NOVEMBER / DECEMBER 2023 # 70

the Ophthalmologist™

Visions of the (Very Near) Future

The cutting-edge technologies and therapies that are destined to shape the ophthalmic space for years to come

14 – 23

SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL

GA unravels so much

Save retinal tissue by slowing progression[1-3]

INDICATION

SYFOVRE® (pegcetacoplan injection) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

IMPORTANT SAFETY INFORMATION

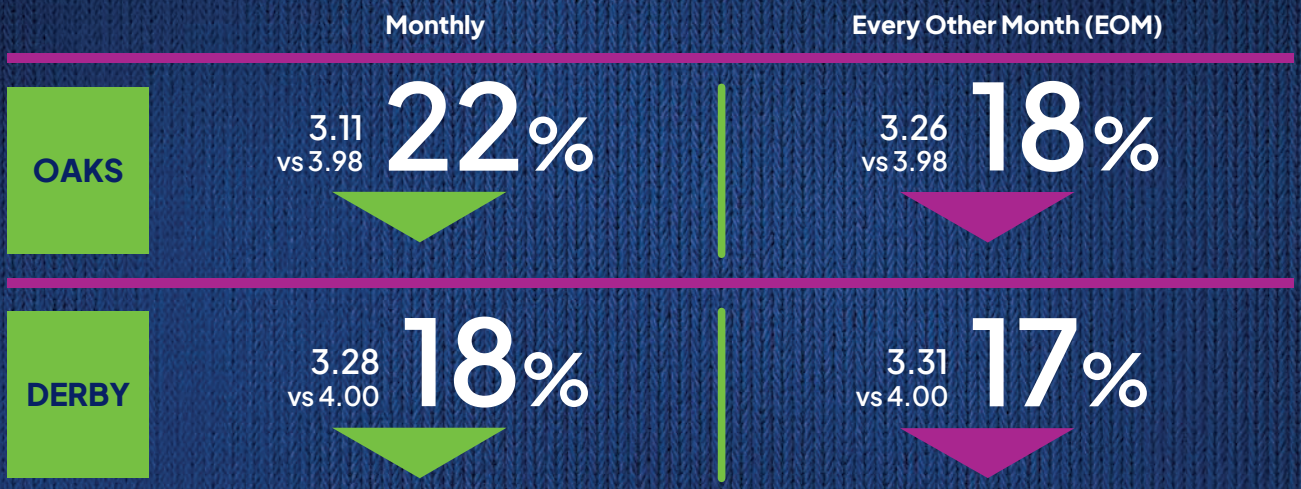
CONTRAINDICATIONS

- SYFOVRE is contraindicated in patients with ocular or periocular infections, and in patients with active intraocular inflammation

WARNINGS AND PRECAUTIONS

- **Endophthalmitis and Retinal Detachments**
  - Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
- **Neovascular AMD**
  - In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.
- **Intraocular Inflammation**
  - In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves, patients may resume treatment with SYFOVRE.

SYFOVRE achieved continuous reductions in mean lesion growth rate* (mm^2) vs sham pooled from baseline to Month 24[1]



SE in trials (monthly, EOM, sham pooled): OAKS: 0.15, 0.13, 0.14; DERBY: 0.13, 0.13, 0.17.

*Slope for baseline to Month 24 is an average of slope of baseline to Month 6, Month 6 to Month 12, Month 12 to Month 18, and Month 18 to Month 24.[1]
Based on a mixed effects model for repeated measures assuming a piecewise linear trend in time with knots at Month 6, Month 12, and Month 18.[1]
GA=geographic atrophy; SE=standard error.

Explore the long-term data

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

- **Increased Intraocular Pressure**
  - Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥5%) are ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, conjunctival hemorrhage.

Trial Design: SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multi-center, 24-month, Phase 3, randomized, double-masked trials. Patients with GA (atrophic nonexudative age-related macular degeneration), with or without subfoveal involvement, secondary to AMD were randomly assigned (2:2:1:1) to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly, SYFOVRE EOM, sham monthly, or sham EOM for 24 months. Change from baseline in the total area of GA lesions in the study eye (mm^2) was measured by fundus autofluorescence (FAF).[1,4]

References: 1. SYFOVRE (pegcetacoplan injection) [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; 2023. **2.** Pfau M, von der Emde L, de Sisternes L, et al. Progression of photoreceptor degeneration in geographic atrophy secondary to age-related macular degeneration. *JAMA Ophthalmol*. 2020;138(10):1026–1034. **3.** Bird AC, Phillips RL, Hageman GS. Geographic atrophy: a histopathological assessment. *JAMA Ophthalmol*. 2014;132(3):338–345. **4.** Data on file. Apellis Pharmaceuticals, Inc.

Please see Brief Summary of Prescribing Information for SYFOVRE on the adjacent page.

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SYFOVRE® (pegcetacoplan injection), for intravitreal use
BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please see SYFOVRE full Prescribing Information for details.

INDICATIONS AND USAGE

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CONTRAINDICATIONS

Ocular or Periocular Infections

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Active Intraocular Inflammation

SYFOVRE is contraindicated in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

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Neovascular AMD

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Intraocular Inflammation

In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves patients may resume treatment with SYFOVRE.

Increased Intraocular Pressure

Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

Clinical Trials Experience

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

A total of 839 patients with GA in two Phase 3 studies (OAKS and DERBY) were treated with intravitreal SYFOVRE, 15 mg (0.1 mL of 150 mg/mL solution). Four hundred nineteen (419) of these patients were treated in the affected eye monthly and 420 were treated in the affected eye every other month. Four hundred seventeen (417) patients were assigned to sham.

The most common adverse reactions (≥5%) reported in patients receiving SYFOVRE were ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage.

Table 1: Adverse Reactions in Study Eye Reported in ≥2% of Patients Treated with SYFOVRE Through Month 24 in Studies OAKS and DERBY

Adverse Reactions	PM (N = 419) %	PEOM (N = 420) %	Sham Pooled (N = 417) %
Ocular discomfort*	13	10	11
Neovascular age-related macular degeneration*	12	7	3
Vitreous floaters	10	7	1
Conjunctival hemorrhage	8	8	4
Vitreous detachment	4	6	3
Retinal hemorrhage	4	5	3
Punctate keratitis*	5	3	<1
Posterior capsule opacification	4	4	3
Intraocular inflammation*	4	2	<1
Intraocular pressure increased	2	3	<1

PM: SYFOVRE monthly; PEOM: SYFOVRE every other month

*The following reported terms were combined:

Ocular discomfort included: eye pain, eye irritation, foreign body sensation in eyes, ocular discomfort, abnormal sensation in eye

Neovascular age-related macular degeneration included: exudative age-related macular degeneration, choroidal neovascularization

Punctate keratitis included: punctate keratitis, keratitis

Intraocular inflammation included: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, anterior chamber flare

Endophthalmitis, retinal detachment, hyphema and retinal tears were reported in less than 1% of patients. Optic ischemic neuropathy was reported in 1.7% of patients treated monthly, 0.2% of patients treated every other month and 0.0% of patients assigned to sham. Deaths were reported in 6.7% of patients treated monthly, 3.6% of patients treated every other month and 3.8% of patients assigned to sham. The rates and causes of death were consistent with the elderly study population.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of SYFOVRE administration in pregnant women to inform a drug-associated risk. The use of SYFOVRE may be considered following an assessment of the risks and benefits.

Systemic exposure of SYFOVRE following ocular administration is low. Subcutaneous administration of pegcetacoplan to pregnant monkeys from the mid gestation period through birth resulted in increased incidences of abortions and stillbirths at systemic exposures 1040-fold higher than that observed in humans at the maximum recommended human ophthalmic dose (MRHOD) of SYFOVRE (based on the area under the curve (AUC) systemically measured levels). No adverse maternal or fetal effects were observed in monkeys at systemic exposures approximately 470-fold higher than that observed in humans at the MRHOD.

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.

Lactation

Risk Summary

It is not known whether intravitreal administered pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. Animal data suggest that the risk of clinically relevant exposure to the infant following maternal intravitreal treatment is minimal. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when SYFOVRE is administered to a nursing woman.

Females and Males of Reproductive Potential

Contraception

Females: It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with intravitreal pegcetacoplan. Advise female patients of reproductive potential to use effective contraception during treatment with SYFOVRE and for 40 days after the last dose. For women planning to become pregnant, the use of SYFOVRE may be considered following an assessment of the risks and benefits.

Pediatric Use

The safety and effectiveness of SYFOVRE in pediatric patients have not been established.

Geriatric Use

In clinical studies, approximately 97% (813/839) of patients randomized to treatment with SYFOVRE were ≥ 65 years of age and approximately 72% (607/839) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies. No dosage regimen adjustment is recommended based on age.

PATIENT COUNSELING INFORMATION

Advise patients that following SYFOVRE administration, patients are at risk of developing neovascular AMD, endophthalmitis, and retinal detachments. If the eye becomes red, sensitive to light, painful, or if a patient develops any change in vision such as flashing lights, blurred vision or metamorphopsia, instruct the patient to seek immediate care from an ophthalmologist.

Patients may experience temporary visual disturbances associated either with the intravitreal injection with SYFOVRE or the eye examination. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured for:
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SYF-PI-17Feb2023-1.0

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AI: The Future No Longer

"How will AI impact ophthalmology?" There's no time left to answer.

With "ophthalmology of the near future" as our main theme this month, it's fitting to begin this issue with another look at that now-ubiquitous question, "What is the future of AI in ophthalmology?" I say ubiquitous because AI has been an increasingly popular thread at ophthalmology meetings for closing in on a decade. For that reason – and given the advances of the last five years, particularly – perhaps it's time to change the question to: "How are we using AI in ophthalmology now?"

Or perhaps: "Why now?"

Indeed, that was the question posed by Josef Huemer, Consultant Ophthalmologist for Medical Retina at Moorfields Eye Hospital NHS Foundation Trust, London, at this year's ESCRS meeting in Vienna, Austria. Since 2000, there have been more than 3000 publications focused on AI in ophthalmology. The technology has provided FDA-approved applications for retinal diseases like diabetic retinopathy (DR) and age-related macular degeneration (AMD). And it has shown promising results in intraocular lens positioning, confocal microscopy, cataract grading, capsular bag diameter prediction, and diagnosing keratoconus, to name a few. Huemer also points out that "much progress has been made in finding signs of Parkinson's Disease on OCT scans."

"We have the proof of concept," he says. "The interesting bit now – the difficult part – is how do we make the best use of our data sets? How do we ensure they are representative? How can we translate what we have learnt from, say, DR and other diseases, with clinical safety?"

A pressing concern, certainly, is how AI can enhance and exaggerate bias when it comes to dealing with diverse populations. Deep-learning systems must be subject to "robust validation processes in multi-ethnic cohorts to avoid biases," says Huemer. One promising example is the UK DR screening program, which includes a multi-ethnic population. "This could serve to see if AI works equally well for everybody, and does exactly what we want it to do."

On the other ever-present (if more provocative) question – "Will AI replace doctors?" – Huemer is less concerned. There are cases where such a development will be useful, he says; for example, triaging patients or performing routine tasks that are time consuming and tedious for humans. But for subspecialities such as uveitis, "a doctor with great clinical expertise will always be better."

"Let's not see AI as a threat, but rather as an opportunity," Huemer concludes. "Doctors were not keen when the thermometer was introduced to measure body temperature, and that has not replaced us. Nor has the use of OCTs replaced retina specialists."

Julian Upton
Group Editor

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the Ophthalmologist

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Upfront

Research
Innovation
Trends

One Eye on the Clock

Stanford University researchers develop a method to identify diseases associated with aging of the eye

Researchers at Stanford University have developed a new method to measure ocular aging (1). "TEMPO stands for Tracing Expression of Multiple Protein Origins," says Vinit Mahajan, senior author of the study. Using this technique, the team were able to find 26 biomarkers of ocular aging out of 6,000 proteins extracted from vitreous humor and aqueous humor. "We could figure out which cells in the eye were making the proteins we found," explains Mahajan. "We found really specific protein expression signatures for photoreceptors, retinal endothelial cells, and amacrine cells, and we could track each cell type's health in various diseases."

The team created an "AI proteomic clock" that enables them to see exactly which of these proteins accelerate ocular aging, as well as indicating that patients who were suffering from certain diseases, such as diabetes, also showed accelerated aging. They now plan to apply the method to other diseases. "The eye is full of neurons, so neurons in brain disease might share molecular changes," says Mahajan.

Finally, Mahajan believes TEMPO could aid personalized medical treatment and, in turn, increase success rates for drug candidates. "TEMPO could be used to enroll patients most likely to respond to therapy. And after a trial drug was started, TEMPO could help determine if the drug started working at the molecular level – something that might be detectable a long time before clinical improvement."

Given that around 90 percent of drug candidates currently fail in clinical trials, any improved predictive and diagnostic capability delivered by TEMPO would be welcome. "It's as if we're holding these living cells in our hands and examining them with a magnifying glass," Mahajan says. "We're dialing in and getting to know our patients intimately at a molecular level, which will enable precision health and more informed clinical trials."

Reference

1. *J Wolf et al., "Liquid-biopsy proteomics combined with AI identifies cellular drivers of eye aging and disease in vivo," Cell, 186, 4868 (2023). PMID: 37863056.*

INFOGRAPHIC

Out of Steam

The rise of independent sector providers comes with a steady decline in NHS ophthalmic staff

The Royal College of Ophthalmologists **2022** workforce census highlights the impact of COVID-19 on ophthalmic staff shortages and practice

The report found that **81 PERCENT** of NHS eye units are concerned about patient backlogs following COVID-19

SPOTLIGHT ON ARVO

We help you keep up to date with the latest vision research from ARVO's journals

Observing Optical Density
Researchers investigated whether the optical density ratio (ODR) of subretinal fluid (SRF) on optical coherence tomography (OCT) differs between choroidal nevi and melanomas. The results – taken from 128 patients with choroidal melanoma and 71 with choroidal nevi – indicated that ODR was significantly higher in melanomas compared with nevi. PMID: 37788003.

Healthcare Disparities
A retrospective TVST study of cataract patients determined that patients with limited English proficiency (LEP) have higher rates of diabetic retinopathy (DR) when compared with patients proficient in English. Highlighting healthcare disparities that currently exist within ophthalmology, the researchers recommend other studies examining how language disparities affect LEP patients. PMID: 37796496.

Homelessness Vision Crisis
Researchers characterized ophthalmic disease and vision-related quality of life using questionnaires among patients seeking eye examinations at Health Care for the Homeless (HCH) in Baltimore, Maryland, USA, observing high ophthalmic disease prevalence. The study suggests a need for more targeted solutions to meet the eye care needs of homeless populations. PMID: 37922150.

Oxidative Stress
Examining oxidative stress markers in 90 ocular rosacea patients and 30 healthy controls, researchers identified several markers in the serum and tears of individuals with ocular rosacea linked to the clinical signs of meibomian gland dysfunction (MGD). The results suggest oxidative stress could be an indicator for MGD severity. PMID: 37843493.

FEVR Findings
Comparing eye biometric characteristics from 50 early-stage familial exudative vitreoretinopathy (FEVR) patients and 50 healthy controls, researchers found that FEVR eyes had smaller axial length, white-to-white diameter, anterior chamber depth, and anterior lens surface curvature radius, but larger central corneal thickness and lens thickness. PMID: 37850946.

CSCR Gender Differences

New study uncovers gender-specific differences in central serous chorioretinopathy

While it has been noted that men are more likely to develop central serous chorioretinopathy (CSCR) than women, there is also a question about gender-specific differences in responses to the condition. In answer to this, a new retrospective study published in Eye (1) examined 109 eyes of 58 patients (28 females and 30 males). The researchers employed a newly validated multimodal imaging classification system to classify both "Simple" and "Complex" CSCR, with visual acuity outcomes and differences being analyzed. The researchers concluded that while men tended to have higher rates of recurrence and progressive vision decline of CSCR, women were more likely to exhibit choroidal neovascularization (CNVM) as a sequela of CSCR.

Reference

1. *N K Sahoo et al., "Gender differences in central serous chorioretinopathy based on the new multimodal imaging classification," Eye, [Online ahead of print] (2023). PMID: 37925559.*

76 PERCENT of NHS eye units do not have enough consultants to meet the current demand

74 PERCENT OF EYE UNITS ARE CONCERNED ABOUT THE IMPACT OF OUTPATIENT BACKLOGS ON PATIENT CARE

58 PERCENT of eye units have said that independent sector providers delivering NHS-funded services have had an adverse effect on patient care and ophthalmology services

See references online at: top.txp.to/out/of/steam

Credit: Rawpixel.com

Fatty Acids Versus ROP

A 30-month follow-up study indicates that supplementation with docosahexaenoic and arachidonic acids results in better visual acuity in preterm infants

In the US, retinopathy of prematurity (ROP) affects an estimated 14,000 infants annually (1). Most commonly associated with preterm babies weighing less than three pounds at birth, the eye disease can develop into serious cases of myopia, cataracts, glaucoma, retinal detachment, and/or blindness (1).

Previous research has sought to identify preventative measures for ROP. Just this year, Medical College of Georgia scientists found that targeting the bile acid receptor could prevent the development of ROP (2). Similarly, a new study funded by the National Eye Institute, found that an inexpensive, smartphone camera can help doctors identify preterm infants in need of ROP treatment (3).

Adding to this ongoing investigation, a 30-month follow-up of the Mega Donna Mega clinical trial has found that preterm infants develop better visual function by the age of two-and-a-half when given a combination of omega-3 and omega-6 fatty acids (4). The study, conducted at the University of Gothenburg, Sweden, between 2016 and 2019, consisted of 178 extremely preterm (EPT) infants (those born at less than 28 weeks of gestation). After being randomized, roughly half of the children were given a supplementation of docosahexaenoic acid (DHA) and arachidonic acid (AA) – fatty acids currently not included in supplements given to EPT babies after birth.

Although further studies are needed to confirm the clinical utility of DHA and AA, the 2.5-year follow up shows promising results. "The study shows that children who have received the combination supplement had improved visual function, regardless of whether or not they had previously had ROP," said Pia Lundgren, the study's first author, in a University of Gothenburg news story (5). "The improved visual development was thus not only due to the beneficial effect on the retina. The supplement also seems to have improved the brain's ability to interpret visual impressions."

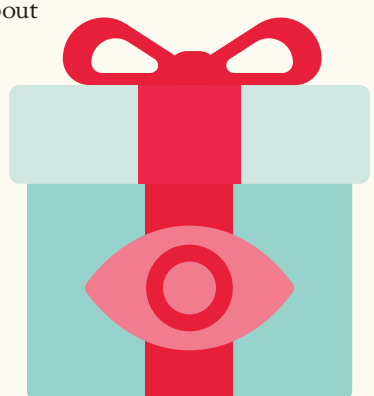
In continued studies on the same group of children, Lundgren added that they would be exploring cognitive and neurological development in more detail.

See references online at: top.txp.to/eat/fatty/acids

Inherited Sight

NIHR research unveils previously undeveloped resource for much needed eye donations

A new National Institute for Health and Care Research (NIHR)-funded UK study has revealed significant untapped potential for eye donations, specifically in the context of palliative and hospice care settings. Surprisingly, the study – conducted in three palliative care services and three hospice care settings in the North, Midlands, and South of England – found that less than four percent of eligible patients had been notified about being able to donate their eyes. As these types of donations are in short supply, these findings could provide a viable remedy to the shortage. The researchers also point to changes in practice that are needed to ensure that end-of-life patients are offered these potentially life-changing opportunities.



Reference

1. T Long-Sutehall et al., "Eye donation from palliative and hospice care contexts: the EDiPPPP mixed-methods study," 11, 1 (2023). PMID: 37929829.

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IMAGE OF THE MONTH

The Mastery of the Slit Lamp

Exudative membrane connecting the anterior capsule to the cornea

Credit: Yang Zhang, Beijing Tongren Hospital, China.

The image was taken on the Haag-Streit BX 900 slit lamp, and was a finalist in this year's Haag-Streit Slit Lamp Imaging Competition.

Would you like your photo featured in Image of the Month?
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QUOTE OF THE MONTH

"Every ophthalmologist I know has a passion outside of work. This may be a dedication to family, youth sports, running, charity work, travel, or music. Avid pursuit of these interests makes us happier and healthier. They enrich our lives through connections to our communities and provide valuable perspective outside of ophthalmology. And I believe all of these things make us better doctors."

Andrew Lam, MD, ophthalmologist and best-selling author *(bit.ly/3FYGjD2)*

Eye Image Credit: Pixabay.com

Eye, Robot

Ophthalmologists were able to discern human from AI-generated responses with 61 percent accuracy

Despite revolutionizing the medical landscape, a rise in medical misinformation has caused a major concern about the safety and reliability of LLM chatbots, especially in niche specialties such as ophthalmology.

To better explore the clinical effectiveness of AI-powered technologies, US-based researchers compared the quality of ophthalmic advice generated by an LMM chatbot with those of board-certified ophthalmologists (1).

In total, 200 pairs of questions and answers were evaluated. A board of eight ophthalmologists were able to discern human from AI-generated responses with 61 percent accuracy. However, chatbot answers were not perceived to be significantly more harmful than human responses in relation to incorrect information, likelihood and extent of causing harm, and agreement with perceived consensus in the medical community.

The results seem to suggest that LLMS can, in fact, provide astute and appropriate ophthalmic advice to patient queries of varying complexity. So, will there come a time when AI technologies fully replace physicians for some tasks?

Reference

1. *A Bernstein et al., "Comparison of Ophthalmologist and Large Language Model Chatbot Responses to Online Patient Eye Care Questions," JAMA Netw Open, [Online ahead of print] (2023). PMID: 37606922.*

In My View

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

(Real-World) Knowledge Is Power

Why real-world data is especially important in the treatment of retinal diseases

By Christopher Brittain, Vice President and Global Head of Ophthalmology Product Development at Roche/Genentech

The importance of quality real-world data in advancing the treatment of retinal diseases really cannot be overstated. Although clinical trials, of course, remain the gold standard when it comes to ensuring that any new retinal medications are safe and effective, they are sadly not without their blind spots. Older patients, people with multiple chronic conditions, individuals from hard-to-reach communities, and individuals from some ethnic and diverse communities are just some of the groups that have been historically underrepresented in clinical trials. And yet they will still ultimately make up a proportion of the people who receive retinal treatments out in the real world. And let's not forget that clinical trials must have a finite duration, meaning they can only tell us so much about the long-term use of a treatment.

When it comes to leading causes of vision loss, such as age-related macular degeneration, diabetic retinopathy and retinal vein occlusion, there is something of a data gap in robust long-term outcomes. Some treatments have shown huge promise in delivering positive outcomes in clinical trials, but have not yet fully realized this in day-to-day use. This can be attributed partially to the high burden of treatment – in particular, the need for frequent eye injections – which leaves many patients undertreated and not able to achieve the best possible vision outcomes. Additionally, clinical trial data sets are unlikely to provide insights into how healthcare professionals swap people from an existing treatment option to a new medication with a different mode of action.

So how do we close this gap? Real-world data has a pivotal role to play in connecting what we observe in clinical trials and what we know about day-to-day treatment outcomes for patients. As the name suggests, real-world data is intended to closely capture real-life routine practice outside of the highly controlled clinical trial setting. As a result, it encompasses the full complexity of patient demographics, comorbidities, treatment adherence, and extended use, a large transition away from the controlled inclusion and exclusion criteria of a randomized controlled trial. The data itself can take many forms and come from a wide range of sources, including surveys, patient registries, electronic health records, Health Authority adverse event reporting databases and non-interventional studies. The various information streams allow for important new insights about the long-term safety, effectiveness, and use of

"Although clinical trials, of course, remain the gold standard when it comes to ensuring that any new retinal medications are safe and effective, they are sadly not without their blind spots."

treatment options in practice. When taken together with what we know from clinical trials, real-world data has the potential, overall, to provide a much richer clinical picture of the current treatment landscape for retinal diseases.

Of course, collecting real-world data has its challenges – the flip side of capturing such a wide range of measures and outcomes is that the quality of data collection and sources can vary widely. Real-world data is also arguably more vulnerable to biases in selection and interpretation outside the strict controls of clinical trials. And all these challenges make statistical analyses more complicated. With the rise of remote monitoring technologies, and electronic health records, ensuring patients are fully aware and informed of how their data is going to be collected, stored, and used is also critical.

At Roche/Genentech, we embrace the challenge, investing significantly in generating robust real-world data across our ophthalmology treatments. Our program of real-world studies, investigates all aspects of treatment patterns, and long-term safety and efficacy of approved ophthalmology treatments. These are all factors that drive decisions in routine clinical practice. We also work closely with the vision loss community to ensure our real-world data studies are advancing inclusive research. Our ongoing research, for example, examines treatment response in historically underrepresented populations with macular edema, including African Americans, Hispanics, Indigenous populations and Asian Indians.

Not only do we strive to generate real-world data that will be of use to the wider ophthalmology community, but we also use those data insights to shape our own research and development programs. For example, understanding that treatment burden has been a driver of the gap between clinical trial and real-world outcomes in retinal diseases has focused our efforts on i) treatment options with the potential for longer dosing schedules that can maintain vision with fewer injections, ii) remote monitoring technologies that can help patients get the support and care they need with fewer clinic visits, and iii) providing better patient education and support to enable participation of patients from underrepresented minority groups in clinical trials.

Ultimately, as the saying goes, knowledge is power. Whether informing better treatment protocols for doctors and patients, guiding regulatory and reimbursement decisions, or helping pharmaceutical R&D scientists identify how they can make the biggest difference to patients, real-world data is the key to unlocking a brighter future for people living with retinal diseases.

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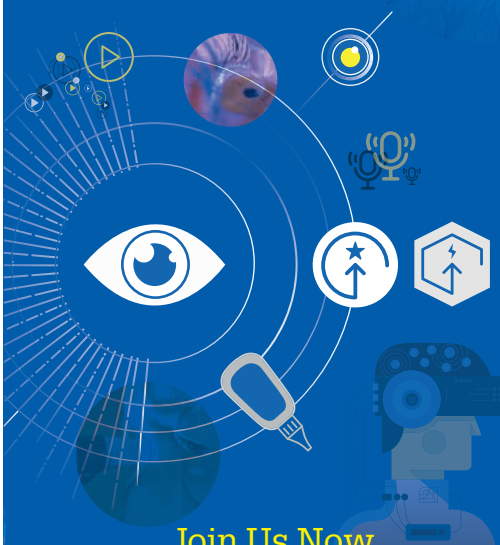

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Credit: CORE

VISIONS OF THE (VERY NEAR) FUTURE

SIT BACK AS WE EXPLORE JUST SOME OF THE CUTTING-EDGE TECHNOLOGIES AND THERAPIES DESTINED TO SHAPE THE OPHTHALMIC SPACE FOR YEARS TO COME

Credit: Eric Rosenberg

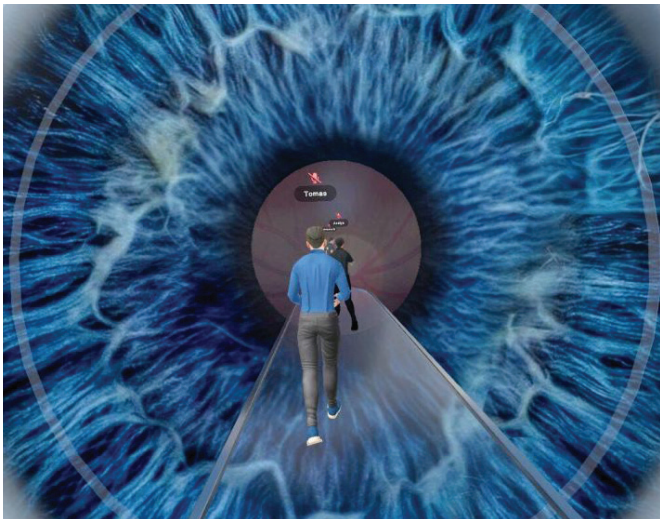
The application of cutting-edge technologies in ophthalmology continues apace – a handful of devices and solutions announcing themselves noisily, others having a quieter impact. As this march of progress gathers inevitable pace, we look at a range of innovations and treatments and explore how they are poised to transform, upgrade, and expedite eye care practice.

To paraphrase, cannibalize, and indeed misinterpret a much-used quotation from "cyberpunk" writer William Gibson: The future is already here – and it's coming your way!

EVOLVING VR

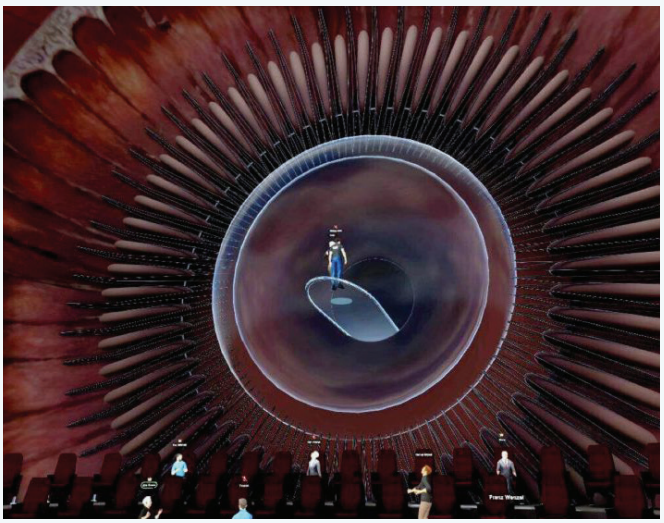
The year is 1962 and you are riding a motorcycle through the neon blur of Brooklyn, New York… or so you think. The scene in question is from Morton Heiling's 1962 3D film for his "Sensorama" system – the first virtual reality (VR) platform of its kind, which immersed its users into a seemingly real world (1). Over 60 years later, VR has weaved its way into not just entertainment, but also healthcare and education.

With its emphasis on imaging, highly precise microsurgical procedures, and multimodal diagnostic testing, ophthalmology lends itself rather beautifully to the implementation of VR and augmented reality (AR). In fact, Ophthalmic graduate medical



Credit: Eric Rosenberg

education in the United States has seen an increase in the use of virtual eye surgery simulators from 23 percent in 2010 to 73 percent in 2018 (2). While covering a wide array of ophthalmic specialties, VR's most significant impact is felt in the field of ophthalmic education and training, with the Eyesi Surgical



Credit: Eric Rosenberg

> "AT FVR WE UNDERSTAND THE IMPORTANCE OF 'FUTURE PROOFING' OUR PLATFORM; WE FOCUS ON ENSURING OUR TECHNOLOGY IS FLUID AND EVER EVOLVING."

Simulator, PixEyes, and Microvistouch all vying for attention in a relatively new but growing market that sees promise in supporting the next generation of eye care professionals (2).

Perhaps the newest development in VR for ophthalmology comes from MetaMed – a US-based company that aims to inspire global connectedness and extend VR across healthcare (3). MetaMed conducted the first ever live-streamed three-dimensional (3D) surgery in the metaverse in 2022, and has thus redefined what it means to educate in the 21st century. "Our mission has and continues to be bringing in top academic institutions and surgeons from across the globe into our virtual environments for the purpose of education and learning," MetaMed's co-founder, Eric Rosenberg, tells us.

MetaMed's VR platform offers immersive environments in which participants can control their own avatars and interact – much as they would at an in-real-life meeting, all while learning from presented content, including 3D surgical videos. "While we may not be active in VR surgical training simulation, we do hope to collaborate with companies and services that are heavily present and building in this space. At the end of the day, we see ourselves as the future of education and collaboration independent of physical location or geopolitical borders," explains Rosenberg.

Alcon is one such company present in the VR surgical training. Indeed, the Swiss-American pharmaceutical company has spent years developing the Fidelis VR Ophthalmic Surgical Simulator (4). This VR system is the first-of-its-kind to place phaco technology – Alcon's Centurion Vision System with Active Sentry – within a VR environment, enabling surgeons to experience all the steps of cataract surgery through haptic feedback. "While developing our training platform, our measure for success was that the virtual environment felt like an actual operating room," says Global Director and Head, HCP Training & Education, Rustin Floyd. "As a result, our team spent an incredible amount of time perfecting the look, feel, sound and interface of Fidelis, and surgeons are letting us know that the experience actually feels real." Another key feature of the Fidelis platform is its ability to connect surgeons with other remote users within the same virtual operating room, enabling them to watch videos together, participate in group discussions, and coach on surgical technique.

Retina is next on Alcon's VR radar with glaucoma and surgical complications management. "The great thing about our pipeline is that it allows us to bring VR into all of our developments," adds Floyd. "The opportunities for virtual reality are endless – it's just a matter of staying close to customers and giving them what they need the most."

In a similar vein, FundamentalVR (FVR) is making waves with the development of its VR platform (5). Using low cost and light-weight hardware, the FVR system is both accessible and portable, supporting residents and attending physicians – across both anterior and posterior segments – globally. "At FVR we understand the importance of 'future proofing' our platform; we focus on ensuring our technology is fluid and ever evolving. We are continuously integrating updates and new technologies to enhance our platform offering," says Vice President of Ophthalmology, Ashlie Leal. "We will continue to expand our Ophthalmic portfolio. We have recently announced an exciting partnership with the American Academy of Ophthalmology to develop procedures in the ophthalmic pediatric space."

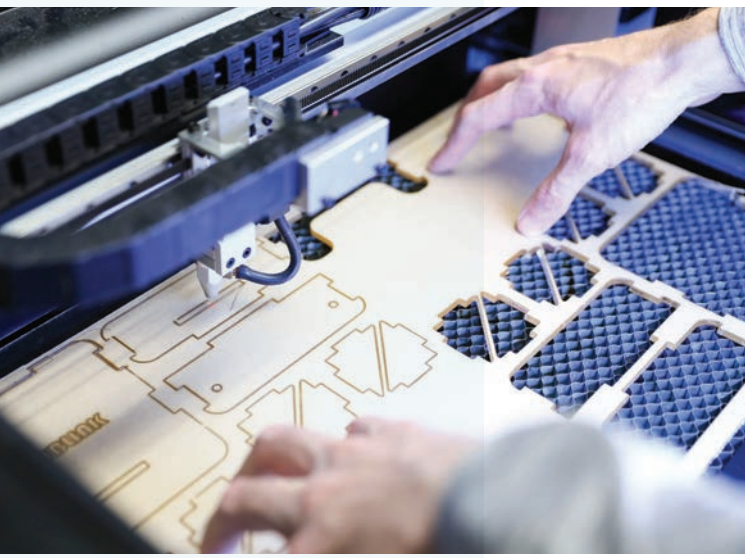
We have certainly come a long way since Morton Heiling's 1962 3D experiment, and, without doubt, there will be more exciting VR developments to come in the ophthalmic environment.

NEW DIMENSIONS IN MODELING

3D printing, also known as additive manufacturing (AM), has advanced significantly in recent years. Working by adding materials in a layer-by-layer fashion, the process has led to the realization of a wide range of technologies, materials, and applications. In the field of ophthalmology, this has culminated in the development of orbital implants, ocular prosthesis, and ophthalmic models (6).

Since 2014, the Center for Ocular Research & Education (CORE) has been at the forefront of advancements in 3D technology in ophthalmology. CORE's development of 3D models representing the front of the eye has enabled researchers to evaluate how new products, including eye drops, contact lenses, and drug-releasing contact lenses will affect the eye, without harming human subjects. Alongside developing 3D models, CORE has also used 3D printing to create custom occluders for children and hands-on-educational products, such as OcuBall to teach clinical skills.

Building on its impressive array of products, CORE is currently developing models for the back of the eye using 3D printing and 3D bioprinting, incorporating cells into the output. Its other efforts include creating miniature models that stimulate various diseased eye states to inform better treatment options; working on ways to use 3D printing to fabricate various ophthalmic devices; and using 3D printing to develop drug-releasing contact lenses and other anterior segment devices. "The underlying concept is leveraging 3D printing to create individualized solutions, including custom-sized contact lenses with customized drug doses for individual patients," says Chau Minh-Phan, Research Assistant Professor at CORE. "In much the same way as in other fields, the biggest impact of this technology will be in areas of ophthalmology that necessitate custom fabrication. Here, 3D printing will reduce cost and time, and provide production flexibility compared to conventional manufacturing methods."



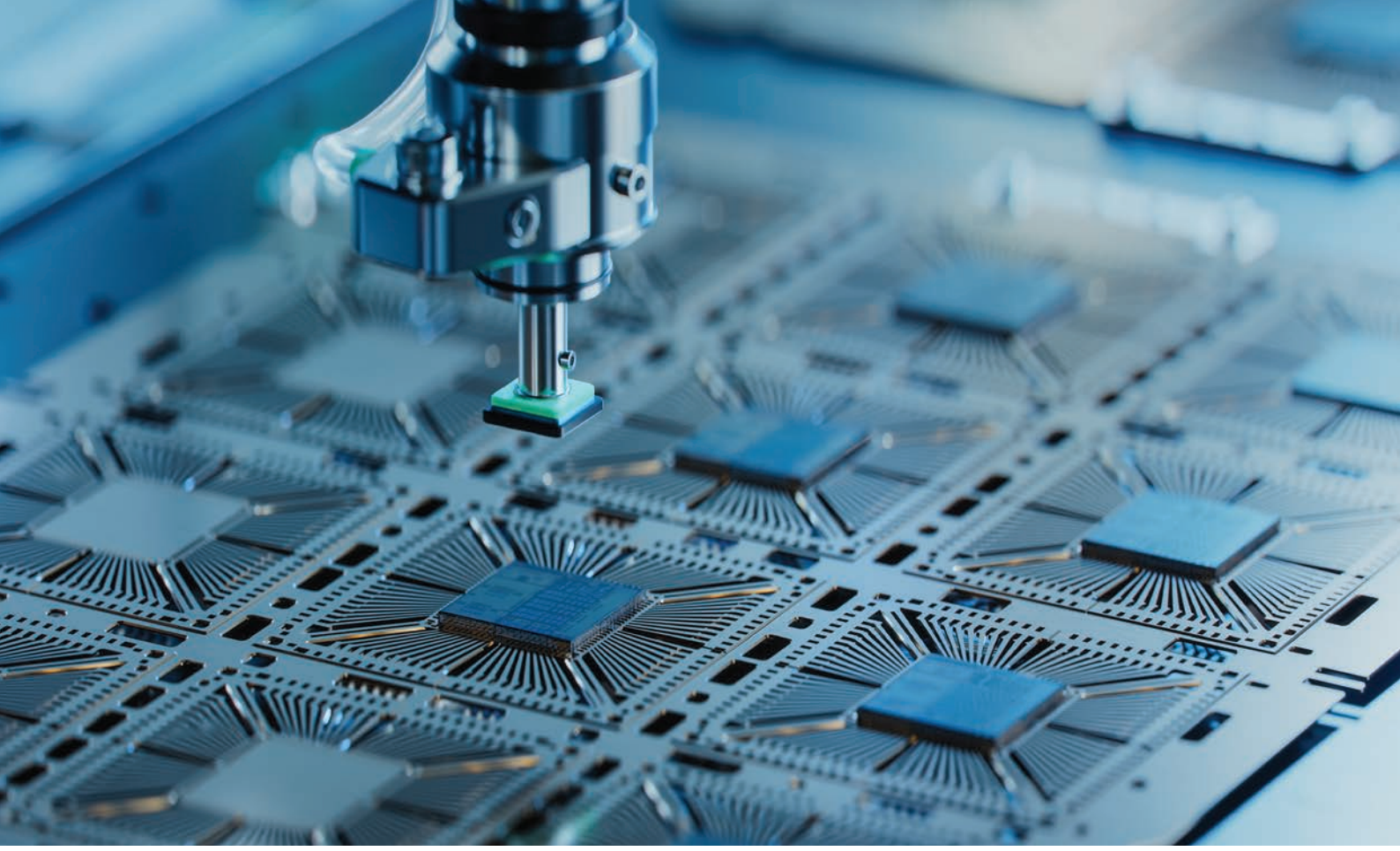
Credit: CORE

Credit: CORE

CORE delivered several innovations at the 2023 ARVO conference (7), but it's clear that there is plenty of room for growth. "The potential of this technology might unfold in ways we have not yet imagined," says Minh-Phan. "One thing is clear, though: 3D printing will undeniably play a role in our future, whether the effect is large or subtle remains to be seen."

Taking a closer look at advancements in 3D technology, Kapil Bharti, Senior Investigator at the National Eye Institute (NEI), shared with us follow-up data on the NEI's development of 3D outer blood-retina barrier (oBRB) tissue. Designed to provide a more in-depth understanding of AMD disease pathology, the oBRB model has now expanded to also include immune cells in the choroid. Researchers have also developed isogenic patient tissues, enabling a more detailed investigation of different genes and gene mutations in different cell types, especially pertaining to the retinal pigment epithelium (RPE).

"As the cost of 3D-bioprinters continues to drop precipitously and as labs continue to develop robust protocols to make different eye cells from patient stem cells, 3D-bioprinting of eye tissues is likely to become a standard practice in labs. This will allow us to do our discoveries on human (not animal) tissues," says Bharti. "Not only will this reduce the usage of animals in biomedical research, it will also provide more relevant data. So, we are really excited to pursue this technology in my group."



NOTABLE NANOTECHNOLOGY

As esteemed cryptographer and computer scientist, Ralph Merkle, once remarked, "Nanotechnology is an idea that most people simply do not believe." But if one remains faithful that such invisible technology actually exists, nanotechnology's potential was clear to the Chair of the Department of Ophthalmology and Visual Science at Rutgers New Jersey Medical School, Marco Zarbin, back in 2010 (12), providing therapeutic value through "full-scale monitoring, regulation, development, restoration, defense, and improvement of human natural systems at the cellular level."

Drug delivery applications of nanotechnology could well be the most attractive, lowest hanging fruit in ophthalmology – especially as there are several pressing "anatomical and physiological challenges which serve as obstacles to effective drug delivery, including the tear film, cornea, conjunctiva, sclera, vitreous, inner limiting membrane, blood-aqueous barrier (BAB), and blood-retinal barrier (BRB)." So say the authors of a recent paper in Advanced Drug Delivery Reviews highlighting the potential of cell-targeted, dendrimer-based therapies in a "new era" ocular drug delivery (13).

Dendrimers – compounds previously described as "the newest class of macromolecular nano-scale delivery devices" (14) – are highly defined artificial macromolecules that offer a range of beneficial characteristics for drug delivery, including chemical stability, solubility, and low cytotoxicity, as well as having the ability to "efficiently encapsulate drugs and allow tunable release rates" (15).

Explaining how dendrimers could be used for sustained posterior segment drug delivery, Rangaramanujam M. Kannan, co-director of the Center for Nanomedicine at the Wilmer Eye Institute and first author on the aforementioned paper, notes, "The dendrimer nanoparticles are administered systemically, but target the disease-associated cells in the choroid/retina. Once they are there, they can stay there for at least 30 days and provide sustained therapy. Therefore, the pharmacodynamic effect may last even longer."

Such therapies are arguably safer as well, according to Kannan: "It benefits patients because intravitreal delivery is avoided or reduced, minimizing inconveniences associated with them." With easier delivery and an improved safety profile, such treatments could facilitate earlier stage treatments of certain diseases, such as AMD and DME.

"[Dendrimers] target key cells associated with pathology, enabling disease cell-targeted delivery!" Kannan says. "This is a holy grail in many ways. Because the dendrimer-drug conjugates are cleared intact through the urine from off-target organs, systemic side effects are minimized, enabling an improved therapeutic index for the drugs." The systemic dendrimer-drug therapies (D-4517.2) devised by Kannan and his team are now undergoing phase II trials for wet AMD and DME and, if successful, will be followed by larger phase IIb/phase III trials.

Credit: Shutterstock.com

BETTING ON BIONIC IMPLANTS

Although bionic technology already exists within ophthalmology, the journey towards commercial viability has been problematic. One of the major players involved has already veered dangerously close to bankruptcy; Second Sight Medical Products, which developed the only extant FDA-approved bionic eye implants, had to discontinue both their Argus I and Argus II models in 2019 due to financial difficulties. With its stock price rapidly falling, Second Sight's commercial future looked bleak until February 2022, when the company announced a merger with biopharmaceutical company Nano Precision Medical (NPM).

Despite these setbacks, companies outside the US continue to develop their own retinal implants. In Paris, for instance, Pixium Vision is currently undergoing feasibility trials for their Prima System (8) – an implant proposing to offer age-related macular degeneration (AMD) patients bionic vision. Pixium's CEO, Lloyd Diamond, believes its device represents further advances for the technology: "The Prima System has demonstrated restoration of form vision, and that's very important because other technologies created phosphenes, but now we are talking about the patients actually being able to see forms and shapes." As if reiterating Diamond's claims at the developmental capabilities of such technology, the market for retinal implants remains set to see a "steady growth rate of 7.5% by 2031" (9).

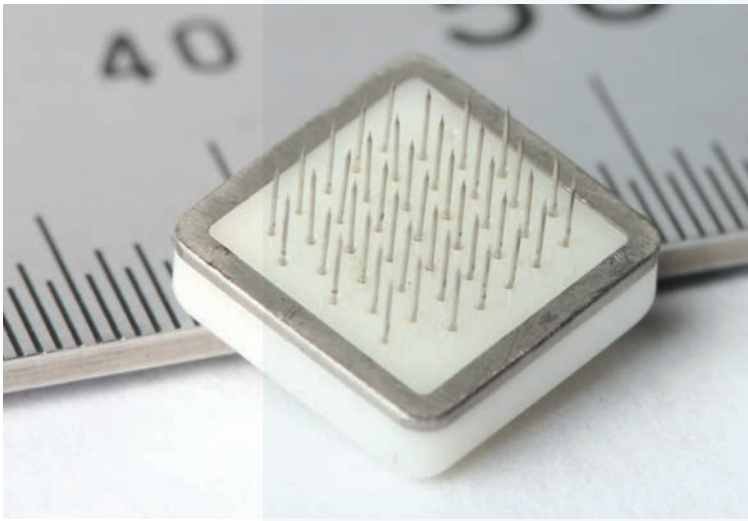
Running parallel to retinal implant development, research into neural implants – which bypass the visual processing of the eyes to send signals straight to the brain's visual cortex – continue to make headway. Indeed, before Second Sight's 2022 merger, the company had already begun to divest R&D time into the Orion Visual Cortical Prosthesis System (10). Still in clinical trials, it will be interesting to see if neural implants really do offer a potential alternative to retinal implants.

When asked about the future of bionic eye implants, Yan Tat Wong, author of a Journal of Neuroengineering study investigating how phosphene mapping might improve neural prosthetic outcomes (11), is adamant there's still work to be done. "The last few decades have seen amazing leaps forward in technology, but major 'discovery science' questions remain unanswered," he says. "My prediction is that we will see a greater linking between implant development – smaller implants with more electrodes that don't damage bodily tissue – and the neuroscience of how our brains work."

With caveats, specialists like Wong appear confident in theevolution of these implants, but the near future of the technology remains uncertain. As witnessed with Second Sight, the principal hurdle to mainstream market adoption is the issue of scalability. "The challenge isn't so much in the performance of the technology; the challenge will be in the ability to efficiently manufacture the implant," says Diamond. "Our next-generation implant will have up to 10,000 electrodes and these electrodes are three-dimensional; and so the industrialization of the technology will be our primary challenge."

> "THE CHALLENGE ISN'T SO MUCH IN THE PERFORMANCE OF THE TECHNOLOGY; THE CHALLENGE WILL BE IN THE ABILITY TO EFFICIENTLY MANUFACTURE THE IMPLANT."

Can this mass production challenge be overcome by the companies still heavily invested in bringing the technology to market? Well, if utilitarianism edges forward as the primary motivating factor behind production, implants – both retinal and neural – may eventually result in vision restoration for people all over the world.



Gennaris Implant. Credit: Yan Tat Wong

THE REGENERATION GAME

Barring the total prevention of the onset of ocular disease in the first place, ocular regeneration could be considered the ultimate ambition when it comes to ophthalmic disease management. The ability to go beyond treating symptoms and halting progression towards regenerating damaged eye tissue, reestablishing natural ocular structures, and, ultimately, restoring patient vision is a dream of many – but how far away are we?

To answer that question, we must look back at the trends in this field over the past decade or so. According to Ali Djalilian, a recognized authority on ocular surface regeneration and the Searls-Schenk Professor of Ophthalmology at the University of Illinois College (UIC) of Medicine's Department of Ophthalmology, there have been five primary areas of innovation in ocular regenerative therapy advancements:

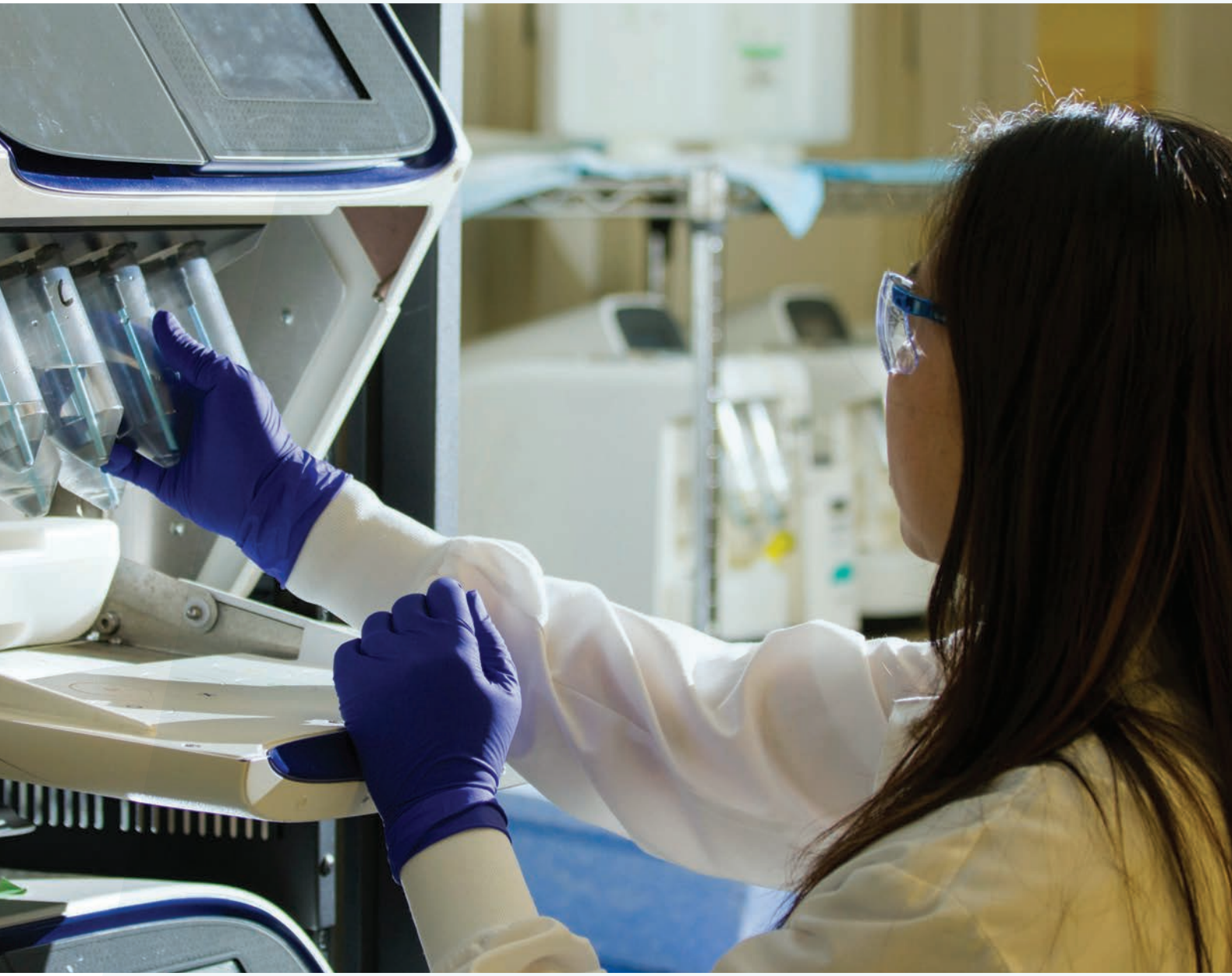
- Cell-based therapy – major advancements in this area have been the use of cultured corneal endothelial cells by Shigeru Kinoshita's lab, and the demonstration of the efficacy of mesenchymal stem cells (MSCs), and MSC-derived extracellular vesicles as a regenerative therapy by Djalilian's lab at UIC.
- Gene therapy – correcting the underlying genetic cause of genetic ocular diseases. Of particular interest is the use of gene editing within the eye using CRISPR-based therapies. An example of this is voretigene neparvovec (Luxturna) which has been approved for the treatment of inherited retinal disease.
- Tissue engineering – the development of bioengineered ocular tissues, through organoids, or more recently, 3D bioprinting (as highlighted above), could alleviate shortages of donor tissues and improve transplantation surgery outcomes.
- Neuroprotection and neurogeneration – the development and application of therapeutic agents capable of preventing cell death of optical neurons, as well as restoring both function to damaged neurons, as well as neuronal numbers in diseases such as neurotrophic keratopathy and glaucoma. The topical nerve growth factor cenegermin is the leading product in this space.
- Drug delivery – development of sustained drug delivery systems, such as ocular implants and micropumps, for the treatment of chronic ocular conditions, that aim to reduce the need for frequent injections and improve patient compliance.

"TARGETED DELIVERY IS ESSENTIAL TO PRECISELY REACH THE AFFECTED AREAS WITHOUT HARMING HEALTHY TISSUE – A SIGNIFICANT CHALLENGE DUE TO THE EYE'S COMPLEX ANATOMY."

Beyond these established areas, there are other emerging areas within ocular regenerative therapies, such as optogenetics – which has the potential to restore vision by making non-photosensitive cells responsive to light, theoretically bypassing damaged photoreceptors – and nanoparticle-based therapies (also highlighted above) that may be capable of delivering drugs or genes directly to specific cells on the ocular surface and target disease.

Though ocular regenerative therapies cover vast and very different areas of scientific innovation, they are united in both their focus and the obstacles that they face, say Djalilian and Mohammad Soleimani – a cornea specialist and member of Djalilian's lab. "Ocular regenerative therapies must address several crucial areas to be effective, safe, and meet patient needs," they explain. "Targeted delivery is essential to precisely reach the affected areas without harming healthy tissue – a significant challenge due to the eye's complex anatomy. Once there, therapeutics and regenerated tissue need to remain viable long-term without repeated treatments, all while withstanding ocular environmental stress." Beyond this, for successful translation into clinical practice, ocular regenerative therapies will also need to be scalable and accessible, integrate with existing therapies with standardized processes, and take into account both ethical and regulatory considerations.

If meeting all of these needs seems like a steep challenge, Djalilian offers some hope, believing that we are beginning to see the positive changes that ocular regenerative therapies



Credit: Unsplash.com

could bring to the ophthalmology space. "Currently, given the trajectory of ocular regenerative therapies, the field is on the cusp of remarkable advancements, encompassing treatments for both the ocular surface and the entire eye, driven by breakthroughs in various scientific domains," he says.

Alongside its incorporation into clinical practice, ongoing research in regenerative therapies will continue to enrich the medical community's understanding of ocular disease, propagating further superior diagnostic and therapeutic strategies that yield greater long-term patient satisfaction.

It is clear that advances in the field of regenerative medicine can give rise to incredible possibilities within the near future of eye care, and it is to this end that Djalilian and Soleimani continue to push forward. "This rapidly evolving field offers clinicians the opportunity to engage in and contribute to groundbreaking work, furthering their professional development," they explain. "Overall, the progression of ocular regenerative therapies is set to revolutionize eye disease treatment, offering new hope to patients and opening new frontiers for clinicians dedicated to restoring and preserving sight."

See references online at: theophthalmologist.com

WEBINAR

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Interventional Glaucoma: A Year in Review

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Ike Ahmed, MD and the faculty share their evolving treatment algorithm and discuss the continuing momentum of this proactive approach.

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The INNOVATORS

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TAKING THE PRESSURE OFF

Alcon's CENTURION® Vision System with ACTIVE SENTRY® continues to light the way forward for cataract surgery

Originally launched in 2013, Alcon's CENTURION® Vision System has developed significantly over the years. The launch of ACTIVE SENTRY® in 2019 – engineered for stable phaco performance across a variety of vacuum levels – signalled a major change in ophthalmology, enabling surgeons to perform cataract surgery at a more physiological intraocular pressure (IOP). The advanced technology enabled surgeons to feel confident operating at more physiological IOP, without compromising anterior chamber stability, surgical efficiency, or ocular safety (1-4).

Although high levels of irrigation pressures were historically necessary because of technological limitations in phaco systems, these high levels may have undesirable clinical ramifications. These included greater postoperative anterior segment inflammation, more corneal edema, and disruption of the anterior vitreous face. It is for all these reasons that Alcon R&D worked to build a solution that could help surgeons perform cataract surgery at a more physiologic IOP.

ACTIVE SENTRY® was designed to reduce post-occlusion surge and maintain anterior chamber stability by adjusting for IOP fluctuations (5,6). Maintaining the same surgical efficiency as compared to higher intraoperative IOP settings, the more physiological IOP reduces stress on the posterior capsule-anterior hyaloid membrane barrier during cataract surgery (7). Similarly, it can support the health of the anterior segment, with studies showing less postoperative corneal swelling (8-12), greater endothelial cell protection (8-10), and less anterior segment inflammation (8, 9, 11, 12).

Aside from the more physiological IOP, the system boasts an array of innovative features. When occlusion break occurs, the ACTIVE SENTRY® Handpiece works with QuickValve™ technology to provide real-time surge minimization ensuring consistent volume and IOP maintenance (1,2). The first-of-its-kind irrigation pressure sensor, located in the handpiece itself, detects changes in the anterior chamber as they occur, delivering acute responsiveness at every stage of cataract surgery (13,14).

With its innovative features and unwavering commitment to physician and patient well-being, Alcon's CENTURION® Vision System with ACTIVE SENTRY® stands as a testament to the pursuit of excellence in modern ophthalmology, setting new standards and ensuring a brighter future for cataract surgery.

For important product information on CENTURION® Vision System, please see your local Directions for Use, or visit MyAlcon.com. Refer to operator's manual for a list of indications, warnings and precautions.

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THE FUTURE OF LEARNING: A SAFE AND REALISTIC TRAINING ENVIRONMENT FOR ROP MANAGEMENT

New technology developed by Haag-Streit is set to change the landscape for ROP training and management

Approximately 14,000 preterm infants in the United States develop retinopathy of prematurity (ROP), making it one of the leading causes of preventable childhood blindness worldwide (1). While an early diagnosis can prevent its progression, performing a retinal examination on a premature infant poses significant challenges.

Until now, residents have learned to perform the examination on the infant patient, a situation that often results in reduced heart rhythm and additional stress. This issue inspired Swiss medical device company Haag-Streit to develop The Eyesi Indirect Ophthalmoscope ROP: a high-fidelity augmented reality simulator.

But how does the technology work? The simulator consists of a head mounted display, a patient model head, and mimics of lenses and scleral depressor. When trainees wear the ophthalmoscope device, they are presented with an immersive 3D simulation of the patient. Correct positioning of the lens is essential to view the inner eye structures. As trainees use the scleral depressor to examine the peripheral retina, they experience realistic haptic feedback from the rubber model eye, enhancing the lifelike experience. The child's presumed behavior in reaction to the examination, such as crying, is also included in the simulation.

The Eyesi Indirect Ophthalmoscope ROP allows trainees to practice and gain experience in device handling and decision-making, independent from hospital routine and patient flow. The embedded curriculum teaches the main characteristics of ROP and how to recognize the different zones and stages for deciding on appropriate control intervals and/or the need for treatment. Moreover, the simulator offers objective feedback and evaluation of a trainee's performance.

With the capacity to prepare trainees for more precise examinations in real-life scenarios, the simulator is set to change the landscape for ROP training and management. Customers can expect the technology to be released in January 2024.

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THE ANALYSIS ADVANTAGE

MS-39 combines Placido disc corneal topography with high-resolution OCT-based tomography for the most advanced analysis of the anterior segment

Understanding the lay of the land is a key part of planning and, ultimately, success. Although this process requires expertise and discernment on the part of a practitioner, having the right tools within the ophthalmologist's toolkit makes it easier to get the job done, and done well. C.S.O is dedicated to offering eye care practitioners the best diagnostic ophthalmic instruments, and with MS-39, the company presents practitioners with the most advanced all-in-one device for the analysis of the anterior segment of the eye.

As a leading ophthalmic device, MS-39 harnesses high-resolution, spectral domain optical coherence tomography (SD-OCT) technology. It allows for detailed analysis of the curvature, elevation, refractive power and thickness of multiple layers of the cornea, including the epithelium, Bowman membrane, and stroma, with a resolution of 3.6 µm in tissue. Compared to Scheimpflug technology, OCT technology is less affected by the scattering of opaque tissues, making the maps of irregular and pathologic corneas generated with MS-39 more reliable than those created with Scheimpflug based devices. Additionally, MS-39 uses Placido disc technology, which provides the highest accuracy for measuring the anterior corneal surface curvature, elevation, and refractive power. Through Placido disc corneal topography, MS-39 is also able to provide tear film break-up time analysis.

The MS-39's combination of these two innovative technologies gives clinicians unparalleled insight and clarity into the anterior segment structures through 16 mm diameter cross-sectional images – something appreciated by anterior segment specialists. Further, the device provides access to exam information through its collation into well-packaged diagnostic summaries, ensuring that users can obtain the data that they need when they need it. Beyond anterior segment clinical diagnostics, MS-39 can also be used in corneal surgery for refractive surgery planning by enabling the earlier detection of keratoconus, thus improving patient selection. Moreover, the device's Ray-Tracing-based IOL calculation module is helpful for approaching candidates for cataract surgery who have previously undergone refractive treatments. MS-39's additional tools allow it to perform advanced analysis of the tear film and accurate pupil diameter measurements.

Ultimately, the MS-39 is designed to give anterior segment specialists the most accurate view of their ocular surroundings, so that they can make the most informed decisions and achieve the highest levels of success for their patients.

TACTILE REALISM

Does HelpMeSee's Eye Surgery Simulator Phacoemulsification Course represent a new pedagogical paradigm for cataract surgeons?

Phacoemulsification – the most commonly performed type of cataract surgery worldwide – is an essential technique in any future cataract surgeon's armamentarium. HelpMeSee's latest educational offering, the Eye Surgery Simulator Phacoemulsification Course, is a first-of-its-kind, full procedural virtual-reality (VR) training platform aimed specifically at teaching this popular technique. The five-day course comprises full procedural training – from making the initial clear corneal incision, performing a capsulorhexis and ultrasound emulsification of the nucleus, to insertion of the foldable intraocular lens, and eventual stabilization of the eye and wound hydration. These activities challenge trainees not only in their skill execution, but also in how they handle decision-making, time management, and any unexpected situations.

By using the state-of-the-art HelpMeSee Eye Surgery simulator, trainees are presented with a comprehensive view of the entire cataract surgery procedure, allowing them to understand how individual tasks fit into the broader context, while equipping them with the skills needed to perform the entire procedure with fluidity and confidence. The full procedural simulators are also equipped with advanced features, such as realistic anatomy, high-fidelity visual and haptic feedback based on live human tissue data, and various clinical scenarios, ensuring a highly immersive experience.

But the training offers much more than life-like visual and tactile realism; as trainees learn the order of operations and how to navigate seamlessly from one task to the next, an expert surgeon instructor remains on hand to facilitate their eventual transition into live surgery. The instructor also serves to accurately simulate the dynamics of a real-life operating room environment, aiding the trainee in learning how to communicate and work collaboratively with a full team. Emulating the efficacy already established in simulated aviation training – whereby prospective pilots have unlimited attempts to reach competency – trainees are then objectively assessed by the instructor for their readiness to transition into supervised live surgery.

As well as offering a scalable solution to the global shortage of qualified ophthalmic surgeons, this technology works to bridge the existing educational gap between training and live surgery, offering both medical students and already established surgeons an opportunity to practice their surgical skills in risk-free and educationally conducive surroundings – a virtual space where their real-life skills can be honed to perfection.

ADVANCING THE FIELD

VABYSMO® ▼(FARICIMAB) – DUAL INHIBITION, RETINAL DRYING, AND EXTENDED DURABILITY

Roche Products Ltd. has commissioned this feature and is responsible for the placement and information provided. For healthcare professionals only.

Neovascular age-related macular degeneration (nAMD) and diabetic macular oedema (DMO) continue to be among the leading causes of vision loss globally (1, 2). One of the latest treatments developed to provide an effective option for clinicians and patients is the first and only bispecific antibody approved for the eye, Vabysmo® (3).

Vabysmo is engineered to target and inhibit two signalling pathways, which are linked to a number of vision-threatening retinal conditions by destabilizing blood vessels, causing new leaky blood vessels to form and increasing inflammation. Dual inhibition of angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A) results in improved anatomical outcomes, including retinal drying (4, 5, 6). Vabysmo is approved in more than 80 countries around the world for people living with nAMD and DMO, with approximately 2 million doses distributed globally, including over 200,000 doses in the UK (7).

"Once faricimab was approved by NICE I adopted it into our service and it's had a big impact on both patients and our capacity," explains Aires Lobo, Consultant Ophthalmologist and Clinical Director, Moorfields Eye Unit at Bedford Hospital. "We have been able to treat more patients and extend the time between appointments to 12 weeks after the fifth intravitreal injection for around 40% of the nAMD patients, including both those switching from anti-VEGF therapy and treatment naïve patients."

Roche's ever-expanding programme of real-world studies includes more than 8,500 participants in almost 30 countries. These studies are investigating everything from the impact of extended intervals between dosing on vision outcomes, to treatment patterns, to the long-term safety and efficacy of Vabysmo®.

Roche remain committed to transform treatment outcomes in nAMD and DMO. With clinical and real-world data supporting the potential of Vabysmo (7, 8, 9), as well as its nomination for "Best Pharmaceutical Product" in the 2023 Prix Galien USA Awards (10), the future looks promising for retinal diseases.

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Date of Preparation November 2023 / M-GB-00015173

Prescribing information for Great Britain only.

▼ Vabysmo® (faricimab): 120mg/mL solution for injection. Single use vial containing 6mg faricimab / 0.05mL

Please refer to Summary of Product Characteristics (SPC) prior to use of Vabysmo. **Indications:** For the treatment of adult patients with neovascular (wet) age-related macular degeneration (nAMD) or visual impairment due to diabetic macular oedema (DMO). **Dose and Administration:** Vabysmo must be administered by a qualified healthcare professional trained in intravitreal injections. Always record batch number. *nAMD:* 6 mg (0.05 mL solution) administered by intravitreal injection under aseptic conditions every 4 weeks for the first 4 doses. Thereafter, treatment may be individualised using a treat-and-extend approach following an assessment of the individual patient's anatomic and visual outcomes. The dosing interval may be extended up to every 16 weeks, and extensions in increments of up to 4 weeks should be considered, based on the physician's judgement of the individual patient's anatomic and/or visual outcomes. If anatomic and/ or visual outcomes change, the treatment interval should be adjusted accordingly, and interval reductions of up to 8 weeks may be implemented if deemed necessary. Treatment intervals shorter than 21 days between injections have not been studied. *DMO:* 6 mg (0.05 mL solution) administered by intravitreal injection under aseptic conditions every 4 weeks for the first 4 doses. Thereafter, treatment may be individualised by using a treat- and extend approach following an assessment of the individual patient's anatomic and visual outcomes. Extend dosing intervals from every 4 to every 16 weeks, with extensions in increments of up to 4 weeks based on physician's judgement of anatomic and/or visual outcomes. If these change, the treatment interval should be adjusted accordingly and interval reductions of up to 8 weeks may be implemented. *nAMD and DMO:* Schedule monitoring between dosing based on patient status and at the physician's discretion. Vabysmo is intended for long-term treatment. Discontinue Vabysmo if visual and/or anatomic outcomes indicate no benefit. See SPC for instructions on method of administration. **Contraindications:** Ocular or periocular infections. Active intraocular inflammation. Hypersensitivity to faricimab or excipients. **Precautions:** Patients should report promptly any symptoms of intravitreal injection- related reactions. Vabysmo has not been studied in patients with poorly controlled glaucoma or in diabetic patients with uncontrolled hypertension. Exercise caution in patients with poorly controlled glaucoma. Monitor and manage intraocular pressure (IOP) and perfusion of the optic nerve head. Do not inject while IOP is ≥30 mmHg. Systemic adverse events including arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors, including Vabysmo. There is a potential for immunogenicity. Patients should inform their physician of any signs or symptoms of intraocular inflammation which might suggest hypersensitivity. Vabysmo administered in both eyes has not been studied. Exercise caution in patients with risk of retinal pigment epithelial tears. There is limited experience in the treatment of DMO patients with HbA1c over 10%, patients with high-risk proliferative diabetic retinopathy (DR), or nAMD and DMO patients with active systemic infections. Withhold treatment in patients with: rhegmatogenous retinal detachment, stage 3 or 4 macular holes, retinal break, treatment related decrease in Best Corrected Visual Acuity (BCVA) of ≥30 letters, performed or planned intraocular surgery within the previous or next 28 days. Do not administer concurrently with any other VEGF inhibitor. Women of childbearing potential should use effective contraception during and for at least 3 months following treatment. Avoid during pregnancy unless benefit outweighs the potential risk to the foetus. Vabysmo is not recommended during breast-feeding as risk to infant cannot be excluded. See SPC for details. Patients should not drive or use machines until visual function has recovered. **Adverse Events:** For more information, see SPC.

Very Common: cataract *Common:* conjunctival haemorrhage, vitreous detachment, vitreous floaters, retinal pigment epithelial tear (nAMD only), increased IOP, eye pain, increased lacrimation, corneal abrasion, eye irritation. *Serious:* uveitis, vitritis, endophthalmitis, retinal tear, rhegmatogenous retinal detachment, traumatic cataract.

Legal Category: POM. **NHS Costs:** 1 vial £857.

Marketing Authorisation Number:

Vabysmo is authorised in Great Britain - PLGB 00031/0927.

Supplied by: Roche Products Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, United Kingdom.

Vabysmo is a registered trade mark.

Prescribing information for Northern Ireland only.

▼ Vabysmo® (faricimab): 120mg/mL solution for injection. Single use vial containing 6mg faricimab / 0.05mL

Please refer to Summary of Product Characteristics (SPC) prior to use of Vabysmo **Indications:** For the treatment of adult patients with neovascular (wet) age-related macular degeneration (nAMD) or visual impairment due to diabetic macular oedema (DMO). **Dose and Administration:** Vabysmo must be administered by a qualified physician experienced in intravitreal injections. Each vial should only be used for the treatment of a single eye. Always record batch number. *nAMD:* 6 mg (0.05 mL solution) administered by intravitreal injection under aseptic conditions every 4 weeks for the first 4 doses. Thereafter, an assessment of the disease activity based on anatomic and/or visual outcomes 20 and/or 24 weeks after treatment initiation is recommended. If no disease activity, consider treatment every 16 weeks. If disease activity, consider treatment every 8 or 12 weeks. *DMO:* 6 mg (0.05 mL solution) administered by intravitreal injection under aseptic conditions every 4 weeks for the first 4 doses. The dosing interval may be extended up to every 16 weeks (4 months), in increments of up to 4 weeks. If anatomic and/or visual outcomes change, the treatment interval should be adjusted accordingly. Treatment intervals shorter than 4 weeks between injections have not been studied. *nAMD and DMO:* Schedule monitoring between dosing based on patient status and at the physician's discretion. Vabysmo is intended for long-term treatment. Discontinue Vabysmo if visual and/or anatomic outcomes indicate no benefit. See SPC for instructions on method of administration.

Contraindications: Hypersensitivity to faricimab or excipients. Active or suspected ocular or periocular infections. Active intraocular inflammation.

Precautions: Patients should report promptly any symptoms of intravitreal injection-related reactions. Vabysmo has not been studied in patients with poorly controlled glaucoma or in diabetic patients with uncontrolled hypertension. Exercise caution in patients with poorly controlled glaucoma. Monitor and manage intraocular pressure (IOP) and perfusion of the optic nerve head. Do not inject while IOP is ≥30 mmHg. Systemic adverse events including arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors, including Vabysmo. There is a potential for immunogenicity. Patients should inform their physician of any signs or symptoms of intraocular inflammation which might suggest hypersensitivity. Vabysmo administered in both eyes has not been studied. Exercise caution in patients with risk of retinal pigment epithelial tears. There is limited experience in the treatment of DMO patients with HbA1c over 10%, patients with high-risk proliferative diabetic retinopathy (DR), or nAMD and DMO patients with active systemic infections. Withhold treatment in patients with: rhegmatogenous retinal detachment, stage 3 or 4 macular holes, retinal break, treatment related decrease in Best Corrected Visual Acuity (BCVA) of ≥30 letters, subretinal haemorrhage involving the centre of the fovea, performed or planned intraocular surgery within the previous or next 28 days. Do not administer concurrently with any other VEGF inhibitor. Women of childbearing potential should use effective contraception during and for at least 3 months following treatment. Avoid during pregnancy unless benefit outweighs the potential risk to the foetus. Vabysmo is not recommended during breast- feeding as risk to infant cannot be excluded. See SPC for details. Patients should not drive or use machines until visual function has recovered.

Adverse Events: For more information, see SPC. *Very Common:* cataract *Common:* conjunctival haemorrhage, vitreous detachment, vitreous floaters, retinal pigment epithelial tear (nAMD only), IOP increased, eye pain, lacrimation increased, corneal abrasion, eye irritation. *Serious:* uveitis, endophthalmitis, vitritis, retinal tear, rhegmatogenous retinal detachment and traumatic cataract

Legal Category: POM. **NHS Costs:** 1 vial £857.

Marketing Authorisation Number:

Vabysmo is authorised in Northern Ireland - EU/1/22/1683/001

Supplied by: Roche Products Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, United Kingdom.

Vabysmo is a registered trade mark.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard Adverse events should also be reported to Roche Products Ltd. Please contact Roche Drug Safety Centre by emailing welwyn.uk_dsc@roche.com or calling +44 (0)1707 367554

As Vabysmo is a biological medicine, healthcare professionals should report adverse reactions by brand name and batch number

M-GB-00013193 Date of Preparation: August 2023

the Ophthalmologist

POWER *List*

NOMINATIONS FOR 2024 ARE NOW OPEN!

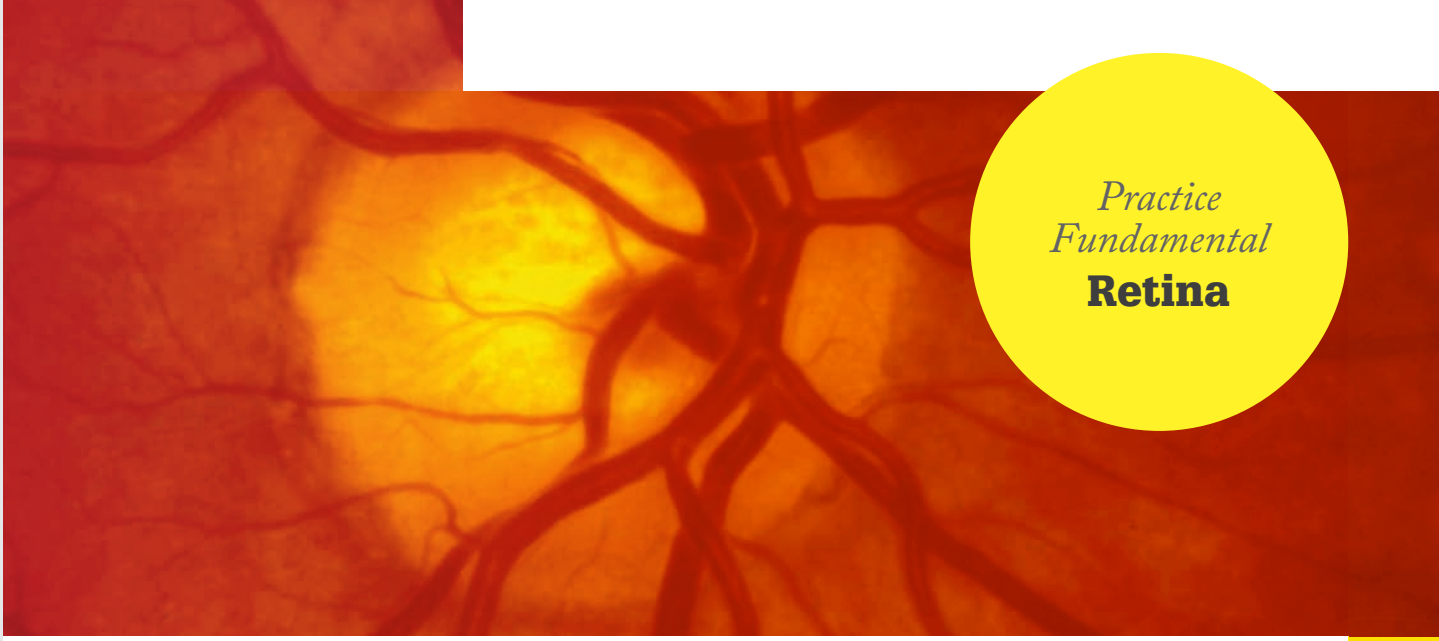
Back for its 11th year, the Power List celebrates global ophthalmology's most impactful visionaries and leaders.

It's time for you to nominate an outstanding individual whose work, dedication, and trailblazing has left you in admiration of their achievements.

Perhaps there's a mentor that the next generation couldn't do without? A surgeon who leads from the front line? Or a researcher who has achieved incredible things, overcoming all obstacles? Now is your chance to put them on a pedestal.

Just head to our website, add your nominee's details to the form, and let us know why you feel they should have their place on the Power List 2024.

NOMINATIONS CLOSE JANUARY 31, 2024



ROP research. A cohort study of 706 infants screened for retinopathy of prematurity (ROP) found that public health insurance was linked to a higher risk of neurodevelopmental problems in cognitive, language, and motor domains. The study suggests that socioeconomic factors may impact the neurodevelopment of high-risk infants, and indicates the safety of early anti-VEGF treatment for ROP. PMID: 37883103.

Deep-learning algorithm to predict GA progression. Study shows a convolutional neural network-based deep learning algorithm predicted progression from intermediate age-related macular degeneration (iAMD) to geographic atrophy (GA) from a volumetric spectral-domain optical coherence tomography (SD-OCT) scan; findings suggest that automated prediction of imminent GA progression could facilitate clinical trials aimed at preventing disease and guide decision-making on screening frequency or treatment initiation. PMID: 37856139.

A good patch. Is there a new way to treat primary macular hole retinal detachment (MHRD) in highly myopic patients? A new study describes a new surgical technique that uses human amniotic membrane (hAM) epiretinal patch for treating this patient group. Four days after implantation in a 60-year-old highly myopic man, OCT showed the hAM patch to be well integrated with the retina. Nine months later, the macular hole was closed, the retina attached and the hAM patch adhered to the retina with no postoperative adverse events. The results indicate that epiretinal hAM implant could be an easier technique for treating MHRD in highly myopic patients. PMID: 37820366.

Nature or nurture? Researchers from Germany set out to assess if and how central visual areas are altered in a vertebrate brain – in this case a zebra fish – depleted of any and all signals from retinal ganglion cells throughout development. They found that signals emitted by retinal axons influence the pace of neurogenesis in visual brain areas, but do not detectably affect the specification or wiring of downstream neurons. Researchers say that the more we know about these processes, the closer we can get to answering the famous question – what is nature and what is nurture? PMID: 37758715.

RVO and COVID. Retinal vascular occlusion (RVO) could be one of the potential long-term consequences of COVID-19, a new retrospective cohort study has reported. Examining 46 healthcare organizations across the US, with over 1.4 million patients' data analyzed, the researchers found significantly higher risks of branch retinal vein occlusion in COVID-19 patients compared with those who had not been infected. PMID: 37824812.

IN OTHER NEWS

Discarding the syringe. *A new Cell Reports Medicine report suggests that researchers from the University of Illinois might be on their way to developing a novel age-related macular degeneration (AMD) treatment aimed at delivering medication via drops rather than regular intravitreal injections. PMID: 37794584.*

Connecting the dots. *Researchers assessing the presence of intraretinal hyper-reflective foci (IHRF) – dots, indicating a number of retinal conditions in OCT scans in 1,339 individuals over a two-year period, found an increased count in the outermost layers of the retina, with the hyper-reflective dots essentially presenting an eye in severe distress. PMID: 37790320.*

Lord of the ring. *Study shows that negative dysphotopsias (ND), which occurs in a small percentage of pseudophakic patients during the post-operative phase, can be counteracted by a ring-shaped insert (ND Ring), a sulcus-fixated device that keeps the intraocular implant intact whilst addressing the unintended visual phenomena. PMID: 37753932.*

AI: Shaping the Future of Medicine

How AI-integrated retinal imaging is revolutionizing contemporary eye care

By Andrzej Grzybowski and Kai Jin

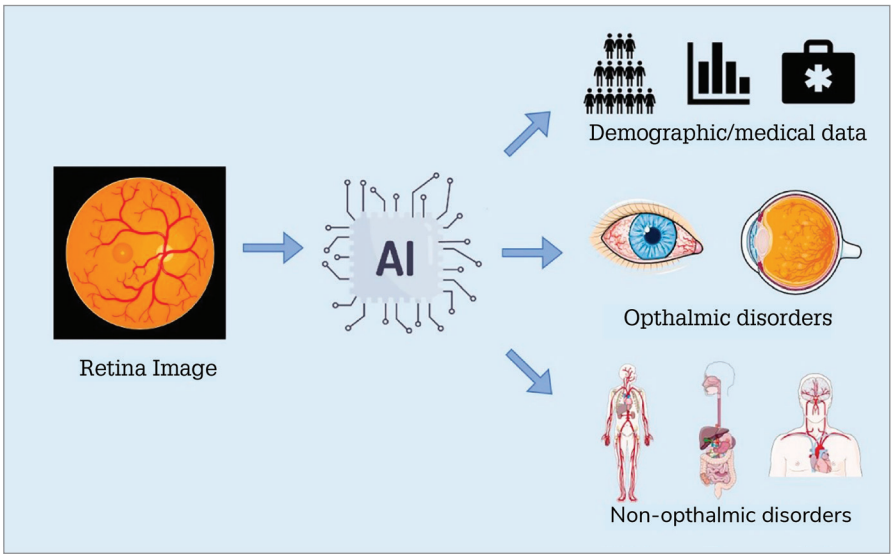


Figure 1. Overview of the applications of AI algorithms based on retinal photos.

The integration of artificial intelligence (AI) with multimodal data analysis, including eye imaging, presents a revolutionary approach to not only diagnosing eye diseases, but also predicting systemic conditions affecting various body systems (1), including the brain and cardiovascular system (2) (see Figure 1). This radical change in imaging approaches has the potential to redefine medical diagnostics and enhance our understanding of the interplay between age, sex, and race in disease pathology.

In contemporary ophthalmology, the fusion of data from diverse sources, such as optical coherence tomography (OCT), fundus photography, and genetic profiling, allows for a comprehensive evaluation of ocular health (3). AI-driven algorithms can process these multimodal datasets to detect early signs of ocular diseases, such as glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy (4), aiding not only early disease diagnosis, but also helping track disease progression.

Beyond eye-specific conditions, the integration of multimodal data holds immense potential for predicting other systemic diseases. For instance, in the case of neurological diseases, AI analysis of ocular data can help to identify subtle changes in the retina associated with Alzheimer's disease (5), Parkinson's disease (6), and multiple sclerosis, facilitating early diagnosis and monitoring of these conditions, and potentially paving the way for personalized treatment strategies. Alongside genetic and clinical data, retinal imaging can also contribute to the prediction of cardiovascular diseases (7), such as hypertension and atherosclerosis. To assess cardiovascular risk, AI analyzes retinal vessel caliber and morphology, enabling timely interventions to prevent heart disease and stroke.

The incorporation of demographic data into AI-based ophthalmic analysis is also a burgeoning field. Advanced AI algorithms can quantify age-related changes in the eye, including lens opacity, retinal thickness alterations, and macular degeneration (8); understanding these changes in the context of aging is critical for accurate diagnostics and treatment planning. Recent research is also being conducted into exploring sex-based differences in eye anatomy and disease susceptibility (9), with studies suggesting that women may be more prone to certain eye conditions like dry eye syndrome (10), and AI can aid in deciphering the nuances of these sex-related disparities in ocular health.

In terms of AI-applied race recognition in medical imaging, we can say it is an evolving frontier. Recognizing any racial disparities in disease prevalence and outcomes can be essential for addressing healthcare inequities (11), and AI can contribute to this field by analyzing medical images for race recognition and subsequently investigating the impact of race on disease susceptibility and progression. Incorporating gathered race-specific data into diagnostic and treatment algorithms can also enable more tailored and equitable healthcare delivery, accounting for genetic and environmental factors that vary across populations.

"Beyond eye-specific conditions, the integration of multimodal data holds immense potential for predicting other systemic diseases."

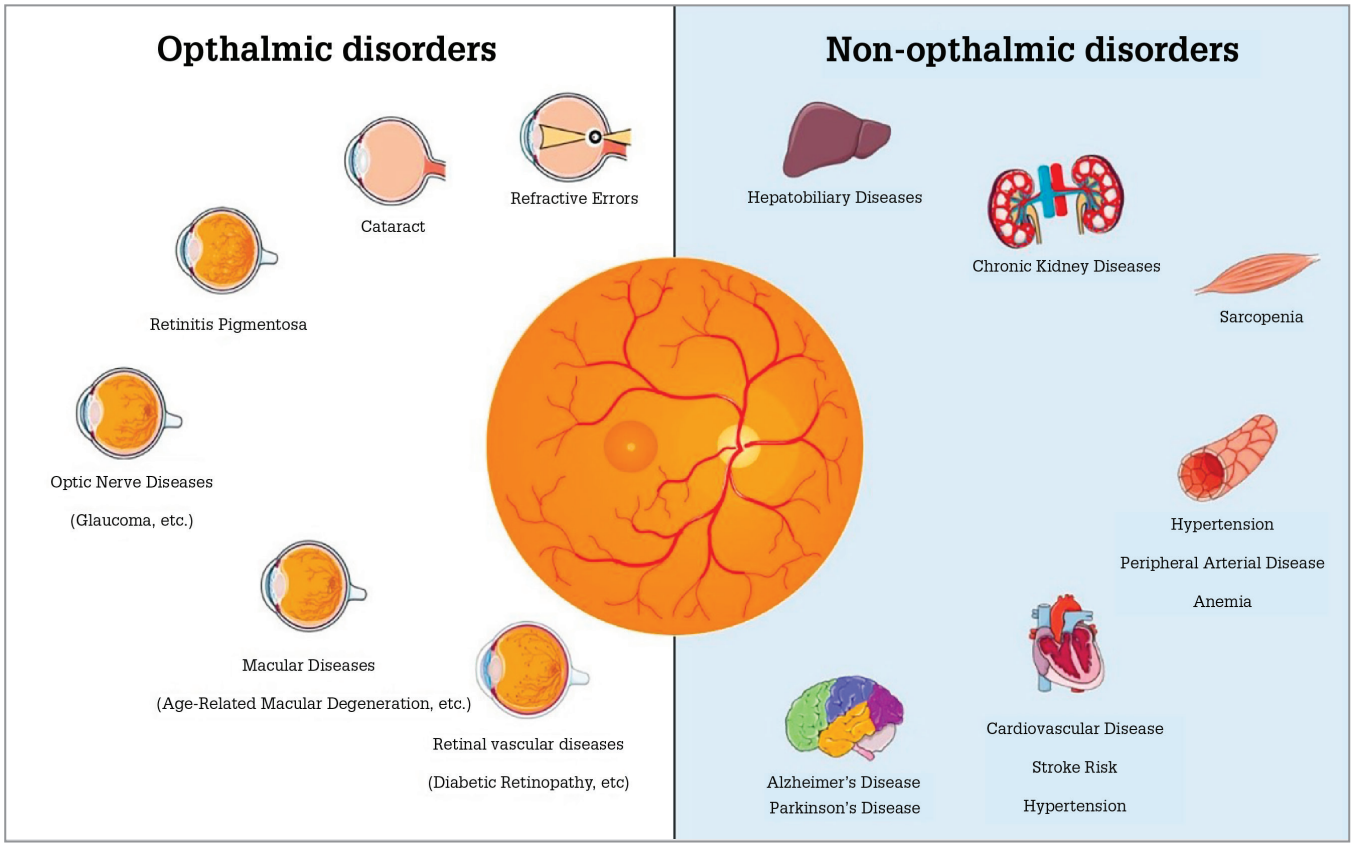


Figure 2. The application of retinal photo-based AI in both ophthalmic and non-ophthalmic conditions.

Andrzej Grzybowski, Professor of Ophthalmology, CEO, Foundation for Ophthalmology Development, Poznan, Poland, and EVER President-Elect.

Kai Jin is a doctor and research scientist at the Eye Center, the Second Affiliated hospital of Zhejiang University School of Medicine. His current research interests are in retina, imaging, artificial intelligence, and personalized medicine. He received his PhD in 2018 and has an outstanding publication record, with 54 publications in peer-reviewed international journals. Jin's Scopus Scientific Citations number is 1092 and his Hirsch index is 18. In the past year, Jin was awarded the WILEY Top Cited Article Award and the National Scholarship.

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AI Alliance

RetinAI and RCA partnership aims to transform the retinal space through AI

Artificial Intelligence (AI) is undoubtedly revolutionizing the medical landscape. In enhancing diagnostics, treatment plans, and healthcare processes, the technology's possibilities are near endless. Now, a strategic alliance between RetinAI and the Retina Consultants of America (RCA) is placing AI at center stage.

By combining RetinAI's expertise in AI-powered clinical and imaging data management with RCA's knowledge of providing specialist retinal care throughout the US, the partnership aims "to transform the retinal space" and provide enhanced patient care.

Here, Carlos Ciller, CEO of RetinAI, tells us what the collaboration means for the retinal space and how it will further drive AI technologies in the medical industry.

Carlos Ciller

How did the collaboration between RetinAI and RCA come about?

In 2020, as RCA was adding more retina specialists to its team, David M. Brown – the head of RCA's Medical Leadership Board – started discussions with the RetinAI group about their RetinAI Discovery platform and AI models. Prior to the partnership announcement in July 2023, a test pilot project was conducted to gauge how RetinAI's system and AI-based biomarker analysis and platform could enhance data analysis for retina experts. Both parties realized that by combining RetinAI's technology with RCA's expertise, we could change the depth and understanding of patients and diseases.

What are the primary goals of the partnership?

In our mutual quest to fight vision-threatening diseases with data-driven decisions, one of the primary goals of the partnership is to improve patient outcomes. To this end, RetinAI and RCA are building the most comprehensive real world evidence database for ophthalmology in the US, linking clinical data with biomarker insights from quality-driven imaging data. More specifically, we plan to expand into retinal diseases such as age-related macular degeneration (AMD), diabetic macular edema (DME), and diabetic retinopathy (DR), and other areas of cardiovascular and neurodegenerative diseases where retinal imaging plays a role. By Q4 2023,we plan to have insights available for geographic atrophy.

How do you foresee the partnership advancing AI-driven technologies in the medical industry?

We see AI becoming a powerful engine to unlock knowledge about patterns and trends in real-world data that cannot be easily seen through traditional analyses. In the future, we'll see this technology seamlessly integrated into routine medical care, into clinical and pharmaceutical research, helping healthcare stakeholders in their decision-making and supporting target-based R&D pathways for new therapies and diagnostics.

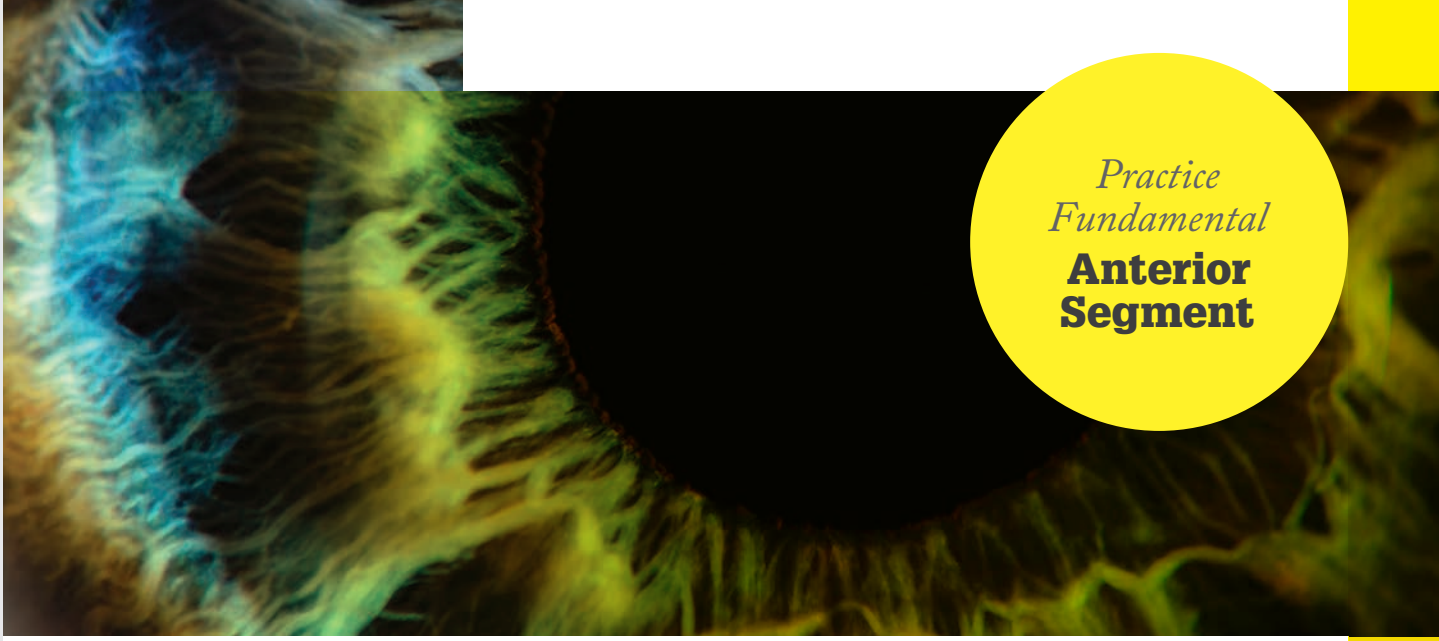
How are you ensuring the secure handling and protection of patient data, given the sensitive nature of medical information involved?

Data privacy and security are top priorities for both RCA and RetinAI. Only de-identified and fully anonymized records under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) compliance will be considered as part of our collaboration, and we have implemented safeguards to protect the confidentiality, integrity, and availability of any electronic protected information.

How does the partnership align with RetinAI's long-term growth strategy?

We hope to significantly improve vision and health outcomes for patients globally by enabling the right decisions sooner in healthcare. We see this partnership broadening our ties to ophthalmology and expanding into other disease areas with the development of the real-world evidence (RWE) database, bringing an unprecedented level of insight and knowledge to the healthcare community.

As leaders in advanced data management and AI analytics for ophthalmology, adding RWE solutions will strengthen our role in driving better data-driven decisions through technology advancement.



Practice Fundamental

Anterior Segment

Left is (al)right. A retrospective, single-center study included 300 patients who underwent phacoemulsification surgery by a single, right-handed surgeon. Patients were divided into two groups according to whether the surgeon used his dominant or non-dominant hand during surgery. The study demonstrated that cataract surgery performed by a single surgeon can be effectively and safely performed using both hands on patients in a real operating theatre environment. PMID: 37977225.

A green light? A study compared transcriptome sequencing results of three cohorts of mice: young control, untreated aged, and those treated by epigallocatechin gallate (EGCG), the most potent antioxidant in green tea to assess its affect on age-related cataract (ARC). Researchers were able, for the first time, to show the inhibitory effect of EGCG on lens clouding in mice, as well as reveal the mechanism of action via the RASSF2/AKT pathway, providing a theoretical basis for the target use of EGCG as a therapeutic. PMID: 37979829.

Seeing color. To determine the racial inequalities in utilization rates and intraoperative complications of cataract surgery, researchers retrospectively identified patients who underwent cataract surgery at a tertiary academic center and recorded best corrected visual acuity, slit lamp findings, and surgical timeline (3). They found that Black patients experienced more delays in receiving cataract surgery, but were more adherent with postoperative follow-up. Additionally Black patients were a lot less likely to receive premium IOLs than white patients. PMID: 37975843.

Connected threads. University of Auckland researchers investigating the prevalence, risk factors and severity of corneal tomographic features of keratoconus in Down syndrome (DS) found that over a quarter of the participants were affected by keratoconus, with eye rubbing being a significant risk factor for the development of keratoconus. Although DS patients with suspected keratoconus and those without had similar minimum pachymetry, they had several significantly different parameters. Keratoconus screening with corneal tomography is recommended for early detection. PMID: 37963802.

ECD flex and center. To determine the reproducibility of endothelial cell density (ECD) measurements offered by Konan CellChek D specular microscopy, researchers compared ECD values in 54 donor corneas by two different ophthalmologists comparing the center and flex-center automated cell count methods. Although the ECD values are reproducible with both methods, the flex-center method tended to output higher values for ECD, particularly in the case of low ECD. PMID: 37951743.

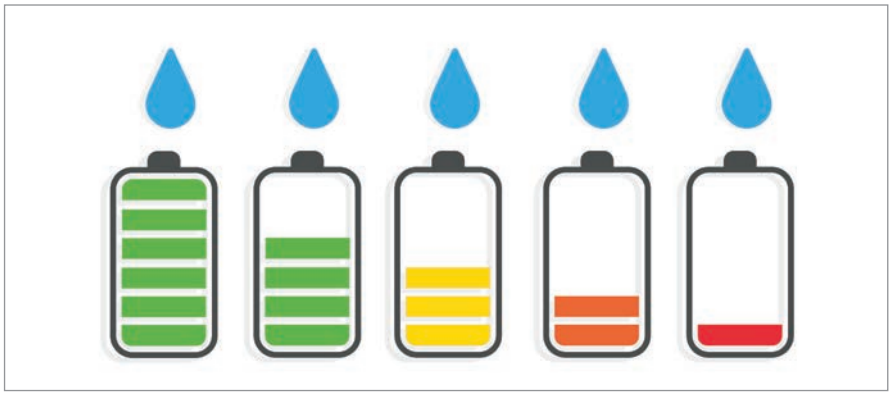
IN OTHER NEWS

At risk. *Researchers identify the risk factors for detecting fibrous ingrowth in first-time keratoplasty recipients, concluding that these factors should be closely monitored for corneal decompensation. PMID: 37647130.*

OSST outcomes. *Elderly patients with less or no systemic immunosuppression exhibit overall favorable outcomes after allogeneic ocular surface stem cell transplantation. PMID: 36727885.*

Looking at lenses. *Both corneal and scleral contact lenses provide visual improvement in eyes after simple limbal epithelial transplantation with residual corneal scarring, without causing adverse effects. PMID: 36728263.*

Combining indexes. *The Tomographic and Biomechanical Index (TBI) is a useful parameter for screening subclinical and frank keratoconus in topographically normal eyes. PMID: 36973879.*



Crying Out for Recharge

Is a newly developed tear-based battery the future for smart contact lenses?

Although they are still very much a work-in-progress, smart contact lenses look set to revolutionize the eye care field and maybe society as a whole. The technology has the potential – due to its wearability and the fact that everyone (or almost everyone!) has eyes – to usurp smartphones as the favored form of portable computing for the masses.

As the tech continues to advance (1), there are hopes that so too will the wearer's ability to use smart contact lenses for more than just vision enhancement – taking advantage of apps and other inbuilt features in the same way they would with their smartphones. A range of features are already in development. Alongside the apps that come as standard on a traditional smartphone (compass, calendar, etc.), smart contact lenses could, for example, combine augmented and mixed reality, allowing wearers to see virtual objects in the real world. And should the wearer have fantasies about being in the SAS, the lenses could switch into night vision mode. They could also be equipped for health monitoring – e.g., allowing users to monitor their blood-glucose levels and their intraocular pressure/temperature, a feature that would be of particular interest to glaucoma patients.

To replicate these kinds of smartphone applications, smart contact lenses will require "invisible computing," (2) which takes the form of a non-intrusive device, effectively invisible to the user, which performs essential computing functions and adapts to the wearer's individual needs so that information is only displayed when it is necessary. For this to become a reality, however, lens batteries need to be further miniaturized and will have to be, if not totally organic, then at least biocompatible with, and non-toxic to, the human eye.

So, are we any closer to this kind of technology being commercially realized?

Most recently, scientists at the School of Electrical and Electronic Engineering, Nanyang Technological University, Singapore, have invented a biofuel-charged miniature battery (3), which could provide a solution to charging smart lenses. Created from biocompatible materials and free from wiring or toxic materials, the flexible battery is as thin as a human cornea and stores electricity when immersed in saline solution.

Seok Woo Lee, an associate professor at Nanyang Technological University who led the research, explains: "To satisfy the safe environment requirements of human eyes, all the battery materials applied in our lens battery are biocompatible. Since the ions required by the reaction are all contained in tears, tears can perform as the electrolyte, which eliminates the potential risks caused by the additional electrolytes" – that is, the battery could also be powered by the wearer's own tears.

However, as the researchers note in a recent press release, for every 12 hours of contact lenses wear, tears only add one extra hour of battery charge, meaning that for the time being, even bawling your eyes out for a considerable period of time won't be enough to keep the batteries powered. But Lee explains that "users can store the lens in the container overnight while sleeping, and the lens can be charged by just being immersed in the glucose solution."

Though innovative in itself, the battery cannot yet be incorporated into the body of the smart contact lens. "Further research will focus on the improvements in the electrical current amount the battery can discharge to make it able to provide sufficient power to the embedded electronic devices on the smart contact lens," says Lee, adding that "the required area of the battery is reduced and the circuit design may be simplified as well."

The research team has now filed for a patent for the device through NTUitive, Nanyang Technological University's innovation and enterprise company, and is currently in talks with several contract lens companies about implementing the technology into devices. "The industry has been looking for a thin, biocompatible battery that does not contain heavy metals," says Murukeshan Vadakke Matham, an associate professor at the School of Mechanical & Aerospace Engineering, NTU, who was not involved in the study. This invention, then, could go some way to meeting some of the industry's unmet needs.

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1. *Forbes, "Mojo Vision's Smart Contact Lens: Ready For Real-World Testing," (2022). Available at: https://bit.ly/46uyXma.*
2. *Medium, "Invisible Computing Will Be All Around Us," (2020). Available at: https://bit.ly/3LQyO4J.*
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For Cataract Success, Get Ahead of DED

Preoperative treatment of DED and lid margin disease is absolutely essential

Preoperative treatment of DED and lid margin disease is absolutely essential in helping us meet three important goals: prevent postoperative infection; obtain accurate measurements for IOL calculations; avoid postoperative aberrations that can result from an unstable ocular surface (particularly with multifocal lenses).

I explain these goals to patients every day so they understand why we need to spend a few weeks treating DED before surgery. It all begins with accurate screening, which includes recognizing the unique symptoms of concurrent DED and cataracts.

Screening cataract patients for DED

The cataract workup includes refractive preoperative measurements. I get two sets of keratometry (K) readings, one manual and one with my biometry device, as well as topography. To help detect DED, I check the results for consistency, looking for incongruous K readings, irregular mires, or unusual topographies. If I find a problem, then we need to treat DED and repeat preoperative measurements later.

In addition, I get an accurate history. You can use a DED questionnaire, but I also choose to talk to cataract patients to differentiate between cataract-induced blurriness and fluctuating vision resulting from an unstable tear film. For example, patients might want cataract surgery because they "can't read," but when we talk about it, they say they're able to read for an hour before their vision gets blurry – that's an unstable tear film until proven otherwise.

For objective testing, I do a detailed slit lamp exam, including corneal staining. I carefully examine the lid margins, express the meibomian glands, and check the TBUT. I also rely on osmolarity to help detect DED and gauge its severity.

DED treatment and retesting

Cataract patients are eager to get their surgery, so I want the treatment plan to deliver rapid results. Everyone gets preservative-free artificial tears, to moisturize and lubricate the ocular surface without any detrimental preservatives. Drops containing povidone, as well as hyaluronic acid (HA) and trehalose, may be particularly useful.

In mild cases, artificial tears and lid hygiene (scrubs and warm compresses) are sufficient. If the lid margin disease is more advanced, I might do a short course of azithromycin or erythromycin. In cases of staining or inflammation, I typically add a two-week course of a mild steroid, such as loteprednol or fluorometholone. I do not typically prescribe immunomodulators perioperatively because they take time to become effective; plus, I don't want patients to have too many drops around the time of surgery. However, I do frequently recommend immunomodulators for long-term maintenance.

After two weeks, if patients' new K values and topography look good, we're ready to choose an IOL. Occasionally, if I'm not confident that a patient will reliably manage their chronic DED post-surgery, I might not recommend a multifocal or premium lens because they'd have vision problems months later without ongoing management of DED.

Classic case: DED changes refraction

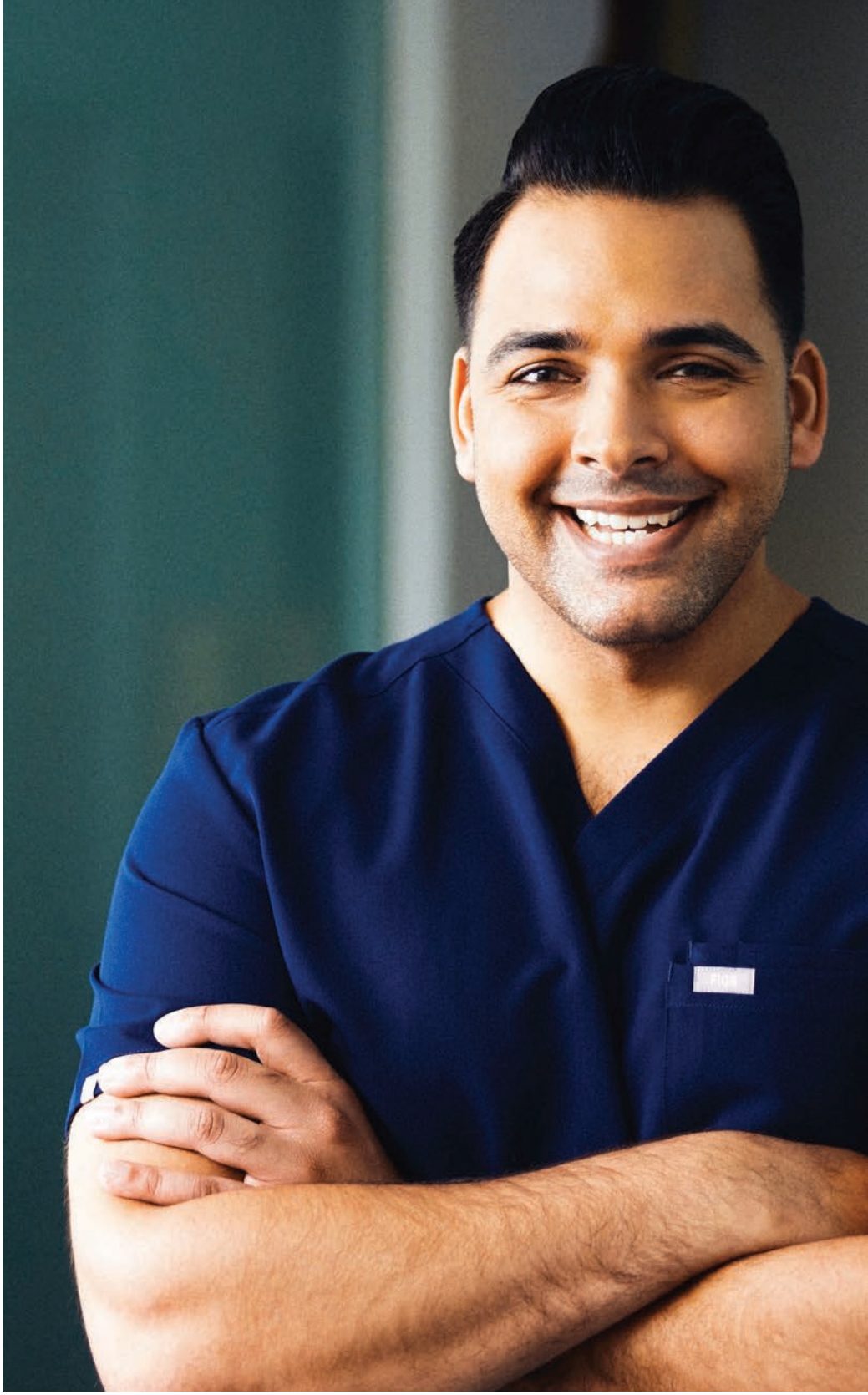
A patient with cataracts was referred to me for toric IOLs to correct three diopters of astigmatism. My topographer verified the three diopters but, on close inspection, the mires had a divot at around 1 o'clock, so they weren't circular. A red hot spot in the same area meant the topography didn't reflect astigmatism's classic bowtie. I found that the patient had a rapid TBUT and there was evidence of moderate lid margin disease. We treated the surface with preservative-free artificial tears and a two-week course of azithromycin, as well as hygiene and warm compresses.

When the patient came back two weeks later, the hot spot was gone and the placido rings were more regular. Remarkably, the amount of astigmatism had dropped from 3 to 0.5 diopters. If I had selected a toric lens based on this patient's initial measurements, he would be living very unhappily with 2.5 diopters of induced astigmatism. It's a classic case that underscores just how much cataract outcomes depend on preoperative treatment for DED.

Kenneth A. Beckman, MD, FACS.

Into the Unknown

Rising Star Arjan Hura discusses what may be in store for the future of refractive surgery and ophthalmology at large



What does the future of ophthalmology, and refractive and cataract surgery, look like?

It is a simple question but one that is difficult to answer with certainty. Understanding and keeping on top of trends within ophthalmology is important for ensuring that patients receive the best possible care. However, one cannot truly know what the future holds. Our field is one that evolves rapidly, and often in unforeseen ways. Companies or technologies can emerge that seem to hold promise or seem poised to revolutionize ophthalmic care, but later they end up not working out. For example, maybe the results don't pan out clinically or there are issues with the companies on the back-end with financing or market uptake. Thus, making predictions about the future of ophthalmology with any level of certainty is difficult. However, there are a lot of exciting developments taking place that may give an indication of where our future is headed.

I personally find one of the most exciting aspects of innovation in ophthalmology to be technological advancement. New intraocular lenses (IOLs) are released on an almost annual basis, and every few years there are developments in laser technology. Additionally, we are seeing amazing advancements in gene therapeutics, sustained drug delivery, and cell therapy across all subspecialties of ophthalmology. As a refractive surgeon, I have my eye on a few developments, particularly lenticular addition and subtraction, refractive indexing, and phakic IOLs. I also feel that we are accelerating towards next-generation IOL technology in the form of modular IOLs, accommodating IOLs, and post-

operative adjustable IOLs. I predict that we will see technology that mimics the natural human crystalline lens, or that is superior to it, within the next few decades.

"My attention is laser-focused on refractive and cataract surgery, so when I see developments in this space, I pay attention and try to stay informed and abreast of where things are headed."

Adapting while advancing

Our field is anything but static, which is why I firmly believe that in order to predict the future, one must constantly be studying industry, the latest peer-reviewed literature, and the latest technology, as well as espousing a mindset of adaptation. If you truly enjoy what you do, putting in time to study and refine your craft outside of your normal work hours should feel natural. The ophthalmologist who remains curious and a life-long learner will not be caught off guard by where the field is headed next. My attention is laser-focused on refractive and cataract surgery, so when I see developments in this space, I pay attention and try to stay informed and abreast of where things are headed. Being primed on current developments allows one to gauge their personal interest in any burgeoning advancement and to appropriately decide where to commit their time. Interest in a certain area will allow for more informed and targeted conversation with industry, may lead to the ability to participate in clinical trials, may lead to investing opportunities, and at the very least will lead to more knowledge, which will make one more perspicacious when it comes to patient care. Patients often ask if there is a better medication or technology that is coming down the pipeline that may serve them better – the ophthalmologist who understands where the future is headed will be able to confidently make the appropriate recommendation.

Shape while being shaped

Although it is impossible to know for sure what the future holds, it is important to remember that we are the ones currently practicing ophthalmology in this era, so it is our duty to contribute to our field and to the generations of patients that will benefit as a result of our careers and lifetimes. My current personal interests are studying how to potentially reverse cataractogenesis, next-generation IOLs, and laser vision correction. I encourage all of my colleagues to see how they can give back to ophthalmology and medicine at large. If you find something interesting, look to see if there is an opportunity (or create one) for collaboration with others with similar interests in research, education, clinical practice, or innovation. The future will not invent itself – we are the ones that must work to actively shape what we hope to see in the future of ophthalmology.

Arjan Hura is a refractive, cataract, and anterior segment surgeon at the Maloney–Shamie Vision Institute, California.

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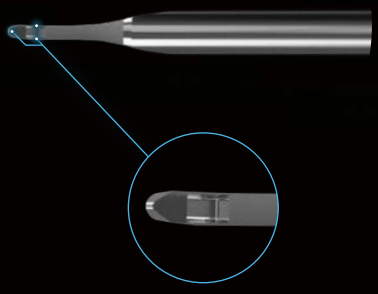

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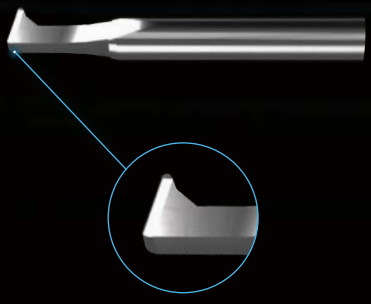

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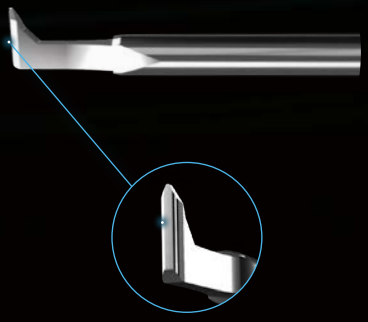

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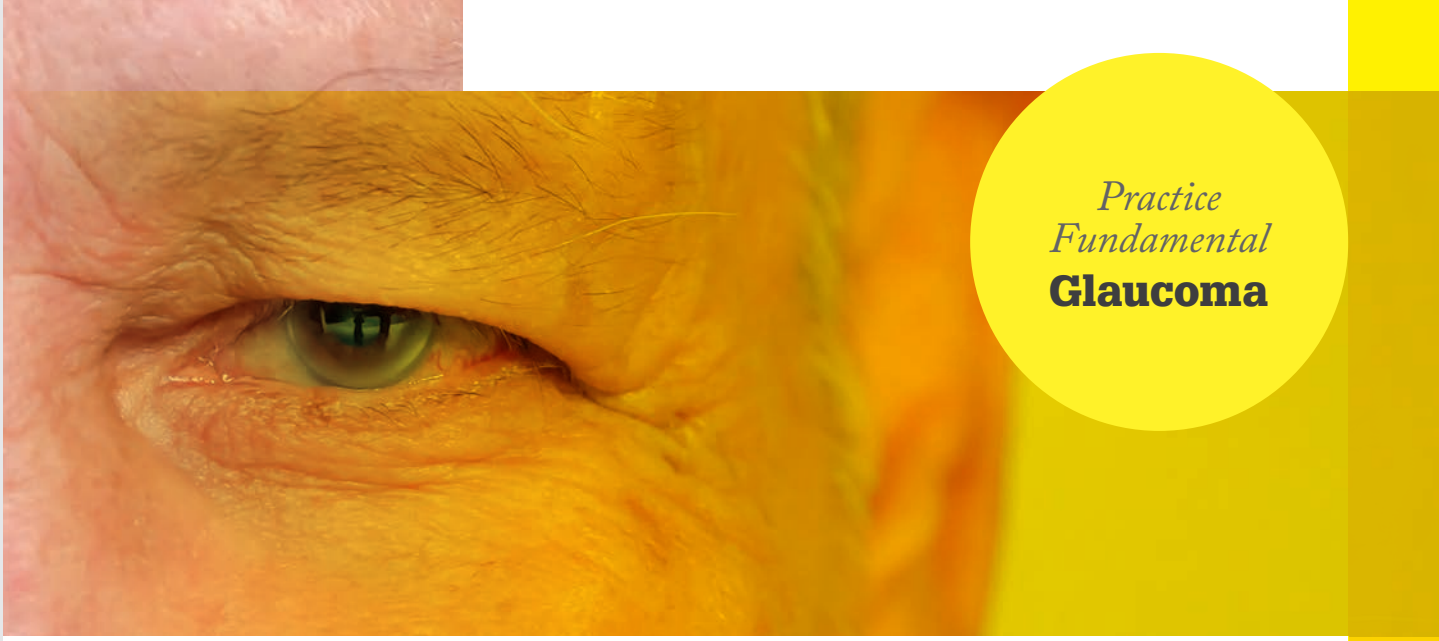


A vicious circle. Researchers exploring the role that circular RNAs (cirRNAs) play in the underlying mechanisms of glaucomatous neurodegeneration injected microbeads into the anterior chamber to generate a model of glaucomatous neurodegeneration. Using this model they were able to distinguish glaucoma patients from cataract patients by detecting the levels of cirRNA-glycine receptor α2 subunit gene (cGlra2) in aqueous humor. PMID: 37819813.

Glaucoma–Alzheimer's link. A national cohort study from Sweden has added to the pre-existing evidence suggesting a potential link between glaucoma and neurodegenerative diseases. The study took data from 324,730 glaucoma patients, plus 3.2 million controls with no prior signs of dementia, discovering that primary open-angle glaucoma and normal-tension glaucoma were both associated with a higher risk of vascular dementia and Alzheimer's disease, whereas primary angle-closure glaucoma only resulted in an increased risk of vascular dementia. PMID: 37839560.

MvD: up in smoke. To determine the impact of smoking on choroidal microvasculature (MvD) in glaucoma, a cross-sectional study imaged 223 eyes of 163 patients who had completed a questionnaire on smoking from the Diagnostic Innovations in Glaucoma Study, with optical coherence tomography angiography. MvD was observed in a higher percentage of eyes with smoking history. PMID: 37899137

Under pressure. Authors of a Nature Scientific Report highlight that certain blood pressure medications could potentially increase the risk of glaucoma, before acknowledging that the use of such antihypertensive medications likely indicates pre-existing comorbidities that run their own risks of glaucoma. On balance, the authors note that the long-term use of these medications was generally very low risk. PMID: 37758842.

Seeing the good life. Is visual field index a good predictor of quality of life in glaucoma patients? A cross-sectional, mono-centric study on glaucoma patients using the NEI-VFQ 25 and Glaucoma Symptom Scale (GSS) to assess quality of life, and Humphrey Field Analyzer to examine visual field, found that there was a correlation between the visual field index and the quality of life of patients with glaucoma, and their visual and non-visual ocular symptoms and functions across the spectrum from the worst to the best eyes. The data supports using visual field index as an important metric instrument when following up with glaucoma patients. PMID: 37731713.

IN OTHER NEWS

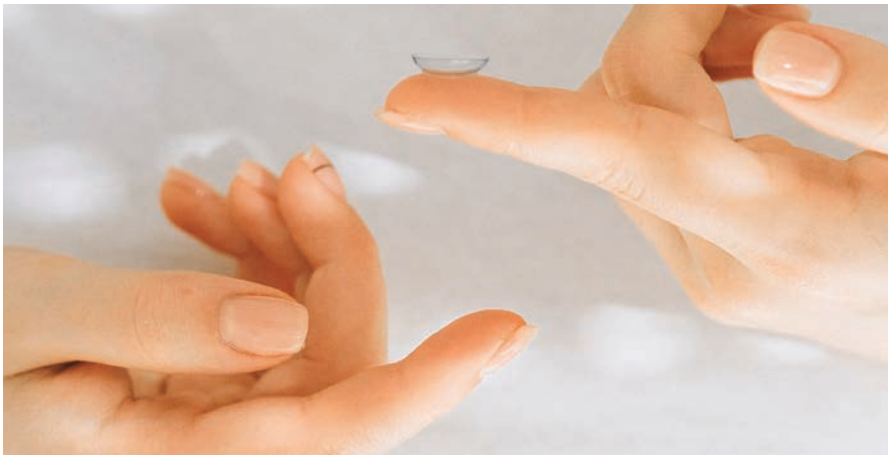
Ask away. *Researchers exploring whether African American glaucoma patients feel able to ask questions to their eye care providers found that very few tended to ask all of the questions that they had. PMID: 37524828.*

Gene survey. *Researchers analyzing the associations between variants of mechanosensitive ion channels, and primary open-angle glaucoma (POAG) identified two rare coding variants of the PIEZO1 within the NEIGHBORHOOD consortium dataset that had protective effects, one of which alters a canonical splice donor site. PMID: 37741866.*

POAG and PACG biomechanical properties. *A retrospective analysis comparing corneal visualization Scheimpflug technology (CST) parameters between eyes with primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) found that there were no differences in age, central corneal thickness, IOP or antiglaucoma eye drop use. PMID: 37568510.*

One Size Does Not Fit All

Important factors to consider when selecting premium IOL technologies for patients with glaucoma



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The micro-invasive glaucoma surgery (MIGS) revolution has ushered in completely new thought processes about glaucoma management. Many of the new MIGS options are performed at the time of cataract surgery. Given that they can be performed ab-interno through the same temporal clear corneal incision as the phacoemulsification, there is little change in surgically induced astigmatism, resulting in predictable and consistent refractive outcomes in most cases.

Although newer, advanced intraocular lens (IOL) technologies can come with known risks including glare, haloes, or loss of contrast sensitivity, mild to moderate glaucoma patients with the well-controlled disease need not automatically be dismissed when it comes to so-called premium IOLs.

What are the main IOLs?

Toric IOLs can be considered in patients with reasonable visual potential regardless of severity or type of underlying eye pathology. Toric IOLs help maximize visual acuity and avoid distortions or asthenopia common with spectacle-based astigmatism correction, without the additional risk of glare, halo, or reduced contrast sensitivity. On the other hand, the multifocal IOLs today use diffractive optics to create multiple focal points on the retina, meaning that less total light is needed to create a single image. Most importantly, the rings used to create the diffractive optics come with a warning of post-operative glare or halos, which patients with severe glaucoma may be more prone to having.

Extended depth of focus IOLs (EDOF) also uses diffractive technology to elongate the primary focal point. This technology also comes with limitations: elongating the focal point also means less total light is dedicated to a single crisp image. EDOF lenses can carry warnings of a post-operative loss of contrast sensitivity. Still, it is often well tolerated by glaucoma patients without significant visual field defect or loss of foveal sensitivity.

How to match glaucoma patients to the right IOL

With increasingly earlier diagnoses at earlier ages, a number of minimally invasive options to keep IOP under control, and an increased number of patients who value the quality of life, glaucoma patients deserve to be informed of the advanced technology IOL options that are available to them – with careful consideration of the risks and benefits attached. In light of this, we present a list of considerations to help determine what IOL best suits a glaucoma patient's specific needs.

Understanding patient goals

Every patient will have different priorities or goals: for some, complete freedom from glasses is their only priority; others may want to reduce their dependence on spectacles but wish to minimize the risk of glares, haloes, or loss of contrast sensitivity. These different requirements call for different treatment options. To achieve the former reliably and practically, the use of multifocal IOLs or a blended vision approach would be the best option. For the latter, the EDOF selection would provide a good balance between the range of vision and the reduced multifocal-related risks.

Additionally, it is important to ensure that patients understand the difference between "spectacle freedom" and "spectacle independence." It might be beneficial to discuss that the "spectacle independence" of the EDOF IOLs should provide a better "range of vision" compared with monofocal or their current experience with presbyopia, typically achieving an uncorrected vision for computer and dashboard distance.

What is most bothersome to the patient?

Similar to goals, it is important to understand what symptoms of cataracts are bothering the patient the most. A cortical cataract patient experiencing significant glare and halos at night preoperatively would likely not be pleased should they experience postoperative glare and halos after a multifocal IOL. Similarly, those with color desaturation or contrast loss may be disappointed by the results, especially at night, of an EDOF IOL. Alternatively, any patient with mild to moderate myopia or early presbyopia with sufficient near vision may be disappointed when only distance vision is achieved, even when sufficiently consulted.

Glaucoma severity and progression

Those with mild or pre-perimetric glaucoma would benefit from multifocal or EDOF IOLs to a much greater

IOL	Patient Goals	Glaucoma Severity	Type of Surgery	Type of Glaucoma	Other Eye Diseases	Worst Cataract Symptoms	CW Cord
Multifocal EDOF Monofocal	Spectacle Free	Mild	MIGS	POAG	NPDR	Blurry Vision	0.0 mm – 0.4 mm
EDOF Monofocal	Spectacle independence ("range of vision")	Moderate	MIGS	PACG	Dry AMD	Glare, Haloes, Blurry Vision	0.0 mm – 0.6 mm
Monofocal	Better vision	Severe	Tubes, Filtering	PXF, Traumatic	Wet AMD, PDR, BRVO	Glare, Haloes, Color, Contrast	> 0.6 mm
Toric IOLs	ANY	ANY	ANY	ANY	ANY	ANY	< 0.7

Table 1.

degree than those with a small inferotemporal island that might not align with the refractive elements of the lens. Additionally, glaucoma that is so severe that vision now appears dim may not experience the same brightness or contrast sensitivity with an EDOF or multifocal compared with a monofocal. Similar to glaucoma severity, glaucoma progression must also be considered. A glaucoma progression analysis spanning 10 years with minimal change is much more reassuring for premium IOLs than a patient whose IOP is not well controlled on maximum medication with the risk of further surgery in the future.

Type of surgery

The type of surgery performed at the time of the cataract extraction may also factor into IOL choice. The majority of angle-based MIGS recovery and refractive outcomes are nearly identical to cataract surgery alone. Different types of glaucoma often inform the anatomy of the eye. For example, those with pseudoexfoliation or traumatic glaucoma may have areas of zonular weakness that could increase the risk of complications during the cataract extraction as well as postoperative decentration or postoperative tilt. To a greater degree than monofocals, premium IOLs are reliant on proper centration of the eye's optical system for maximal effect of the diffractive elements. If this cannot be reasonably guaranteed due to underlying pathology, monofocal choices are likely safer – but this must be decided in conversation with the patients.

Retinal disease and IOLs

There is limited evidence that patients with retinal disease should be discouraged from multifocal IOLs. Although patients who have mild eye diseases, including age-related macular degeneration, would likely benefit from an EDOF IOL, the same cannot be said for any patients suffering from subfoveal or active macular pathology. Instead of benefiting their vision, the premium IOLs could hinder vision further by the parsing of available light. Patients with high axial myopia may have an increased risk of TORIC IOL rotation in the immediate postoperative period. Use of capsular tension ring, ensuring complete removal of viscoelastic from behind the IOL, avoidance of overinflation of the eye at the conclusion of the case, activity precaution on the day of surgery, as well as discussion of possibly needing an IOL rotation procedure would be prudent.

Lens exchanges

The final thing to consider is that surgeons offering multifocal, EDOF, or even toric IOLs should be comfortable with lens exchanges and have the ability to offer refractive laser enhancement at no additional cost.

On balance…

Although it may be safer to avoid implanting premium IOLs in all patients with glaucoma, this may significantly hinder the opportunity to gain spectacle freedom and increased quality of life gained by premium IOLs in stable, mild to moderate glaucoma patients. Some of the happiest and most grateful glaucoma patients are those who underwent a successful MIGS combined with premium IOL. As long as both the surgeon and the patient understand the risks, benefits, and alternatives to specific treatment options, it is important that glaucoma patients are offered the same opportunities for spectacle freedom and independence as any other cataract patients.

Matthew Hirabyashi, Resident at the University of Missouri–Columbia

Jella An, Vice Chair for the Wilmer Eye Care Network at the Wilmer Eye Institute, Baltimore

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The Long View on Presbyopia

Marguerite B. McDonald considers the unmet needs in presbyopia correction – and the new topical agents that may be able to address them

Over the course of my career, I have been fortunate to witness and contribute to innovative developments in presbyopia correction, including laser refractive surgery, corneal procedures like conductive keratoplasty, and corneal onlays and inlays that have offered millions of patients the gift of spectacle independence.

What has been missing all along is a safe, effective, reversible, and noninvasive solution for the middle years – from approximately age 40 to whenever patients are ready for lens surgery. The onset of presbyopia in one's 40s is the first real sign of aging for many people. It is a particularly unwelcome shock for emmetropes and successful contact lens wearers, who suddenly find themselves wearing glasses for the first time.

In an ongoing quest to help patients in this age group, I was an early prescriber of pilocarpine 1.25% drops (Vuity, Allergan/AbbVie) and continue to offer them to patients. Although some clinicians have not been actively offering Vuity, I take the long view. It is the first entrant to the market in an entirely new category. Just as with Restasis and Crystalens – the first in their own categories of dry eye therapies and premium IOLs – we have had to learn important lessons about miotic drops for presbyopia after launch. Additional entrants to the market – the second and third waves

Marguerite B. McDonald

of innovation – will have the benefit of those lessons learned and will hopefully continue to advance the science to better serve patients.

Here are some of the still unmet needs in topical presbyopia correction that new agents may be able to address.

1. Minimize the number of drops

Certainly, a drop that lasts all day without re-instillation is desirable. I'm excited about the potential for Brimochol PF (Visus Therapeutics), a presbyopia-correcting drop containing carbachol and brimonidine, which together provide the duration of effect that may better meet patient needs. We could also see the introduction of a topical formulation that isn't a drop at all: Eyenovia's Optejet technology, which delivers a fine mist to the eyes, could alleviate the concerns of patients who don't like using drops. The delivery technology is being tested with once-daily pilocarpine 2% (NCT05114486). I am interested to see whether a spray is effective and whether it can be delivered without smearing makeup.

2. Increase the responder rate

Manufacturers can secure approval of their presbyopia-correcting drops by demonstrating a statistically significant difference in the number of responders (people who achieve a three-line gain in near vision without losing distance vision) between the study drug and the control group. Presbyopia-correcting drops with a higher and longer responder rate are needed for doctors to feel more confident in routinely prescribing them.

3. Reduce symptoms

I think we'd all prefer to have a drop that doesn't cause headaches, brow ache, stinging/burning, or a sensation of dimness. However, brow ache as a symptom is also telling us that the ciliary body is stimulated by the drug, and that can have consequences for the retina. Phentolamine, the active ingredient in Nyxol (Ocuphire), blocks pupillary dilation, so it may be safer for high myopes – or former high myopes who have had LASIK already – to use without risking a retinal detachment (RD). The downside of phentolamine is that the drug causes significant redness for a few hours. Ocuphire is testing Nyxol with and without a low-dose pilo "booster" that would be used the next morning. We need to see additional study data to know whether the disadvantage of a two-step drug regimen will be offset by greater safety.

Although often positioned as a "tolerability issue," the symptom of redness is problematic because it conflicts with one of the reasons people are interested in a presbyopia-correcting drop in the first place. Pilocarpine has a direct effect on muscarinic receptors, providing a vasodilator effect that contributes to redness. Brimonidine, the second drug in Brimochol PF, is a sympatholytic alpha-2 agonist that whitens eyes, so it may have an advantage in addressing this common cosmetic issue with topical presbyopia drops. Brimonidine also has the advantage of preventing pupillary dilation and, by altering aqueous dynamics, increases the bioavailability of carbachol, thereby extending the duration of its pinhole effect.

Another contributor to redness and to stinging/burning symptoms is the low pH of some drops relative to the physiologic pH of human tears. In storage, pilocarpine is stable at a pH of 4.5 – far lower than the pH of tears (7.4). An incompatible pH can make drops uncomfortable, induce tearing, and reduce corneal permeability and bioavailability as well. The manufacturers of Vuity went to great lengths to ensure that, although their drop contains pilocarpine, it reaches a tolerable pH of 6.5 within a minute or two as the drop un-ionizes. Aceclidine also requires an acidic pH for stability, and initial phase II results with topical aceclidine (NCT03201562) showed that 35–39 percent of patients experienced mild to moderate instillation site pain. Headache has also been reported with aceclidine despite some evidence there may be some degree of pupil selectivity demonstrated in iris and ciliary body explants (2).

4. Turn back the clock on the lens

Best of all would be a way to treat the lens that reverses the protein misfolding and aggregation that causes presbyopia in midlife and eventually cataract in later years. Novartis evaluated UNR844, a lipoic acid choline ester that was reported to reduce disulfide bonds in the lens proteins to restore elasticity, but discontinued the program after poor phase II clinical trial results. Visus Therapeutics also has an interesting small molecule in early-stage development with the goal of preventing and reversing cataract and presbyopia. In preclinical studies, an α-crystallin inhibitor compound has been shown to restore the natural chaperone activity of native lenticular α-crystallins, restore lens elasticity, and reverse lens opacity in human lens explants (3).

The areas above are the four major items on my personal wish list for the next couple generations of presbyopia-correcting drops and disease-modifying agents to better serve our patients. I believe that we will see new products coming soon that address at least some of these unmet needs.

Pharmaceutical companies don't bear all the responsibility for improving outcomes with topical presbyopia drops. We as clinicians have also learned that patient education and patient selection are absolutely critical. We have to describe potential side effects and tell patients what to look for, when to return for a potentially serious complication, and how long to expect minor side effects to last.

For my patients who are appropriately counseled and highly motivated, Vuity has been quite successful. Patients love the reversibility and ease of a topical presbyopia solution. As science marches on, I believe this decade will be a watershed moment for the treatment of presbyopia.

See references online at: top.txp.to/presbyopia

The Role We Play

How the power of mentorship extends far beyond the individual, through the community, and into the future

By Dagny Zhu, Medical Director and Partner at NUVISION Eye Center, California, and Power List Rising Star

Mentorship is a key component in the professionalism, excellence, and constant improvement of our field. Whether through official mentorship programs and fellowships or unofficial mentorships and electives, good mentors demonstrate and cultivate the skills and qualities needed for their mentees to thrive, while ensuring these skills are transferred and built upon – across generations. Reading these words, you are likely picturing the people who had – and continue to have – a formative impact on you and your development, speaking volumes about the power of mentorship and having good role models in one's life. Throughout my career to date, I have had the privilege of standing on the shoulders of many in our field – individuals who have demonstrated the difference we can make by offering up our shoulders as platforms for the next generation.

Like many, my first role model existed way before I decided to pursue ophthalmology. At the age of three, my mother and I immigrated to the US from Shanghai, China, along with my father. Unfortunately, my parents divorced when I was very young, and my mother raised me as a single mom, working tirelessly to provide for the two of us. She waitressed seven days a week, alongside attending night school on weekdays to study English. Her work ethic made a long-lasting impression on me, as did experiencing firsthand the benefits one experiences when somebody works in service of another. This served as an inspiration for me, motivating me to work hard, concentrate on my studies, and pursue a career as a physician so that I could give back to my mother, and also positively impact those around me. My mother has continued to inspire and motivate me as I have progressed through my career. She is the first of an ever-growing group of role models I aspire to emulate.

For the many and the few

Mentorship can benefit everybody, but can be particularly beneficial for those within minority groups – something I can personally attest to. Gender inequity in ophthalmology is well documented in the form of pay gaps and disparities in grant amounts, authorship, and leadership positions. Although our field is doing many wonderful things to reach gender equity and make it easier for women to become ophthalmic surgeons, increasing the number of women in leadership roles and boosting the number of female mentors are important in achieving this goal. Especially in a male-dominated field like refractive surgery, I struggled to find women mentors in my first few years of practice to emulate. In fact, at one of my very first job interviews, I was awkwardly asked by the senior surgeon when I was planning to have children. Learning from (and building a professional relationship with) someone who has been through similar struggles and has already navigated further through the field can help mentees overcome many hurdles – especially those shared. Knowledge is power and, when shared and applied from generation to generation, can lead to significant change and the breaking down of walls – and glass ceilings.

One example highlighting the multigenerational impact of mentorship is that of Marguerite McDonald. A pioneer of refractive surgery, McDonald served as the first female president of ASCRS and was the first surgeon to perform laser excimer treatment, really paving the way for women in ophthalmology and acting as a role model and mentor to many entering into the field. Several of McDonald's mentees, having themselves broken down further barriers and become established in the field, have paid forward the gift of mentorship to those in the next generation of ophthalmologists – including myself. As one link in this chain of mentorship, I am incredibly grateful to all the women in ophthalmology today, especially those in leadership positions. They give me something to aspire to, and show me that, yes, my goals are achievable – more so now than ever; I can't even imagine the obstacles they had to overcome back in the day, when it was even more of a male-dominated field. Their passion, intelligence, and drive keep pushing me forward, and make me want to do better for our field.

Modern mentorship

As time has progressed, the methods available to us for advancing our careers, networking, and finding role models and mentors have expanded. As a mentor, there are a couple of new platforms that I use alongside the traditional methods to help upcoming generations of ophthalmologists. "Mend the Gap" is a Healio podcast that I co-host with

Cathleen McCabe, Susan Macdonald, Laura Enyedi, and Laura Periman (some of my current mentors), in which we explore gender disparities in healthcare and seek to move the needle towards equity. These women, along with so many other female leaders including Sheri Rowen, Neda Shamie, and Audrey Talley Rostov, set the example for how I want to carry myself throughout my career—with beauty, intelligence, humility, and respect.

Through "Mend the Gap," we reach a wide-ranging and engaged audience, and offer a platform for the giants in our field to share their knowledge, expertise, and experiences. Of course, women could never have gotten as far as we have without men who lifted us up along the way, so one of our first episodes was dedicated to "Men who Champion Women," featuring ophthalmic pioneers including Thomas Oetting, David Chang, Randall Olson, and William Trattler. Bill, in particular, opened so many doors for me and has been an incredibly kind and generous role model to the next generation of young eye surgeons. Although a podcast cannot provide the personal, one-to-one aspect of mentorship, it absolutely can provide an opportunity for women entering the medical field to hear from people who look like them on the issues that affect us all. Naturally, some of the topics that we cover on the podcast are difficult – recently we covered how women can better advocate for themselves in job contract negotiations, as well as sexual harassment discrimination within ophthalmology – but they are crucial to discuss. We want to equip women in ophthalmology – and medicine as a whole – with the information, advice, and knowledge gathered by their predecessors to help them navigate difficult scenarios, if they should ever arise.

Social media is another tool I have harnessed in my mentorship of others. With a social media following of over 100,000 across platforms, I have thousands of premedical students, medical students, and residents following my journey whom I am privileged to help guide along their own paths. When I was in training, I was under the impression that once I left academia, there would be no way for me to work with students and residents. However, in reality, I have learned that you absolutely can still do this – especially if it is a passion and you make it a priority. In fact, I continue to conduct many of my research projects with students and trainees who found me on social media.

By joining the lineage of ophthalmic mentorship, we are reinvesting what we have gained from those who came before us into those coming after. I am grateful that I've been able to give back by using social media as a tool to mentor the next generation, and I look forward to continuing to take more of them under my wing. It is my belief that as you and I continue to do this, we are not just benefiting the individual (who themselves will hopefully pay it forward), or even the field of ophthalmology as it currently stands, but the future generations of eye care professionals (and patients) to come.

A Vision for the Future

Sitting Down With… Sascha Fauser,
Global Head of Ophthalmology, Pharma Research and Early Development (pRED) Vice President, Roche

Tell us a bit about yourself and your career to date – was there a particular moment you decided to specialize in ophthalmology?

My current role is in research and development, but my background is as a practicing ophthalmologist. I spent over 16 years in the clinic seeing patients, specializing in medical and surgical retina. I also hold a position as Professor of Ophthalmology at the University of Cologne, Germany.

I can't really say there was ever an exact moment I decided to pursue ophthalmology; for me, it was more about naturally following my interests. In medical school, one of my earliest passions was exploring the molecular and genetic causes of disease, and, at that time, ophthalmology was really leading the way for the discovery of many monogenetic diseases. So, I suppose I came into ophthalmology via molecular genetics, and I have never regretted it.

What led you to make the move from the clinic to working in research and development?

Similar to my entry into ophthalmology, moving from the clinic to research and development definitely felt like a natural progression. Throughout my time as a practicing retinal surgeon, I was also active in research – this led to my being recruited as the lead of the dedicated ophthalmology pharma research and early development (pRED) group at Roche.

It is a change I have embraced; I get the chance to work with colleagues from many different areas, including fellow clinicians, academic partners, computer scientists, and manufacturing experts. Ultimately, it is a real privilege to work in a space with the resources, the connections, and the patience required to deliver the next generation of treatments that could improve the lives of millions of people.

What do you think is the next big "frontier" in the treatment of retinal vascular diseases?

There are two main components to this. First, the delivery of the next big breakthrough in retinal disease treatment. Around 15 years ago, vascular endothelial growth factor-A (VEGF-A) inhibitors revolutionized eye care by offering an effective way to treat certain retinal diseases, but we now understand more about the potential limits of this approach. For instance, not everyone achieves a good outcome with anti-VEGFs. It is plausible that these complex diseases cannot be treated by targeting only one cytokine. Additionally, we're pushing up against an "efficacy ceiling" with anti-VEGF treatments. This is something the team I work with is laser-focused on: how can we break this status quo? It's a significant challenge, and one Roche is tackling from multiple angles. As a community, I believe we are making great strides, and I'm optimistic that the next big breakthrough is on the horizon.

Secondly, it's going to be critical to move beyond control of disease and towards more preventative and even regenerative treatment approaches. We all know our population is aging, and with that, we expect to see significant increases in retinal diseases. We're not there yet, but the science and the technology are definitely maturing, and so my belief is that we will be able to shift from treating vision loss towards reversing, and even curing it, in the not-too-distant future.

How can combination therapies improve the standard of care?

Combination therapies are exciting as they have the potential to address the mechanisms driving retinal disease from multiple angles at once, with several potential benefits. First and foremost, the potential vision outcome improvements for patients. It may be the key to surpassing the efficacy ceiling of anti-VEGF treatments. Additionally, combination therapies have the potential to reduce treatment burden by using lower doses of complementary therapies rather than relying on escalating doses of monotherapy. In the future, if we can successfully develop several combination therapies targeted to different retinal disease pathways, it would offer flexibility to tailor the treatment approach to individual patients. This approach would ensure we are really delivering the best vision outcomes on a case-by-case basis. It is a rapidly advancing area, and I am looking forward to seeing how it delivers over the coming years.

Which pathways do you think are good candidates for new treatments?

That is the big question! Currently, there is a great deal of excitement about targeting inflammatory processes, which contribute to the development and progression of various retinal conditions. There has been a lot of buzz around this as a potential treatment target on the conference circuit this year, and it's certainly something the Roche pRED team and I are actively working on.

Beyond this, we know that, for some individuals who don't respond so well to anti-VEGF therapy, additional factors can limit the vision gains they are able to achieve. It seems logical that the mechanisms underlying these processes will also be good candidates for future targeted treatment.

Thinking about the next year or so, what new developments are you most excited to see?

I think we're seeing the most progress in retinal diseases at the moment. There are many new technologies – for example, new antibody formats that cover more aspects of disease than ever before, and many exciting diagnostic tools coming through. The key now will be to see how these can best be translated to tangible benefits to patients. I also remain deeply interested in advances in molecular genetics, and I think we're going to see some promising updates about gene therapy candidates for a range of eye conditions.

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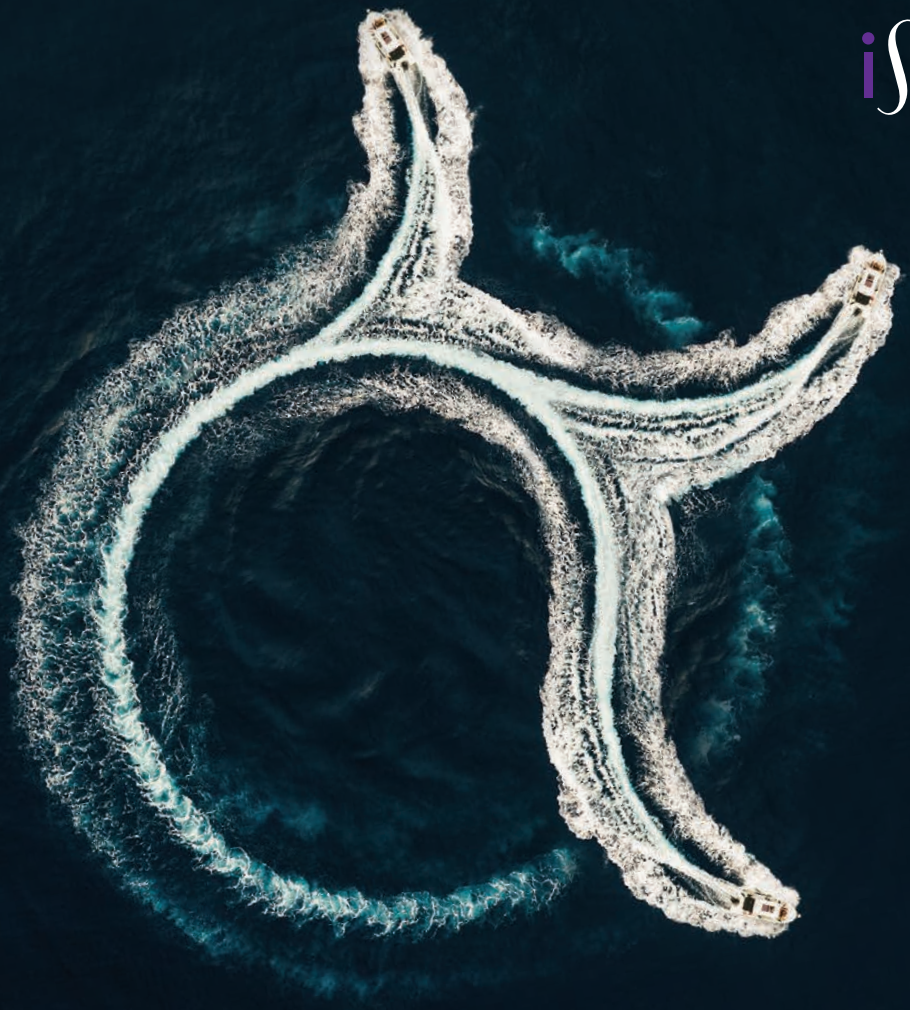

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REFERENCE

1. Sarkisian SR Jr, Grover DS, Gallardo M, et al; iStent infinite Study Group. Effectiveness and safety of iStent infinite trabecular micro-bypass for uncontrolled glaucoma. *J Glaucoma.* 2023;32(1):9-18.

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