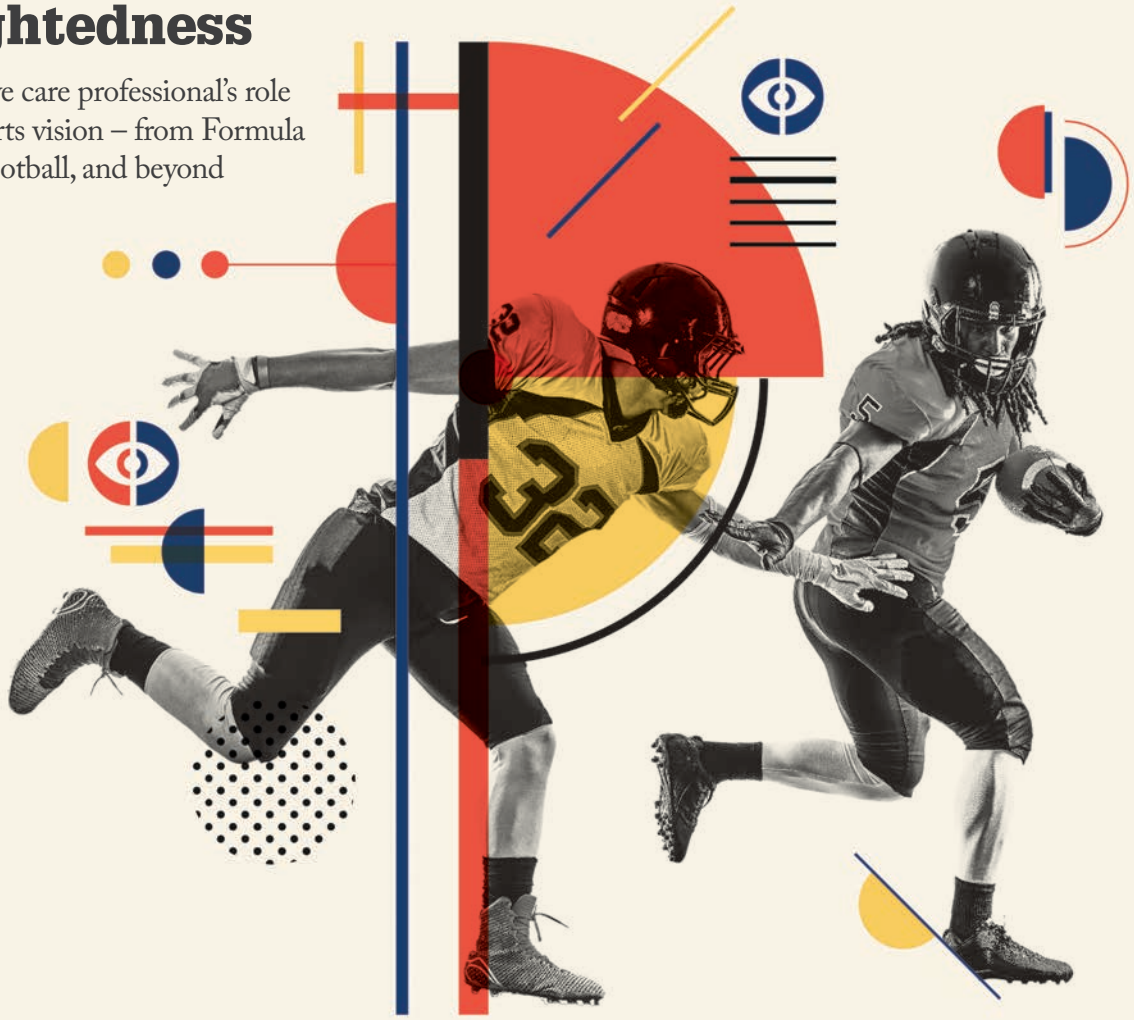
MAY / JUNE 2022 # 61

the Ophthalmologist™

Sport-Sightedness

The eye care professional's role in sports vision – from Formula 1 to football, and beyond



WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

304 BINGO CARDS

Inspired by a real patient with Wet AMD.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

REGENERON

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777 Old Saw Mill River Road, Tarrytown, NY 10591

PROVEN VISUAL OUTCOMES AT YEAR 1 IN THE VIEW STUDIES

Fewer injections with EYLEA Q8 vs ranibizumab Q4

Demonstrated in the largest phase 3 anti-VEGF trials completed to date in Wet AMD (N=2412)[1-3]

Proportion of patients who maintained vision (<15 ETDRS letters lost of BCVA) at Year 1 from baseline[1-3,*]

	Primary Endpoint (Year 1)	
	VIEW 1	VIEW 2
EYLEA Q4	**95%** (12.5 injections†)	**95%** (12.6 injections†)
EYLEA Q8‡	**94%** (7.5 injections†)	**95%** (7.7 injections†)
ranibizumab Q4	**94%** (12.1 injections†)	**95%** (12.7 injections†)

*Last observation carried forward; full analysis set.
†Safety analysis set.
‡Following 3 initial monthly doses.

Vision was maintained at Year 1 with ≈5 fewer injections with EYLEA Q8 vs ranibizumab Q4

EYLEA was clinically equivalent to ranibizumab.

VIEW 1 and VIEW 2 study designs: Two multicenter, double-masked clinical studies in which patients with Wet AMD (N=2412; age range: 49-99 years, with a mean of 76 years) were randomized to receive: 1) EYLEA 2 mg Q8 following 3 initial monthly doses; 2) EYLEA 2 mg Q4; 3) EYLEA 0.5 mg Q4; or 4) ranibizumab 0.5 mg Q4. Protocol-specified visits occurred every 28 (±3) days.[1] In both studies, the primary efficacy endpoint was the proportion of patients with Wet AMD who maintained vision, defined as losing <15 letters of visual acuity at Week 52, compared with baseline.[1]

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH WET AMD AT HCP.EYLEA.US

anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4, every 4 weeks; Q8, every 8 weeks.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Data on file. Regeneron Pharmaceuticals, Inc. **3.** Heier JS, Brown DM, Chong V, et al; for the VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537-2548. doi:10.1016/j.ophtha.2012.09.006

Please see Brief Summary of Prescribing Information on the following page.

03/2021
EYL.21.02.0019

EYLEA® (aflibercept) Injection
For Intravitreal Injection

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

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

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
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Tarrytown, NY 10591

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

EYL.20.09.0052

Embracing the 42 Percent

Is it possible to remove burnout from our reality?

Recently, a friend mentioned to me a statistic that, at first, was difficult to understand. Apparently, we should all be resting for 42 percent of our day. In other words, out of every 24 hours, at least 10 should be devoted to sleep, leisure, and connecting with others – so something other than work or life admin tasks, with no exceptions!

And that wasn't the end of my friend's argument; apparently, if we don't devote 42 percent of our time to rest, it will come back to haunt us – in the form of burnout – and, ultimately, we will have no choice but to pay back this borrowed time (and more).

My friend cannot lay claim to this concept. It actually comes from a book by Emily and Amelia Nagoski – the former a health scientist, the latter a music professor (1). Now, I wonder whether you are shaking your head in disbelief or if you recognized the value of this equation a long time ago. But even in ophthalmology – a specialty commonly regarded as providing the best work-life balance (as Dr Glaucomflecken's sketches would have us believe) – 52 percent of female ophthalmologists report feeling burned out (2). During the COVID-19 pandemic, burnout affected 56 percent of ophthalmologists and resulted in a reduction of working hours, and increasing the time spent on exercise, hobbies, and other leisure activities (2). And a US survey showed that ophthalmologists employed in academic and hospital settings reported higher burnout rates than those working in large private practices (3).

Burnout never used to be a concept I worried about; in fact, when my boss insisted that I should take my annual leave regularly throughout the year to prevent it, I would smile, nod, and then dismiss the advice. Then, 2020 came – and things changed. With many of our usual emotional outlets closed off to us, the concept of burnout started popping up everywhere. Like me, you may have found yourself laughing at burnout-themed tweets – and then carrying on working (either the professional sort or the unpaid kind at home). Is the solution simply embracing that 42 percent?

Quite possibly. And I find that celebrating wins – big and small – can also help. Speaking of which, all of us at Texere Publishing will be blowing out the candles on our 10th birthday cake this June – but mainly we'll be raising a glass to thank our wonderful readers, contributors, and partners who made it possible. Cheers!

Aleksandra Jones
Editor

Reference

1. *E Nagoski, A Nagoski, Burnout: The Secret to Unlocking the Stress Cycle. Ballantine Books: 2019.*
2. *Medscape, "Ophthalmologist Lifestyle, Happiness and Burnout Report 2022." Available at: https://bit.ly/3GEUVqT.*
3. *JA Sedhom, "Physician burnout in ophthalmology: a national survery," J Cataract Refract Surg, [Online ahead of print] (2021). PMID: 34596630.*

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A Sport-Sighted Vision: The People images are sourced from Shutterstock.com

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Neurotrophic keratitis is a degenerative disease that warrants immediate attention[1]

oxervate®
(cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

OXERVATE is the first FDA-approved pharmacologic treatment that targets the root pathogenesis of neurotrophic keratitis (NK)[2]

Cenegermin-bkbj, the active ingredient in FDA-approved OXERVATE, is structurally identical to the human nerve growth factor (NGF) protein made in ocular tissues.[3]

Endogenous NGF is a protein involved in the differentiation and maintenance of neurons and is believed to support corneal integrity through three mechanisms (in preclinical models): corneal innervation, tear secretion, and epithelial cell growth.[3-5]

In clinical studies, with a single 8-week course of therapy:

- Up to **72%** of patients with NK achieved complete corneal healing*†[2]
- **80%** of patients who achieved complete corneal healing remained completely healed at 1 year (REPARO trial)[6]

OXERVATE is a recombinant human nerve growth factor indicated for the treatment of neurotrophic keratitis.

Important Safety Information

WARNINGS AND PRECAUTIONS

Patients should remove contact lenses before applying OXERVATE and wait 15 minutes after instillation of the dose before reinsertion.

ADVERSE REACTIONS

The most common adverse reaction in clinical trials that occurred more frequently with OXERVATE was eye pain (16% of patients). Other adverse reactions included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, and increase in tears (1%-10% of patients).

Please see additional Important Safety Information on accompanying page and full Prescribing Information, including patient information, at OXERVATE.com/prescribing-information.

You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Dompé at 1-833-366-7387 or Usmedinfo@dompe.com.

TREAT NK TODAY
OXERVATE.com/HCP

*Study NGF0212 (REPARO): 52 patients per group; European patients with NK in one eye; 72% of patients completely healed; key findings were after 8 weeks of treatment; 6 times daily; vehicle response rate 33.3%.[2] Study NGF0214: 24 patients per group; US patients with NK in one or both eyes; 65.2% completely healed; vehicle response rate 16.7%.[2,7]
†Complete corneal healing was defined as the absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of OXERVATE treatment.[2]

References: 1. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579. **2.** OXERVATE (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) [US package insert]. Boston, MA: Dompé U.S. Inc.; 2019. **3.** Voelker R. New drug treats rare, debilitating neurotrophic keratitis. *JAMA*. 2018;320:1309. **4.** Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol*. 2017;232:717-724. **5.** Muzi S, Colafrancesco V, Sornelli F, et al. Nerve growth factor in the developing and adult lacrimal glands of rat with and without inherited retinitis pigmentosa. *Cornea*. 2010;29:1163-1168. **6.** Data on file. Dompé U.S. Inc.; 2021. NGF0212. **7.** Pflugfelder SC, Massaro-Giordano M, Perez VL, Hamrah P, Deng SX, Espandar L, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy. *Ophthalmology*. 2020;127:14-26.

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US-OXE-1900180.02 02/21

oxervate®
(cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

Brief Summary of Safety

Consult the full Prescribing Information for complete product information.

INDICATIONS AND USAGE

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

Contact lenses should be removed before applying OXERVATE and may be reinserted 15 minutes after administration.

If a dose is missed, treatment should be continued as normal, at the next scheduled administration.

If more than one topical ophthalmic product is being used, administer the eye drops at least 15 minutes apart to avoid diluting products. Administer OXERVATE 15 minutes prior to using any eye ointment, gel or other viscous eye drops.

Recommended Dosage and Dose Administration

Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

ADVERSE REACTIONS

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

In two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary There are no data from the use of OXERVATE in pregnant women to inform any drug associated risks.

Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects in offspring at clinically relevant doses.

Animal Data

In embryofetal development studies, daily subcutaneous administration of cenegermin-bkbj to pregnant rats and rabbits throughout the period of organogenesis produced a slight increase in post-implantation loss at doses greater than or equal to 42 mcg/kg/day (267 times the MRHOD). A no observed adverse effect level (NOAEL) was not established for post-implantation loss in either species. In rats, hydrocephaly and ureter anomalies were each observed in one fetus at 267 mcg/kg/day (1709 times the MRHOD). In rabbits, cardiovascular malformations, including ventricular and atrial septal defects, enlarged heart and aortic arch dilation were each observed in one fetus at 83 mcg/kg/day (534 times the MRHOD). No fetal malformations were observed in rats and rabbits at doses of 133 mcg/kg/day and 42 mcg/kg/day, respectively. In a pre- and postnatal development study, daily subcutaneous administration of cenegermin-bkbj to pregnant rats during the period of organogenesis and lactation did not affect parturition and was not associated with adverse toxicity in offspring at doses up to 267 mcg/kg/day. In parental rats and rabbits, an immunogenic response to cenegermin-bkbj was observed. Given that cenegermin-bkbj is a heterologous protein in animals, this response may not be relevant to humans.

Lactation

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

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older [*see Clinical Studies (14)*].

Geriatric Use

Of the total number of subjects in clinical studies of OXERVATE, 43.5 % were 65 years old and over. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis and Mutagenesis Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD). In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

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Blanket Coverage

How a single gene target may be the way forward for combating retinal degeneration

We are constantly learning more about genetic contributions to eye conditions – through both advancements in technology and work in the lab. But is the genetic information we uncover about diseases useful if many genes contribute to a single condition? Developing a therapeutic for one genetic contributor may help, but it may also result in a one-dimensional and potentially ineffective treatment for a disease that is multifaceted and multifactorial.

Researchers from Trinity School of Genetics and Microbiology in Dublin, Ireland, may have found a single gene target with a blanket coverage effect on treating impaired vision – and perhaps even blindness. The *SARM1* gene has been shown to drive the process of retinal ganglion cell (RGC) degeneration and ultimately causes visual impairment and blindness (1). Suppressing *SARM1* in a mouse model protected spatial vision, increased RGC survival, and preserved axonal density in the optic nerves for four months. In essence, the group found that, by suppressing *SARM1*, they were able to combat mitochondrial dysfunction – a hallmark contributor to many ocular and neurodegenerative diseases – in the retina at a tissue level and at a functional level.

Although this research is promising, there is quite a way to go before therapeutics can be made available. Nonetheless, the work offers hope that we may one day be able to treat diseases that affect the optic nerve, such as glaucoma. Aside from the ocular applications, the positive effect of *SARM1* suppression also stretches to neuronal cells (2) – meaning that the gene may be a viable target for neurodegenerative diseases, such as Alzheimer's disease, that are characterized by mitochondrial dysfunction.

References

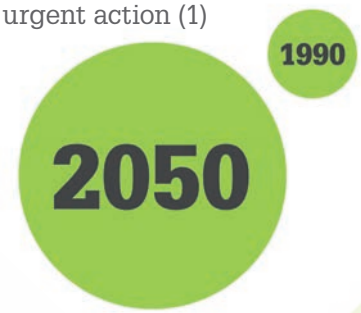
1. *LK Finnegan et al., Int J Mol Sci, 23, 1606 (2022). PMID: 35163535.*
2. *GJ Farrar et al., Trends Genet, 29, 488 (2013). PMID: 23756086.*

INFOGRAPHIC

Eye Health for All

The Right to Health program has been helping marginalized groups in Pakistan and Bangladesh access eye health services

Worldwide blindness is set to triple by **2050** without urgent action (1)



The Right to Health project in Pakistan and Bangladesh has helped

2.3 million

people access eye care

BUSINESS IN BRIEF

We go through the recent business announcements from the world of ophthalmology – so you don't have to!

- RetInSight, a spin-off from the Department of Ophthalmology & Optometry at the Medical University of Vienna, Austria, develops AI-based software solutions. The company has obtained a CE mark for its RetInSight Fluid Monitor, designed for innovative neovascular AMD monitoring (1).
- Bettina Hohberger, a researcher from the Eye Clinic at the Friedrich Alexander University in Erlangen, Germany, has received the Xtreme Research Award from Heidelberg Engineering for her investigations into chronic fatigue syndrome associated with long COVID (2).
- Roche's wet AMD treatment, faricimab, is the first therapy approved for the UK market using the Access Consortium – a collaboration of regulators from the UK, Australia, Canada, Singapore, and Switzerland whose aim is to increase cooperation, avoid duplicating regulatory processes, and get treatments to patients faster (3).
- BRIM Biotechnology has entered into a partnership with ORA, an organization facilitating ophthalmic research. They are working together on late-stage clinical development of BRM421 for the treatment of dry eye disease (4).
- Visus Therapeutics has signed an exclusive agreement with Zhaoke Ophthalmology to commercialize BRIMOCHOL PF and Carbachol PF – two preservative-free, long-lasting eye drops designed to address presbyopia – in Greater China, South Korea, and some territories in South Asia (5).

Bettina Hohberger.

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1. *Available at: https://bit.ly/3LVGpMl.*
2. *Available at: https://bit.ly/3GDHZBG.*
3. *Available at: https://bit.ly/3GxAR9R.*
4. *Available at: https://bit.ly/3GtDolv.*
5. *Available at: https://bit.ly/3a9G8IE.*

Eye Spy

Screening for neurological diseases using your phone? There's an app for that!

A research group from the University of California in San Diego, US, is pushing the functionality of smartphones through an application that turns the phone's native technology into a pupillometer (1).

Specifically, the team repurposed facial recognition technology, which uses a front-facing near-infrared camera, alongside the "selfie" camera to track pupil size changes with sub-millimeter accuracy – measurements that could one day be used as digital biomarkers for neurological diseases, such as Alzheimer's and ADHD.

By developing an app that turns most smartphones into a cheap and accessible pupillometer, the team is paving the way for more large-scale community screenings, which could not only aid in detection but also improve our understanding of neurological disease.

With a certain demographic in mind, the researchers incorporated features to help make the app as user friendly as possible. The team is also working ondevelopment of a version of the app that works on smartphones without facial recognition technology.

See references online.

The focus was on women, older people, those with disabilities and transgender communities

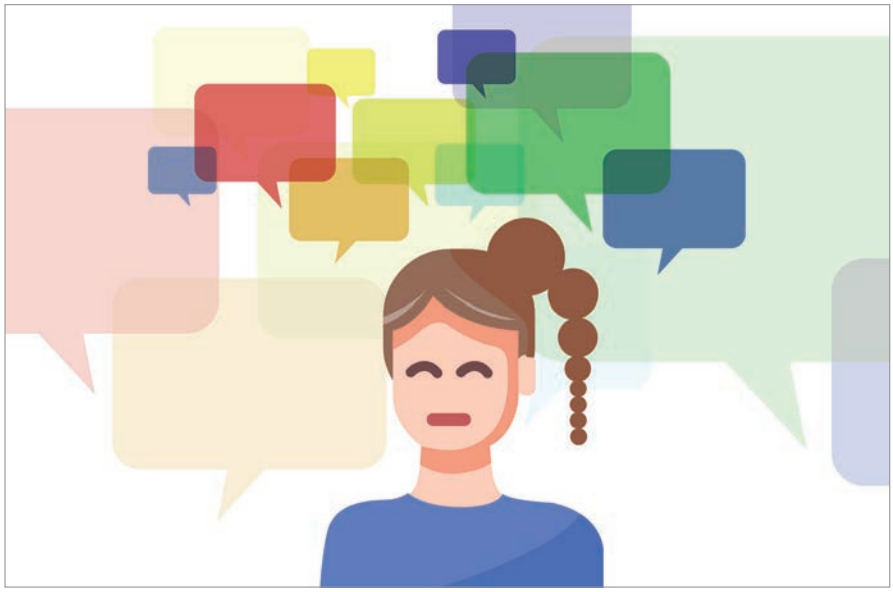
Result:

850,000
cataract surgeries

847,000
prescriptions

1 million
non-surgical treatments

See references online at: top.txp.to/eye/health/for/all



Hard to Imagine

Identifying aphantasia begins with looking at our eyes

What is the stimulus of the eyes? The answer to this seemingly simple question may be more complex than it initially appears. Researchers at the University of New South Wales (UNSW) School of Psychology in Kensington, Australia, have investigated the connection, or lack thereof, between the mind's eye and the body's physiological response in people with aphantasia – the inability to picture images within one's mind.

"When we visualize a beach, most of us have the experience of 'seeing' that image in our mind; however, a small proportion of individuals report that they do not see anything when they imagine," study author Rebecca Keogh explains. "To date, aphantasia identification has relied purely on self-reports. We have been doing a lot of research into visual imagery and aphantasia over the past few years and have been trying to develop better ways to measure visual imagery ability without relying on self-reports, such as questionnaires."

Building on work by Bruno Laeng and colleagues, who showed that the pupillary light response observed when we imagine pictures of differing brightness is the same, although to a lesser degree, as when physically seeing those images (1), the UNSW researchers found that reported imaginary strength correlated with the magnitude of the pupillary light response observed. They also found that aphantasic individuals, who report a lack of imagery, display no pupil change in response to attempting visualization (2). This is the first objective, physiological measure of aphantasia, and it highlights the fact that pupil responses can be driven by mental processes as well as external stimuli.

What's next for the UNSW research team? "We hope to extend this research by looking at whether we get similar effects when people imagine complex images, such as scenes. So far, our visual imagery measurements have used visualization of basic shapes (such as triangles in the pupillometry study and gabor patches in our binocular rivalry study). If we could develop a measure of how vividly someone can imagine a complex scene, this would allow for one of the first objective measures of scene imagery," says Keogh. "We are also aiming to modify this study to see if we can use web cameras to measure the size of the pupil, so that people can measure their own ability to visualize (or, in the case of aphantasia, inability to visualize) at home."

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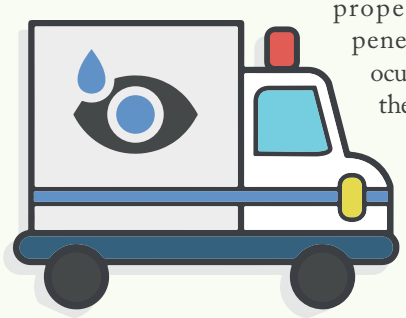
1. *1. B Laeng, U Sulutvedt, Psychol Sci, 25, 188 (2014). PMID: 24285432.*
2. *2. L Kay et al., Elife, 11, e72484 (2022). PMID: 24285432.*

Special Delivery

The pain of being outside of delivery range may be over for the posterior segment

These days, access to speedy food deliveries from a variety of specialists largely depends on your location – you're much more likely to be spoiled for choice in a big city than in rural areas. It's not that different with drug delivery in the eye; the anterior segment (the inner city of the eye) has plenty of options, while the countryside-like posterior segment is complaining about the lack of drug delivery in their area –as well as the non-existent 5G coverage.

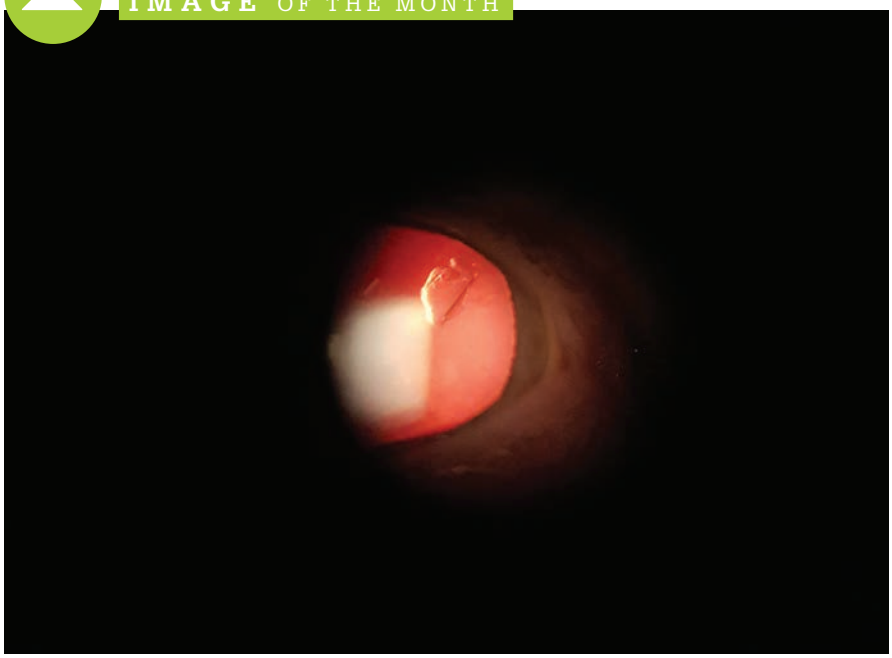
But the posterior segment may not be limited to home cooked meals any longer! Researchers from Kyushu University in Fukuoka, Japan, have developed a gel-in-water nanoemulsion that improves the delivery of topical drugs to the posterior segment, with maximum therapeutic efficiency. The nanogel emulsion was developed using beeswax as a gelator during ultra-sonification, which creates nanocarriers smaller than 250 nm and with physical properties that increase penetration and improve ocular permeability through the deep layers.



See references online.

KINDLY AND UNCONDITIONALLY SPONSORED BY
HEIDELBERG ENGINEERING

IMAGE OF THE MONTH



Breaking Away

The image shows a posterior capsule rupture, a side effect of an intravitreal injection.
Credit: Rainer Lässer and Francesco Comacchio, ophthalmologists at the Hospital of Merano, Südtirol, Italy.

Would you like your photo featured in Image of the Month?
Send it to edit@theophthalmologist.com

QUOTE OF THE MONTH

"My research shines a spotlight on the impact of surgical hiatuses amongst individual groups. It unveils that trainees experience more negative challenges, which can in part be ameliorated by simulation training, and that females report childcare five times more than male colleagues as a barrier to accessing learning resources."

Laura Maubon, current Young Ophthalmologist Lead for the UK and Ireland Cataract and Refractive Society

Retinal Revelations

Will mapping the RPE lead us in the direction of new discoveries?

If you've ever found yourself in a field, surrounded by seemingly endless space with no idea which way to turn, you'll likely appreciate the benefits a detailed map can offer. Similar principles apply to navigating the retinal pigment epithelium (RPE), which National Eye Institute researchers have now mapped morphometrically for the first time (1).

Using AI-based software to analyze cell morphology, the team identified five concentric RPE cell subpopulations, which they named P1 to P5, that had differing cell areas, fluorescence, aspect ratio, hexagonality and number of neighbors. This explains why retinal degenerative diseases affect specific regions of the RPE; individual populations showed differing susceptibilities to monogenic and polygenic retinal diseases when the eye maps of AMD and non-AMD eyes were compared. In particular, P1 was missing in most AMD eyes.

Knowing that these different RPE subpopulations exist is the first step toward understanding them – and toward the development of more precise cell and gene therapies for specific degenerative eye diseases. Like geographical maps, this morphometric map may ultimately reveal a way forward in treating, or even preventing, these diseases.

References

1. *M Soanes et al., Engineering Reports (2021). DOI: 10.1002/eng2.12355.*
2. *University of Birmingham (2021). Available at: http://bit.ly/2P0AMF5.*

THE OPHTHALMOLOGIST'S
TIME MACHINE: CHAPTER 4

How Charles Babbage beat Hermann von Helmholtz in the race to invent the ophthalmoscope

With Andrzej Grzybowski

Charles Babbage was a famous English mathematician, inventor, and polymath, and he is regarded by some as the father of computing. Between 1828–1839, he occupied the Lucasian Chair of Mathematics at the University of Cambridge, UK – a prestigious post that has been held by the likes of Sir Isaac Newton and Stephen Hawking. Like his contemporaries, Babbage yearned to push the bounds of knowledge and innovation – and one of his dreams was to build a "difference engine" that could automatically compute values of polynomial functions; he hoped to introduce mechanical computations similar to early computers. Though work on a prototype began, it was never finished because of a lack of financing – when work stopped, the machine had 25,000 parts and weighed 13.6 tons.

Towards the end of his life, Babbage designed a more complex "analytical engine" that represented a transition from mechanized arithmetic to fully-fledged general-purpose calculations. The proposed machine would be programmed with punched cards, have memory for 1,000 numbers of 40 decimal digits, and contain some elements that are still used in modern computers. In 2002, the first full-size "difference engine" was built; the culmination of a 17-year project, the machine was faithful to the original designs at the Science Museum in London and was capable of returning results to 31 digits.

Alongside these two engines, Babbage devised several other inventions, including the "black-box" recorder for monitoring the state of railway lines, theater lights that used colored filters, hinged flap shoes for walking on water, the metal frame attached to the front of locomotives that clears the tracks of obstacles (also called a cow-catcher), the dynamometer car, and – most important to our field – the ophthalmoscope.

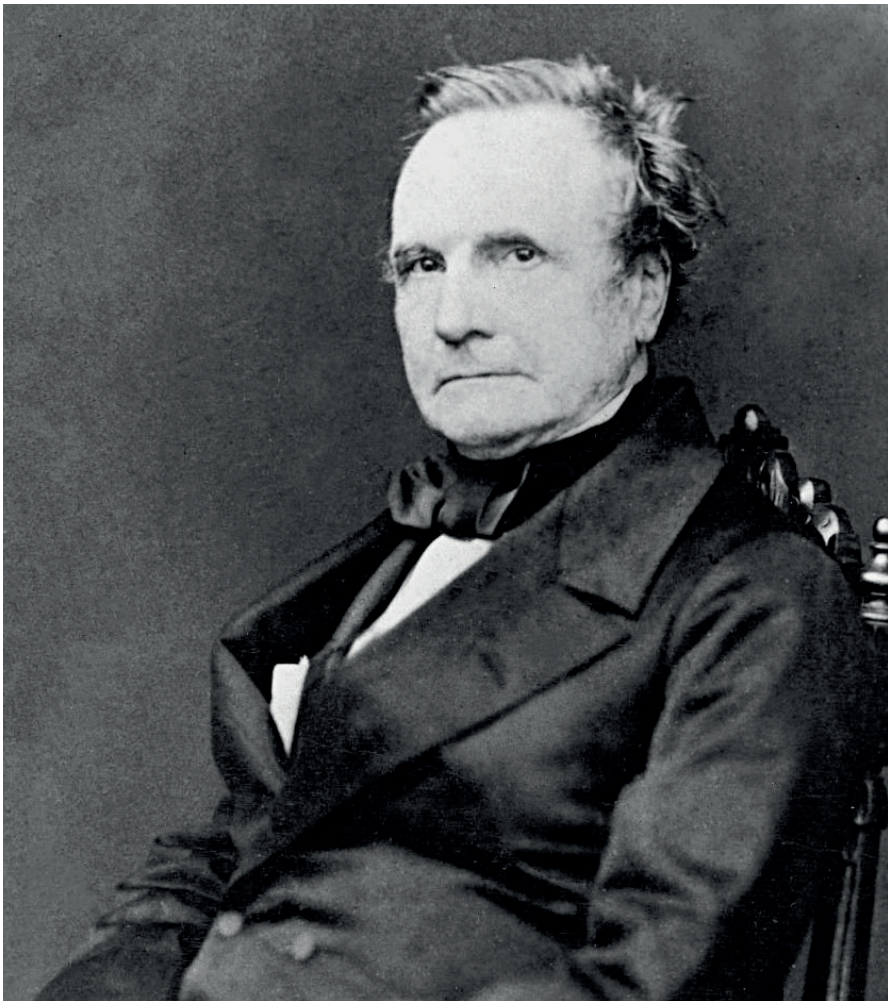


Figure 1. Charles Babbage.

Babbage constructed the ophthalmoscope in 1847 and showed it to Thomas Wharton Jones – a prominent ophthalmologist and lecturer at Charing Cross Hospital in London, who would later become Professor of Ophthalmic Medicine and Surgery at University College London. Unfortunately, Wharton Jones was blind to the value of Babbage's ophthalmoscope – likely due to his myopia, which might have left him unable to use it. According to Wharton Jones, who described the device in 1854, Babbage's 'scope "consisted of a piece of plain mirror, with the silvering scraped

Figure 2. Punch cards for Babbage's never-completed Analytical Engine.

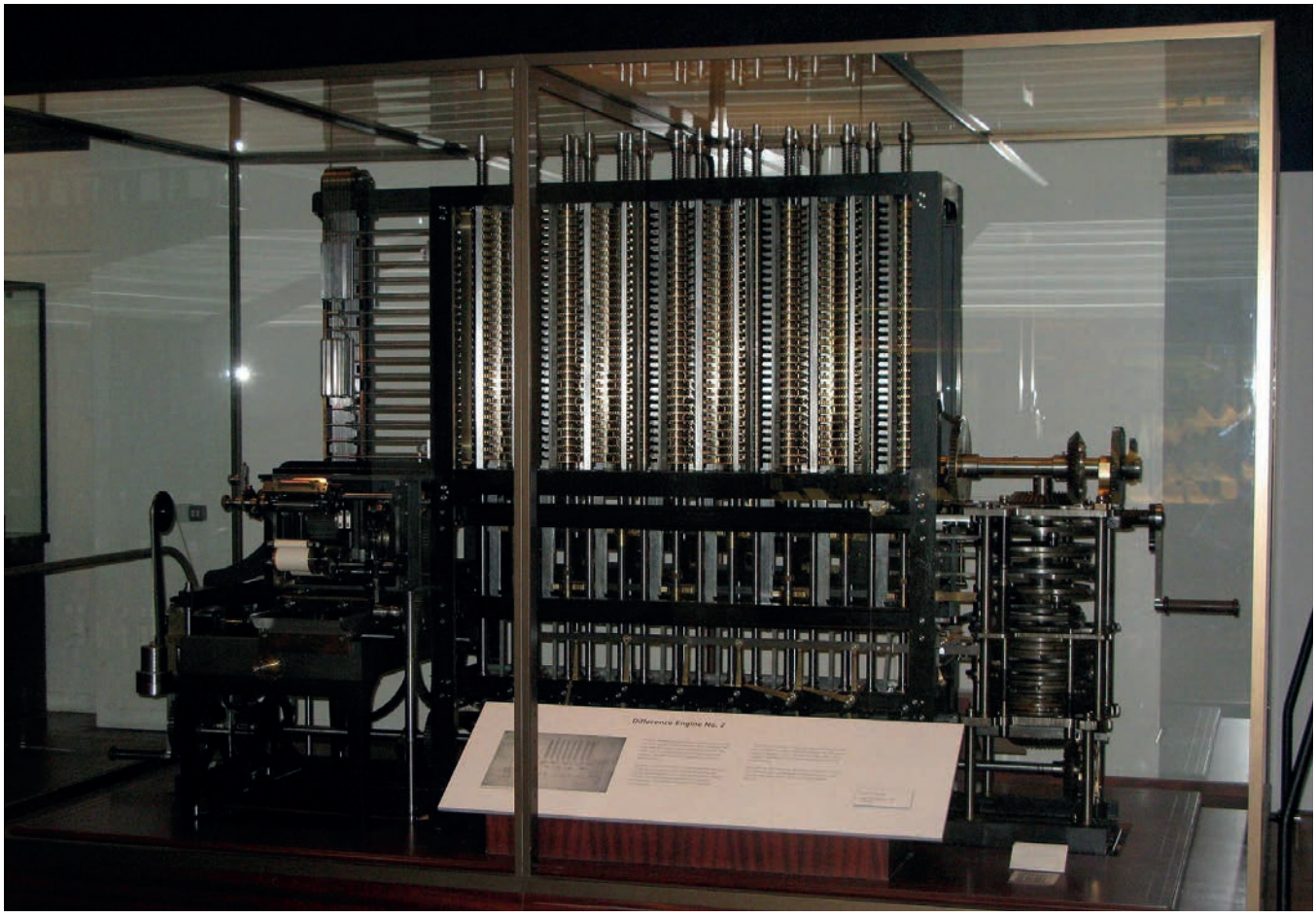


Figure 3. The Difference Engine, constructed by the Science Museum based on the plans for Charles Babbage's Difference Engine No. 2. Photo by geni, 2008, Permission: GFDL CC-BY.

off at two or three small spots in the center, held within a tube at an angle so that rays of light falling on it through an opening in the side were reflected to the eye to be observed." The investigator looked through the clear spots of the mirror from the other end. This concept was later successfully adapted and used in later models by Epkens, Donders, Coccius, Meyerstein, and others.

But what led Babbage to develop the ophthalmoscope in the first place? The consensus is that his problems with bilateral monocular diplopia, which he was able to partially correct with the use of a pinhole or concave lens, may have directed his attention to the fundus of the eye in an attempt to discover the origin of his own affliction.

Just three years later, in 1850, Hermann von Helmholtz constructed his own ophthalmoscope that revolutionized ophthalmology.

Andrzej Grzybowski is a Professor of Ophthalmology and Chair of the Department of Ophthalmology, University of Warmia and Mazury, Olsztyn, Poland, and Head of the Institute for Research in Ophthalmology, Foundation for Ophthalmology Development, Poznań, Poland. He is also an expert in the history of ophthalmology, with over 100 peer-reviewed articles published in this area. He is a member of AAO Museum of Vision's Program Committee, curator of ESCRS Archive, and founder of the history section at EVER. He is the president of the Polish Society for History and Philosophy of Medicine, and Editor-in-Chief of Archives of History and Philosophy of Medicine, and Historia Ophthalmologica Internationalis, the only journal devoted solely to the history of ophthalmology.

See references online.

In My View

Experts from across the world share a single strongly held opinion or key idea.

Clear-Cut Classification

Providing simpler intraocular lens nomenclature for the benefit of patients, manufacturers, and doctors alike

By Sheraz Daya

The evolution of intraocular lenses with a variety of mechanisms of action, each attempting to improve lens performance, has resulted in complex and poorly understood terminology. Much of this has stemmed from manufacturers trying to differentiate themselves from the competition in an attempt to capture market share. In my opinion, they should perhaps be more concerned about collaborating with their rivals to grow the overall business – but that is a topic for another discussion.

Universally accepted nomenclature is needed to communicate effectively. Often mechanisms of action are confused with optical and visual performance, the classic example being the term EDoF or "extended depth of focus," whereby many ophthalmologists associate EDoF with fewer dysphotopsias. The ANSI standard for EDoF lenses requires implants to have intermediate vision (67 cm) of 20/30 in 50 percent or more of recipients, but there is no mention of dysphotopsias. However, returning to fundamentals, the term EDoF, borrowed from photography, is in reality "extended depth of field" and should really only be applied to small aperture lenses.

"Universally accepted nomenclature is needed to communicate effectively."

Observing manufacturers all wishing to jump on the bandwagon of having an EDoF offering was a source of amusement to many ophthalmologists. However, the mechanisms used to achieve the phenomenon of improved range of focus did not really follow the principle of elongating the conoid of Sturm and used diffractive, zonal refractive or a combination along with others like optimizing chromatic aberration. This resulted in similar dysphotopsias caused by bifocal and trifocal lenses, though professed to be less in magnitude. More concerning was the misinformation provided to patients who were informed that having so-called EDoF lenses would result in fewer halos, starburst and

glare. This misinformation set false expectations for patients, who still faced dysphotopsias and compromises in their reading ability.

Several members at the European division of the American European Congress of Ophthalmic Surgery (AECOS) informally discussed the myth of EDoF equating to less dysphotopsias and the arising confusion with the variety of lenses being manufactured. This led to the creation of a committee by me and four other members of AECOS Europe with the objective of looking further into the issue and identifying ways to simplify terminology and classify lenses. The purpose of this initiative was to provide a systematic approach that would deliver cognitive ease for all stakeholders: patients, ophthalmologists, and manufacturers, avoiding misunderstanding.

Considering the defining principles of good nomenclature and classification, we determined on parameters for our system: simple, stable, uniform set of rules, room for further additions with language that could be easily understood, where relevant, by all parties and in particular patients. An example of good classification is the 4C system created by Shipley and employed by the Gemological Institute of America for classifying diamonds. The 4Cs of Color, Clarity, Cut and Carat simplified what was previously a complex process.

To decide the components needed, the issues concerning each stakeholder group were considered. Component issues of lens behavior were identified and differentiating terminology was crafted by the members of the committee.

The common denominator "Lens Performance" was broken down into three main components: range of focus, mechanisms of actions, and dysphotopsias. The committee acknowledged that lens performance was not just about the optical device alone and included a number of other important variables, but, to avoid complexity, decided that the variables could not be incorporated. These included corneal optical performance (presence of aberrations), postoperative pupil size, axial length and conoid of Sturm, neuroadaptation, and patient expectation management.

"Often mechanisms of action are confused with optical and visual performance, the classic example being the term EDoF or "extended depth of focus," whereby many ophthalmologists associate EDoF with fewer dysphotopsias."

Classified outcomes

Range of focus was classified using the following terms: Monofocal, Monofocal Plus, Increased Range of Focus (IRoF) and Full Range of Focus (FRoF).

Mechanism of action of the lens included Accommodation, Small Aperture (true EDoF), Diffractive, Zonal Refractive, Combined, and Other.

Dysphtopsias were classified with the following terms: Glare, Halos, Starbursts, and Other (to include less frequent issues like waxy vision syndrome).

Attempting to classify available high-performance lenses, specifically regarding range of focus, we invited manufacturers to complete a questionnaire. Responses were unfortunately not as good as hoped and could not be reliably considered. The inclusion criteria for each category are something that will need further clarification and consensus from the board of AECOS.

Accepting that no classification is perfect, especially where elements are subjective and variables, such as neuroadaptation and expectation management, have considerable influence, the proposed classification system does fulfil its objective of simplifying intraocular lenses, based on the range of focus provided, mechanism of action, and magnitude of dysphotopsias. We are very pleased to see good acceptance of this terminology, which is now becoming commonplace amongst ophthalmologists.

Acknowledgments: AECOS Europe and the Lens categorization working group: Sheraz Daya, Eric Mertens, Francesco Carones, David Shahnazaryan, Joaquin Fernandes.

Sheraz Daya is Medical Director of the Centre for Sight, East Grinstead, UK. He has been an innovator and leader in refractive and cataract surgery. He has both led and been involved in classification systems and consensus panels and avidly supports good use of language that facilitates communication amongst stakeholders.

A SPORT-SIGHTED VISION

How eye care professionals help athletes achieve their peak performance

Perspectives gathered by Aleksandra Jones and Geoffrey Potjewyd

Meet the specialists who have ventured into the sporting arena. Here, we present viewpoints and stories from the lives of eye care experts working with baseball, Premier League soccer, Formula 1 racing, and international rugby teams, and more.

The Eye in Team

How I built my career in sports and performance vision

By Daniel Laby

At the start of my ophthalmic career, I didn't plan to get involved in sports vision. I was never a huge sports fan, and I'm not very good at sports myself. Of course, growing up in the US, you are never far away from a game (I was even present at the last game at the original Yankee Stadium), but I wasn't a sports fanatic.

I did my ophthalmic training at the George Washington University in Washington, DC, and I went on to do a Pediatric Ophthalmology fellowship at UCLA's Jules Stein Eye Institute in Los Angeles, California, US. Our program director and Chief of Pediatric Ophthalmology and Strabismus, Arthur Rosenbaum, wanted all fellows to pick a project to work on. He mentioned a project that a previous fellow had started, which involved working with the Los Angeles Dodgers, looking at the baseball players' vision. It sounded interesting, but I really wanted to pursue my own project, and not finish someone else's, and I took it on the condition that I would be in charge and would make decisions on subsequent publications. Rosenbaum agreed, and that was the beginning of my career in sports and performance vision!

WORKING WITH LA DODGERS

As part of my project, I saw the Dodgers annually for about 18 years (or you could count it in seasons), starting in 1993, and only stopped working with them following the move of their practice location from Vero Beach, Florida, to Camelback Ranch-Glendale, Arizona. Even when I lived abroad, they would still bring me back every spring to carry on the work. Based on the research my team conducted while working with the Dodgers, we published our first paper in sports vision (1), which, I believe, was also the first paper on sports and performance vision published in any major ophthalmic journal. At that time, most ophthalmologists weren't very positive about working on athlete's vision, considering it to be the domain of optometrists and vision therapists, with no solid science behind it. But, as I became really interested in understanding how athletes' visual systems differ from those of the general public, that didn't stop me.

I was never particularly interested in the surgical aspects of ophthalmology, even though I performed Strabismus surgeries for 25 years. Instead, I've always been trying to find out more about how our brains use vision to make decisions that translate into actions. Over the years, attitudes of the ophthalmic community have changed – partly as a result of the refractive surgery boom – and sports vision has become a more popular topic among ophthalmologists, bringing more eyecare professionals to the field. Several good evidence-based publications on this topic have also changed the minds of many ophthalmologists and got them interested in this field, and in optimizing people's vision and performance even in the absence of ocular pathologies.

> *"Many athletes and teams reach out to me directly, but I also proactively contact some big names and teams, like those in the English Premier League."*

PROMOTING SPORTS VISION

At the start of my sports vision career, eye care professionals working with sports teams and athletes weren't paid beyond out-of-pocket expenses; our time wasn't compensated, so I was doing this work (which involved conducting research and writing publications) on top of a busy pediatric ophthalmology and Strabismus practice, working seven days a week. Slowly, this changed, and as I began to get paid for my sports vision work, I could devote around half of my working time to it, with the other half still spent at my pediatric practice. Now, while I still see my young patients, most of my week is spent on sports vision science. Some of this work takes place at my New York City office, but most of it involves working directly with teams at different locations around the world.

Many athletes and teams reach out to me directly, but I also proactively contact some big names and teams, like those in the English Premier League. It still surprises me how many big teams with huge budgets don't even consider evaluating players' vision as an important aspect of their performance. This is why the highly publicized project I worked on with Trent Alexander-Arnold from Liverpool FC in the UK was so important – it has opened people's eyes to the potential of improving sportspeople's visual performance

Liverpool F.C. and England international soccer player, Trent Alexander-Arnold, alongside Daniel Laby.

and – in turn – their results. I traveled to Liverpool on two occasions, to test and to train Alexander-Arnold. This work was documented in the Red Bull movie available online (titled "Trent's Vision"), documenting work we did together, the training Alexander-Arnold completed, and how his results improved. I have also published a film on my sports vision YouTube channel analyzing how aspects we worked on together impacted a later Liverpool FC game.

I have seen a whole spectrum of team management approaches, from extremely old fashioned to very forward-looking. I tend to work with teams taking the latter approach, as they aim to look at an array of tools, they can leverage to maximize performance. These include psychological aspects, sleep science, nutrition, and – of course – vision. Appreciation of the human body built from many different systems, and getting different professionals in all these areas to work with each other is crucial to improving performance and results. These days, the science behind these processes and interactions is well documented, so those in charge of improving athletes' performance ought to be well aware of it.

HELPING HANDS

When I go to work with a sports team, we usually have between 100 and 150 people to screen in a few days, so I often ask for help, often locally to where the team is based. Ophthalmologists appreciate the idea of working with a professional team and mixing with athletes. I also have great contacts who are always happy to exchange thoughts with me, and these include David B. Granet, Professor of Ophthalmology and Pediatrics at the Shiley Eye Institute of University of California in San Diego, and Bruce Mitchel Zagelbaum who practices in Manhasset, New York.

I hugely value relationships with researchers, such as Lawrence Gregory Appelbaum from the Department of Psychiatry at the University of California in San Diego, with whom I have just published an editorial in Frontiers in Human Neuroscience (2). In Europe, I work closely with Michel Guillon who practices at the Ocular Technology Group in London, UK. I have loved learning from researchers such as the late Richard Masland, Former Distinguished David Glendenning Cogan Professor of Ophthalmology and Neurobiology, and Jeremy M. Wolfe, Professor of Ophthalmology and Radiology at the Harvard Medical School in Cambridge, Massachusetts, US, with focus on retina functions and visual perceptions, respectively.

THE SPORTS VISION PYRAMID

I have created a framework to understand the role of all vision interventions – testing, training, and more – and how they can all be used to improve performance. I have called it the sports vision pyramid, as it has a very strong base, and tapers to a point at the top. This pyramid has five levels, and if they are not all laid out in the correct order, and the bottom functions are not optimized well enough, the whole structure won't be stable. As each of the levels is improved individually and in order, the top of the pyramid – field performance – will also improve.

At the bottom of the pyramid are the monocular visual functions: visual acuity, contrast sensitivity, and ability to see things at all distances that appear for a short time. This is something that each eye can do by itself, and that's why we test each eye separately, using a test (see below), showing the athlete targets from around 13 feet away, for a short time, and we evaluate the results. If the visual acuity isn't what it needs to be, it can be addressed with training, with contact lenses or spectacles, or appropriate surgical procedures, while contrast sensitivity issues can be addressed with tinted lenses, for example. The next level is stereo vision – looking at how both eyes work together to create depth perception. This function is critical to know how far things away are. Then, it's decision making based on visual information. Following that, it's all about a visually guided motor action so that the body follows the decision.

In 2019, I published a paper with my colleagues showing how visual acuity – the bottom of the pyramid – impacts on the batting performance of baseball players (3). We also published a paper looking at the US Olympic team of 157 athletes taking part in the Beijing Olympics in 2008, and we demonstrated

different visual functions of athletes representing different sports (4), but in any case, if you optimize each of the pyramid levels, the overall performance will improve.

TESTS AND INTERVENTIONS

Having abandoned the Snellen chart, which I deem wholly inadequate, I have worked with Alcon to develop a test – called the adaptive visual performance testing system – that is now used in ophthalmic drug testing, sports vision, military education, and other high-performance areas. It uses small targets shown to the patient for short amounts of time (such as 300-800 milliseconds) to reflect real-world scenarios. The test has been shown to correlate to performance in the field (3).

When talking about refractive interventions, it's important to realize that 20/20 vision is a very weak standard in everyday life, but especially in sports, so refractive experts have to aim for much more. For young athletes, we aim to achieve 20/12, perhaps 20/15. Some of them achieve 20/08, which is typically considered to be the limit of human vision. Also, for athletes, small refractive errors can make a really big difference.

We have a whole host of interventions available beyond refraction, including games, augmented reality, virtual reality, and various applications available on tablets or computers.

RESULTS

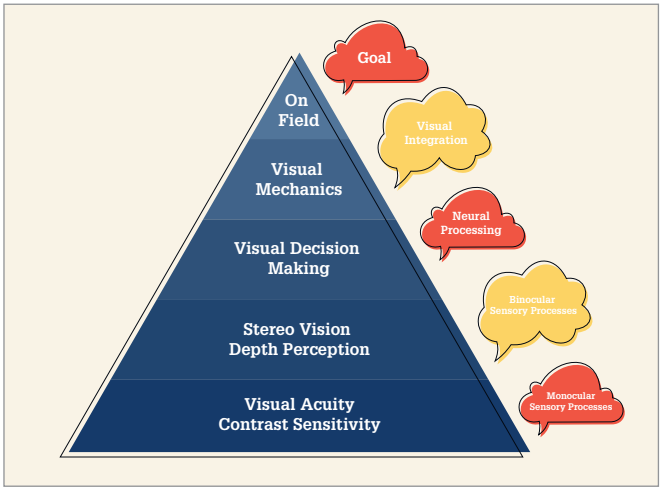
In 2004, I worked with a Dominican-American baseball outfielder, Manny Ramirez, who played in Major League Baseball for 19 seasons. My team developed a training scheme that helped him with his hand-eye coordination and decision-making. That year, he became the Most Valuable Player at the World Series, and he used our training as a warm-up before every game for the rest of his professional career.

In 2013, I worked with Stephen Drew, a Boston Red Sox infielder. We selected contact lenses with a small refractive correction for him and straight away he helped seal the World Series for the team.

I can confidently say that there's no other ophthalmologist who has worked with as many champions among athletes and teams as I have, and I have around 10 championship rings to prove it.

FUTURE DIRECTIONS

I work with baseball teams and players a lot, and I don't have much capacity for additional work in the baseball field, but I would like to make my sports work an all-year-round occupation, rather than just seasonal. This is why I have been looking at professional soccer teams to work with, and I would like to do more work with the Premier League and Champions League teams, other European league teams as well as additional NBA, NHL, or NFL teams. That's where the top players, with the top performing visual systems are! Every day, we are learning new things about the visual system, and it is fascinating to see how much we can learn from those at the top of the scale.



The sports vision pyramid.

I have always been attracted to solving problems in ophthalmology that didn't have very clear solutions – like Strabismus surgeries. I enjoy looking at new directions and coming up with fresh ideas to give an edge to the teams and athletes I work with. The more education on sports vision there is, the more people will reach out to specialists to help them get the vision to achieve their goals. This, in turn, will result in more investment from corporate entities for research to build an even bigger evidence base for sports vision. Sports and performance vision is a great field for those who don't want to follow existing formulas in ophthalmology but want to have an opportunity to come up with new solutions. Let's keep this field a true scientific discipline, based on solid research, with statistical data from randomized, double-blind and prospective studies. Scientific rigor and high scrutiny really matter in this field!

I have watched the field of sports and performance vision develop greatly, bridging ophthalmology and optometry, as well as vision research, to the benefit of teams, athletes, and everyone else – as everyone can all use the testing and training methods developed for the highest-performing humans. I share a lot of my knowledge and expertise on my YouTube channel in video presentations and TED talks, so it is available for everyone to learn from.

Daniel Laby is an ophthalmologist specializing in sports and performance vision, as well as pediatric ophthalmology and Strabismus. He practices in New York, USA.

See references online.

A Sporting Spectacle

How can technology break down the barriers to participation in rugby?

By Julie-Anne Little

Almost all sporting events pose some risk to the eyes – a flying tennis ball here, a stray finger on a basketball shot block, and I don't need to mention how boxing or other fighting sports can cause eye injuries – there are so many ways that our most precious organ can be damaged. This high risk of injury has led to the implementation of compulsory visors in the North American Ice Hockey top division, the National Hockey League (NHL), and an investigation into how visors would reduce injuries in the National Football League (NFL). Of course, there are plenty of contact sports where helmets are not included in the equipment list – and that makes visors a more complicated addition.

Rugby is one of these sports. On the rugby pitch, hands, feet, and even the ball can cause damage to eyes – but, at the same time, spectacles are prohibited because the physical nature of the sport makes them extremely dangerous to be worn on the field. However, there is now an answer to these woes. World Rugby have created – with my team's help (1) – protective goggles that can include prescription lenses.

"The federation wanted to increase access to the sport, especially at a grassroots level, while better protecting players."

EYE-VIS AWARENESS

World Rugby recognized that the no-spectacles rule excluded potential participants who, for whatever reasons, weren't able to wear contact lenses. The federation wanted to increase access to the sport, especially at a grassroots level, while better protecting players. Although sporting eye injuries are not common, they are often serious; wearing eye protection vastly diminishes the chance of an ocular injury.

There have been a few high-profile cases that have raised

New Zealand Rugby international Ardie Savea, wearing his World Rugby goggles during a match against Wales.

Julie-Anne Little.

awareness of eye care in rugby. Irish rugby union player Ian McKinley – a major "poster boy" – was blinded in one eye after a studded boot hit his eye in a rugby game. He managed to return to professional rugby and even play internationally – thanks to a lot of hard work, as well as goggles to protect his functioning eye. Thankfully, such injuries are rare, but these incidents really highlight the importance of protecting sight. For McKinley and others like him, retiring would have been the only option without the protection of the goggles.

And so, with the two angles of participation and protection in mind, World Rugby decided to incorporate sports eyewear into the Laws of the Game. And it's fair to say that the study my team conducted for the federation wasn't within the realms of our usual work! Specifically, World Rugby asked for our optometric and optical expertise to assess the quality of the goggles. The remit fitted very nicely with my expertise – and it was a really great trial to work on.

SCOUTING REPORT

The study was essentially a wearability trial. We wanted rugby players' views and experiences of how successful the goggles were in helping them to access and play the sport without impeding sight. We also wanted to drill down into any emerging issues and whether they could be ameliorated in some way – for example, ease of cleaning, performance in different weather conditions. And, of course, we looked at the safety of the goggles in play.

Our main findings were positive: the goggles were a helpful addition. Notably, there were a large number of young people (up to 18 years old) using the goggles – likely a reflection of the lower likelihood of people under 18 being contact lens wearers but still wanting to play rugby.

But there were some challenges with the goggles – fogging being one key issue. Just like wearing a mask with glasses, it is annoying when fogging occurs! Given that rugby is played all across the world, different humidities and weather conditions will need to be taken into account. The comfort of the design was another concern – in particular, the thickness of padding and the pressure around the nose; the padding is required to ensure the actual goggles are not in contact with the player's face, but resulted in some scrapes around the nose and face.

Both of these issues were highlighted in the paper and will need to be addressed by the manufacturer of the goggles.

GRAND DESIGNS

World Rugby also asked me to evaluate the goggles in more detail; for example, how they would fit different face shapes and work with different optical prescriptions. As you can imagine, if someone is very short- or long-sighted, it will have significant implications for the optical insert placement. Indeed, I recommended the need for clearer instructions for the opticians and optometrists who would be glazing the optical inserts into place. Another key recommendation was the need for additional sizes – especially given that the goggles were also intended to increase participation. My family and I have been involved in community level rugby for some years – and I even played a bit at university, and it's easy to see the benefits of the goggles for inclusion in sport.

Julie-Anne Little is a Senior Lecturer in Optometry and Vision Science and Associate Research Director, School of Biomedical Sciences, Ulster University, UK

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Eyes on the Tries

We interview Dan Morris, the Welsh Rugby Union Match Day Ophthalmologist on his role in the team

HOW DID YOU GET INTO SPORTS OPHTHALMOLOGY, AND IN PARTICULAR, WELSH RUGBY?

I suppose that I was just in the right place at the right time. I did a sports medicine degree during my training, which I've always been interested in and nearly ended up pursuing full time. My sporting experience would still open some of the right doors. As it transpired, when I arrived in Cardiff, UK, there had been a couple of high-profile injuries to elite rugby players that hadn't been dealt with very well in the acute setting, and they wanted someone to be around for the matches – so I offered to help out! That was about 10 years ago. With my background in sports medicine, it was easier to slip into the role within the team.

The Welsh Rugby Union medical team is a lot like the multidisciplinary teams (MDTs) I'm part of at the University Hospital of Wales, where I'm a general ophthalmologist, but also an oculoplastic and orbital surgeon. The success of that Welsh Rugby Union medical team relies on good teamwork, good communication, good leadership – the whole is certainly much greater than the sum of the parts within that team.

Rugby isn't the only sport which I've been able to offer ophthalmic help to – I also help out with the Welsh Football Association games, and the British Boxing Board of Control.

SO HOW INGRAINED ARE YOU INTO THE TEAM? IS IT JUST A MATCH DAY ARRANGEMENT OR MORE?

It's a home arrangement, where I provide medical cover for the players of both teams when they're in the Principality Stadium, the Welsh national stadium in Cardiff. I don't travel with the squad; the team has its own team doctors and physiotherapists who will travel wherever the team goes, and they get in touch with me between matches if there are any eye or orbital problems. The whole medical team works together with the squad inside of matches and training, but also outside of those times. It's also common for them to give me a phone call if they have an issue when they're up in Scotland, or wherever they might be. If it's needed, I might get one of my colleagues up there to see them. We're only providing stadium cover for the for the teams, but not the crowd – we can't do anything if they decide to pour beer in each other's eyes!

Dan Morris.

WHO IS PART OF THE MEDICAL TEAM?

We've got emergency medicine doctors, anesthetists, a neurosurgeon, orthopedic surgeons, maxillofacial surgeons, a dentist, us – the eye care team, and then an awesome team of paramedics. It's quite a big team, and we could deal with almost anything in the medical room. There have been high profile cardiac arrests of late, so we've got all the wherewithal for resuscitation and intubation.

SO HOW DOES A MATCH DAY WITH THE MEDICAL TEAM PLAY OUT?

Everyone's got a role to play in the medical room. There's a briefing a couple of hours before the match, and a debrief afterwards to discuss the injuries and anything we could do to improve management and communication. We meet the visiting team doctors and physios to discuss who wants to do any stitching that arises, which is what I have to do sometimes. It's also important that we discuss who is performing which role for the head injury protocols, because they're obviously a big issue these days. Ultimately, we're just making sure everyone's reading from the same script so that we provide the best medical care that we can.

THAT MAKES SENSE TO ME, BECAUSE YOU'RE THE ONLY ONE I COULD FIND! SO HOW COMMON ARE EYE INJURIES IN RUGBY, AND WHAT ARE THE BIGGEST DANGERS?

Thankfully, they are not too common. During the game I might be called upon to examine an eye or stitch a laceration anywhere on the face; brows and foreheads are most common so I can put my oculoplastic skills to good use with occasional eyelid lacerations as well. I also help the maxillofacial team with other facial injuries – for example if any ears are hanging off or sliced lips. I've dealt with corneal abrasions, hyphemas, and then, of course, blowout fractures are pretty common. Between ourselves and the maxillofacial surgeon we have the majority of eye care covered for the game.

We also often help out between matches with the rehabilitation of players who might have eye problems, such as double vision. We also have follow ups with players that are local; we see them afterwards to follow them up. If they've come from abroad, or further afield, then we'll try and set up a follow up with an ophthalmologist closer to home – unless they're English, of course, when they get sent packing!

I'm always happy to lend a hand with anything else that needs to be done as part of the bigger team. If you've got someone with multiple injuries, or they are having significant problems with pain, for example, I can help out the anesthetists and the emergency medicine doctors, or show the orthopedic surgeons how stitching is done properly

I GET THE IMPRESSION YOU SUPPORT THE WELSH RUGBY TEAM, TOO?

Yes, but I have English, Welsh, and Italian blood in me, and my wife is Scottish, so the Six Nations Tournament is an interesting time in our house. But, because we're living in Wales, and I'm working with the Welsh team, I proudly support Wales.

One of the great things about the rugby and the Six Nations is that it's always a good opportunity for a laugh and some banter between fans. The rivalries are usually quite happy ones – it's great when the French come over, and we're all singing together in the pub afterwards. And the Welsh are an easy team to support in the rugby, as it's so ingrained into the Welsh culture from grassroots up – so it's a great sport to be part of in Wales.

"We had to stitch up the great New Zealand player Richie McCaw's forehead in the World Cup actually, no pressure there."

HOW HAVE THE INJURIES SUSTAINED IN RUGBY CHANGED OVER THE YEARS?

There used to be a lot of eye gouging – I have rugby players in my clinic in Cardiff who had career-ending injuries and lost an eye because of gouges during rugby matches, and they're pretty horrendous injuries. Gouges can be devastating to the eye and the eye socket, which has led to them being outlawed now. So not only will you be sent off and banned for doing it, you might well face a criminal prosecution if you start gouging people in the eye these days.

The big game changer for such injuries was when Hawk-Eye (a computer vision and monitoring system) was introduced for international matches, bringing cameras everywhere and the technology and personnel to use it in real time; it is very difficult to get away with professional fouls nowadays. Hawk-Eye allows the referee to immediately ask the Hawk-Eye technicians to let them see all the views available and make an informed decision. We'll often go in at halftime and review the footage with the Hawk-Eye cameras, and we catch these cheeky little gouges going on in rucks. Referees come down on them really hard, which is great for player welfare and less work for me to do! There are occasional gouges, often just by mistake, but the offending player will still get sent off

even if it was an accident. This all means that players know they must keep their hands away from eyes now, which is fantastic news.

Concussion is an important topic at the moment, in rugby and across many sports. We've really got to stay ahead of the game to protect players – there have been some high-profile players getting dementia early, as with other sports. With eye symptoms being fairly common in concussion, we're often involved when there's blurred vision, double vision or even loss of vision. We had one Welsh player who went completely blind after a line-out concussion in a French game. That obviously caused a lot of stress to the player, his family, and the team doctors. But his scans were normal and thankfully his vision returned the next day. Visual symptoms are a sign of significant concussion.

WHAT IS THE PRESSURE LIKE, WHEN YOU'RE TREATING A SPORTSPERSON ON THE INTERNATIONAL STAGE?

There's a lot of time pressure when you're stitching someone up during a match, as you've got that 10-minute blood window before they're not allowed to come back on, so if they need a head injury assessment, you've really got to be a fairly swift technician and get those stitches in sharp – and the player is also raring to get back on the field. We had to stitch up the great New Zealand player Richie McCaw's forehead in the World Cup actually, no pressure there... But you just chat away with the player, trying to keep their mind off the procedure and get them out back in the game as quickly as you can. It really is a privilege to be part of it – trying to deliver high-quality medical care to elite athletes during huge international matches. This work really brightens up my February, March, and the time with the rest of the games. The players are also great guys, truly professional, who work and train so hard, and are genuinely grateful for the help you're giving them. I almost feel their pain when they suffer from career threatening injuries. It can be the end of their careers, so it's gratifying to get their injuries sorted, and to see players like George North and Alan Wyn Jones come back from injury – they're talismanic people!

It's all voluntary, so we're not paid to do it, but we do get a few perks occasionally! We do it because we love the game of rugby and want to give the players the best possible care.

WHAT ADVICE WOULD YOU GIVE TO READERS WHO WOULD LIKE TO BE THEIR FAVORITE SPORTS TEAM'S OPHTHALMOLOGIST?

There are various courses you can do, not for just ophthalmology, but also for general sports medicine and pitch side medical care, but for me, it was serendipitous. It is about luck, and being in the right place at the right time, but you can create your own luck to a certain degree. I've always said that you've got to actually put yourself in the position to get the job, and work hard at it. These days, it is much more difficult as a trainee to get the time to get involved in extra activities like this, but you can still do it; you just have to be tenacious and beaver away. And you're not going to become a "sporting ophthalmologist" as such; you have to offer a variety of skills. So doing either a part time Sports Medicine degree, or a similar course, would help. Also, just offering to help out at your local club with general medical issues can be a big step in the right direction. My kids play hockey, ski and do other sports, so if they have injuries, I've always got a bag in the back of my car and help out. You can also work at slowly making the right contacts, and offering to be helpful when people want you.

WHAT WOULD BE YOUR DREAM OPHTHALMOLOGY JOB?

To be the ophthalmologist for a British Lions Rugby tour of course, not that they've ever asked for one! But, otherwise, I've already got my dream sporting ophthalmology role with the Welsh Rugby Union.

IS THERE ANYTHING ELSE YOU'D LIKE TO MENTION?

As a result of my sporting ophthalmology work, I represent the Royal College of Ophthalmologists on the Council of the Faculty of Sport and Exercise Medicine (UK). This Faculty, which will hopefully be a Royal College in its own right one day soon, promotes and accredits sports physicians, but also promotes exercise for treatment and prevention of cardiovascular disease, and improving mental health. As medics and ophthalmologists, we should be having that discussion about exercise with our patients improve health as a whole, and reduce the risk of AMD, diabetes and cardiovascular eye problems, such as vein occlusions. Exercise is so important and it's a cheap "prescription" to offer people.

I also do some charity work with the Welsh Rugby Charitable Trust who look after injured rugby players, especially those with spinal injuries – it's good to be able give a little back to injured players for the sacrifices they have made.

Dan Morris is a specialist in cataract and oculoplastic surgery based in Cardiff, Wales, UK, and is the match ophthalmologist for the Welsh Rugby Union.

A Career of Speed

My memories from years spent with Formula 1 Brazilian Grand Prix drivers and crews

By Milton Yogi

The period between 1991 and 2001 was a very good time for the annual Formula 1 Brazilian Grand Prix in São Paulo. It was also a period when I was extremely fortunate to serve as the circuit ophthalmologist, supervising eye care of the drivers, also known as pilots, and their crews. I was invited by the organizers to join the medical crew, and when they were happy with the job I did in the first couple of years, I was invited back again for the following several years. I was the first ophthalmologist to bring equipment from their office, bringing with me my slit lamp, an indirect and direct ophthalmoscope, a Snellen chart, and other equipment to support me – an approach that was very much appreciated by the organizers as they felt I was able to perform a better level of service.

My main role was to be on hand to help with ocular injuries. Fortunately, there were no major injuries during my tenure, but I was well prepared for all eventualities. We had larger surgical teams on standby in case their support was needed. What I mostly attended to were minor injuries sustained by the Formula 1 mechanics. There was one instance when I had to help an American pilot, Michael Andretti, who drove for McLaren. He suffered a major crash right where by the start of the track and I was really close by and attended to his injuries, not only as an ophthalmologist, but also as an emergency physician.

DREAM COME TRUE

I have been a big Formula 1 fan since I was seven years old. In the 1970s, when I was growing up, Brazil had an amazing driver named Emerson Fittipaldi (he won the Formula One World Championship and the Indianapolis 500 twice, and the CART championship once), and watching his career got me into following the sport closely.

When I started my role as the Grand Prix circuit ophthalmologist, I proceeded to build relationships with crews on different teams so I could learn more about Formula 1's inner workings. I got access into their boxes and found out a lot about their work. That meant so much to me, as I'd always wanted to see the parts of the Grand Prix that are hidden from the general public.

Milton Yogi with Michael Schumacher.

I also got to spend time with pilots, including such legends as Ayrton Senna and Nelson Piquet. They would invite me into their boxes and everyone always treated me with utmost respect. Not all team doctors were as big fans of Formula 1 as I was, so drivers and crews really related to me.

> *"Not all team doctors were as big fans of Formula 1 as I was, so drivers and crews really related to me."*

Senna had a dream of winning the Grand Prix in Brazil, his home country. It always seemed to escape him, and in 1991, as he was in the lead, in mild rain, his gearbox broke down. He took his final laps of the race with one gear, without anyone knowing that at the time. It was something that had never seemed possible. As Senna crossed the line at winning speed, I was lucky to be in the pit wall. It was truly a dream come true for me and I will never forget that. I was also there for the champagne shower at the podium!

FORMULA 1 VISION

Apart from perfect visual acuity, racing drivers have extraordinary reflexes. They react very quickly while driving,

Ayrton Senna with his pit crew.

but also when accidents happen. The position in a racing car cockpit tube – a tiny, confined space – is almost horizontal, and when I tried it myself, I couldn't understand how drivers were able to see anything. They have a very unusual perception of things ahead of them and around them. They train their vision and reflexes all the time. Each successful driver has their own personal trainer who not only looks after their overall physical shape, but also their reflexes. I had the opportunity to check the vision of one driver, Thierry Boutsen, who at the time raced with Williams. He needed a check up to renew his super licence, and I was asked to conduct his tests.

Many times, Brazil has been announced as the country best supporting emergency healthcare in Formula 1 events, and having participated in this sport at such a high level makes me very proud. I decided to do things my way: bring my equipment and arrange the space in the best way I could to provide support (working on it for up to a week ahead of each event) and I'm extremely happy I did that, as it helped me provide the best possible care for pilots and their crews, which then came to be regarded as best practice.

Milton Yogi is the Coordinator at MY/Learning Study Group and Managing Director at IPEPO – Instituto da Visão in São Paulo, Brazil.

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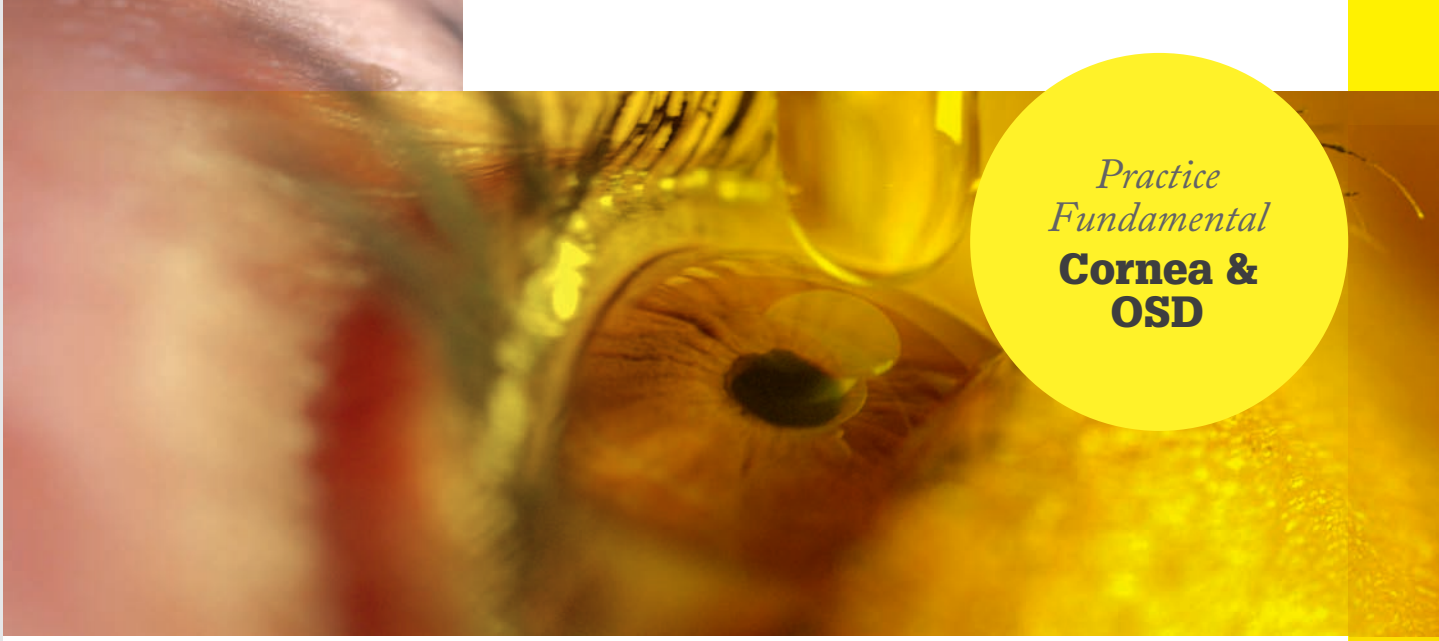

Tears of joy. Researchers from Osaka University, Japan, have discovered a way to grow 3D lacrimal gland-like organoids, which have notable morphological, immunolabeling characteristics and gene expression pattern similarities to native lacrimal glands, replicate aspects of the tear duct, and differentiate into mature lacrimal glands when transplanted into animals with partial or no tear ducts. The organoids are grown from human induced pluripotent stem cells.

Peculiar TK. Researchers have found an unusual corneal presentation of trachomatous keratopathy, with amyloid deposits being identified in 16 of 29 eyes when retrospectively scanning histopathological records of patients undergoing keratoplasty over a three-year period. This form of trachomatous keratopathy was distinct from the usual presentation of dense leucomatous, vascularized cornea scarring in trachoma and has resulted in novel reporting of endothelial changes and formation of guttae.

Thank me, laser. A prospective comparison of dry eye and corneal sensation in individuals undergoing LASIK and SMILE showed that SMILE has a reduced corneal denervation compared with LASIK in the early stages that followed surgery, and this effect diminished after a year. There was no difference in dry eye symptoms between the groups.

Deep detection. Researchers have developed deep learning algorithms, using anterior segment images retrospectively acquired from 194 microbial keratitis patients, able to rapidly discriminate between fungal keratitis and microbial keratitis. This convolutional neural network model, using ensemble learning, demonstrated the best performance in discriminating between fungal keratitis and bacterial keratitis when compared to single architecture models, indicating that it has the potential to act as a tool for rapid provisional diagnosis in microbial keratitis patients.

Dry eye depression? A secondary cross-sectional and longitudinal assessment of data from the Dry Eye Assessment and Management (DREAM) randomized clinical trial of 535 participants found that patients who screened positive for depression displayed worse dry eye symptoms and overall signs of dry eye, but similar inflammatory markers compared to patients that had dry eye but screened negatively for depression. This association between depression and severe symptoms and signs of dry eye disease (DED), gives more credit to depression being a DED comorbidity.

IN OTHER NEWS

Defying gravity… and aging. *A method of transporting corneas preserving buccal tissue and cartilage may employ zero gravity corneal storage, helping to slow down the aging processes.*

Aiming dry high. *Loss of sex steroid hormones produced by 3-HSD enzymes may lead to dry eye disease, but can be resolved by non-steroidal local NMN treatment.*

Date with density. *Low post-operative endothelial cell density following DMEK has been linked to difficult surgeries.*

Fuchs' associations. *Newly diagnosed Fuchs' endothelial dystrophy is strongly associated with ocular allergic conditions, geographical region, residential status, and income.*

A gift horse. *The ocular surface variably expresses SARS-CoV-2 cellular entry proteins, with a very low rate of positivity.*

See references online at:
top.txp.to/thank/me/laser

A RAPID Revolution

Making the gold standard for endothelial corneal disease treatment safer and easier

By Peter Szurman and Annekatrin Rickmann

Over the past few years, Descemet membrane endothelial transplantation (DMEK) has become the gold standard for treating endothelial corneal diseases. This is a result of numerous innovations that have shaped it into a standardized, minimally invasive procedure. One important milestone was the provision of pre-prepared, precut lamellae (LaMEK) from specialized tissue banks to external transplantation centers. This has enabled more surgeons to benefit from high-quality, quality-assured lamellae.

Through the approval of DMEK RAPID in 2021, the next breakthrough has been reached. Surgeons can now receive pre-prepared DMEK lamellae preloaded in an injector, for direct injection into the eye without further manipulation, enhancing both the safety and ease of DMEK surgery.

Change in transplant surgery

The revolution of corneal surgery by DMEK can be attributed to its particularly gentle approach, where visual rehabilitation is much faster and more effective than other methods, postoperative follow-up is easier, and rejection rate is lower.

The KHERI Research Institute of the Sulzbach Eye Hospital have been on the forefront of DMEK innovation, with their contributions being pivotal to its success. One example of this is the world's first DMEK injection system for touchless lamellar corneal transplantation, which they introduced in 2011 and has already been used to perform 60,000 corneal transplantations worldwide (1). Two years later, a new "liquid bubble" technique was introduced, a particularly gentle and safe preparation technique for transplanting donor lamella (2, 3).

Specialized cleanroom tissue bank for lamellar transplants

Since 2016, the Knappschaft Tissue Bank in Sulzbach has been one of the most modern cleanroom facilities in Europe for the production of high-quality corneal transplants. The donor network now consists of 17 German donor hospitals, with the tissue bank having a capacity of 1,000 certified transplants annually. As an official partner of the German Society for Tissue Transplantation, transplants are processed under the highest-quality standards, and are made available to the Sulzbach Eye Clinic and external transplant clinics. In 2021, one in every eight corneal transplants transplanted in Germany came from Sulzbach.

The Knappschaft Tissue Bank particularly specializes in the production of pre-prepared corneal lamellae (Precut-LaMEK). Lamellar grafts require a particularly high manufacturing quality compared to classic full transplants, which the cleanroom tissue bank meets as a result of the entire manufacturing process being subject to a strict, certified quality-assurance system.

Precut LaMEK: a success

Precut is the new trend in DMEK surgery. This is due to the challenging manual preparation process, which has driven more transplant centers to source pre-prepared, precut lamellae

Credit: Image from Shutterstock.com

to improve safety and quality of grafts. Although experienced anterior segment surgeons learn implantation relatively quickly, manual preparation of donor lamella poses risks. Manual dissection of the lamellae, which are only about 15 µm thick, is usually performed in the operating room shortly before the start of the procedure and can be incorrectly prepared with possible graft loss. Similarly, "fresh" graft preparation in the operating room is neither standardized nor validated.

One solution to this problem is to transfer the production of lamellae to specialized tissue banks. In Germany, only two tissue banks, Sulzbach and Hanover, are approved to produce and market pre-prepared lamellae.

By using pre-prepared lamellae, the surgeon avoids the risk of incorrect preparation and graft loss. With LaMEK, the surgeon receives a pre-prepared lamella that has been quality-controlled with regard to density, morphology, and vitality of the endothelial cells and has been produced in a standardized manufacturing process in a certified cleanroom. The risk of the preparation lies entirely with the manufacturing tissue bank.

This has led to a high acceptance rate. To date, more than 2,000 pre-prepared LaMEK have been produced in Germany, with the preparation success rate being over 95 percent.

How safe are pre-prepared DMEK lamellae?

Comparisons between the long-term effects after DMEK transplantation with Precut-LaMEK and lamellae prepared immediately before surgery showed that after six months, when assessing graft failure, endothelial cell count and visual acuity, there was no significant difference between patients who received pre-prepared grafts and those who received lamellae prepared immediately pre-op. In particular, there was no higher graft failure owing to the use of pre-prepared grafts (4). This demonstrated the safe use of pre-prepared lamellae, as shown in US studies. There was no evidence of a toxic effect of the dextran-containing culture medium (5).

Europe-wide introduction of DMEK RAPID

The Europe-wide approval of DMEK RAPID, as the first preloaded transplantation system for minimally invasive DMEK transplantation, signposted the achievement of the next important step in the evolution of DMEK (6).

For the first time, clinicians have the option of using a pre-prepared and preloaded DMEK lamella which is ready to use. These grafts can be injected directly into the eye without further manipulation, as shown in Figure 3, simplifying transplantation, allowing numerous ophthalmic clinics and external surgeons to perform non-contact, standardized transplantation without risk of dissection. These advantages enhance the safety and ease of DMEK surgery.

The foundation of the DMEK RAPID transplantation system is its patented "ready-to-use" design. Like Precut-LaMEK, the lamella is prepared in advance in the tissue bank but is additionally loaded into the DMEK RAPID injector system and are ready for direct use by the surgeon. The graft does not need to be manipulated or drawn into the injector cartridge; if necessary, the lamellae can be restained within the closed system.

First pre-prepared DMEK RAPID delivered

In December 2021, the world's first DMEK RAPID were delivered to German external transplant clinics.

REGISTRATION STUDY AT THE SULZBACH EYE CLINIC

A comparison of cell loss and endothelial cell viability after transport between the new DMEK RAPID injection system and Precut-LaMEK (7) showed no significant difference when observed in the viewing chamber. Both groups demonstrated comparable low cell loss, indicating that the transport of preloaded grafts has no negative impact on graft quality and viability.

The Knappschaft Tissue Bank in Sulzbach is currently the only cornea bank manufacturing and shipping these high-quality, pre-prepared DMEK lamellae under cleanroom conditions, using the liquid bubble technique. The lamellae are then preloaded in approved locations throughout Germany.

The Sulzbach Eye Clinic has used the DMEK RAPID system to treat patients for three years and because of the innovations it has brought to DMEK, the demand from patients and referring physicians has increased dramatically. In 2021, the milestone of 500 transplantations was reached, making the Sulzbach Eye Clinic one of the largest corneal transplant centers in Germany. DMEK RAPID is currently being rolled out across Europe; the approval process is already well-advanced in most European countries, especially Italy and the Netherlands.

Peter Szurman is Chief Physician and Annekatrin Rickmann is Senior Physician and Head of Cornea Section, Sulzbach Eye Clinic, in Sulzbach, Germany.

See references online.

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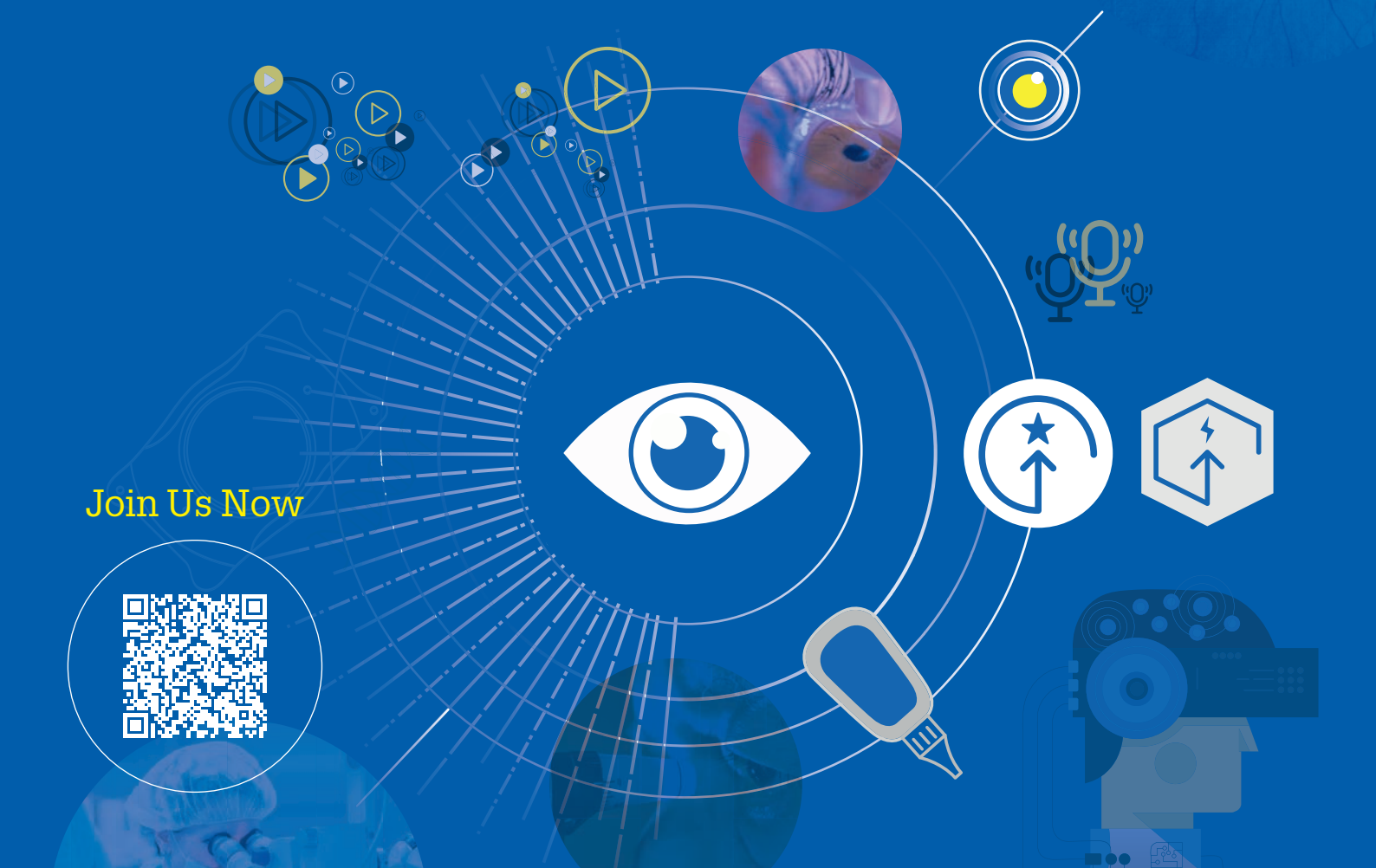

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Practice Fundamental

Cataract & Refractive Surgery

Simulating surgeons. Looking to identify the best training tool for novice surgeons, researchers evaluated the performance of experts tasked to create continuous curvilinear capsulorhexis on three commercially available surgical simulators. Although the surgeons performed the fastest on models believed to most closely approximate human capsular tissue, other simulators proved more accurate.

Wrong suspect? An experimental study designed to quantify damage to the corneal endothelium resulting from the flow of a balanced salt solution during phacoemulsification found that the volume of the balanced salt solution alone was not a major contributing factor to endothelial cell damage and loss.

Sims vision. Deciding on the right IOL can be a big decision for patients and ophthalmologists. But what if you can experience multifocal IOL function before cataract surgery? Researchers have developed an IOL simulator for this exact purpose. Using a trial lens frame adapter, lens tube, concave lens, spacer, wet cell, and the all-important IOL, it is possible to let patients try before they buy.

Partial decline. Researchers evaluating the refractive, visual, and morphometric changes of 481 eyes over five years after implantation with a foldable iris-fixed phakic intraocular lens (pIOL) to correct myopia or astigmatism observed slight myopic changes in refraction and visual acuity, in patients with Artiflex Myopia or Myopia Toric pIOLs, attributed to cataract formation and increased axial length.

Surgery in a bottle? Researchers have undertaken the first study testing the effects of the topical administration of oxysterol compounds on the optics of the lens. Oxysterol compounds have previously been found to interact with proteins essential for lens transparency, and as a result have been touted as potential anti-cataracts drugs.

Fear of the unknown. Two thirds of adults aged 50-80 who have considered having or had elective surgery in the past five years express concerns about pain and discomfort, almost half of them worry about the associated costs, and over a third are concerned about having someone take care of them after the surgery. After the procedure, 79 percent of patients previously in excellent or good health were satisfied with the outcome. Specialists are warning against postponing medical procedures, including elective surgeries, and advise seeking help from "prehabilitation" clinics.

No screening. The US Preventive Services Task Force commissioned a systematic review to evaluate evidence of screening for impaired visual acuity in asymptomatic adults over 60. It has concluded there isn't currently enough evidence to assess the balance of harm and benefit of a screening.

IN OTHER NEWS

Cataract causes. *Development of cataracts has been associated with two protein ion channels, TRPV1 and TRPV4, which act as sensors for control mechanisms of the eye lens. Now, a study aims to discover the exact biological mechanisms within the cells on the lens' surface responsible for cataract creation.*

Drawing near. *A study based on UK Biobank data has found a significant increase in myopia rates in 40–69-year-olds, and that its associations with education, ethnicity, and sex have also changed over time.*

Pre-school cataracts. *Modern therapies for retinoblastoma can cause secondary cataracts, but after cataract surgery risk there is a low risk of recurrence and extraocular spread.*

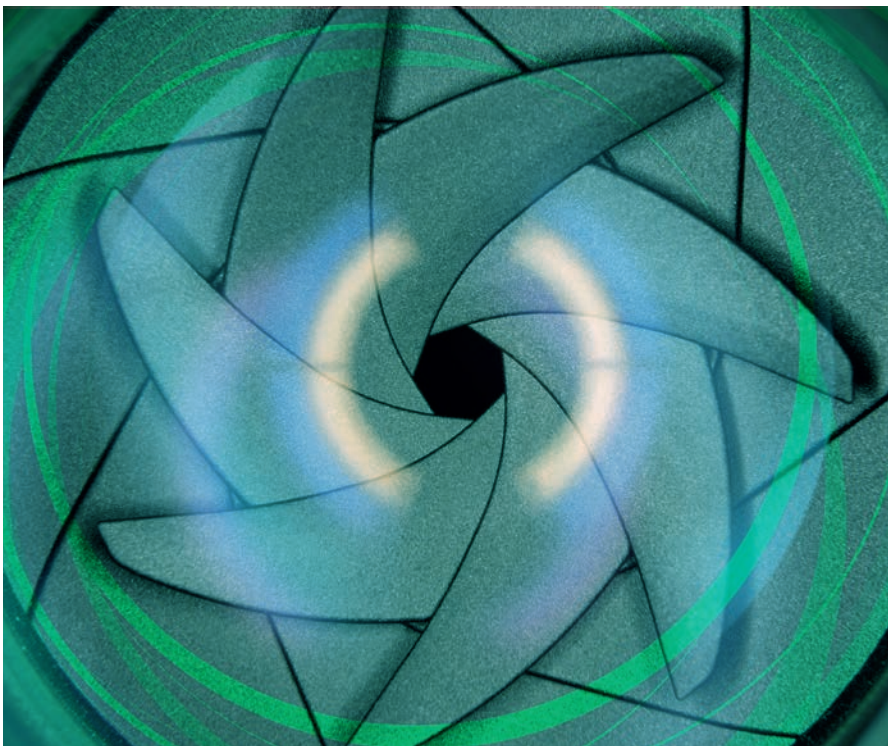
Eye on Alzheimer's. *A shared pathology is identified between lens and brain with Alzheimer's disease (AD) hallmark amyloid-β found in cataracts of age-related AD cases.*

See references online at: top.txp.to/wrong/suspect

A Pseudophakic Problem-Solver

Are pupil-modulating presbyopia-correcting drops the future of customizable vision correction for the pseudophakic population?

By Sumit "Sam" Garg



Credit: D-Kuru from Wikimedia Commons

Pupil-modulating presbyopia drops rely primarily on the principle of pinhole optics. Channelling light through a smaller central aperture, created pharmacologically in this case, sharpens vision under most lighting conditions and increases the depth of focus. Pinhole optics have already been leveraged, with good refractive results, for implanted devices in the form of corneal inlays and small-aperture IOLs. Now, with the introduction of VUITY and several other miotic-based presbyopia-correcting drops, pinhole optics may prove to be an ideal solution for some of the common postoperative problems we encounter as cataract surgeons.

New and upcoming drops modulate the pupil using familiar agents such as pilocarpine, carbachol, and brimonidine. Although these agents have long been available in some form, they were not practical for daily presbyopia correction. New formulations have been optimized using lower concentrations of the active ingredients and advanced vehicles expected to offer better penetration, more comfortable instillation, and reduced side effects. VUITY drops contain a low concentration of pilocarpine and were designed to quickly adjust to physiologic pH to improve tolerability of the acidic active ingredient. A fixed-combination preparation from Visus Therapeutics (BRIMOCHOL PF) includes the sympatholytic alpha-2 agonist, brimonidine to inhibit contraction of the iris dilation muscle, potentially reducing ocular surface redness due to the vasoconstrictive effects of brimonidine on the conjunctival vessels. Nonclinical studies have also indicated that brimonidine may reduce ciliary body contraction and markedly increase carbachol bioavailability, resulting in increased duration over carbachol monotherapy.

A better range of vision

The largest group of pseudophakic patients potentially set to benefit from drops are those who have already had cataract surgery with a monofocal IOL. Offering these patients topical drops to temporarily improve their near vision could be a significant lifestyle enhancer.

The evidence from FDA trials of surgical small-aperture technologies suggests pinhole optics preserve patients' distance acuity (1, 2). In ongoing clinical trials for presbyopia-correcting drops, the FDA is requiring manufacturers to demonstrate that products can achieve near vision gains with less than one line loss of distance vision. This provides confidence in trying these drops in pseudophakes who already have good distance vision but desire a more functional range of vision for all or part of their day.

Addressing residual error

Predictably, many of our pseudophakic patients don't have great uncorrected near or distance vision. For patients who still need to wear distance correction after cataract surgery, presbyopia-correcting drops could offer the option of wearing single-vision glasses, especially in unfamiliar environments, and being less dependent on bifocals or progressive spectacles. Spectacle multifocality creates blur on the downgaze and impairs edge-contrast sensitivity and depth perception, increasing the risk of falls (3).

Presbyopia-correcting drops may also help patients with up to 1.5 D of residual astigmatism see better (2, 4). By blocking aberrated peripheral light rays, pinhole optics improve astigmatism tolerance. In patients wearing glasses primarily for astigmatism and near vision, this effect could provide less spectacle dependence during the work day or for social activities.

Dealing with dysphotopsia and aberrations

We know from looking at modular transfer function graphs that visual quality is always better with narrower pupils. The pinhole effect of blocking stray light and unfocused peripheral light has added benefits of minimizing not only regular astigmatism and defocus, but also the impact of irregular corneal aberrations on vision. We have post-Radial Keratotomy patients whose incisions have caused hyperopic shift and fluctuating vision throughout the day. A smaller pupil makes them less sensitive to those fluctuations. I believe such patients will ultimately benefit the most from a small-aperture IOL. In the meantime, presbyopia-correcting drops give them a chance to test out pinhole optics in advance and perhaps carry them through for a few years before they are ready for lens surgery.

We also have patients in our practices who received early presbyopia-correcting IOLs with a high add power, which typically provided excellent near vision but with more dysphotopsia at night. While some patients neuroadapted to them, others found the glare and halo disabling at night and have had to restrict night driving. I have sometimes treated these patients with topical brimonidine because of its action in preventing pupillary dilation which, in a presbyopia drop, is complementary to constricting the pupil. Should drops like BRIMOCHOL PF be approved in the future, a drop in the non-dominant eye at nighttime may also help to prevent defocus-related glare and halo from the IOL in patients whose primary issue is dysphotopsia.

Prescribing considerations in pseudophakes

So far, presbyopia-correcting drops have only been tested in pseudophakes in a few clinical trials, and clinical experience with VUITY, at the time of this writing, is still limited. There are still questions to be answered about how well these drops will work for a pseudophakic population. My hope is that pupil modulating drops will work well bilaterally, without any loss of distance acuity or significant dimness. A 2019 review of small-aperture strategies for presbyopia reported that perceived brightness through a small aperture is greater than what would be expected from theoretical calculations (5). However, we still want to monitor how well new presbyopia-correcting drops perform in dim light.

We may want to exercise caution in prescribing the drops for patients who already have reduced contrast sensitivity from optic neuropathy or macular degeneration. It may become more important to get a baseline pupil size in patients, especially if they are elderly or on medications that already tend to affect pupil size. These patients might not respond to miotics for presbyopia at all, or may be more challenged by dim light. Additionally, just as with presbyopia-correcting IOLs, it will be important to appropriately manage the ocular surface. Pinhole optics won't work very well if the patient has superficial punctate keratitis in the center of the pinhole. Importantly, it is prudent to perform a dilated fundus exam and discuss the risk of retinal complications that miotics may exacerbate in some at risk eyes.

There will likely be some variability in effectiveness, due to refractive status, age, or other patient factors we don't yet fully understand. However, unlike IOLs or corneal inlays, patient response isn't necessarily a cause for immediate concern. If one particular drop doesn't work, patients can stop using it or wait for one with a better side effect profile or longer duration of effect to hit the market. This new category is full of promise, both for routine correction of presbyopia and for resolving tough postoperative problems.

Sumit "Sam" Garg is Professor of Ophthalmology, Vice Chair of Clinical Ophthalmology, and Medical Director at the Gavin Herbert Eye Institute at the University of California – Irvine, USA.

He is a consultant to Allergan, CorneaGen, Johnson & Johnson Vision, and Visus Therapeutics.

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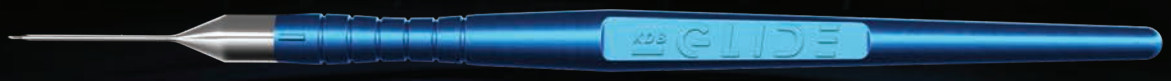

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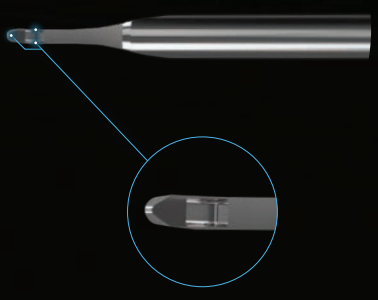
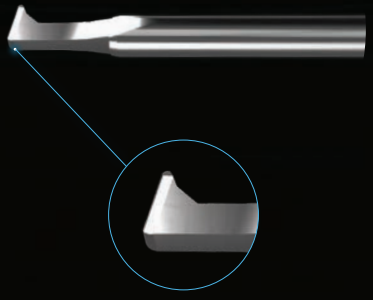
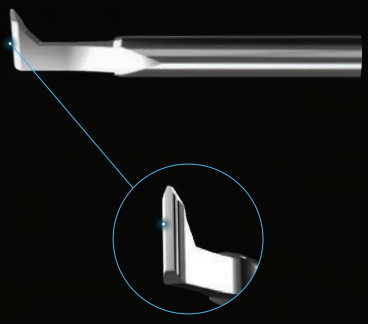


ROUNDED HEEL



TAPERED SIDES & FOOTPLATE



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Practice Fundamental

Glaucoma

Analyzing AI. The capability of AI as a glaucoma diagnostic tool was assessed in a meta-analysis. Having searched databases for studies that developed or investigated AI use for glaucoma detection using fundus and OCT images, researchers saw the potential of AI to revolutionize glaucoma care, but concluded that AI is not ready for implementation into clinical care as issues such as standardizing grading protocol, implementing external data validation, and analysis across different ethnicity groups are yet to be addressed.

Trust the process. Data postprocessing reduces variability of visual field data, and can be used to more effectively track glaucoma progression. Researchers applied a dynamic structure–function (DSF) model to a database from 118 glaucoma eyes. They found that without compromising specificity, DSF-predicted measurements to identify progression produced similar or better data sensitivity to noise, which can be applied to existing visual field data to evaluate patients who may be at risk of glaucoma progression.

Ringing true. A case-control study using nationwide population-based data from Taiwan, using data from the country's National Health Insurance Research database for patients with a first-time diagnosis of tinnitus, showed a slight association between primary open angle glaucoma patients and tinnitus, indicating a higher risk of developing tinnitus within this patient group. However, the underlying mechanisms are yet to be discovered.

Surgical dilemma. A study of the long-term success of surgical intervention in Thai primary congenital glaucoma patients found that primary trabeculotomy and primary combined trabeculectomy showed the highest long-term success rates whereas primary diode transscleral cyclophotocoagulation (TSCPC) demonstrated the lowest efficacy, with no successful outcomes after 48 months. All surgery types assessed, apart from TSCPC, had comparable cumulative one-year success rates.

Fun in the sun. The SUN project finds that adhering to Mediterranean lifestyle is significantly associated with lower risk of glaucoma. Certain healthy habits were used to quantify Mediterranean lifestyle adherence: Mediterranean diet, moderate consumption of alcohol (no binge drinking), having never smoked, good levels of physical activity, low TV exposure, an afternoon nap, meeting up with friends, and low body mass index.

See references online at: top.txp.to/trust/the/process

IN OTHER NEWS

Tracking change. *A new method of tracking glaucoma progression enables visualization of this change in a two-dimensional structural and functional space.*

Protein protection. *If Sigma 1 receptors protecting retinal ganglion cells are missing, astrocytes may not be able to secrete supportive factors for neurons, leading to glaucomatous damage.*

Calcium equilibrium. *Damage to nanotubes connecting pericytes in glaucoma patients – due to calcium deficits – leads to neurovascular deficits.*

Genetic risk. *Immediate IOP elevation and iritis incidence after prophylactic laser peripheral iridotomy was higher in Black primary angle closure patients.*

Studying stem cells. *Researchers investigated human stem cells made into retinal ganglion cells, attempting to slow down glaucoma progression or even reversing vision loss.*

From Too Few Drops to DSLT

Introducing a more efficient approach to treat glaucoma patients who cannot maintain eye drop adherence

By Gerd U. Auffarth

Ophthalmologists are aware of the challenges facing glaucoma management, particularly regarding patient compliance. In our clinic at the University of Heidelberg, we see patients at various stages of glaucoma development – from undiagnosed to early onset and post-operative. These long-term patients often have issues with adherence. No matter how specific the instructions given when prescribing eye drops, a large percentage of glaucoma patients will not take them correctly (1, 2). Though it is understandable that patients sometimes forget to instil their drops, maintaining compliance when treating a lifelong disease like glaucoma is crucial.

Managing patients with poor adherence

When patients return to the clinic, it is important not to rely on pressure measurements, as sometimes patients forget their drops, only remembering to take them before their next appointment to lower the pressure – behaviour known as "white coat adherence."

Neglecting eye drops can cause irreversible damage in one to two years, and, when a patient is not in a position to understand this damage, it is better to recommend other treatment options.

In most of these cases, patients are given a time frame of between one and five months to improve their compliance. If it is clear that they have not been adhering to their medication over multiple visits, it becomes necessary to tell them that they must undergo a different procedure to lower the pressure. As a doctor, it is important to differentiate between patient profiles and observe how they react; depending on the patient, you may need to make it clear that there is no way for them to continue without intervention.

At this point, the language used to counsel the patient becomes of crucial importance. Many patients can be persuaded to undergo a "treatment" or a "procedure," if they understand that it will reduce the need for eye drops. However, there will always be patients who are afraid to undergo "surgery." Patients who have done their research will further understand that glaucoma surgery is not like cataract surgery,

Gerd Auffarth.

where the results are more instant. There will be hospital time, significant healing time involved to realize the results, and a chance of side effects, such as hypertonia or some blood in the eye. Ultimately, the more invasive the recommended

"As glaucoma is a lifelong disease, we need diverse ways of managing glaucoma patients in the long term."

intervention is perceived to be by patients, the more reluctant they will be – and that's why less invasive procedures have higher patient acceptance.

Enter DSLT?

As glaucoma is a lifelong disease, we need diverse ways of managing glaucoma patients in the long term. Though treatment may commence with eye drops, the lack of compliance can lead to the need for even more eye drops – but that only highlights the imperfect nature of the treatment. The idea of a simple, non-invasive procedure with nearly instant impact and a high likelihood of reducing the need for eye drops is extremely appealing to me and other doctors – especially when compared with the alternatives: more drops or invasive surgery. Direct selective laser trabeculoplasty (DSLT) could fill a real gap.

DSLT represents a gentler, non-contact primary treatment therapy for open-angle glaucoma patients which, in initial studies, appeared to be as effective as selective laser trabeculoplasty (SLT), while still being a rapid, non-contact, and automated treatment (3). With the impending release of the results of the GLAUrious randomized control trial (4), we expect to see clinical results to support this conclusion.

This procedure is straightforward to perform, with a touch of a single button, and does not exclude the possibility for further surgeries, if necessary. In healthcare systems like Germany's, DSLT could provide a new early intervention option and even first-line treatment in glaucoma management. In other countries, where patients cannot afford eye drops and have little access to follow-up visits, this type of automated procedure, without the need for significant resources or a surgical theater, could also be valuable. There are, in fact, many scenarios in which this treatment would be appealing.

In our own clinic, integrating this methodology as a routine application would be fairly simple as we have already begun to move away from "last-resort" type surgeries, such as trabeculectomy, towards a mixed treatment approach, including SLT and the PRESERFLO MicroShunt (Santen). And that is thanks to our strategy of detecting and treating glaucoma patients much earlier. Thus, for a certain group of patients, DSLT can certainly be implemented as a first-line treatment option, before or instead of prescribing drops.

What makes the promise of DSLT even more interesting is the rapid treatment time and elimination of a gonio lens; patients will not have to endure an uncomfortable procedure, and ophthalmologists and their teams will experience greater efficiency in the clinic.

Gerd U. Auffarth is Professor and Chairman of the Department of Ophthalmology, University of Heidelberg; and Director of the International Vision Correction Research Centre, David J. Apple International Laboratory for Ocular Pathology, Germany.

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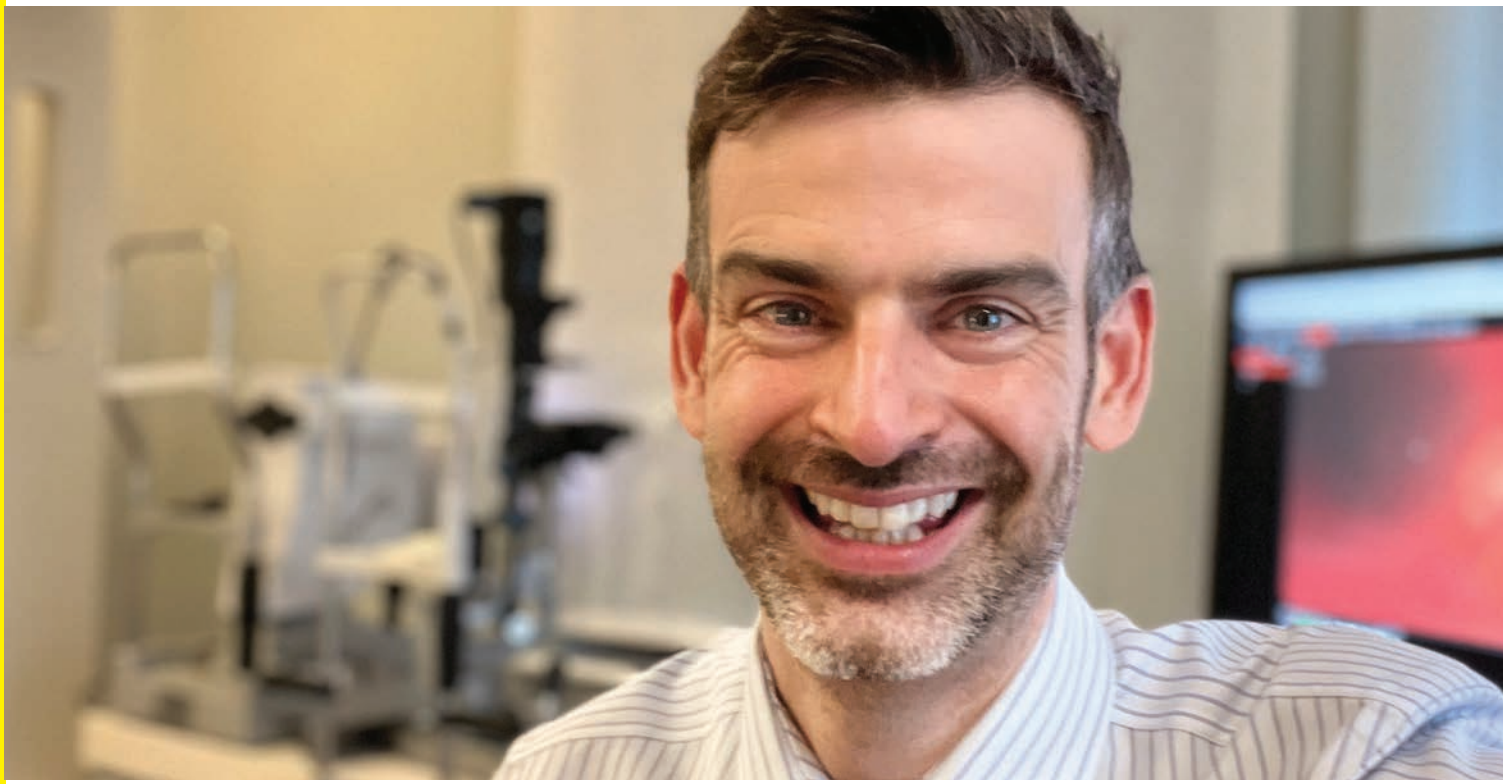
Dan Lindfield.



From the Rooftops

Two recent updates in the glaucoma field that are definitely worth shouting about

By Dan Lindfield

The LiGHT study changed glaucoma practice in 2019 (1). Many practitioners used this evidence to inform a discussion of primary drops versus primary selective laser trabeculoplasty (SLT) for ocular hypertension (OHT) and glaucoma, resulting in two valid primary treatment options. Now, the UK's National Institute for Health and Care Excellence (NICE) has assessed the burgeoning evidence and recommended that SLT should be the only therapy offered at diagnosis, with medication reserved for those patients unwilling to receive, unsuitable for laser, or where laser is not available (2). NICE defines UK practice, but the ripples can be felt across Europe, Asia and the US. It's great to see SLT allowed the prime position that I feel it should have. Hopefully, the number and availability of SLT devices increases quickly, as demand is large. The next logical step is to study whether we can safely extend patient follow-up duration (to 18 or even 24 months) subject to an adequate response to SLT and if other criteria are met. Predictable effect without adherence/compliance issues and greater diurnal flattening of IOP may well allow our overstretched services to decompress our lower risk patients due the added confidence SLT confers to their care.

A shift in MIGS disease control metrics

The HORIZON study looking at five-year data on Hydrus Microstent is a real shift in the quality of evidence supporting MIGS devices (3). We've progressed from IOP results muddied by the phaco effect, to more representative device-only outcomes, not only for efficacy but safety, quality of life, and – most recently – cost–benefit data. However, until now, disease controlmetrics have not been well studied or proven. We extrapolate target IOP from studies 20-40 years old but the preliminary results from HORIZON suggest that Schlemm's canal scaffolding can lower the rate of visual field loss by 47 percent across all patients enrolled (and includes control for the cataract surgery element alone). I'm reserving full judgement until the full paper emerges later this year, but this sort of data is really moving the field forwards. We need data like this to fuel better discussion with our patients about the benefits of all MIGS procedures and back up our negotiations with payors as the MIGS arena become more divergent, expensive and popular.

Recent Research Ruminations

Despite pandemic-related challenges, we – researchers in Beijing, China – have managed to make promising progress in glaucoma research, with a few major breakthroughs

By Ningli Wang

Previous findings suggested that elevated trans-laminar cribrosa pressure difference (TLCPD), instead of IOP itself, is a vital factor for the development of glaucoma (1). Further investigating the effect of focal lamina cribrosa (LC) defect on glaucoma progression, we explored the binocular comparison of LC defect within 93 NTG patients with asymmetric visual field loss. LC defects were found to be more common in eyes with better visual fields and exhibited lower peak IOP. Then, evaluating ocular parameters in patients (one eye with LC defect and the other without), we found eyes with LC defect to exhibit significantly better mean deviation, lower IOP, but longer axial length and larger tilt ratio. The rebalance of TLCPD mediated by focal LC defect may be the reason for the delay of glaucoma progression. These results were confirmed in rhesus monkeys. We therefore hypothesize that the spontaneous channel may connect the intraocular cavity and subarachnoid space, leading to fluid diffusion and reduced IOP. As a result, TLCPD is rebalanced in a lower level, potentially inhibiting glaucomatous optic neuropathy progress.

The American Academy of Ophthalmology's Preferred Practice Patterns highlights low cerebrospinal fluid pressure (CSFP) as a risk factor for primary open angle glaucoma. However, retinal vasculature changes following CSFP reduction have not previously been studied. Recently, we performed OCT-A scans in patients undergoing diagnostic lumbar puncture and showed a CSFP reduction (2). Vessel density in the macular region decreased significantly after CSFP reduction. We also identified a significant relationship between CSFP reduction and macular parainferior vessel density decrease. However, the optic nerve head vessel density did not change after CSFP reduction. Additionally, choroidal thickness significantly decreased in the subfoveal and peripapillary region after CSFP reduction and a significant association between CSFP and the ratio of small to medium vessel layer to total choroidal thickness was found. This is the first demonstration of dynamic vascular changes after CSFP reduction in humans and provides more clinical evidence on the diagnostic paradigms for glaucoma.

Finally, transscleral cyclophotocoagulation (TSCP) has been described as a safe and effective treatment, providing excellent IOP control in malignant glaucoma and acute primary angle closure (APAC) patients. Our previous studies provided clinical signs that TSCP induced damage or inflammation may change the structure of the anterior vitreous (3), lowering posterior pressure and causing a backward movement of the lens-iris diaphragm. This leads to anterior chamber deepening and reopening of angle in prolonged APAC and younger patients with chronic angle closure glaucoma (CACG). Recently, we found further evidence of vitreous modification caused by a fixed dosage of TSCP in three young patients with CACG, and some porcine eyes and rabbit eyes in vitro (4). This suggests that low dose TSCP with an audible "burst" could be used as an anterior vitreous modification procedure, having a significant effect on the management of young CACG patients.

"Vessel density in the macular region decreased significantly after CSFP reduction."

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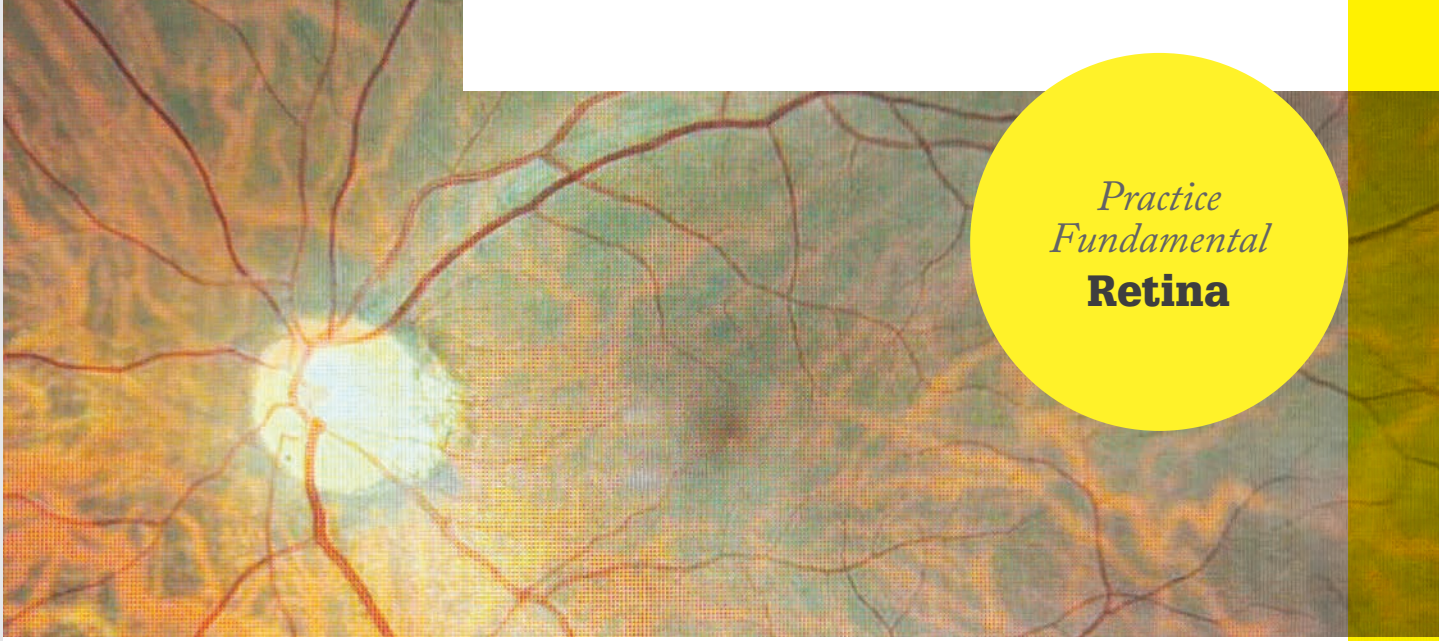

Retinal A to Z. Five subpopulations of distinctly different cells were found in the RPE layer – researchers used AI to analyze single-cell resolution images. Five concentric RPE populations were identified, along with subpopulations with different susceptibility to monogenic and polygenic retinal diseases. These findings will help the development of specific cell and gene therapies to target retinal diseases.

Optical powerhouses. A research group from the National Eye Institute in Bethesda, Maryland, US, has shown that mitochondria aggregated by mammalian photoreceptors act as a microlens and focus light entry into the outer segment, remodeling themselves to alter light concentration. This phenomenon is essential in improving resolution – the insight given from this study is relevant to clinical ophthalmic imaging, and may help early diagnosis of retinal diseases.

Unintended consequences. Researchers analyzing health insurance claim records of over 213,000 American men found an increase in the risk of serous retinal detachment, retinal vascular occlusion, and ischemic optic neuropathy in those who regularly use phosphodiesterase type 5 inhibitors (PDE5Is), used in the management of erectile dysfunction. This data is important, as previous results on this subject are conflicting and epidemiological data are non-existent. People using PDE5Is will need to be aware of these adverse events, and alert their physicians at the first sign of trouble.

Double trouble. A study of 502 participants assessed associations of the two most common genetic risk loci for AMD with disease progression: CFH-CFHR5 on chromosome 1 and ARMS2/HTRA1 on chromosome 10. The risk of disease onset was increased in people who carried two risk alleles for each of the loci. The findings suggest that AMD disease progression is associated with these loci through distinct biological mechanisms, and warrant consideration when designing clinical trials.

New foundations. A In vivo correction of an Rpe65 mutation by adenine base editor has been demonstrated to prolong the survival of cones in a mouse model of Leber congenital amaurosis. The findings highlight base editing as a potential gene therapy that could confer long-lasting retinal projection.

Ophthalmic oracle. Relative telomere length (RTL) is now associated with risk of AMD, but only in women. A previous link between physiological aging and RTL had been established, so researchers sought to establish a link to AMD in a 2,262 strong, elderly cohort. The results are in tune with levels of reactive oxygen species levels and higher telomerase activity in women.

IN OTHER NEWS

Sight after death. *Scientists describe how they were able to revive retinal neurons and restore light signalling in the post-mortem mouse and human retina.*

Road to recovery. *A recent study shows that a treatment for retinal vein occlusion has long-lasting advantages for vision – but patients require ongoing treatment.*

'Allo 'Allo! *A clinical trial of allogenic RPE transplant patch has shown it survive for two years post implantation, with researchers looking to secure FDA approval.*

In the womb. *UK's National Health Service is rolling out a non-invasive test capable of identifying babies' risk of developing retinoblastoma – in utero. The test, developed at Birmingham's Women's and Children's Foundation Trust, uses a maternal blood sample and has almost 100 percent accuracy, enabling treatment straight after delivery.*

See references online at: top.txp.to/retinal/AZ

On the Right Track

Using AI to map and track retinal changes could revolutionize diagnosis and treatment of advanced Dry AMD

By Konstantinos Balaskas

Age-related macular degeneration (AMD) is a huge issue for eyecare professionals – and one that will only grow with time. Wet AMD accounts for a large proportion of outpatient hospital activity and is a major area of interest in ophthalmology – from both a clinical and academic viewpoint. But AMD doesn't have only one vision-threatening form, and dry AMD, with its advanced stage of geographic atrophy (GA), still has no effective treatment. Patients are left in a hopeless situation and ophthalmologists can only monitor the gradual progression of visual impairment. We are now in an era of very intensive academic activity to search for GA treatments and a number of molecules show good promise – some already in late clinical trials. Aside from the lack of treatments available, there is also the challenge of detecting GA at its early stages, and quantification of disease progression is particularly difficult.

This vast unmet need inspired me to look at this condition in more depth, including disease management and its effect on capacity pressures in the UK's already overburdened National Health Service (NHS). Did you know that ophthalmology accounts for 10 percent of all outpatient activity in the NHS – more than any other medical specialty?

Our research team is considering how automation through AI could help alleviate the burden for patients, doctors, and the healthcare system. Specifically, we have developed a deep learning algorithm for the detection and quantification of GA that performs a specialist assessment in a fully automated manner (1). Using OCT images, the algorithm tracks disease progression in just two seconds and brings consistency and repeatability in an assessment that suffers from great interobserver variability – even between experts. Precisely quantifying GA progression means patients can be better characterized earlier to maximize the window of opportunity for therapeutics. And it could also lead to improved patient selection for clinical trials. A major challenge for eye departments that store large databases of OCTs is to quickly identify patients who are eligible for a clinical trial, so they tend to rely on traditional labor-intensive approaches of manual screening of clinical and imaging records. Imagine how valuable it could be to apply an AI model to an entire OCT database within a local hospital environment, identifying the cases of GA, and then selecting patients whose stage of progression is more suitable for a particular clinical trial.

Dry AMD versus AI

In wet AMD, there is usually an episode of bleeding or swelling at the back of the eye, which causes a significant and noticeable change in vision. This will in most cases cause alarm and prompt patients to seek immediate medical assistance and treatment to prevent or reverse progression. GA, on the other hand, progresses slowly over time, causing areas of wear and tear at the back of the eye which grow at an unpredictable pace, in a sense creeping up on the patient. Patients tend not to seek expert advice early as they often don't realize a problem has developed in their eye until a lot of damage has already been done. Consequently, there is an obvious need to improve dry AMD and GA screening and tracking, as well as objectively monitoring the progression of affected retinal areas – a very challenging task.

The imaging modality device of choice for both types of AMD and many other retinal conditions is OCT. Tracking GA lesion progression over time with 3D OCT scans requires manual delineation and segmentation of complex scans that often consist of over 100 individual images. Manual processing of all the images would be unrealistic in real-life clinical practice. It would be therefore infeasible to consistently and accurately monitor the behavior of the disease and to assess the efficacy of any potential treatment. Hence, this process is a prime candidate for automation.

Our automated method uses Deep Learning (a form of AI) to quickly quantify retinal atrophy over consequent patient visits, offering an accurate representation of the stage and extent of atrophic Dry AMD and helping the ophthalmologist decide if treatment is needed and if so, how well the patient is responding to treatment. When decisions are based on standardized, reliable, repeatable quantification of the area of atrophy, it is expected that better clinical outcomes from emerging treatments will be achieved. And for patients, it also means shorter visits and less time spent in crowded hospital waiting rooms. When we were developing this AI system, the average time required for an expert human

grader to segment a geographic atrophy lesion on OCT was 43 minutes; our Deep Learning model can achieve the same task in 2.04 seconds, on average.

At the London City Road campus of Moorfields Eye Hospital, we administer more than 100 intravitreal injections for the treatment of Wet AMD every day. Although treatment decisions for Wet AMD are primarily guided by OCT scans, these are mostly assessed in a qualitative way. Just by looking at the scan, we can tell whether the condition is getting worse, better, or is stable. In GA, the situation is very different. Disease progression is too subtle and the changes are too slow to visually track by human experts with the level of precision needed to discern short-term progression. Hypothetically, if a GA treatment became available and the patient population requiring intravitreal injections doubled, the need of an automated, fast and accurate monitoring system will be ubiquitous. Not only would this help physicians and patients to jointly make the decision on whether treatment is warranted, but also when and how frequently it should be given.

Inside the algorithm

To explain how the algorithm works, we should go back to the basics of Deep Learning. The algorithms are exposed to a large number of examples – in this case, retinal OCT images – and they start to recognize patterns. Next, they are able to recognize similar patterns in images they have not seen before. My team used data from a phase II clinical trial – the FILLY study, which assessed the efficacy of a novel GA therapeutic. We manually graded multiple images from volume OCT scans – resulting in approximately 6,000 individual manually graded images – and used them to train the Deep Learning model for the detection and monitoring of retinal atrophy. The algorithm was then exposed to a rigorous testing phase applying it to a distinctly different data set not previously seen by the algorithm. In our case, the performance of the algorithm – expressed by a statistical metric called the dice similarity score – was 0.96, which is extremely high.

"In wet AMD, there is usually an episode of bleeding or swelling at the back of the eye, which causes a significant and noticeable change in vision."

It is relatively easy for an AI model to perform well when exposed to data from patients with similar traits to those it was trained on. The real test is when it is exposed to a data set from a completely distinct healthcare setting. And that's why it's important to note that our OCT algorithm was tested against a data set from a patient population completely distinct, geographically and temporally separated from the population used for training. (The FILLY study had patients from the US, Australia and New Zealand, whereas our external validation data set was from Moorfields Eye Hospital patients.)

But there are still challenges ahead. An AI model alone is a sophisticated piece of code with no clinical utility in isolation. AI implementation requires further infrastructure development, and particularly a user interface allowing clinicians to import OCT scans which will then enable visualisation of the AI output to clinicians and researchers in a digestible and user-friendly format. Cloud-based deployment and information security are additional major priority areas for consideration. Ahead of clinical implementation, approvals from the Medicines and Healthcare Products Regulatory Agency (MHRA) and potentially other regulatory authorities are an essential pre-requisite.

The system could also be applied to other ophthalmic disease areas. In essence, we developed four different deep learning models, one for each retinal layer that is a constituent feature of GA. As a by-product of that, we can now tune these models to detect changes in individual layers that have distinct profiles of impairment or degeneration, particularly in inherited eye diseases.

On the horizon

A really common question AI experts are asked is, "How soon do you think we will have it in our clinic?" People used to be conservative with their answers but, as the field develops, we are becoming more optimistic! Now that we are able to develop such models "in house" using our own resources, I am more positive about the future of point-of-care AI-based decision support systems. It might still be a matter of few years, but it's no longer in the distant future – for this clinical application of AI decision support systems in retinal disease, at least. We can also envisage a longer-term future with AI processing high-dimensional data including multi-modal imaging, but also clinical data, genetics, proteomics, and more. With the increasing importance of the Internet of Things, data from remote monitoring devices will eventually also be integrated and processed through AI systems, with the over-arching objective to inform personalized treatment plans best suited for the needs of each individual patient.

See references online.

The Winning Formula

Sitting Down With… Douglas Koch, Professor and Allen, Mosbacher, and Law Chair in Ophthalmology, Cullen Eye Institute, Baylor College of Medicine, Houston, Texas, USA

When did you first think of becoming a physician and an ophthalmologist?

My father, a radiologist, talked of how he loved patient care and the intellectual stimulation of practising medicine. Becoming a physician appealed to me from a young age, but I was a latecomer to ophthalmology as a career choice. In my small hometown of Port Huron, Michigan, one of our parents' friends was ophthalmologist Nicholas Douvas. Nick developed one of the first vitrectors, and ophthalmologists from around the world traveled to Port Huron to learn from him. This was incredibly unusual for our slightly rural small town. Nick was also my ophthalmologist and fit me with PMMA contact lenses when I was 13; that was life-changing.

Despite all of this, I wasn't exposed to ophthalmology in the clinic until the start of my fourth year at Harvard. I took a rotation at Massachusetts Eye & Ear and was astonished by the magic of examining and treating the human eye and the unbelievable intricacies of eye surgery. I had applied to pediatric residency, but I immediately pulled those applications in favor of ophthalmology. Of course, I misspelled it "opthalmology" on my applications…

My subspecialization in cataract and refractive surgery was even more serendipitous. In my final year of residency, I secured the fellowship I had sought in pediatric ophthalmology and strabismus (yes, kids again…). However, a few months before graduating, as I was scrubbing with Jared Emery – our amazing faculty cataract surgeon – he paused, looked at me, and asked if I would consider joining him as a partner at Baylor in Houston, Texas. By then, I was committed to Marcia, my future wife and a native Houstonian, and a week later the pediatric fellowship program informed me that my funding for the fellowship "fell through." It was a dream choice for me… and another abrupt career change.

When did you know you had made the right career choice?

On the first day of my ophthalmology rotation, when I looked at an eye with the slit lamp. Over time, I have come to realize that I am very visually oriented. I am pretty hopeless at memorizing syndromes, but images stay with me. I love the visualization our field allows. I was incredibly fortunate to find such a great fit.

Do you ever imagine having followed a different path?

In college, I toyed with the idea of becoming a professional French horn player, but I saw the challenges such a career entailed. I have many friends who are musicians and love their careers, but I have no regrets about my decision. Music remains an important part of my life, though; I help run Bach Society Houston and play the piano (at a very amateur level).

Who do you see as your most valued mentors?

There have been so many, but I will mention three: i) my chairman of 30 years, Dan Jones, who taught me the importance of painstaking attention to detail and was remarkable for the personal touch in the care he provided for his patients; ii) Jared Emery, who taught me so much but, above all, the elegance of surgery performed with precision and grace; and iii) Stephen Obstbaum, who brought me onto the editorial board of the Journal of Cataract and Refractive Surgery and mentored me in the nuances of editing, managing a journal, and more.

What is your greatest achievement?

That's an easy answer: teaching students, residents, and fellows. This is the most deeply satisfying part of my career. I have had the opportunity to work with so many spectacular students and young physicians. Seeing them flourish, become brilliant clinicians and surgeons, and make meaningful contributions to our field is the greatest reward I could ask for.

From a research standpoint, I would list two things. The first is my interest in improving the accuracy of IOL calculations, especially in challenging situations. In 1989, my colleagues and I published the first paper showing the unexpected outcomes of IOL calculations in post-RK eyes, which started my career-long work in this area. My second is my team's work pointing out the impact of posterior corneal astigmatism on astigmatism management in cataract surgery; this has transformed the way toric IOLs are calculated.

Are there any aspects of your job you dislike?

The hardest part of my job is guiding patients to set appropriate expectations. You can never tell what will make a patient upset or afraid. Yesterday, in succession, I saw a 20/40 post op patient who was ecstatic and a 20/20+ patient who was miserable. Helping patients work through these issues is a huge part of caring for them.

Do you remember any individual patients your work has helped?

In the mid-1980s, my chairman, Dan Jones, referred a prominent patient to me. He had undergone cataract surgery in New York City, and the surgeon targeted both eyes for myopia instead of targeting the monovision that the patient had achieved with contacts and had requested. At that time, there were some uncertainties with IOL labeling; there was no ORA, no formula for calculating IOL exchanges, and no proven formula for calculating IOL power in a pseudophakic eye. And, of course, the IOL had a 6-mm PMMA optic. I removed the IOL, placed it in a water bath, read the power with a lensometer, and made an educated guess for the new IOL, all under the watchful eye of my chairman. The patient was 20/20 on day one and has been an incredibly generous supporter of our research ever since, culminating in the huge 10-year grant I received last year. So much for early retirement…

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