AUGUST 2018 # 24

the Ophthalmologist™

Good Business

The story of Epipole – a balancing act of doing the right thing and running a sustainable company.

POWER TO PREVAIL

As demonstrated in phase 3 clinical trials evaluating BCVA,* as measured by ETDRS letters, in patients with Wet AMD, Macular Edema following RVO, DME, and by ETDRS-DRSS† in DR in Patients with DME,[1] as well as your clinical experience

Start with EYLEA for proven efficacy outcomes[1]

AMD = Age-related Macular Degeneration; DME = Diabetic Macular Edema;
DR = Diabetic Retinopathy; RVO = Retinal Vein Occlusion.

Dosing driving efficacy outcomes across all indications.[1]
Learn more at EYLEA.us/dose

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with

- Neovascular (Wet) Age-related Macular Degeneration (AMD): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).
- Macular Edema following Retinal Vein Occlusion (RVO): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly).
- Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in Patients with DME: The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

ADVERSE REACTIONS

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

Please see adjacent Brief Summary.

*Best-corrected visual acuity.
†Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale: an established grading scale for measuring the severity of DR.

Reference: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. May 2017.

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

10/2017
US-LEA-13945

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA package insert for full Prescribing Information.

1 INDICATIONS AND USAGE

EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:

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

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

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

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments. Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Dosage and Administration (2.7) and Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure. Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.7)*].

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

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

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

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

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

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

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

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

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

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

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

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

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

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

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

6.2 Immunogenicity. As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept [*see Clinical Pharmacology (12.1)*], treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Data

Animal Data

In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.

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

8.2 Lactation

Risk Summary

There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential

Contraception

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

Infertility

There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment [*see Nonclinical Toxicology (13.1)*].

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

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

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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

Issue Date: June 2017
Initial U.S. Approval: 2011

Based on the May 2017 EYLEA® (aflibercept) Injection full Prescribing Information.

REGENERON

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Advanced Glaucoma Technologies North American Forum

Join Ike Ahmed and a panel of world-leading experts in the field of glaucoma surgery for a live discussion. The live and online program will provide ophthalmologists with an impartial and authentic body of content that addresses many of the questions, concerns or barriers to adoption of MIGS and other technologies. Registrants will also have the opportunity to interact with the discussion and direct questions to each of our experts.

Broadcast live from The Harold Pratt House, New York, NY, USA; October 6, 2018.
Invitations to be distributed soon.


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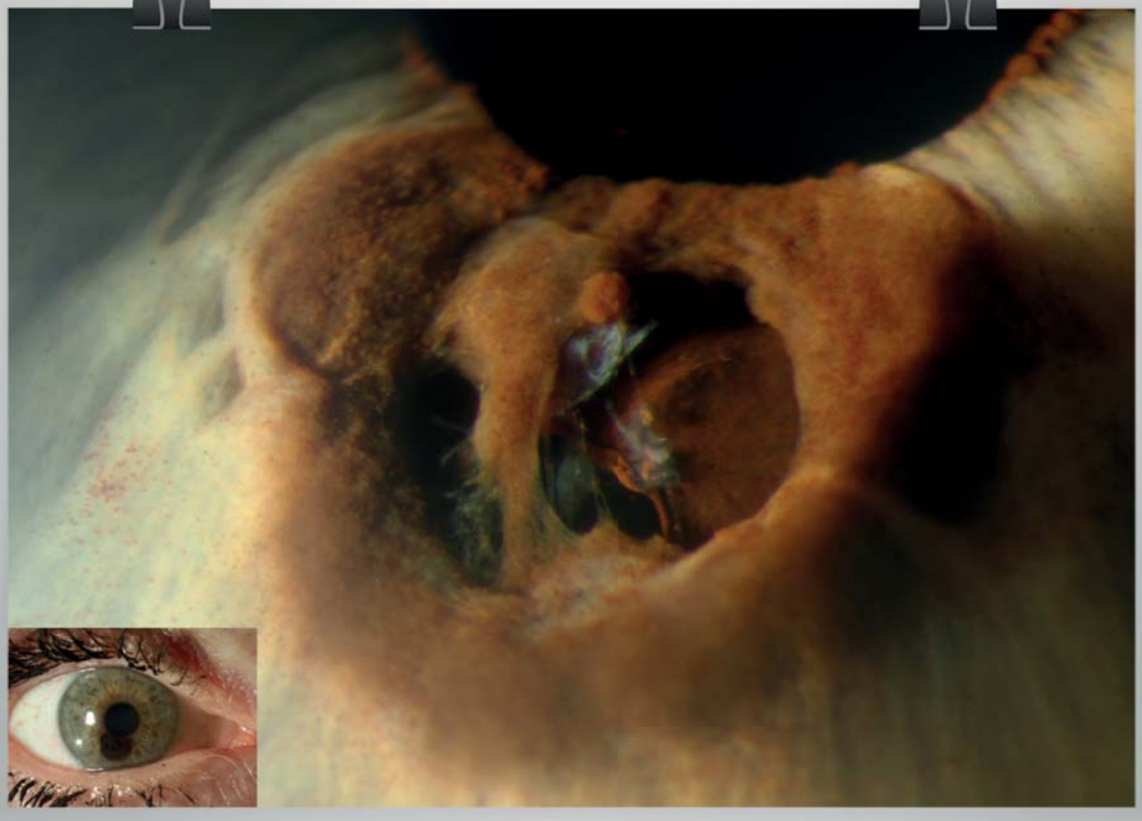
Image of the Month



Pele: Goddess of Volcanoes

This image was submitted to us by Houston Sharpe III, an ophthalmic imaging specialist with 10 years of ophthalmic experience in imaging and clinical operations. It shows a high magnification slit lamp image of a large iris nevus, resembling a broiling volcano. Sharpe also acts as Chair of the Scientific Exhibit Committee for the Ophthalmic Photographers' Society.

Credit: Houston Sharpe III, ophthalmic imaging specialist.

Do you have an image you'd like to see featured in The Ophthalmologist? Contact edit@theophthalmologist.com.

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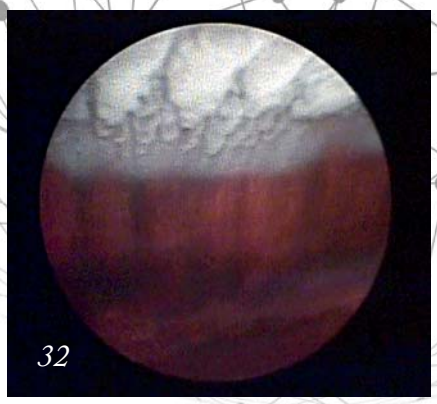

On The Cover

A representation of meeting the ophthalmic needs of neglected communities worldwide.

Upfront

In My View

Feature

In Practice

NextGen

Profession

Sitting Down With

the Ophthalmologist

ISSUE 24 - AUGUST 2018

Change of address
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General enquiries
www.texerepublishing.com
info@texerepublishing.com
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Distribution
The Ophthalmologist North America (ISSN 2398-9270) is published monthly by Texere Publishing, 175 Varick St, New York, NY 10014. Periodical Postage Paid at New York, NY and additional mailing offices.
POSTMASTER: Send address changes to Texere Publishing ,175 Varick St, New York, NY 10014
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OCTOBER 25, 2018

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CELEBRATING

10 YEARS

OF INNOVATION

UNITING OVER 1000 LEADERS

IN THE DEVELOPMENT OF GROUND-BREAKING OPHTHALMIC TECHNOLOGIES

Modern Medicine's Makeunder

What goes up must come down. And what goes forward can always come back to serve the many, not the few

Craig Robertson shares the story of Epipole in our cover feature (page 16) – and it was a tale we were more than keen to tell. Founded to help bring advanced yet inexpensive imaging technologies to neglected countries, Epipole has centered its business model on 'doing good' – but have experienced commercial success along the way.

Clearly, companies need to make money, not only to keep the 'lights on', but also to drive research and development, and to iteratively improve upon technologies and treatments. But it seems to me that, with the wonders of the modern world, there exists the potential for disruptive low-cost solutions that can make a huge difference to those who need it most. And that's precisely what Robertson and his team have focused on; through cunning, perseverance (and not the pursuit of profit), they have adapted high-tech imaging solutions to provide inexpensive and portable fundus imaging devices – and all without compromising quality.

And they're not alone in providing neglected markets with feasible solutions. In our June issue, Sean Ianchulev shared the story of miLOOP, the low cost microinterventional cataract surgery device that is helping to tackle the backlog of global cataract blindness (1). For countries or rural communities where phaco machines aren't readily available – or affordable – the device is proving to be a gamechanger. Many surgeons in more technologically-advanced markets are also praising the device for its simplicity and its effectiveness in hard cataracts. Even the humble ophthalmoscope, which does not come with a prohibitive price tag for many, received a makeunder: back in 2017, William J Williams, Andrew Blaikie and John Sandford Smith told their wonderful story of Arclight, the $6 ophthalmoscope that is improving eyecare for millions (2).

There will always be a place for advanced technologies that push ophthalmology and medicine into exciting new realms of possibility – as well as the markets and interest to support them. But equally, there is also a place – and, as Epipole exemplifies, a market – for more affordable, more portable, or more efficient solutions that increase the accessibility of healthcare. It delights me to see companies risking it all by driving development in a different direction or by putting a positive spin on the concept of a 'makeunder' – in doing so, they are satisfying unmet need across the globe.

Ruth Steer
Managing Editor

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1. *Sean Ianchulev. "What Goes Around". The Ophthalmologist, 22, 38–40. Available at: http://bit.ly/miloop.*
2. *Ruth Steer. "Ophthalmoloscopy for all". The Ophthalmologist, 09, 18–27. Available at: http://bit.ly/arclightoph.*

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 edit@theophthalmologist.com

Where Are They Now?

Re-dropping the needle: topical anti-VEGF therapy revisited

In June 2017, we reported on a study that demonstrated topical delivery of anti-VEGF antibodies to the posterior segment, and how the findings showed the potential to release AMD patients from the burden of monthly injections (1). The hero? Cell penetrating peptides (CPPs) that can act as chaperones to facilitate the uptake of anti-VEGF complexes.

In their 2017 publication, the team – led by Felicity de Cogan of the University of Birmingham, Birmingham, UK – showed that CPP-anti-VEGF complexes successfully reached the posterior segment in rat and porcine eyes, and that they could reduce lesion size in a mouse model of choroidal neovascularization (2).

But where are they now? The group have pushed their treatment one step further, and recently shown that topically applied CPP complexes (with either bevacizumab or ranibizumab) can reach the retina in both rabbit and porcine eyes, and have also quantified how much anti-VEGF was delivered (3). Also, Macregen, Inc, now owns the pending patents for the treatment, and a collaboration between the US-based company and the team is in place to develop novel therapies for AMD and other eye diseases. On the collaboration, de Cogan said: "We welcome the commercial investment and expertise from Macregen so we can deliver a structured research and development program that should bring concrete benefits to people with AMD and eye diseases" (4).

With proof of concept studies currently being expedited, and clinical trials set to start as early as Q2 in 2019, how soon might patients be able to "drop the needle?"

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1. *Ruth Steer. "Dropping the needle". The Ophthalmologist, 42, 10–11 (2017). Available at: http://bit.ly/dropneedle*
2. *F de Cogan et al., "Topical delivery of anti-VEGF drugs to the ocular posterior segment using cell-penetrating peptides", Invest Ophthalmol Vis Sci, 58, 2578–2590 (2017). PMID: 28494491.*
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Eat to Beat AMD

Meet the foods halting AMD progression – and those responsible for 'speeding' it up

What do Shanghai and San Sebastian have in common? According to science – more than you think. A team at the University of Auckland, led by Naoko Chapman, has found that Oriental and Mediterranean diets are beneficial for those at risk of AMD.

Their systematic review (1) analyzed 18 studies and found that adherence to a Mediterranean diet – characterized by high consumption of fruits, vegetables, legumes, wholegrains, and nuts – decreased risk of late AMD progression. Similarly, an Oriental diet pattern – which resembles the Mediterranean diet in volume of fruit, vegetables, legumes, tomatoes, and seafood – decreased association with early and advanced AMD prevalence. In contrast, the high-glycemic Western diet pattern – categorized as having a high intake of red meat, high-fat dairy products, processed meat, fried potatoes and refined grains, as well as alcohol consumption of more than two units per day – increased association with early and advanced AMD prevalence.

"When I started this research I was looking for a simple answer," says Chapman. "However, the evidence showed that there were multifactorial influences of diet and food intake on the incidence and progression of AMD." The upshot? "Health professionals need to check that their own views of what constitutes a healthy diet are consistent with the evidence base, and help patients consider – what might be for some far-reaching – changes in diet".

These findings add weight (no pun intended) to existing research that has focused on modifiable risk factors, such as diet and antioxidant supplementation, to protect against AMD. And the evidence keeps mounting. Researchers at the University of Sydney, Australia, assessed the dietary intake of flavonoids in 2,856 adults aged 49 years and younger, with 2,037 followed up 15 years from baseline (2). They found each 1 standard deviation (1-SD) increase in flavonoid intake – the bioactive compounds found in tea, chocolate, red wine, fruit, and vegetables – was associated with a reduced likelihood of AMD. Furthermore, study participants that reported eating ≥1 orange – a key source of flavanones – per day were found to have a reduced risk of late AMD 15 years later compared with those who didn't consume oranges at baseline (odds ratio: 0.39; 95% CI, 0.18–0.85).

So how many oranges are needed to prevent the onset of AMD? Apparently, as little as one a week. Bamini Gopinath, lead author on the associated study (2), says, "We were not hugely surprised that certain flavonoids were protective against the risk of AMD, but what did surprise us is that oranges, which contribute to the intake of a particular flavonoid subclass – flavanone – were so strongly protective against late AMD."

Gopinath's study provides further evidence that flavonoids could be capable of not only reversing oxidative stress and inflammation-associated damage, but also improving vascular function and thus, possibly the clinical features of AMD. "Dietary modifications can not only slow the evolution of established AMD, but represent one of the only means of delaying the onset of the condition," she says. "Therefore, paying attention to what we're eating could help to minimize our risk of developing AMD."

References

1. *NA Chapman, "Role of diet and food intake in age-related macular degeneration: a systematic review", Clin Exp Ophthalmol (2018). PMID: 29927057.*
2. *B Gopinath, "Dietary flavonoids and the prevalence and 15-y incidence of age-related macular degeneration", Am J Clin Nutr (2018). PMID: 29982448.*

The Pitter-Patter of Tiny Diagnoses

A simple yet accurate model could help streamline ROP screening

Every year, retinopathy of prematurity (ROP) affects between 400 and 600 infants in the US (1). ROP continues to be a leading cause of strabismus, amblyopia, and severe near-sightedness in premature babies – and can lead to total vision loss, if not diagnosed and treated quickly. And therein lies the problem: the current model has low specificity for predicting which premature infants are most at risk of severe ROP; only 5–10 percent of those selected for a screening examination go on to receive treatment. But that looks set to change – thanks to a new model that boosts accuracy while maintaining, or even improving upon, sensitivity (1).

"Prior approaches were successful but limited by development studies that were too small, resulting in overfitted models and relatively complex calculations," says Gil Binenbaum, who led the study. "But despite these limitations, we suspected we could combine successful ideas from each group of investigators into a more effective approach." And thus, a hybrid model was born.

Together with a multi-hospital team he analyzed 7,483 premature infants born in 29 hospitals in the US and Canada between 2006 and 2012 in a retrospective cohort study. Infants included were at risk of ROP and had a known ROP outcome. "We knew we had to use as large a cohort as possible so that we could develop a new model that is easy to use and more accurately identifies all premature infants who are at high-risk of developing severe ROP," said Binenbaum (2).

The study identified six key criteria that could be used to determine whether a child should receive a screening examination for ROP: birth weight (BW) below 1,051 grams (about 2.3 pounds), gestational age (GA) at birth younger than 28 weeks, hydrocephalus, and slow weight gain during three time periods between the ages of 10 and 40 days. Using these six criteria, they were able to correctly predict 100 percent of infants with "type 1 ROP" – those requiring treatment – while reducing the number of premature infants who would undergo examinations by 30.3 percent.

Binenbaum added, "The criteria we developed were highly sensitive; in fact, they were slightly more sensitive that the current screening guidelines, and yet they were much more accurate than the current guidelines."

Current ROP screening criteria – based on BW, GA at birth, and a third, poorly defined screening criterion for heavier, older infants – relies on the judgement of the neonatologist. Under these guidelines, 70,000 infants are examined annually in the US – 69,400 more than have the disease. As these recommendations have the potential to significantly reduce the number of eye examinations being performed, could they ease the burden for parents, nurses, and doctors, who are already dealing with other issues associated with premature birth?

"Using these modified screening criteria could potentially reduce the number of babies who need to be examined by almost a third, which would be beneficial for those infants, and allow us to focus all our efforts on treating those who are at high risk for retinal detachment and blindness," says Binenbaum. "The next step is to validate these encouraging results in a second large clinical study before actually using the new criteria in practice."

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Reading Between the Lines

Are deficits in visual function more frequent in children with developmental dyslexia?

Developmental dyslexia (DD) is a common learning disability, estimated to affect between 5 and 10 percent of the US population (1). Although researchers agree on its origins, there are still facets of the disorder that are not fully understood – including whether visual processing deficits are more prevalent in children with DD. Now, an observational study involving 29 school-aged children with DD and 33 typically-developing (TD) children has attempted to provide an answer (2).

In the study, participants spent two hours undergoing psychoeducational testing, comprehensive eye examinations, and visual function measures – assessing vergence, accommodation, and ocular motor tracking. Ocular motor tracking was evaluated two ways – with a printed test and infrared eye tracking – and all parametric analyses for the vision measures were adjusted for age and sex. Children with DD exhibited more deficits in peripheral visual function – specifically vergence, accommodation, and/or ocular motor tracking – than the non-randomized group of TD children: 23 children (79 percent) in the DD group had deficits in one or more domain of visual function, compared with 11 children (33 percent) in the TD group ($p<0.001$).

The findings on frequency are clear, but what about the possible cause of these deficits? Uncertainty remains. For now, the authors simply offer a suggestion: "assessment of vergence, accommodation, and eye movements may be helpful in the initial evaluation of children with dyslexia and will supplement the findings of a comprehensive ophthalmologic examination and a detailed literacy evaluation."

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Down in the ~~Mouth~~ Eye

Digging into the relationship between dry eye disease and depression

Dry eye disease can certainly be unpleasant and uncomfortable for those affected – but do the symptoms contribute to depression? According to a recent study in women with signs and symptoms suggestive of Sjögren syndrome, the answer appears to be yes.

A research team led by John Gonzales from the University of California, San Francisco, CA, USA, turned to the Sjögren's International Collaborative Clinical Alliance (SICCA) registry, which has 3,514 patients enrolled from nine international research sites (45.2 percent of participants in the registry have a definitive Sjögren's syndrome diagnosis). All female participants from the registry (n=3,185) were included in their study, and assessed for depression, keratoconjunctivitis sicca, patient-reported symptoms of dry eye, and overall health.

Overall prevalence of depression in the cohort was 34.9 percent, which the authors noted was "much higher than the 10 percent found in the general population" (1) – perhaps unsurprising given their place on the registry. However, patients who reported dry eye symptoms had a higher odds of depression ($p<0.001$, compared with symptom-free participants). Moreover, specific dry eye symptoms, such as burning or stinging, were also associated with a higher odds of depression ($p<0.001$ versus no symptoms). Counterintuitively, more pronounced keratoconjunctivitis sicca (OSS ≤5) was associated with a lower odds of depression – but the authors describe the finding as potentially "artefactual."

As well as increasing our understanding of the relationship between dry eye symptoms and depression, the authors identified that further investigation to understand the relationship between these two diseases – and the role that neuropathic pain might play – could help improve quality of life for patients.

Reference

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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 edit@theophthalmologist.com

Decisions Must Be Data-Driven

More information on factors influencing cataract surgery outcomes is needed – for the good of our patients

In consultation with Mary K. Daly, Chief of Ophthalmology, Veterans Affairs Boston Healthcare System, MA, USA.

In an ever-changing healthcare environment, research and data are imperative. So why are policy decisions made without enough relevant data to drive those decisions? Case in point: in February 2018, National Public Radio reported that "your eye surgeon may have to do 'double duty' as your anesthetist under a new policy by health insurer Anthem" (1). A clinical guideline released by Anthem in response said "it's not medically necessary to have an anesthesiologist or nurse anesthetist on hand to administer and monitor sedation in most cases." So imagine, you (or your mom or dad), needs cataract surgery. Someone is going to cut into your eye, relatively routine, but what does that actually mean? Be prepared: the surgeon who should be concentrating all of their education, skill, and focus on the delicate intraocular surgery to provide your best long-term chance of great vision, may now be distracted by the intraoperative control of your blood pressure levels, pain management, monitoring of your heart rhythm, and overall comfort during the often (but not always) short procedure.

In 2018, Anthem Insurance denied payment for anesthesia coverage during cataract surgery procedures. Put yourself in the patient's shoes: imagine having cataract surgery and because your ophthalmologist isn't comfortable operating without an anesthesiologist, you receive a bill for the anesthesia component that your insurance company will not cover. What do you do? Do you find an ophthalmologist who is comfortable operating in an office-based setting? What if you have comorbidities that put you at a higher risk of complications, or anxiety? Does your ophthalmologist have the support staff to identify and account for it preoperatively? What if an issue occurs and no anesthesiologist is present – how is the ophthalmologist supposed to focus on the surgery itself as well as try to manage any systemic issues with anesthesia?

The fact that the decision to not pay anesthesiologists was made without supporting data and literature to drive that decision is not just an economic issue, but an ethical one too. It's why organizations like the AAO and the ASCRS are fighting this stance – and why we need more data on how a patient's physical status impacts cataract surgery outcomes.

The American Society of Anesthesiologists (ASA) classification was developed in the 1960's, and evaluates the overall physical status of patients prior to surgery. The grading system is a significant predictor of postop outcomes in vascular and general surgery cases. In neurosurgery, high ASA classification is a risk factor for major medical complications; and high ASA status is also a predictor of postop morbidity and mortality after cardiac and major non-cardiac operations. Of the six ASA classes, four are relevant to ophthalmology, but their relationship with ophthalmic postop outcomes is not well understood. Moreover, though large often referenced studies have evaluated the burden and cost-effectiveness of preop testing for cataract surgery, they did not assess the visual and vision-related quality of life (QOL) outcomes.

A commonly cited database study by Schein et al. (2) concluded that preop testing did not appreciably increase the

safety of cataract surgery. But when you actually read this publication, it didn't look at visual outcomes – which many would agree are of utmost importance to an ophthalmologist. Additionally, the majority of patients (64.3 percent) were ASA class I and II – the healthier end of the spectrum. Another study by Cavallini et al. (3) compared the incidence of ophthalmic and systemic complications in patients randomized to either preop testing or no testing, and reported no difference. However, as the preop characteristics in those two groups were not reported, it is not actually clear if the groups were similar or different in terms of physical status. Further, as the study excluded patients taking anti-coagulation medications or insulin, 'sicker' patients were removed – probably the very patients that need to be studied.

Another paper by Chen et al. (4) reported that preop testing before cataract surgery occurs frequently – but is costly. This study is often referenced, but it didn't actually look at periop or postop outcomes – neither systemic nor ophthalmic; it was basically a cost analysis. Because outcomes were not assessed, the utility of this study needs to be interpreted with caution. Unfortunately, it is a showcased study in a prominent journal – and insurance companies look to articles like this when making policy decisions.

Ophthalmologists are under increasing economic pressure to streamline the preop workup of our patients, yet we lack data showing how systemic preop testing impacts outcomes. Ultimately, decisions on how we approach the preop workup – and surgery – should be based on those factors that have been proven to achieve the best outcomes for our patients. In the US Department of Veterans Affairs (VA), outcomes data is of critical importance, and the VA is a leader in this area. To analyze the relationship between systemic disease and outcomes of cataract surgery, Mary K. Daly, Chief of Ophthalmology at VA Boston, along with her colleagues at other VA sites across the USA, evaluated the relationship between ASA class and postop outcomes through a retrospective review of the ophthalmic surgery outcomes database (OSOD) (5). The OSOD project was designed to assess and enhance the quality of cataract surgery, and contains data from almost 5,000 cases at five VA centers, including ocular and systemic comorbidities, visual acuity, and vision-related QOL. Their analysis showed that cataract surgery improved visual acuity and vision-related QOL in all patients, but outcomes were lower in patients with a higher ASA class (III and IV). Moreover, intraop floppy iris syndrome, iris prolapse, corneal stromal edema, clinically significant macular edema (CSME) and postop hospital admission within 30 days were unanticipated periop events seen more often in patients of higher ASA class. A higher ASA class was shown to increase the risk of CSME and admission to the hospital postop. Eight patients died within 30 days of surgery, all of whom had higher ASA classes. They also identified a significant association between a history of COPD and 30 day postop mortality (all cause death). Patients with COPD can be fragile, and further research to help optimize them for elective, but potentially life-changing and vision-restoring surgery, is required.

Why are these results timely and important? Having this information can help determine levels of risk, properly inform patients, help set reasonable expectations and maximize outcomes by minimizing those risks. We should offer patients the level of care needed to give them the best chance at a great outcome. That level of care (e.g., extent of preop testing, type of anesthesia) may vary depending on the patient's systemic and ophthalmic comorbidities, and it is critical to provide valid research in this area which prevents insurers from enforcing blanket 'one-fits-all' policies which are essentially denials of payment.

The important work of the US VA might be limited in terms of its retrospective design and demographic, but it is a jumping board. The protocols and reimbursement levels for preop testing and assessments by US physicians for visual restorative cataract surgery are extremely variable, and there is much we can gain on this topic, not only for the benefit of our patients, but for insurance companies. There might be a lot of economic pressure, but more studies investigating stratification of risk for patients based on their underlying health issues and comorbidities are needed to drive policy and practice decisions. It can be a challenging area to study, but our surgical colleagues – particularly cardiothoracic surgeons – are very good at looking at morbidity and mortality, and complications relevant to their procedures. Indeed, there exists a large corpus of literature pointing to systemic risk factors that influence postop outcomes for their patients.

Ophthalmology is following suit, but much more work needs to be done to gather and analyze data that evaluate the relationships between systemic disease, anesthesia requirements, and vision-related outcomes of cataract surgery. The vision and quality of life of our patients depend on it. The VA in the USA is advocating and leading the way.

The views expressed in this report are those of the author and do not necessarily reflect the position or policy of the United States Department of Veterans Affairs or the United States government.

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GOOD BUSINESS

In a sector strongly driven by shareholder value, is 'doing the right thing' a sustainable business model?

By Craig Robertson

I took an unusual route into ophthalmology. After training in mathematics, I worked on artificial intelligence (AI) optimization before moving into medical devices. The transition was kicked off by a conversation with the Optos Chief Technical Officer David Cairns; their product development programs needed the kind of mathematical expertise I could offer. And, in fact, I was predisposed to work in ophthalmology because, as a young person, I'd seen my grandmother go blind due to diabetic complications. The speed of her sight loss was shocking, and the experience never left me – and so it became a powerful motivator in my efforts to improve the management of diabetic retinopathy (DR).

I joined a small prototyping team at Optos, and stayed there for several years working on some incredibly advanced devices. I learnt a lot – Optos is a bit like a University – but, after a while, I began to wonder about the company business model. True, Optos was making the best devices on the market – but as a major PLC, its core aim was to enhance shareholder value, so it focused on the territories that returned the most revenues. Commercially, that makes perfect sense, but I couldn't help asking myself: what about the other 194 territories on Earth? Once I'd posed that question, there was no going back. I left Optos on a Friday, seven years ago, and started Epipole the following Monday. My aim? To build inexpensive ophthalmic imaging devices for neglected populations.

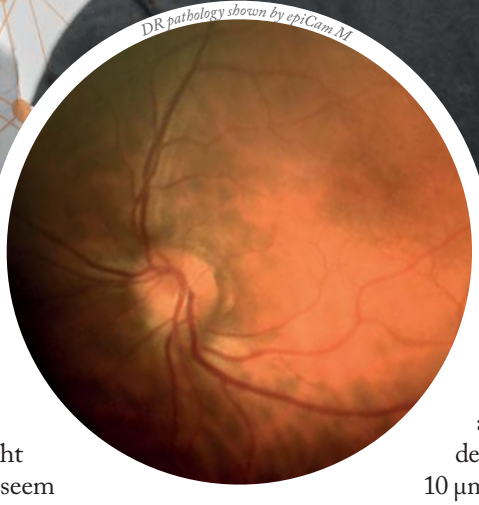
Life isn't always a beach

My first job was to track down Bob Henderson, a retired engineer who had invented the key Optos instrumentation. Eventually, I found him in Ko Samui in Thailand – though asking him to return to Dalgety Bay on the Scottish coast felt like I was pushing my luck, he came back. Suddenly, Epipole was a team of two. Having buy-in from one of the finest optical engineers in the world was a great boost for me, but when I showed Bob a sketch of my idea for a low-cost fundus camera, he just looked

Box 1: The epiCam M

- 1.3 megapixel camera
- Covers 52 degrees in a single shot, with over 100 degree reach
- Operates in amber spectrum (590 nm), which can help differentiate between oxygenated and deoxygenated blood
- No reflex from surface of retina or cornea
- Main application: DR

Craig Roberston holding an epiCam fundus camera



DR pathology shown by epiCam M

at it and said: "No." And that was the start of two guys shutting themselves away in a tiny pitch-black optics room for months on end.

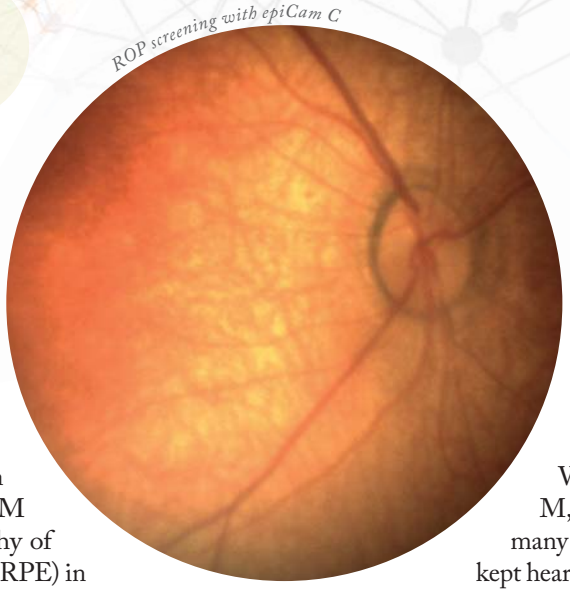
It wasn't easy. We were trying to solve problems which, for all we knew, might have been unsolvable; many ideas that seem great on paper are confounded when they meet biological tissue. Perhaps the hardest thing about building an ophthalmoscope is that the illumination and the optical axis are on top of each other – all the system wants to do is send reflex back to your sensor! We worked on that problem for about a year and, just as we started to question our sanity, we finally made a series of discoveries that fixed the issue. It was a hugely cathartic moment for us, and opened up the way to device prototyping.

Aiming high – and small, and wide

Our first fundus camera, the epiCam M (see Box 1), was conceived to improve the diagnosis of DR. We designed everything about this device from the ground up – the chassis, the optics, the electronics, firmware, software – everything. Nothing similar had been done before, so we were inventing as we went along – and we set ourselves a couple of ridiculously severe engineering constraints.

Firstly, we wanted to diagnose DR with a high degree of sensitivity – specifically, by detecting very small microaneurysms (below 10 μm). I didn't realize how large that hurdle was until we started work! Secondly, we wanted the device to be suitable for any community where DR is an issue, from remote parts of South America to rural China. And that limits size. If you're taking it to rural communities, it must be portable. It also restricts the price: a rural doctor making $6,000 a year won't buy a $30,000 camera.

The result was better than we could have hoped for: not only did we limit the size and price of the device for our markets, but we also met and exceeded our technical goals. To control camera costs and dimensions, we designed an electronics board (which in itself is something of a work of art!) that permits us to download data via a USB cable and display on a separate screen. Hence, the device does not need a large battery, or a screen, or a computer – the camera body needs only to house the optics. In terms of performance, we achieved a detection limit of about 8 μm



ROP screening with epiCam C

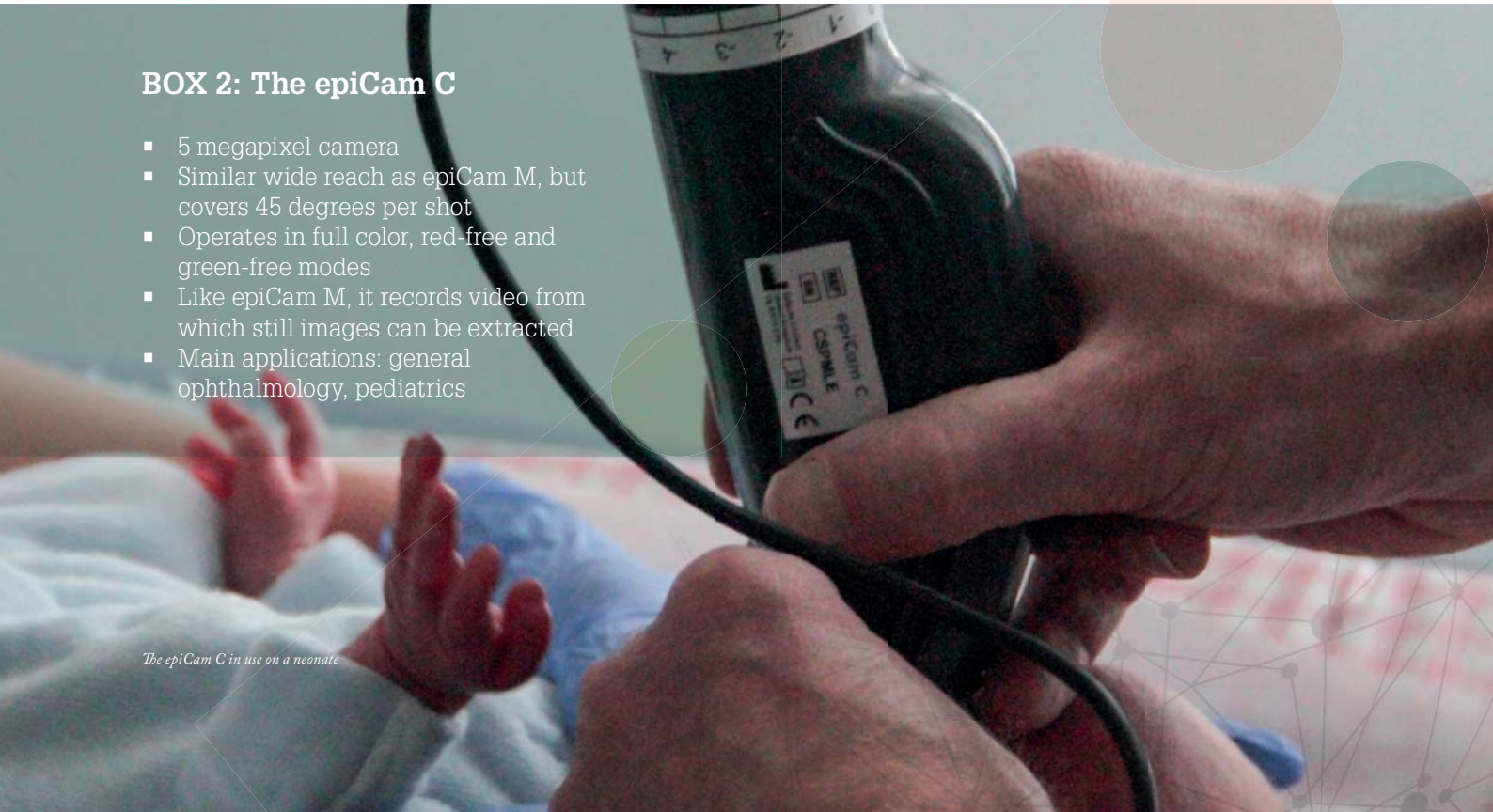
at the back of the eye – which is plenty because microaneurysms are only 'problematic' when they reach 30–40 µm. We also provided the device with a very wide reach – well over 100 degrees horizontally and vertically, which can help detect pathologies that might be missed by other devices. Indeed, examination of my own eyes with epiCam M identified a congenital hypertrophy of the retinal pigment epithelium (CHRPE) in the periphery, which a market-leading competitor device could not detect. Being able to look around the eye and see pathology beyond 45 degrees, instead of relying on a static view, makes a huge difference. Furthermore, the unique video capability we have incorporated allows observation of the retina in real time as a living tissue. It also supports efficient triage – the doctor can very rapidly examine all around the fundus, which can help make a real difference to clinical practice. The video capability also encourages novel basic science; for example, some are using epiCam M to study blood flow through the eye – you can see vessel dilation and contraction in real time. Others have used it to observe hypoxic changes in the fundus at high altitude. As well as diagnosing DR, the device is also capable of examining related applications, such as the tortuosity of blood vessels, and observing cholesterol platelets. Anecdotally, we have been told by users that it has been useful in a wide range of other systemic conditions.

Next generation

While we were developing the epiCam M, I continued seeking feedback from as many clinicians as I could speak with. And I kept hearing about the need for a better system of diagnosing and monitoring retinopathy of prematurity (ROP). This serious pathology can lead to a lifetime of blindness, and is increasing in frequency with the number of surviving premature neonates. Listening to this feedback, we started developing a second device specifically aimed at ROP: the epiCam C (see Box 2). The device is based on non-contact technology: with a working distance of 13 mm, our device doesn't touch the infant at all, so an examination is a less stressful experience for all concerned. In fact, clinicians have used our device in the incubator while the child is actually asleep! By contrast, other devices on the market are full-contact and require extensive preparation time. We knew it was important to move away from that strategy.

BOX 2: The epiCam C

- 5 megapixel camera
- Similar wide reach as epiCam M, but covers 45 degrees per shot
- Operates in full color, red-free and green-free modes
- Like epiCam M, it records video from which still images can be extracted
- Main applications: general ophthalmology, pediatrics



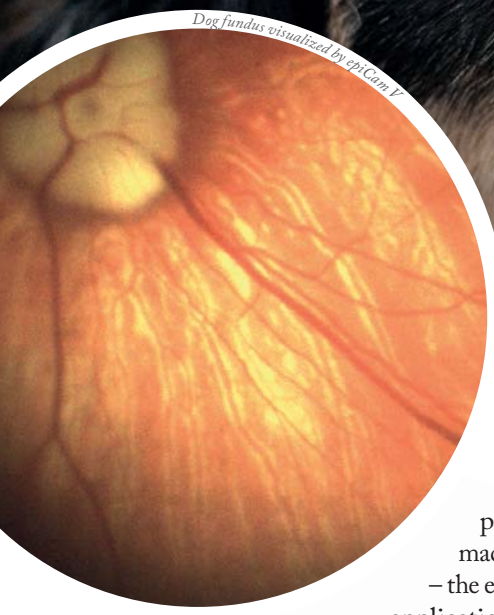
The epiCam C in use on a neonate

Box 3: The epiCam V

- Video capabilities and 5 megapixel camera
- Non-contact imaging
- Low power illuminant that can be adjusted to suit the reflectivity of the tapetum
- 45 degree field of view with reflex-free images

The epiCam V in use

Bengal Eagle Owl being imaged by epiCam V



Dog fundus visualized by epiCam V

Cat fundus visualized by epiCam V

Furthermore, epiCam C is a full-color, video rate ophthalmoscope, making it applicable to general ophthalmology indications as well as pediatrics. We've also made a variant of epiCam C – the epiCam V – for veterinary applications (see Box 3), which benefits from low power illumination that can be adjusted to suit the reflectivity of the tapetum – the reflective choroid layer found in most animals. Incidentally, some of the comparative work we see from zoo vets – looking at retinas of Sumatran tigers and Bengal eagle owls and vicunas and monkeys – is just fascinating.

Testing times

One of the problems we had to solve when developing our devices was how to test them. Our solution was to develop a proprietary model eye (See Box 4: Model Testing) to assess device performance in terms of resolution and field of view. We now have two versions of this model eye. The first has field rings and a calibration guide (a US Air Force 1951 resolution target), and is designed to test resolving power and performance of ophthalmic equipment – both ours, and that of the competition. The second version is available with a range of printed retinas and serves as a training aid. During its development, we had to invent a way to print onto a hemisphere at 10 times normal resolution, which was a little awkward!

We have also combined our model eyes with our model head for a training and demonstration system – something we've found to be a massive hit wherever we take it. Increasingly, we get requests for customized models: for example, eyes with various pathologies or bespoke field targets at the back of the eye. One of our clients requested placement of camera sensors at the position of the macula, to exactly simulate what the macula would perceive through the optics of the human eye. And we've even launched a dog model head and eye for training veterinary ophthalmologists in the use of epiCam V.

Digesting feedback

Throughout our journey so far, customer feedback has been essential in letting us know we're on the right track in terms of meeting global clinical needs; for example, revisions to the first generation of epiCam devices were heavily influenced by feedback from Zia Carrim, an ophthalmologist based in Mauritius. The epiCam made a great difference to his clinic, where he sees some very serious cases, but he could still point out areas where we could tweak the device.

Similarly, when I was in India in 2013, I had a very useful meeting with Professor Azad at the All India Medical Institute. He was only going to give me five minutes, but when he realized I was interested in what he actually needed, rather than just trying to sell him something, he gave me two hours! Such market research is incredibly valuable – I learnt about his workload, the kind of diseases they see, how they treat them, and what their needs are now and in the future. In the same way, we get fantastic input from the veterinary community, which helps us improve the epiCam V.

With any suggestions we get from users immediately going into improving the device, we've managed to make the devices better and better over the last five years. It helps being a small company, because we can react very quickly to accelerate product development. In fact – and this may upset the engineers – I am willing to say that I think the epiCams are now design-complete.

"Customer feedback has been essential in letting us know we're on the right track in terms of meeting global clinical needs."

Global position

Our credo is to 'do good' while remaining commercially sustainable. Few companies achieve that – especially in the medical device space. But our model is different – and that's how we can supply low-priced devices to doctors and charities operating in resource-poor locations. The underserved communities will remain our true focus, but I do believe our cameras could be used in the developed world too. Though it's true that the UK has gold standard DR screening systems, it's also true that if the NHS relies entirely on hugely expensive desktop systems, then the number will remain limited. Wouldn't it be better if every GP had access to a simple, low-cost device, so that they could routinely screen every one of their at-risk patients; for example, anyone over 70? However, for that to happen, we'd need to generate political support – and that's perhaps a bigger mountain to climb than those we've already conquered!

Doing good and doing well

The opportunity to apply my knowledge to the field of ophthalmology has become a very important part of my life. I believe Epipole is doing something very valuable – the number of undiagnosed diabetics is far too high, and without improved diagnostics we will see a huge number of people developing DR. Of course, there are other pressing clinical needs in ophthalmology, and we intend to address those, too. In fact, we are going after all the other important eye diseases, one by one, starting with AMD and glaucoma. At the same time, we hope to develop our model eye system into a range of training aids – for retinal laser surgery technique instruction. And we are now prototyping a low-cost version of the model eye, which we hope will extend

Epipole model eye mounted in head

the opportunity to trainee ophthalmologists and optometrists.

When we started Epipole, we set ourselves three key targets: i) to make a device that would have a significant clinical impact in the real world; ii) to provide video output rather than relying on static images; and iii) to visualize the retina at high resolution and with a wide field of view. These challenges involved setting and overcoming extremely high engineering hurdles, and I am very proud of our achievement. At the same time, we've also built a company that does good, while being commercially sustainable. It's a fine line to walk!

Box 4: Model Testing

- Corneal shell equivalent to human cornea
- Crystalline lens analogous to lens of human eye
- Axial length identical to that of human eye
- Water-filled; refractive index extremely close to that of vitreous humor
- Customizable to a range of needs: printed retina, different pathologies, sensors at macula
- Fits in model head for convenience and familiarization
- Manufactured by sophisticated 3D-printing – tolerance at the micron scale
- Precise model of human eye for testing or demonstrating any fundus camera or similar device, or for training in the use of such devices
- Users: academia, industry, hospitals

Early epiCam in use in Indonesia

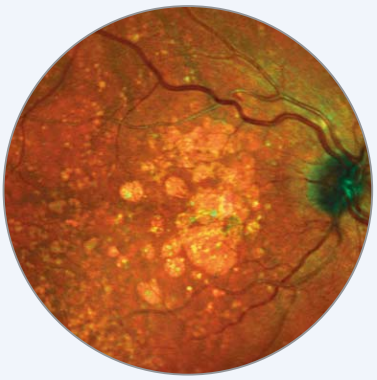
Epipole model eye

The Epipole team

Model dog head for training in veterinary ophthalmology

Technology to Empower: Diagnostics

Decisions come from data – it's why technologies play such an integral role in managing patients. Whether it's initial diagnosis, assessing response to treatment, or monitoring disease progression – or even acquiring the most accurate information to guide surgical procedures – diagnostic technologies are crucial for ensuring that appropriate and timely decisions are made. Here, leading ophthalmic companies showcase their latest diagnostic technology, and explain what these advances mean for you and your patients.



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TruTrack Active Eye Tracking is patented technology that uses a second laser beam to actively track the eye during OCT scanning to avoid motion artifacts. It effectively "freezes" the retina, allowing you to capture the precise OCT image you want, even if the patient blinks or moves. The retinal recognition technology automatically repositions the OCT scan in the same anatomic location at follow-up for incredible accuracy. Detect changes as small as 1 micron and confidently monitor disease progression over time. To learn more about the DNA of SPECTRALIS visit www.spectralis-oct.com.

**The SPECTRALIS OCT Angiography Module has not been cleared by the FDA for use in the United States.*

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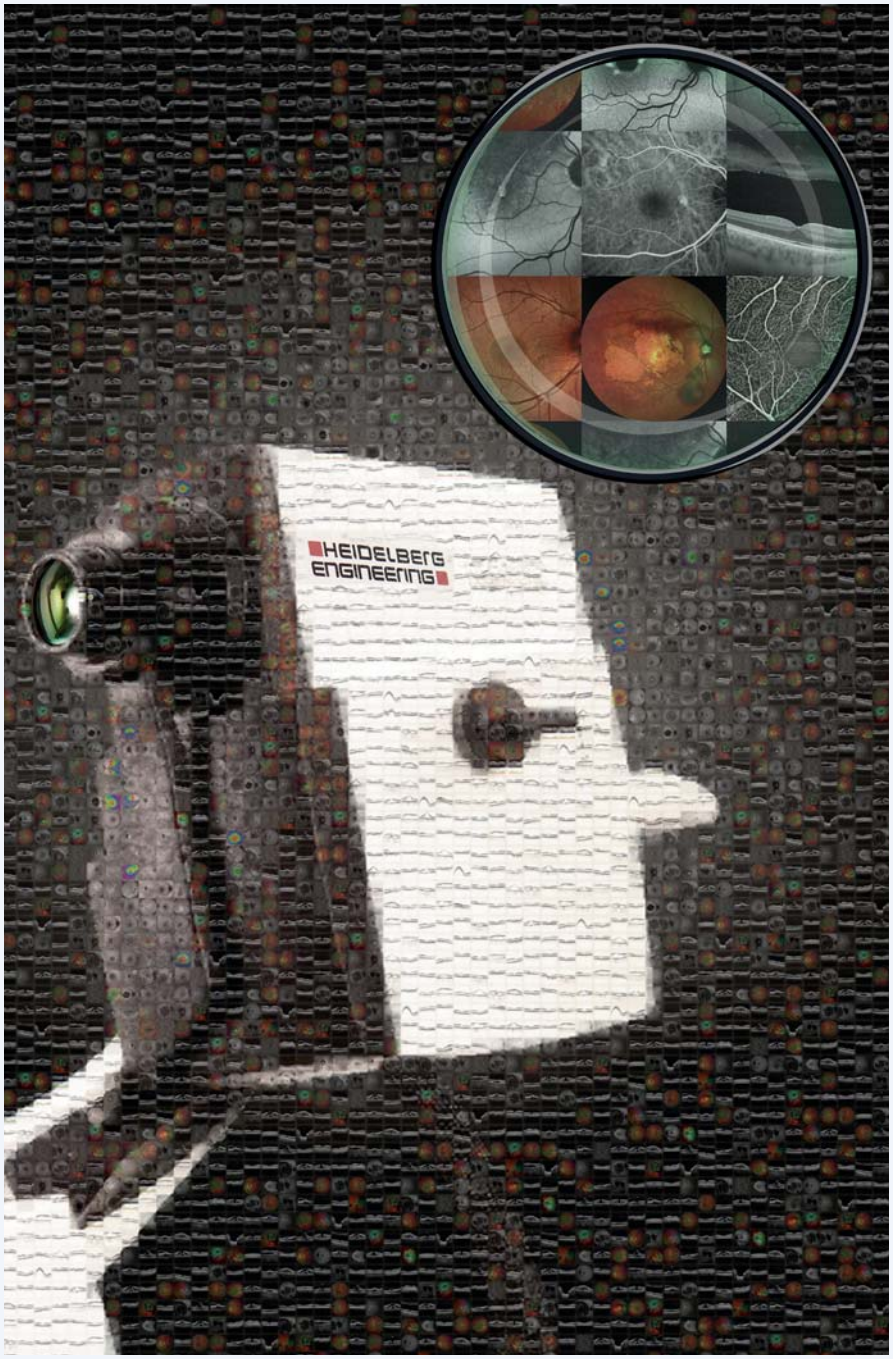

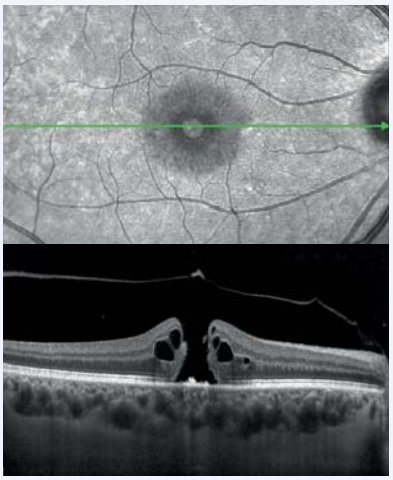

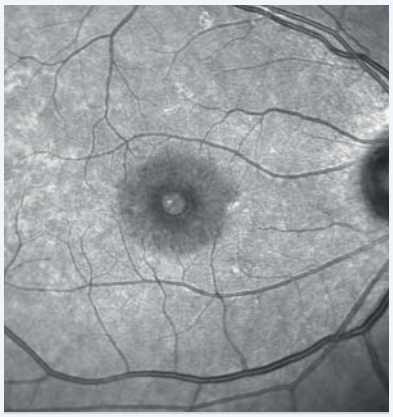

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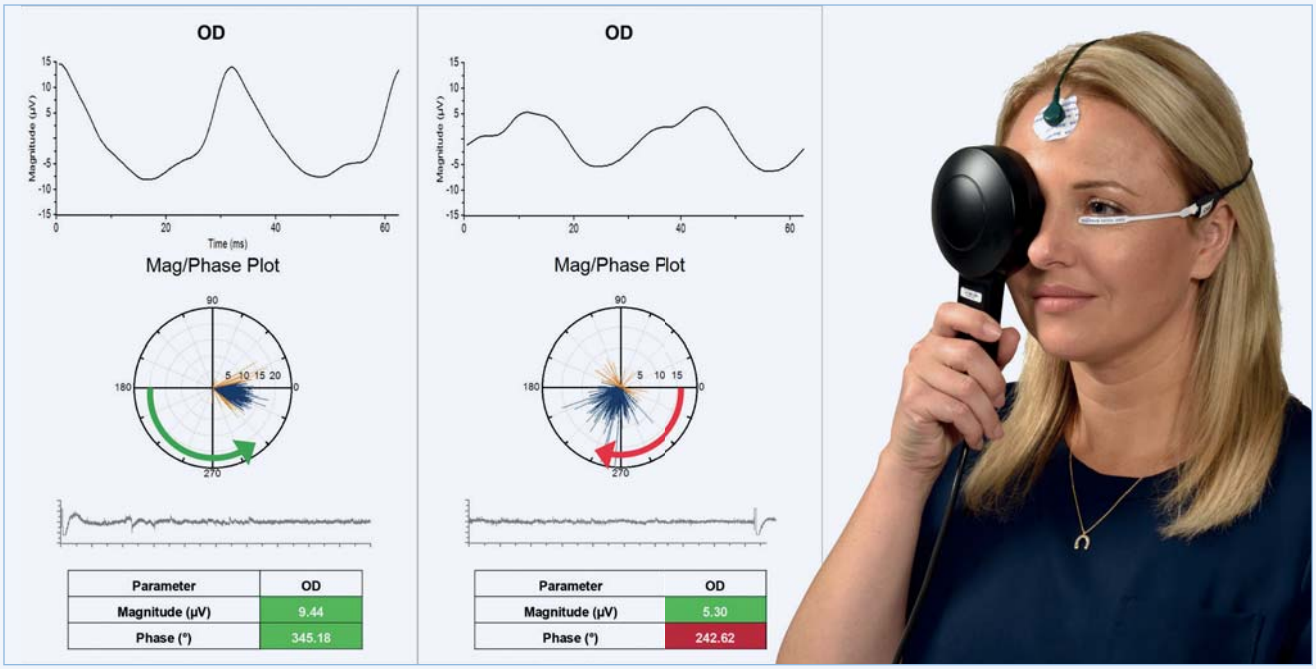

FILLING THE VOID

Modern visual electrophysiology for the eye care practice

When it comes to retinal disease, information is key. Knowing more about the health of the vision system enables early detection, as well as enhanced patient management post-treatment, which leads to better visual outcomes for the patient.

As the world-leader in modern visual electrophysiology, Diopsys®, Inc., has done more than any other company to advance the use of electroretinography (ERG) and visual evoked potential (VEP) in eye care practices – and provide eye care professionals with **objective and functional** information on the health of their patients' vision systems.

With OCT providing objective structural information, fundus photography providing subjective structural information, and visual field testing providing subjective functional information, modern electrophysiology provides the objective functional information that eye care providers need – filling the 'information void' in most practices.

Diopsys' unique patented technology was created with practice-based eye care professionals in mind, and features space-efficient designs, streamlined testing protocols, and intuitive color-coded reports based on documented reference ranges. Three unique platforms – Diopsys® NOVA™ (cart), Diopsys® ARGOS™ (tabletop) and the NEW Diopsys® RETINA PLUS™ (carry case) – accommodate practices of all sizes, and each system can be customized with a full suite of visual electrophysiology modules:

- *Diopsys® ffERG / Flicker (full field ERG)* tests record the retina's response to flashes of light – reflecting the electrical activity of cone and bipolar cells – and provide objective functional information about global retinal health. Clinically effective in helping to manage retinal disorders, such as diabetic retinopathy, central retinal vein occlusion, retinal concerns obscured by media opacities and uveitis (1–5), Flicker vision tests use intuitive color-coded reports to help physicians evaluate retinal disease severity (1,2), predict retinal ischemia (2–4), quantify retinal function loss and recovery (1, 2, 5), and monitor retinal function for appropriate and timely treatment (1, 2, 5).

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- *Diopsys® ERG (pattern ERG)* tests record the retina's response to a phase-reversing patterned stimulus and provide objective functional information on the performance of retinal ganglion cells. Effective in helping physicians diagnose and manage diseases including glaucoma, age-related macular degeneration (AMD) and diabetic edema (6–8), ERG tests identify 'stressed' cells at a subclinical stage – sometimes years earlier than OCT (6). Starting treatment at this early stage – before evident structural defects – can help extend patient sight.
- *Diopsys® mfERG (multifocal ERG)* provides objective information on localized retinal function, and helps physicians recognize the first signs of drug-induced retinopathy (9, 10). As most ocular side effects of drug-induced toxicity are reversible after cessation of therapy if detected early (10), mfERG can help physicians co-manage patients more efficiently.
- *Diopsys® VEP (visual evoked potential) testing* objectively records the conductivity of the visual pathway in response to a phase-reversing patterned stimulus, and provides important diagnostic information on the functional integrity of the entire visual system, from the anterior segment to the visual cortex. Useful for detecting and monitoring many types of visual abnormalities, it is often used for the diagnosis and management of neuro-visual disorders, such as optic neuritis, amblyopia, and vision problems caused by traumatic brain injury (11-13).

Testimonials

"The only objective, functional method at our disposal for diagnosing and managing retinopathies and glaucoma is ERG. Thankfully, scientific advances from Diopsys® have enabled this testing modality to be incorporated into the clinic. ERG testing has more than proven its worth in evaluating retinal pathologies, which means that I use the Diopsys® device in my clinic daily."
William Ayliffe, FRCS, PhD, Consultant Ophthalmologist, Lister Hospital, London, UK.

"Accessible, modern visual electrophysiology devices from Diopsys® provide objective measures of function and are useful in following progression of disease, or response to treatment. Pattern ERG is particularly useful when visual field testing is difficult to perform. Most importantly, though, it provides a mechanism to diagnose glaucoma at an earlier stage – when it is in a reversible state. Thus, pattern ERG testing represents a powerful tool to aid clinical decision making, especially regarding when to start therapy to avoid vision loss from glaucoma progression."
André Mermoud, MD, Medical Director, Genolier Swiss Visio Network SA, Clinique de Montchoisi, Lausanne, Switzerland.

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TWO IN ONE

Anterior segment tomography and IOL calculation all-in-one device: the OCULUS Pentacam® AXL

All surgeons want the best for their patients, and when it comes to refractive outcomes, anterior segment analysis plays a key role. The Pentacam® and Pentacam® HR provide a gold-standard in anterior segment tomography. Now meet the newest member of the family – the Pentacam® AXL.

Based on the trusted Pentacam® HR system, which offers high-resolution Scheimpflug imaging, the Pentacam® AXL offers the additional feature of axial length measurement – a crucial part of accurate IOL calculation and customized IOL selection. Through partial coherence interferometry biometry, the Pentacam® AXL collects several successive axial length measurements; patient eye movement is detected by the pupil camera and corrected for, and a 3D model of the anterior segment based on ray tracing allows for the correction of individual optical distortions. Using fourth generation IOL formulas, the system can automatically calculate IOL power. Because the total corneal refractive power (TCRP) map shows the influence of the posterior corneal surface with regard to total corneal astigmatism axis, magnitude and regularity, the IOL calculation software can account for posterior corneal astigmatism. The software also accounts for prior refractive surgery and pre-existing conditions, ensuring a reliable IOL power calculation for any IOL type in both virgin and post-refractive eyes.

The upshot? The Pentacam® AXL enables full screening before corneal refractive and cataract procedures. Laser vision correction procedures can be planned effectively; patients can be screened for existing diseases such as Fuchs endothelial dystrophy or angle-closure glaucoma; prior refractive surgeries can be detected; and crystal lens densitometry can be used to plan femtosecond laser-assisted cataract surgery (FLACS). Now, accurate IOL calculation can also be achieved – as well as customized IOL selection regarding multifocal, toric and aspheric IOLs, all from one device.

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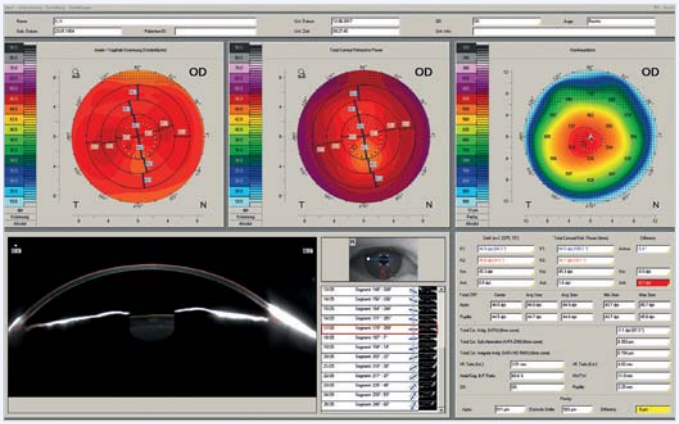

Figure 1. TCRP map for the right eye.

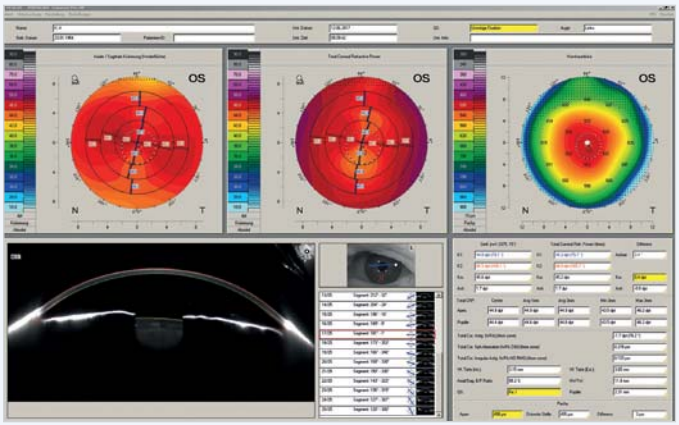

Figure 2. TCRP map for the left eye.

Figure 3. IOL calculations.

Pentacam® AXL in Action

A case study by Ina Conrad-Hengerer, MD, University of Heidelberg, Germany.

A 63-year-old woman presented with subjective loss of visual acuity and increased glare. Corrected distance visual acuity (CDVA) was reduced in both eyes; 20/63 (-0.5 D -1.0 D × 98°) in the right eye and 20/40 (-1.0 D -0.75 D × 75°) in the left eye. Examination of the anterior segments revealed senile cataract without corneal pathology. Before medical mydriasis or further examinations, Scheimpflug imaging and anterior segment analysis by Pentacam® AXL was performed. The postoperative target refraction was emmetropia for distance, and fundoscopy showed no macular changes.

The TCRP map showed increased corneal astigmatism of the axial topography from 0.9–1.6 D (right eye) and from 1.4–1.8 D for the left eye, respectively (Figures 1 and 2). Usually, toric IOL implantations are considered based on spectacle correction and anterior corneal keratometry values – but that approach would not have identified this result. Total spherical corneal aberrations (6 mm zone) were 0.353 µm (right eye) and 0.305 µm (left eye), revealing that an asphericity-correcting IOL could be a good option. Total corneal irregular astigmatism (4 mm zone) was 0.154 µm (right eye) and 0.145 µm (left eye); as 0.3 µm is the recommended limit to avoid photic phenomena, multifocal IOLs could be offered to this patient.

The IOL calculations are presented in Figure 3. Femtosecond laser-assisted cataract surgery followed by implantation of monofocal aspheric toric IOLs was performed (right eye, +18.0 D 1.5 D/6°; left eye, +18.0 D 2.25 D/6°). One day after surgery, UDVA was 20/20 in both eyes, increasing to a UCVA of 20/16 one month after surgery. Objective refraction measured by Nidek AR310A was +0.25 D 0.25 D/110° (right eye) and plano -0.25/60° (left eye).

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In Practice

Surgical Procedures
Diagnosis
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Stop the Processes?

Reducing IOP by targeting the ciliary body; two physicians present two different approaches

In the quest to move away from topical management of glaucoma – and the associated issues, including non-compliance – the field has seen a shift towards surgical management, with a boom in minimally invasive technologies transforming glaucoma care. One such option is cyclophotocoagulation – a procedure which targets the ciliary body epithelium to modulate aqueous production and lower IOP. Here, two surgeons share their preferred cyclophotocoagulation approaches, and talk through how – and why – they perform them.

ECP Explained

Top tips for endoscopic cyclophotocoagulation – an ab interno approach

By Brian Francis

At a Glance

- *Many surgical approaches focus on reducing IOP by improving outflow*
- *Cyclophotocoagulation reduces inflow – and thus IOP – by decreasing aqueous production*
- *Endoscopic cyclophotocoagulation (ECP) directly targets the ciliary processes for treatment via an ab interno approach*
- *Gain top tips from my own experiences, and learn how ECP has benefited my patients.*

Glaucoma is epidemic worldwide – and the number of people affected is set to increase to 79.6 million by 2020 – 74 percent of which will have open angle glaucoma (OAG) (1). Although a multifactorial disease, the primary treatment approach is IOP reduction to prevent further damage to the optic nerve. First-line therapy with topical hypotensive medications is effective when used according to direction; however, these can be limited by poor compliance or insufficient efficacy. It's why multiple surgical IOP-lowering treatment options are also available and in development, each of which targets different outflow and filtration pathways (see Surgical management of IOP). Of these, treatments that target aqueous production are gaining in popularity.

It was first discovered in 1905 that severing the ciliary body could decrease IOP (2). In the 1960s, transscleral ultrasound radiation was used to achieve the necessary destruction (3). Since then, multiple methods of cyclodestruction have been popularized, including cyclophotocoagulation through a transpupillary route, or a contact or non-contact transscleral route (4). Transscleral cyclophotocoagulation (TSCP) – in which ciliary processes are targeted from an external approach with a Nd:YAG or diode laser – has been through several iterations since it was first introduced in the 1970s. In 1992, Martin Uram introduced the use of an intraocular endoscope paired with a diode laser to achieve cyclophotocoagulation using an ab interno approach (5). Endoscopic cyclophotocoagulation (ECP) applies 810 nm wavelength light directly onto the ciliary processes, with positioning visualized by the surgeon through the endoscope. Here, I overview my top tips for performing ECP, and share some case studies of its use.

ECP: Top Tips

Anterior segment approach

- The key to this approach is to treat as many ciliary processes as possible. Even with a 360 degree treatment, the posterior aspect of the processes can be missed. For a significant effect it is advisable to treat 360 degrees, including in between each process. Many surgeons do not treat the intervening space between each process, but as the ciliary epithelium completely encompasses each process – including between the peaks and valleys – it is advisable.
- Titrate the power to achieve a good effect with whitening and shrinking of each process, taking care not to over-treat and cause them to 'pop'. Laser power can be adjusted manually and length of delivery controlled by the foot pedal. Proximity of the probe to the process being treated is important as being too close can result in delivering too much energy – I have found that it is ideal to have six to 10 processes within view.
- Thoroughly inflate the ciliary sulcus with a heavy viscoelastic until the iris nearly touches the cornea. Healon GV (Johnson&Johnson Vision) is my choice, because there is no bubble formation, the higher molecular weight maintains the space, and I find it easier to remove than others. Pushing the iris forward and the lens back will give you the space in which to work.
- A 2.2 mm limbal clear corneal incision works well. Too large an incision may cause the loss of viscoelastic, resulting in poor inflation. When complete, ensure the removal of all the viscoelastic. I have found that some form of irrigation and aspiration is typically needed to avoid pressure spikes. Flushing with BSS and trying to 'burp' it out may not be sufficient.
- For the anterior approach, I prefer the patient to be pseudophakic. It is possible to treat a phakic eye, but it is much more difficult. If the patient is aphakic and vitrectomized, do not try to inflate the sulcus with viscoelastic – use an anterior chamber maintainer, which will preserve the integrity of the globe while the surgery is performed.

Pars plana approach

- Execute a pars plana incision, generally with a 20 or 19 G MVR blade or a 2.2 mm keratome. Perform the procedure through a standard three port vitrectomy or a two port vitrectomy with an anterior chamber maintainer. Place the vitrector in one port and the endoscope in the other. View with the endoscope and perform a limited vitrectomy. Then perform the ECP procedure. Once accomplished, switch hands and perform a vitrectomy and ECP with the other hand from the opposite side. I find this technique works quite well even for anterior segment surgeons.
- For the pars plana approach, it is advisable to avoid 360 degree treatments – a greater portion of the ciliary epithelium is treated due to improved access to the entire length of the ciliary processes. This is especially true with ECP Plus (see below), which includes not only the pars plana approach but treatment of all of the ciliary processes along with approximately 1–2 mm of pars plana. This treatment may result in acute IOP reductions and should be used with care to avoid hypotony.

General top tips

- To facilitate treatment of the ciliary processes via the anterior or posterior approach, scleral depression may be used. This maneuver splays out the processes, allowing for more complete treatment of the processes and the areas in between. If ECP becomes challenging due to significant anterior segment pathology, such as posterior synechiae, consider the pars plana approach.
- Anterior and posterior synechiae can typically be severed to facilitate access to the ciliary sulcus. In some cases, residual lens material or posterior iris synechiae are discovered. Removal is possible if necessary, however, these can sometimes be circumvented by manipulation of the probe. This will require an adjustment of the power as the probe tip will generally be in close proximity to the ciliary processes. As previously stated, if these are severe consider a pars plana approach.
- The most common complication of ECP is inflammation, and this needs to be managed thoroughly. Treatments can include intracameral

dexamethasone (600–1,000 µg), subconjunctival dexamethasone, and IV or topical steroids. Oral prednisone can also be administered postoperatively. I find it best to treat aggressively at first, and then taper relatively quickly to avoid extended treatment. As steroid response can occasionally mask IOP lowering, taper the steroid once inflammation is controlled and reevaluate the IOP if the desired IOP has not been reached.

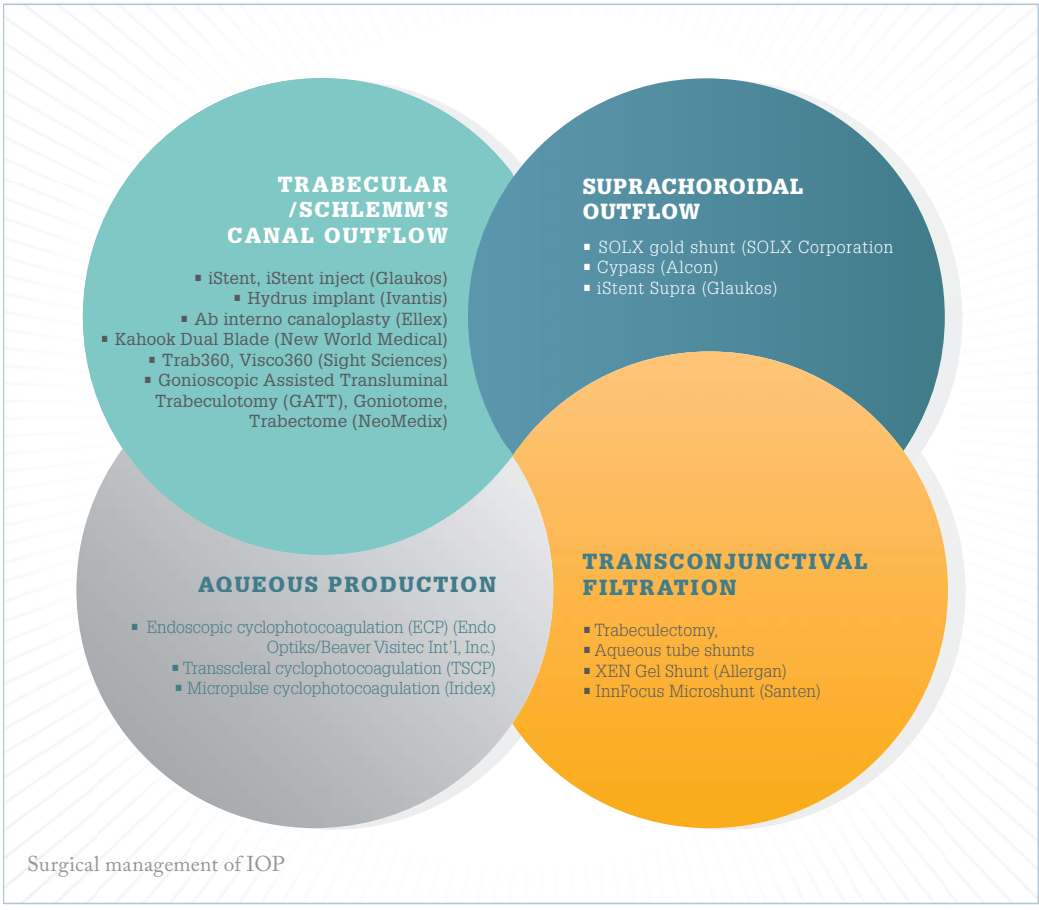
ECP: case by case

Many other surgical options are only available to patients with OAG, but ECP can be used in a wide spectrum of glaucoma patients – either OAG or chronic angle-closure – as well as at any disease stage. For patients with refractory glaucoma who have failed other procedures, the ECP Plus procedure (ECP via a pars plana approach combined with vitrectomy and pars plana laser treatment) has been shown to be effective (6). ECP can also be effectively combined with any other outflow surgery, and because techniques can be readily learned by anterior segment surgeons, it can be used in combination with cataract surgery.

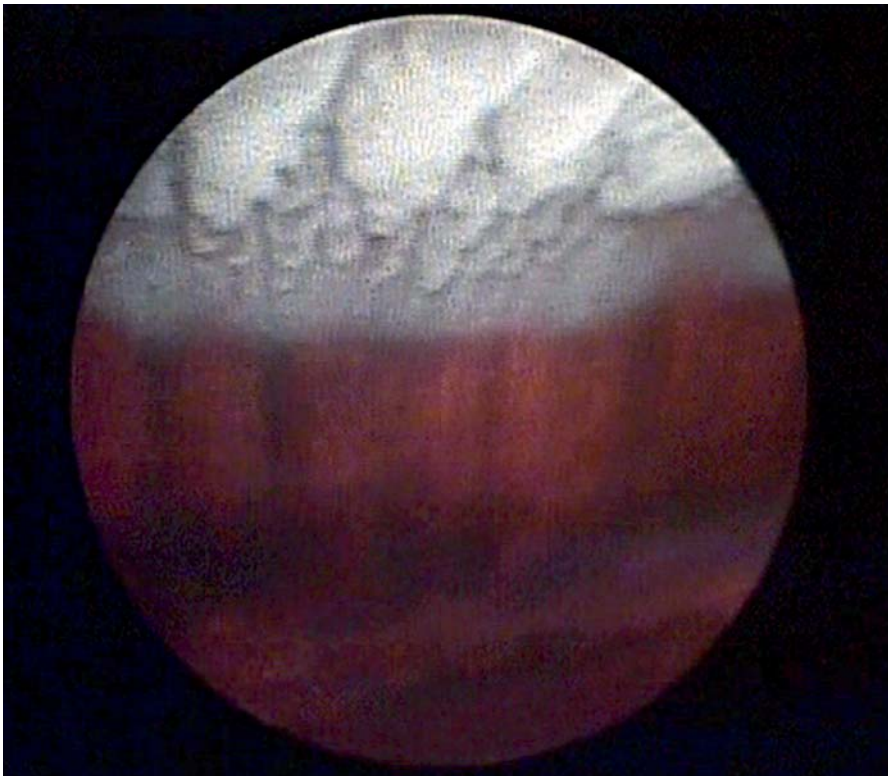
The flexibility of ECP in the glaucoma treatment paradigm is illustrated in the following three cases.

Case 1

A 68-year old Asian female with a history of mixed mechanism glaucoma and chronic angle closure presented with moderate glaucoma damage. Her cup-to-disc ratio was 0.75, and her pressures were controlled at 16 –18 mmHg with two medications (latanoprost at night and timolol in the morning). Her visual field tests were stable with a mean deviation of approximately -6.0 dB. The patient manifested visually significant cataracts (best corrected visual acuity, 20/60). After discussion with the patient, we decided to combine cataract surgery with ECP; because of the patient's



Surgical management of IOP


ECP plus: Ciliary epithelium is photocoagulated on the ciliary processes as well as a row along the pars plana at the base of the processes.

angle closure, we determined that reducing aqueous production was a better option than angle-based outflow procedures. Following combined cataract surgery with ECP, she initially maintained her glaucoma medications. We then tapered off her medication, and her IOP now sits between 15–17 mmHg without any medications. Her visual field tests are stable and her visual acuity has improved to 20/20.

Case 2

A 32-year old Caucasian female presented with symptoms of intermittent angle closure, including headaches, eye pain, and visual phenomenon – particularly at night time. Gonioscopy and anterior segment OCT revealed that she had appositional angle closure in three to four quadrants. The patient was also hyperopic with a +2.25 D correction. The first treatment, a laser iridotomy, was successful at creating a patent opening, but the patient was still experiencing symptoms of intermittent angle closure. Repeat gonioscopy verified that the angles were still quite narrow, and the patient had a plateau-type approach, some phacomorphic component, and that the peripheral iris was also very anteriorly displaced.

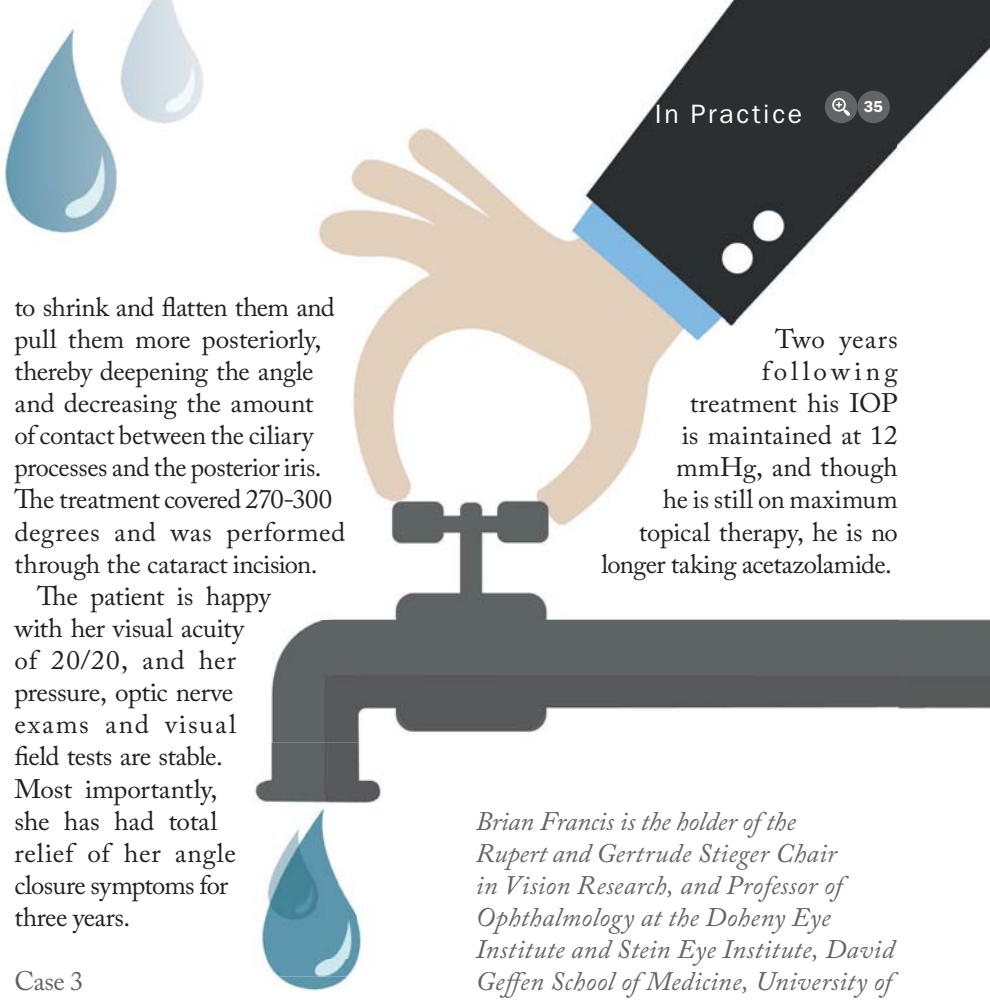
Ultrasound biomicroscopy (UBM) verified the very narrow angles and also revealed some anterior lens vault. Very prominent, anteriorly rotated ciliary processes were pushing the peripheral iris anteriorly. Pilocarpine treatment was tried, but the patient had severe side effects including decreased vision. Repeat laser iridoplasty was an option as it was somewhat effective previously, but the patient considered this to be a "band-aid" measure that would not last, so we discussed incisional surgery. Even though her vision was 20/25 with a clear lens, we opted for lens extraction combined with endoscopic cycloplasty (ECPL) to improve her anatomical abnormality. The ciliary processes were treated with laser to shrink and flatten them and pull them more posteriorly, thereby deepening the angle and decreasing the amount of contact between the ciliary processes and the posterior iris. The treatment covered 270-300 degrees and was performed through the cataract incision.

The patient is happy with her visual acuity of 20/20, and her pressure, optic nerve exams and visual field tests are stable. Most importantly, she has had total relief of her angle closure symptoms for three years.

Case 3

This final case is a 72-year old Latino male with advanced primary open angle glaucoma (POAG). His cup-to-disc ratio was 0.90 in one eye and 0.95 in the other, with IOP at 16 –18 mmHg. Both eyes had previous trabeculectomies and Baerveldt aqueous tube shunt implants. Both of these surgeries failed to adequately control IOP, and the patient was receiving maximum topical medication to maintain his target pressure of below 15 mmHg. The patient was lost to follow-up for one year and when he returned, he was also taking oral acetazolamide 500 mg twice daily because the drops alone were not controlling his IOP. He was uncomfortable taking the acetazolamide and experiencing side effects, including tingling, fatigue and gastrointestinal symptoms, prompting him to return to me for a new option.

At this point, his central vision was still 20/25 but he had severe visual field constriction. Talking through the options, we decided to perform ECP on each eye at separate sessions. Each received 360 degrees of ECP from an anterior approach.



Two years following treatment his IOP is maintained at 12 mmHg, and though he is still on maximum topical therapy, he is no longer taking acetazolamide.

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Reassessing TSCP's Role

Transscleral cyclophotocoagulation as an in-office approach to glaucoma management – and an earlier option in the treatment paradigm

The TSCP procedure.

By David Gossage

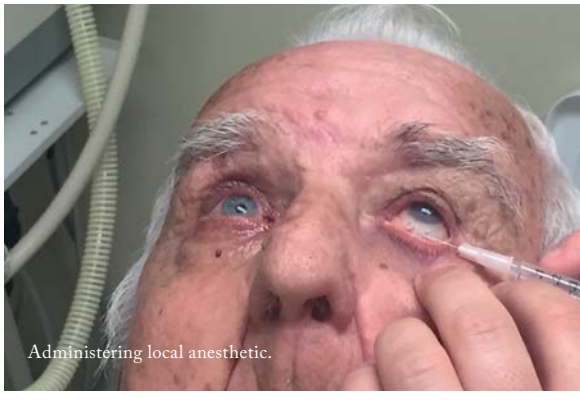
Traditionally, cycloablation procedures to lower IOP have been reserved for patients at – or near – the limit of maximum tolerated medical or surgical therapy, or for patients with refractory glaucoma. One such procedure is transscleral cyclophotocoagulation (TSCP). Performed in the office or in the OR using an 810 nm laser and a transscleral laser delivery probe, TSCP involves ciliary body destruction by targeting the ciliary epithelium to reduce aqueous humor production and therefore lower IOP.

Though effective, cyclophotocoagulation treatments can have some limitations and associated risks. One important limitation of traditional cyclophotocoagulation is the requirement for anesthesia. The treatment endpoint is ablation of the ciliary body in the superior and inferior regions, often marked by an audible 'popping' sound. As this is painful for the patient during treatment, anesthetic is required in the form of retrobulbar block, heavy sedation or general anesthesia in the OR. Although retrobulbar block is feasible, it comes with its own risks and potential complications, including retrobulbar hemorrhage, ocular perforation (especially in patients with high myopia or staphyloma), diplopia, retinal artery and vein occlusion, risk of perforating the nerve sheath or optic nerve damage. The TSCP procedure itself has also been associated with complications, such as hypotony, hyphema, vision loss, and inflammation that can lead to pain or discomfort after treatment.

As such, clinical decisions surrounding cyclophotocoagulation – and other cyclodestructive procedures – often balance safety and efficacy with quality of life, meaning that many physicians are not prepared to damage the ciliary body unless the prospect for disease progression and visual field loss are substantial.

However, I believe that the role of TSCP for glaucoma management can be reassessed. With new techniques and technologies available it should no longer be considered only a 'last resort' treatment, but rather used earlier in the disease process and in patients who have good vision.

MicroPulse technology – a treatment delivery mode in the Cycloe G6 laser console from Iridex – separates a continuous wave laser beam into segments, delivering targeted pulses of energy to the ciliary epithelium to modulate aqueous production. There is also some evidence that shows that segmented laser energy delivery augments the aqueous outflow pathway by constricting and expanding ciliary muscles (1). As the laser is applied with a duty cycle of 31.3 percent, energy is only delivered for around a third of the treatment application. Between pulses of energy, the tissue can cool, preventing a build-up of thermal energy and thermal spread. The reduction in overall energy also means that there is less pain and discomfort for the patient, which raises the potential to perform TSCP as an in-office procedure, using only local anesthesia – an approach we use for many of our patients.



Administering local anesthetic.

At a Glance

- *Transscleral cyclophotocoagulation (TSCP) destroys the ciliary processes, and lowers IOP by reducing aqueous humor production*
- *Although an effective procedure, TSCP is often considered a 'last resort' because of the discomfort of the procedure, the need for anesthesia or deep sedation, as well associated risks and complications*
- *As newer technologies become available, the role of TSCP should be reassessed such that it can be considered earlier in the treatment paradigm*
- *Using a segmented laser, TSCP can be used as an in-office procedure under local anesthesia.*

In-office TSCP

In our clinic, we introduce MicroPulse TSCP to patients who are currently receiving IOP-lowering therapies. We find

it a nice adjunct to most existing treatment approaches, and most of the cases I have performed are in individuals who have previously received laser trabeculoplasty. Previous argon laser trabeculoplasty (ALT) is not a contraindication, even though it yields destruction of the trabecular meshwork.

Local anesthesia

We begin the procedure by using a cotton tip to apply topical anesthesia to both the superior and inferior conjunctiva. We then inject local anesthetic (0.5 cc of 2 percent lidocaine with epinephrine) subconjunctivally to numb the globe, and allow it to diffuse for about 10 minutes. After the patient is comfortable, we set the laser at 2,000 mW of power with a 31.3 percent duty cycle.

The treatment

Laser is applied in 10-second passes along the entire inferior or superior region of the eye, for a total of 90 seconds of treatment time per hemisphere. The 3 and 9 o'clock positions should be avoided because of the long ciliary nerves. Unlike previous versions of cyclophotocoagulation, there is no visible – or audible – tissue destruction to use as a treatment endpoint. Instead, treatment duration is decided at the surgical planning phase. For example, a treatment time of longer or shorter than 90 seconds may be used depending on the extent of IOP-lowering needed, and treatment duration can be titrated specifically to patients. Use of a lid speculum throughout the procedure is discretionary; some patients find it uncomfortable, and it is possible to simply hold the lids open while applying the laser.

Post-procedure

After the procedure, we ask patients to apply a topical corticosteroid QID for one week. We typically see the patient back in the office at one week, one month, and three months post-procedure, depending on how their IOP is responding. As far as outcomes, we usually aim for patients to reach a target IOP rather than attempting a percent or numerical reduction in IOP; however, in our experience, 35 percent to 40 percent reduction in IOP can be expected.

Our experience

We have found several advantages to performing in-office TSCP under local anesthesia. It is more time efficient than performing a retrobulbar block, or administering heavy sedation or general anesthesia – whilst also avoiding associated risks. There is no 'downtime' waiting for the OR staff to turn a room around or waiting for patients to be prepped for surgery. And that allows the treating physician to manage their time more appropriately. There is also less cost to the patient and insurance company because OR/ambulatory surgery center and anesthesia fees can be avoided. Moreover, as deep sedation or general anesthesia are not needed, we can verbally communicate with the patient during the procedure; not only do patients feel more comfortable as we apply the laser, but they can also inform treating staff if there is any pain or discomfort. So far, no patients have asked us to stop the procedure because of pain or discomfort.

The procedure is non-invasive, and easily repeatable if necessary. In summary, as new technologies become available, it is time to consider the potential of TSCP as an in-office approach to treating glaucoma – and not just for patients who have a poor prognosis or refractory disease.

David Gossage is a comprehensive ophthalmologist at Gossage Eye Institute and Optical, Hillsdale, MI, USA. Gossage reports that he receives compensation from Iridex for scientific lectures.

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Research advances
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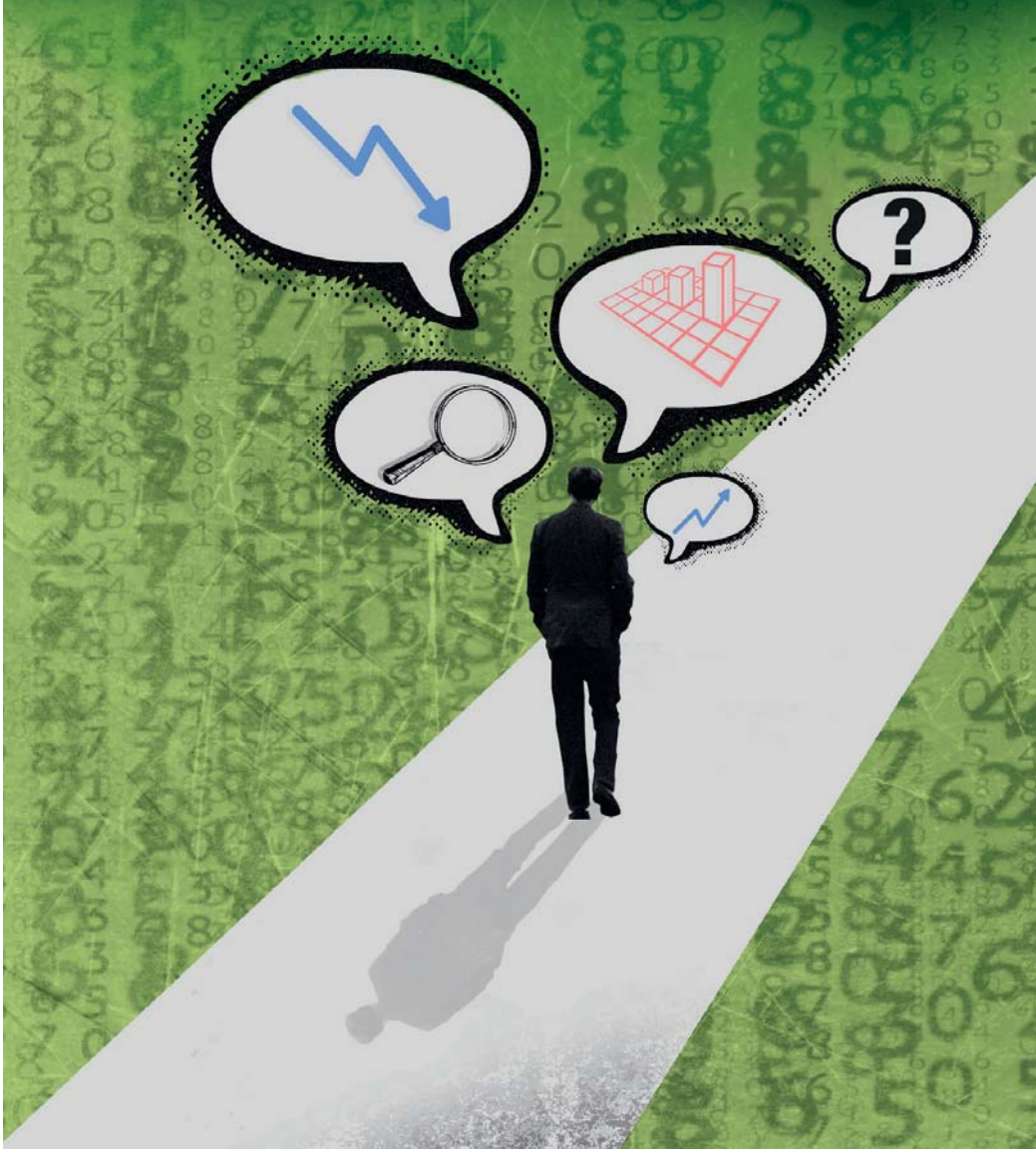
Surprising Associations, Surprisingly Available

Clinical records harboring useful data are there for the taking – we just need to access and analyze them

By Anthony Khawaja



With clinical care comes patient-specific records of medication history and disease outcomes. Today, these data are better captured and curated, and more widely available than ever before – which is exciting because such information from routine clinical care can readily provide important and unexpected insights into drug effects or disease biology. Our recent investigation (1) into potential associations between glaucoma risk and systemic medications is testament to this. Our idea was to assess every medication class for its potential contribution to the probability of developing serious glaucoma. But with hundreds of drug classes to independently analyze, we needed a very large number of patient records to get statistically meaningful results.

Big ideas need big data

Luckily, my collaborators had access to (and were familiar with) the Truven Market Scan Data Set (2) - a database comprising US insurance claims from nearly 200 million patients. These records were generated through routine clinical care, and so are not as rigorous as trial data; nevertheless, they include key facts, such as which patients had glaucoma and of what type, what procedures they underwent and what medications they had been prescribed. It was exactly what we needed.

"Routine clinical care can readily provide important and unexpected insights into drug effects or disease biology."

At a Glance

- *Expert interrogation of large medical records databases may yield important insights into drug effects and disease biology*
- *From a medical insurance claims dataset, 423 drug classes (1,763 drugs) were assessed for an association with glaucoma risk (6,130 test records, 30,650 controls)*
- *Unexpected findings included a 26 percent higher risk of POAG associated with calcium channel blocker prescriptions, and a 30 percent lower risk associated with SSRI prescriptions*
- *Much can be learned from clinical databases, and findings from these studies can open the door to research novel disease pathways.*

"At this stage, the associations between particular drug classes and POAG seem to be genuine."

We developed a methodology (Box 1) to interrogate the Truven dataset and analyze potential associations between systemic drug use and development of primary open angle glaucoma (POAG). In brief, we matched two populations of patients – those with POAG who had received a glaucoma procedure, and patients who had undergone cataract surgery but had not been diagnosed with any form of glaucoma. We then compared prescription drug use in the preceding five years. And it was exciting! With such a large patient group, we could test all 423 drug classes yet maintain statistical validity. I felt sure that we would discover something new. And we did.

Box 1: Methodology Outline

- Analyzed US insurance claims database containing medical records for >170 million patients
- Test population: patients with POAG who had received a glaucoma procedure
- excluded: patients with other forms of glaucoma
- Control population: patients who had undergone cataract surgery without a glaucoma diagnosis
  - excluded: patients with glaucoma or undergoing non-routine cataract surgery
- Alternative control population: patients with any visit to an ophthalmologist
- A total of 423 drug classes (1,763 drugs) were assessed, used in the five years preceding POAG procedure in 6,130 test patients, matched to 30,650 controls
  - alternative control population: 6,269 tests matched to 43,883 controls
- Association of drug use with POAG was analyzed by logistic regression using standard statistics packages (SAS, STATA and R)
  - Drug classes significantly associated with POAG were separately analyzed for dose-response effect on POAG risk

SSRI	*Beta-blockers*	*Calcium channel blockers*
• 30 percent lower risk • Odds ratio (95% CI), 0.70 (0.61–0.82) • $P=1.04\times10^{-15}$	• 23 percent lower risk • Odds ratio (95% CI), 0.77 (0.72–0.83) • $P=2.71\times10^{-14}$	• 26 percent higher risk • Odds ratio (95% CI), 1.26 (1.18–1.35) • $P=1.78\times10^{-11}$

Table 1. Top three drug classes significantly associated with POAG risk

Surprise, surprise

One of the clearest signals we identified was an association between beta-blocker use and reduced glaucoma risk – an effect known since the 1960s and caused by the ability of systemic beta-blockers to lower IOP. We were pleased to find this, as it was rather like an internal control, proving to us that our model was working. But another observation really caught our attention; although a number of associations were evident (Table 1), two drug classes stood out in particular.

Firstly, we found a strong association between calcium channel blocker prescriptions and increased POAG risk; the scale of the increased risk (26 percent) was remarkable, and the statistical significance very high ($P=1.8\times10^{-11}$). Previous studies have hinted at a possible link between calcium channel blockers and glaucoma, but never revealed a consistent association. To find such a strong signal was therefore completely unexpected. Secondly, we found an even stronger and larger-scale association between selective serotonin reuptake inhibitors (SSRIs) and decreased POAG risk; the protective effect for SSRI users is ~30 percent as compared with non-users, and the statistical significance is even higher than for calcium channel blockers ($P=1\times10^{-15}$ and $P=6\times10^{-24}$ in analyses based on the alternative control population). We also found a marked

dose-response effect: longer SSRI use was associated with a progressively lower risk of having a glaucoma procedure.

As we only have observational data at this stage, we cannot be certain of a causative relationship between drug use and altered POAG risk. In theory, the increased risk associated with calcium channel blockers could instead be caused by the high blood pressure – the symptom the drugs are prescribed to treat, rather than the drugs themselves. However, this seems unlikely, as our analysis indicates that ACE inhibitors – the commonest antihypertensive class in the study – showed no significant association with glaucoma risk. Similarly, we found no association between POAG risk and anti-depressive classes unrelated to SSRIs (such as tricyclics). A separate statistical analysis revealed no association between depression diagnosis and POAG risk. Therefore, it is possible that the protective association observed with SSRIs is a function of drugs that interfere with serotonin reuptake. Another theoretical possibility is prescribing patterns: for example, physicians may be less likely to prescribe SSRIs for POAG patients. But our finding of a clear correlation between increasing SSRI use and progressively lower risk of POAG counteracts any role played by prescribing patterns. At this stage, the associations between particular drug classes and POAG seem to be genuine.

What's going on?

Right now, we're not sure what our findings mean – but we know they merit further investigation into potential mechanisms driving disease. The SSRI association could be mediated through serotonin pathways in ocular tissues, but this is currently a poorly understood field. Serotonin receptors are expressed in retinal ganglion cells (3) – but also in the iris and ciliary body. Some have suggested that serotonin pathways affect pupil diameter, which then contributes to glaucoma risk. And there is also some evidence that serotonin receptors may directly affect IOP (4). Getting to the bottom of serotonin's role in ocular biology will be a fascinating journey.

The mechanisms driving the calcium channel blocker association also require some unraveling given that both low blood pressure and hypertension diagnosis are associated with increased glaucoma risk (5). There is evidence that the higher risk of glaucoma with lower blood pressure is only seen in patients receiving antihypertensive treatment (6); it is possible that the increased risk is not due to low blood pressure per se, but due to other effects on the optic nerve by specific antihypertensives such as calcium channel blockers. The relationship certainly needs investigating because hypertension is a common comorbidity in glaucoma, and so many patients are taking calcium channel blockers – in fact, Japanese physicians sometimes prescribe these drugs to protect against glaucoma...

What next?

Although clinical practice shouldn't change because of our findings, we do think our data reveal important information and interesting hypotheses to explore. One of our imminent next steps is to repeat our work using another dataset, such as the UK BioBank. If the associations still hold in an independent data set, it warrants further work; we must establish the biological basis of the effect – for example, by investigating whether these drugs can modulate glaucoma risk in animal models.

Our findings could also guide fundamental research into disease mechanisms; for example, the role of serotonin pathways in glaucoma etiology. POAG is complex and multifactorial; certainly, IOP is not the whole story, as high IOP patients don't always get glaucoma, and low IOP patients sometimes do. As we still don't understand much of the biology that underlies this disease, we need new hypotheses. And datasets, such as the one we investigated, could suggest specific avenues to explore.

"Getting to the bottom of serotonin's role in ocular biology will be a fascinating journey."

Currently, we are investigating the relative risk associated with different calcium channel blockers. We are also examining associations between systemic medications and relevant ocular features, such as cup-to-disc ratios. More generally, there is still so much to do with datasets like Truven. I think we are 'missing a trick' because nobody has investigated associations between systemic medications and macular degeneration or diabetic retinopathy. Given that patients with these conditions are older and more likely to be receiving systemic medications, we really need to understand how different drugs might affect disease progression and response to medication, or even to surgery. Database 'mining' can really help this kind of investigation, and can generate novel and surprising discoveries. It's

also a very cost-effective approach: interrogating existing records doesn't incur the costs associated with getting informed consent from – and running tests on – each of several hundred new patients. The data is already available. We just need to take more advantage of the new insights available to us.

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A View to the Future

By identifying vision problems early, we can unlock children's true learning potential

By Andrew Morgenstern

Most learning, cognition, and perception – maybe as much as 80–85 percent – is mediated through vision. Although researchers cannot be exact on this statistic, they have found significantly lower achievement test scores (1), reduced letter and work recognition, receptive vocabulary, emergent orthography (2), and verbal and performance intelligence quotients (3) among children with uncorrected hyperopia. It is also known that vision-related problems are more prevalent in children with learning disabilities compared with the entire population (4).

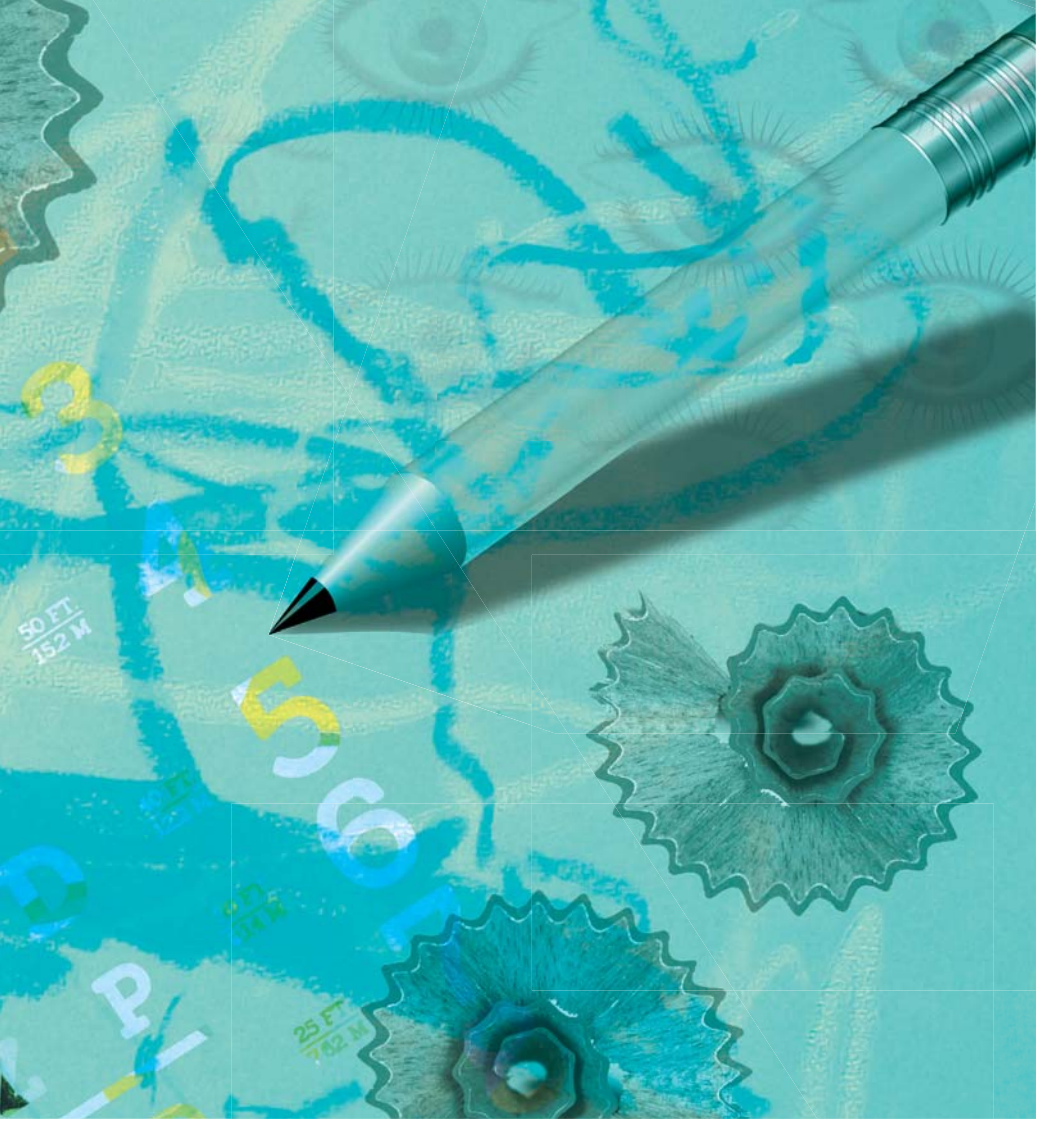
At a Glance

- *Vision assessments and comprehensive, dilated/cycloplegic eye examinations are critical to ensure that children succeed in school, and to prevent academic issues at all levels*
- *An estimated one in five preschool children in the US has a vision problem, yet less than 15 percent of preschoolers receive an eye exam by an eye care professional*
- *Inadequate vision may cause children to become frustrated with learning, enhancing the likelihood of need for special education*
- *Reports have found that as many as 70 percent of juvenile criminal offenders tested had undetected vision problems that affected learning.*

Inadequate vision may cause children to become frustrated with learning, enhancing the likelihood of underachievement and/or a need for special education. These children can develop a negative self-image, exhibit behavior problems, and even drop out of school. Reports have found that as many as 70 percent of juvenile criminal offenders tested had undetected vision problems affecting learning (5, 6). The societal consequences of inadequate vision care for children is significant, and the effect on workforce quality and productivity is obvious. As vision problems that can affect learning are often related to refractive error, vision evaluations are imperative in children, and especially in the management of children with learning disabilities. Here, I overview the current 'state of play', and how best to approach visual testing in children to unlock their learning potential.

IEPs

In 2005, the enactment of the Individuals with Disabilities Education Act ensured educational services for all children with disabilities, and led to the creation of Individualized Education Programs (IEPs) (see Box: What is IEP?). To assess the relationship between success in the academic setting and vision-related problems, Jeffrey Walline and Erica Johnson from The Ohio State University College of Optometry (Columbus, OH, USA) compared the prevalence of ocular findings among children on IEPs with population-based samples. Ohio requires that a first-time IEP student who hasn't been examined in the past nine months undergo a comprehensive eye examination with a licensed eye care professional within three months (8). Data for 255 children reported to have an IEP was



Box 1: What is IEP

An IEP is a legal document that spells out educational objectives for a child with a disability. It includes a child's present levels of academic achievement and functional performance, measurable academic and functional goals, alternate assessments aligned to alternate achievement standards (if necessary), and a description of necessary special education services, supplementary aids, and accommodations. A team of school psychologists, teachers, school nurses, speech/language teachers, and medical specialists are tasked with setting measurable goals and establishing a guide for the child's special learning needs (7).

analyzed and, of the 179 children who required some form of treatment, 124 had better than 20/40 entrance visual acuity (VA) in both eyes, meaning that they would have passed the school's vision evaluation because the condition did not affect their distance vision (9).

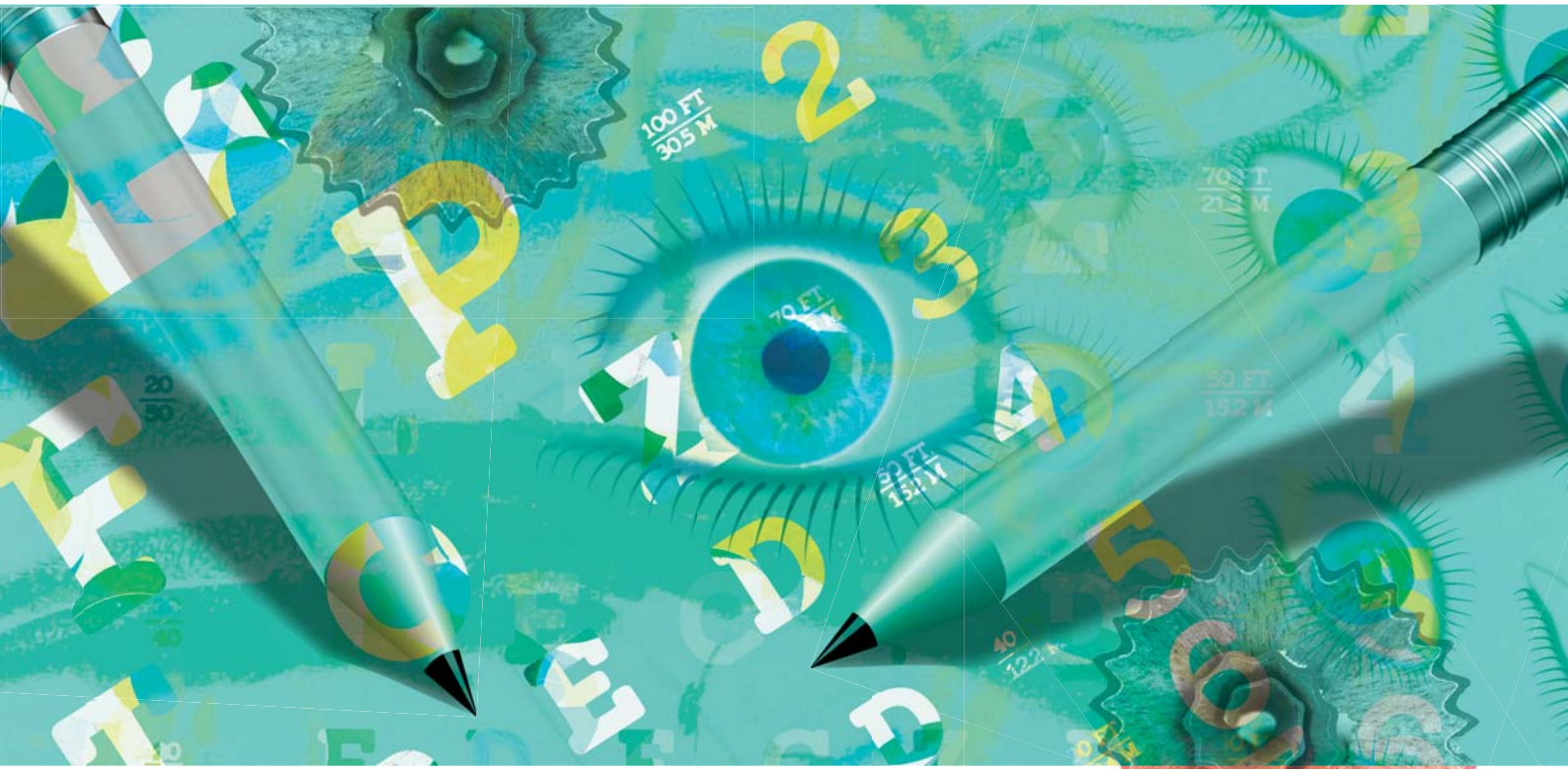
"Children with IEPs have a significantly higher prevalence of myopia, hyperopia, astigmatism, anisometropia and strabismus than most population-based samples in the literature," wrote Walline and Johnson. "Many of these vision problems would be undetected by vision evaluations based on distance VA, illustrating the need for comprehensive vision examinations for children who are struggling academically."

The need for better early recognition

In children with developmental and intellectual disabilities, early recognition of visual disorders is especially important. The American Optometric Association (AOA) reports that an estimated one in five preschool children have vision problems and that one in four school-age children wear corrective lenses. I am a committee member and the chief methodologist for the recently released AOA Evidence Based Clinical Practice Guidelines (CPG) (10). Our pediatric guideline is truly a comprehensive and multidisciplinary effort between optometrists, ophthalmologists, pediatric experts and laypeople. We are proud of the work, and it was accepted by the US Department of Health and Human Services Agency for Healthcare Research Quality National Guideline Clearinghouse in record time (11).

According to the CPG, the assessment of VA for infants and toddlers (through two years of age) may include preferential looking VA, fixation preference test and visual evoked potential. For refraction, cycloplegic retinoscopy and noncycloplegic retinoscopy are listed.

VA in preschool children aged three through five years should be measured with symbol optotype or letter matching. The CPG states that a refraction should include objective and appropriate subjective assessment of the child's refractive status. The refractive error measurement should be analyzed with other testing data that may include static retinoscopy, cycloplegic retinoscopy and autorefraction. Binocular vision, ocular motility, and accommodation assessments should be performed.



Creating a safety net

An estimated one in five preschool children in the United States has a vision problem, yet less than 15 percent of preschoolers receive an eye exam by an eye care professional (12). The National Center for Children's Vision Health shows that 10 states have no preschool or school-age vision evaluation requirements, and only 17 that do include preschoolers.

The Lions KidSight USA Foundation is a nationwide program that runs vision-testing events. It reaches more than one million children per year through state and local programs, many known as KidSight. The coalition seeks to brings together Lions groups that perform device-based testing on preschool and school-aged kids as an alternative way to detect ocular abnormalities that, when addressed by an eye care professional, can ensure children have every opportunity to reach their intellectual potential.

Screening programs cannot lead to the earlier diagnosis and treatment of ocular or vision problems without follow-through (comprehensive eye exam). Outreach programs may, however, identify some children at risk for vision problems who can then be referred to an eye care professional to receive a comprehensive eye exam, definitive diagnosis, and appropriate treatment.

The Colorado program

In 2017, the Colorado KidSight program screened more than 54,000 children. Executive Director Holly Rutherford, says: "We use the Plusoptix device specifically designed for children. We screen children six and younger for the following vision problems: myopia, hyperopia, astigmatism, strabismus, anisocoria and anisometropia. Some of these vision problems are risk factors for amblyopia." According to the National Eye Institute, amblyopia is the most common cause of visual impairment among children, affecting approximately 2–3 percent (13). Unless it is successfully treated in early childhood, amblyopia usually persists into adulthood. It is also the most common cause of monocular visual impairment among young and middle-aged adults – all reasons to catch potential problems early in childhood.

More than 6,000 children in the program were referred for a comprehensive eye exam because a problem had been detected. Most children in the program are referred for astigmatism, and a significant number have multiple vision problems, she says. The highest rates of referral are in the metropolitan areas of the state, where there are low incomes and diverse neighborhoods; rates of referral are typically much lower in rural areas. "The rate of referral in Colorado is 11.1 percent, however, we have school

"Children with untreated vision problems are left behind before they even start school"

districts with significantly diverse student populations, where our rate of referral is about 20 percent. In one pocket, the rate soars to 30 percent," she notes. About 25 percent of the state's population is Hispanic, a group with higher rates of astigmatism and anisometropia (12). "These kids are truly at risk because parents in these communities don't always speak English, and come from cultures where there is no history of vision screening or correction because of a scarcity of doctors or treatment facilities." They also tend to have lower incomes, no insurance, and are often working several jobs to make ends meet, making a visit to the eye doctor difficult to accomplish, she adds.

Rutherford knows firsthand of the "snowball effect" a child's unidentified vision problems has on school performance and behavior, resulting in problems for teachers, trips to the school nurse and the consideration of an IEP evaluation. "Sometimes I will get a letter or a phone call that really hits home," she says, describing a preschool child who was scheduled for IEP testing because he was struggling to focus in class. During a vision screening, a problem was identified and the child received glasses. Within a couple of weeks, the teacher told the school nurse to cancel the evaluation due to the child's improvement. "This is an instance where a child is performing poorly, and because of the vision evaluation and the subsequent comprehensive eye examination by an eye care professional. The problem was fixed and there was an immediate difference in how the child is able to learn," says Rutherford. "Evaluations for special services are expensive, so the school district saves money if we identify a vision problem that can be treated. It is an extra bonus."

Doing it for the kids

"While state and federal governments and others work to improve educational opportunities for children, more work needs to be done to address one of the elemental issues affecting literacy today: poor vision in children," writes Joel Zaba, an expert on relating vision to child and adult learning problems, literacy and school performance. "Essentially, the children with untreated vision problems are left behind before they even start school."

There is no question that vision problems have a severe impact on children's ability to learn. Left untreated, poor VA can thwart educational achievement and stunt overall literacy. To ensure children have the necessary vision skills to be successful, preschool and school-aged children must have a comprehensive eye examination as they progress through their school years. The take home message is that "You can't treat what you don't see". The mindboggling fact is that the majority of these problems are very commonly treatable. The only way we can help these kids is if their problem is detected and they are referred for comprehensive eye examination.

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Year of the Woman

Sitting Down With… Bonnie An Henderson, Partner at Ophthalmic Consultants of Boston, and Clinical Professor at Tufts University School of Medicine Boston, MA, USA.

What inspired you to become a cataract and refractive surgeon?

Coming from a family of physicians, it was expected that I'd be a physician too. I'm lucky the hereditary trait of being a doctor was passed down to me. I didn't realize it when I finished my medical training, but looking back, I'm fortunate the field I selected was perfect for my skill set. My desire to become an ophthalmologist was down to my experience with David Campbell during my ophthalmology elective. He's a brilliant glaucoma specialist with an insatiable curiosity, but he's also a kind, ethical, humble person who treated his patients with compassion and his staff with respect.

Who inspires you today?

I know it sounds like a cliché – but my mom. She's the most hard working, loving, generous person that I know. She was always there when I needed something and always supportive, regardless of the situation. I can't think of a better inspiration.

You called the last 12 months the "year of the woman" – why is that?

Many of the large ophthalmic organizations were led by women; Cynthia Bradford was president of AAO, Emily Chew was president of ARVO, Cynthia Mattox was president of the AGS, Beatrice Cochener was the president-elect of ESCRS, and I served as president of ASCRS. We were able to work together to discuss issues regarding governmental regulations in the US, and we were successful in lobbying to reduce the measures and penalties to the PQRS and Value-Based Modifier Programs, as well as blocking the MedPAC's recommendation to move physicians towards Advanced Alternative Payment Models.

What's it like for women in ophthalmology?

Thankfully, ophthalmology is one of the more progressive specialties when it comes to gender roles, with many champions for equality. The number of female ophthalmologists continues to grow every year. In fact, when I graduated medical school over 20 years ago, the class was already 50/50 male/female. However, men still dominate surgical subspecialties, which reflects in the 4:1 ratio of male to female practicing ophthalmologists. The challenges that women face in ophthalmology are not unique. They are the same challenges that women face in all industries, and in all fields of medicine.

What are you doing to help?

I'm working on a conference called EnVision Summit. The inaugural event will be held in February 2019 in Puerto Rico, and will focus on empowering women to lead in their field of specialty. Unlike other medical conferences, EnVision Summit fosters a welcoming environment that is open to families. We understand the challenges of advancing in a career while juggling the needs of personal life. This organization offers unique opportunities for new and experienced physicians to discuss issues of clinical importance, develop mentoring opportunities and facilitate collaborations for research. A major theme of this summit is how to conduct clinical research, with a spotlight session led by Malvina Eydelman, the Senior Medical Advisor of the US FDA Ophthalmic Devices Division.

What was the highlight of your ASCRS presidency?

As part of a three-year collaboration with the Outpatient Ophthalmic Surgical Society (OOSS) and others, we created new specialty-specific guidelines for ophthalmic instrument cleaning and sterilization in the US. If the ASCRS hadn't stepped in, longstanding practices for processing eye instrumentation could have been cited by surveyors as deficiencies that would warrant loss of ASC licensure or coverage. These are the types of challenges that individual physicians cannot combat alone. We need a strong organization, such as the ASCRS, to represent us and voice our unified protest. Being part of something greater than one individual was a rewarding experience.

How do you think ophthalmology will change in the coming years?

Technologic advances seem to evolve more rapidly in ophthalmology than other industries. The explosion of IOLs, use of lasers, development of injectable medications for retinal diseases and the surgical innovations in glaucoma are just a handful of the incredible changes that have occurred in the past decade. Hopefully future advances will allow patients to be less dependent on eyedrops for glaucoma, less dependent on corrective spectacles, and medical therapies will decrease visual morbidity from age-related diseases and endocrine disorders. Globally, I hope that the rate of blindness from cataracts will have drastically decreased as more patients have access to affordable cataract surgery.

What's exciting you right now?

The focus on presbyopia correction. Not only because of the explosion of new IOLs, but also the new medical developments to prevent lens hardening. This field is in its infancy and will continue to grow over the next few decades.

Finally, what's your advice for future leaders?

Remember when your parents told you that you can do anything? They were right. I've found that it is possible to do nearly anything. You may never be a professional ball player, but within ophthalmology, people can achieve any goal. It's important to remember this and strive for the best. Whether that means to become the best clinician, the best educator or the best researcher, it's all possible with perseverance, hard work and creativity.

CHOOSE A SYSTEM THAT EMPOWERS YOUR EVERY MOVE.

Technique is more than just the motions. Purposefully engineered for exceptional versatility and high-quality performance, the **WHITESTAR SIGNATURE® PRO** Phacoemulsification System gives you the clinical flexibility, confidence and control to free your focus for what matters most in each procedure.

Let's talk.

Contact your phaco specialist today.
WHITESTARSIGNATUREPRO.COM

Rx Only

INDICATIONS: The WHITESTAR SIGNATURE® PRO System is a modular ophthalmic microsurgical system that facilitates anterior segment (cataract) surgery. The modular design allows the users to configure the system to meet their surgical requirements. **IMPORTANT SAFETY INFORMATION:** Risks and complications of cataract surgery may include broken ocular capsule or corneal burn. This device is only to be used by a trained, licensed physician. **ATTENTION:** Reference the labeling for a complete listing of Indications and Important Safety Information.

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