NOVEMBER 2016 # 03

# the Ophthalmologist



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BromSite™
(bromfenac ophthalmic solution) 0.075%
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### Indications and Usage

BromSite™ (bromfenac ophthalmic solution) 0.075% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

### Important Safety Information

- **Slow or Delayed Healing:** All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite (bromfenac ophthalmic solution) 0.075%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- **Potential for Cross-Sensitivity:** There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.
- **Increased Bleeding Time of Ocular Tissue:** With some NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

  It is recommended that BromSite be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
- Use of topical NSAIDs may result in keratitis. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.
- BromSite should not be administered while wearing contact lenses. The preservative in BromSite, benzalkonium chloride, may be absorbed by soft contact lenses.
- The most commonly reported adverse reactions in 1% to 8% of patients were anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain, and ocular hypertension.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

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

NSAID=nonsteroidal anti-inflammatory drug.

**References: 1.** BromSite [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2016. **2.** Hosseini K, Hutcheson J, Bowman L. Aqueous humor concentration of bromfenac 0.09% (Bromday™) compared with bromfenac in DuraSite® 0.075% (BromSite™) in cataract patients undergoing phacoemulsification after 3 days dosing. Poster presented at: ARVO Annual Meeting; May 5-9, 2013; Seattle, Washington. **3.** Bowman LM, Si E, Pang J, et al. Development of a topical polymeric mucoadhesive ocular delivery system for azithromycin. *J Ocul Pharmacol Ther.* 2009;25(2):133-139. **4.** ClinicalTrials.gov. Aqueous humor concentration of InSite Vision (ISV) 303 (bromfenac in DuraSite) to Bromday once daily (QD) prior to cataract surgery. https://clinicaltrials.gov/ct2/show/results/NCT01387464?sect=X70156&term=insite+vision&rank=1. Accessed July 18, 2016. **5.** Si EC, Bowman LM, Hosseini K. Pharmacokinetic comparisons of bromfenac in DuraSite and Xibrom. *J Ocul Pharmacol Ther.* 2011;27(1):61-66.


SUN-OPH-BRO-014 09/2016

SUN OPHTHALMICS

# BromSite™ (bromfenac ophthalmic solution) 0.075% Brief Summary

## INDICATIONS AND USAGE
BromSite™ (bromfenac ophthalmic solution) 0.075% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

## DOSAGE AND ADMINISTRATION
### Recommended Dosing
One drop of BromSite should be applied to the affected eye twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days postsurgery.

### Use with Other Topical Ophthalmic Medications
BromSite should be administered at least 5 minutes after instillation of other topical medications.

### Dosage Forms and Strengths
Topical ophthalmic solution: bromfenac 0.075%.

## CONTRAINDICATIONS
None

## WARNINGS AND PRECAUTIONS
### Slow or Delayed Healing
All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite (bromfenac ophthalmic solution) 0.075%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

### Potential for Cross-Sensitivity
There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

### Increased Bleeding Time of Ocular Tissue
With some NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that BromSite be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

### Keratitis and Corneal Reactions
Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

### Contact Lens Wear
BromSite should not be administered while wearing contact lenses. The preservative in BromSite, benzalkonium chloride, may be absorbed by soft contact lenses.

## ADVERSE REACTIONS
### Clinical Trial 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 clinical practice.

The most commonly reported adverse reactions in 1–8% of patients were: anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain and ocular hypertension.

## USE IN SPECIFIC POPULATIONS
### Pregnancy
Risk Summary
There are no adequate and well-controlled studies in pregnant women to inform any drug associated risks. Treatment of pregnant rats and rabbits with oral bromfenac did not produce teratogenic effects at clinically relevant doses.

Clinical Considerations
Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of BromSite during late pregnancy should be avoided.

Data
*Animal Data*
Treatment of rats with bromfenac at oral doses up to 0.9 mg/kg/day (195 times a unilateral daily human ophthalmic dose on a $mg/m^2$ basis, assuming 100% absorbed) and rabbits at oral doses up to 7.5 mg/kg/day (3243 times a unilateral daily dose on a $mg/m^2$ basis) produced no structural teratogenicity in reproduction studies. However, embryo-fetal lethality, neonatal mortality and reduced postnatal growth were produced in rats at 0.9 mg/kg/day, and embryo-fetal lethality was produced in rabbits at 7.5 mg/kg/day. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Lactation
There are no data on the presence of bromfenac in human milk, the effects on the breastfed infant, or the effects on milk production; however, systemic exposure to bromfenac from ocular administration is low. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bromfenac and any potential adverse effects on the breast-fed child from bromfenac or from the underlying maternal condition.

### Pediatric Use
Safety and efficacy in pediatric patients below the age of 18 years have not been established.

### Geriatric Use
There is no evidence that the efficacy or safety profiles for BromSite differ in patients 65 years of age and older compared to younger adult patients.

## NONCLINICAL TOXICOLOGY
### Carcinogenesis, Mutagenesis and Impairment of Fertility
Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (129 times a unilateral daily dose assuming 100% absorbed, on a $mg/m^2$ basis) and 5 mg/kg/day (540 times a unilateral daily dose on a $mg/m^2$ basis), respectively revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the bacterial reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (195 and 65 times a unilateral daily dose, respectively, on a $mg/m^2$ basis).

## PATIENT COUNSELING INFORMATION
### Slow or Delayed Healing
Advise patients of the possibility that slow or delayed healing may occur while using NSAIDs.

### Concomitant Topical Ocular Therapy
If more than one topical ophthalmic medication is being used, advise patients to administer BromSite at least 5 minutes after instillation of other topical medications.

### Concomitant Use of Contact Lenses
Advise patients not to wear contact lenses during administration of BromSite. The preservative in this product, benzalkonium chloride, may be absorbed by soft contact lenses.

### Sterility of Dropper Tip/Product Use
Advise patients to replace the bottle cap after use and do not touch the dropper tip to any surface as this may contaminate the contents.

Advise patients to thoroughly wash hands prior to using BromSite.

**Rx Only**

**Distributed by:** Sun Pharmaceutical Industries, Inc. Cranbury, NJ 08512


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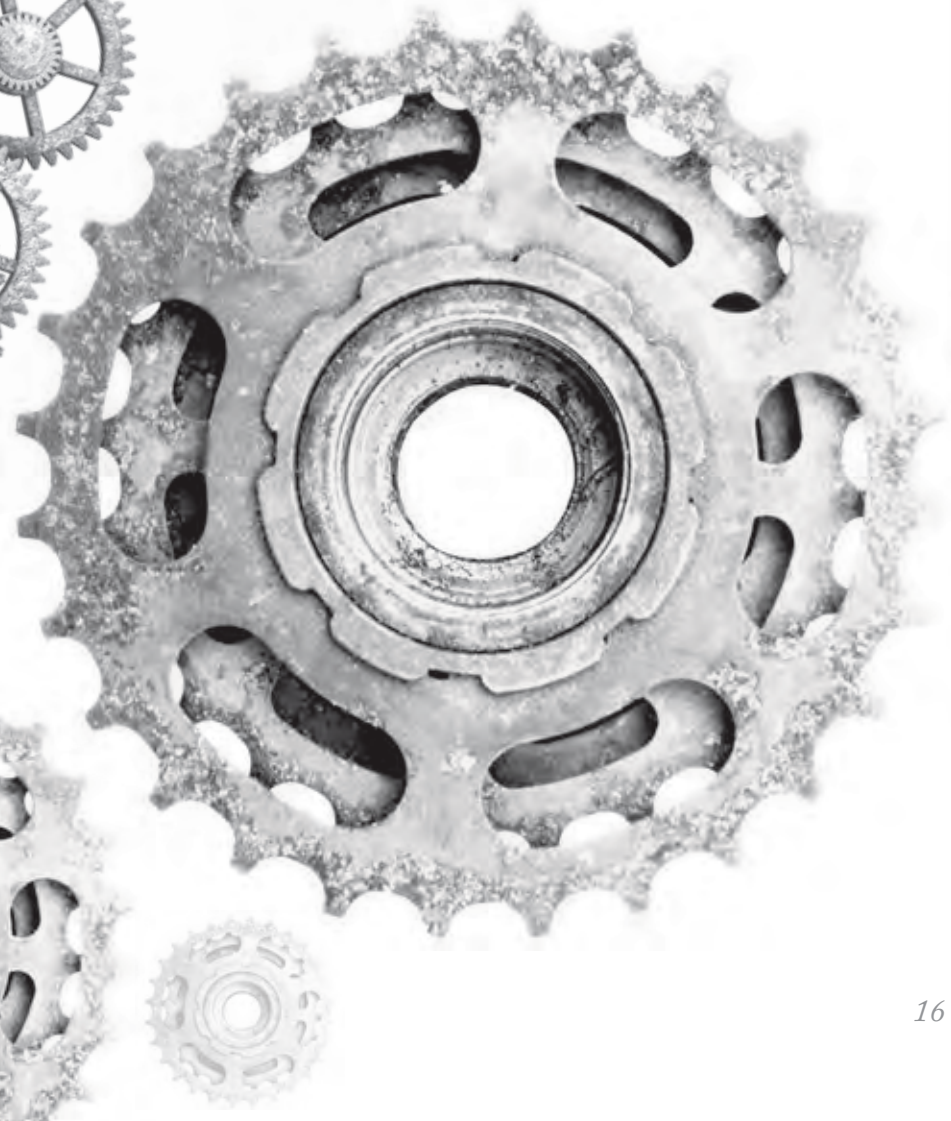

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## In Practice



## NextGen



## Profession



## Sitting Down With




the **Ophthalmologist**

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# Embrace the Unknown

*Strength lies in combining our differences, not by hanging on to our similarities*

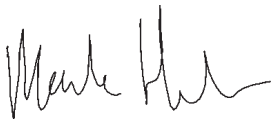


Last month, while in Chicago for the annual meeting of the AAO, I was fortunate to be invited to two, extremely worthwhile events. The first was the International Council of Ophthalmology's (ICO) roundtable on leadership development – the essence of the meeting being ICO president Hugh Taylor's drive to make the organization's governing committees more representative of the people it serves – a move away from the perception of the ICO as a club of "old men and their grandfathers" (or as Hugh later put it more succinctly, just "pale, male and stale") towards an ICO that is full of color, youth and a more equal gender balance.

From a purely functional viewpoint, being inclusive and embracing diversity gets results. A diverse team derives the benefit of a wider range of experiences, viewpoints and problem-solving approaches – in other words, it increases the collective intelligence of a team. But it turns out being inclusive is hard. The opening speaker at the roundtable, the Rwanda-based consultant ophthalmologist, Ciku Mathenge, told of her journey towards being more inclusive herself. There are a number of inherent biases in everyone: she found that her professional biases were seniority, whether someone worked in a public or private hospital, where they trained. Ciku explained that you have to understand your "default," what your automatic associations and biases are, and how they might hold you back. This is why stereotypes are so harmful – the example given being "African doctors have poor English" and it would be hard work taking them on as a resident. This might be true in some cases, but it's not an accurate reflection of reality: Ciku urged people not to take it at face value. You have to "look for data that shows you that your bias is wrong, recognize a stereotype for what it is, and pull it apart for the myth that it is." She explained that such attitudes rob organizations of diversity and the increased collective intelligence that it brings: you must challenge them. I agree wholeheartedly.

That same evening, I attended the OWL Annual Signature Event. OWL is no longer a contraction of "Ophthalmic Women Leaders," it now stands for "Ophthalmic World Leaders," but the tagline "Advancing Diversity in Leadership" remains. It was interesting to hear when Marsha Link won the Visionary Leader Award that until recently, this award was called the Visionary Woman Award – and that this change was a marker of just how far OWL – an organization already devoted to challenging a diversity imbalance (here, gender) had come. I think OWL and the ICO are singing from the same hymn sheet – and I hope they both see great benefits from this enlightened approach.

**Mark Hillen**
*Editor*



# Upfront

*Reporting on the innovations in medicine and surgery, the research policies and personalities that shape the practice of ophthalmology.*

*We welcome suggestions on anything that's impactful on ophthalmology; please email mark.hillen@texerepublishing.com*

## Hard Graft

### Might crosslinking patch grafts placed during glaucoma drainage device implantation eliminate conjunctival erosions?

Glaucoma drainage devices (GDDs) can be a great option for intraocular pressure reduction in some patients with glaucoma or ocular hypertension, with reductions equivalent to those achieved with trabeculectomy in some cases, and with fewer complications (1), although "fewer" does not equal "none." Conjunctival erosions can occur in 5–10 percent of patients, exposing the tube or shunt, and putting the patient at risk of number of complications, including endophthalmitis (2, 3). One way to lower this risk is to cover the GDD with a "patch graft" during surgery, and short-duration studies have certainly reported good outcomes from using donor cornea tissue (4, 5).

However, this is a precise art: if the graft is too thick, it may lead to bleb formation (or other complications), and if too thin, it may fail (6). Ideally, patch grafts need to be strong enough to provide sufficient and durable support to the cornea to prevent device exposure, yet thin enough to avoid inducing complications. Cue corneal crosslinking…

Recognizing the value that the approach could offer in this scenario, one research group have taken anterior lenticules from Descemet's stripping automated endothelial keratoplasty (DSAEK) corneas (300–350 µm), and "augmented" the tissue via UV-riboflavin crosslinking. They then implanted the crosslinked grafts over the drainage device in 10 patients undergoing GDD surgery. Interim 6-month results (7) were presented at the recent EVER congress in Nice, France and demonstrated no intra- or post-operative complications, with no grafts becoming eroded or GDDs becoming exposed.

The study is anticipated to last 36 months, but from these interim results, the researchers note "UV-riboflavin crosslinking of corneal tissue appears to be a safe modification of GDD surgery." Understandably, the team note that "prospective randomized trials are needed to compare augmented tissue with standard corneal grafts, and to define the optimal surgical strategy" – but it's certainly one strategy to file under "why didn't we think of that one before?" *RS*

*References*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5. *O Spierer et al., "Partial thickness corneal tissue as a patch graft material for prevention of glaucoma drainage device exposure", BMC Ophthalmol, 16 (2016). PMID: 26920383.*
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# Club Med

## Adopt the Mediterranean diet, cut the risk of developing AMD

There's reasonable evidence that the "Mediterranean diet" – adhering to the dietary habits of the Greeks, Italians and Spanish (in the 1940s and 1950s, at least) – is health giving. One meta-analysis found that all-cause mortality, and the risk of cancer, cardiovascular disease, and neurodegenerative like Alzheimer's and Parkinson's disease were all reduced by adherence to this diet (1). And it looks like we can add "protective against the development of AMD" to that list, too.

In an extension of the previously published COIMBRA eye study, that assessed the prevalence of AMD in Portugal (2), Silva et al. (3) looked at subjects with or without early AMD to determine how adherence to the Mediterranean diet, key dietary nutrients and lifestyle factors associate with the disease.

Participants were asked to complete food frequency questionnaires, and their adherence to a Mediterranean diet was evaluated using a well-established adherence scale – mediSCORE (4). mediSCORE values ranged from 0–9, with scores equal to or greater than six defined as high adherence to a Mediterranean diet. The team used a commercially available nutrition analysis software package (Food Processor Plus, ESHA) to determine the micronutrients (such as vitamins or trace elements) that participants managed to ingest during the time in this part of the COIMBRA study.

What they found was that AMD prevalence was lower in the subjects with high adherence to the Mediterranean diet (mediSCORE ≥6) compared with subjects with a mediSCORE of less than 6 – in other words, high adherence to the Mediterranean diet was associated with a lower chance of developing AMD. However, it wasn't just the Mediterranean diet. Physical activity and fruit and micronutrient consumption were significantly higher in participants without early AMD. One novel finding was that caffeine intake appeared protective against AMD too.

According to one of the researchers, Joao Figueira, "Given these findings, ophthalmologists should consider recommending a Mediterranean-style diet to their patients." Next steps? The team plan to continue their studies, including further dietary assessments and future re-screening of patients without AMD to determine if they develop the disease. *RS*


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1. *F Sofi et al., "Adherence to Mediterranean diet and health status: meta-analysis", BMJ, 337, a1344 (2008). PMID: 18786971.*
2. *L Cachulo Mda et al., "Prevalence of age-related macular degeneration in Portugal: the Coimbra eye study – Report 1", Ophthalmologica, 233, 119–127 (2015). PMID: 25677077.*
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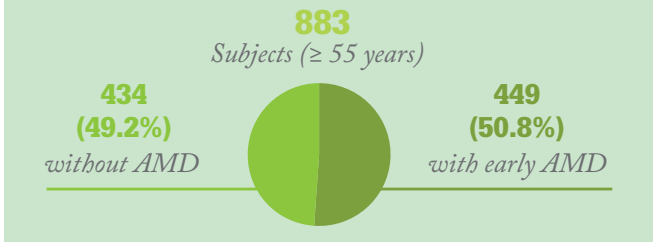


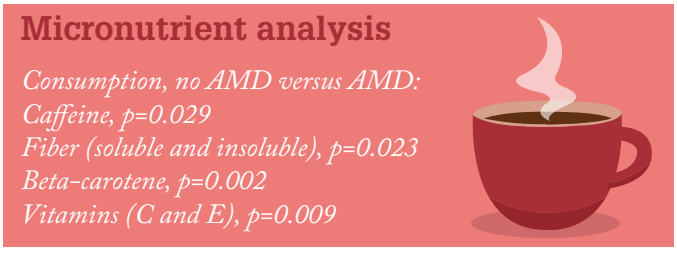


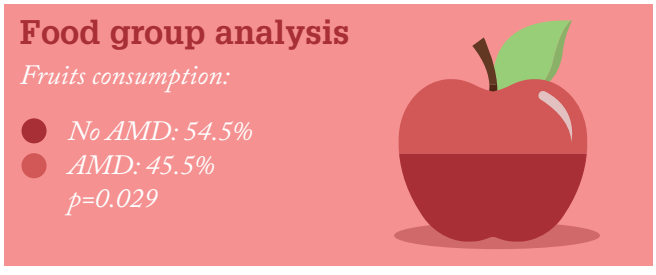


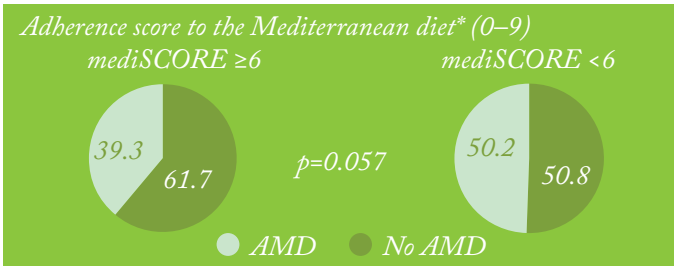


**mediSCORE adhesion scale (0–9). A value of 1 (beneficial) was attributed to consumption of: vegetables, legumes, fruits, cereals, fish and monounsaturated lipids above sex-specific median; meat and dairy below sex-specific median; 10–50 g/day alcohol (men) or 5–25 g/day (women). A score equal to or greater than 6 defined high adhesion to the Mediterranean diet.*

# The Multi-Drop Doctrine

## Waiting between eyedrop instillations: dogma or duty?

Do you need to wait five minutes between administering eyedrops? Does the second drop really wash out the first? That's the dogma (1), but is there concrete evidence to support it?

It's intuitive that if a drug isn't diluted and washed away by another, its absorption, and action, will be greater, and topically administered drugs do take time to be absorbed. On the other hand, not having to wait between eyedrop instillations would be considerably more convenient for patients – and should reduce the frequency of missed doses because, for example, the patient didn't have 20 minutes to spare that morning to take four eyedrops, or their mind wandered between drops three and four. Is the wait really that necessary?

To answer this question, a team from Centre Hospitalier Universitaire (CHU) de Caen in France tested the effect of a five-minute time interval between the administration of two different topical mydriatic agents (2). In 20 volunteers (40 eyes), they applied one drop of 10% phenylephrine and added one drop of 0.5% tropicamide immediately afterwards, or following a five-minute interval. Using digital photographs taken in photopic conditions, two observers compared pupil-to-iris surface ratios, finding that the relative pupil surface area was significantly increased with the five-minute wait (observer 1, p=0.004; observer 2, p=0.006) compared with the serial, immediate administration of the topical mydriatics.

The team therefore confirmed that convenience cannot trump pharmacokinetics: if patients are instilling multiple drops, they need to "take a break" of at least five minutes between them. *RS*

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2. *P Saguet et al., "A 5-minute time interval between two different dilating eyedrops increases their combined effect", Poster presented at the European Association for Vision and Eye Research; October 6, 2016; Nice, France. Poster #T108.*

# To Peel or Not to Peel?

## Does peeling the ILM when removing the ERM lead to better outcomes? That is the question

If a patient presents with an epiretinal membrane (ERM), it's likely that they'll eventually undergo vitrectomy and an ERM peel as treatment. In recent years, an increasing proportion of surgeons have added in another step: staining and peeling of the internal limiting membrane (ILM) (1). The belief is that removing the ILM helps reduce the chances of an ERM recurrence, as this removes any residual ERM cells that might have been left on the surface of the ILM, and that the ILM can act as a scaffold for their proliferation. On the other hand, ILM peeling is known to cause mechanical trauma to the retinal nerve fiber layer, but the effects are transient, and don't appear to affect visual outcome. But most studies assessing the pros and cons of peeling are retrospective – and inconclusive.

A team of researchers from Thessaloniki and Athens in Greece, and Moorfields Eye Hospital in the UK decided to try to obtain a more definite answer to the question "to peel or not to peel?" They performed a randomized controlled trial that compared the functional and anatomical outcomes of eyes (n=102) of patients (n=102) that underwent an ERM peel, with (n=50) or without (n=52) ILM peeling (2). All patients were aged ≥18 years, with an OCT-confirmed idiopathic ERM, binocular distortion, BCVA of ≤90 ETDRS letters, and intraocular pressures of ≤23 mmHg.

At 12 months after surgery, the mean change in distance BCVA was 0.30 ± 0.24 LogMAR (15 ETDRS letters) in the ILM peel group, and 0.31 ± 0.23 LogMAR (14 ETDRS letters) in the non-peel group (Figure 1a). The differences in distance BCVA, central retinal thickness and metamorphopsia between the two patient groups were not found to be statistically significant (Figure 1b, c) – suggesting that ILM peeling provides no additional benefits to patients undergoing an ERM peel. No ERM recurrence was seen in either group, although the length of follow up (12 months) may not be enough to rule out of the possibility of recurrence in some patients. However, a greater proportion of patients experienced anatomical disturbances (the formation or persistence of intraretinal cysts) in the ILM peel group, but this did not appear to affect visual outcomes.

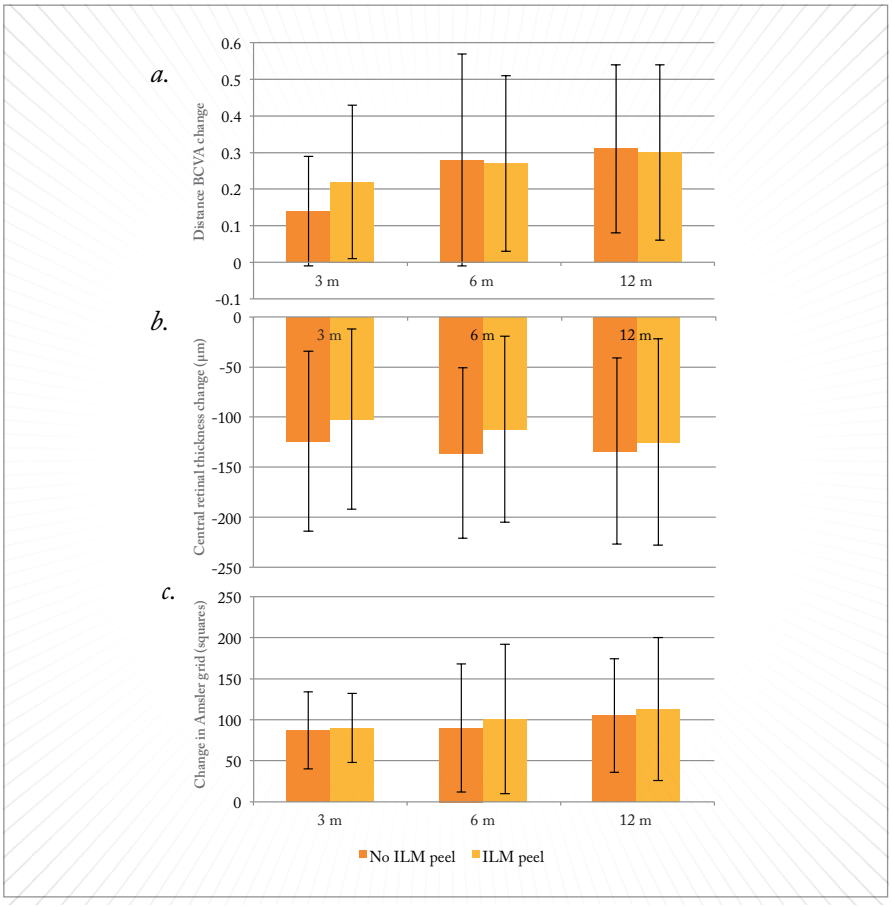


Figure 1. Change from baseline values at post-operative months 3, 6 and 12 for (a) BCVA, (b) central retinal thickness, and (c) Amsler grid squares. BCVA, best-corrected visual acuity; ILM, internal limiting membrane. Error bars: standard deviation.

The study authors concluded that ILM peeling doesn't result in better outcomes following ERM removal, and that ILM removal may have some downsides too. *RM*

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2. *P Tranos et al., "The role of internal limiting membrane peeling in epiretinal membrane surgery: a randomized controlled trial", Br J Ophthalmol, [ePub ahead of print] (2016).*

# High On a Low Supply?

## OCT angiography discriminates between POAG, NTG and normal patients

The first three papers describing OCT angiography (OCT-A) didn't examine the vasculature of the eye with the technology, they examined blood flow in the outer layers of the brains of rats (1–3). It was actually the fourth that examined the human eye; in 2012, Jia et al. (4) compared optic nerve head (ONH) flow in patients with preperimetric glaucoma (PPG; n=4) with normal subjects (n=4), and found that ONH flow was significantly lower in the PPG group.

Today, OCT-based analysis of the peripapillary retinal nerve fiber layer (RNFL) thickness is a commonly performed method of detecting glaucoma and assessing its progression, but OCT-A is rapidly becoming an extremely useful method of diagnosing and staging glaucoma progression. When you perform OCT-A in normal eyes, you see a dense microvascular network around the optic disc – but this annular network is attenuated both globally and focally in patients with glaucoma, which results in reduced blood flow (5–6). The question is now: can OCT-A be used to differentiate between different types of glaucoma?

To find out, Scripsema et al. (7) examined 92 subjects who had either no glaucoma, normal tension glaucoma (NTG) or primary open-angle glaucoma (POAG), and performed perimetry, assessed RNFL and used OCT-A to generate peripapillary density maps of each patient (Figure 1).

There were three key findings. The 4.5 $mm^2$ scans showed that annular perfused capillary density (PCD) in patients with

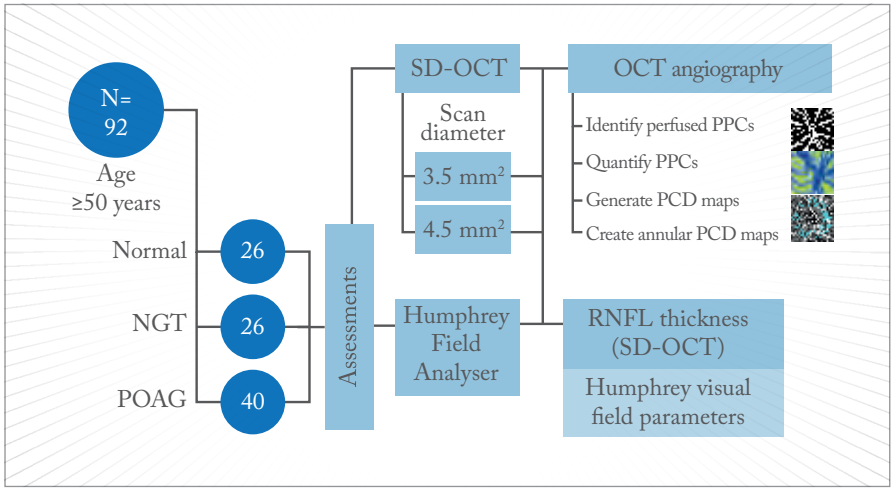
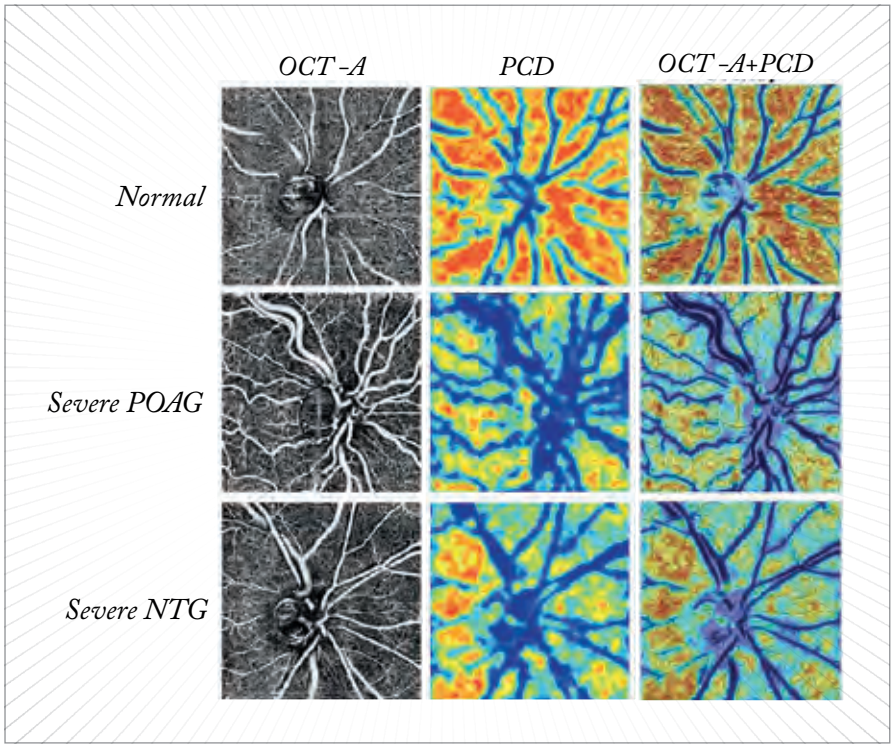



Figure 1. Study design and assessed parameters. NTG, normal-tension glaucoma; POAG, primary open-angle glaucoma; PPC, perfused peripapillary capillaries; PCD, perfused capillary density.




Credit: Nicole Scripsema, Shelley Mo, Toco YP Chui, Richard Rosen. New York Eye and Ear Infirmary of Mount Sinai.

Figure 2. Perfused capillary density (PCD) maps: normal vs. primary open-angle glaucoma (POAG) vs. normal-tension glaucoma (NTG). Adapted from (1).

POAG (34.24 ± 6.76 percent) and NTG (37.75 ± 3.52 percent) was significantly lower than in patients without glaucoma (42.99 ± 1.81 percent; $p<0.01$ and $p<0.01$, respectively). There was also a moderate correlation between annular PCD values and RNFL thickness. When the researchers used linear regression analysis to compare the annular PCD from the 4.5 $mm^2$ scans to the

Humphrey Visual Field (HVF) mean deviation, HVF average deviation and RNFL thickness, respectively, they found that all comparisons showed statistical significance (P<0.05).

In terms of differentiating between types of glaucoma, however, the color-coded PCD maps were of greatest utility (Figure 2), showing that POAG and NTG patients had a reduction in perfused capillaries that progressed in size when comparing early, moderate, and severe glaucoma groups – or in other words, the areas lacking perfused capillaries become larger as glaucoma progresses. In POAG, the pattern of blood flow loss closely matched the optic nerve fiber loss, and in NTG, the pattern of blood flow loss – while not significantly different from open-angle glaucoma – tended to be more diffuse.

There are a number of reasons why this study represents a welcome advance. The identification of vascular factors that are indicative of NTG should help to detect the disease earlier, and in addition to enhancing our knowledge of glaucoma pathophysiology, OCT-A of perfused peripapillary capillaries around the ONH should also help with monitoring the disease's progression, and also represents a new – and potentially very useful – biomarker for use in future clinical studies. *MH*

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# This Month in Business

## The FDA approves pre-filled ranibizumab syringe, HOYA extend global reach, and CZM announce new appointment

- The FDA have approved Genentech's pre-filled ranibizumab 0.5 mg syringe for the treatment of patients with wet age-related macular degeneration and macular edema after retinal occlusion. The syringe is expected to be available in early 2017.
- Envisia Therapeutics has released interim results from its ongoing 12 month Phase II study assessing a single administered dose of extended-release travoprost in five patients with glaucoma. Results demonstrate a 26 percent decrease in IOP nine months after administration.
- Allegro Ophthalmics has announced topline results from its Phase IIb DEL MAR trial evaluating ALG-1001 (Luminate versus bevacizumab monotherapy in patients with diabetic macular edema. Both the primary and secondary endpoints (non-inferiority to bevacizumab in best-corrected visual acuity and mean change in central macular thickness, respectively) were met at 20 weeks.
- HOYA announced an agreement to acquire Performance Optics and its subsidiaries VISION EASE and Daemyung Optical, expanding the Japanese company's global reach.
- Abbott announced Q3 2016 sales of $5.3 billion. Sales for medical optics totaled $296 million – an increase of four percent on an operational basis which the company attributed to cataract products in their premium IOL segment. Johnson & Johnson is expected to complete acquisition of Abbot Medical Optics in early 2017.
- Novaliq has appointed Christian Roesky as CEO, effective November 1, 2016. Bernhard Günther – the former CEO – will commence the new role of Chief Innovation Officer.
- Steven Schallhorn has been appointed Chief Medical Officer for Global Ophthalmic Devices at Carl Zeiss Meditech.

# In My View

*In this opinion section, experts from across the world share a single strongly-held view or key idea.*

*Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of ophthalmology. They can be up to 600 words in length and written in the first person.*

*Contact the editor at mark.hillen@texerepublishing.com*

## The Right Design

### Successful clinical trials – it's all about the endpoints

*By Philip J. Rosenfeld, Professor of Ophthalmology, Bascom Palmer Eye Institute, Miami, Florida, USA*

As William Feuer, a marvelous biostatistician and colleague, once said "If you design a clinical trial properly, there is no such thing as a failed study." And, this is the truth: while a treatment may fail to achieve its pre-specified efficacy endpoint and prove beneficial to patients – the study has not failed, just the treatment. At the very least, a successfully executed study will give you a definitive answer, either yes or no. Moreover, the study outcomes should help you refine the design of future trials by providing additional natural history data. After all, showing that a treatment doesn't work saves money, allows better allocation of resources, and prevents patients from being exposed unnecessarily to treatments. Similarly, there is nothing more frustrating than having a potentially valuable drug that could be a breakthrough therapy, but it fails to prove itself in a clinical trial, because the study was not designed correctly and appropriate endpoints were not chosen properly. Companies throw hundreds of millions of dollars at the clinical development of drugs, and they may be effective. But if the trials are designed poorly or conducted improperly, then what's ahead is heartbreaking: all that effort, and you're still left with questions as the results don't answer the question you asked.

There is so much work that goes into writing an experiment and running a clinical trial that you absolutely have got to get an answer at the end of it. And this means designing a "bulletproof" clinical trial: setting up the study and necessary controls so you know the results will be meaningful. Designing appropriate studies is a constant and dynamic process of education, renewal and improvement that everyone has to go through, so if you're just starting to get involved as a clinical trial investigator, what I would recommend is this: embrace the learning process and get started with an established industry-sponsored trial. It gives you an appreciation of how complicated it is to run a clinical trial. There are so many study design and compliance issues that an investigator needs to be aware of before setting out on their own to design and enroll a clinical trial. And, I have been there: by getting involved in the photodynamic therapy trials for neovascular AMD, I learned a tremendous amount that gave me the experience I needed to move forwards and look at anti-VEGF therapy and the role of OCT imaging.

Another piece of advice is to be prepared to pivot and go where the research takes you. Don't be so fixed in your idea and approach that you are not going to learn from what you – and others – are doing. About six years ago, I pivoted and decided to investigate dry AMD, and I realized that we didn't have endpoints or imaging modalities that could give us more reliable quantitative measurements about disease progression, so I have spent a number of years using spectral domain and swept source OCT to come up with clinical trial endpoints that we can employ in dry AMD trials (1).

In my view, it is essential that we develop endpoints that can be used at earlier stages of AMD, and we propose to focus on intermediate AMD through using drusen volume as a predictor of disease progression (1). In November 2016 there is going to be an important

meeting involving the NEI, ARVO, and the FDA focusing on clinical trial endpoints for dry AMD, and I hope that we are able to reach a consensus on how best to design and conduct these trials to test novel therapies that we so desperately need.

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# Dropping the Ball

**Non-adherence is a bigger threat to optimal outcomes than missed appointments in glaucoma management – and much easier to hide**

*By Ivan Goldberg, Clinical Associate Professor, Ophthalmology, University of Sydney; Head, Glaucoma Unit, Sydney Eye Hospital; Director, Eye Associates, Sydney, Australia*

When talking about medication and treatment, "compliance" and "adherence" are sometimes used interchangeably. But they're different: "compliance" is old-fashioned, describing a meek patient blindly following advice from an all-knowing, paternalistic doctor. "Adherence" is a team effort – treatment is decided by the doctor and patient together. Adherence can be defined as the extent to which a patient's behavior (e.g. drugs, diet, and lifestyle changes) coincides with the clinical prescription. Non-adherence can be defined as either intentional or accidental failure to follow the program created with the physician.

Glaucoma management today is mainly focused on IOP reduction, and there are a number of medical (and surgical) avenues to achieve it. The choices we make as clinicians are a balance of benefits versus risks for that particular patient, and their likelihood of adhering to the management program. But how common is non-adherence? For eye disorders in general, the number is extremely high, at 70–75 percent (1). We might wonder why people don't adhere to and persist with their programs when it's clearly in their own interests to do so. The reasons are multifaceted, but it's clear that many of our patients aren't taking their medications, and frankly, we're pretty hopeless at telling which ones. It's always the "other doctors" who have non-adherent patients, not us! What are the risk factors? According to one study group, only a few patients said that costs, side effects, or other medications presented a barrier (2), even though we know that these factors are important in other patient populations. According to the WHO, the reasons for non-adherence are therapy-, condition-, and patient-related, and influenced by the healthcare system and socioeconomic factors. The take-home message is that there isn't any one factor affecting adherence, and the factors can change over time.

So what do we do about it? We need to address it at every opportunity by asking open questions, trying to track the prescriptions a patient asks for, following up with people who don't show up, and in patients who are progressing, considering non-adherence as a possible cause.

There's also a link between non-attendance and non-adherence. Regular clinic attenders are more likely to be adherent, and vice versa (3). The number of visits seems to be important – a recent study found that four visits a year appears to double the odds ratio of adherence. Missed appointments are easy to spot, and can be minimized be reminding patients of appointments, and following up.

We need to remember that patients won't reliably tell us what they're not doing, partly because they don't want to disappoint us, and partly because, as they quite reasonably say, "How can you expect me to remember what I have forgotten to do?"

There are physical barriers to consider too, i.e., getting the drop from the bottle into the eye. Instillation techniques are infamous for being disastrous – in one study 35 percent of patients in a glaucoma center rammed the bottle in their conjunctival sac and poured the contents until they cascaded down their cheek (4). Another 15 percent were "high-altitude bombers," hoping for the best, and five percent deliberately put the drop on their cheek and rolled their heads around in an attempt to get it in their eye! Of these patients, 25 percent didn't succeed and 13 percent didn't know they had failed.

Missing drops (whether through timing or targeting) are hidden from the doctor, and possibly even the patient. They can be disguised, willfully or inadvertently, and they can be denied. Ultimately, it's the failure to get the agent to the receptor that leads to a failure to achieve results, resulting in less than optimal outcomes. We need to pay attention to non-adherence, and remind our patients that the drugs we prescribe for them simply can't work if they aren't using them.

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# Refractive Surgery's Personalized Revolution

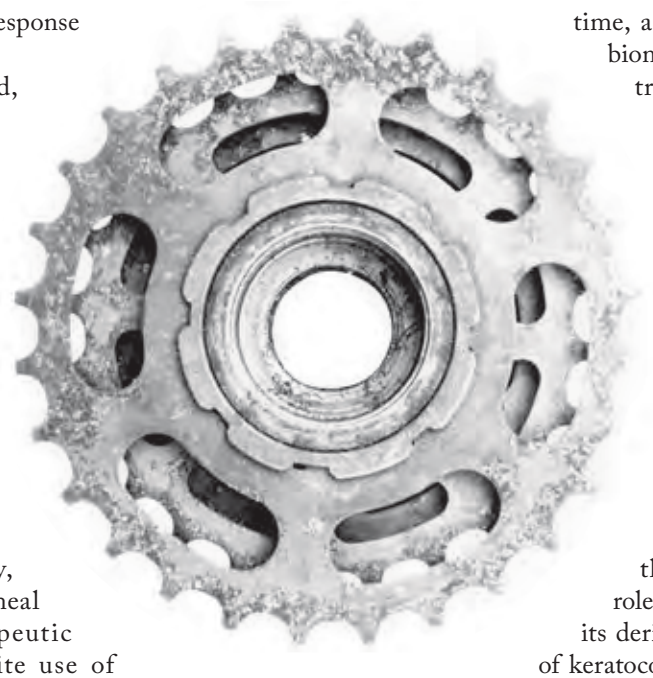
A better understanding of corneal biomechanics through computer modeling will transform the way we approach refractive surgery

*By William J. Dupps Jr.*

Ophthalmologists have been leveraging the cornea's biomechanical response for refractive purposes for over a century. The first reported case of astigmatic keratotomy dates back to 1885 (1), and keratorefractive surgery – as well as our understanding of how the cornea responds to it – has continued to develop ever since. Today, we have access to advanced imaging techniques that are able to measure the minute alterations in corneal shape that drive changes in the optical performance of the eye. Although most established forms of refractive surgery have satisfied rigorous safety and effectiveness criteria, there is an increasing desire among surgeons and patients to further optimize individual outcomes and postoperative stability. To meet this need, I believe we need a better working appreciation of corneal structural mechanics – not just an abstract intuition about mechanical responses (or weakly correlated predictors of those responses), but practical tools that can consolidate the complexities of a three-dimensional (3D) structural response problem into personalized guidance that can be used in our daily clinical practice.

## Corneal biomechanics over the years

Arguably, surgeons had a greater appreciation for the importance of corneal biomechanics when refractive surgery was purely incisional. Not long after Tsutomu Sato began experimenting with anterior and posterior keratotomy for refractive correction and Svyatoslav Fyodorov refined radial keratotomy for myopia, ophthalmic surgeons were routinely exploiting their working knowledge of the biomechanics of the cornea to produce refractive change. But when laser ablation arose as the dominant mode of refractive correction in the 1990s, a narrower concept of refractive surgery as pure "shape subtraction" was adopted. That view neglected, or at least minimized, the contribution of the corneal biomechanical response to surgical outcomes.



As the 1990s progressed, awareness of the practical importance of biomechanics began to re-emerge. This was a period of rapid evolution of corneal imaging technology that saw more widespread use of Placido topography and introduction of new optical tomography devices. Several clinical phenomena suggested the continued relevance of biomechanical factors, even in laser refractive surgery, including: unexpected corneal flattening in phototherapeutic keratectomy (PTK) despite use of optically neutral ablation profiles; the need for empirical adjustment of the programmed laser treatment through surgeon nomograms; evidence of late post-radial keratotomy refractive drift; refractive regression after LASIK or PRK in some patients; and most importantly, postoperative corneal ectasia. These and other observations prompted a more nuanced understanding of the role of biomechanics: even in refractive procedures where biomechanical change is not the primary mechanism of action, it remains an important, often performance-limiting influence on treatment precision and stability.

The early 2000s saw the introduction of femtosecond lasers in refractive surgery. Far more impactful than just making "bladeless" LASIK a possibility, this technology supported unprecedented levels of treatment reproducibility in refractive surgery by enhancing the precision of the flap creation process and revitalizing incisional procedures by offering a highly customizable alternative to manual astigmatic keratotomy. At the same time, it ushered in a new class of intrastromal procedures such as small incision intrastromal lenticule extraction (SMILE) that made it possible to correct refractive error while deliberately sparing the corneal stroma's most mechanically resilient anterior layers.

Building on their experimental work in the mid-1990s, Theo Seiler and his team reported the first clinical use of corneal cross-linking (CXL) in 2003. This was a momentous breakthrough in clinical ophthalmology and a major milestone in the timeline of corneal biomechanics: for the first time, a treatment that enhanced corneal biomechanical properties was used to treat keratoconus, a condition in which a deficit in corneal material properties is the final common pathway to progression. Just two years later, a commercially available tool for measuring corneal biomechanical properties (the Ocular Response Analyzer, Reichert Instruments) was introduced and broke through the first major barrier to understanding and using biomechanical measurement in clinical practice. Hundreds of studies have followed that have further established the role of this measurement method and its derivatives as independent predictors of keratoconus and Marfan syndrome, post-LASIK ectasia risk, and even progression of glaucomatous visual field and nerve fiber layer loss. More recently, the Corvis ST from Oculus was introduced, and it provides direct visualization and measurement of corneal deformation behavior in one corneal meridian, and major progress is now being made toward full spatial mapping of corneal elastic properties using technologies such as OCT elastography and Brillouin scattering microscopy. These newer technologies have the potential to detect localized abnormalities in biomechanical properties and produce a patient-specific 3D corneal biomechanical fingerprint. With further study, they will likely lead to breakthroughs in assessing ectasia susceptibility in refractive surgery candidates and establishing a prognosis in young keratoconus suspects facing decisions about early intervention with CXL.

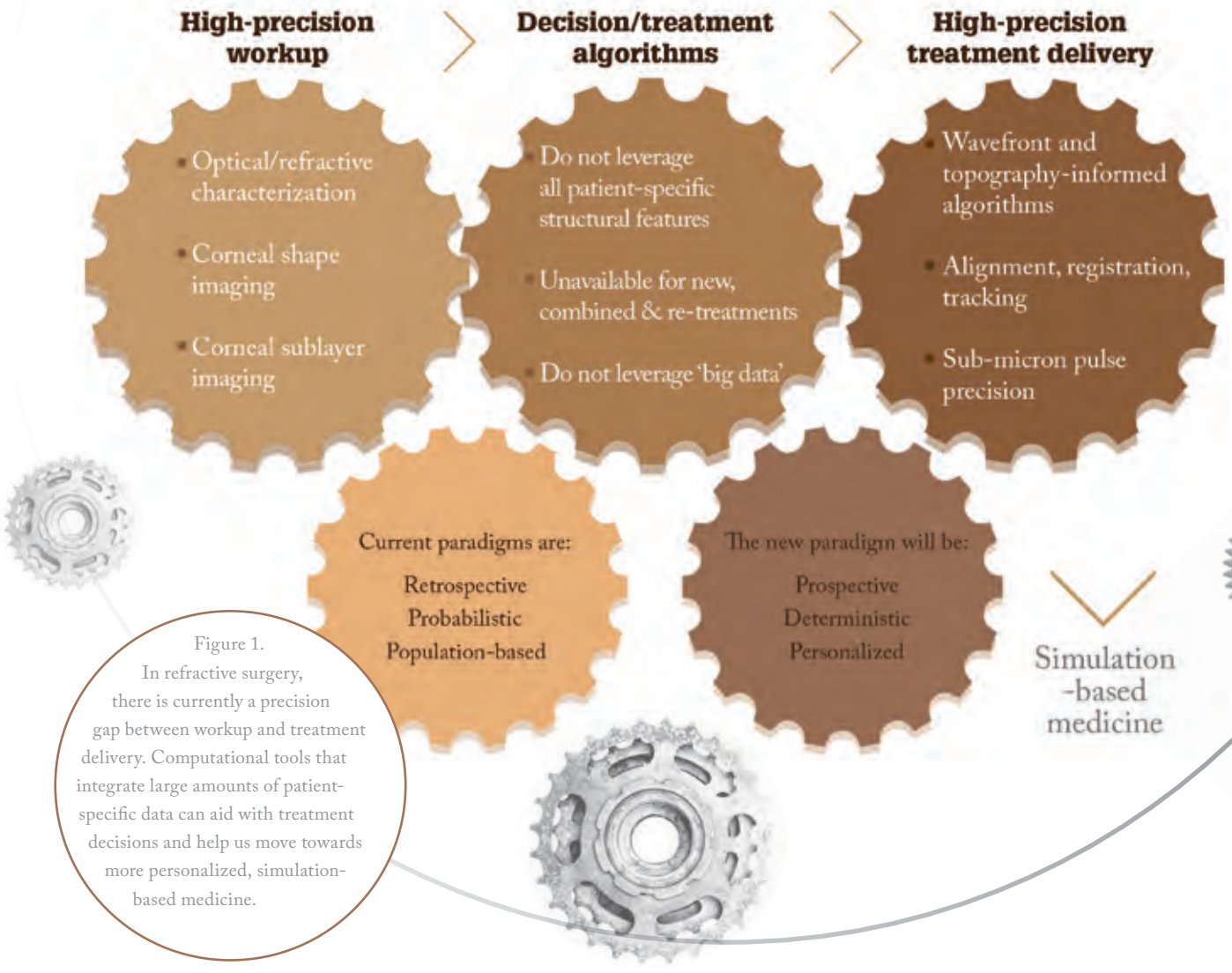



Figure 1. In refractive surgery, there is currently a precision gap between workup and treatment delivery. Computational tools that integrate large amounts of patient-specific data can aid with treatment decisions and help us move towards more personalized, simulation-based medicine.

## Individualized treatment planning: The missing link

It's clear that, remarkable advances have been made in measurement and treatment technologies in cornea and refractive surgery (Figure 1). We have very precise clinical tools to characterize the 3D anatomy of the eye and its optical performance. We have excimer and femtosecond laser systems with sub-micron pulse precision and tracking systems that offer exquisite opportunities for customizing treatments, and more sophisticated UV delivery systems for customized CXL are already available outside of the US. Devices for mapping the corneal biomechanical properties are around the corner. But when it comes to treatment planning, current paradigms have not kept pace with the dramatic growth in available information for preoperative planning or the precision of treatment systems. By leaving an enormous amount of patient data on the table, some of which is very likely to enhance the ability to predict an individual's outcome, the precision of the entire treatment process is limited by the coarseness and low patient specificity of the planning tool.

The current degree of personalization varies greatly across procedures. In CXL for keratoconus, a standardized treatment is typically used for all candidate patients without modification. Most conventional excimer laser treatment algorithms and nomogram software make use of a very limited subset of data, namely the refractive sphere and cylinder and perhaps a corneal curvature value. Even though maps of corneal elevation, curvature and thickness are usually obtained preoperatively, this information is used only to determine candidacy for surgery and not as input for the treatment algorithm. Wavefront-guided and topography-guided ablation algorithms are exceptions, and

by incorporating whole-eye aberrations or anterior corneal elevation data, these procedures provide a higher level of personalization than convention treatments. Even with over 90 percent of myopic LASIK patients achieving 20/20 or better vision, there is an opportunity to improve predictability, and results in hyperopic and higher astigmatic corrections are less predictable. Emerging treatments such as crosslinking for lower refractive errors may not have obvious treatment algorithms to take into clinical trials, and nomograms for intracorneal ring segments and astigmatic keratotomy are more qualitative with less predictable outcomes. Algorithm modifications for combined treatments (for example, PRK and CXL), enhancement procedures, and treatments in atypical corneas (like relaxing incisions after keratoplasty) are either absent or only minimally patient-specific. Even though all of these procedures involve biomechanical interactions with the cornea, we don't have a unifying method for planning that is grounded in structural principles.

*"Even though all of these procedures involve biomechanical interactions with the cornea, we don't have a unifying method for planning that is grounded in structural principles."*

### Closing the precision gap with simulation-based planning

Current paradigms for optimizing outcomes in our patients are retrospective, probabilistic, and population-based. Nomograms are based on historical outcomes, and de novo outcomes are predicted by calculating the average historical response of a minimalistic representation of the new patient. Such history-based nomograms are helpful, and when they are specific to the surgeon, can capture environmental variables that influence outcomes. But thanks to computational advances and the increasing availability of high-resolution patient data, we are moving toward a more prospective, structurally deterministic, and personalized approach through simulation-based medicine.

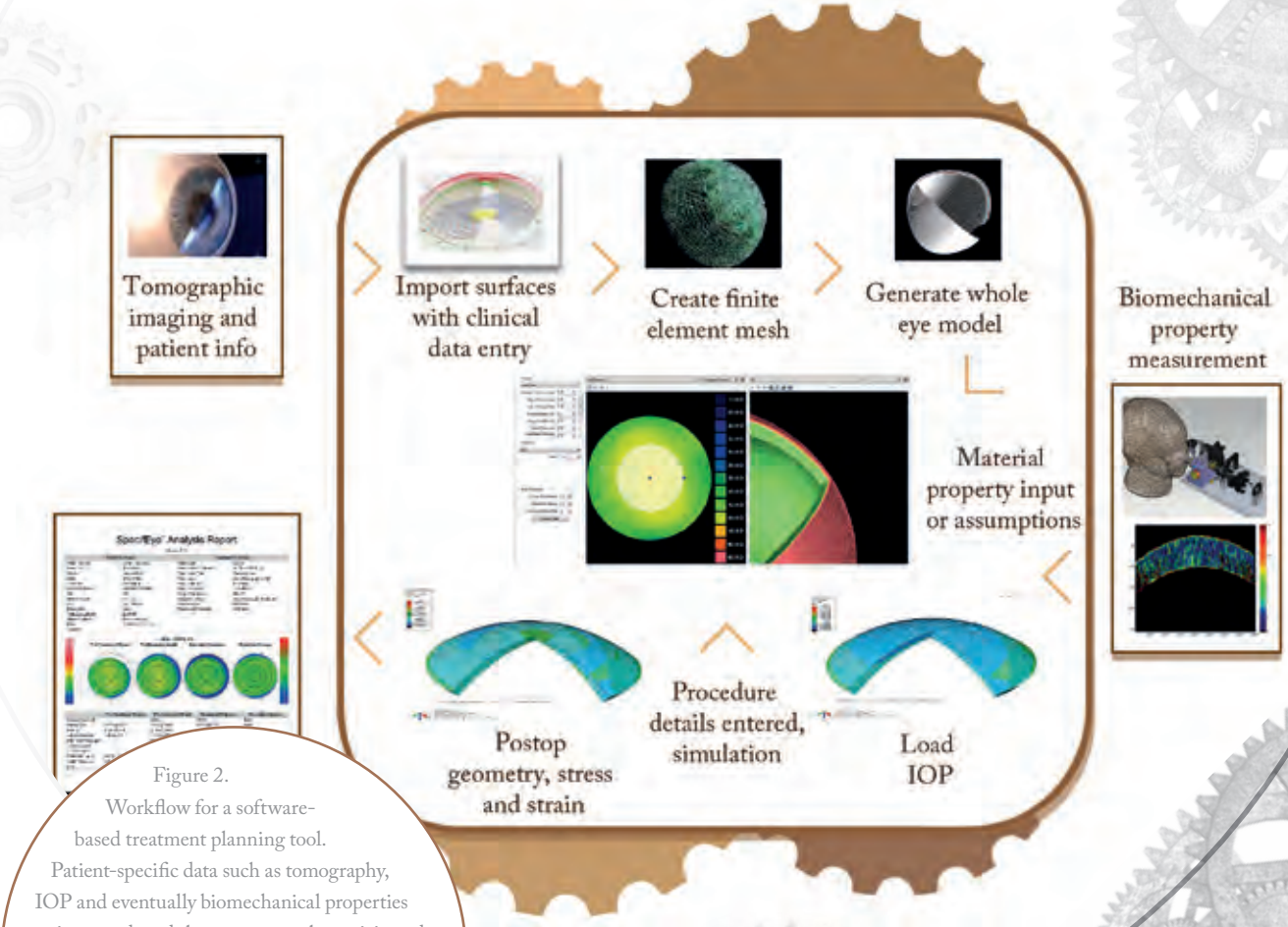



Figure 2. Workflow for a software-based treatment planning tool. Patient-specific data such as tomography, IOP and eventually biomechanical properties are imported, and the user enters the anticipated surgical parameters. Reports are generated showing the predicted outcome based on simulation and other machine learning strategies. The box includes the personal computer software processes and web-based finite element solver.

The relationship between corneal shape and visual performance is one of nature's finest examples of a structure-function relationship, and presents an enormous opportunity for ophthalmology to lead in the area of simulation-based medicine. Investigation of computational biomechanical models as tools for predicting refractive surgery responses dates back to at least 1989. Our group and others have escalated efforts to apply such models to clinical prediction, and with proper validation, I believe they will change how we approach corneal and refractive surgery. It was computational modeling that demonstrated how strain redistribution leads to localized flattening in CXL, that tested hypotheses of keratoconus progression, and that provided a virtual trial for showing the potential of customized CXL patterns to maximize topographic normalization in keratoconus and correct myopia, hyperopia, and astigmatism without weakening the cornea. Studies examining the performance of models for predicting outcomes in LASIK and assessing biomechanical risk of ectasia are underway. Modeling has the makings of a universal planning tool, one that could dramatically increase the utility of biomechanical measurements by leveraging them in simulations.

The greatest advantage of modeling is that it provides a mechanism for combining nearly everything we know about and

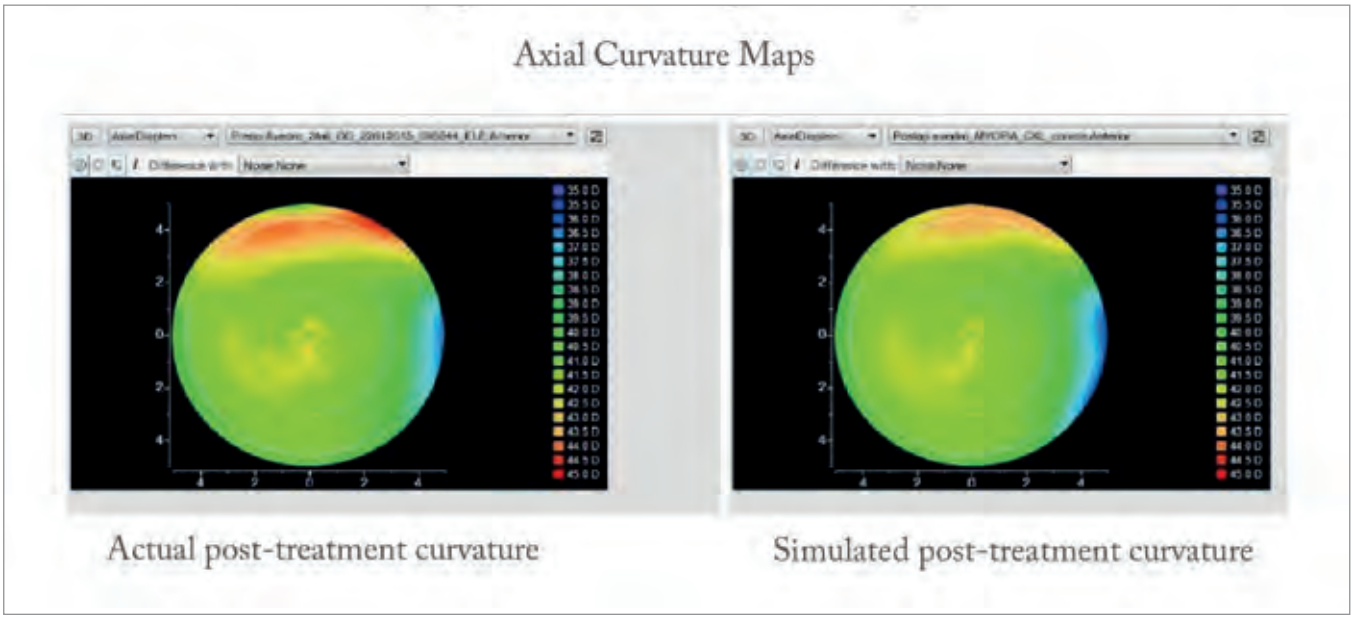



Figure 3. Example comparing the clinical and model-predicted axial curvature maps of a myopic crosslinking procedure. The predicted change in central curvature was -0.99D and actual change was -0.90D.

can measure from the patient's eye and the proposed treatment. It then allows the user to subject the virtual version of that eye to that treatment, observe the predicted outcome, and consider the results during the planning of the actual treatment. Figure 2 gives an overview of the workflow that we are developing to automate the process, and Figure 3 offers an example of a modeling result comparing the clinical and model-predicted axial curvature maps of a myopic crosslinking procedure from a collaboration between our laboratory, Avedro, and Burkhard Dick's group in Bochum, Germany. In addition to importing patient data such as corneal geometry, axial eye length, clinical refraction, and eventually biomechanical properties, the model allows detailed specification of all surgical parameters and performs ray-tracing on pre- and post-treatment surfaces to estimate refractive change and higher order aberrations. Aside from its potential as a surgical guidance tool, modeling is currently being used to test hypotheses, explore novel treatment designs, refine treatment algorithms in preclinical simulations, and perform stress and strain-based risk assessments – all on a personal computer.

## 'Big data' will support even better prediction

The vision of the future of surgical planning that I've presented here focuses on 'big data' in the context of the individual: ensuring that the predictive model knows as much as possible about the eye and the treatment for the most effective "n of one" study possible. I have highlighted how this approach differs from the current approach of 'customizing' treatment based on historical outcomes for the average eye using regression equations that are agnostic to most of the available data and that do not explicitly account for the important structural effects we reviewed early in this article. The current approach is useful for reducing systematic error in prediction as long as the right information is included in the statistical analysis. But our knowledge of what is important to include is imperfect, especially for newer treatments and atypical eyes, and nomograms can only account for inter-individual differences in outcomes if they capture the personal factors that drive those differences.

However, this does not discount the value of big data beyond the individual eye. The rich datasets that are collected through the modeling process and the predictions that are generated across many simulations for many eyes and many procedures are an important source of model refinement and continuous improvement. Aggregating these results and comparing to actual outcomes data will allow automated learning mechanisms to provide "smarter" nomogram suggestions that incorporate structural predictions along with empirical performance information.

Imagine the refractive practice of five years' time – one where the "precision gap" has been bridged by refined treatment planning technologies and greater levels of personalization. I believe that in that timespan, we will also incorporate corneal

biomechanical measurements into our workflow. These tools will support increasingly more accurate predictions of the outcomes of procedures, and help identify which procedures and which treatment parameters will generate the most optimal outcome possible for each patient. We will be able to more objectively screen patients for refractive procedures using structural information in a data-driven, computationally-assisted process, one that helps us rule out eyes that aren't safe for surgery and proceed with greater confidence in ambiguous cases.

*"Imagine the refractive practice of five years' time – one where the 'precision gap' has been bridged by refined treatment planning technologies and greater levels of personalization."*

Today's surgical outcomes are excellent. But with better utilization of rich patient-specific datasets and computer modeling of structural mechanics, we can narrow the precision gap in refractive surgery planning. As a result, tomorrow's surgery will be safer, more predictable, and characterized by even better outcomes.

*William J. Dupps Jr. is a cornea and refractive surgeon at the Cole Eye Institute with appointments in Ophthalmology, Biomedical Engineering and Transplant at Cleveland Clinic, and an Adjunct Associate Professor of Biomedical Engineering at Case Western Reserve University in Cleveland, Ohio. He is founder of OptoQuest Inc., a Cleveland Clinic company focused on commercial translation of biomechanical measurement technology and a clinical modeling tool, SpecifEye™.*

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## A Concise Clinical Timeline Of Corneal Biomechanics

**1960s**
Biomechanics leveraged widely to produce incision-mediated refractive change

**1980s**
Photoablative refractive surgery is introduced and conceptualization of surgery as "shape-subtraction" undermines appreciation of importance of biomechanics

**Late 1980s**
First published finite element model of corneal refractive surgery

**1990s**
More widespread use of high-precision corneal imaging technology. Biomechanics in photoablative surgery increasingly recognized as an important source of outcome variability and instability (fluctuation, regression, ectasia)

**2000s**
Introduction of femtosecond laser for precision creation of flaps, incisions and eventually intrastromal lenticules and pockets

**2003**
Demonstrated potential of crosslinking to stabilize progressive biomechanical disease

**2005**
First clinical instrument commercialized to measure corneal biomechanics

**2010s**
Computational modeling used to explain flattening effect of crosslinking, test hypotheses of keratoconus progression, and show potential for using personalized crosslinking patterns to maximize topographic normalization in keratoconus and produce refractive effects – without weakening the cornea

**Today**
Accelerated development of tools for mapping corneal biomechanical properties and software for simulation-based treatment planning

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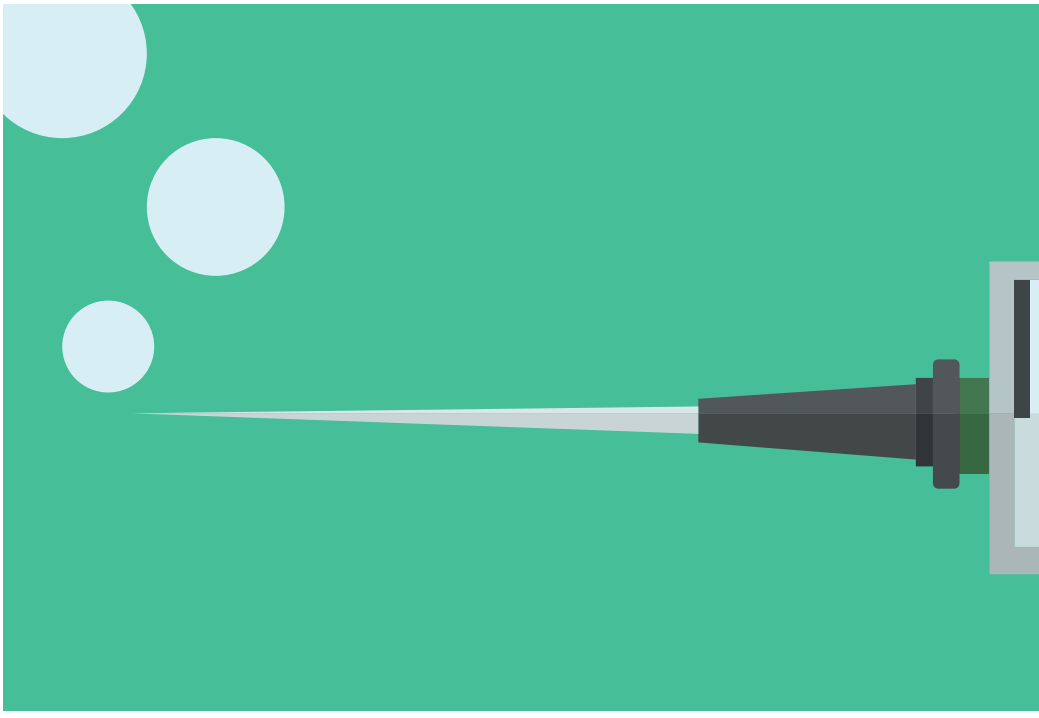
# In Practice

*Surgical Procedures*
*Diagnosis*
*New Drugs*

# The Importance of Good PR

## Pneumatic retinopexy – an effective (and inexpensive) alternative to vitrectomy and scleral buckling?

*By Paul Tornambe*



I advocate pneumatic retinopexy (PR) for the treatment of retinal detachment, and have done so for nearly 30 years. I presented the results of a multicenter clinical trial comparing PR to scleral buckling at the 1988 AAO congress, and even today, I still think that for many patients with retinal detachment, PR has the best chance of restoring pre-detachment vision.

### Buckle up?

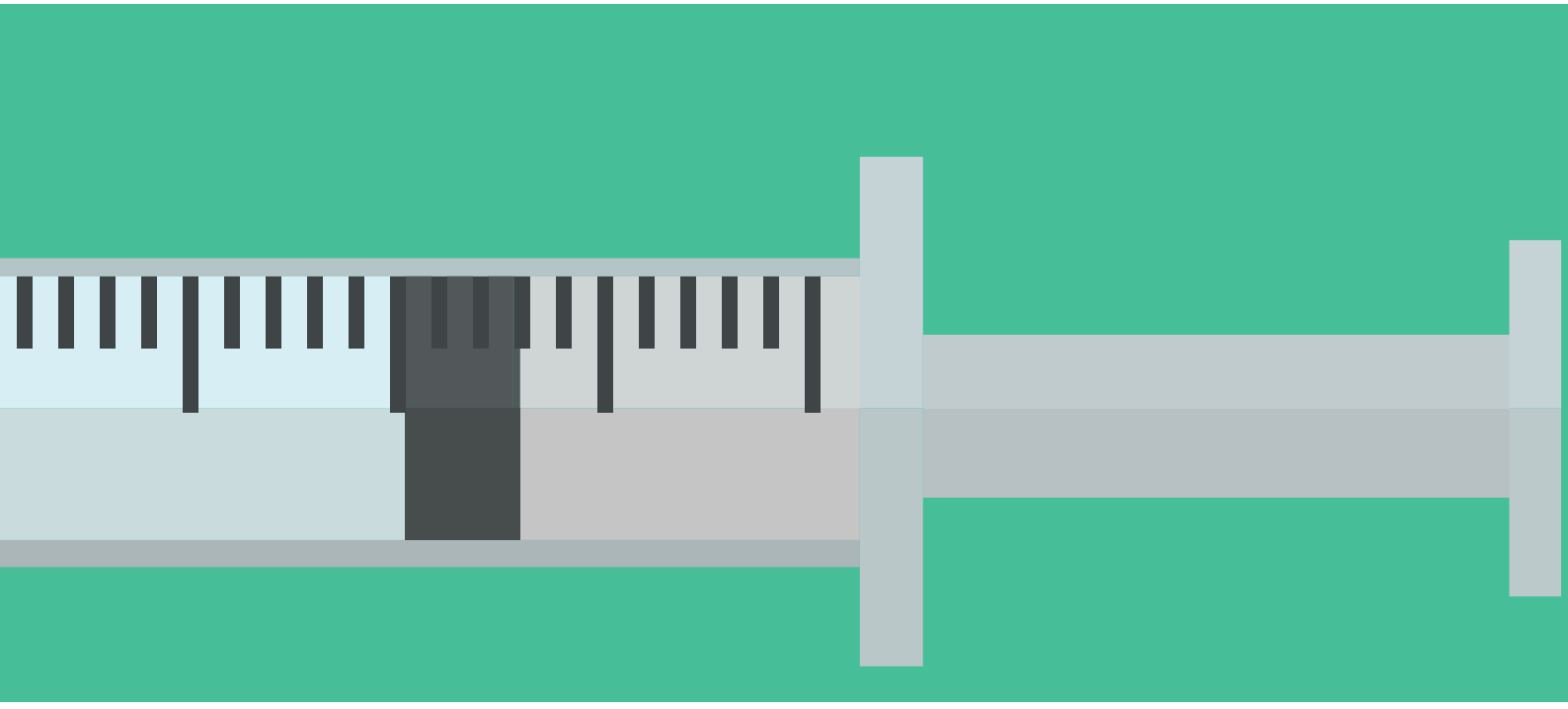
In 1989, I participated in one of the largest clinical studies of PR ever performed – a multicenter, randomized, prospective trial that compared the outcomes of PR and scleral buckling in 198 patients (1). Patients were carefully selected for inclusion in the trial: they had to have retinal break(s) no greater than one clock hour in size, that were within the superior two thirds of the fundus, and only patients without significant proliferative vitreoretinopathy were enrolled. What we found was that the single-operation success rates with PR and scleral buckling were 73 percent and 82 percent, respectively, which additional laser or cryopexy increased to 81 and 84 percent, respectively. It is important to note that VA continued to improve by about 10 percent between six months and two years after the procedure, likely caused by restoration of the normal macular architecture. Indeed, in patients who had preoperative detachment of the retina, 20/50 or better vision was achieved after 2 years in 89 percent of eyes that received PR, and only 67 percent that underwent scleral buckling.

*"I still think that for many patients with retinal detachment, PR has the best chance of restoring predetachment vision."*

Now, the surgeons who participated in this trial were all fellowship trained and had prior experience of both PR and scleral buckling, yet the results differed significantly between the centers – the scleral buckle and PR success rates varied from 57 to 100 and 43 to 83 percent, respectively (1).

### *At a Glance*

- *Pneumatic retinopexy (PR) is not as popular an approach to retinal detachment repair as I believe it should be: it costs little to perform and produces good results*
- *You can't separate the surgeon from the surgery. The surgeon's technique and ability to find all the breaks, and the patient's involvement in positioning correctly postoperatively all affect the outcome*
- *Careful consideration of patient selection, pre-op preparation, technique, post-op care and patient positioning are all crucial factors for successful PR*
- *Reimbursement for PR has been cut recently, encouraging more expensive OR-performed procedures; but in my opinion, for the right patient, PR remains a valid and inexpensive choice*



When we examined our results more closely, what we found was that you can't separate the surgeon from the surgery. Case selection, the surgeon's ability to find all the breaks, surgical technique and correct postoperative positioning all factor into the outcome. So what did we find were key to successful PR? And what happens to eyes with failed PR?

## Defining success

In the trial, 99 percent of detached retinas were ultimately reattached. I decided to take a more contemporary look at failed pneumatics, so I reviewed 43 consecutive primary detachments that I repaired with PR since September 2012, where I had at least one year of follow-up. One third were pseudophakic, and in one third the macula had detached preoperatively. PR successfully attached 81 percent of eyes with a single procedure, and final attachment was 100 percent. One eye developed proliferative vitreoretinopathy. Macula attachment did not influence single operation success, and neither did phakic status – which means that pseudophakia is not a contraindication to performing PR.

To attach the eight failed cases, 11 procedures were needed. In the one PVR case, silicon oil was inserted and later removed. Overall, 86 percent of all eyes attained 20/40 or better acuity, and all failed eyes attained 20/40 or better acuity. So at one year, even eyes which failed the first PR ultimately did well.

## Cutting the wrong costs?

Hypothetically, if we compare the cost of performing 43 vitrectomies with a 90 percent success rate, with the cost of performing PR with an 81 percent success rate, PR (including reoperations) is less than half the cost of vitrectomy – and a failed PR does not disadvantage the eye when it comes to ultimate anatomic attachment or visual recovery. Unfortunately, the Centers for Medicare & Medicaid Services (CMS) in the US has defined single operation success as the primary quality measure for retinal detachment repair.

My colleagues and I have shown that single operation success does not necessarily equate to best vision or least cost, and hope that CMS will reconsider this erroneous definition of quality, and reconsider recent cuts to PR, which encourage more expensive, OR-based procedures. If surgeons are ever compensated based on their outcomes and cost, I suspect PR will become very popular.

*Paul Tornambe is Director of the San Diego Retina Research Foundation and founder of Retina Consultants San Diego, California, USA.*

*Reference*

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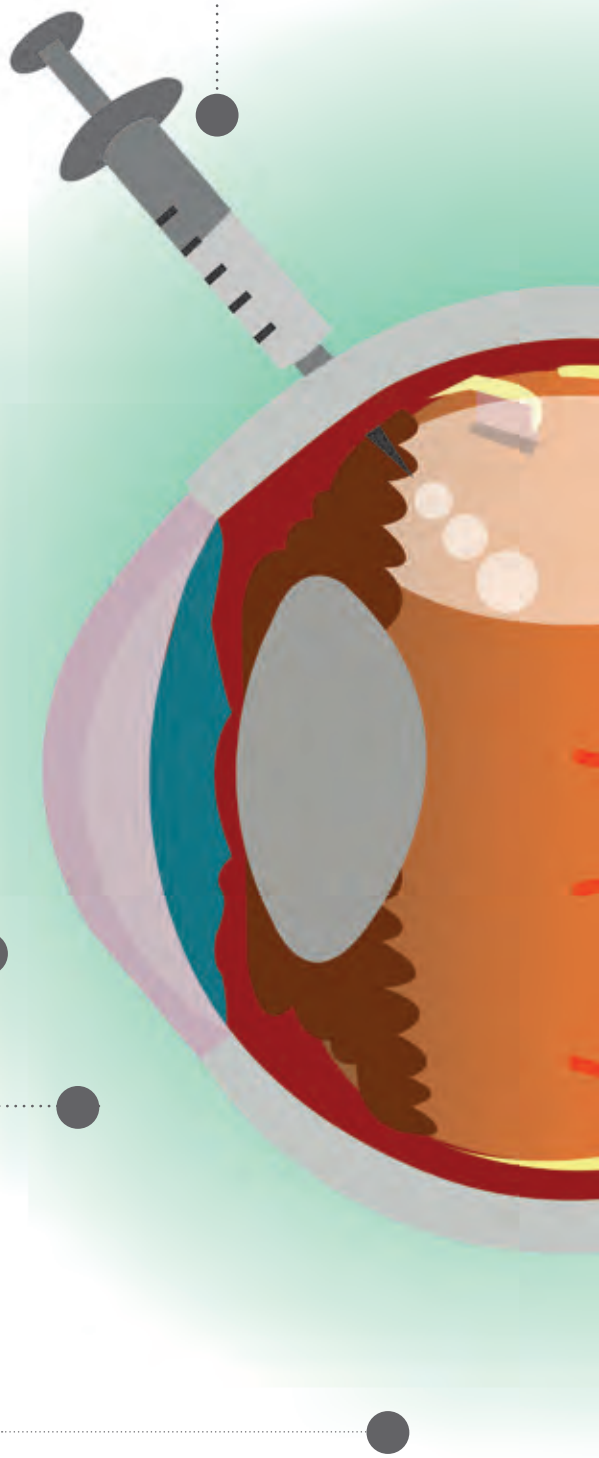
# PR – 10 Steps to Success

*1. Pick the right patient*

- With PR, the patient is your cosurgeon, and you need to make sure they have the physical and mental capacity to perform postop positioning.

*2. Pick the right eye*

- Make every effort to assess the vitreoretinal interface, find all the breaks and regions of subretinal fluid accumulation (a three mirror lens may help), note lens status and chamber depth.
- Multiple breaks or extensive lattice degeneration suggest an abnormal vitreoretinal interface. If the fellow eye has a giant tear, PR might not be a good idea.
- Ideally, the break should not extend below the horizontal.



*3. Pre-op prep and anesthesia*

- Subconjunctival anesthesia is usually adequate, and I do all the procedures in my office.

*4. Immediate cryo vs. deferred laser*

- Avoid excessive cryotherapy.
- If the break is highly elevated, inject the gas, position the patient, and apply laser the next day.

*5. Paracentesis*

- Perform a paracentesis prior to gas injection, with a 30 G needle on a plungerless syringe. This helps avoid issues like hard eye, pain, iris incarceration, arterial occlusion and displacement of the bubble into the anterior chamber.

*6. Gas selection*

- Use a half cc of 100% SF6, but consider C3F8 if the eye is large, the break is posterior, or if multiple breaks are present.

*7. Injection technique*

- I inject using a one cc syringe with a 32 G needle, with the exact amount of gas I plan to inject preloaded in the barrel of the syringe.
- With the patient supine, I inject the gas into the superior temporal quadrant, away from large breaks.
- The injection is made perpendicular to the eye wall, and the needle is inserted about 4 mm into the eye.
- To avoid subretinal gas, never inject inferiorly.

*8. Steamroller*

- The streamroller maneuver is used to debulk subretinal fluid, by rolling the bubble towards the break, pushing subretinal fluid back into the vitreous cavity.
- It is performed to prevent displacement of subretinal fluid into the detached macula, or into flat inferior breaks.

*10. Postop care*

- I prescribe a steroid-antibiotic combination for five days, and I position as much as the patient can tolerate for the first 24 hours – and I always see the patient the next day.
- Inferior subretinal fluid not involving the macula may be managed conservatively, because in some cases it may take weeks to resolve.
- If the macula is still detached after a few days, the break is open or there is an unrecognized break, I usually go directly to vitrectomy – do not delay the rescue operation.
- In my experience if minimal cryo is used and the patient is reoperated upon promptly, failed cases do well.

*9. Positioning*

- Proper patient positioning is crucial to success.
- I use the Tornambe Pneumo Level (Escalon) on the patch to aid positioning.
- Some patients don't listen, so in these cases make sure a family member knows how to position the patient.

# Adding Another String to Your Bow

## How and why I started offering laser vitreolysis at my practice

*By Inder Paul Singh*

Around 30 percent of the general population have symptomatic floaters, yet the impact of this common visual phenomenon on patient quality of life remains grossly underestimated (1). Few cataract patients presenting with visual dysfunction, such as glare and poor night vision, are expected to tolerate and grow accustomed to their symptoms, yet this remains the standard response to patients with floaters who present with a similar level of debilitating visual impairment. This "wait and see" approach does not stem from a lack of effort from ophthalmic professionals – for most the treatment options really are wait-and-see or vitrectomy – and the latter procedure isn't without risk either (2). But there is a third option: laser vitreolysis. This procedure has been around for years, but perception was that the risks mostly outweighed the benefit of the procedure, and this rendered it a very niche offering. However, in recent years, significant technologic strides have taken laser vitreolysis from a potentially risky treatment option for floaters to a potentially very beneficial one instead.

*At a Glance*

- *Laser vitreolysis-based floater treatment has existed for years, but a number of issues – principally, suboptimal visualization of the vitreous – limited both their success and adoption rates*
- *Today's multimodal Nd:YAG lasers allow the entire vitreous to be clearly visualized and can pull "double duty" – standard procedures (like Nd:YAG capsulotomies) and laser vitreolysis too*
- *If you scratch the surface, there is a considerable volume of patients that want to have their floaters dealt with*
- *I share the story of how I added modern laser vitreolysis to my practice, and the lessons I learned along the way*

### Selecting the right patient

While almost everyone will be affected by floaters throughout their lifetime, in clinical practice, the focus is always on those with disabling floaters.

The type of floater that patients – both phakic and pseudophakic – present with most frequently is the Weiss ring (Figure 1a; Figure 2). As these are often located in the middle or posterior vitreous, they are easy to see and typically straightforward to treat, regardless of lens status – and eliminating them results in very satisfied patients even after a single treatment. I have found in my practice that younger patients – in their 30s, 40s and 50s – and postoperative cataract surgery patients more commonly present with amorphous clumps (Figure 1b). As large masses, these types of floaters have a significant impact on patients' daily lives, especially in patients who may rely on high levels of visual function to do their job. It is not entirely clear why postoperative cataract patients often complain of floaters, but it has been suggested that these patients may have a lower tolerance for floaters due to an expectation of perfect vision after surgery, or because they have a clearer media after lens replacement.

When considering laser vitreolysis for floater removal, I have found it essential to select the right patients – and there are three components to this. Firstly, I never treat a patient who doesn't have any visual complaints from their floaters. Secondly, I only perform the procedure on patients who have had symptoms without resolution for at least 4–6 months. Thirdly, I only treat floaters that I can clearly see, so it's important that the location, size and density of the floater can be visualized. If it's located close to the nerve, retina or phakic lens, and it doesn't move after asking the patient to look up, down, right and left, I tell the patient it's not safe to do the procedure. Instead, we wait until a future date to see if the floater has moved.

I also think it is essential to manage the patient's expectations of the procedure. An analysis carried out by my practice has shown that one laser session adequately dissolves a single Weiss ring in more than 90 percent of patients (3), but when the floater is a large amorphous clump that is very dense, it can take 2–3 sessions to achieve near 100 percent patient satisfaction. This is simply because the laser creates a small plasma reaction rather than a large explosion, so the 400–600 shots delivered in a single session may only get rid of 50 or 60 percent of a very large dense clump. Alternatively it may break the large floater into smaller pieces that become troublesome a few months down the line. It is therefore important to advise all patients with a large amorphous clump on preoperative examination that they are likely to need a second or third treatment session.

Also key to setting patient expectations is "painting a clear picture" of how the procedure is performed. Many patients hear the words "laser treatment" and envisage a long, painful procedure with a convoluted aftercare regime. I make sure all of my patients understand that floater removal is an in-office procedure that takes on average less than 10 minutes, and has no post-operative recovery

period, pain, patches or eye drops. I have found that explaining the procedure to my patients helps them realize it really is a minimally invasive procedure that lets them go about their daily life straight away, and this decreases their apprehension and makes them feel more comfortable.

### Targeting floaters

To date, I've performed over 1,400 laser vitreolysis procedures and have found clear retinal visualization imperative for safe and successful floater removal, as a surgeon needs to be able to see where the retina is to obtain much-needed spatial context. In my practice, I use a multimodal Nd:YAG laser (Figure 3), and although this works just like a standard Nd:YAG laser, it is more suitable for safe and effective floater destruction because the aiming beam, laser and light source in the slit lamp visualization tower are all coaxial – something that ensures its user can view floaters in the middle of the vitreous and posterior segment, all the way to the retina. In comparison, standard Nd:YAG lasers may only visualize vitreous behind the posterior capsule, meaning they cannot effectively target floaters (as these mostly reside between the middle and posterior vitreous). Other benefits of a multimodal Nd:YAG laser for vitreolysis include the ability to visualize anterior floaters (which is crucial in phakic patients to ensure that the lens is not "hit") and improved safety over standard Nd:YAG lasers. This is because standard Nd:YAG lasers have energy beam profiles that follow a Gaussian curve, whereas the newer laser that I use has a truncated 3 ns energy beam, which improves efficiency by decreasing the amount of energy dispersion in the eye, meaning lower energy laser beams can be used to vaporize floaters. The nonlinear relationship between energy on the laser and amount of energy dispersed in the eye also means that we can increase the energy level of the laser and not worry about too much energy in the eye – for instance, a change in energy level from 1 mJ to 5 mJ only increases the convergence zone from 110 to 115 µm.

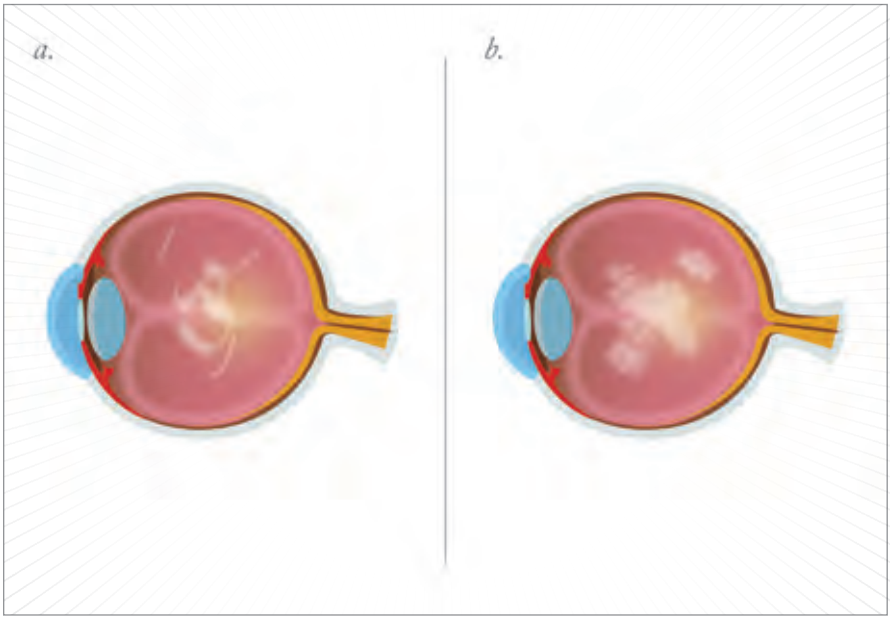


Figure 1. Schematic diagrams depicting a Weiss ring (a) and an amorphous clump (b).

Performing laser vitreolysis with a multimodal Nd:YAG laser is very similar to performing laser peripheral iridotomies and capsulotomies with a standard laser, where a lens, viscoelastic agent, topical anesthetic and preoperative dilation are all required. The only real difference between the conventional procedures and laser vitreolysis is understanding the visualization through the laser and lens, and this can involve a little acclimatization. The most effective way of getting used to this type of visualization (just as with any other procedure) is simply to practice. It can take up to 20 cases to feel really comfortable with going up to higher energies and visualizing the floaters. My advice to those who are new to the procedure is that it all begins with the retina. If you view the vitreous and notice that both the floater and the retina are in focus, you're too close to the retina. If the floater is in focus but the retina isn't, you can feel confident that you have enough spatial context to fire the laser without damaging the retina. Viewing the floater through the vitreolysis lens during the preoperative exam can also allow the surgeon to get used to what it looks like before beginning the procedure. Another tip for visualizing floaters is to use a higher level of magnification. While I use around 10x magnification for capsulotomies, I go up to 16x magnification with vitreolysis lenses because this provides the best view of both the retina and the floater, and ensures sufficient spatial context to confidently and safely vaporize the floater.

### Growing your practice with a multiuse laser

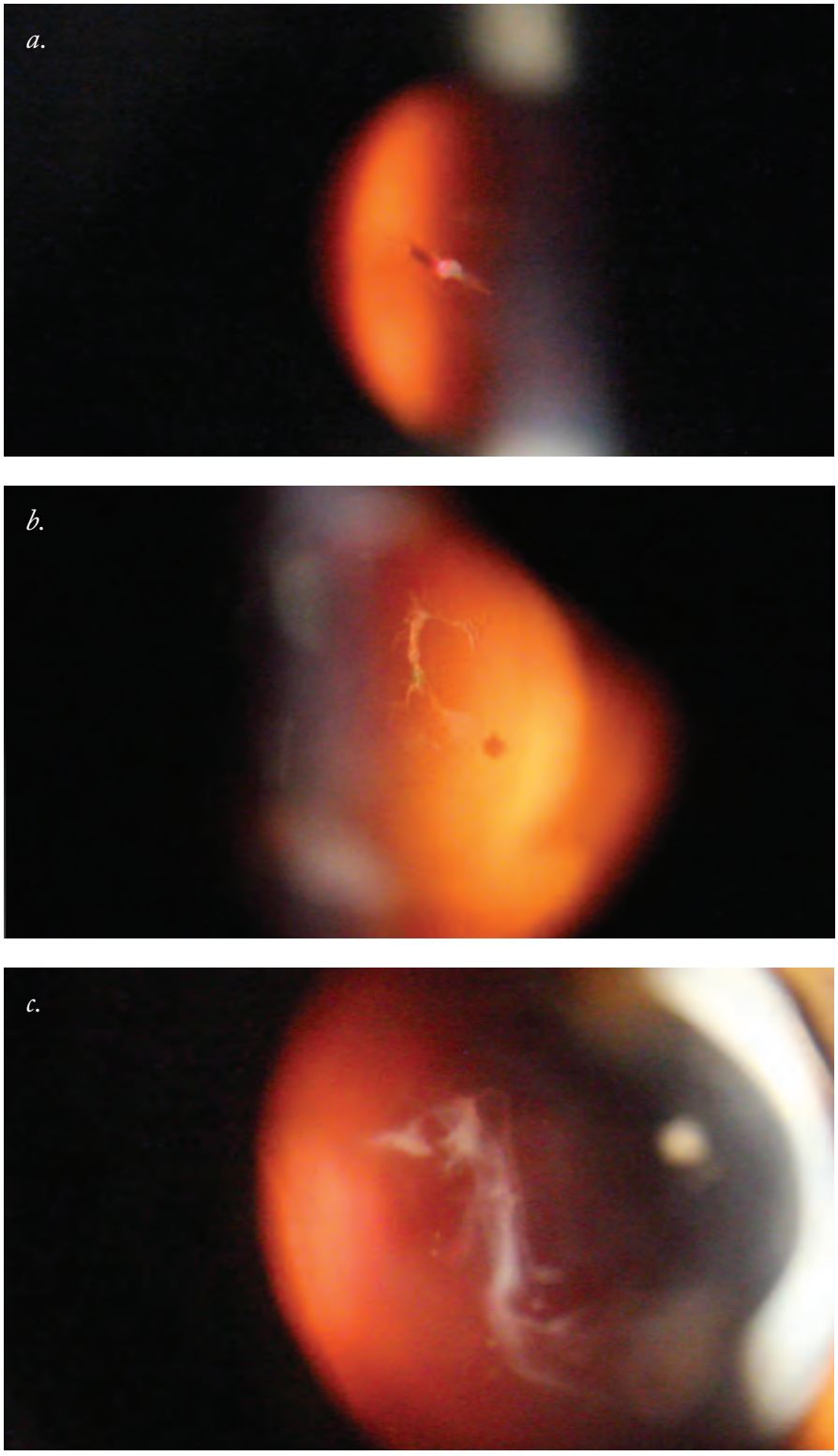
Introducing a multimodal Nd:YAG laser into my ophthalmology practice three years ago has proven immensely beneficial, not only in terms of profitability, but also for staff morale, patient satisfaction and the overall

reputation of the practice. As a single device that can be used for all Nd:YAG laser-based eye procedures, as well as laser vitreolysis, it has provided a new stream of patients and revenue to our practice. While several sources for obtaining this new stream of patients exist, local optometrists and ophthalmologists are an invaluable source, particularly when you are just starting out.

Using a multi-pronged approach is ideal for maximizing the impression your clinic makes on such referrers. When I treat a patient who also sees an optometrist, I always encourage them to go back and let their optometrist know how happy they are with their results and how easy they found the process. I do the same thing for primary care physicians. Happy patients are the best testament of the efficacy of the procedure and if they return to their optometrists and ophthalmologists full of praise for laser vitreolysis, that puts a practice in a great position to receive future referrals from these local sources.

Secondly, when I first started to offer the procedure I held a few seminars to help educate local optometrists on floater removal with laser vitreolysis. These were structured as continuing education (CE) credit lectures, in which I shared procedure videos, patient testimonials, and addressed questions and misconceptions about the procedure. This was in addition to sending out email-based newsletters and distributing pamphlets to the area's optometrists to further educate. Adopting these types of strategies as well as encouraging patients to be vocal about their results and satisfaction have proven to be really effective at driving referrals. We also wrote articles for local newspapers informing the public of this procedure that were also published online.

It is also important to realize that a sizeable amount of target patients may already exist within your patient




Credit: Inder Paul Singh.

Figure 2. Weiss ring floaters viewed on axis (a, b) and a large floater viewed on partial axis (c).

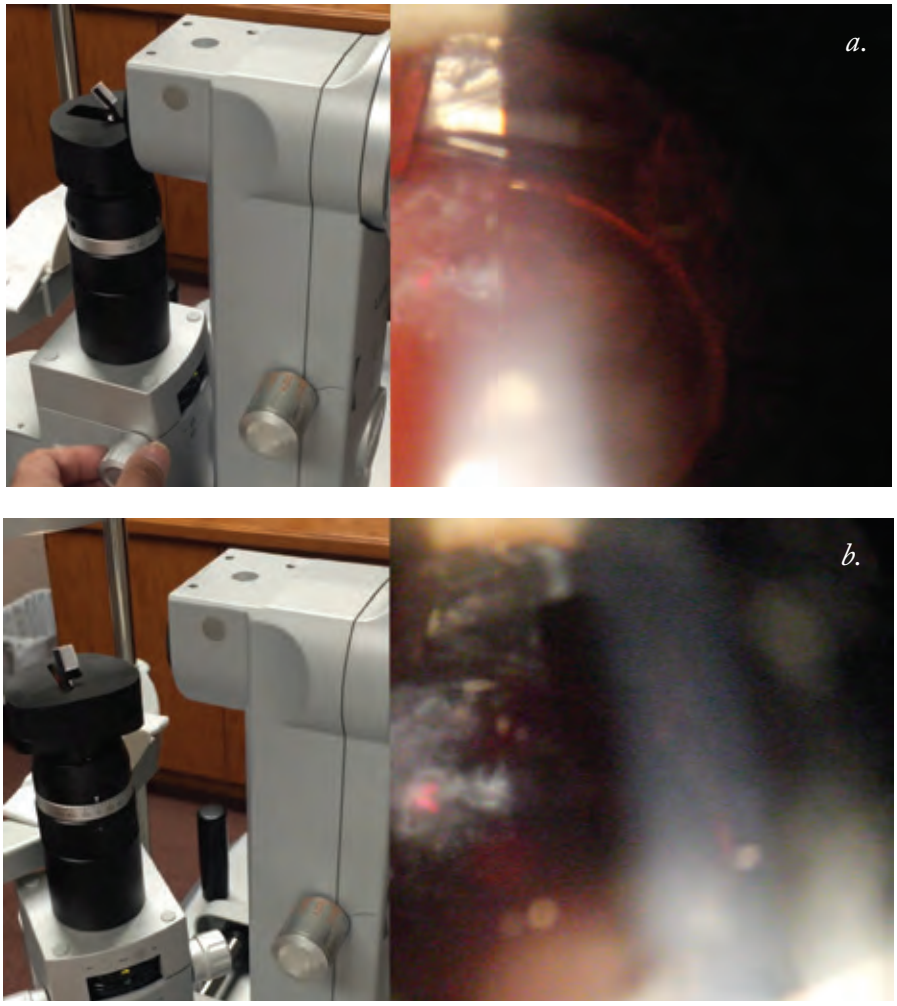



Figure 3. The Nd:YAG multimodal laser in use and the view through vitreolysis lens showing the laser targeting of floaters in a patient's eye.

database. I relied on educating my own staff to generate those first few patients because I realized a lot of the patients who stood to benefit from floater removal were already in our practice. However, as these patients with disabling floaters had spent years being told that nothing could be done about their floaters, they had conditioned themselves to never tell their eye doctor about them. It was therefore important to encourage my staff to start letting existing patients know that something could now be done for them, and for me to do the same. Indeed, the first 100–200 patients I treated were from my own practice database. If I spotted floaters during an examination, I simply started asking patients if the floaters bothered them. I was amazed at how often their eyes lit up and they said: "You mean you can remove them? Really? Let's go for it!"

## Destined for great things

I truly believe that laser vitreolysis with multimodal Nd:YAG lasers is set to become a popular procedure within ophthalmology practices. The key thing to understand is that today's laser vitreolysis is not the same procedure as that of the past. Some doctors may be apprehensive because they've heard about low success rates, but this relates to old technology. It's analogous to cataract surgery: the outcomes achieved by cataract surgery from 30 years ago quite simply do not compare what is achieved, as a matter of routine, today. The difference in efficacy and safety is staggering, and that's because of the advances in the technology used. It's the same principle with laser vitreolysis, in that multimodal Nd:YAG lasers deliver results that are worlds apart from those achieved years ago, and evidence of this can be seen by the number of satisfied patients who receive the procedure. A retrospective observational study performed within my practice involved 296 eyes of 198 patients with floaters (aged 38–89 years) and revealed a 93 percent satisfaction rate following laser vitreolysis (3).

It is clear to me that laser vitreolysis is set to become a popular procedure in ophthalmology practices and given the impact of symptomatic floaters on daily life, I am confident this change is one that will be greatly welcomed by affected patients.

*Inder Paul Singh is President of The Eye Centers of Racine & Kenosha, Wisconsin, USA.*

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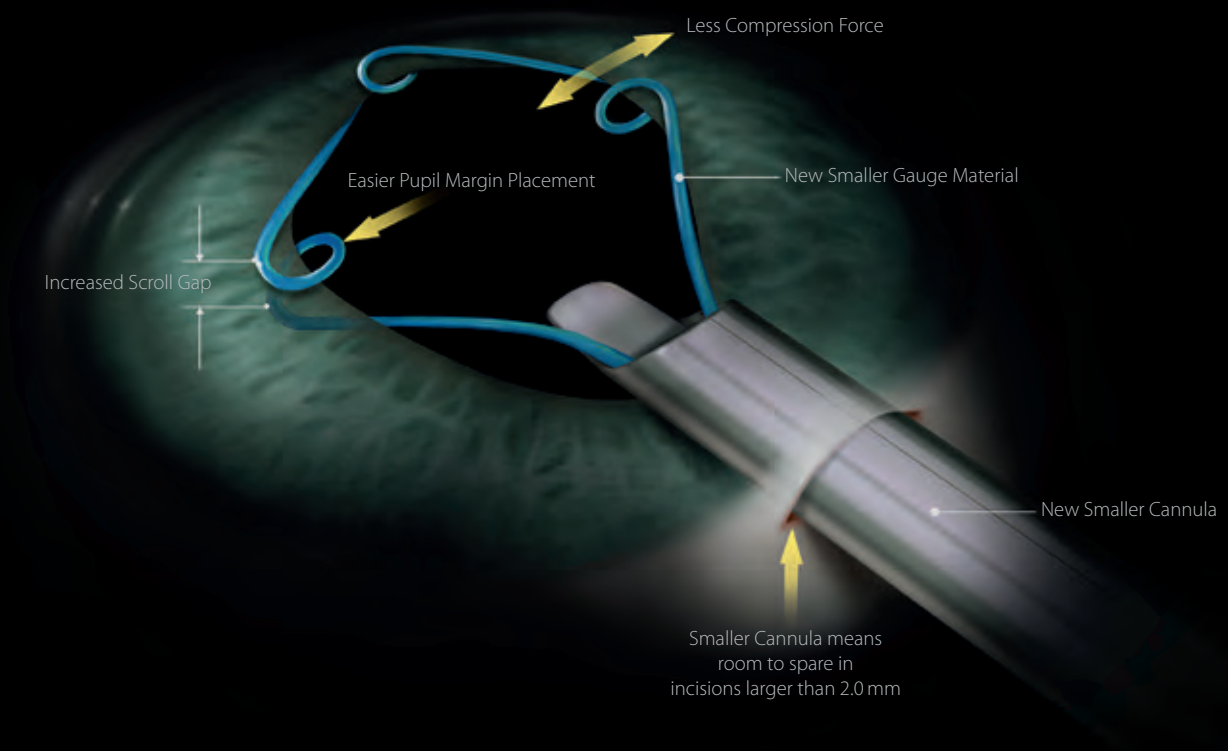
# Introducing Malyugin Ring 2.0

## Nothing's Changed... Except For Everything




When contemplating what the next version of the Malyugin Ring should provide surgeons and their patients, we established three goals:

1. Provide the same or better safety as surgeons have experienced and has made the Malyugin Ring "classic" the standard of care for pupil management.

2. Make it easier to place and remove from the pupil margin.

3. Allow for entry in 2.0mm incisions and more room in wounds larger than that.

After several years of work, we are proud to introduce the Malyugin Ring 2.0. The second generation of the Malyugin Ring that also can be used in 2.0mm incisions.

Mayugin Ring 2.0 requires no surgical technique changes for you, and we believe that you will find it easier to use, that you will appreciate the extra room it affords, and be glad to know that it has softer compression characteristics (in fact Malyugin Ring 2.0 exerts less than half as much pressure on the iris than the "classic" Malyugin Ring).

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# NextGen

*Research advances*
*Experimental treatments*
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# Shock Treatment

## Can electrostimulation of the ciliary muscle delay the loss of accommodation experienced in early presbyopia?

*By Luca Gualdi*

Old age brings with it an ocular inevitability: presbyopia. Everyone becomes presbyopic to some degree as they age. Today, it can be dealt with non-surgically with spectacle or contact lens use, or surgically with procedures like clear lens exchange, corneal inlay implantation, and a number of laser refractive approaches. But another strategy for correcting presbyopia is under development – electrostimulation therapy to restore the accommodation of the lens and the ciliary body.

### Swimming against the current?

Electrostimulation of the eye isn't a new concept – previous studies have explored its applications in glaucoma, retinal dystrophy, AMD, and progressive myopia, and it's garnered some positive results with few reported side effects (1–3). However, this isn't a popular area of research – a search using the terms "electrostimulation" AND "eye" in PubMed produces only 25 results.

Presbyopia is caused by two factors – as people age, their ciliary muscles progressively weaken, and their crystalline lenses start to lose elasticity. Resorting to near-vision glasses only weakens the ciliary muscle further (as it starts to become "lazy"), meaning that people become increasingly dependent on those spectacles with time. But what if we could give the ciliary muscle a workout? We propose that electrostimulation can be used to restore the loss of accommodation experienced by patients with early presbyopia – and we set out to study the efficacy of micro-electrostimulation of the ciliary body as a noninvasive presbyopia treatment.

*"We propose that electrostimulation can be used to restore the loss of accommodation experienced by patients with early presbyopia."*

We enrolled people aged between 40 and 50 years, who had early presbyopia no greater than +1.50 D, and were either emmetropes or low hyperopes. We excluded pseudophakes and those with any ocular pathologies or neuropathies, those on medications that could influence the accommodative response, and people with demyelinating or vascular diseases that might affect the ocular influx to the ciliary body. People with cardiac pacemakers or who were affected by epilepsy were also excluded.


Figure 1. Components of the electrostimulator kit (CE 0051) including a contact lens, syringe, and current generator.

### A ciliary body workout

The medical device we use to carry out this procedure is CE marked, and comprises a contact lens, a syringe (which can be used for suction, but which is optional), a cable, and a generator that supplies a square wave biphasic compensated micro-continuous electrical current (Figure 1). The current induces passive exercise of the ciliary body by generating a rhythmic, low-voltage, contraction and relaxation of the ciliary

### *At a Glance*

- *There are a number of options for the treatment of presbyopia, which range from spectacle/ contact lens use, to multifocal intraocular lens or corneal inlay implantation*
- *Electrostimulation of the ciliary body might be the latest (nonsurgical) addition to that list*
- *An initial trial found that the procedure was not painful, had no apparent side effects, and appeared to positively impact presbyopia*
- *It turns out that demonstrating improvements in accommodation is technically challenging – but was achieved by combining anatomical, subjective and objective data*

Figure 2. The contact lens 20 mm-diameter rigid scleral lens is connected to four 3 mm electrodes, which are in turn directly connected to the electrostimulating device.

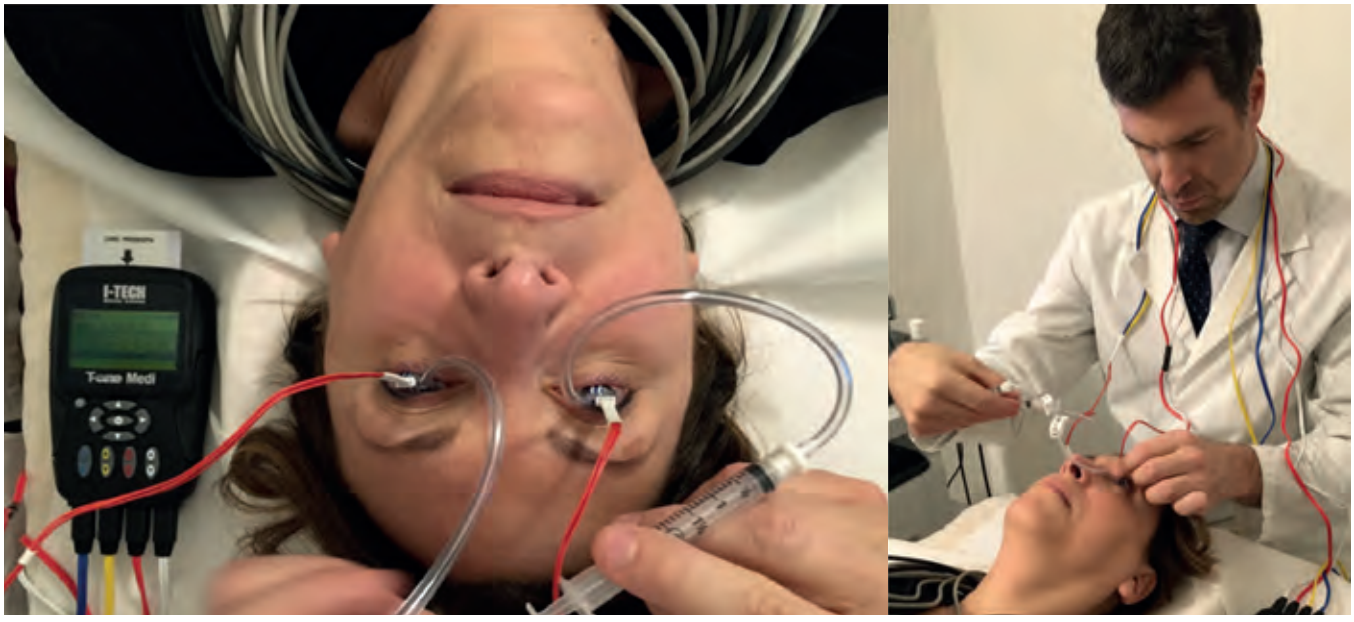


Figure 3. Bilateral electrostimulation using the device.

muscle. During the treatment there is also a rhythmic contraction of the pupillary muscles, which alternate between miosis and mydriasis – the "workout."

The contact lens we use is a 20 mm-diameter rigid polycarbonate scleral lens (Figure 2). The internal side is placed in contact with the bulbar conjunctiva – but makes no contact with the cornea. Four 3 mm electrodes are connected to the core of the contact lens, which are in turn directly connected to the electrostimulator device.

An anesthetic drop is used before the treatment begins; during stimulation, the patient may feel a small tingling effect on the lids or in the whole eye, but this has not been reported to be painful. The procedure can be performed bilaterally (Figure 3), but when used for the first time, it is better to do only one eye. This is partly because the cables that connect the lens to the device are soft, and if the suction is not correct (which can happen, particularly during the learning curve) they may move, reducing the effect of the treatment and potentially even damaging the corneal epithelium in extreme cases. It also means the patient cannot use their other eye to keep their pupils centered. A speculum can also be used if necessary, which can be helpful to visually ensure that the electrodes are in the ciliary body region, about 3.5 mm from the corneal limbus. After eight minutes of stimulation, the contact lens can be removed (taking care to avoid touching the corneal epithelium), completing the treatment. As the procedure is, in many ways, similar to the application of contact lenses, it should not need to be performed in an operating theater.

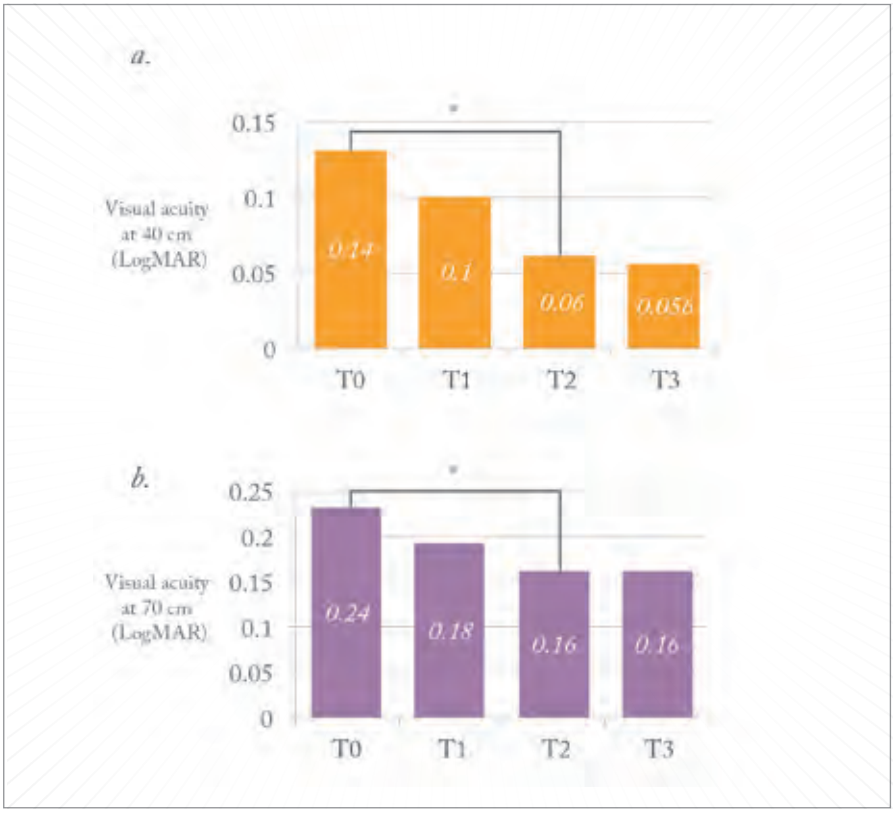


Figure 4. Mean visual acuity (LogMAR) at baseline (T0), treatment 1 (T1), treatment 2 (T2) and treatment 3 (T3) at 40 cm (a) and 70 cm (b). *T2 vs. T0, $p<0.05$ (Student's t-test).

## Objective challenges

Our initial results were very encouraging, with all the participating subjects showing improvement in accommodation. Using a Jaeger chart, we saw an increase of almost one character – and increases of around one character were also observed using a LogMAR chart at near (40 cm) and intermediate (70 cm) distance (Figure 4). Reading speed also showed improvement – reading times dropped (Figure 5), and more words could be read per minute. Reading from a LogMAR chart in dim light conditions was also improved with treatment (Figure 5). We also measured subjective accommodation amplitude using the Duane test, and found that, on average, patients were able to focus 6 cm closer than before treatment.

As the treatment is based on a passive induction of a stimulus, the exercise, like any stimulation of a muscle, must be repeated to maintain the effect. Based on our early results, we would suggest an "attack dose" of four treatments within two months (one every 10–15 days), and afterwards, to maintain the effect, one treatment every three months – but the frequency of treatments can be customized to the patient's requirements.

We had our initial results and some positive feedback, but we faced a challenge. How could we demonstrate the effects of the device objectively? This proved difficult – we struggled to find an instrument that could accurately and reproducibly measure the accommodation of the eye. Following a review of the literature, we decided to use ultrasound biomicroscopy (UBM) to study accommodation pre- and post-stimulation, as it allows for visualization of structures in the posterior chamber, and can be used to study the changes that occur during accommodation (see Figure 6). After stimulation, we collected all of this data and found that there was an increase in crystalline lens thickness, a decrease in posterior ray of curvature, and a dramatic decrease in anterior ray of curvature – this translated into a reduction in total spherical aberration. We also examined internal spherical aberration (which is mainly the aberration induced by the lens) and saw a reduction of longitudinal spherical aberration too.

*"How could we demonstrate the effects of the device objectively?"*

So far, we have compared our anatomical data to both our subjective and objective data, with good results: every significant improvement we saw in patients using subjective data (such as LogMAR and reading speed) corresponded with an improvement in UBM and aberrometry data. We have presented our initial findings at several congresses (4–6) and now plan to submit our work for publication in a peer-reviewed journal.

## Optimization and IOP

When it comes to refractive surgery, choosing the right treatment for a 40 to 50 year-old presbyope can be difficult – and some treatments are more invasive and more permanent than others. Electrostimulation of the ciliary body may provide a new, nonsurgical option to help delay the development of early presbyopia. Through follow up and

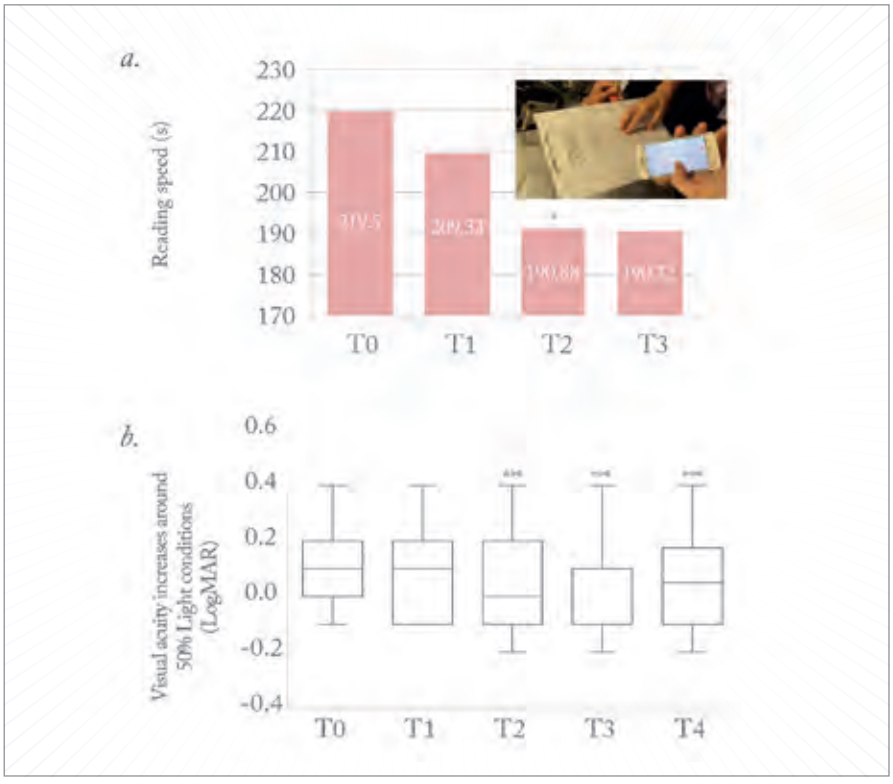


Figure 5. Mean reading speed time (seconds) using MNREAD charts (a) and visual acuity in dim light conditions (b) at baseline (T0), treatment 1 (T1), treatment 2 (T2) and treatment 3 (T3). *T2 vs. T0, p<0.05; *** p<0.001 vs. T0.

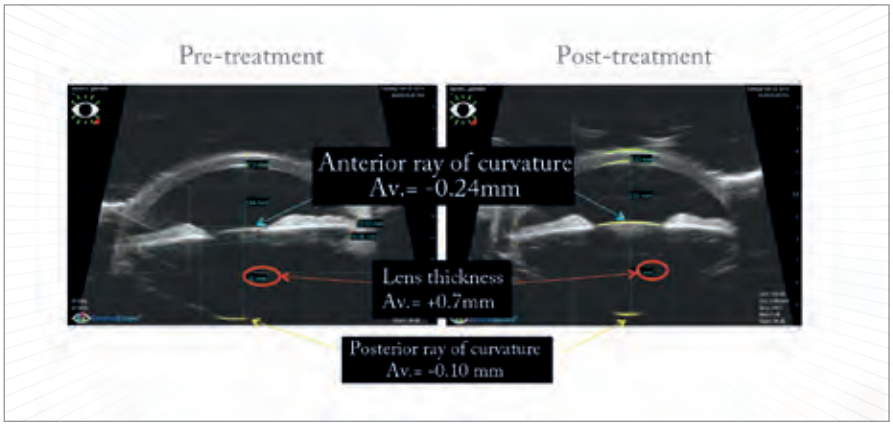


Figure 6. Ultrasound biomicroscopy images (taken under accommodation), obtained pre- and post-stimulation.

further study, we hope to confirm the effects we have observed with our electrostimulation approach to date. We also hope to upgrade and optimize our methods (in particular, our stimulation parameters and patterns) in order to try to achieve even better results, both in patients with presbyopia and even in other disease states, such as glaucoma, as previous work has shown that ciliary muscle stimulation can also positively effect IOP (7). In any event, exploring the potential of electrostimulation in ophthalmology could lead to some electrifying advances!

*To see a video of the technique, head online to our YouTube channel: http://top.txp.to/LG-ciliary-muscle*

*Luca Gualdi is a surgeon at the DOMA Eye Clinic, Rome, which specializes in ocular diagnostics, cataract and refractive surgery, and the treatment of keratoconus.*

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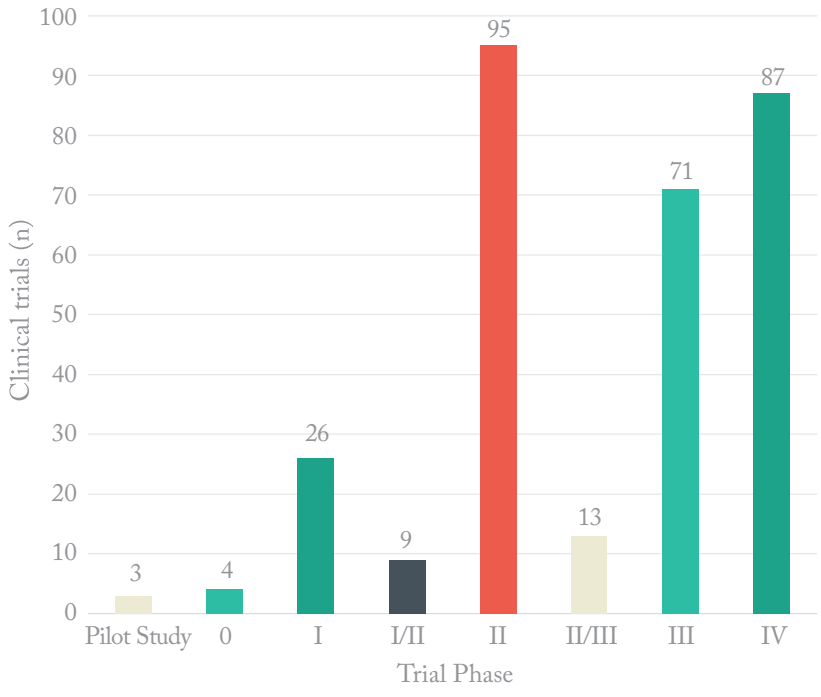
# Dry Eye Clinical Trials

*By Ruth Steer*

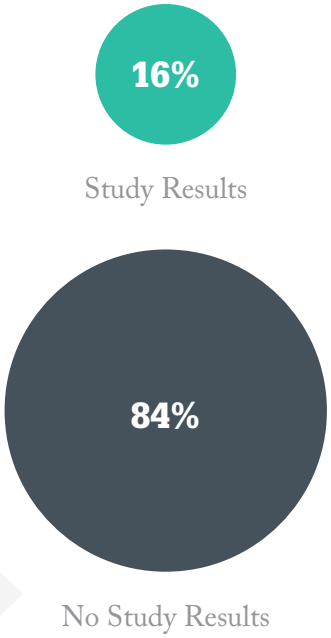
It's estimated that there are nearly 100 million people worldwide who have some form of dry eye disease (DED) – and that between 10 and 30 percent of patients aged over 50 years have this disorder. However, most people with DED go undiagnosed, and for those who do receive a diagnosis, the most commonly offered treatment is artificial tears. Diagnosis can be challenging – in some, signs fail to match the symptoms, and in others, symptoms fail to match the signs, and this is partly why it's one of the most underdiagnosed eye conditions in the world today. Dry eye symptoms can be the result of many disorders – meibomian gland dysfunction, tear fluid insufficiency, allergy, LASIK, and many autoimmune diseases, in addition to being a side effect of many commonly prescribed drugs – and it's a market that's potentially one of the largest in eyecare. To find out where the clinical research into dry eye has been focused, and where ongoing clinical trials might take the field, we performed an analysis of dry eye clinical trials on clinicaltrials.gov.

We searched clinicaltrials.gov for: "dry eye," "Meibomian" and "Sjögren," and analyzed the data in Microsoft Excel 2013. Inappropriate records were excluded, and the full text of each record examined for additional details to be recorded into the spreadsheet.

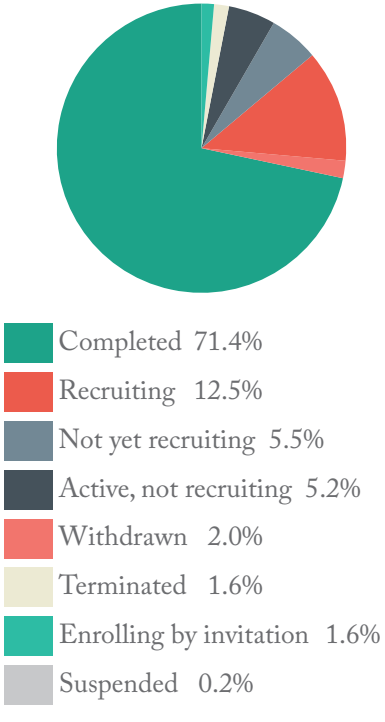
## Trial Phase




## Dissemination of Results




## Trial Status

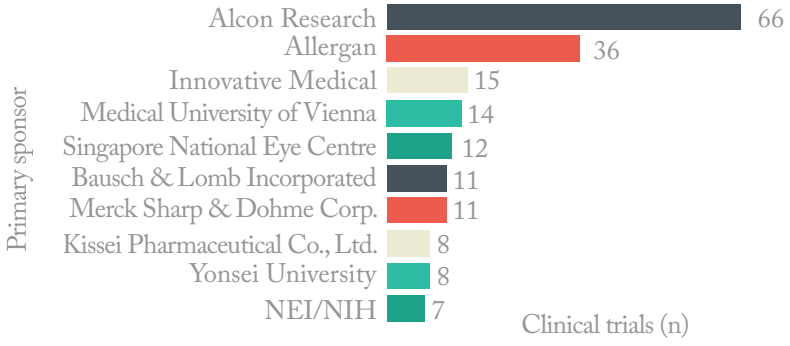


## Funding Source

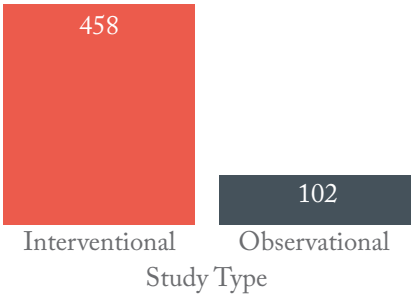
| 301 | 170 | 58 | 14 | 6 | 4 |
|---|---|---|---|---|---|
| Industry | Other | Other, Industry | NIH | Industry, Other | Other, NIH |

| 2 | 1 | 1 | 1 | 1 | 1 |
|---|---|---|---|---|---|
| U.S. Fed, NIH | U.S. Fed, Industry | U.S. Fed | NIH, Industry | U.S. Fed, Other | NIH, Other |

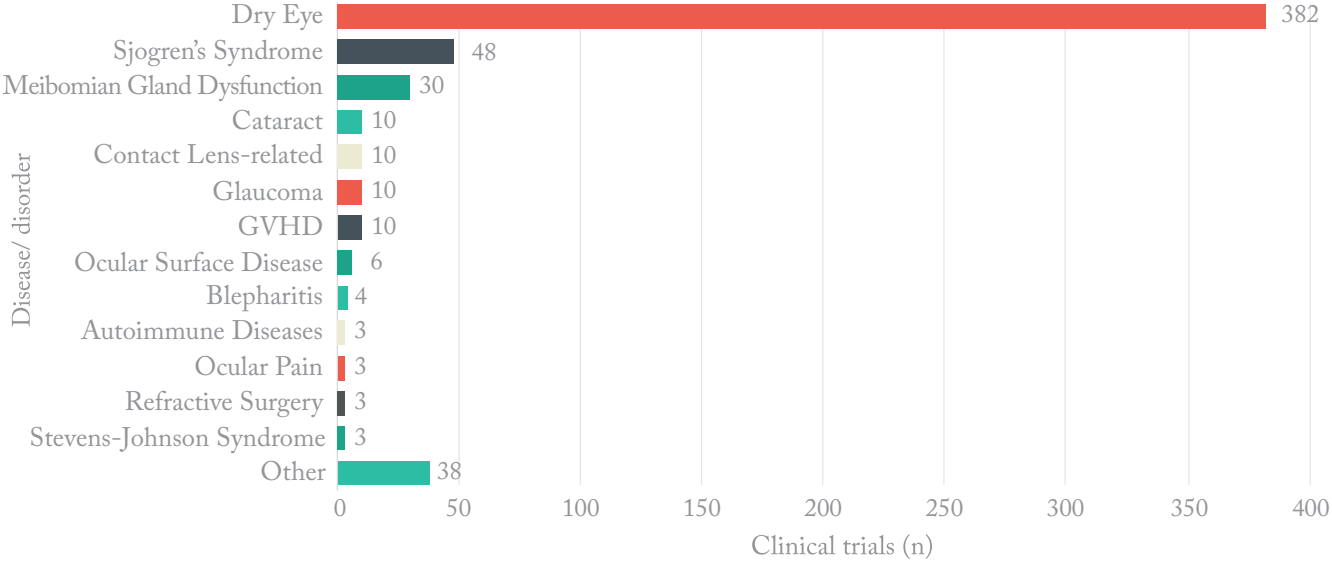
## Principal Sponsor

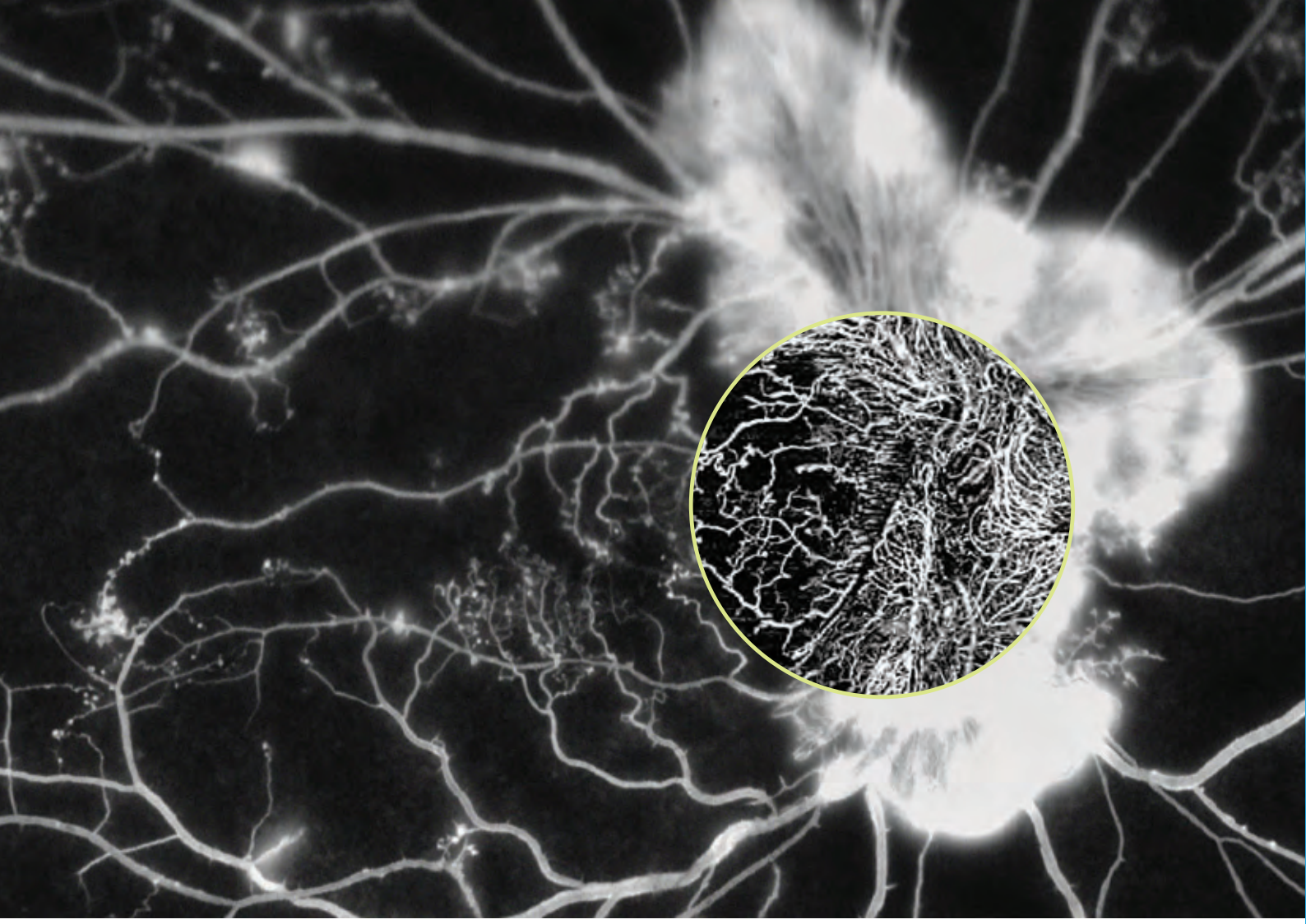



## Interventional or Observational?




## Disease/ Disorder Focus





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# Profession

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# Taking Control

## Managing your online reputation is key, but what about your offline reputation?

*By Robert Melendez*

I used to be a very private person when it came to social media. But when I was studying for my MBA, this changed. My professors and classmates told me things like "If you are out of sight, you are out of mind," and "People aren't going to be thinking of you when it is time to be invited to a presentation or lecture – you need to have some presence and build some networks." It was around this topic of networking, and its importance, that my interest in managing online reputation began. The first thing I did was join LinkedIn. I then joined Facebook briefly, before immediately shutting it off as I thought there was too much drama for what I wanted. But I then started to see the value of it, both professionally and personally. You have to control your professional reputation, because if you don't control it, somebody else will.

*At a Glance*

- *More and more patients are turning to the internet to search for physicians to fulfill their health and eyecare needs*
- *In a highly competitive field, managing your online reputation is crucial, particularly in today's era of social media*
- *The best way to do this is to take control of the information available online about you by maintaining a professional presence online*
- *I share my tips, and explain how managing your online reputation actually starts with your offline reputation*

### The value of online reputation

Over the past several years I have had more and more patients tell me they found me online. And as patients increasingly turn to the internet to search for physicians, it is becoming key that you have a strong online persona – there is a lot of importance in branding yourself and your practice. To do this, you need to take control of your online reputation, so that when patients Google your name, you will be in control of at least part of the information that they see – and this will dilute anything negative that may be out there too.

Most people that I speak to about this say "I know I need to do it, I just don't know how to get started." This shouldn't stop them. There's plenty of help out there: in publications, in the friendly advice of other physicians, and in companies who are geared up to help with exactly this sort of thing. But whilst many see the value of online reputation, a frequent response I have heard is "I will never join social media." And why is this? Because of the fear of negative comments. In my opinion, you should welcome all comments, as it is an opportunity to make things better. As an ophthalmologist, you have to be willing to expand your horizons and try to improve, even if you feel like you have something perfected. There is always room for improvement, even if it is just a little bit, so you should never shy away. Receiving negative feedback online also allows you to respond and potentially resolve any issues. Honestly evaluate and ask yourself "How am I doing?" It could be that maybe your wait times are too long, but acknowledging it, evaluating it, and sharing it with the public – as opposed to hiding it – means you're only going to come out on top. If responding to negative feedback makes you uncomfortable, then you should wait until you feel more comfortable before responding appropriately.

### Taking control

I think that all ophthalmologists should have a professional presence online, and for this, I would recommend creating a "killer" website and a professional Facebook page.

> *"You have to control your professional reputation, because if you don't control it, somebody else will."*

There are numerous benefits to having a professional Facebook page. As well as using it for patient education and awareness, patients can learn as much about you as you wish to disclose. For instance, you can highlight attending at a conference – which shows patients that you are committed to learning and advancing your career. Additionally, setting up a page is free, you can put as much information on as you would like, and the user-friendly aspect means developing and updating the content is fully in your (or your staff's) control.

Slightly less in your control are the numerous physician review sites which are out there, the two most common in the US being HealthGrades and Vitals. To see what your potential patients are seeing, I would recommend that you find and read your reviews on these sites. Search for all names you may go by – not just the medical name on your diploma – and believe me, you will be

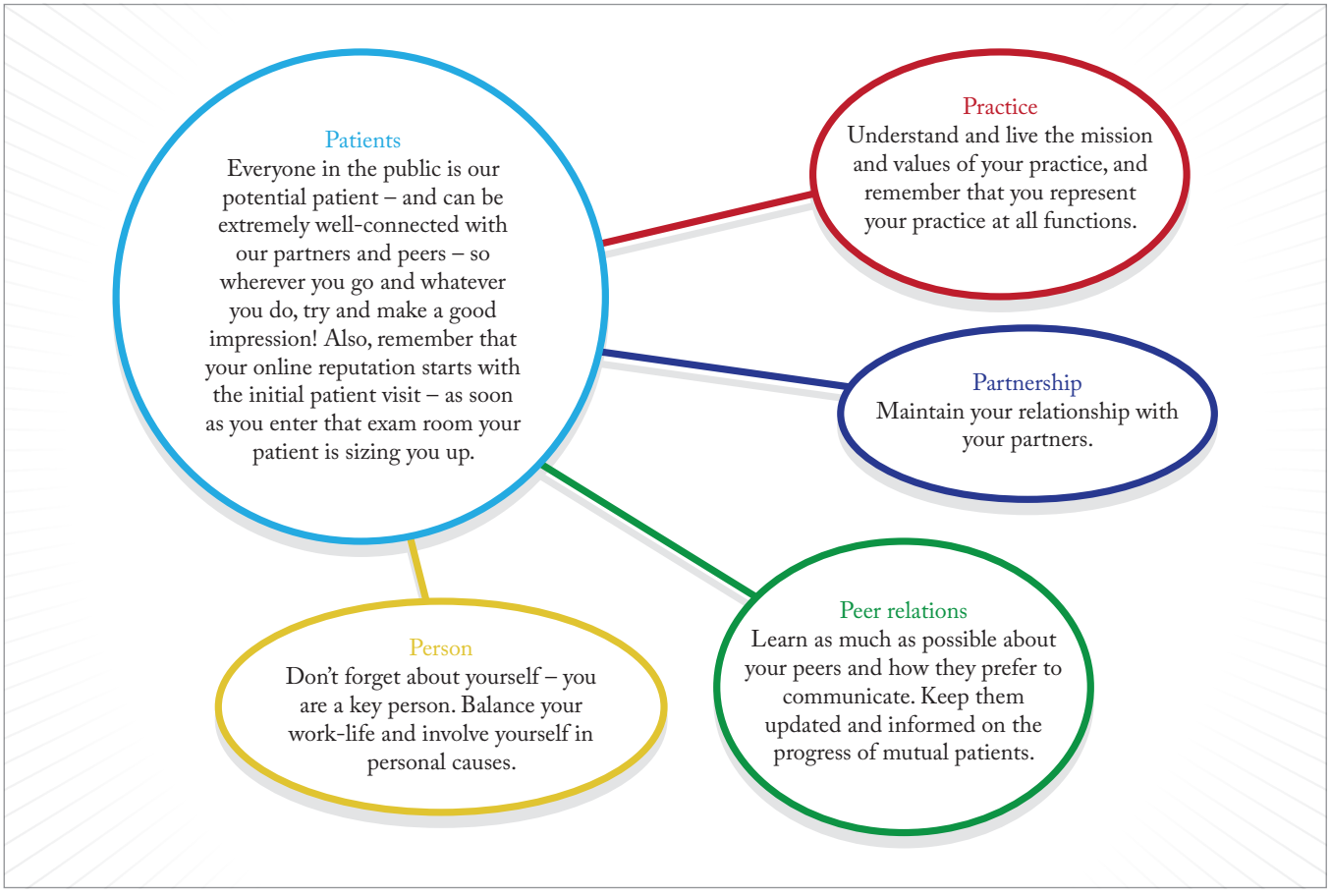


Figure 1. Managing your reputation with the public and The Five Ps.

surprised what comes up on the first few pages of Google. When doing this, it is important to remember that you are seeing what patients are seeing, and if you don't like what you see, take control! We have the power to ensure that the information about us on these sites is correct, so register your name on HealthGrades, vitals etc., upload a professionally-taken photo of yourself and correct any potential errors which may be on those pages. I would also strongly recommend registering your practice on Google – not only does this direct patients to an official website, registration is free (1).

## It all starts offline

Over the past seven years since becoming interested in social media, I have been intrigued by how it has developed. But managing your online reputation is not as simple as maintaining an impressive social media presence – it actually starts with your offline reputation. And if you're not doing a good job offline, you're not going to succeed no matter how many brilliant marketers you hire to make you look good online. A few years ago, I came up with something I like to call "The Five Ps" that focuses on areas where you can actively manage your reputation (Figure 1). Patients are central to this, as your reputation starts with the initial visit, and continues at every point of patient contact with yourself, your practice, your partners and your peers in the community. Remember that word of mouth is "king" – a happy patient may tell three people about their positive experience, but an unhappy patient may tell 10 about their dissatisfaction, and with social media, this effect is only amplified.

*Robert Melendez is a comprehensive ophthalmologist and partner at Eye Associates of New Mexico and an assistant clinical professor in the Department of Surgery/Division of Ophthalmology at the University of New Mexico in Albuquerque. He is also executive director of The Juliette RP Vision Foundation.*

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# See the Bigger Picture

**Information sharing between eyecare professionals is far more difficult than it should be. How do we improve it?**

*By Dawn Sim*

It's an exciting time to be working in ophthalmology. Advances in imaging technology are revealing more about ocular disease, and the combination of "big data" and artificial intelligence strategies (such as Moorfields and Google DeepMind Health's recent collaboration) is set to transform the diagnosis and detection of disease from images of the eye. However, a crucial ingredient for the successful integration of these technical advances into the real world of clinical practice is the existence of platforms that accommodate them, and the foresight of building infrastructure to support these promising technologies. A natural starting point for this, I believe, will be in the field of teleophthalmology, which relies heavily on both acquiring images of the eye and an electronic means to review, report, and relay information to the patient. In an ideal setting, an image will be acquired in a place convenient to the patient and an artificial intelligence algorithm will read the scans and generate an instantaneous report for the patient. A remotely located expert in the relevant ophthalmic subspecialty could then validate this report, communicate health advice to the patient and/or advise the need for a face-to-face encounter or repeat scan. Arguably, this utopia is within our reach today, but understanding its barriers and identifying practical solutions will be key in realizing this in our day-to-day practice.

*At a Glance*

- *It's remarkable, that still today, patients resort to taking photos of OCT images and retina scans acquired by their optometrist to share with their ophthalmologist*
- *This is due to a lack of integrated systems that allow referrers to easily communicate with ophthalmologists*
- *What's needed is a system that's image platform-agnostic; a cloud-based solution that accepts multiple, standardized formats*
- *Such a system is about to be tested in the UK and the hope is that software like this will enhance collaborative care, improve the patient pathway and pave the way for new technologies*

## Learning lessons from radiology

In a typical workflow, a patient will see an optometrist or a general practitioner (GP) – or both – before being referred to an ophthalmologist. But as they move along their patient journey, it seems that no-one is sharing their eye images. Incompatible file formats and image management systems along that patient journey can mean that there is no easy way for ophthalmologists to quickly access high-quality image scans. Occasionally, referrals may come to an ophthalmologist with a poor quality image – often, as a black and white grainy printout, or a single snapshot of an OCT scan (as opposed to the 100 image volume scan of the macula), or worse, a smartphone photo of a scan acquired by the patient or a relative. These archaic methods of communication is not only insufficient for effective triage, it renders the pursuit of collaborative care or new technology adoption invalid. It also creates more work – if there's any ambiguity at all, you absolutely need to perform your own OCT scans and retinal photographs.

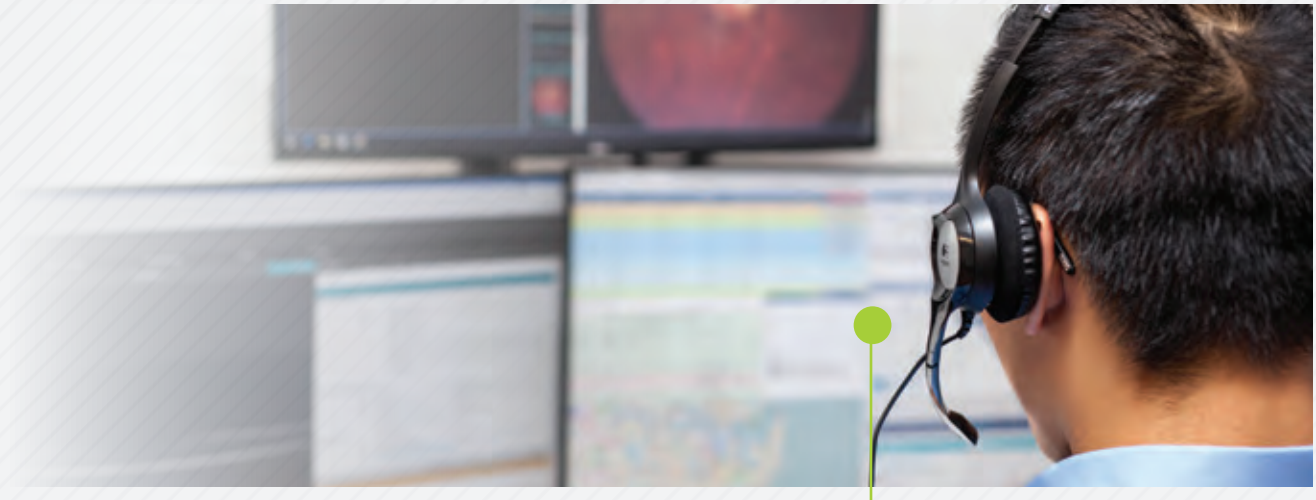
One of the main barriers holding us back is legacy technology. Something as simple as an OCT image cannot be read using the proprietary platforms provided by the different OCT manufacturers – and in many cases, the imaging data is encrypted! This is reminiscent of the situation that radiology was in more than 30 years ago; where radiologists using different imaging devices could not decode or share their images. However, the disruptive technology of computerized tomography (CT) and magnetic resonance imaging (MRI) scans that all but made single frame X-rays obsolete, proved a tipping point for the field. This era saw the development of Digital Imaging and Communications in Medicine (DICOM) – a means of standardizing medical imaging and patient information across different devices. DICOM was first co-developed in 1985 by the American College of Radiology and the National Electrical Manufacturers Association, yet it took almost 10 years to take its current form today; an almost universally accepted industry communications standard for medical images. DICOM (as with any industry standard) has its limitations, however it has created an interoperable and open system that has been central to advancements in the field of radiology.

Ophthalmologists now face a similar challenge but in a very different time. We are at the height of the digital age, as compared with our radiology colleagues who broached this problem when the World Wide Web was merely a toddler. Surely we can make our OCTs, visual fields, and autorefractometers talk to each other and feed into an electronic health record system? It is therefore incongruous that this hard-won interoperability seems a lot easier in radiology than in ophthalmology. In reality, an ophthalmic DICOM does exist, but it is used by few, and many OCT manufacturers continue to utilize closed formats that require users to "pay extra" for DICOM capabilities. As tech-loving ophthalmologists, we are naturally lured by new inventions – the promise of a higher definition scan, improved motion tracking, instantaneous 3D rendering. In effect, for these big tech dreams to be realized we must concurrently build infrastructure and platforms to bring this to our patients.

# Example of an Automated Patient Journey

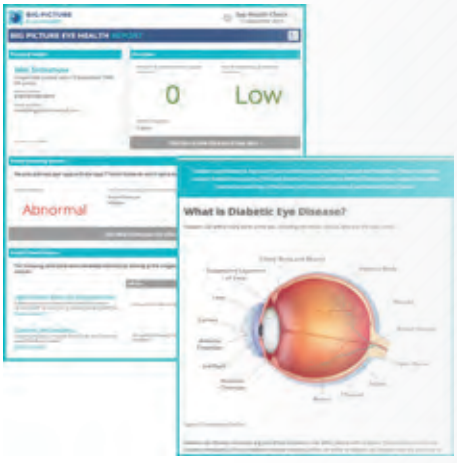
*Step One*

Customer visits primary healthcare provider who scans their eye at a kiosk, which incorporates advanced eye scanning technology including OCT. Scans are then instantly and securely uploaded to the cloud-based platform.



*Step Two*

Customer eye scans and relevant history are reviewed and reported on remotely by eyecare specialists.




*Step Three*

Using input from specialists, the software automatically generates a detailed eye health report for the patient, including educational content and a referral to an ophthalmologist, or optometrist if necessary. The detailed report can be shared with any healthcare provider participating in the patients care.

### Could we have a solution?

I was introduced to a software company based in Sydney that had the foresight to develop such a platform to solve this problem. Big Picture Eye Health was founded by Tom McKinnon, a medical practitioner who saw the crevice between new technology and integrative platforms, and he hopes to revolutionize how images are taken, assessed, and reported on by eyecare specialists.

*"For big tech dreams to be realized we must concurrently build infrastructure and platforms."*

The primary aim of Big Picture was to find a solution for streamlining the patient's eyecare journey – to develop a platform that covers the entire pathway and works with all imaging devices. Over the past three years, his team of software engineers and physicians have been working on developing exactly this – an interoperable software platform, integrating eyecare expertise with advanced eye scanning technology and decision support algorithms. The platform combines multiple elements of comprehensive eyecare; an iPad-based patient registration, patient-directed consent and history taking, remotely controlled eye scanning equipment, image compression technology and software diagnostics culminating in a cloud platform for scan review, referral management and patient communication. Although the platform is capable of performing eye scans, one of its most important features is that it is fully DICOM compliant and works with all medical imaging devices.

The platform stores all patient scans and information in a single secure location and can be accessed from anywhere through a web browser. This not only facilitates international collaboration, but also should be invaluable for the increased global mobility of patients, as it offers patients ownership and freedom of control of their own eye scans and health data, while ensuring that no information is lost along their eyecare pathway. As research has shown that many patients leave medical consults not really knowing what the plan is or where to go from there, the platform's personalized online portal would mean that patients will not only be able to access their actual eye scans, but also review a summary of their care, details of the follow up plan, and relevant educational materials. (See Sidebar: Example of an Automated Patient Journey). Another element of the software is its structured approach to analysis and reporting, which includes a user-friendly interface for referral, according to patient location and support algorithms that calculate validated risk scores – these risk scores are based on parameters such as age, duration of diabetes, HbA1c etc., and are available to both patients and eye specialists. In the future, the platform may also be used as a personalized health education tool.

### Ophthalmology in the cloud

Empowered patients are increasingly demanding convenience – healthcare services need to be accessible, efficient and of a high quality. To avoid lengthy waits in the eye clinic, a model of eyecare that incorporates teleophthalmology into routine clinical practice means that patients could be monitored more frequently than they are now. For example, a patient with high risk dry age-related macula degeneration (AMD) could choose to have an OCT scan every month, then have that scan reviewed and the results reported back to them by their own ophthalmologist. The patient would only need to see their specialist once or twice a year, and yet have their eyes closely monitored; this would allow conversion to wet AMD to be detected early, and facilitate rapid commencement of therapy. For those without known eye disease, this form of opportunistic screening may uncover refractive errors or eye pathology that would benefit from visual aids and/or specialist intervention.

### Looking ahead

The platform is scheduled to launch in Australia before the end of the year, and will be accompanied by an all-in-one eye imaging kiosk, which includes OCT, fundus cameras, autorefractors, and visual field assessments. With their kiosk situated in the community and the cloud-based platform, Big Picture will be the first in the world to attempt to make one interoperable platform that seamlessly covers the entire patient journey. A collaborative study between the company and Moorfields Eye Hospital is also planned to take place in the United Kingdom, and let's hope that this software is the first of many new technologies that our industry will embrace to drive significant improvement in the way that critical eyecare information is accessed and communicated amongst professionals – all in the name of better patient care.

*Dawn Sim is a Consultant Ophthalmologist at Moorfields Eye Hospital, and Institute of Ophthalmology, University College London, United Kingdom, and Global Medical Lead of Big Picture Eye Health.*

# Dual Blade, Single Purpose

**Malik Kahook wanted a better way to image the trabecular meshwork in cadaver eyes, and designed and built a blade that was capable of removing tissue strips intact. The Eureka! moment came when he realized it could be used to lower IOP in glaucoma patients too**

*Malik Kahook, Slater Family Endowed Chair in Ophthalmology, Vice Chair of Clinical & Translational Research, and Chief, Glaucoma Service, University of Colorado, USA, tells his story of creating the Kahook Dual Blade.*

Where did the idea for the Kahook Dual Blade (KDB) come from?

We have a busy translational research program here at the University of Colorado, and one project was imaging the trabecular meshwork (TM). Harvesting the TM from cadaver tissue is difficult – it's a bit like wet tissue paper, and is hard to remove in one piece in order to perform anatomically correct imaging. This limitation made me take a step back and design a device with the properties I needed.

Around 40 versions came and went before we began honing in on the ramp that exists after the distal-most point of the device, which stretches the tissue and raises it above the normal plane of the TM. We worked hard to find the geometry that functioned best, and then went on to create the blade with help from outside contractors. One day when harvesting tissue, I realized what we had, and said "Wait a second, we could use this to perform goniotomy surgery in patients with glaucoma!" It seems obvious now, but innovation often leads you in a different direction to your original goal.

What motivated you to pursue your idea?

In glaucoma surgery, our gold standard is trabeculectomy; if that fails, we'll perform tube shunt surgery. These procedures are effective, but they're associated with adverse events, and since they were introduced, we've been trying to improve our toolkit. When I saw how well the KDB worked in cadaver tissue, it was a natural decision to try and use it to improve surgical outcomes in my patients. I thought if we could cleanly remove the TM without leaving significant tissue leaflets behind and open a pathway for fluid to exit the eye, this could have a significant impact on how we address high IOP. And since glaucoma is a disease of the TM, we're removing the root cause of raised IOP, without disrupting other tissues.

What outcomes have you seen?

We've seen a decrease in IOP (around 5 mmHg) for six months in a large cohort of patients, and a significant decrease in the number of topical medications required, with around 70 percent of our patients decreasing their dependence by at least one drug (1–4). New World Medical launched the device in the US last year, and we're following around 120 patients as part of an initial survey. We'll soon have one-year data on this group, and right now, all the indications suggest that we'll see that this 5 mmHg drop is sustained beyond six months.

We're currently looking at all patient types – those with mild, moderate, or severe disease, and with many different forms of glaucoma – we're even having great success in very advanced glaucoma cases. Unlike some glaucoma surgeries that are only approved in conjunction with cataract surgery (which can be an obstacle for pseudophakic patients, and create reimbursement issues in the US), we've successfully used our device in both phakic and pseudophakic patients. The benefit to the patient is that they can have this procedure done prior to (and hopefully obviating the immediate need for) a trabeculectomy or drainage device. It's a huge success if we can push away a trabeculectomy or drainage device for a year or two, and even better if we can push it off into the distant future so that we're not even thinking about it, and I think we're starting to see that. I've seen this robust IOP lowering firsthand in my own patients, and I've observed that combining the procedure with cataract extraction adds IOP lowering efficiency, and a more significant drop in medication dependence.

What feedback have you received?

The device has been marketed in the US since November 2015, and is now available in Europe and Canada. My US-based colleagues are seeing the same things – a significant lowering of IOP and a decrease in medications. They're also using the device in many forms and stages of glaucoma. Some are choosing to use it in combination with cataract surgery, and others are using it on their pseudophakic patients, or even patients who had cataract surgery with a MIGS device in the past, who need their IOP lowered further. I'm seeing a lot of excitement about the variety of patients that the device can be applied to – all without reimbursement concerns. I believe the KDB could become a key tool for glaucoma surgeons – instead of perfecting a large repertoire of procedures to treat glaucoma, the KDB offers surgeons versatility, and great outcomes in a wide range of patients.

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4. *Data on file with New World Medical*

# Everybody be COOL

**Sitting Down With... David Huang,** Peterson Professor of Ophthalmology and Professor of Biomedical Engineering at Oregon Health and Science University (OHSU), Portland.

You're a co-inventor of OCT – and lauded for it. How does this feel?
Of course it is wonderful to know that this invention has been successful, useful, and beneficial to tens of millions of patients on an annual basis. I couldn't have anticipated it at the beginning and I am very happy to see it grow over the years – the technology is always getting better and there are more diseases where it is useful.

OCT was your PhD project – at the time, did you have any inkling of how far it might advance?
Well, no! I knew there were many ways forwards. Back at the start, we thought of many ideas to make OCT faster, as we realized this was the key to making it more powerful and useful. But implementing these general ideas was challenging. I have been surprised and gratified by the number of high-caliber people who came into the field and moved it forward. A big milestone was the development of spectral domain (SD)-OCT back in 2003 – that really required deep understanding of the physics behind OCT. As a researcher, it is challenging to operate in this incredibly competitive field with so many innovative people and strong research groups. But it is also exhilarating to watch the rapid progress the field has made!

What are your thoughts on the future of OCT?
Over the next 10–20 years I think the potential lies in improving speed, decreasing cost, and making it more compact. Swept-source OCT can operate at higher speeds than SD-OCT, and once it is two or four times faster there will be a real clinical and commercial advantage despite the higher cost initially. There is also potential to put multiple swept-source systems and beams on a single chip, which would continue to improve speed and eventually decrease cost. If you are buying a system now, I don't actually think that swept-source has a lot of advantage, but in the long run, I think it will dominate at some point.

Do you consider yourself to be an inventor?
I actually do think that's my primary job. I am not sure where the ideas come from – the solutions just occur to me as I think about engineering and clinical problems. My clinical practice keeps me familiar with clinical problems: it lets me know what technological innovations are needed to improve clinical application or inspires inventions tailored towards specific diseases. I was able to develop disease-specific inventions because of my knowledge in ophthalmology, but others, like the angiography algorithm, came more from my understanding of the physics of light-tissue interaction.

How do you think mobile diagnostics will change the future of ophthalmic care?
I think they will be very important, especially in the ophthalmic space. When you look at a heart valve or other invasive technology, it is very hard to imagine a smartphone being involved, but if you are trying to check vision or measure refraction, a smartphone with a nice camera can do a lot. Amblyopia risk factors, myopia progression, keratoconus, retinal diseases and glaucoma – I think that these all have the potential to be followed at home through mobile devices, or by primary care physicians rather than specialists.

You run the Center for Ophthalmic Optics and Lasers – the COOL lab. What can we expect to see in the next few years?
The COOL lab is special because it is a vertically integrated research group with the capability to develop advanced OCT prototypes and algorithms, and take them from the bench to multi-center clinical trials. Right now we are really focused on OCT angiography, and we hope to improve the hardware and software to advance the capabilities of wide-field angiography and reduce artifacts. We also hope to advance clinical applications by conducting clinical studies and serving as a reading center for larger trials.

What do you enjoy most about your job?
If I can have an idea for a better design of an imaging system, or a more efficient algorithm, then I feel very satisfied because we are able to take the field forward in a clever way. It is also gratifying to see other investigators pick up these ideas and further improve them. Seeing them used clinically on a wide scale is most satisfying.

Reflecting on your career so far, are there any "do's" and "don'ts" that you would share?
In my experience, finding collaborators and clinical investigators who really care about advancing the technology and its applications is invaluable. If you do this, you really need to cultivate and help them, and share credit. The research enterprise depends on a few people who are the main driver of progress, and it is very important that those people feel valued.

As for "don'ts," I would say don't get stuck in a rut – it is important to learn when to quit. You have to learn to bet on the winners and fold on the losing hands, because no matter how clever you are you always end up going in some blind alleys, both in terms of teams that won't work or projects that have low significance or are too technically difficult. Sometimes this is just a matter of timing. Like when we were trying to do swept-source in the 1990s and it was extremely difficult, but now it is making progress in leaps and bounds.

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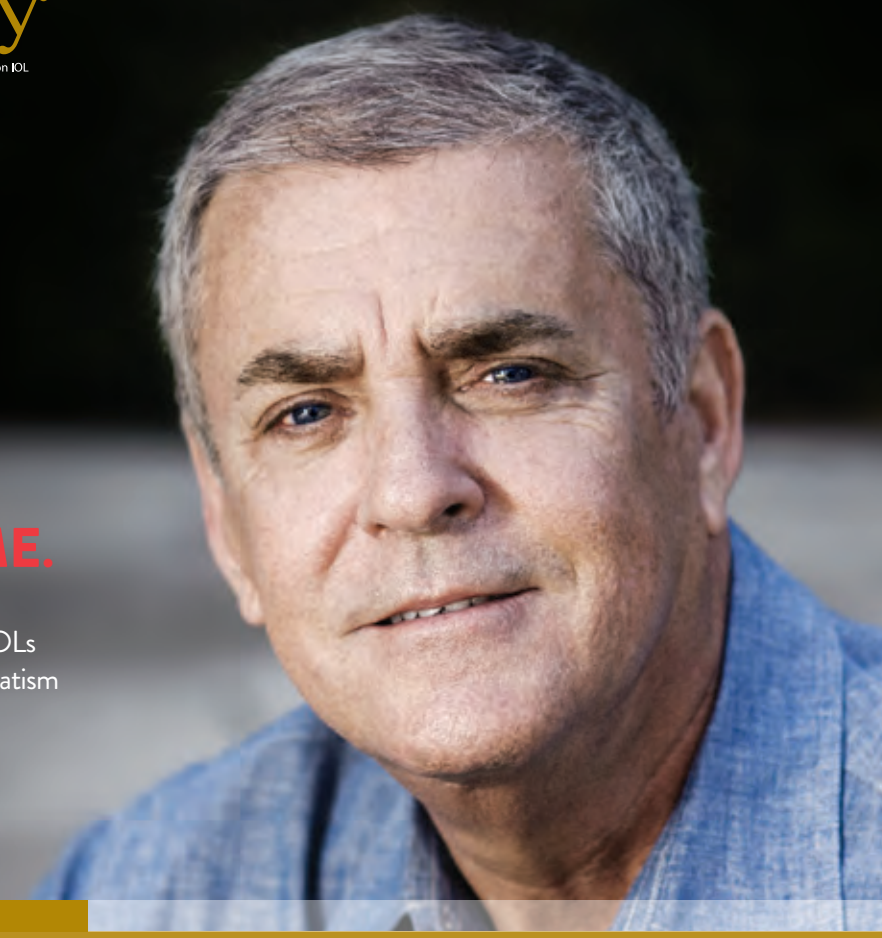

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