for carcinogenic activity in long-term animal studies. Latanoprost acid is a main metabolite of latanoprostene bunod. Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime rodent bioassays, was not carcinogenic.

Fertility studies have not been conducted with latanoprostene bunod. The potential to impact fertility can be partially characterized by exposure to latanoprost acid, a common metabolite of both latanoprostene bunod and latanoprost. Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

### 13.2 Animal Toxicology and/or Pharmacology

A 9-month toxicology study administered topical ocular doses of latanoprostene bunod to one eye of cynomolgus monkeys: control (vehicle only), one drop of 0.024% bid, one drop of 0.04% bid and two drops of 0.04% per dose, bid. The systemic exposures are equivalent to 4.2-fold, 7.9-fold, and 13.5-fold the clinical dose, respectively, on a body surface area basis (assuming 100% absorption). Microscopic evaluation of the lungs after 9 months observed pleural/subpleural chronic fibrosis/inflammation in the 0.04% dose male groups, with increasing incidence and severity compared to controls. Lung toxicity was not observed at the 0.024% dose.

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U.S. Patent Numbers: 6,211,233; 7,273,946; 7,629,345; 7,910,767; 8,058,467.



Based on 9464800 11/2017 VYZ.0055.USA.16 Issued: 11/2017

# Only VYZULTA Expands the Trabecular Meshwork with the Power of Nitric Oxide[1-5]

Visit **VYZULTANOW.COM** to learn more.


## DUAL ACTION:

› VYZULTA increases aqueous humor outflow by targeting the **uveoscleral pathway** with latanoprost acid and the **trabecular meshwork** with nitric oxide[1,6]

## PROVEN EFFICACY:

› VYZULTA decreased mean IOP up to **9.1 mmHg** from baseline in clinical trials of up to 12 months[6]

## DEMONSTRATED SAFETY:

› **6%** of patients in pivotal trials reported **hyperemia**[6]

› **6 out of 811** patients on VYZULTA in pivotal trials **discontinued** treatment[1]

## INDICATION

VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

## IMPORTANT SAFETY INFORMATION

- Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent
- Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation
- Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA should generally not be used in patients with active intraocular inflammation
- Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema
- There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients

## IMPORTANT SAFETY INFORMATION (CONTINUED)

- Contact lenses should be removed prior to the administration of VYZULTA and may be reinserted 15 minutes after administration
- Most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%)

**For more information, please see Brief Summary of Prescribing Information on previous page.**

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**For more information about VYZULTA and how it works, visit VYZULTANOW.com**

IOP=intraocular pressure

BAUSCH + LOMB

VYZULTA®
(latanoprostene bunod ophthalmic solution), 0.024%

glaucoma needs some endpoint that acts as a proxy for reversing a given disease characteristic. As of now, that endpoint has not been identified.

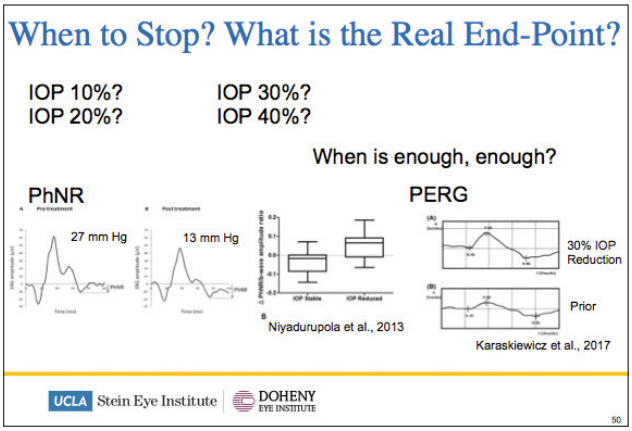


**FIGURE 4. THE ENDPOINT IN IOP**
The field of glaucoma heavily relies on IOP to manage patients, even with IOP's primary limitation—the lack of a standard target for lowering.

As an example, one potential biomarker is electrophysiology, which is a measurement of bioelectrical activity within the visual pathway and can reveal RGC function. Most commonly employed, pattern electroretinograms (PERGs) can specifically determine RGC function before and after IOP reduction in newly diagnosed, non-treated preperimetric glaucoma and early-stage POAG.[14] PERG data has pointed to the fact that significant IOP-lowering can improve RGC function as assessed by PERG amplitude in preperimetric and early-stage POAG patients.

An additional type of electrophysiological recording that specifically measures RGC function but that has received less attention has been has been photopic negative response (PhNR). Using electroretinogram PhNR, researchers have also revealed improvements in glaucomatous and ocular hypertensive eyes by observing significant increases in raw PhNR amplitudes and PhNR b-wave amplitude ratios post IOP-lowering therapy.[15]

Therefore, active research on electrophysiology in glaucoma is ongoing, as a result of significant debate regarding the measurement's utility for glaucoma diagnosis. Consensus might determine it to be an endpoint for assessing when IOP-lowering treatment has been sufficient. I have similar hopes for For OCTA. Investigators are trying to reveal how OCTA reveals glaucoma risk (similar to IOP) and how it might be able to guide IOP lowering (as with electrophysiology).

For example, Kim et al., obtained OCTA images in POAG eyes before and three months post-trabeculectomies to determine microvasculature shifts in the deep ONH and peripapillary tissues, and correlate the changes with those in the lamina cribrosa curvature.[16] They calculated VDs in various segmented layers—prelaminar tissue, lamina cribrosa, peripapillary retina and peripapillary choroid. Researchers performed SS-OCT volume scanning of the ONH on the same day as OCTA to examine alterations in the lamina cribrosa curvature. Multivariate analyses determined that post-trabeculectomy increases in lamina cribrosa VD, revealed by OCTA, were associated more with reductions in the lamina cribrosa curve than IOP.

In another review, authors wrote that OCTA could highlight restored vascularity post-IOP lowering with eyedrops.[17] The same authors, had earlier used OCTA to evaluate young, newly diagnosed OAG and ocular hypertensive individuals whose untreated, high IOP had dropped OCTA signal by at least 50%. After IOP-reducing therapy, their OCTA signals significantly improved in the eye.[18] Thus OCTA signal improvements due to treatment in early glaucoma could be an early measure of sufficient IOP-lowering to preserve visual fields. Other groups have used OCTA to reaffirm these findings.[19,20]

## Future of OCTA

OCTA is a new and powerful tool to assess blood flow in the presence of glaucomatous disease. However, I am waiting for more published research to establish how to utilize the data that I can acquire from the imaging modality and whether to perform OCTA on every patient. I'm optimistic that the results will bear out that OCTA is advantageous for clinical evaluation of glaucoma risk and guiding patient treatment.

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President's Lecture

# New Ideas for Primary Angle-Closure Glaucoma

*Robert M. Feldman, MD*

Primary angle-closure glaucoma (PACG) is a type of glaucoma that we hadn't talked much about in the United States until recently. However, statistics reveal that this form of disease is rapidly becoming more prevalent due to shifting demographics and an aging population. We know that the lens gets larger with age, decreasing space for the anterior segment.

In 2010, 15.7 million people worldwide reportedly were diagnosed with angle closure worldwide.[1] The number of global PACG cases was projected to increase 18% between 2012 and 2022, according to one study.[2] Growth of the Asian population—46% in the United States alone between 2000 and 2010—meant the Asian population was expected to represent 87% of ACG cases by 2020.[3,1] Factor in an exploding senior population—the U.S. 65-year-old-and older segment could almost double from 43.1 in 2012 to 83.7 million by 2050—and it's apparent the situation is quite serious.[4]

Consequently, our thinking about the angle has begun to change. Day et al. wrote in 2012 that PACG was more common than previously thought and that all primary glaucoma cases should be considered to be PACG unless the anterior chamber angle was shown to be open on gonioscopy. Clearly, the ACG landscape is shifting. Fortunately, the field has some new strategies to effectively treat and manage the angle-closure patient.

## PACG Characteristics

A primary angle closure (PAC) suspect generally presents with an anatomically occludable angle closure—of at least 180 degrees in the posterior trabecular meshwork [TM]—on gonioscopy in primary gaze. This is often with no identifiable anatomic or syndrome-related causes. Other features include superior peripheral anterior synechiae (PAS), intraocular pressure (IOP)>21 mmHg, pigment deposition on the TM surface, and evidence of a previous ACG event such as Glaukomflecken or sector iris atrophy.[5,6]

Diagnosis of PACG includes presentation of PAC plus evidence of glaucoma or existing damage in the optic nerve disc, retinal nerve fiber layer, or the visual fields. PAC and PACG are placed in two categories based on the degree of angle closure and extent of pupillary block: 1) acute, and 2) chronic (sub-acute and primary). Since management of acute ACG patients hasn't changed much, it is useful to focus on new ideas about managing the chronic patient.

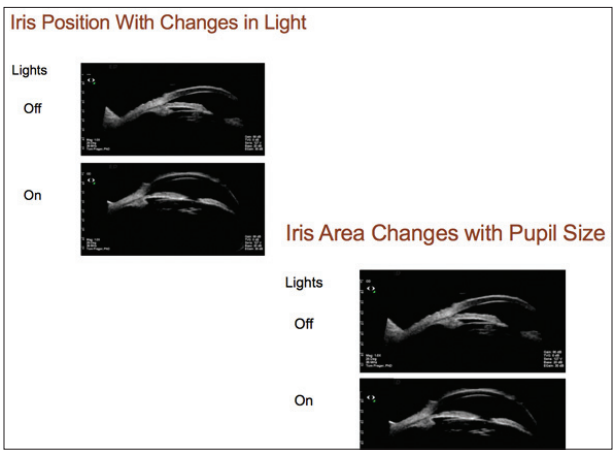
In sub-acute PAC, patients often complain of chronic migraines or ocular discomfort typically in the evenings, and intermittent rainbow haloes around lights. This type of angle closure is more common in plateau iris configuration, caused by a large or anteriorly positioned ciliary body that leads to mechanical TM obstruction. It is more common in younger patients and is not normally detected on slit lamp exam unless a gonio lens is employed. Management requires eliminating angle closure as in other forms of PAC.

Chronic PACG, the most common form of angle-closure disease, is usually an appositional angle closure with or without permanent PAS, resulting in periodic or sustained elevated IOP. TM damage can occur from proximity to, and increased contact with, the iris. The associated block of aqueous humor outflow and a more forward lens may increase pressure behind the iris such that the iris bows forward. Patients are usually asymptomatic, so diagnosis is based entirely on gonioscopy. PAS tends to occur superiorly, and compression gonioscopy can help distinguish between appositional and synechial closure.

Chronic PACG can develop in patients who previously had open angles, so it's key to continue doing gonioscopy as patients age. By the same token, not all narrow eyes go on to develop angle closure. Risk factors include a large lens, a more severe angle, and shifts in iris thickness and position, and choroidal thickness.

## Iris Position, Pupil Size & Choroidal Volume

In PAC suspects and PACG, dynamic changes have been shown to occur over time in iris volume, pupil size and accommodation, and choroidal volume. Iris volume and pupil differences can be seen with room lights on and off. In normal eyes, in a dark room, the iris and pupil are more dilated and pulled away from the crystalline lens; with the lights on, the iris flattens out (reducing pupillary block), and the pupil returns to its normal size.




**FIGURES 1 AND 2. IRIS POSITION WITH LIGHTS ON AND OFF**
In a normal iris, the position with the lights off is more dilated and pulled away from the zonules and lens. With the lights on, the iris flattens out, reducing pupillary block.
*Images: Robert M. Feldman, MD*

A retrospective study evaluating a Chinese population of PAC suspects, and PACG and normal eyes found significant differences in iris behavior in dark compared with light conditions.[7] Logistic regression analysis showed that lens vault (p=0.002) and iris area

loss per pupil density increase (p=0.017) were risk factors for an occludable angle.

A prospective study assessing PAC suspects found that larger iris volume, smaller anterior chamber volume and greater pupil diameter were associated with smaller angle width.[8] Using swept-source anterior-segment optical coherence tomography (AS-OCT) imaging, researchers reported that mean iris volume decreased after pupil dilation in open-angle and angle-closure eyes, with less reduction in eyes with smaller anterior chamber volume.

Turning to choroidal volume, researchers prospectively looked at 162 PAC spectrum eyes to determine if increased choroidal thickness was a risk factor for PAC. They used enhanced-depth imaging OCT to compare macular choroidal thickness in PACS, PAC, and PACG eyes, and 87 healthy controls.[9] Researchers found that PAC eyes had thicker choroids than control eyes at all macular locations (all p<0.05). Li, et al. reported similar changes.[10] The team determined that choroidal thickness was greater in PACG than healthy eyes, although it didn't differ between moderate and severe cases.

## Imaging the Angle

We have three primary imaging modalities to visualize the anterior segment: ultrasound biomicroscopy (UBM); Scheimpflug and dual-channel rotating Scheimpflug; and anterior segment (AS)-OCT.

UBM penetrates deeper into the eye for a view behind the iris, to assess, for example, the status of the ciliary body when diagnosing plateau configuration. Unfortunately, the imaging technique has relatively poor resolution. Scheimpflug, on the other hand, uses light scattering to image the anterior segment, with resolution down to a few microns axially. But problematically, the wavelength doesn't enable the viewer to see into the angle recess. So, it's less useful for glaucoma evaluation.

AS-OCT, however, offers a wavelength of light that improves illumination of the angle recess. Light penetrates further through tissues such as the sclera and limbus to increase visualization of the angle, cornea, iris, and lens. Useful AS-OCT measurements for the angle are: trabecular iris surface area (TISA); angle opening distance (AOD); angle recess area (ARA); and trabecular iris circumference volume (TICV). Importantly, TICV helps identify predictive parameters for development of angle closure. Though many individuals will never be diagnosed with PAC, we treat many suspects to save the vision of future patients.

To determine the effectiveness of AS-OCT images and information for the angle, my team compared interobserver, intervisit, and interinstrument agreement between gonioscopy and Fourier-domain AS-OCT in classifying open and narrow angle eyes.[11] The findings revealed that intervisit agreements were moderate to excellent between gonioscopy (0.53 to 0.86) and AS-OCT (0.57 and 0.85). However, when grading angles using the most posterior structures, AS-OCT was not as good, as it tended to show narrower angles than gonioscopy, possibly because it's done in a darker-light setting.

## Band of Extracanalicular Lamina: A New Marker

One area of imaging interest to glean important structural information about the angle has been the scleral spur, located between the ciliary muscle and the TM. However, identification of the scleral spur, especially in the eye's superior and inferior regions, has been challenging. This led my group to identify a new landmark on AS-OCT imaging adjacent to Schlemm's canal that we named the band of extracanalicular lamina (BELL). Previous studies in the literature reported BELL as the TM shadow located behind Schlemm's canal.

Surgically, when dissecting a deep scleral flap, BELL can be seen at a point at the limbus where scleral fibers change direction. In immunohistochemistry, the structural change is apparent on haemotoxylin and eosin (H&E) staining.

We also developed software to manually identify scleral spur on AS-OCT. Initially, our team located the landmark on 2D images, which have a higher resolution than 3D imaging, and then translated the desired site of interest onto 3D imaging using the software.

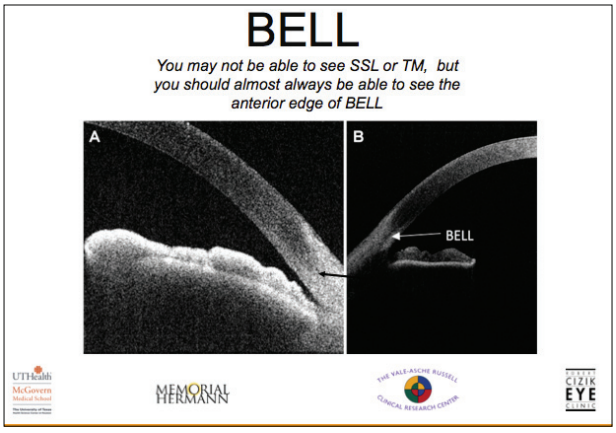


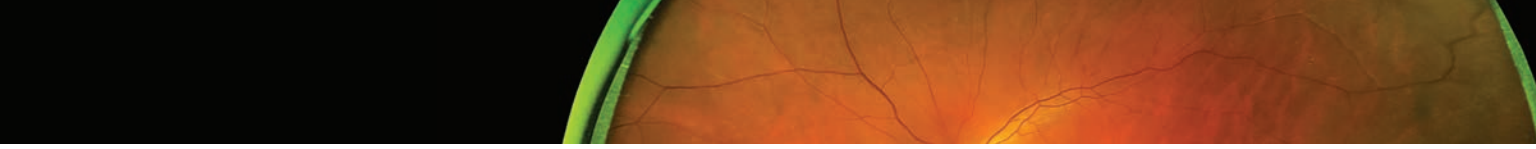

**FIGURE 3. BELL**
Historically, identification of scleral spur, especially in the eye's superior and inferior regions, has been challenging. This led my group to identify a new landmark in AS-OCT imaging adjacent to Schlemm's canal that we named the band of extracanalicular lamina (BELL).

We then deciphered how many slices would be necessary to manipulate the images to acquire TICV measurements. It turned out that we needed TISA data from 156 scans and eight angles to determine the iris volume. Once BELL and iris volume measurements were available, we created a normative database for several parameters using AS-OCT—factors that might be affected by angle closure. And we came up with threshold figures to demonstrate that treatment was effective.

Our study introduced TICV as a new AS-OCT measurement that determines the volume of the peripheral angle and establishes age-adjusted reference ranges in normal and open-angle eyes.[12] We calculated TISA and TICV at 500 and 750 µm, and performed analyses of covariance to examine the effect of age and its interaction with spherical equivalents. Our resulting paper reported on the 303 angles we evaluated.[12] The outer border of BELL was observed in 288 angles (95%), TM was found in 220 angles (73%), and SC was seen in 120 angles (40%). Overall, TICV showed an age-related angle-volume reduction (p=0.035) associated with disease. In addition, greater angle volume was associated with greater myopia for all age groups, except those older than 65 years, probably because many of those individuals had already had their lenses out.

## LPI & Current Therapy

Laser peripheral iridotomy (LPI), a procedure in which a laser is



used to create an opening in the peripheral iris, is often employed as a treatment for occludable narrow angles. Though we could send many patients early for LPIs and not bother obtaining TICV measurements or monitoring them, the reality is LPI is not a totally benign procedure. Some of my most miserable patients complain post-LPI of a line of light across their vision. One of my patients wound up having a trabeculectomy the night after I performed an LPI because I had unintentionally released pigment during the procedure.

Factors that decrease the threshold for LPI are elevated pressure, evidence of PAS or closure, or someone who works away from home for months at a time. In addition, LPI is not effective in the setting of plateau iris without sulcus or pupillary block, though a rare type of plateau iris exhibiting a degree of pupillary block might help some patients.

Studies show LPI is relatively successful for angles in the mid-term, though long-term benefits have not been borne out. My team evaluated post-LPI subjects for initial treatment of PAC, CPAC, and CPACG.[13] About two-thirds of individuals had at least 10 degrees of opening, which is fairly good, and all suspects without evidence of angle closure also opened with LPI. However, we found that most people who underwent LPI required future interventions for IOP lowering or improved visual acuity.

A retrospective study evaluated the long-term outcome of subjects treated with LPI who had iridotrabecular trabecular apposition or PAS, and fellow eyes with narrow angles, as well as IOP <22 mmHg at diagnosis.[14] Mean follow-up was 8.5±5.53 years. Though no apposition or PAS was observed in 84% of eyes post-LPI, at 10 years, 38.7% had increased IOP, and 17.3% required medication. Younger patients and those with no apposition or PAS after LPI had a better prognosis ($p<0.01$).

So ACG patients can buy several years of relief with LPI. However, the vast majority are going to need further treatment, whether that's medications, a trabeculectomy, or lens extraction.

Looking at ways to assess patients post-LPI status, my team evaluated changes in patients' TICV values using AS-OCT before and after LPI.[15] We found a modest, though significant, increase in average angle parameters. So, TICV was successful in quantitatively measuring the effectiveness of LPI in the treatment of PAC spectrum disease. We looked back at these findings in a retrospective study with a mean follow-up of 57 months.[16] Seventy-two percent of PACS eyes required medications by last follow-up; however, only two suspects converted to glaucoma. So, it's important to keep a close eye on patients and treat when necessary.

Another procedure, iridoplasty also known as gonioplasty, uses low-energy laser burns to the peripheral iris to widen the anterior chamber angle or break PAS. One retrospective chart review showed that about 70% of procedures didn't work at five years.[17] The study was performed on all patients with plateau iris syndrome treated with argon laser peripheral iridoplasty (ALPI). The primary outcome was incidence of needing IOP-lowering medications or surgery (filtering or phacoemulsification). The majority of individuals (77%) required additional surgery, so as a result, we have abandoned iridoplasty.

My team evaluated whether cataract extraction (CE) was more effective than LPI for addressing the angle and found on AS-OCT considerably more angle opening from CE than LPI.[18] In 28 PAC spectrum eyes, TISA and TICV measurements spiked once the lens was out. In particular, TICV750 increased by 174% after CE and by 102% after LPI ($p<0.001$).

Another team analyzed primary lens extraction vs. LPI in Japanese patients with CACG and PAC, who were followed for six months.[19] The mean postoperative IOP went down and number of medications dropped with lens extraction; yet, in LPI, mean postoperative IOP and number of medications stayed the same. That being said, six months is a relatively short time to get a real answer.

In addition, the landmark EAGLE study compared the effectiveness of clear lens extraction, with LPI and medications in subjects with PAC and PACG, who had pressures over 30mmHg.[20] Researchers found that taking out the lens was more effective and cost-effective long-term than LPI and medications; vision, visual acuity, pressure and the angle all improved with clear lens extraction, and individuals who had their lenses out had less need for additional glaucoma surgery than LPI (one vs. 24). As such, clear lens extraction might be a viable option for PAC and PACG patients.

An important consideration is that some candidates might be pre- or early presbyopes, and a 40-something-year-old probably will not like having their lens removed, despite the option of multifocal lenses. However, sometimes, this route is necessary. Additional factors to assess are refractive error, availability of further treatment, and the amount of PAS. A person with 270 degrees of PAS will not benefit from cataract surgery.

## Predicting the Angle Closure Patient

Our goal is to predict PAC suspects who will progress to full disease. We did a retrospective review to determine and validate thresholds of anterior chamber angle parameters in open vs. narrow-angle eyes using AS-OCT images.[21] The best predictors of disease were TICV and AOD. A less complex criterion, AOD can be obtained using a single measurement, while TICV's 360-degree calculations offer greater precision in sensitivity and specificity. We also know that 3D measurements, especially using TICV, have the best discriminative ability for detecting narrow angles. So, those would be the AS-OCT data to focus on to predict progression.

Moreover, the Kansara, et al. study looking at effects of LPI vs. CE told us that the angle, even with plateau iris configuration, will open more with lens extraction.[14]

We can help prevent angle closure purely by detection and determining who we need to treat and when. The medical imperative is to use all of our existing and new tools to differentiate individuals who need treatment early from those who don't.

*Dr. Feldman is chair of the Department of Ophthalmology and holds the Richard S. Ruiz Distinguished University Chair at the McGovern Medical School of the University of Texas Health Science Center in Houston.*

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Intraocular Pressure

# IOP Variability: Causes & Clinical Significance

*Arthur J. Sit, MD*

A wealth of studies reveals that lowering intraocular pressure (IOP) is currently the only effective treatment for glaucoma. We know that IOP is an important biomarker for monitoring therapy effectiveness and progression in glaucoma. But, in order to optimally affect IOP management and patient outcomes, we have to fundamentally understand eye pressure's unique characteristics and tendencies.

First and foremost, IOP is dynamic. Research has taught us that pressure varies rapidly, constantly and by large magnitudes; that it tends to be higher during dark than light circadian phases; and that it can fluctuate as much as 10 mmHg or more over 24 hours—even from one hour to the next.[1,2]

Though many factors affect IOP, this discussion will focus on on how changes in circadian rhythms, and body and head position influence patient pressures. Once we grasp the scope of IOP fluctuation and its implications, we can better recognize how these shifts can impact glaucoma development, progression, and prognosis, and understand what strategies and technology might potentially help minimize IOP fluctuation.

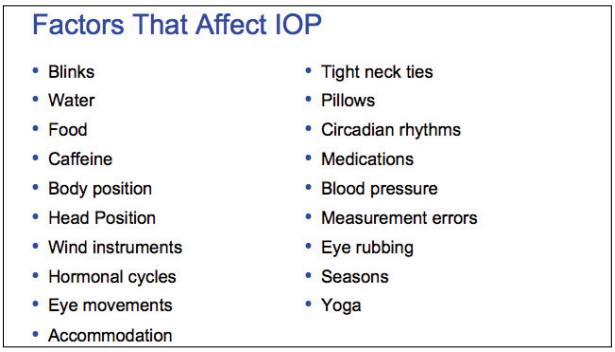



**FIGURE 1. FACTORS THAT AFFECT IOP**
Many factors affect IOP, including circadian rhythms, and body and head position.
*Images: Arthur J. Sit, MD*

## How Circadian Rhythm & Body Position Changes Alter IOP

To see how circadian rhythms and body position influence IOP, it's helpful to look at seminal experiments performed by Liu, et al.[3] The researchers, as part of a sleep study, measured IOP every two hours for 24 hours using a pneumotonometer in untreated glaucoma patients with newly diagnosed abnormal optic discs or visual fields (VFs). Their findings revealed that nocturnal supine IOP was higher than diurnal upright IOP in both glaucoma patients and normal subjects.

Research is increasingly showing us that IOP, when measured in the same body position, is often relatively stable. But, turn the body upside down, and pressure goes up dramatically. One team studied individuals performing the yoga headstand pose Sirsasana and correlated ocular biometric parameters with IOP changes.[4] The increases in IOP during the posture were twice the baseline readings, with two-fold increases across all age groups, irrespective of ocular biometry and ultrasound pachymetry.

A few years ago, my team systematically evaluated IOP changes with head and body position alterations in young, healthy individuals using pneumotonometry measurements.[5] In the sitting position, we randomized subjects to neck in neutral, flexion, and extension; in the recumbent position, we randomized them to supine, and right and left lateral decubitus. The results: Neck extension and flexion resulted in elevated IOPs, with neck flexion yielding higher pressures than extension. All recumbent positions had higher pressures than upright ones with the neck in neutral. And, in lateral decubitus positions, the dependent (lower) eyes tended to have higher pressures than non-dependent eyes.

## Aqueous Humor Dynamics & IOP Fluctuations

To understand the mechanisms of IOP variability, it's necessary to evaluate aqueous humor dynamics. Researchers have learned that aqueous humor exits the eye through two pathways, trabecular and uveoscleral. IOP is affected by the aqueous humor production rate, uveoscleral outflow rate, aqueous humor outflow facility, and episcleral venous pressure. A modified Goldmann equation can model steady-state IOP as a function of these parameters, and measurement

of these parameters is key to understanding aqueous humor dynamics.

In the 1960s, Jones and Maurice developed a new method to measure the rate of aqueous humor flow rate using fluorescein.[6] They added fluorescein to the cornea to form a depot such that aqueous humor production would wash away the fluorescein over time. Brubaker and colleagues subsequently developed a fluorophotometer to make measurements of fluorescein concentration practical in human eyes and enable aqueous humor flow rate measurements.[7]

Researchers have used tonography—a dynamic test of the eye's ability to recover from acute IOP elevation—to measure aqueous humor outflow facility. Grant developed a method where a weighted tonometer was placed on the eye of a supine patient to artificially raise IOP and observe subsequent IOP decay curve to estimate outflow facility.[8] Scientists initially had used the electronic Schiotz tonometer for measurements, although the technology has evolved over time. A few years ago, my team introduced a digital version of the Schiotz tonometer and recorded data from a computerized tonography system to determine outflow facility.[9]

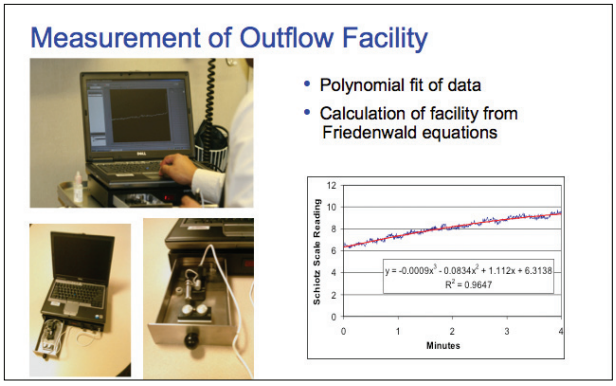



**FIGURE 2. MEASUREMENT OF OUTFLOW FACILITY**
A few years ago, my team introduced a digital version of the Schiotz tonometer to record data from a computerized tonography system that performed curve fitting and determined outflow facility with the aid of Friedenwald equations.

Measuring episcleral venous pressure (EVP) historically involved the Ziemer venomanometer.[10] The device's "balloon" was placed against the eye, and the user would turn up the pressure with a dial until the episcleral vein collapsed. At a time point when the vein was said to be "half-blanched," the user would read the pressure. The problem was that the "half-blanched" endpoint was vague, and therefore, measurements were highly variable.[11]

In an effort to improve the device, my team added a motor drive, pressure transducer and high-definition video camera, and created software to assist with automatic measurement of the amount of vein collapse.[12] This enabled us to visualize the veins, as we ramped up the pressure and automatically collapsed episcleral veins. We measured the pressure from the transducer and combined it with the vein measurements from the video. We determined that pressure in the veins was equivalent to pressure when the veins just started to collapse.

Uveoscleral flow has been the most difficult parameter to quantify using aqueous humor dynamics due to its poorly defined nature, the lack of a noninvasive technique to measure it, and the resulting need to calculate it from other data. The only direct measurements of uveoscleral flow in human eyes were obtained by Bill and Phillips in patients with presumed uveal melanomas, scheduled for enucleation.[13] The duo perfused radioactive iodine, enucleated the eyes, and assessed where iodine collected. Based on the volume of iodine in the uveoscleral system, they found that 4% to 10% of total flow went through the uveoscleral tract. (However, most indirect measurements find that uveoscleral flow accounts for 30% to 50% of total flow.)

## Understanding IOP Fluctuations During Body Position & Circadian Changes

Researchers have used aqueous humor dynamics to understand the causes of IOP changes with different body positions and circadian rhythms.

Brubaker and his team used a tilt table to calculate aqueous humor production rates in altered body positions. In one experiment, they put subjects into various degrees of tilt and measured their IOPs.[14] Minor tilt, ±15 degrees, yielded subtle pressure changes and no alterations in aqueous humor flow rates. Greater tilt, ±50 degrees, led to more significant IOP changes. When subjects were head down, pressure shot up, but surprisingly, aqueous humor production rates decreased. As a result, the team concluded that changes in aqueous formation were relatively pressure-insensitive and did not account for the IOP changes with body position.

Our team studied aqueous humor outflow facility using tonography in upright and supine positions, and found outflow facility did not change between the positions, although IOP increased when supine.[15] So, IOP elevations weren't due to changes in outflow facility either.

To evaluate EVP fluctuations with various body position changes, we used our automated episcleral venomanometer to measure the changes in young, healthy individuals between supine and semi-prone positions.[16] IOP elevations in the semi-prone position were similar to those in EVP (p=0.18), suggesting that IOP changes with body position could be explained by EVP.

Turning to circadian changes, Brubaker and his team, over several decades, measured aqueous humor production during the day and night in healthy individuals, and in glaucoma patients. They consistently found that aqueous humor production dropped by about 50% at night.[17-19] As a result, one might expect that IOP would also decrease significantly at night. But, sleep studies by Liu, et al.[3] showed that IOP stayed relatively stable between day and night unless body position changes were introduced.

In an effort to understand this phenomenon, we used our sleep laboratory to analyze healthy individuals with regular sleep patterns.[20] We measured aqueous humor flow rates, IOP, outflow facility, and EVP during the mid-diurnal period (2pm to 4pm). Then we calculated uveoscleral flow from other variables via the modified Goldmann equation. We re-measured the variables during the mid-nocturnal period (2am to 4am) and compared them with ones measured during the diurnal period.

Similar to Brubaker, my team found that aqueous humor production dropped by about 50% at night. IOP didn't change substantially from day to night in seated or supine positions, although outflow facility fell by about 15% from day to night. EVP tended to be a noisy measurement, but it didn't have any significant changes from day to night. Plugging this data into the modified Goldmann equation, my team determined that about 38% of total flow went through the uveoscleral

system. At night, it fell by about 95%, so only about 5.6% of total flow went through the uveoscleral system. Therefore, the decrease in aqueous humor production at night was compensated by the reduction in aqueous outflow facility and uveoscleral flow. The eye wanted to keep pressure constant and that's how it accomplished it at night.

### Looking to Clinical Trials for IOP Variation Significance

Although these findings are interesting scientifically, clinicians want to see evidence that IOP variations matter for patient management. Most of our information comes from retrospective analyses of large clinical trials. The results can sometimes be contradictory, but they do indicate a link between IOP fluctuation and progression in specific populations.

Starting with the Advanced Glaucoma Intervention Study, investigators reported that subjects with low mean IOPs experiencing high variability between evaluations were more likely to have VF progression. In contrast, the rate of VF progression in individuals with high mean IOPs was not affected by the degree of IOP variability between visits.[21] However, not all studies have revealed similar findings.

The Early Manifest Glaucoma Trial uncovered that mean IOP was an important risk factor for IOP progression, but IOP fluctuation did not place subjects at greater risk for disease advancement.[22] Somewhat similarly, the Collaborative Initial Glaucoma Treatment Study, which randomized individuals to medical or surgical therapies to evaluate the impact of IOP control on progression during open-angle glaucoma (OAG) treatments, found that measures of IOP variability, including maximum range and standard deviation, were not predictive of glaucoma progression in surgical subjects.[23] However, in medically treated subjects, the measures of IOP variability were independent risk factors for glaucoma progression.

Recently, the cross-sectional Los Angeles Latino Eye Study assessed IOP variation on glaucoma progression in subjects three times at initial visits and three times at four-year follow-up evaluations.[24] From those six measurements and a large enough sample size, investigators deduced that IOP variation (i.e., maximum standard deviation and range) was only associated with progression if subjects started with low IOPs, although it was not associated with disease advancement in individuals with high IOPs.

Further data for the importance of IOP fluctuations in glaucoma comes from use of the Triggerfish (Sensimed)—a sensor made of a silicone contact lens containing an embedded strain gauge that can quantify changes in cornea curvature with IOP fluctuations, providing a 24-hour IOP pattern.[25] In a multicenter, retrospective study, De Moraes used data from 445 eyes in the Triggerfish consortium, and stratified it into VF fast progressors (more than one decibel per year) and slow progressors (less than one decibel per year) based on mean deviation.[26] Then he looked at 55 variables and cofactors, most related to variability, and determined that 24-hour parameters from the Triggerfish were better at predicting VF progression than Goldmann pressures taken during the day, due to large intra-visit variations.

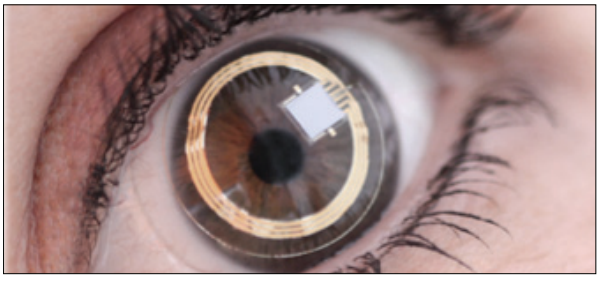


**FIGURE 3. TRIGGERFISH CONTACT LENS SENSOR**
The Triggerfish (Sensimed) is a contact lens sensor made of a silicone contact lens that contains an embedded strain recording gauge to quantify changes in cornea curvature with IOP fluctuations.

### Glaucoma Therapy for 24-Hour IOP Control

Given the evidence that IOP fluctuation is a risk factor for glaucoma progression, at least for some populations, effective monitoring and management of IOP changes around the clock is a high priority. Researchers have tried to evaluate glaucoma therapies for effectiveness of IOP control throughout the 24-hour day. Much of this work has been performed at the UCSD sleep laboratory. In one study, researchers compared the prostaglandin analog latanoprost with the beta-blocker timolol (an aqueous suppressant) in controlling IOP during the day and night.[27] Both drugs had good efficacy throughout the day, but timolol showed no improvements at night, while latanoprost continued to have a modest effect. Considering that aqueous humor production is already at a basal level during sleep, it's not surprising that further suppression by timolol would be challenging.

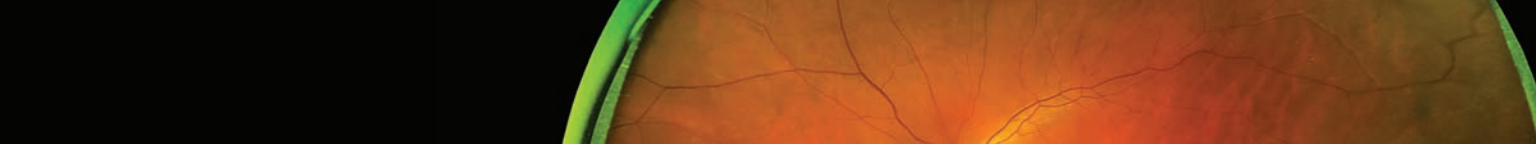
In another study from UCSD, researchers administered the alpha-agonist brimonidine (another aqueous suppressant) in ocular hypertension or newly diagnosed OAG patients three times a day—in the morning, afternoon, and before bedtime.[28] The drug had good efficacy throughout the day but produced no effect at night. The team also compared the diurnal and nocturnal effects of aqueous suppressants brinzolamide and timolol on IOP in subjects receiving latanoprost monotherapy. Both therapies had good diurnal additive effects, but timolol had no additional nocturnal benefit, while brinzolamide exhibited a small effect.

Recently, at the University of Colorado, pilocarpine was evaluated as an adjunct to prostaglandin and determined to have a statistically significant additive effect during the day and night.[29] Pilocarpine increases outflow facility by contracting the ciliary muscle, pulling on the scleral spur and stretching the trabecular meshwork, so it makes sense that this strategy would have some nighttime effect. Another study out of Greece demonstrated the value of improving outflow facility by comparing IOP control over a 24-hour period in patients treated with trabeculectomy with mitomycin C vs. maximum tolerated medical therapy.[30] Researchers determined that surgery patients had lower pressures at night than during the day, in contrast with medically treated patients, who continued to experience nocturnal elevations.

So, the bad news is that most medications are less effective at night, due to the ineffectiveness of aqueous humor suppression during sleep. On a positive note, treatments that target outflow facility or uveoscleral flow have shown a nocturnal effect and given us some effective treatment options.

### Continuous IOP Monitoring

In order for clinicians to optimize disease management, continuous IOP monitoring of patients has emerged as an essential unmet need.[31] Two paradigms are emerging—temporary and permanent. Temporary monitoring is a less invasive, contact lens-based approach to measure pressure over 24 to 48 hours. Permanent monitoring



involves surgically implanting devices.

Temporary continuous IOP monitoring is not a revolutionary concept. In 1958, David Maurice developed a device to take ambulatory IOP measurements that was essentially a wearable Schiotz tonometer.[32] And in the 1970s, Greene and Gilman molded silicone contact lenses with embedded strain gauges to the eyes of rabbits to measure IOP swings.[33] However, the lenses were not suitable for clinical use because they had to be molded to individual eyes and had wires protruding from the side.

The Triggerfish has advanced efforts to improve temporary continuous monitoring with wireless technology to enable true ambulatory measurements of IOP patterns; however, the strain gauge obtains measurements in millivolts rather than millimeters of mercury. In fact, the Triggerfish was not FDA approved for IOP measurement, but to detect peak patterns of IOP variation over a maximum of 24 hours. Given the device's lack of true IOP measurement, investigators have aimed to determine its agreement with existing methods and its clinical utility.

The team at UCSD, led by Dr. Weinreb, compared Triggerfish contact lens sensor (CLS) patterns in one eye and pneumotonometry IOP patterns in the contralateral eye, and found the two patterns were almost identical.[34] Their team also looked at the timing of patterns and acrophases, i.e., peaks, and determined that CLS peaks occurred in the same pattern as those in the contralateral eyes using IOP. However, amplitudes from the CLS vs. those from pneumotonometry showed no correlation, indicating that CLS measurements were not equivalent to IOP measurements.

To gauge the reproducibility of CLS patterns, Mansouri, et al., repeated measurements in two sessions over 24 hours, and revealed a moderate, but highly individual, association.[35] In one example, a 53-year-old male with glaucoma using a PGA in a fixed combination, measurements indicated good correlation. However, in another example, a 20-year-old glaucoma suspect, possibly a student with irregular sleep patterns, yielded a poor relationship between patterns.

Several groups of investigators have tried to determine the clinical value of CLS data. A Hong Kong team looked at primary angle-closure glaucoma patients and found statistically significant differences in circadian IOP fluctuations between progressive and stable PACG eyes, using CLS.[36] They suggested that large IOP fluctuations might be associated with disease progression in PACG eyes. A study from Japan looking at healthy vs. normal-tension glaucoma eyes found the range of IOP pattern fluctuations to be greater in NTG than non-glaucomatous eyes, but no difference in IOP itself.[37] They suggested that 24-hour continuous IOP readings might be useful to distinguish NTG from non-glaucomatous eyes.

The Triggerfish CLS has been shown to to aid in assessing 24-hour patterns and those associated with glaucoma progression, representing a significant step forward in continuous IOP monitoring. But questions remain about how frequently to perform the measurements, how to address signal noise issues and how to calibrate the devices to mmHg.

## Surgically Implanted IOP Monitoring Devices

Permanent IOP monitoring might offer some advantages over temporary strategies. Since the devices are implanted in the eye and controlled remotely using wireless power, they tend to have less signal noise issues within the eye. But the technology may be limited to certain patients such as those with advanced glaucoma, or those having surgery for glaucoma or cataracts.

The idea of telemetric IOP monitoring also is not a new one. In 1967, Carter Collins placed into rabbit eyes a pressure sensor he called a bubble tonometer, in which two coils changed distance and capacitance with compression which could be measured externally and correlated with IOP.[38] In the early 1990s, Svedbergh introduced a concept for a pressure sensor on an intraocular lens that was remotely detected by a spectacle-mounted device, but there is no record of it being successfully implanted into living eyes.[39]

Schnakenberg and colleagues furthered this idea with better wireless technology, and integration of an encapsulated IOP sensor equipped with telemetric signals.[40-42] After implantation in enucleated pig and rabbit eyes in vivo, the researchers compared sensor measurements with pneumotonometry, and determined that the implanted system worked with similar precision as traditional tonometry. However, the device was never commercialized.

Implandata is the first company to develop a pressure sensor approved for use in human eyes (it holds the CE Mark in Europe). Their device includes a silicone rubber encapsulation ring with an antenna and chip housing eight capacitive pressure sensors that could be inserted into the sulcus. A reader above the eye powers the chip that determines the pressure by averaging the value from the sensors. Todani, et al., implanted the wireless IOP transducer (WIT) into the eyes of six rabbits after extracapsular lens extraction, and measured IOP at intervals by pneumotonometry, the WIT and manometry.[43] The WIT appeared to be well-tolerated in rabbit eyes and demonstrated high concordance with direct manometry measurements.

In the first human implant with a WIT, the device went through a large incision, 5mm, at the time of cataract surgery.[44] The WIT was well-tolerated, yielding no overt signs of toxicity or other adverse events. However, the incision was much larger than what is normally used for modern cataract surgery, and the device was much thicker than devices (e.g., intraocular lenses) normally placed in the sulcus during surgery.

In a subsequent study evaluating one-year WIT results in a series of patients, some individuals experienced pupil and iris transillumination defects, mild to moderate pupillary distortion, and pigment dispersion after surgery.[45] Most required iridotomies to prevent angle closure. Also concerning was the pressure data originating from the chip sensors, which showed drift and sudden unexpected changes vs. Goldmann applanation tonometry, making it difficult to interpret the WIT data. Nevertheless, it represents an important step forward in the development of continuous IOP monitoring.

We're making tremendous progress in continuous IOP monitoring as the first devices enter the market, but obstacles persist. For one thing, we need to determine the optimal location to place sensors in the eye. Some sensors have been implanted in the sulcus, but there may be other or better locations. Long-term safety and stability, and signal drift also have been issues that need to be addressed.

## Looking Ahead

Since IOP variation has been shown to be a risk factor for glaucoma pathogenesis and progression in susceptible populations, and IOP fluctuations are constant, this area of research is very active. We are optimistic about new 24-hour monitoring devices and therapies that

might provide better IOP control throughout the circadian cycle. It's clear that we can't rely on traditional IOP measurements taken during the day at periodic office visits to reveal the true picture of glaucoma.

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**ABOUT THE OPTOMETRIC GLAUCOMA SOCIETY**

The Optometric Glaucoma Society's (OGS) mission is to promote excellence in the care of glaucoma patients through professional education and scientific investigation. For more information: www.optometricglaucomasociety.org

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

**This Brief Summary does not include all the information needed to use VYZULTA safely and effectively. See full Prescribing Information for VYZULTA.**

# VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024%, for topical ophthalmic use.

**Initial U.S. Approval: 2017**

## 1 INDICATIONS AND USAGE

VYZULTA™ (latanoprostene bunod ophthalmic solution) 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

## 4 CONTRAINDICATIONS

None

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Pigmentation

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% may cause changes to pigmented tissues. The most frequently reported changes with prostaglandin analogs have been increased pigmentation of the iris and periorbital tissue (eyelid).

Pigmentation is expected to increase as long as latanoprostene bunod ophthalmic solution is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes are likely to be reversible in most patients. Patients who receive prostaglandin analogs, including VYZULTA, should be informed of the possibility of increased pigmentation, including permanent changes. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17) in full Prescribing Information]*.

### 5.2 Eyelash Changes

VYZULTA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and the number of lashes or hairs. Eyelash changes are usually reversible upon discontinuation of treatment.

### 5.3 Intraocular Inflammation

VYZULTA should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation as it may exacerbate this condition.

### 5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. VYZULTA should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

### 5.5 Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

### 5.6 Use with Contact Lens

Contact lenses should be removed prior to the administration of VYZULTA because this product contains benzalkonium chloride. Lenses may be reinserted 15 minutes after administration.

## 6 ADVERSE REACTIONS

The following adverse reactions are described in the Warnings and Precautions section: pigmentation (5.1), eyelash changes (5.2), intraocular inflammation (5.3), macular edema (5.4), bacterial keratitis (5.5), use with contact lens (5.6).

### 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 the clinical trials of another drug and may not reflect the rates observed in practice.

VYZULTA was evaluated in 811 patients in 2 controlled clinical trials of up to 12 months duration. The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

Latanoprostene bunod has caused miscarriages, abortion, and fetal harm in rabbits. Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (IV) to pregnant rabbits at exposures ≥ 0.28 times the clinical dose. Doses ≥ 20 µg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat when administered IV at 150 mcg/kg/day (87 times the clinical dose) *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

*Animal Data*

Embryofetal studies were conducted in pregnant rabbits administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 19, to target the period of organogenesis. The doses administered ranged from 0.24 to 80 mcg/kg/day. Abortion occurred at doses ≥ 0.24 mcg/kg/day latanoprostene bunod (0.28 times the clinical dose, on a body surface area basis, assuming 100% absorption). Embryofetal lethality (resorption) was increased in latanoprostene bunod treatment groups, as evidenced by increases in early resorptions at doses ≥ 0.24 mcg/kg/day and late resorptions at doses ≥ 6 mcg/kg/day (approximately 7 times the clinical dose). No fetuses survived in any rabbit pregnancy at doses of 20 mcg/kg/day (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0.24 mcg/kg/day (0.28 times the clinical dose). Malformations included anomalies of sternum, coarctation of the aorta with pulmonary trunk dilation, retroesophageal subclavian artery with absent brachiocephalic artery, domed head, forepaw hyperextension and hindlimb malrotation, abdominal distention/edema, and missing/fused caudal vertebrae.

An embryofetal study was conducted in pregnant rats administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 17, to target the period of organogenesis. The doses administered ranged from 150 to 1500 mcg/kg/day. Maternal toxicity was produced at 1500 mcg/kg/day (870 times the clinical dose, on a body surface area basis, assuming 100% absorption), as evidenced by reduced maternal weight gain. Embryofetal lethality (resorption and fetal death) and structural anomalies were produced at doses ≥ 300 mcg/kg/day (174 times the clinical dose). Malformations included anomalies of the sternum, domed head, forepaw hyperextension and hindlimb malrotation, vertebral anomalies and delayed ossification of distal limb bones. A no observed adverse effect level (NOAEL) was established at 150 mcg/kg/day (87 times the clinical dose) in this study.

### 8.2 Lactation

Risk Summary

There are no data on the presence of VYZULTA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for VYZULTA, and any potential adverse effects on the breastfed infant from VYZULTA.

### 8.4 Pediatric Use

Use in pediatric patients aged 16 years and younger is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

### 8.5 Geriatric Use

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

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Latanoprostene bunod was not mutagenic in bacteria and did not induce micronuclei formation in the *in vivo* rat bone marrow micronucleus assay. Chromosomal aberrations were observed *in vitro* with human lymphocytes in the absence of metabolic activation.

Latanoprostene bunod has not been tested for carcinogenic activity in long-term animal studies. Latanoprost acid is a main metabolite of latanoprostene bunod. Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime rodent bioassays, was not carcinogenic.

Fertility studies have not been conducted with latanoprostene bunod. The potential to impact fertility can be partially characterized by exposure to latanoprost acid, a common metabolite of both latanoprostene bunod and latanoprost. Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

### 13.2 Animal Toxicology and/or Pharmacology

A 9-month toxicology study administered topical ocular doses of latanoprostene bunod to one eye of cynomolgus monkeys: control (vehicle only), one drop of 0.024% bid, one drop of 0.04% bid and two drops of 0.04% per dose, bid. The systemic exposures are equivalent to 4.2-fold, 7.9-fold, and 13.5-fold the clinical dose, respectively, on a body surface area basis (assuming 100% absorption). Microscopic evaluation of the lungs after 9 months observed pleural/subpleural chronic fibrosis/inflammation in the 0.04% dose male groups, with increasing incidence and severity compared to controls. Lung toxicity was not observed at the 0.024% dose.

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# Only VYZULTA Expands the Trabecular Meshwork with the Power of Nitric Oxide[1-5]

Visit **VYZULTANOW.COM** to learn more.


## DUAL ACTION:

› VYZULTA increases aqueous humor outflow by targeting the **uveoscleral pathway** with latanoprost acid and the **trabecular meshwork** with nitric oxide[1,6]

## PROVEN EFFICACY:

› VYZULTA decreased mean IOP up to **9.1 mmHg** from baseline in clinical trials of up to 12 months[6]

## DEMONSTRATED SAFETY:

› **6%** of patients in pivotal trials reported **hyperemia**[6]

› **6 out of 811** patients on VYZULTA in pivotal trials **discontinued** treatment[1]

## INDICATION

VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

## IMPORTANT SAFETY INFORMATION

- Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent
- Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation
- Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA should generally not be used in patients with active intraocular inflammation
- Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema
- There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients

## IMPORTANT SAFETY INFORMATION (CONTINUED)

- Contact lenses should be removed prior to the administration of VYZULTA and may be reinserted 15 minutes after administration
- Most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%)

**For more information, please see Brief Summary of Prescribing Information on previous page.**

**References:**

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**For more information about VYZULTA and how it works, visit VYZULTANOW.com**

IOP=intraocular pressure

BAUSCH + LOMB

VYZULTA®
(latanoprostene bunod ophthalmic solution), 0.024%