September / October 2024
#75

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NORTH AMERICA

For the treatment of all stages of neurotrophic keratitis (NK)

NOT JUST ANY SOLUTION

A RESOLUTION

Complete and long-lasting resolution of NK for most patients*[1-4]

- **Up to 72% of patients** achieved complete corneal healing in clinical trials*†[1-3]
- **80% of these patients** remained healed at 1 year (REPARO trial)*[4]

*Resolution was evaluated in clinical trials as complete corneal healing, defined as the absence of staining in the lesion area and no persistent staining in the rest of the cornea after 8 weeks of treatment and as <0.5-mm lesion staining at 48-week follow-up.[1-3]

†Key study findings were after 8 weeks of treatment, 6 times daily. REPARO (Study NGF0212): 52 patients with Stage 2 or 3 neurotrophic keratitis (NK) in 1 eye per group; 72% (36/50) of patients completely healed; vehicle response rate 33.3% (17/51). Study NGF0214: 24 patients with Stage 2 or 3 NK in 1 or both eyes per group; 65.2% (15/23) completely healed; vehicle response rate 16.7% (4/24). Last post-baseline observation carried forward; chi-squared test. Patients without any post-baseline measurements were excluded from the analysis.[1-3]

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

Important Safety Information

WARNINGS AND PRECAUTIONS

Use with Contact Lens

Contact lenses should be removed before applying OXERVATE because the presence of a contact lens (either therapeutic or corrective) could theoretically limit the distribution of cenegermin-bkbj onto the area of the corneal lesion. Lenses may be reinserted 15 minutes after administration.

Eye Discomfort

OXERVATE may cause mild to moderate eye discomfort such as eye pain during treatment. The patient should be advised to contact their doctor if a more serious eye reaction occurs.

ADVERSE REACTIONS

In clinical trials, the most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Eye pain may arise as corneal healing occurs. Other adverse reactions occurring in 1% to 10% of OXERVATE patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, photophobia, tearing, and headache.

USE IN SPECIFIC POPULATIONS

Pregnancy

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

Lactation

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

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in pediatric patients 2 years of age and older is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in children.

INDICATION

OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

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

To report ADVERSE REACTIONS, contact Dompé U.S. Inc. at 1-833-366-7387 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

References: 1. OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) [US package insert]. Boston, MA; Dompé U.S. Inc.; 2023. **2.** Bonini S, et al. *Ophthalmology*. 2018;125:1332-1343. **3.** Pflugfelder SC, et al. *Ophthalmology*. 2020;127:14-26. **4.** Data on File. Clinical Study Report (NGF0212). Dompé U.S. Inc., 2016.

See more clinical data
OXERVATE.com/hcp

Dompé

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

Brief Summary of full Prescribing Information

Consult the full Prescribing Information for complete product information, available at www.oxervate.com/prescribing-information.

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

General Dosing Information

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

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

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

Recommended Dosage and Dose Administration

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

WARNINGS AND PRECAUTIONS

Use with Contact Lens

Contact lenses should be removed before applying OXERVATE because the presence of a contact lens (either therapeutic or corrective) could theoretically limit the distribution of cenegermin-bkbj onto the area of the corneal lesion. Lenses may be reinserted 15 minutes after administration.

Eye Discomfort

OXERVATE may cause mild to moderate eye discomfort such as eye pain during treatment. The patient should be advised to contact their doctor if a more serious eye reaction occurs.

ADVERSE REACTIONS

Clinical Trials Experience

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

In two clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95). The majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Eye pain may arise as corneal healing occurs.

Other adverse reactions occurring in 1% to 10% of OXERVATE patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, photophobia, tearing, and headache.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of OXERVATE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye disorders: eye irritation, blepharitis (including eyelid margin crusting and eyelid edema) and corneal neovascularization.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Lactation

Risk Summary

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

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

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

Impairment of fertility

Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD).

In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

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Remembering Sir Harold Ridley

November 2024 marks the 75th anniversary of an invention that went on to revolutionize ophthalmology

The invention of the intraocular lens (IOL) changed ophthalmic practice forever. On November 29, 1949 Sir Harold Ridley performed the first IOL operation on a 45 year-old woman at St Thomas' Hospital, London, disrupting one of the basic tenets of surgery that one should never deliberately put a foreign body into the eye. The lens was designed by Ridley, John Pike of Rayner, and John Holt of ICI, and manufactured by Rayner in Brighton, UK. With this procedure Ridley forced a major rethinking of surgical principles.

Ridley's invention marked the beginning of modern ophthalmic surgery, with the subsequent evolution of the IOL into the safe, and reliable implants we all use today. It also marked the beginning of a major change to improve surgery and paved the way for the era of implantable prosthetic biodevices, which has impacted many medical fields over the last few decades.

At the time, the innovation was unfortunately marred by hostility within the academic establishment in the US and Europe. But by the late 1970s IOLs and implantation procedures had undergone many improvements, and Ridley's invention had become an accepted option for the optical correction of aphakia. Ridley was subsequently accorded due recognition, receiving many awards and honours, including Fellowship of the Royal Society. He was knighted in 1999.

UKISCRS will be marking the 75th anniversary of the first IOL implantation with a celebration conference at the Leonardo Tower Hotel, London on November 28-29, 2024. This special once-in-a-generation conference will feature the Royal College, the Irish College of Ophthalmology, the British & Eire Association of Vitreoretinal Surgeons, and the UK & Eire Glaucoma Society. There will be a presentation of the best new findings in UK IOL research. Also, the current Presidents of ESCRS, APACRS, ASCRS and the International Intraocular Implant Club, which was founded by Sir Harold in 1966, will discuss where cataract surgery needs to progress further and what surgery will look like at the 100th anniversary! It will be a fitting celebration of one of the most influential ophthalmologists of modern times.

Paul Ursell
President, UKISCRS; Consultant Ophthalmic Surgeon, Epsom & St Helier NHS Trust, UK.

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POAG Preferences

Survey finds that younger ophthalmologists prefer laser trabeculoplasty over topical medication for first-line POAG treatment

Credit: AdobeStock.com

As the glaucoma landscape shifts, with more efficacious and safe treatments becoming more widely available to the general public, it seems reasonable that practitioner's preferred methods will align with this wider range of options. To this end, the Journal of Glaucoma compiled a 33-question study to survey ophthalmologists' first-line treatment choices for glaucoma, specifically primary open-angle glaucoma (POAG).

The survey was distributed across an American Society of Cataract and Refractive Surgery (ASCRS) database, and included questions on the practitioner's country of practice, length of time in the field, glaucoma fellowship training details, and primary treatment preferences for POAG patients (e.g., topical medication versus laser trabeculoplasty or intracameral sustained release implants).

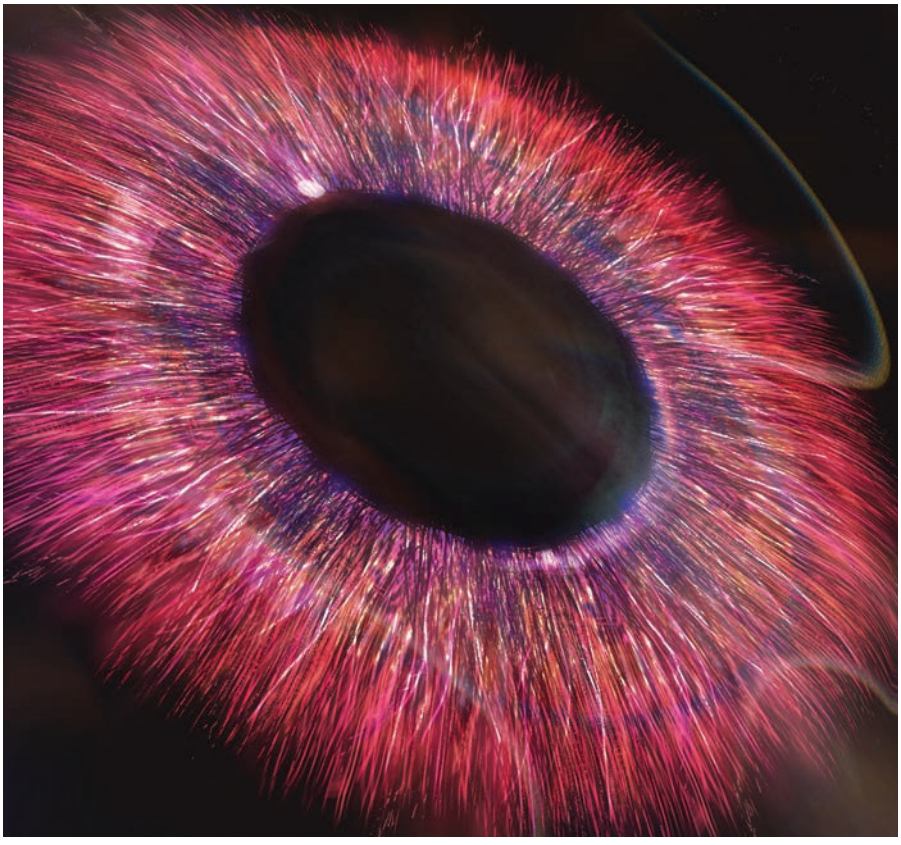
Of the 19,246 surveys sent to respondents in 2021, 252 (1.3 percent) were completed and returned. The study revealed that 73.6 percent of the respondents preferred to use topical medication for first-line POAG treatment, as opposed to 26.4 percent who preferred laser treatment as their starting point. "Given that the survey was performed in 2021, I was both heartened and a little surprised that 26 percent of respondents were already offering SLT [selective retina therapy] as first-line treatment," says Douglas Rhee, the study's lead author and Chair of the Department of Ophthalmology and Visual Sciences, Case Western Reserve University School of Medicine.

The research team also observed that a majority of respondents from both sets preferred to use a trabecular meshwork bypass stent in cases where POAG was moderate and there was a visually significant cataract. Although they are not certain about why this method is preferred, the authors speculate that "it is likely reflective of a shift in preferred practice and community standards based on the relative safety and efficacy of this combined approach."

The authors believe the study results highlight a continuing unmet need for education on evidence-based treatment results for POAG. It is "a snapshot of the community standard," says Rhee. "For those offering SLT first, you can be reassured that you are not alone aside from being supported by a very high quality of science amassed over two decades." Individual patient factors will determine what is best for an individual patient, Rhee adds, "but based on the clinical science and the available treatments in 2024, I believe that SLT first should be the new community standard."

Reference

1. *DJ Rhee et al., "Primary Practice Patterns for the Initial Management of Open Angle Glaucoma," Journal of Glaucoma, 33, 671 (2024). PMID: 38874528.*



Galaxy Eye

"This digital painting was created to honor my experience with the expansive, beautiful field of ophthalmology."

Credit: Allison Kufta, medical student, University of Illinois College of Medicine at Chicago

QUOTE *of the month*

"Change and innovation are constants in the field of medicine, and ophthalmologists must embrace these changes, incorporating new technologies and techniques into their practice."

Ivo Ferreira, Co-Founder and CEO of Oftalmo University

3D Printed Intraocular Lenses

Proof-of-concept study showcases stereolithographic rapid prototyping of IOL-like designs

UK researchers have introduced a 3D printing system (1) that could improve the manufacture of intraocular lenses (IOLs) for cataract and refractive surgeries worldwide.

"Though current IOLs are of high quality and effective in restoring vision, each eye is unique in its anatomical structure and biometric measurements," says Aram Saeed, study author and Associate Professor of Healthcare Technologies at the University of East Anglia. "3D printing can significantly enhance the traditional manufacturing process for IOLs by enabling greater customization and complexity in design."

The University of East Anglia system could also enable multiple lens designs to be printed simultaneously on one printer; in the future, this process could even be combined with advanced imaging technologies to produce lenses that fit patients' eyes optimally, reducing the need for adjustments or complications after surgery.

PMID: 38762982.

The Future-Ready Surgeon

How ophthalmologists can master tomorrow's techniques and redefine excellence in their profession

Contemporary ophthalmologists must not only master their surgical skills, they must also embrace a dynamic approach to learning and skill development – an approach that prioritizes continuous improvement, adaptability, and holistic well-being. To achieve this level of expertise, surgeons need to engage in deliberate practice, receive constant feedback, and maintain a high level of performance – all while balancing their personal lives to avoid burnout and stress.

The importance of being trainable

A critical aspect of elite performers – whether in sports, arts, or medicine – is their ability to be trainable. They should thrive on learning from excellent mentors and coaches across various disciplines. Unfortunately, this culture of continuous mentorship and cross-disciplinary learning is often missing in the surgical field. To bridge this gap, we must focus on two key strategies: simulation training and active learning.

Simulation training

Simulation training is the most efficient way for adult learners to acquire and refine skills. It allows for the repetition of tasks, objective feedback, and contextual interference, which helps surgeons to simulate various clinical scenarios, and to make decisions, solve problems and think independently based on whatever scenario they encounter. Regardless of their level of expertise, surgeons can benefit from simulation training by:

1. **Enhancing psychomotor skills**. Fine motor skills, synchronization with two pedals, viewing in 3D through a microscope, and other microsurgical skills.
2. **Developing cognitive skills**. Understanding surgical principles, decision-making and problem-solving, as well as situational awareness.
3. **Cultivating mental skills**. Often overlooked, mental skills include maintaining a steady focus, achieving a "state of flow," building confidence during challenging situations, and managing one's emotions effectively.

Active learning

Active learning can be incorporated into simulated environments through various methods, each tailored to enhance surgical training:

1. **Deliberate practice.** Focused, repetitive practice of specific skills until they are mastered.
2. **Feedback loops**. Continuous objective feedback on performance to guide improvement.
3. **Scenario-based training.** Simulating real-life surgical scenarios to develop decision-making and problem-solving skills.
4. **Team-based learning**. Collaborative exercises that mimic operating room dynamics, improving communication and teamwork.
5. **Reflective practice**. Encouraging self-assessment and reflection on performance to identify key areas for improvement.

Achieving excellence: A holistic approach

To become a modern, future-ready surgeon, one must adopt a comprehensive training approach that includes controlled rest periods, a balanced diet, and mentorship for both emotional control and work-life balance. This holistic approach ensures that surgeons are not only technically proficient, but also that they are mentally resilient and capable of maintaining their emotional well-being.

The role of mentors and coaches

Mentorship and coaching play crucial roles in the development of an ophthalmologist. The best surgeons in the world often have access to a variety of mentors who provide guidance, support, and insights from different perspectives. In ophthalmology, this culture is not always as prevalent as it should be. Encouraging a mentorship model that includes both regular feedback and guidance from experienced surgeons can significantly enhance the learning curve and skill acquisition of younger surgeons entering the profession.

Embracing change and innovation

As we look towards the future, the role of the ophthalmologist will continue to evolve. Technological advancements, new surgical techniques, and a deeper understanding of human physiology are all contributing to the changing landscape of ophthalmology. The future-ready surgeon must be adaptable, innovative, and open to new ways of thinking and practicing. Change and innovation are constants in the field of medicine, and ophthalmologists must embrace these changes, incorporating new technologies and techniques into their practice. This not only improves patient outcomes, but also keeps the surgeon at the forefront of their field.

Redefining excellence

The future-ready surgeon is one who is always learning, always improving, and always striving for excellence. By redefining excellence in ophthalmology and focusing on holistic training approaches, we can ensure that surgeons are well-prepared to meet the challenges of the future and provide the best possible care for their patients.

Refractive & cataract surgeon Ivo Ferreira is CEO of Oftalmo University, Mexico.

Gene Detectives

How early genetic testing for inherited retinal diseases (IRDs) can empower patients to take proactive control of their eye health

Professor Hanno Bolz, Human Genetics, Bioscientia Institute for Medical Diagnostics GmbH, Ingelheim, Germany

Dr Philipp Herrmann, Inherited Retinal Disease Clinic at the University Eye Hospital Bonn, Germany

Janssen Pharmaceutica NV, a Johnson & Johnson company, has funded the development and publication of this article, including a consultancy fee for Professor Bolz and Dr. Herrmann. The views expressed in the article are those of the authors and publisher, and do not necessarily reflect the views of Janssen Pharmaceutica NV and/or Johnson & Johnson.

Although relatively rare in the general population with a prevalence rate of around 1:1380, inherited retinal diseases (IRDs) still affect approximately 5.5 million people worldwide (1), making them collectively the leading cause of vision loss for individuals aged between 15 and 45 years old (2). For patients with a potential IRD, genetic testing can act as an important tool in helping ophthalmologists identify the genetic basis of a retinal disease, with around 56-76 percent of IRD patients being accurately diagnosed through the use of next-generation sequencing (NGS) which often includes quantitative readout for copy number variant analysis (3, 4). Being able to accurately uncover the cause of vision loss can provide patients with answers that will put them back in control of their eye health, from understanding the cause (genetic vs. non-genetic) potential of disease progression and extent (isolated vs. syndromic) and risks to other family members (mode of inheritance), to determining their eligibility for clinical trials or emerging targeted treatments (5, 6, 7).

However, a current lack of awareness around IRDs often results in delays in diagnosis for these patients. A multinational European survey conducted in 2021 found that the time to genetic diagnosis can vary among countries, from around four weeks to over 10 years in some extreme instances (8). To work towards addressing this issue of prolonged waiting times and delayed diagnostics, it is imperative that eye care specialists work closely together with other specialists, combining their clinical and genetic expertise to help people suspected of an IRD receive testing and diagnoses sooner.

But how can we ensure that more people suspected of having an IRD are tested earlier? And what are the first steps towards achieving an accurate diagnosis?

"From a geneticist's perspective, first of all we have to confirm or rule out whether a disease is indeed a genetic, inherited issue," explains Professor Hanno Bolz, head of Bioscientia Human Genetics, Ingelheim, Germany. "In many cases, a genetic cause is obvious because of the phenotype – retinitis pigmentosa (RP), for example, is a monogenic trait, albeit non-genetic phenocopies do exist (9) – and/or familial occurrence, but a genetic diagnosis always helps to clarify (5) – as soon as we come across a gene mutation, we can be sure that this mutation is the cause of the disease. In contrast, and as in cases of other inherited conditions, a non-genetic cause is much harder or even impossible to prove."

"We could still do better as a whole community to be aware of these huge developments we've seen in the last decade in the field of genetic medicine."
– Dr Philipp Herrmann

One of the most common types of gene therapy within ophthalmology, Bolz adds, is *RPE65* gene (replacement) therapy. Mutations in the *RPE65* gene are responsible for both RP and Leber congenital amaurosis (LCA), a group of genetically diverse congenital retinal dystrophies (10). As is well documented within ophthalmology, LCA is characterized by congenitally severe visual impairment (11). In case of *RPE65*, there is a therapeutic window before photoreceptor cells will undergo degeneration (11), meaning it's crucial for genetic testing to be performed as early as possible. Bolz stresses it is important that, "as soon as the patients receive their diagnosis, they know what gene they should be interested in", going on to recommend organizations like Foundation Fighting Blindness and PRO RETINA, which provide patients with the most up-to-date information on their specific disease, as well as giving patients the ability to upload their data onto its patient registry.

Much like LCA, early genetic detection for all IRDs to ensure early and accurate

Normal Vision

Progressive Vision Loss due to Retinitis Pigmentosa

Normal Vision

Progressive Vision Loss due to Retinitis Pigmentosa

diagnosis is essential. It allows patients greater decision-making in regards to their disease, the ability to better identify appropriate treatment opportunities or clinical studies they may be eligible for, and, ultimately, improve their outcomes (5).

"You're sitting there with the patient and often they've been running around in circles," says Philipp Herrmann, head of the Inherited Retinal Disease Clinic at the University Eye Hospital Bonn, Germany. "At that point, different doctors have looked at their eye and assessed what sort of disease it might be, the patient has good phenotyping, and yet still they have a feeling that they've not got the right diagnosis. So genetic testing is really about closing that chapter, stopping the patient from feeling like they're running in circles and pinpointing the actual gene mutation that is causing the disease. I think this is also a psychologically important step for IRD patients."

This early diagnosis achieved through genetic testing can help to improve the health literacy of the patient, empowering them to make informed decisions as to their future care and treatment (12, 13). This sense of patient empowerment is a finding that has been reported previously in the cases of other rare diseases, and it is this type of empowerment – the sense of autonomy over one's body and healthcare decisions – that has been documented to contribute towards more sustainable healthcare systems across Europe (14).

It should also be noted that genetic testing can be applicable to any age group (5): "For example, if you have a very young patient, there could be hidden extra-ocular symptoms that you only discover through gene testing (7)," notes Bolz. "But then you may also meet adult patients with, say, diabetes – those common conditions that occur alongside vision issues – and still it can be due to a single gene defect (7). We encounter that all the time: Patients who have all kinds of long-term health problems and have been dealing with those issues for decades already, and they have been misdiagnosed or not diagnosed at all, and then you can suddenly clarify that through gene testing. We can sometimes encounter very surprising diagnoses in older people, where we see that their long-term health problems can all be traced back to the same genetic cause. For example, a patient with early retinal degeneration, diabetes, high blood lipids, short stature and developmental delay may be diagnosed with Alström syndrome through the detection of *ALMS1* mutations (15) – and suddenly everything falls into place."

In the case of Germany, where both Bolz and Herrmann are based, Herrmann states that "there are many labs that offer genetic testing – also for eye diseases – and so, because of high-throughput NGS technology, the production of data is no longer bottlenecked." Bolz adds, "In Europe we are very privileged to have access to genetic testing and treatments for everyone through national healthcare systems, more or less independent from insurance status. Taken globally, I think that is a very privileged position to be in."

However, Bolz admits that even with this high level of testing available to the general public, there can still occur situations "where patients have to find out, to some extent on their own, where to go and what they might have." As such, for ophthalmologists "it's very important to communicate all the information about these rare diseases to patients, and to refer any patients suspected of having an IRD to specialist clinics, such as the one in Bonn, where they can get the right diagnostics and treatment."

And Herrmann confirms that while this level of genetic testing is broadly available throughout Germany, this is not necessarily the case for every European country (8): "We're currently working on having this type of access available on the same level throughout Europe. For a large swathe of

the European population it exists to some degree, so that's good. But there is room for improvement on that level, definitely."

Speaking of improvement, advances in molecular diagnostic technologies and therapies – as evidenced in NGS tests and, more recently, in CRISPR development – have resulted in significant improvements in how we understand IRDs, as well as increasing our likelihood of correctly identifying causative variants in individuals with IRDs; NGS is enabling geneticists and clinicians to better diagnose IRDs. These advancements also spotlight the need for increasing awareness of human genetics on a broader scale, as well as how CRISPR therapy – though still in its preclinical stages – could open up future personalized treatment options for patients (5, 16).

This shifting landscape has also brought into focus the need for better training in genetic diagnostics for ophthalmologists. That said, ocular genetics has now been introduced as a subspecialty within the profession, and though at the moment it's mostly confined to academia, this new specialty does seem to be witnessing an upsurge in training programs and fellowships aimed specifically at genetic testing for ophthalmologists (17).

"Overall," Herrmann reflects, "we could still do better as a whole community to be aware of these huge developments we've seen in the last decade in the field of genetic medicine." On this point, Bolz is in agreement with Herrmann: "I think the interaction and cooperation between ophthalmologists and geneticists is very important – to exchange information and knowledge, and to discuss what can be done, in terms of the timely diagnostic implementation of new technologies, and the possibilities they offer." As the first lab worldwide, Bioscientia recently launched diagnostic long-read whole-genome sequencing for sensory disorders such as retinal dystrophies (18), marking a major milestone for diagnosing those tricky cases that can confound even the greatest minds of ophthalmology.

"We need a complete paradigm change," adds Herrmann. "In the last few decades, we have seen this huge evolution in the field of genetic testing (19). But from the patients' perspective, especially if they are a bit older, they come from a period where a doctor would say, 'Well, you have an IRD, you're going to be blind, you don't have to come back.' Sometimes you can see that bleak outlook remains, lingering from the past. Now that we have such innovative technology at our fingertips, this reality has completely changed."

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Access All Areas: *Recognizing Global Education Impact 2024*

We profile six institutions committed to developing access to eye care and ophthalmology education around the world


Robert N. Weinreb

Last year, The Ophthalmologist launched its annual Recognizing Global Educational Impact feature to celebrate those institutions and programs that are leading the way in tackling global health inequality. Now, we add six more entries to this prestigious roll call, from an institution with nearly 200 years of history to a program providing low-cost but versatile devices to low- and middle-income countries.

Although they vary significantly in size and scope, each new entry shares the common goal of making global access to eye care and ophthalmology training more equitable and affordable – drawing new generations from diverse backgrounds into the profession and fostering cutting-edge technologies that bring treatment advancements to some of the world's poorest areas.

University of California San Diego and Shiley Eye Institute

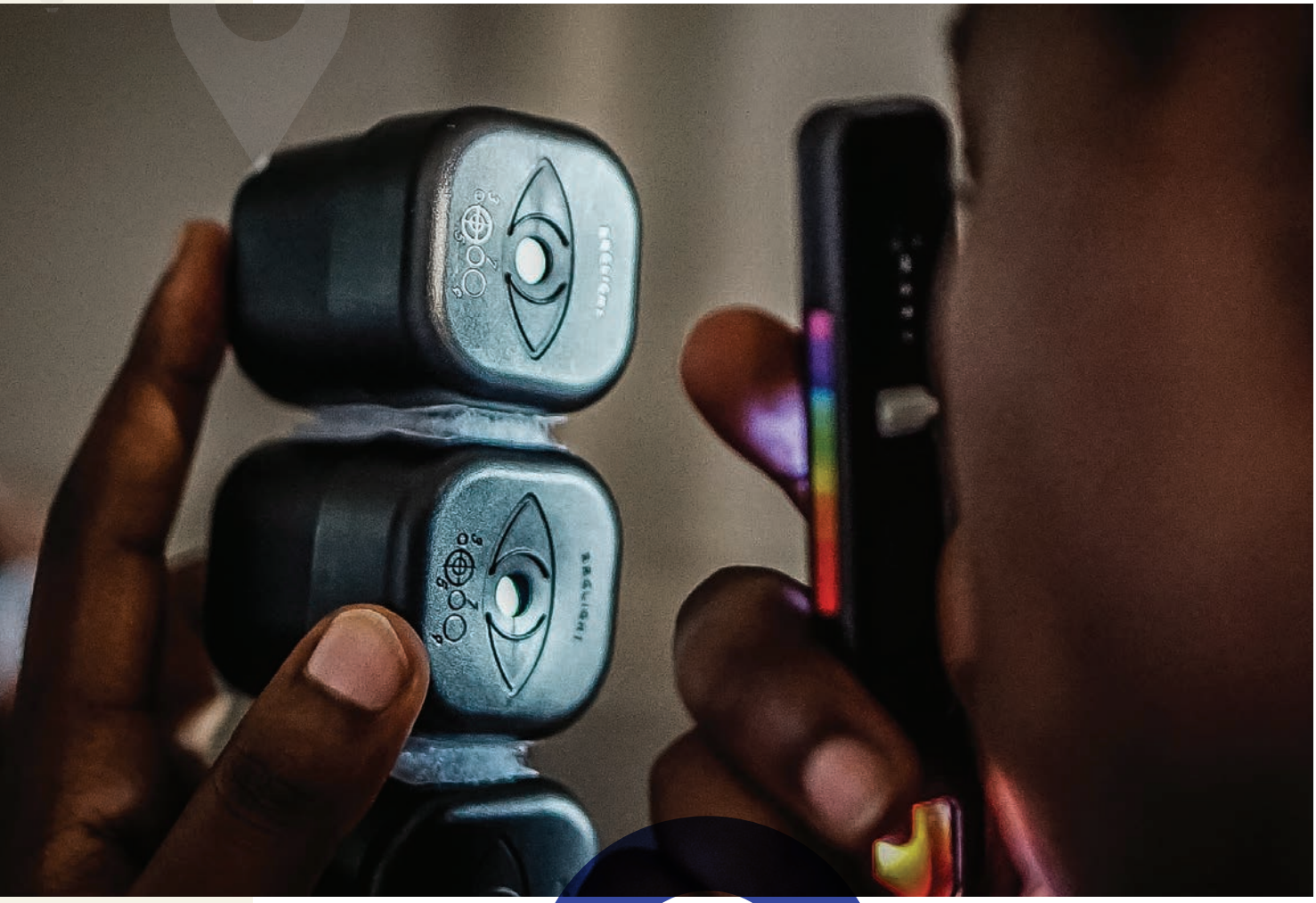
Location: La Jolla, California, USA

The Department of Ophthalmology at the University of California San Diego (UCSD) began its journey in 1983 with a modest, three-room clinic. Today, its Shiley Main Building, New Shiley Wing, Ratner Children's Eye Center, Jacobs Retina Center, and Hamilton Glaucoma Center spans 91,000 square feet. It stands as the only academic institution in the San Diego area with comprehensive programs for the clinical care of patients with eye disorders, advanced research on surgical techniques and treatments of eye diseases, and education in ophthalmology.

The institution has several clinical programs, including the UCSD EyeMobile for Children, which has completed over 225,000 vision screenings in underserved communities at the US-Mexico border region and has provided free comprehensive eye exams and glasses for those in need. Giving student interns the opportunity to assist with providing these services, the program has inspired many of them to pursue careers in ophthalmology.

Trainees mentored by faculty can participate in a free clinic. According to Robert N. Weinreb, Chair and Distinguished Professor of Ophthalmology at the Shiley Eye Institute, "the majority of UCSD medical students who have entered ophthalmology and worked in the Free Clinic cite this experience as a major factor in influencing their specialty decision." Diversity, in this regard, is something the institution holds dearly. "In all UCSD training

Shiley Eye Institute, University of California San Diego



The Arclight is specifically designed for low-resource settings

programs, there is a strong emphasis placed on trainee diversity, including those from populations under-represented in medicine and research, and global reach," Weinreb adds.

The current academic year alone has trainees from a wide range of countries, including Mexico, Saudi Arabia, Poland, Thailand, Lebanon, Malaysia, The Philippines, Ghana, and Nigeria. Many prior trainees now serve as leaders and department chairs across the world.

UCSD has also been selected for a National Institutes of Health (NIH) initiative that supports a year-long training program at the intersection of ophthalmology and artificial intelligence/data science. This pairs trainees with mentors to foster the next generation of ophthalmologists and vision scientists.

https://shileyeye.ucsd.edu/

Arclight Project

Location: University of St. Andrews, UK

The Arclight Project, based at the University of St. Andrews' School of Medicine, is a social enterprise that aims to support health workers in low- and middle-income countries by equipping, training, and empowering them to diagnose and manage eye and ear diseases with confidence. The centerpiece of the project is the Arclight: a compact, all-in-one ophthalmoscope, loupe, and otoscope specifically designed for low-resource settings, and for training or backup purposes.

The Arclight benefits users from students and novice health workers to experienced specialists. It eliminates the need for replacing bulbs or worrying about dead batteries, and

can be attached to a smartphone camera to capture clinical images. The design allows for easy examination of the optic nerve, eardrum, anterior segment of the eye, eyelids, and skin, and possesses LED illumination that ensures accurate diagnoses with minimal infrared and ultraviolet exposure. For ear examinations, users can also insert the speculum to clearly view the ear canal and tympanic membrane.

"The Global Health Team at St. Andrews has played a significant role in its development through research and training, collaborating with eye care NGOs to empower healthcare workers in diagnosing and managing eye and ear diseases," says Karsten Paust, practicing ophthalmologist in Bonn, Germany. "Over 40,000 Arclights have been distributed worldwide with Arclights in use in all six continents – including Antarctica!" The Arclight Project has established training workshops across the globe and collaborated with institutions such as TanZanEye, which teach community level nurses in remote western Tanzania to identify eye disease and refer cataract cases.

Conditions such as diabetic retinopathy and retinopathy of prematurity are becoming increasingly prevalent in low- to middle-income countries, where screening programs are often limited and resources are scarce. Gaining access to traditional medical instruments, in this regard, can be challenging. This is why Arclight is particularly promising: its low-cost, easy-to-use and offers a solar-powered function that doesn't require ongoing consumables. The WHO has even recommended the device in its newborn eye care guidelines and is featured as an International Approved Supplier for the Prevention of Blindness, according to Paust.

The device is sold for profit in high-income countries to subsidize provision and training in those parts of the world where it can have the most impact.

https://medicine.st-andrews.ac.uk/arclight/

John A. Moran Eye Center

Location: University of Utah, Salt Lake City, USA

First envisioned in 1979 as a division of the University of Utah's Department of Surgery by ophthalmologist and cornea specialist, Randall J. Olson – who subsequently constructed the first Moran Eye Center building in 1993, aided by a major donation from University of Utah alumnus and namesake John Moran – the John A. Moran Eye Center has witnessed many extraordinary developments within its walls.


Randall J. Olson

The center created the Moran Global Outreach Division in 1994, which aims to give greater accessibility to eye care and surgical services for underserved populations around the world. To date, the Outreach Division has provided volunteer eye care services in more than 25 countries, training local ophthalmologists and health care workers, as well as providing cataract surgeries and vision screenings specifically in areas where access to quality health care is limited.

Known for its strong emphasis on education and training, the Moran Eye Center offers highly competitive residency and fellowship programs, and is committed to training the next generation of ophthalmic researchers and ophthalmologists. This training also includes reaching out to other educational institutions. "Jeff Pettey – Professor and Clinical Vice-Chair of the Moran Eye Center Department of Ophthalmology and Visual Science – and the Moran Eye Center are leading the US effort in this area," says Thomas Oetting, Clinical Professor of Ophthalmology and Visual Sciences at the Carver College of Medicine, University of Iowa. "They have guided our starting program at the University of Iowa and many other institutions. Dr Pettey started the global ophthalmology conference together with the American Academy of Ophthalmology, which has helped colleagues in this area gather to learn new skills and tricks."

Closer to home, the center's local outreach work focuses primarily on the Salt Lake and Summit counties, as well as on the Navajo Nation – in conjunction with the Utah Navajo Health System – of southern Utah. In this work, the team directs their attention to underrepresented populations of the US healthcare system, such as those experiencing homelessness, those without insurance, and former refugees.

In 2021, the center set up the Alan S. Crandall Center for Glaucoma Innovation. Directed by The Ophthalmologist Power Lister and MIGS powerhouse, Ike Ahmed, the center is focused on leading the way to provide better

Credit: Adobestock.com

diagnostics, more effective and safer therapies, more advanced surgical devices, and a deeper understanding of glaucoma and its genetic complexities. The center pursues four key initiatives to achieve this aim: Glaucoma Therapeutics, Translational Research, Neuroprotection-based Therapies, and Global Care.

Moran's Global Outreach Division is focused on training physicians across Africa. Led by Initiative Director, Craig J. Chaya, the team established a glaucoma fellowship training program in Tanzania in 2023, and are currently training three physicians in the region, as well as hosting Tanzanian medical professionals at their base in Utah and beginning a series of remote surgical mentorship training sessions.

Moran's outreach work in Africa also covers Ghana – where for almost two decades the center has trained surgeons at the Komfo Anokye Teaching Hospital (KATH) in Kumasi – Ethiopia, Kenya, and South Sudan, where the Outreach Division is involved with providing much-needed cataract surgeries.

https://healthcare.utah.edu/moran/

Sankara Nethralaya

Location: Chennai, India

Image supplied by Sankara Nethralaya

A non-profit ophthalmology institute based in Chennai, India, was rated as one of the top specialized hospitals in the world by Newsweek in 2020.

Founded in 1978 by the late Indian ophthalmologist, Sengamedu Srinivasa Badrinath, an elected fellow of the National Academy of Medical Sciences, the institute was intended to provide high-quality and affordable eye care to people from all walks of life.

Sankara Nethralaya is equally focused on the promotion of research and training in ophthalmology – since its inception the center has offered fellowship programs in oculoplasty, glaucoma, cornea, vitreo-retinal surgery, and general ophthalmology to postgraduate students, as well graduate training programs.

"The institution has given the country some of the finest ophthalmologists and has elevated the standard of eye care in the Indian subcontinent by training numerous ophthalmologists and optometrists," says Shikha Bassi, Deputy Director of the Department of Neuro-Ophthalmology at Sankara Nethralaya's headquarters in Chennai.

Since the 1990s the institute has expanded its reach across India, and now has 11 branches located in various regions around the subcontinent.

Sridhar Baratan, who undertook a fellowship at Sankara Nethralaya and then worked for eight years performing high-volume cataract surgeries for the center, says, "I had the privilege of being… part of the pioneering team that conceptualized a Mobile Eye Surgery Unit (MESU), in collaboration with IIT [Indian Institute of Technology] in Madras, and this endeavor has given vision to 500,000 patients – and counting – in multiple states in India."

Established in 2011 by Healthcare Technology Innovation Centre (HTIC) before being passed on to Sankara Nethralaya in 2012, the Mobile Eye Surgical Unit is composed of two surgically-equipped buses – which jointly house a sterilization chamber, an anesthetization area, a patient monitoring area, a surgical instrument packing and cleaning area, and an operating theater – that travel to underserved and remote regions within the states of Tamil Nadu, Andhra Pradesh, and Jharkhand.

The buses – one aimed at surgeon and patient preparation, the other known as the surgical vehicle – can be connected by a retractable vestibule, recreating the type of setup one would ordinarily only see in a tertiary care setting. The MESU offers free, high-quality cataract surgeries (one of the leading causes of blindness in India) in remote villages across these three states, with a diesel generator providing power to all electrical equipment in the units. By March 2020, MESU reported that over 16,000 surgeries have been performed by the unit across more than 12 surgical camps.

https://www.sankaranethralaya.org/

John H. Stroger Jr. Hospital of Cook County

Location: Chicago, Illinois, USA

Based in Chicago, Illinois, the John H. Stroger, Jr. Hospital of Cook County offers a highly regarded Ophthalmology Residency Program to four applicants each year through the San Francisco Matching Program, an initiative aimed at matching ophthalmology residency applicants to training programs. Known for its high patient volume, Cook County's program treats around 50,000 patients every year, performing over 2,300 major ocular surgeries and providing its selected residents with significant exposure to the complex orchestrations of eye surgery.

The four-year program is specifically designed to train residents in becoming skilled comprehensive ophthalmologists and subspecialists, and offers a wide range of ophthalmic subspecialties, including cornea, glaucoma, neuro-ophthalmology, oculoplastics, pediatric ophthalmology, retina/vitreous, and uveitis. "As a resident graduate of this program, I can personally attest to the high surgical volume and the invaluable opportunity to work with cutting-edge technology," says Nadezhda Bolton, a board-certified ophthalmologist now based in Tucson, Arizona. "The mentorship provided by the attending staff extends well beyond graduation, as they continue to support and guide former residents throughout their careers. This enduring commitment to professional development is matched by their active involvement in research and contributions to the broader ophthalmology community."

The hospital also prides itself on its approach towards diversity. As Bolton notes, "The clinic's diverse team of residents and attending staff, who come from various cultural and ethnic backgrounds, enrich the training environment and foster a culture of inclusion and understanding."

"With one of the most diverse populations in the country, we ensure each patient is taken care of in a way that makes them comfortable — [by providing] either doctors who speak their language or access to translators 24/7," says Dagmara Danek, an ophthalmologist at the hospital.

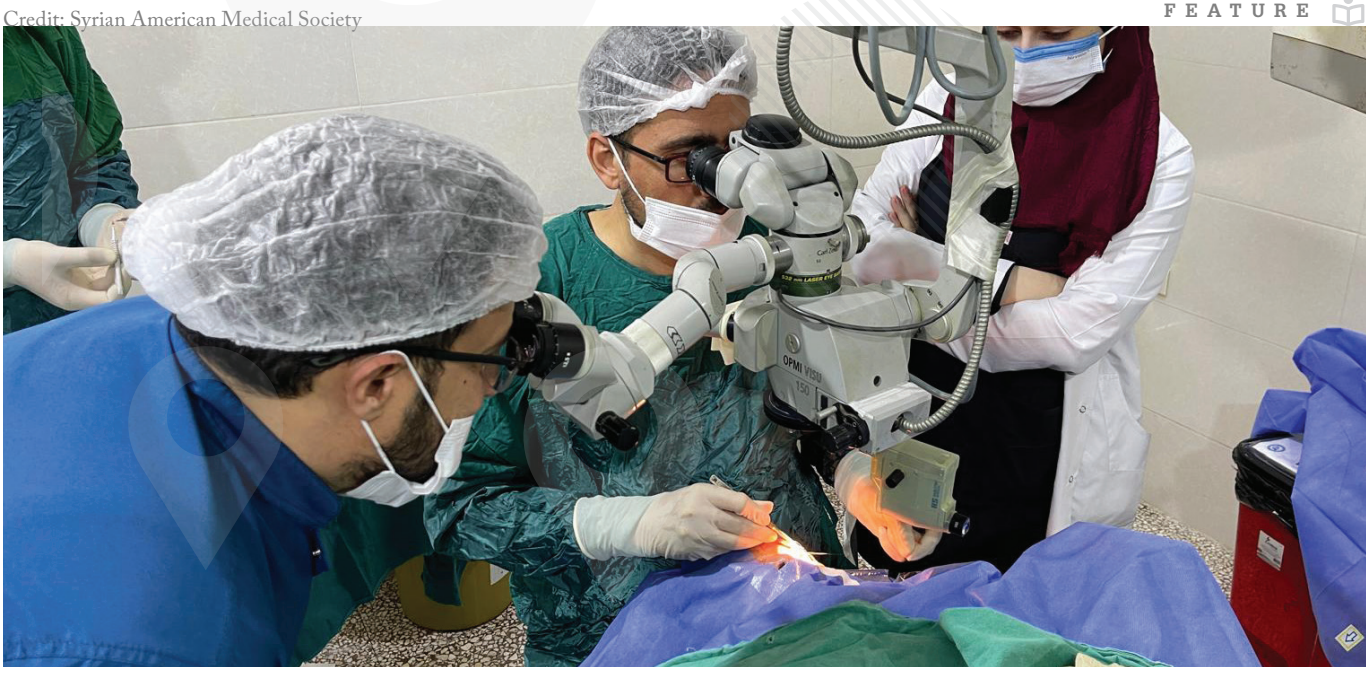
Shweta Chaudhary, another ophthalmologist employed by Cook County, adds: "We take care of patients from all parts of the world with serious ocular illnesses, irrespective of their race, ethnicity, gender, socio-economic status and ability to pay. We train the next generation of Ophthalmologists in house and across the globe, by giving them training in low-resource settings where they learn to manage serious eye conditions medically and surgically with available resources."

The hospital's Innovation and County Education Enrichment (ICEE) Fund is primarily geared towards addressing educational disparities and supporting innovative educational programs across the county. The fund is driven by alumni donations, which are tax-deductible, to ensure residents can continue contributing to advancements in ophthalmology without financial constraints.

Cook County continues to play a significant role in ophthalmology, both domestically and globally. For example, residents – alongside members of other academic medical centers – recently traveled to Guatemala to deliver eye care services to underserved populations in the country.

https://cookcountyhealth.org/locations/john-h-stroger-jr-hospital-of-cook-county/

Credit: Syrian American Medical Society



Syrian American Medical Society

Location: Washington, DC, USA

Founded in 1998 by Syrian and American healthcare professionals, the Syrian American Medical Society (SAMS) is a non-profit organization that was originally intended to provide medical treatment to those affected by the crisis in Syria. Since the outbreak of war in the country in 2011, the organization has shifted its focus to providing humanitarian aid and health care delivery to underprivileged Syrian refugees, internally displaced persons, and any other individuals caught up in zones of conflict and displacement.

Since its creation, the non-partisan society has implemented over ten residency training programs in northern Syria, the region most severely impacted by the war. "Many of these residency programs are managed by local physicians with mentoring and remote supervision from SAMS physician members based in the United States," explains Syrian-born retina specialist, Aref Rifai, who takes regular volunteering eye care missions with the organization.

Most recently, SAMS launched their Surgical Vitreoretinal Fellowship, a fellowship based in a tertiary care hospital in northern Syria. "The program is a one-year program devoted to clinical training in the diagnosis of vitreoretinal patients and surgical management of vitreoretinal diseases," says Rifai. "The retina fellow, based in northern Syria, works closely with the Syrian American physicians based in the United States, through virtual lectures [and] scheduled on-site clinical visits."

SAMS is now involved with launching a retina center in the region, where graduate fellows will receive a certificate of completion and then serve as a member of the academic team. "They will become a Surgical Retina Attending for three years, to help supervise and become mentors for the next cohort of fellows," Rifai says. "This will provide medical and surgical retina services to a large cohort of refugees with limited access to such specialized services"

Credit: Syrian American Medical Society

A SAMS-supported ophthalmology center has also been established in Kafr Lusin, a village in northern Idlib, Syria. The center serves a high volume of patients, including many internally displaced persons, and provides specialist care and medication to those otherwise unable to afford or access eye care services.

SAMS has been working in partnership with the Emory Eye Center, Atlanta – as well as international NGO Medecins Sans Frontieres, and UNHCR (the UN Refugee Agency), who make patient referrals to the team – to deliver eye care to locations like Za'atari, the largest refugee camp in Syria, which houses more than 80,000 refugees, the majority of whom are children. The multi-institutional team provides cataract surgeries, laser procedures, and eye injections, and has set up a pediatric screening program at the camp.

Politically neutral, SAMS continues its mission to protect the eyesight of all civilians in the unpredictable environs of a warzone.

ANTERIOR SEGMENT

Paving the Way for Robotic Cataract Surgery

How deep learning is incorporating AI into femtosecond laser-assisted cataract surgery

AI has come to the forefront of public consciousness in the past few years. From organizing photos on smartphones to self-driving software in automobiles, new applications for AI are discovered every day – especially in the context of healthcare. I believe the potential of AI to refine the precision of surgical devices, enhance surgical efficiency, and improve patient outcomes is truly being realized today.

I recently had the opportunity to delve into the deep learning being done to incorporate AI into femtosecond laser-assisted cataract surgery (FLACS), particularly for diagnostic image segmentation and optimizing fragmentation patterns during cataract surgery. The following is a summary of research recently presented at ARVO and a look at where deep learning, AI, FLACS, and robotic cataract surgery may be headed in the future.

Diagnostic image segmentation

Cornea and lens segmentation. One of the most impressive applications of deep learning in FLACS is the segmentation of Scheimpflug images to precisely identify the boundaries of the cornea and lens, a crucial step in accurately planning and executing cataract surgery.

In a study presented at ARVO, researchers analyzed 973 eyes with AI to delineate these boundaries with remarkable accuracy (1). About 220 eyes were from surgeries performed with the LENSAR Laser System (LENSAR) in a commercial setting, and the remaining eyes were imaged by ALLY (LENSAR) in the following settings: commercial surgeries (n = 628), a clinical study environment (n = 64), precommercial clinical data collection activities of noncataracts (n = 31), and ex vivo scans obtained in a laboratory setting (n = 28).

The researchers manually delineated the boundaries of the cornea and the lens surfaces and performed aggressive data augmentation including illumination changes, noise addition, affine transformations, and histogram stretching to train a deep neural network (DNN) of Scheimpflug images to identify pixels of the anterior and posterior surfaces of the lens capsule and cornea.

All Scheimpflug images included in the study, regardless of the setting, showed delineation of the anterior surface of both the cornea and lens with zero failures to reconstruct these surfaces. However, reconstruction of the posterior surface of the lens failed in five eyes. In three instances, the density of the cataract was too great and obscured accurate identification of the posterior lens. All successful reconstructions were screened for visible surface detection errors. Only one and eight cases of visible surface detection errors were found for the anterior and posterior lens surfaces, respectively. The DNN output produced a usable 3D lens reconstruction and one free discernible error in 99.7 percent and 98.8 percent of cases, respectively.

The researchers concluded that this DNN can be used to repeatedly and accurately identify the boundaries of the cornea and lens capsule at a pixelar level, even in the presence of dense cataracts where the posterior lens capsule is difficult to visualize (Figure 1).

Pupil, limbus, and eyelid segmentation. A separate yet related study presented at ARVO showed that a DNN can also be used to segment iris images and identify the pupil, limbus, and eyelid boundaries from various topography devices with a unified software approach (2). Researchers manually delineated the boundaries of the pupil and visible iris of 604 grayscale topography images and applied a custom pupil warping method to produce augmented copies of each image with the iris manipulated to varying pupil shapes and sizes (Figure 2). A DNN was then trained to label pixels as from the pupil, iris, or neither.

Accurate identification of the pupil and limbus was achieved in all but one eye, and the pupil center error was fewer than 5, 10, and 15 pixels in 98.7 percent 99.5 percent, and 99.7 percent of eyes, respectively. Similarly, the limbus center error was fewer than 5, 10, and 15 pixels in 69.2 percent, 95 percent, and 99.8 percent of eyes, respectively. Dice coefficients of greater than 0.95 was achieved in 95.6 percent, 98.2 percent, and 92 percent of pupil region, composite iris region, and exclusive iris region, respectively.

Clinical applications. The clinical applications of these two related studies are significant. Improving the accuracy of 3D reconstructions of the cornea and lens enhances the precision of FLACS, which has been shown to result in a reduction of overall intraoperative case time. This increased accuracy has also been shown

Figure 1. Sampling of successful segmentations for various cataract morphologies. (Courtesy of Dustin Morley and Mike Evans)

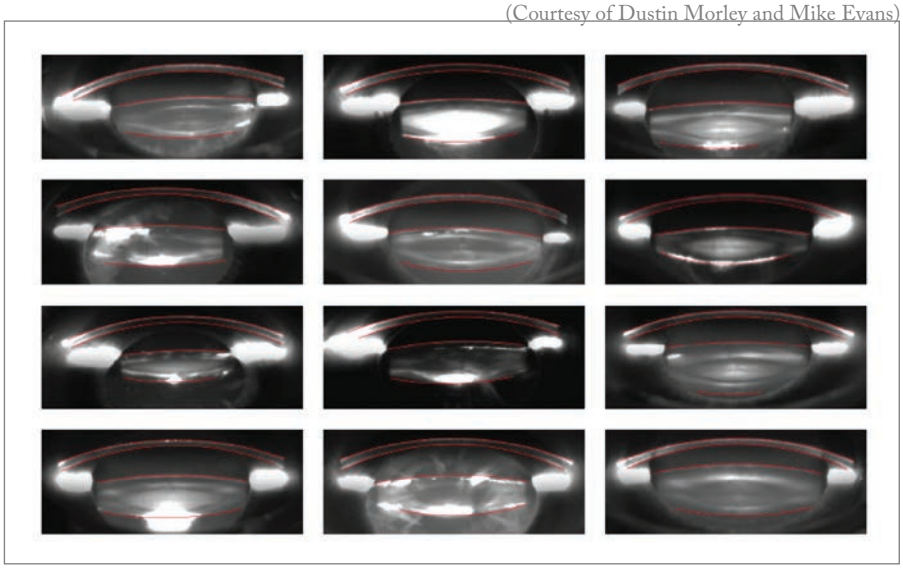
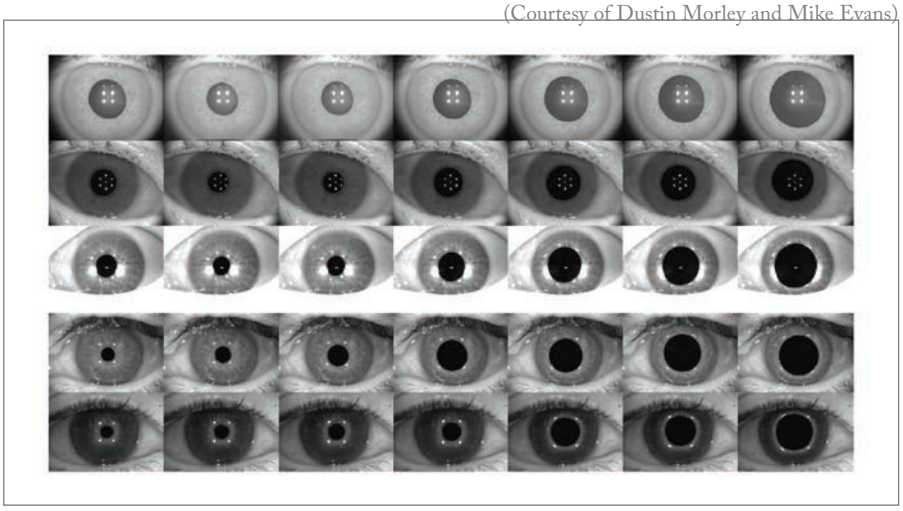


Figure 2. The original topography images were manipulated to create various pupil shapes and sizes. (Courtesy of Dustin Morley and Mike Evans)



to reduce phacoemulsification time for FLACS users, leading to the use of less intraoperative phacoemulsification energy, possibly less corneal edema, and thus, a potential improvement in immediate surgical outcomes and faster postoperative recovery and visual acuity for patients. Additionally, these technological advances can improve device interoperability and enable software to process images from multiple diagnostic devices with little or no modification for iris registration and identification of potential for cyclotorsion when treating astigmatism either with astigmatic keratotomy or guiding toric IOL alignment.

Optimizing fragment patterns

Another exciting development is the application of AI to optimize fragmentation patterns. During a recent LENSAR user meeting, Jonathan Solomon shared his experience working with the company to refine his custom laser fragmentation patterns. Analyzing his baseline settings and then using AI to adjust parameters such as spot spacing led to better cleavage and increased his pattern from a two-plane to a three-plane chop plane. This helped Solomon achieve a 20 percent reduction in his overall case time and decreased the amount of phaco energy he used in routine cases. As with AI-based Scheimpflug image segmentation, the clinical implication of optimizing fragmentation patterns with deep learning is meaningful, including a shorter surgical time, a reduced risk of intra- and postoperative inflammation, faster recovery, and better postoperative day one visual outcomes.

Even for users of this femtosecond laser technology who may not have the opportunity to work directly with the manufacturer to refine their personal fragmentation patterns, the benefits of these advancements are very accessible. The data and improvements generated from the collaborative efforts of researchers and key clinicians are integrated into the next-generation models of DNNs, resulting in software upgrades that benefit all those who use the technology in clinical practice. This democratization of advanced surgical techniques ensures that we can all leverage innovations to improve our practice and patient outcomes, especially in complex cases like dense cataracts and eyes with zonulopathy.

Forward progress

Looking ahead, the integration of AI and deep learning into FLACS paves the way for the next frontier – robotic cataract surgery. This potential future will be driven by sophisticated AI algorithms capable of processing big data to perform precise surgical tasks. While we are still in the early stages of robotic cataract surgery, the progress made by the researchers working on these developments is a crucial step toward making robotic cataract surgery a reality.

Incorporating AI and deep learning into FLACS underscores the transformative shift currently happening in our field. As we continue to embrace AI in ophthalmology, we are not only advancing our current practice but also laying the groundwork for the future of cataract surgery.

It is an exciting time to be in this field.

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

See references online at: top.txp.to/robotic/cataract/surgery

GLAUCOMA

Unraveling Glaucoma's Genetic Tapestry

Key questions for a new era of precision medicine in glaucoma

By David Mackey, Vice President of the Asia Pacific Academy of Ophthalmology, Councillor for the Australian Academy of Health and Medical Sciences, Councillor of the Royal Australian and New Zealand College of Ophthalmology

Glaucoma has long been recognized as a disease underpinned by a complex interplay of genetic and environmental factors. Over the past 25 years, the field of glaucoma genetics has evolved from constructing glaucoma family trees for gene discovery using linkage analysis and gene screening, through to large population and cohort studies for genome-wide association studies (GWAS) and developing polygenic risk scores – all of which could have profound implications for clinical practice.

At the outset, our understanding of glaucoma genetics was anchored by identifying specific genes with Mendelian inheritance patterns, such as myocilin and CYP1B1. These discoveries, heralded as breakthroughs at the time, offered valuable insights into the genetic underpinnings of the disease. Myocilin genetic testing in families could identify those carrying mutations and at high risk of developing glaucoma, and even today we are still weighing evidence as to whether one of hundreds of variations in myocilin are disease-causing mutations, benign polymorphisms, or variants of unknown significance.

Relatively early on, it became apparent that the Mendelian genes accounted for only a fraction of glaucoma cases. The advent of GWAS established a new era in glaucoma genetics, enabling researchers to cast a wider net in their quest for genetic determinants of the disease. Through GWAS, hundreds of genetic loci associated with glaucoma have now been discovered. From the *LOXL1* gene implicated in exfoliation glaucoma, to the *TMCO1* and *CDKN2BAS* genes linked to primary open-angle glaucoma (POAG), the genetic landscape for glaucoma has expanded exponentially, with hundreds of genes contributing to the polygenic nature of POAG (2).

Polygenic risk scores have emerged as a powerful tool in the armamentarium of glaucoma genetics; indeed, an individual's risk score provides a nuanced assessment of genetic susceptibility to the disease. By integrating information from multiple genetic variants, a polygenic risk score can provide personalized risk estimates, enabling more targeted approaches to screening, prevention, and treatment. However, the utility of these scores hinge on their validation across diverse populations; notably, most studies to date have predominantly focused on Northern European cohorts.

Taking this into account, it is important to note that ethnic diversity in genetic studies is paramount for ensuring the generalizability and equitable application of genetic findings. Despite the disproportionate burden of glaucoma among individuals of African ancestry, their representation in genetic research remains inadequate – a fact that highlights systemic disparities in research funding and participation. As such, efforts to address these disparities are imperative to guarantee that genetic insights are applicable across diverse populations, so that they can inform tailored approaches to glaucoma management – wherever it is most needed.

In the clinical arena, the integration of genetic information could revolutionize patient care. From risk stratification to personalized treatment algorithms, genetics has the potential to usher in a new era of precision medicine in glaucoma. But challenges abound – from the interpretation of genetic variants to the ethical implications of genetic testing and counseling.

With all of these factors to consider, several key questions loom large in the glaucoma genetics space: How do we translate genetic discoveries into actionable insights for clinical practice? What are the implications of genetic testing for disease screening and management? And how do we ensure equitable access to genetic testing and its benefits across diverse populations?

If we're able to answer these questions, collaborations between glaucoma geneticists, researchers, and clinicians could help us achieve a realistic future in which there are no cases of glaucoma-associated blindness.

See references online at: top.txp.to/genetic/tapestry

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Future Treatment of Leber Hereditary Optic Neuropathy

Why mitochondrial base editing in unaffected carriers may achieve the best outcome for Leber Hereditary Optic Neuropathy

By Byron L. Lam, Mark J. Daily Professor, Bascom Palmer Eye Institute, University of Miami, Florida, USA

Ophthalmologists typically intervene once disease symptoms manifest, but, in some cases, the best visual outcomes are achieved by treating before any signs or symptoms appear. Indeed, this may be true for Leber Hereditary Optic Neuropathy (LHON). Emerging gene therapy techniques involving mitochondrial DNA editing in unaffected LHON carriers hold promise for optimizing visual outcomes. They have the potential to reduce disease penetrance and lower the conversion rate of carriers to symptomatic LHON; these interventions may also mitigate retinal ganglion cell loss if optic neuropathy eventually develops. In other words, a proactive approach could significantly improve the prognosis for individuals at risk of LHON (1).

Treating LHON is challenging due to its complex nature. Only a fraction of such genotype carriers will experience visual loss, with the specific triggers remaining undetermined. The window for effective treatment narrows early in the course of the condition as significant functional and anatomical deficits in retinal ganglion cells are present in both asymptomatic and symptomatic eyes. These deficits can be measured by pattern electroretinogram and OCT GCIPL thickness (2). Additionally, some LHON patients may experience spontaneous partial vision improvement months after the onset of visual loss, which can complicate the evaluation of treatment effectiveness (3).

One current clinically-tested gene therapy for LHON, with the G11778A mutation, involves indirectly delivering a normal ND4 protein to the mitochondria. This is done by introducing a nuclear-encoded version of the mitochondrial ND4 gene into the nucleus of retinal ganglion cells. The gene is then transcribed into mRNA, transported to the cytoplasm, and translated into the ND4 protein, which is subsequently transported to the mitochondria. Phase III clinical trials of this allotopic gene therapy have shown good safety and unexpectedly resulted in partial bilateral improvements in visual acuity. From the worst visual acuity recorded during the trial, treated eyes improved by nearly three lines, while untreated eyes improved by 2.5 lines. The final mean visual acuity levels after gene therapy were approximately 20/400 in both eyes.

Future clinical trials should include a randomized control group who do not receive gene therapy in either eye. This would better assess the treatment effect by determining whether the reported bilateral visual acuity changes are significantly different from the natural progression of the disease, sham treatments, or placebo treatments. Other promising LHON advanced medicine treatment strategies, which may offer superior outcomes compared to allotopic expression gene therapy, are currently in development. These approaches include direct DNA delivery into the mitochondria and mitochondrial base editing systems. And while using CRISPR systems with guide RNA to edit the mitochondrial genome presents significant challenges (mainly because the double membranes of the mitochondria block DNA entry), novel mitochondrial DNA editing strategies are being developed to overcome this obstacle.

Treating LHON genotype carriers before the onset of the disease using mitochondrial base editing techniques may yield solid visual outcomes. It is a preventative approach that could reduce disease penetrance by lowering the conversion rate of carriers to symptomatic LHON and minimize retinal ganglion cell loss if LHON does develop. However, there are several feasibility challenges to be considered first. LHON has a low carrier conversion rate, thus a clinical trial would need to be conducted over several years and require a large number of both treated and untreated participants. To assess the therapy's effectiveness, a composite outcome criterion would also need to be developed. This would incorporate the methodology of multiple primary endpoints, such as conversion rate and visual outcomes when LHON develops.

Though these challenges are daunting, the nature of diseases often requires innovative solutions that may seem impractical. Human ingenuity, however, knows no bounds – and it is time to think outside the box. Despite the obstacles, advancing our approach to treating LHON and similar conditions demands bold and creative strategies that push the boundaries of current medical and scientific capabilities.

See references online at: top.txp.to/hereditary/optic/neuropathy

RETINA

Unlocking Retina's Potential

The University of Edinburgh's decade-long history of developing retinal imaging methodologies that can detect both ocular and systemic diseases

By Janice English

Frequently referred to as a "window to the brain", the retina has been known for decades to offer up biomarkers for many diseases, ocular and otherwise. But it is only now that the full extent of this observation is being realized. Thanks to advances in optical coherence tomography (OCT) screening, imaging specialists in 2024 have the means to identify the early indicators of many conditions. In addition, research projects around the world are laying the foundations to make optimum use of new drugs becoming available (drugs such as lecanemab and donanemab for Alzheimer's, Syfovre and Izervay for geographic atrophy, and Ocrelizumab for MS), which will have a profound effect on millions of lives.

"In the future [optometrists and ophthalmologists] could be examining more than eye health, by looking at changes to brain health, risk of stroke and cardio-vascular disease that may be five or ten years away in their patient's future," says Tom MacGillivray, Principal Investigator in the Centre for Clinical Brain Sciences, University of Edinburgh, UK. "This [development] could elevate the entire role of optometry, and we need clinical pathways to address this very soon. We have the potential to spot signs of change years ahead, opening the door for many new treatments."

MacGillivray adds that optometrists can now "see the in-vivo workings of the brain and the micro-vascularity at work", meaning that signs of systemic, metabolic and neurodegenerative disease can be detected through the eye – diseases such as Alzheimer's, Parkinson's Disease, diabetes, and Huntington's Disease.

Retinal and choroidal cellular layers are providing detailed measurements and are under extensive scrutiny. They are being monitored over time with fast, non-invasive OCT, a modality that is easily integrated into existing workflows.

This immense potential for wider healthcare disease prediction, diagnosis, and monitoring heralds a new era of medicine, a concept that is often labeled "oculomics" or "computational ophthalmology".

Multiple Sclerosis and Alzheimer's Disease progression monitoring via retinal scans is now ten years down the line, with MacGillivray's research providing valuable findings which will aid future diagnosis and drug development.

"Five years ago we started the Future MS longitudinal study, looking at 230 newly diagnosed patients from throughout Scotland," explains MacGillivray. "Our PhD student is segmenting the retinal layers, and looking at angiography in relation to the patients' frailty and cognitive scores. We are also looking at patients who are at risk of stroke and Parkinson's to examine the different signatures of conditions affecting the brain in the retinal tissues and cells. The unique data sets for neuro-degenerative diseases are clearly defined through deep clinical phenotyping."

This type of retinal screening gives contextual changes that can't be evaluated using a traditional bran scan, MacGillivray adds. "By examining these patients, particularly with a family history, they can be assessed and directed to lifestyle changes or prescribed medication in the future. In the next five years we expect to be tracking people who are much younger."

MacGillivray believes that the Heidelberg Engineering SPECTRALIS system "delivers one of the best OCT views possible" for this type of scanning. "We can't do anything without scan data, and highly detailed imaging technology brings many disciplines together," he says. "Looking at how the retina changes over time, how patients are in themselves, and how prescribed medication affects patients, are all facilitated by OCT.

The University of Edinburgh is working alongside Duke University, North Carolina, US, to collaborate on projects focusing on early and late-stage Alzheimer's and Parkinson's diseases, as well as joining forces with other UK-based universities in Belfast, Dundee, and Cambridge for a number of studies. One such study, the PREVENT Dementia study – a study aimed at identifying the earliest signs of dementia in UK and Ireland that is part-funded by the Alzheimer's Association – has been running for over a decade and has more than 700 participants. "We are monitoring people in their 50s and 60s before any clinical symptoms appear," says MacGillivray. "Cambridge leads the MRI brain scanning and we are using retinal scans alongside this to identify micron level changes to nerve tissue and blood vessels."

2003 saw the formation of VAMPIRE (Vascular Assessment and Measurement Platform for Images of the Retina), a collaborative initiative that is focused on developing software and methodologies to advanced retinal imaging. Now in its 21st year, the VAMPIRE research group is driving biomarker discovery and providing valuable insights into the microvasculature of brain and holistic health. Providing technical expertise, and funded by UK research grants, VAMPIRE is playing a crucial role in advancing clinical applications relating to vascular health and disease.

"Finding people best suited for clinical trials, and seeing what changes there are in the blood vessels and tissues of the retina, is opening up targets for new therapies across a broad range of morbidities," MacGillivray exclaims. "It is an extremely exciting time to be working in this field."


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Community Champion

Sitting Down With… Imran Rahman, CEO of CHEC (Community Health and Eyecare), UK

What do you see as the key ophthalmology challenges in the UK?
The whole ophthalmology sector could operate much more efficiently if there was clearer dialogue between primary, secondary, and independent services, and less resistance from all parties around working together.

There's regular commentary that independent sector providers are undertaking too much work, placing acute ophthalmology departments at risk. However, there is little factual evidence of this. These are areas where independent providers can support and reduce sight threatening problems. What I believe the independent sector has done successfully is remove some of the longest waiting times, allowing the NHS to capitalize on the extra capacity this has given to reduce their backlogs. Ultimately, patients want a provider that offers them quick, accessible, safe care, with positive outcomes, free at the point of service.

With technology advancing as it is, there is no reason for waiting lists to continue rising. Community care should be exactly that – all services within one community, working together for the people who live there. It's an ambition of mine to help achieve this, but much needs to change to do so. In particular, there needs to be closer collaboration with the NHS and independent sector to maintain low waiting times and improve patient safety in an agile way, using technology fit for future generations and truly placing patients at the center of discussions.

What obstacles have you faced in your career?
When you're a medical student you get taught how to communicate efficiently, think critically, interpret and relay good and bad news, and how to handle emergency situations – things you don't get exposure to in any other degree. But a medical degree doesn't tell you how to cope with institutionalized issues, such as racism, which – at the time I was looking for my first job – was rife.

During one of my earliest job interviews I was told I might never become an ophthalmic surgeon because of my name. On another occasion, when working with a senior registrar who was Nigerian, he explained he had come across challenges he didn't want to repeat out loud. I decided that, should I ever become a consultant, I would do the right – and obvious – thing, and recruit and reward based on talent, not race.

It sounds simple. We live in a different world today, but to have those issues presented to you in the earliest days of your career sets a certain type of tone. I've built a culture at CHEC – now one of the UK's leading providers of community healthcare – which makes it an open, honest, welcoming place to work. We take an incredibly strong stance against bullying of any kind. As long as our people are taken care of, I feel like we can take on any other challenge that comes our way.

What's your vision for the future of CHEC?
Our ultimate ambition is equity of access to high quality, efficient, and safe healthcare. This is why the mobilization of our community clinics is so important to us right now. We're aiming for each of our hospitals to have at least four community sites supporting it, so patients are offered a choice of convenient locations closer to home with short wait times. This reduces travel time – and therefore expenditure – and being placed in hard-to-reach areas with a standardized level of service helps reduce healthcare inequalities.

This also supports our Net Zero agenda. Up to 3.5 percent of carbon emissions from the NHS are related to patients and staff coming to hospitals and going to appointments. Our community hub and spoke model is designed to reduce carbon emissions as well as support local care delivery

> *"During one of my earliest job interviews I was told I might never become an ophthalmic surgeon because of my name."*

What advice would you give to other practitioners with ambitions to make a real difference to healthcare delivery?
One piece of advice I received when I was thinking about starting CHEC was to do the best you can for patients and everything else will follow. Whether it's your reputation, a great team, awards – none of it will come your way if you don't prioritize the patient every step of the way. Acknowledge and accept you will make mistakes, but minimize the risk of that whenever you can by planning methodically and to great detail. At CHEC, we don't instigate anything until we've fully understood the risk element beforehand, centered around a clinical governance structure.

And finally, never stop learning. My parents instilled in me a great love of education, to the point it is still habitual. Learn from your team, learn from your peers, learn from industries with synergies and surround yourself with the best people. Combine all that and you're sure to leave your mark.

INTERVENTIONAL GLAUCOMA

SHATTERING THE STATUS QUO

Introducing

iDose® *TR*

(travoprost intracameral implant) 75 mcg

The catalyst to advance the interventional glaucoma revolution, helping you and your patients take back control of their treatment journey.

iDose TR is a long duration intracameral procedural pharmaceutical that delivers prostaglandin analog therapy for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.[1]

Actual size
1.8mm x 0.5mm

1. iDose TR (travoprost intracameral implant) 75 mcg Prescribing Information. Glaukos Corporation. 2023.

INDICATIONS AND USAGE
iDose TR (travoprost intracameral implant) is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

IMPORTANT SAFETY INFORMATION

DOSAGE AND ADMINISTRATION
For ophthalmic intracameral administration. The intracameral administration should be carried out under standard aseptic conditions.

CONTRAINDICATIONS
iDose TR is contraindicated in patients with active or suspected ocular or periocular infections, patients with corneal endothelial cell dystrophy (e.g., Fuch's Dystrophy, corneal guttatae), patients with prior corneal transplantation, or endothelial cell transplants (e.g., Descemet's Stripping Automated Endothelial Keratoplasty [DSAEK]), patients with hypersensitivity to travoprost or to any other components of the product.

WARNINGS AND PRECAUTIONS
iDose TR should be used with caution in patients with narrow angles or other angle abnormalities. Monitor patients routinely to confirm the location of the iDose TR at the site of administration. Increased pigmentation of the iris can occur. Iris pigmentation is likely to be permanent.

ADVERSE REACTIONS
In controlled studies, the most common ocular adverse reactions reported in 2% to 6% of patients were increases in intraocular pressure, iritis, dry eye, visual field defects, eye pain, ocular hyperaemia, and reduced visual acuity.

View full prescribing information at iDoseTRhcp.com

Please see full Prescribing Information.
You are encouraged to report all side effects to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.
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