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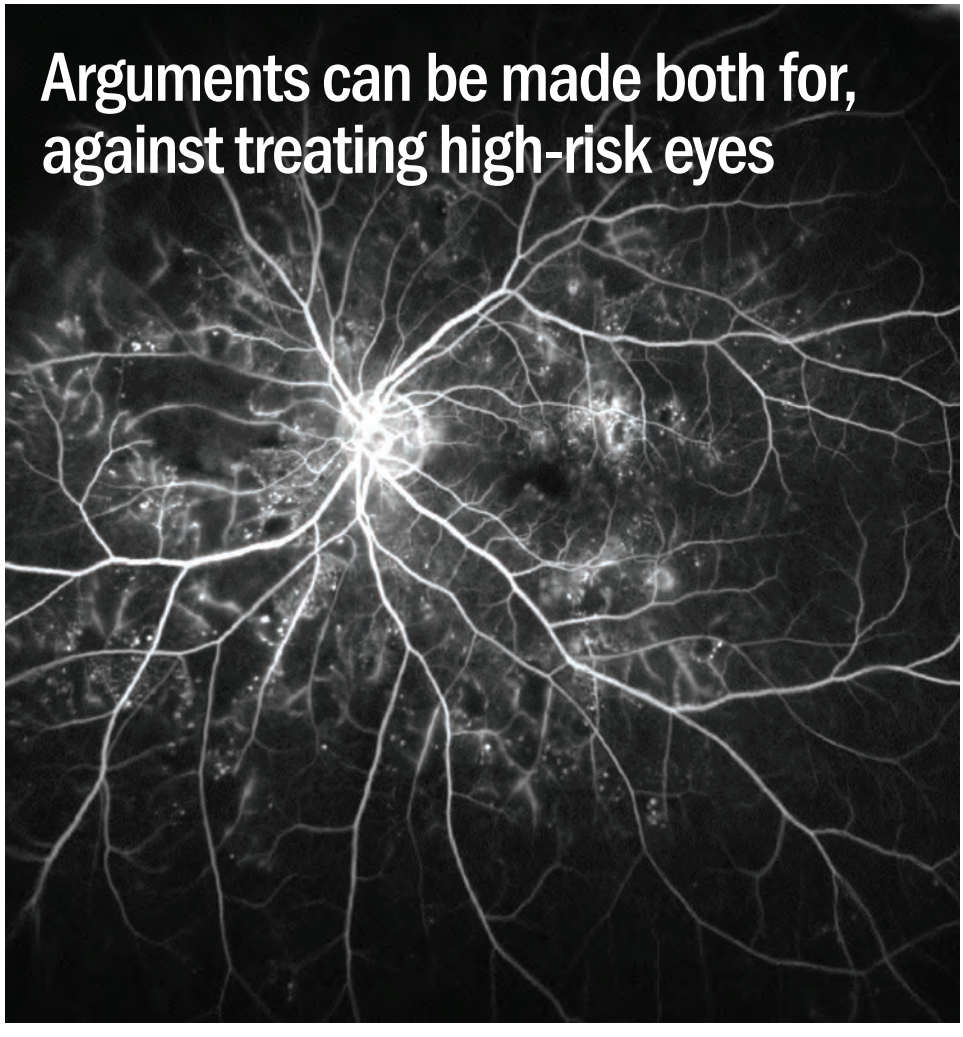
RETINA

Quest for data increases debate over anti-VEGF



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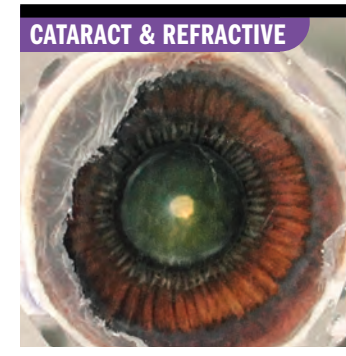

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Hope for inherited retinal, corneal dystrophies

CORNEA

Colour-LED topography

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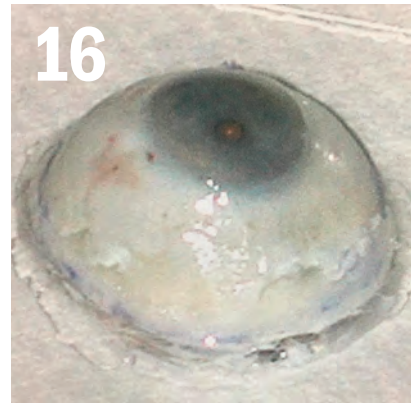

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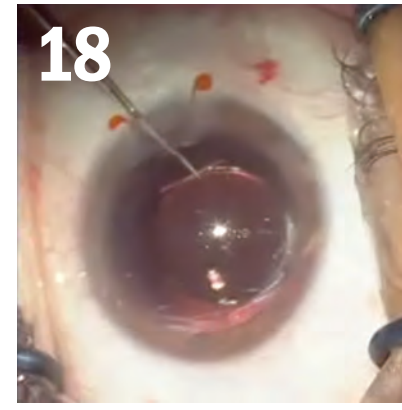

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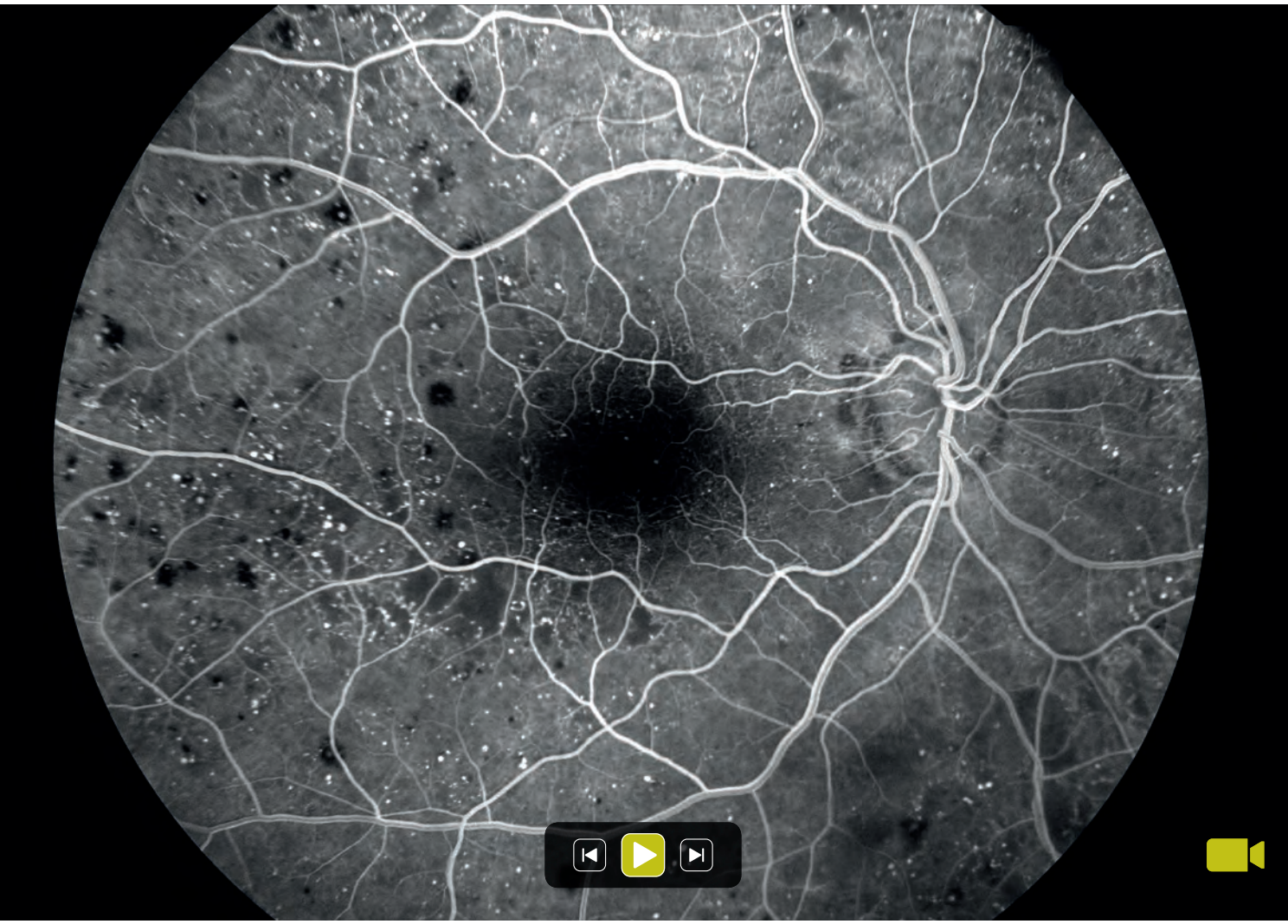

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Hope springs eternal for ophthalmic innovations across the seasons

***Mike Hennessy Sr**, Chairman and founder of* Ophthalmology Times Europe*'s parent company, MJH Life Sciences*

In what has been a busy autumn for ophthalmic conferences, *Ophthalmology Times Europe* is reinvigorated by the depth and breadth of innovation in the global ophthalmic space. In this and upcoming months, we will present coverage from the European Society of Cataract and Refractive Surgeons (ESCRS) in Paris, and the American Academy of Ophthalmology (AAO) in San Francisco, CA, USA, as well as recent conferences in Canada.

We begin with a focus on key research in personalised medicine and gene therapy. Guylene Le Meur, MD, shares how a treatment for patients with confirmed biallelic *TPR65* mutation-associated retinal dystrophy is now available. Next, Rohit Shetty, DNB, FRCS, PhD, explains how biomarkers are being identified in the eye that can provide clues to numerous bodily diseases. "The cardinal rule for clinicians is Do Not Discard. Even something as simple as a Schirmer's strip could provide clues to new biomarkers," he says.

In cataract and refractive news, Gerd U. Auffarth, MD, PhD, explains how understanding the characteristics of available IOL materials provides insights for developing a perfect lens for the future; David Chang, MD, discusses how a light-adjustable IOL can improve patient satisfaction by allowing ophthalmologists to fine-tune and customise patients' refractive outcomes after cataract surgery; Samuel Masket, MD, notes how dysphotopsias may be one of the most under-recognised complications following otherwise unremarkable cataract surgery; and Liliana Werner, MD, PhD, shares how researchers performed a study using cadaver eyes to evaluate the results of using a novel hybrid phaceoemulsfication tip with a polymer overmold. With presbyopia remaining one of the final frontiers of refractive surgery, efforts are under way to develop the real restoration of accommodation, explains Florence Cabot, MD.

In the realm of cornea, doctoral student Mona El Zarif, OD, MSc, says stem cell success is also observed as the use of confocal microscopy establishes a new methodology to count the keratocytes in the corneal stroma, and measure the density of adipose-derived adult stem cells in the implanted tissue, as well as the corneal stroma.

Dipika V. Patel, MRCOpht, PhD, highlights a wide range of anterior-segment imaging technology available today; surgeons must decide which options are best suited for their practices. Also, David P. Pinero, PhD, discusses how colour-LED technology can measure corneas with consistency.

Regenerative medicine and engineering are also making headway in glaucoma therapy, as is evident in a panel discussion led by David J. Calkins, PhD, and Joel S. Schuman, MD. Also, from the annual Sally Letson Symposium in Toronto, Harry A. Quigley, MD, stresses that glaucoma patients are looking for treatments other than daily eye drops. "We need sustained delivery in some form, so patients do not have to remember to take something everyday."

The threshold for treatment with an anti-VEGF agent for diabetic retinopathy without diabetic macular edema is controversial. Two Phase III studies are now investigating aflibercept for moderately severe to severe nonproliferative diabetic retinopathy in patients with good vision, notes Charles C. Wykoff, MD. Eric W. Schneider, MD, highlights a study that was an outgrowth of frustration with his inability to completely dry the macula in a subset of patients with neovascular age-related macular degeneration.

Finally, when it comes to paediatric patients, there is a 5-minute exam that clinicians need to know when presented with a child with an ocular injury—and when referral to an ophthalmologist is warranted.

The message from a prospective study looking at new-onset uveitis risk in juvenile idiopathic arthritis is to encourage patients and families to get the recommended eye exams, says Karen N. Watanabe Duffy, MD.

Michael F. Chiang, MD, says a recent study reveals how diagnostic algorithms may achieve 91% accuracy, outperforming retinopathy of prematurity specialists. "Computer and information technologies are dramatically changing the practice of medicine, and require that people from different clinical and scientific backgrounds work together," he concludes.

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Gene therapy offers hope for cases of retinal or corneal dystrophy

Tests indicate change in functional vision during first year

By Cheryl Guttman Krader;

Reviewed by Dr Guylène Le Meur

Dr Le Meur

In December 2017, voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) became the first gene therapy with a recombinant adeno-associated virus vector for an ophthalmic disease. The story of its relatively short journey from preclinical development to regulatory approval gives hope for the future of gene therapy in ophthalmology, said Guylène Le Meur, MD.

"Currently, many other clinical trials are investigating gene therapy for various inherited retinal degenerations. There are almost 200 patients enrolled in these studies and approximately another 600 patients in studies of gene therapy for other retinal degenerative diseases," said Dr Le Meur, Department of Ophthalmology, Centre Hospitalier Universitaire de Nantes, Nantes, France.

"We can also expect to be seeing gene therapy arrive in the future for inherited corneal dystrophies," Dr Le Meur added.

Voretigene, which is given as a subretinal injection, is also the first pharmacological therapy approved by the FDA for an inherited retinal dystrophy. Specifically, it is indicated for the treatment of adult/paediatric patients with vision loss caused by confirmed biallelic *RPE65* mutations who have sufficient viable retina cells.

"The treatment is given in both eyes, with the second eye injected at least six days after the first. Immunosuppressive therapy with prednisone should be started prior to injection and continued after," she said.

Preclinical studies conducted in a canine model provided proof of concept that the therapy resulted in functional and structural recovery of the retina. Results from the first clinical trial investigating voretigene in patients with *RPE65* Leber's congenital amaurosis were published in 2008, and the paper describing the Phase III results was published in 2017.

The Phase III study included 31 patients, of which about two-thirds were children. Participants were randomly assigned 2:1 to receive bilateral injection of the gene therapy or to a control group that were initially observed and then received delayed therapy after 1 year.

IN SHORT

The era of gene therapy in ophthalmology has begun. A treatment for patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy is now available and there are many ongoing studies of gene therapies for inherited and other retinal degenerative diseases.

Change from baseline to 1 year in functional vision as measured by performance on a multi-luminance mobility test (MLMT) developed specifically for studying the efficacy of voretigene was investigated as the primary endpoint. Testing results showed that two-thirds of the treated patients were able to complete the course at the lowest illumination level, whereas all of the untreated control patients failed to manoeuver the course.

Additional testing showed a benefit of the treatment for improving full-field light sensitivity, and a recent publication showed the improvements are durable with follow-up to 4 years.

Voretigene was approved by the European Union in 2018, but due to stringent criteria pertaining to education and certification of the personnel involved with product storage, preparation, and administration, the gene therapy is currently only available in France and Germany.

Other gene therapy trials for Leber's congenital amaurosis are ongoing. In addition, gene therapies are being developed for choroideremia, Stargardt disease, Usher syndrome, retinoschisis, retinitis pigmentosa, and achromatopsia.

Corneal dystrophies being targeted for gene therapy include lattice, Reis-Bucklers, Thiel-Behnke, and granular corneal dystrophy.

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This article is adapted from Dr Le Meur's presentation at the 2019 Congress of the European Society of Cataract and Refractive Surgeons. Dr. Le Meur is a founder of Horama, which is a biopharmaceutical company developing gene therapies for retinal diseases.

Tear-drop analysis provides a window into diseases of the body

Review helps researchers find biomarkers, reasons, cause, treatment options

By Lynda Charters;

Reviewed by Dr Rohit Shetty


Dr Shetty

Human tears hold many secrets and clues that currently are being unearthed to aid physicians in the diagnosis and prognostication of diseases.

"It is most important to understand the behavior of every facets of a disease, i.e., the bacteria, molecules, inflammation, and they are constantly changing, said Rohit Shetty, DNB, FRCS, PhD. "Even when considering the stem cells and scenarios the body faced decades previously, everything in the bodily system is changing."

Dr Shetty is a faculty member, Department of Ophthalmology, Maastrich University, Maastrich, The Netherlands, and vice chairman, Narayana Nethralaya Eye Institute, Bangalore, India.

In line with this perspective, another point for consideration is that the ophthalmologists can no longer be concerned with only what is happening in the eye. And the changing scenarios regarding food, exercise, and the gut microbiome, are big challenges from a clinical perspective.

Biomarkers and ophthalmology

A biomarker is defined by the FDA as a characteristic, that is measured as an indicator of normal biological and pathogenic processes or responses to an exposure or intervention, including therapeutic interventions. Applying this knowledge in clinical practice is most beneficial for clinicians.

According to Dr Shetty, there is a great need for biomarkers in clinical practice in numerous areas, such as in the differential diagnosis, risk quantification, prognosis, and disease identification.

"The clinical signs and symptoms, imaging, and medical history may no longer be adequate," he said, noting that clinical scenarios such as identifying the predisposition to postoperative complications before refractive surgery and disease progression status, for example, in determining keratoconus stability and unilaterality or asymmetry in the clinical presentation.

Tear-based biomarkers already exist for ocular diseases (keratoconus, dry eye, blepharitis, pterygium, diabetic retinopathy and glaucoma); metabolic disorders (diabetes); autoimmune diseases (thyroid eye disease, Sjögren's syndrome, rheumatoid arthritis, and uveitis); neurological conditions (Alzheimer's and multiple sclerosis), breast and prostate cancers.

"The cardinal rule for clinicians is Do Not Discard. Even something as simple as a Schirmer's strip could provide clues to new biomarkers," Dr Shetty said.

> 'The cardinal rule for clinicians is Do Not Discard. Even something as simple as a Schirmer's strip could provide clues to new biomarkers.'
>
> – Dr Rohit Shetty

Inflammation

What do the biomarkers provide?

"We start redefining the definition itself," Dr Shetty explained.

For example, regarding keratoconus, the first question asked about the disease was whether it was an noninflammatory or inflammatory disorder. Dr Shetty's work to address this question started with tear cytokine/chemokine profiling, which lead him to the observation of extensive inflammation in the epithelium and tears of keratoconus patients.

"This finding provided the insight that we should

IN SHORT

- ***Biomarkers are being identified in the eye that can provide clues to numerous bodily diseases.***

start looking forward for progression status indicator biomarkers in keratoconus," he said.

Tear collection at each visit allowed him and his team to identify changes in the tears that indicated progression or stabilisation of the disease, such as increased matrix metalloproteinase (MMPs).

"Eventually, we saw that some patients were progressing and others were not," Dr Shetty said. "We found significant and distinct differences between those who were and were not. The differences in the various factors in the tears eventually become biomarkers that facilitated decisions to intervene or not."

Stabilisation

The next step after identification is stabilisation, Dr Shetty noted. He and his colleagues experimented with cyclosporine A in his keratoconus patients and found that most with elevated MMPs and inflammatory cytokines can be stabilised with the drug, meaning that not all require immediate surgical intervention.

> 'Eventually, we saw that some patients were progressing and others were not. We found significant and distinct differences between those who were and were not.'
>
> – Dr Rohit Shetty

The investigators also looked at the enzymes that hold collagen together, lysyl oxidase (LOX), the first area of interest and are interesting was also present in the tears.

Evaluation of the peripheral corneal epithelium found that the altered epithelial tissue and stromal expression of specific genes at the corneal cone apex drives the focal structural weakness in keratoconus.

"The LOX was completely different in the cone from the periphery, the latter of which appeared normal," he reported.

Dr Shetty explained that higher LOX levels in the cone epithelium correlated significantly with the optimal outcome after cross-linking. The lower LOX levels indicated that the cross-linking would not be as optimal as with higher levels.

"LOX was a very important biomarker in cross-linking and in progression," he stated.

Dr Shetty also reported a case of ectasia that developed after a SMILE procedure caused by LOX deficiency. Based on this case, his laboratory is working on developing an enzyme-based detection chip that would enable detection of such deficiencies in the patient's tear preoperatively. He said he is hopeful that the prototype will be ready next year.

Molecular signature understanding

Reading the signature is the first important step. Dr Shetty demonstrated epithelial cells with and without stress and the marked changes in the epithelial pattern, which drives keratoconus and dry eye.

The cell shape of stressed cells was severely altered, the intracellular organelles were unclear, and the cell-to-cell transport and interactions were compromised.

"A major factor in oxidative stress is autophagy," he said. "Oxidative stress induces dysregulated autophagy in the corneal epithelium of keratoconus patients. Changes in autophagy drives a disease."

In his investigation, Dr Shetty further discovered that a commercially available lubricant containing trehalose augmented autophagy to ease the stress-induced inflammation in human corneal cells.

"The same biomarkers of autophagy can be changed to start functioning better," he explained.

Another area of investigation, the gut-eye axis demonstrates the emerging roles of the microbiome in ocular immunity and diseases. Microbiome profiling of lead Dr Shetty to the discovery that the bacteria may be linked to keratoconus or dry eye.

Clinical application

A problem that has received extensive investigation is haze development after refractive surgery. After identifying a number of unique markers in patients who develop haze, Dr Shetty carried his experiment a step further to prove that alterations in molecules like PREX1 and transforming growth factor beta were actually causing haze.

Dr Shetty's team found that overexpression of these two biomarkers causes increased fibrosis-associated factors and knockdown of the two resulted in decreased fibrosis-associated factors.

This field of investigation also involves the brain, which, according to Dr Shetty, controls more than what is known. Investigators currently are examining biomarkers in the brain and the role of inflammation in depression.

"We are on a long journey that involves multiple steps from collecting samples to identifying biomarkers to developing a point-of-care kit to determine the root cause of the disorder," Dr Shetty concluded.

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Dr Shetty received research grants from Alcon Surgical, Allergan, Carl Zeiss Meditec, Johnson & Johnson Vision, and Microvision.

Creating the ideal IOL begins with knowledge of lens materials

Several attributes go into formulating the lens of the future

By Cheryl Guttman Krader;

Reviewed by Dr Gerd U. Auffarth

Dr Auffarth

Understanding the characteristics of available IOL materials provides insight for developing a perfect IOL for the future, according to Gerd U. Auffarth, MD, PhD.

The "perfect" material would be optically pure without risk for calcification, glistenings, interaction with substances inside the eye, or long-term degeneration, said Dr Auffarth, chairman, Department of Ophthalmology, Ruprecht-Karls-University of Heidelberg, Heidelberg, Germany.

Consideration would be given to refractive index, which dictates material thickness and therefore surgical incision size. Other issues include Abbe number and optical features of the material that are related to refraction and potential side effects, as well as the opportunity for changeability.

Data on the IOL global market show dominance of acrylic IOLs, with hydrophobic acrylic IOLs accounting for 56% of implants worldwide and hydrophilic acrylics having a 29% market share overall.

Dr Auffarth explained that hydrophobic materials are copolymers related to polymethyl methacrylate. The various hydrophobic acrylics are relatively similar with respect to refractive index, which is approximately 1.5 (range 1.41–1.55), he said.

"High refractive index is one of the advantages of hydrophobic acrylic as an IOL material," Dr Auffarth added. "Other advantages include a low rate of posterior capsule opacification (PCO), rotational stability, resistance against both capsular contraction and Nd:YAG laser-induced damage, and freedom from calcification because the material is inert."

Hydrophobic acrylic IOLs have limitations. An association with negative dysphotopsias is one disadvantage cited for hydrophobic acrylic lenses.

"Reports of negative dysphotopsias with IOLs are mostly limited to individual cases or cases series," Dr Auffarth said. "Though hydrophobic acrylic lenses are often involved, they have the highest market share."

The potential for mechanical damage and glistenings is an issue with hydrophobic acrylic materials. Glistenings, which are fluid-filled microvacuoles within the polymer network, can be present before implantation or develop over time when the lens is in the eye.

"Glistenings are not just a cosmetic issue, because they can have a clinical impact by increasing straylight," Dr Auffarth said. "With the use of an experimental model for accelerating glistening formation, we have found that manufacturers are now doing a good job producing glistening-free lenses."

Hydrophilic acrylate IOLs are mostly made of polyhydroxyethylmethacrylate and other copolymers. Their advantages include foldability and high biocompatibility. Their high water content, however, is a disadvantage because it leads to a risk for calcification when the material is in the aqueous environment within the eye or exposed to air or gas, which can occur during various surgical procedures.

Though it can be difficult to get information from manufacturers about IOL materials in development, through collaboration with a Chinese company (Pillarbio), Dr Auffarth described features of a novel IOL material that is a crosslinked polyisobutylene. The material also has a high refractive index (1.52) and high Abbe number (50), stable physicochemical properties, low modulus, high elasticity, and superb long-term clarity.

"This material appears to resolve current concerns regarding glistenings, dysphotopsias, chronic inflammation, and PCO. The high refractive index and Abbe number also allow for a large optic that would enable retina observation," said Dr Auffarth.

IN SHORT

- ***With acrylic lenses currently dominating the market, the industry continues to consider viable options for IOL materials.***

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This article is based on Dr Auffarth's presentation at the 37th Congress of the European Society of Cataract and Refractive Surgeons. Dr Auffarth receives research grants from many companies that manufacture IOLs.

Light-adjustable IOL technology creates novel treatment window

Postoperative customisation offers physicians multiple options for their patients

By Laird Harrison;

Reviewed by Dr David Chang

A light-adjustable IOL (LAL, RxSight) can improve patient satisfaction by allowing ophthalmologists to fine-tune and customise the patient's refractive outcome after cataract surgery, according to David Chang, MD.

"It shifts the need to do all of our counselling and decision-making preoperatively more to postoperatively," said Dr Chang, clinical professor of ophthalmology at the University of California, San Francisco, CA, USA. "You can let the patient preview different refractive outcomes while they are pseudophakic."

LAL design

The LAL is a three-piece silicone lens with diffusible monomers in the optic. Following a standard phacoemulsification procedure, the ophthalmologist uses a slit lamp equipped with a near-UV light to alter the IOL shape to adjust the patient's refraction.

As the light hits the lens, it initiates polymerisation, causing micron-level changes in the structure of the lens. This allows the surgeon to adjust both the sphere and cylinder, Dr Chang said.

The LAL precludes the need to perform intraoperative aberrometry or to mark the astigmatism axis prior to surgery, because the refraction will be adjusted to correct any astigmatism postoperatively, he said.

Unlike with conventional toric IOLs, the LAL will not rotate, Dr Chang added.

A surgeon can adjust up to 2 D of sphere in either direction using a single treatment, along with up to 3 D of astigmatism, and up to 4.5 D of astigmatism can be corrected with two treatments, he said.

Advantages

Light-adjustable IOLs offer a number of advantages over traditional cataract surgery.

First, they eliminate a significant amount of guesswork on the part of the surgeon. Advances in biometry and IOL formulae have significantly improved the refractive results of cataract surgery.

"We still have to estimate the effective lens position, posterior corneal astigmatism, or surgically induced astigmatism (SIA)," he said. "In addition, many eyes are at higher risk for IOL power surprise, such as those with prior keratorefractive surgery or unusual keratometry or axial lengths."

In a 2018 European Registry of Quality Outcomes for Cataract and Refractive Surgery (EUREQUO) study of 280,000 patients cited by Dr Chang, 27% of cataract surgeries failed to achieve within in a half diopter of the target refraction.

> 'We can let the patient decide postoperatively how much anisometropia is optimal for them, and how much they can comfortably tolerate. If they don't like it, we can then reverse it.'
>
> – Dr David Chang

Dr Chang predicted that, for eyes with astigmatism, an ophthalmologist fresh out of residency should be able to achieve better results with the LAL than the most experienced surgeons now get with the most advanced pre- and intraoperative technologies.

While refractive outcomes can be changed or enhanced with LASIK, many ophthalmologists do not perform keratorefractive surgery, requiring a patient who needs an enhancement to see a second

IN SHORT

- ***The ability to fine-tune and customise patients' refractive outcome after cataract surgery could shift the need for physicians to do counselling and decision-making preoperatively more to postoperatively.***

> 'The best thing is that patients will not have to understand concepts such as depth-of-focus, myopia, astigmatism and anisometropia.'
>
> – Dr David Chang

surgeon. Even then, the patient must wait a few months until the refraction is stable before undergoing a LASIK or PRK procedure.

Better patient experience

In addition to improving the refractive accuracy, Dr Chang hopes that adjustability will improve the patient experience.

European Registry of Quality Outcomes for Cataract and Refractive Surgery (EUREQUO) study (2018)

280,000 patients

27%

of cataract surgeries failed to achieve within 0.5 D of the target refraction

Setting reasonable expectations and helping patients make decisions about their refractive goals during preoperative counselling can be difficult for both the patient and the surgeon.

Patients are sometimes overwhelmed by a bevy of unfamiliar terms and often intimidated by disclaimers that results of surgery may not meet their expectations.

The ability to try different pseudophakic refractive states should reduce preoperative anxiety and confusion, and improve patient satisfaction.

"If you wanted natural distance vision," Dr Chang said, "how would you know what the difference would be between plano and −0.75 with an IOL. If you want to read without glasses, how could you appreciate the difference between being −1.5 versus −2.5? With an adjustable IOL, you can preview these different refractive targets once you have the IOL, and then have your preferred target delivered with an adjustment."

Light-adjustable IOLs will be a great way to deliver customised mini-monovision, Dr Chang noted.

"In addition to achieving good distance vision in one eye, we can try out different amounts of myopia in the second eye," he said. "We can let the patient decide postoperatively how much anisometropia is optimal for them, and how much they can comfortably tolerate. If they don't like it, we can then reverse it."

In theory, the ability to wait until after surgery to demonstrate different refractive options and targets should substantially reduce the amount of time that surgeons must spend preoperatively trying to describe these different options.

"The best thing is that patients will not have to understand concepts such as depth-of-focus, myopia, astigmatism, and anisometropia," Dr Chang concluded. "We can use trial lenses or even a soft contact lens trial to demonstrate postoperatively how increasing or decreasing myopia affects their uncorrected vision."

The LAL is approved by the FDA.

VOTE **Dr Fritz H. Hengerer forecasted** how the LAL might impact the premium cataract market. Go to **Europe.OphthalmologyTimes.com/LAL**

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This article is adapted from Dr Chang's presentation at the 2019 Congress of the European Society of Cataract and Refractive Surgeons. Dr Chang disclosed that he is a consultant at RxSight and Perfect Lens.

New IOL design trends avoid negative dysphotopsias after surgery

Surgeon also uses primary reverse optic capture with positive patient outcome

By Fred Gebhart;

Reviewed by Dr Samuel Masket

Dr Masket

Dysphotopsia may be one of the most under-recognised complications following otherwise unremarkable cataract surgery. Based on subjective symptoms, up to 20% of patents have negative dysphotopsia (ND), a temporal dark shadow after IOL implantation. Other patients have positive dysphotopsia (PD), characterised by light streaks, arcs, central light flashing or star bursts. Some patients may have both ND and PD.

"Overall, dysphotopsia has not been studied particularly well, especially epidemiologically," said Samuel Masket, MD, founding partner, Advanced Vision Care, and clinical professor of ophthalmology, David Geffen School of Medicine, Stein Eye Institute, University of California, Los Angeles, CA, USA.

Early ND symptoms tend to improve over time due to neuroadaptation, but about 3% of cases will have chronic ND at 1 year after surgery.

PD is directly related to square-edge design and the index of refraction of an IOL. The higher the index of refraction, the more complicated the ND. It is a temporal dark arc, similar to the effect of putting blinders on a horse. Unlike PD, there is no good correlation between clinical findings and optical lab findings, Dr Masket said.

Researchers have suggested that square edges can cast ND shadows where rounded edges do not. And some have indicated that ND is also associated with a greater iris to IOL distance and an expanded posterior chamber depth. However, these assertions are not supported in clinical investigations.

Studies reveal increased posterior chamber depth does not cause ND and that any IOL, irrespective of material or edge design, implanted in the capsule bag can result in ND, which resolves when the inciting lens is moved from the bag to the ciliary sulcus. These findings suggest a relationship between the IOL and capsule bag as central to ND.

"Historically, every IOL on the market in the United States has been associated with ND," Dr Masket said. "While ND is likely multifactorial, it is prevented, relieved or improved when the IOL optic edge overlies the nasal capsulotomy, rather than the capsulotomy overlying the optic edge."

Reverse optic capture

Dr Masket published reverse optic capture (ROC), either as a therapeutic or prophylactic measure for ND, in 2011.

A 2018 update with ROC in 43 eyes showed good success. Of 22 eyes with chronic ND, 21 were corrected with secondary ROC and 21/21 contralateral eyes successfully avoided ND using primary ROC. All of the eyes that underwent primary ROC placement had fibrotic PCO that required laser posterior capsulotomy within 3 months of the initial surgery.

> 'Overall, dysphotopsia has not been studied particularly well, especially epidemiologically.'
>
> – Dr Samuel Masket

Dr Masket's original lens was licensed and modified by Morcher. It has CE marking and is being developed as the model 90S.

Two other capsulotomy supported IOLs have been CE marked, he noted, the Tassignon "BIL" (Morcher) and Femtis (Oculentis).

The Tassignon lens has had no reported ND in

IN SHORT

- ***Newer laboratory studies reveal that increased posterior chamber depth does not cause ND and that any IOL, irrespective of material or edge design, implanted in the capsule bag can result in ND, which resolves when the very same inciting lens is moved from the bag to the ciliary sulcus.***

ND: Surgical experience, 58 procedures

THERAPEUTIC

2º Rev Optic Capture: 21/22

IOL Exchange: Bag/Sulcus 6/7

IOL Exchange:Bag/Bag 0/4

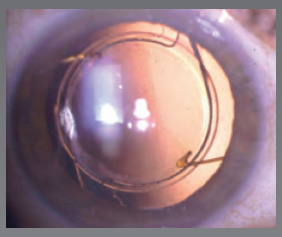
Piggyback IOL: 8/11

Masket S, Fram NR. et al. JCRS 44:6-16 Jan 2018

PREVENTATIVE

1º Rev Optic Capture: 21/21

42/43 eyes with ROC successful



Anti-dysphotopic IOL

US PATENTS 8,652,206
9,433,498

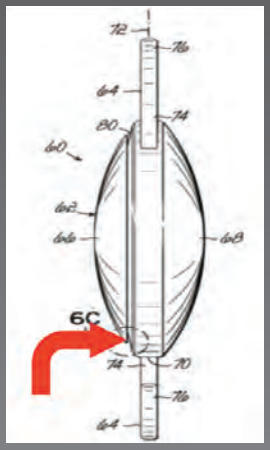
Groove on anterior optic captures the capsulotomy

Part of optic overlies the capsule rather than vice versa

IOL is fixated by anterior capsule

Masket S: Expert Review of Ophthalmology, DOI: 10.1080/17469899.2018.1560263

(Images courtesy of Dr Masket)



several thousand uses and the Femtis has had no ND in its reported series of 384 lenses.

In addition to the absence of ND, capsulotomy-supported IOLs have a more predictable effective lens position, a stable toric axis, absence of capsule contraction, perfect centration when the capsulotomy is centered on the visual axis, reduced higher-order abberations and limited optic tilt.

"There is likely a future for this design concept," Dr Masket concluded.

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This article is based on Dr Masket's presentation at the 2019 Congress of the European Society of Cataract and Refractive Surgeons. Dr Masket is the patent holder for an anti-dysphotopic IOL that is being developed by Morcher GmbH.

Cadaver eyes used to demonstrate capsular safety of hybrid phaco tip

Tool can be useful for both residents, experienced surgeons alike

By Steve Lenier;

Reviewed by Dr Liliana Werner

Dr Werner

Posterior capsule rupture (PCR) is a common complication of cataract surgery, with most ruptures occuring during phacoemulsification, according to Liliana Werner, MD, PhD, professor of Ophthalmology and Visual Sciences and co-director of the Intermountain Ocular Research Center at the John A. Moran Eye Center, University of Utah, Salt Lake City, UT, USA.

Risk factors that increase the likelihood of this occurrence include surgeon experience, operative factors such as a small pupil (3 mm or less), and other comorbidities, such as pseudoexfoliation and diabetic retinopathy.

With a rupture, there may be a loss of vitreous and a worse visual prognosis. Researchers performed a study using cadaver eyes to evaluate and the results of using a novel hybrid phacoemulsification tip with a polymer overmold.[1]

In 2006, Steven Dewey, MD, popularised a needle design with no sharp edges. Studies have shown this has helped reduce the incidence of PCR. The present study evaluates a smooth hybrid needle tip, with a polymer at the distal end made of a proprietary material.

(FIGURE 1) A hybrid phaco needle that features no sharp edges, reducing the incidence of PCR. *(Photo courtesy of Dr Werner)*

Study details

The study compared this tip, with a balanced metal tip.[1] Cadaver eyes were prepared with the Miyake-Apple technique, where the eye is sectioned and the anterior segment glued to a glass slide.

> Researchers performed a study using cadaver eyes to evaluate the results of using a novel hybrid phacoemulsification tip with a polymer overmold.

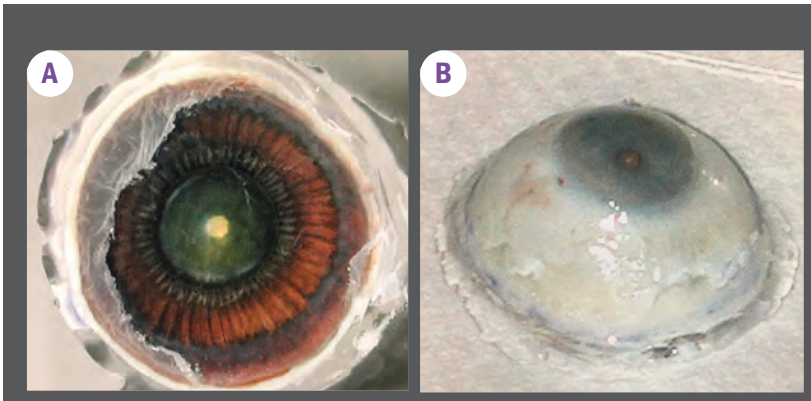
This provides a posterior view of the entire capsular bag and zonular apparatus.

In the first experiment, the tip was used with the bevel pointing down. In the first pair of eyes, the researchers determined the vacuum limit, and found that it could be raised up to 300 mm Hg without having PCR. They determined that for the study, the vacuum would be set to 150 mm Hg.

In the next four pair of eyes, still with the bevel down, the researchers began in each eye with one tip, and increased torsional energy in 5% increments up to 60%. If there was no rupture they switched to the other tip. In this test, the hybrid tip required more

IN SHORT

- ***A needle with no sharp edges can help reduce the incidence of posterior capsule rupture, and a study has evaluated a smooth hybrid needle tip, with a polymer at the distal end.***



(FIGURE 2) **A. The anterior view of a cadaver eye is seen, showing the capsular bag and zonular apparatus. B. The cadaver eye is sectioned using the Miyake-Apple technique, and the anterior segment is flued to a glass slide.** *(Photos courtesy of Dr Werner)*

energy for PCR. This is not representative of a surgical case because the bevel was down.

In the second experiment, the bevel of the tip was kept pointing up. The same process was followed, a tip was inserted and the torsional energy was raised in 5% increments to a maximum of 60%, with a fixed vacuum of 150 mm Hg and flow rate of 30 cc/min.

Again one tip was inserted, and if there was no rupture at 60% the researchers switched to the other tip.

The mean torsional power required for PCR was higher in the hybrid group. To determine if phaco would weaken the capsular bag without did a subanalysis that excluded capsules that were reused, and the results remained significant.

Variables influencing PCR

These six variables all influence PCR. Perhaps playing the most important role are numbers 1 and 5 on the list.

1. **Pressure of the tip against the capsule**
2. **Amount of active vacuum**
3. **Aspiration flow rate**
4. **Gauge of the needle**
5. **Needle sharpness and degree of angulation**
6. **Energy modulation active at the time of contact.**

Limitations

The study results were significant, but it was performed in a small sample size, and was an ex vivo study only.

It is difficult to have a true control in a cadaver eye study. Efficiency must also be considered, as it may be a limiting factor in "safer" needles. Radius needles are slightly less efficient.

> The researchers concluded that this tip can be useful for both residents and experienced surgeons.

A role for the hybrid tip

The researchers concluded that this tip can be useful for both residents and experienced surgeons, and noted that whoever is considering using it should consider all risk factors when choosing a needle tip.

REFERENCE

1. Shumway C, Ellis N, Heczko J, Jiang B, Werner L, Mamalis N. Evaluation of the capsular safety of a new hybrid phacoemulsification tip in a cadaver eye model. *J Cataract Refract Surg*, 2019 (in press).

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Dr Werner has no financial disclosures related to this project.

Into the future: Development of true accommodative IOLs

Research into restoring accommodation—whether on cornea, lens or sclera

By Steve Lenier;

Reviewed by Dr Florence Cabot

Dr Cabot

Like space in the "Star Trek" motion picture series, presbyopia remains one of the final frontiers of refractive surgery, but efforts are under way to develop the real restoration of accommodation.

Over the years, the results of accommodative pseudophakic IOLs have been mixed, but that may be ready to change and the last frontier of ophthalmology may be tamed with new lenses that provide options for surgeons and hope for their patients.

Accommodation and presbyopia involve several ocular structures—the ciliary muscle, pupil, lens, zonule, vitreous, and some brain structures and neural pathways as well. This makes restoring accommodation complex.

Restoring accommodation means creating a device that has a continuously variable, adjustable, active, near-focusing ability. This can be thought of as similar to the auto-focus of a camera. Over the years, several teams have worked on restoring accommodation, whether on the cornea, the lens, or on the sclera.

> Presbyopia remains one of the final frontiers of refractive surgery, but efforts are under way to develop the real restoration of accommodation.

First-generation IOLs

The first generation of accommodative IOLs relied on the Helmholtz theory of accommodation. The lenses are supposed to provide a forward shift, because they have flexible haptics that should respond to the contraction of the ciliary muscle. Results have been disappointing, and the few good results that have been seen were attributed to an increase of optical aberrations rather than an actual movement of the lens.

The Ophthalmic Biophysics Center (OBC) at the Bascom Palmer Eye Institute in Miami, FL, USA, built a unique dual OCT system that provides dynamic imaging, so real-time video of the ciliary muscle can be seen on one side, with the anterior segment seen on the other side.

Researchers used that system to image patients that had received a Crystalens (Bausch + Lomb), a first-generation accommodative lens. They could see that after a 2 D accommodation stimulus the Crystalens was actually showing either a minimal forward axial shift (not able to provide useful accommodation to the patient), or no axial shift at all, or a backward axial shift in some cases.

Modular and multicomponent IOLs

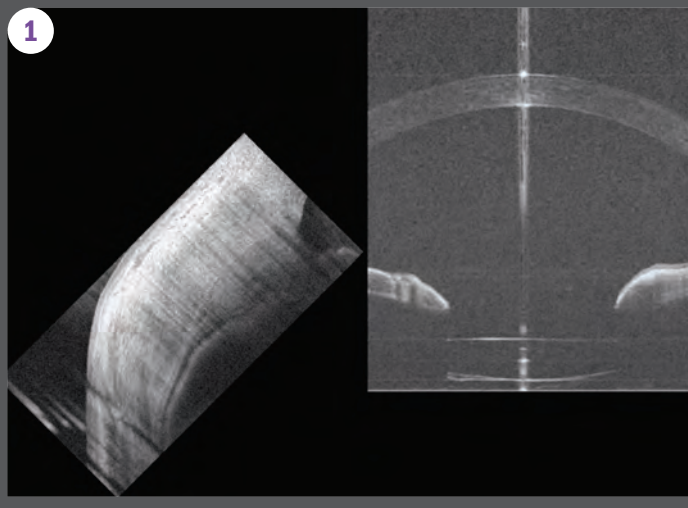
The new-generation accommodative IOLs are modular and multicomponent, and provide postoperative adjustability. In both categories, the exact effective lens position is known. This allows precise IOL calculations and refractive outcomes.

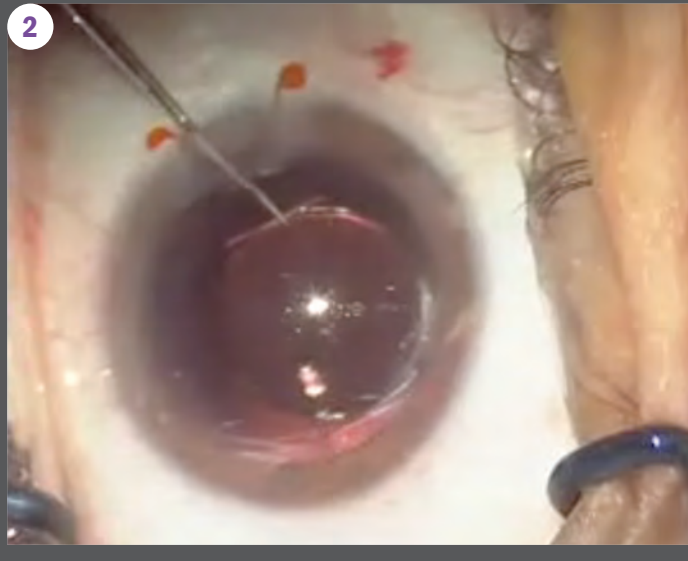
Multicomponent open capsule IOLs

Some lenses do not have continuous adjustability, but allow for an adjustment to be made after the operation, and repeated over time. Within this category there are two subcategories. The first consists of two parts, a base component and an optic component. The Gemini Capsule from Omega Ophthalmics, the Harmoni from ClarVista Medical, and the Precisight from infiniteVision Optics are this type of lens. These keep the capsule open, thus preventing posterior capsular opacification. The haptics stay in the bag while the optics can be

IN SHORT

- ***Restoring accommodation means creating a device that has a continuously variable, adjustable, active, near-focusing ability. This can be thought of as similar to the auto-focus of a camera.***





(FIGURE 1) In this video still, a patient has a Crystalens implant that does not move forward. (FIGURE 2) A Crystalens IOL is injected into the eye of a patient. *(Photos courtesy of Dr Cabot)*

exchanged and adjusted as many times as necessary later on.

Modular IOLs

The other subcategory is a single component lens, with the adjustability achieved through a reshaping of the IOL itself, which is done with UV light or a femtosecond laser. This category includes the Light Adjustable Lens (LAL) from RxSight (adjustment done with UV light a few weeks after surgery), and the femtosecond laser-adjustable system from Perfect Lens, which can be used to reshape any acrylic IOL.

Accommodative IOLs with instantaneous, constant adjustability

These lenses rely on ciliary muscle movements or pupillary changes to provide a real time change in their shape to provide near vision. There are two subcategories here, IOLs that are injected into the bag, and IOLs that are implanted in the sulcus or fixated to the sclera. The main reason for implanting outside of the bag is to avoid capsular bag fibrosis.

In-the-bag IOLs

The Synchrony lens from Visiogen, the WIOL-CF from Medicem, and one of the newest, the Juvene by LensGen, are in this group.

Another interesting concept, just at the experimental level with Sapphire's Elenza, is injecting a chip into the capsular bag, which has a sensor. A change in pupil size can trigger an automatic adjustment exactly like auto focus, and there can also be a remote control used to change the accommodation. Looking further, this could be integrated with artificial intelligence to become even more useful.

Out-of-the-bag IOLs

The NuLens Dynacurve uses the collapsed bag–zonular complex as a diaphragm, which drives a piston system that changes the shape of the lens, and the AkkoLens Lumina is injected into the sulcus and has two optics that slide perpendicular to the visual axis in response to the ciliary muscle for near focus.

Accommodating fluids/lens refilling technology

This technology is utilised by the Nishi Lens Refilling IOL, the Phaco-Ersatz from Ophthalmic Biophysics Center at the Bascom Palmer Eye Institute, the Smart IOL by Medennium, and the Liquilens by Vision Solutions. Despite years of development, it is still difficult to get good results with this type of technology.

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Dr Cabot has no relevant financial interests to disclose.

Colour-LED topography measures corneas consistently in analysis

Guidelines set for anterior topography, aberrometry, total corneal astigmatism

By Laird Harrison;

Reviewed by Dr David P. Piñero

Dr Piñero

Colour-light-emitting diode (LED) technology can consistently measure anterior topography, aberrometry, and total corneal astigmatism, said David P. Piñero, PhD.

But these measurements cannot be used interchangeably with those obtained through Scheimpflug imaging by the Oculus Pentacam, explained Dr Piñero of the University of Alicante, in Alicante, Spain.

He presented the finding at the 2019 Congress of the European Society of Cataract and Refractive Surgeons (ESCRS).

The Cassini Total Corneal Astigmatism is a multi-spot (up to 700), multi-colour (red, yellow, and green) LED tear-film-reflection topography imaging system designed to avoid source mismatch and decrease artifacts caused by shadows.

The system uses ray tracing to process every three spots identified by the software and to define the relevant local elevation. Employing the reflection of seven infrared LEDs for second Pukinje imaging, it measures the centre of the posterior corneal surface.

> 'This . . . technology has shown its usefulness to measure the shape of the anterior corneal surface in different types of eye.'
>
> – Dr David Piñero

Technology shines

"This Cassini technology has shown its usefulness to measure the shape of the anterior corneal surface in different types of eye, including keratoconus and scarred corneas," said Dr Piñero.

Several studies have evaluated the intrasession repeatability of some measurements from the device.

"But I haven't found any paper evaluating the intrasession repeatability of corneal asphericity or corneal higher-order aberrations provided by this device," he said.

Dr Piñero noted that papers by other authors, showed clinically relevant differences in keratometry and other parameters between the Cassini and other devices. So, Dr Piñero and colleagues set out to evaluate the intrasession repeatability of anterior corneal topographic and aberrometric measurements obtained by the Cassini and to compare it with those obtained by the Pentacam in healthy eyes.

Comparisons

They made this comparison in 35 healthy eyes of 35 patients, with an age range of 16–66 years at the, University of Alicante. They obtained three consecutive measurements in each patient to assess the intrasession repeatability. Then they obtained one measurement in each patient with the Pentacam system.

The research team discovered that the within-subject standard deviation for keratometric readings as 0.02 mm, with intraclass correlation coefficient readings of at least 0.992.

In addition, the team also found that the intrasession repeatability for anterior astigmatic measurements was 0.16 D, and for total astigmatic measurements it was 0.05 D. The intraclass coefficient readings were 0.930–0.978.

They found a standard deviation of 0.06 mm for asphericity and 0.03 mm for corneal diameter, "which can also be considered as a good level of intrasession repeatability," said Dr Piñero.

When analysing the repeatability of aberrometry, however, the researchers found "something curious," Dr Piñero explained. "We obtained very good

IN SHORT

- ***Researchers evaluated the intrasession repeatability of anterior corneal topographic and aberrometric measurements obtained by the Cassini imaging system and compared it with those obtained by the Pentacam in healthy eyes.***

correlation coefficients and intraclass correlation coefficients., and within subject standard deviations, for all this Zernike terms for the second order to the fourth order.

"But when we analysed one component of the secondary astigmatism and one component of the quadrafoil, we obtained a limited intrasession repeatability," he said.

Small aberration

According to Dr Piñero, this discrepancy is attributed to the very small amount of aberration. Even a slight difference in a very small difference can appear to be a statistically significant variation.

"This is probably the reason, but we have to investigate more," he said.

On the other hand, the differences between readings of the Cassini and Pentacam devices were statistically significant for keratometry, total astigmatism, asphericity and in some Zernike terms.

"If we analyse the ranges of agreement between these two devices, we find that, for keratometry, it was more than 0.06 mm, which can be considered clinically relevant because this can have an impact, for example, in higher-power calculation of more than 0.5 D," he said.

There were differences in astigmatic corneal components of more than 0.69 D, in asphericity of more than 0.35 mm. There was a trend for the Cassini of obtaining steeper values of curvature, as well as higher values of total corneal astigmatism, he said.

In Zernike terms, there were differences of 0.2 µm for the second order, 0.13 µm for the third order and 0.01 µm for the fourth order.

Conclusions

The research team is poised to continue its work to find additional commonalities.

"More studies are needed to corroborate this consistency of Cassini measurements in pathological or highly aberrated corneas," Dr Piñero concluded. "There are no studies evaluating the repeatability in keratoconus, for example, or the interchangeability with other currently available topography systems also based in Scheimpflug images."

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Dr Piñero has no financial interests in the subject matter.

Sifting through the cream of the crop for anterior-segment imaging

Surgeons must weigh the benefits of the range of options available

By Lynda Charters;

Reviewed by Dr Dipika V. Patel

Dr Patel

A wide range of anterior-segment (AS) imaging technologies are available, but not all of these are of practical benefit for AS surgeons. Some are more useful for diagnosing, managing, and assessing the prognoses of patients undergoing keratoplasty, Dipika V. Patel, MRCOpht, PhD, pointed out.

Dr Patel is professor of ophthalmology, University of Auckland, Auckland, New Zealand.

Preoperative assessment

Ultrasound biomicroscopy (UBM) provides a view of the AS that can be obscured by corneal opacities on slit lamp examination. The surgeon can have a robust view of the anterior chamber depth, angle, lens and anterior capsule, membranes, adhesions, and vitreous in the anterior chamber using UBM, she commented.

The disadvantage of UBM is that the patient must be supine and water immersion is usually needed (although recent models overcome these issues), both of which require patient cooperation or use of general anaesthesia.

"Having the knowledge of the status of the eye behind an opaque cornea aids in planning the surgery as well as discussing the prognosis with the patient," Dr Patel emphasised.

AS optical coherence tomography (AS-OCT), which is a non-contact technology performed with the patient sitting, allows the surgeon to assess the depth of corneal pathology. With the information provided by this imaging, the surgeon can select the most appropriate surgical intervention, she noted, and described a case of stromal haze that developed following implantation of a Kamra inlay (SightLife Surgical) that was removed.

At the slit-lamp, the depth of the haze could not be clearly ascertained. OCT demonstrated that the haze was maximal at the interface, including the location of the inlay, and extended both anteriorly and posteriorly to the deep stroma.

The disadvantages of AS-OCT include poor visualisation of both the ciliary body and through corneal opacities.

In vivo confocal microscopy (IVCM) is useful preoperatively for looking at and differentiating among the endothelial diseases, such as bullous keratopathy, Fuchs' endothelial dystrophy, or ICE syndrome.

Intraoperative observation

Real-time, high-quality images are now accessible using intraoperative OCT with microscope-integrated OCT devices. The images may be viewed through the surgeon's microscope on a heads-up display or an external screen.

> 'Having the knowledge of the status of the eye behind an opaque cornea aids in planning the surgery as well as discussing the prognosis with the patient.'
>
> – Dr Dipika V. Patel

"The availability of these images affects decision-making intraoperatively and is thought to reduce the length of the surgery."

This technology can be applied to deep anterior lamellar keratoplasty (DALK) to evaluate the depth of the needle and dissection, the plane of big-bubble dissection, the residual stromal thickness, and to detect any microperforations. In Descemet's stripping automated endothelial keratoplasty (DSAEK) and Descemet's membrane endothelial keratoplasty

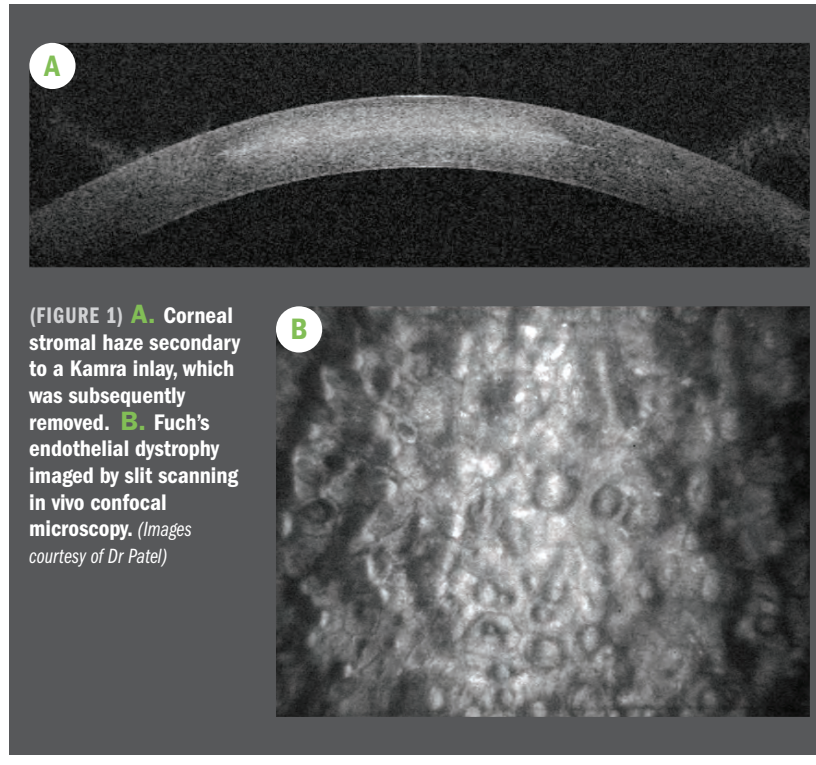
IN SHORT

- ***A wide range of anterior-segment imaging technologies are available today. Some anterior-segment imaging devices are better than others in anterior-segment surgeries, and surgeons must decide which options are best suited for their practices.***

(DMEK), intraoperative OCT can evaluate graft-host apposition, assess the interface fluid, check the graft orientation in DMEK, and facilitate faster positioning of the graft with less manipulation,

The usefulness of intraoperative OCT was evaluated in a prospective multi-surgeon study that included 244 cases of AS surgery. The results indicated that the technology influenced surgical decision-making in 43.4% of cases; 78.3% of surgeons preferred real-time to static image acquisition; and 63.1% of surgeons preferred viewing the images on the external screen.

The limitations of intraoperative OCT include limited details visible on the heads-up display, light scattering and shadowing from surgical instruments, and cost.



(FIGURE 1) A. Corneal stromal haze secondary to a Kamra inlay, which was subsequently removed. B. Fuch's endothelial dystrophy imaged by slit scanning in vivo confocal microscopy. *(Images courtesy of Dr Patel)*

Postoperative examination

AS-OCT facilitates the assessment of grafts in DSAEK and DMEK for thickness, centration, and detachment. This technology influences management considerations such as graft reshaping and repositioning and rebubbling.

"This technology is particularly valuable in cases with an edematous cornea when the view at the slit-lamp is poor," Dr Patel pointed out.

AS-OCT allows the surgeon to assess the graft-host junction after penetrating keratoplasty, in which graft-host malpositioning occurs commonly and is associated with high levels of astigmatism. Dr Patel described the case of a patient in whom the vision decreased a few years after deep anterior lamellar keratoplasty due to recurrent granular dystrophy at the interface.

AS-OCT is also useful for evaluating the extent of epithelial ingrowth, albeit rare, following lamellar endothelial keratoplasty. The technology is also used to monitor patients over time.

IVCM has proven useful to confirm cases of epithelial ingrowth. Dr Patel described an interesting case in which the IVCM images showed epithelial cells with fibrotic areas in the stroma, where epithelium should not be present, she explained.

IVCM and specular microscopy are both useful technologies for determining the prognosis and potential for late endothelial graft failure.

Two long-term studies investigating graft failure after full-thickness or endothelial transplants both found that preoperative donor endothelial density is not predictive of failure, but rather, low endothelial cell density (<1,200 cells/mm^2) 6 months postoperatively is associated with late endothelial graft failure.

"UBM, AS-OCT, intraoperative OCT, IVCM, and specular microscopy are useful for establishing a diagnosis, directing the management and assessing the prognoses of these patients," Dr Patel concluded.

> 'UBM, AS-OCT, intraoperative OCT, IVCM, and specular microscopy are useful for establishing a diagnosis, directing the management and assessing the prognoses of these patients.'
>
> *- Dr Dipika V. Patel*

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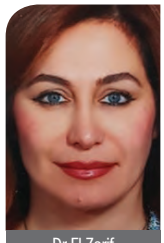
Dr Patel has no financial interest in any aspect of this subject matter.

Microscopy study suggests stem cell success in keratoconus

ADASCs injected into the stromal pocket in keratoconus can transform

By Laird Harrison;

Reviewed by Dr Mona El Zarif



Dr El Zarif

New evidence with confocal microscopy shows that adipose-derived adult stem cells (ADASCs) injected into the stromal pocket of patients with keratoconus can transform into keratocytes, according to Mona El Zarif, OD, Msc.

The use of confocal microscopy to monitor and evaluate the evolution of the stem cells over time is novel, said Dr El Zarif, a doctoral student at Miguel Hernández University in Alicante, Spain, at the 2019 Congress of the European Society of Cataract and Refractive Surgeons (ESCRS).

"It allowed a qualitative and quantitative assessment of the cells," she explained.

The technique establishes a new methodology to count the keratocytes in the corneal stroma, and measure the density of the ADASCs in the implanted tissue, as well in the corneal stroma she said.

Three groups

The researchers compared three groups of adult patients with keratoconus in an experimental, interventional, prospective, consecutive case series. In the first group, five patients were implanted with ADASCs alone without scaffold.

In the second group, five patients were implanted with decellularised human corneal stroma, essentially a scaffold without ADASCs.

"We decellularise the lamina from the donor human cornea stroma," Dr El Zarif noted.

The third group was implanted with ADASCs embedded onto a scaffold made from a decellularised lamina.

"We observed that the automatic count of cells done by the software of the confocal microscopy was not accurate," said Dr El Zarif. "That's why we proceeded with a manual count of cells. We proceeded choosing a good image, a good number of keratocytes and good contrast and quality of illumination."

For anyone wanting to try this approach, she recommends starting the count of cells with 50% illumination and contrast determining a fixed area.

In this study, Dr El Zarif analysed an area of about 0.1 mm and counted the most illuminated and most refringent cells with well-defined edges.

"The dark grey cells are not counted in our study because they don't belong to the plan of observation," she said.

When the researchers could not find any defined structure similar to keratocytes, they considered the tissue in question to be acellular.

By this definition, the decellularised lamina in this study remained acellular a month after implantation.

By contrast, cells in the recellularised lamina after 1 month had structures similar to normal keratocytes and these cells become more similar to keratocytes 6–12 months postoperation.

The researchers used software in the confocal microscope to calculate the density of the cells. They defined cell density as the number of cells multiplied by 10 (cell/mm^2) ± SD.

The results were promising. In the first group, those implanted with ADASCs but no scaffold, the ADASCs appeared round in shape, and more luminous, refringent, and voluminous. The shape of ADASCs changed after 6 months from round to fusiform until after 12 months the morphology of these cells looked like a normal cornea.

In the second group, those patients implanted with decellularised lamina only, the lamina remained acellular for the first month after implantation.

After 3 months, it became recellularised by the patients' own keratocytes.

"There was a migration of keratocytes from the host stroma toward the lamina," said Dr El Zarif.

IN SHORT

- ***The use of confocal microscopy establishes a new methodology to count the keratocytes in the corneal stroma, and measure the density of the ADASCs in the implanted tissue, as well in the corneal stroma.***

The posterior surface of the lamina recellularised before the anterior surface. After a year, the keratocytes populated the lamina in a similar way to a normal cornea stroma.

discoveries in each of the groups. In the first group, the researchers noted a gradual but significant increase of the cellularity of the mid corneal stroma ($P<0.001$).

> 'There was a migration of keratocytes from the host stroma toward the lamina.'
>
> – Dr Mona El Zarif

The third group, implanted with recellularised lamina, showed structures like normal keratocytes after 1 month. These were more voluminous in the posterior surface of the lamina. With some patients they had dendritic shape after one year of implantation.

In all three groups, 12 months after the surgery the researcher noted gradual and significant increase in the cellularity of the anterior and posterior stromas of the patients in comparison to the preoperative density, with a *P*-value for this difference of less than 0.001 in the anterior and posterior stroma.

Mid corneal stroma

As the study progressed, the research team continued to make new

In groups 2 and 3, a significant increase ($P<0.001$) in cellularity in the anterior and posterior surfaces and within the lamina was observed 1 year after surgery.

Cell density

They found that cell density was significantly higher in patients implanted with recellularised laminas than in those implanted with decellularised laminas, both on the anterior surface and within the lamina ($P=0.011$), and on the posterior surface of the lamina ($P=0.029$).

After making its initial findings on cell density, the research team continued to follow up on this measurement.

After 1 year, group 3 had greater cell density than either group 2 or group 1 in the anterior stroma. It had greater cell density than group 2 in the anterior stroma, the anterior surface of the lamina, the mid stroma of the lamina and the posterior surface of the lamina.

Conclusion

In conclusion, Dr El Zarif said, confocal microscopy is an essential tool for the evaluation and monitoring "in vivo" of the ADASCs.

"It allowed a qualitative and quantitative assessment of the cells through the experiment," she said. "And it allowed monitoring of the progressive morphological changes that occurred in the implanted tissue in decellularised and recellularised laminas."

Dr El Zarif added that the technique assisted in determining the change in the cells' densities in the grafted tissue as well as in all the posterior and anterior corneal stroma.

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Dr El Zarif has no financial disclosures to declare.

Regenerative ophthalmology making waves in glaucoma therapy

Stem-cell-based regenerative approaches are showing promise in glaucoma

By Michelle Dalton

Degenerative diseases—including glaucoma—lack effective medical treatment. Stem-cell-based regenerative approaches are being investigated as one approach to potential treatment.

Interest in regenerative technologies has been ongoing for years—some as simple as local tissue repair or as complex as replacing epithelium or endothelium.

As part of the New Horizons Forum at the 2019 Glaucoma 360 meeting, leaders in the topic addressed some of the latest technologies in regenerative medicine and engineering during a panel discussion.

Moderated by David J. Calkins, PhD, University of Vanderbilt, Nashville, TN, USA, and Joel S. Schuman, MD, New York University-Langone Health, New York, NY, USA, the presenters included:

- **Adriana di Polo, PhD, University of Montreal, Canada, and the Louis J. Fox Center for Vision Restoration;**
- **Karl Kador, PhD, University of Missouri-Kansas City School of Medicine;**
- **Kenneth Mandell, MD, PhD, Neurotech Pharmaceuticals Inc.;**
- **Jeffrey L. Goldberg, MD, PhD, Beyers Eye Institute, Stanford University, Palo Alto, CA, USA.**

> 'Insulin can 'talk' to neurons, activate a signalling pathway, and then lead to normal neuronal function.'
>
> – Dr Adriana di Polo

Ganglion cell regeneration

Retinal ganglion cells (RGCs) are complex structures, with all of the electrical information that is transmitted by RGC axons to the brain first being received and integrated by structures called dendrites that emanate from the cell body, according to Dr di Polo.

"One of the first pathological changes that happen after glaucomatous injury is the retraction of RGC dendrites," she said.

Dr di Polo's latest study (with lead authors Luis Alarcon-Martinez, PhD, and Jessica Agostinone, MS), entitled "Regeneration of RGC Dendrites: The Role of Insulin Signaling to Stimulate Connections and Restore Vision in Glaucoma," was simple, she said.

"Can we bring RGCs in glaucoma and after optic nerve injury from a state where their dendrites are retracted and disconnected from important targets within the retina to a situation where they regenerate, reconnect, and then can serve to transmit the important signals that are going to lead to vision?" Dr di Polo asked.

Insulin—which is most associated with diabetes management—belongs to a family of proteins dubbed growth factors. As such, it plays an important role in neuronal function, she said.

"Insulin can 'talk' to neurons, activate a signalling pathway, and then lead to normal neuronal function," Dr di Polo said. By administering insulin two ways (intravenous and via topical eye drops), "we regained that nice complexity versus a group that was treated with vehicle acid control," she added.

There seems to be signals suggesting that the regenerated dendrites also reconnect with their targets, with insulin restoring the synaptic input. When the electrical activity of RGCs upon light stimulation is measured, Dr di Polo said insulin "promotes a very nice restoration of the amplitude of these responses that correspond to retinal ganglion selectivity."

IN SHORT

- ***Stem-cell-based approaches to reverse vision loss in glaucoma are showing good potential.***

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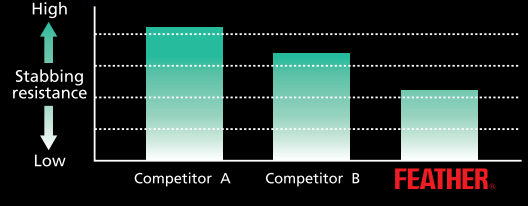

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Meshwork regeneration

Glaucoma is an optic neuropathy, said Dr Du, and the trabecular meshwork regeneration using stem cells may be a key.

"Our hypothesis was that restitution of the trabecular meshwork cell population may improve aqueous humor outflow and lower intraocular pressure (IOP), leading to new treatments for glaucoma." Her lab explored the viability of stem-cell-based therapy to restore the trabecular meshwork function.

The group began by isolating stem cells that were slow cycling, label-retaining cells in vivo.

"These were clonogenic multipotent and they can differentiate into functional trabecular meshwork cells," she said. The group first injected stem cells into the anterior chamber of healthy mice. While the stem cells attached to the trabecular meshwork, the fibroblasts attached "to wherever they can attach."

What this means is that stem cells can become functional cells, but some are still able to remain as stem cells until they are needed elsewhere. The group used a laser to damage part of the trabecular meshwork, then injected the stem cells, which also attached to the wound and repaired the corneal wound at the injection site.

> 'Stem-cell-based therapy for trabecular meshwork regeneration to treat glaucoma is feasible.'
>
> – Dr Yiqin Du

Stem cells suppress the inflammatory response, Dr Du explained. Fibroblasts exaggerated the fibrotic response and the inflammatory response, but, after stem-cell injection, fibrosis was dramatically prevented. Stem-cell-based therapy for trabecular meshwork regeneration to treat glaucoma is feasible.

Tissue engineering, inner retina

Stem cells that are injected into the subretinal space "have been shown to actually migrate into the retina, form synaptic connections, and then actually restore light responses," Dr Kador said.

But is that possible for RGCs, which have a "much more complex integration.

"They have to migrate in and form the synaptic connections with the injured retina, but then they have to also project their axon to the optic nerve. They have to grow through the optic nerve," Dr Kador said.

His lab created a scaffold that can offer physical guidance to replace those lost signals via electrospinning, which allows the researchers to produce micron-sized fibres. They designed a collector in which the fibres would run from an outer rim to an inner core.

"We found 81% of the ganglion cells were then directed to the centre of the scaffold," Dr Kador said.

RGCs produced their longest neurites on a laminin substrate, Dr Kador explained, which led to the development of a hydrogel (Matrigel) "that has a large laminate component that can actually produce those extended neurites" along with a high collagen component.

"When we transplanted the scaffolds that are cell-laden to an actual explant, using Matrigel to seal the tube together, we found that, in 60% of our cases, we are actually able to direct RGCs to the optic nerve head," Dr Kador said. "We can actually seed our RGCs onto our radial scaffolds and mimic the alignment of the retina."

CNTF implants for glaucoma

Neurotech Pharmaceuticals' encapsulated cell therapy has been implanted safely into over 300 subjects, noted Dr Mandell, chief medical officer, Neurotech. "We've shown that it is been viable for more than 2 years and we have the ability to deliver a wide range of proteins from this platform."

In a rare retinal disease (macular telangiectasias type 2), Neurotech delivers ciliary neurotrophic factor (CNTF).

Results of a Phase II study are complete and a 5-year, open-label extension study is under way. Patients treated with sham continued to progress with increasing loss of photoreceptors.

"What we've shown is quite remarkable," Dr Mandell said. "Not only does the CNTF treatment decrease the rate of progression, but between 2 and 3 years, it actually halts disease progression altogether."

He added that some patients have gone 11 years with the device still expressing therapeutic levels of the drug.

In glaucoma, "CNTF promotes the survival of RGCs and optic nerve crush models, and promotes the growth of axons into the visual cortex in animal models," he said.

A multicentre Phase II study is showing promise as a potential glaucoma treatment, he added.

Cell therapy shows promise

Encapsulated cells that excrete CNTF (Renexus, Neurotech) into the back of the eye are showing promise as a treatment for glaucoma in a multicentre, Phase II clinical trial, noted Jeffrey L. Goldberg, MD, PhD.

Humphrey visual field values improved in eyes implanted with the capsules, but declined in eyes treated with sham surgery and in fellow eyes, said Dr Goldberg.

The results are a step in the direction of reversing the vision loss in glaucoma, said Dr Goldberg, who presented the preliminary findings.

Can glaucoma patients benefit from cell-based therapy approach?

Sustained delivery, other treatment options may change landscape

By Louise Gagnon;

Reviewed by Dr Harry A. Quigley

Dr Quigley

The future of glaucoma will likely not resemble the current state of management of the disease, with numerous advances on the horizon, according to Harry A. Quigley, MD.

Delivering the Bryan St. L. Liddy Lecture on the topic of the future of glaucoma therapy during the annual Sally Letson Symposium, Dr Quigley stressed that patients are looking for treatments other than daily administration of eye drops.

"If I quit my career without having gotten rid of eye drops, then I will have failed," noted Dr Quigley, the A. Edward Maumenee Professor of Ophthalmology at Johns Hopkins School of Medicine, Baltimore, MD, USA. "We need sustained delivery in some form, so patients do not have to remember to take something everyday. Sustained delivery of IOP drugs will get around a lot of problems."

One of the advantages of sustained delivery resonates with patients, according to published research, which showed that glaucoma patients would consider these alternatives to daily eye drops if they avoided the need for surgery or showed superior efficacy over eye drops [*J Glaucoma*. 2018;27:328-335].

Patient adherence

Glaucoma patients have been largely left on their own to stick to a daily regimen of using eye drops. Some technology innovations have looked at trying to increase adherence. These include cell phone robo-calls or texts, noted Dr Quigley.

In one study, individuals randomly selected to receive reminders were more adherent to their therapy than those who were not. They increased adherence from 53% to 64% ($P<0.05$). However, there was no statistical change among the 32 participants in the control group [*JAMA Ophthalmol.*2014;132:845-850].

Another innovation is the Kali Drop device, a wireless monitoring device that provides accurate adherence monitoring, uses telephone feedback, and sends data to an ophthalmologist's office in real time.

"It will pop up on your screen if they (patients) have not touched their drops," said Dr Quigley.

Identifying progression

Identifying patients who will experience catastrophic worsening, and ruling out those who will not, can be done by modifying the frequency with which visual field tests are conducted, according to Dr Quigley.

"They represent under 10% of all patients, but we need to identify them as rapidly as we can," Dr Quigley explained.

Conducting an annual visual field test is not sufficient to identify patients who will have rapid progression of disease, underlined Dr Quigley.

"If you will do a (visual) field (test) a year, it will take you 4 or 5 years to detect the patient is worsening, and if they are one of these catastrophic worsening people, by then, the horse is already out of the barn," he said.

Dr Quigley routinely performs five field tests in the first 18 months with a new patient, as well as measuring IOP before initiating medical therapy, in order to detect patients with and without fast disease progression, resuming a schedule of annual visual field tests for those without fast disease progression.

"It is well worthwhile and I explain to the patient why we are doing this, that some people get rapidly worse," he said. "I also explain that at the end of doing this series of tests, we will know that patient is one of the people who will not get worse very fast at all and that patient can be re-assured."

However, better biomarkers are needed to reveal if patients with glaucoma are getting worse and at risk of losing their vision, Dr Quigley pointed out.

Biomechanical changes

One of the avenues of research to help uncover which patients will worsen quickly and which will not, is an

IN SHORT

- ***Sustained delivery is needed to ensure that patients do not have to remember to take their medication every day.***

examination of the biomechanics of the lamina cribosa, according to Dr Quigley.

Researchers have observed that the anterior depth of the lamina cribosa varies according to different IOPs, which can be viewed with optical coherence tomography [*Invest Ophthalmol Vis Sci.* 2017;58:2566-2577].

Additionally, glaucomatous eyes have been observed to not display the same degree of change in the lamina in response to IOP reductions as non-glaucomatous eyes. This observation and understanding the biomechanics of the sclera has led to new insights into the pathogenesis of glaucoma and has revealed new therapeutic targets and novel treatments like rho-associated protein kinase (ROCK) inhibitors [*Transl Vis Sci Technol.* 2018;7:6].

> 'If I quit my career without having gotten rid of eye drops, then I will have failed. We need sustained delivery in some form, so patients do not have to remember to take something every day.'
>
> – Dr Harry Quigley

Sustained-release delivery

Success in animal models is pointing to the sustained release of dorzolamide as a way to lower IOP and protect against the loss of retinal ganglion cells.

In both rat and rabbit glaucoma models, Dr Quigley and colleagues have achieved success with the injection of the therapy as microparticles, to halt the progression of glaucoma [*Mol Pharm*. 2016;13:2987-2995; *Transl Vis Sci Technol.* 2018;7:13].

"We have produced 3-month- long pressure lowering [of IOP] with delivery of one treatment," he noted. "The hope is that it will get to 6 months [between treatments]."

Going forward, researchers aim to take their work to the next step. The ultimate goal is ensuring that patients have positive results and improved quality of life.

Translating this animal research to patients is clearly possible, so that the future scenario of glaucoma treatment would mean patients make a visit to the ophthalmologists a couple of times in the span of a year.

"You would inject the patient every 6 months, and the patient would get in the car and drive home," he concluded. "That should be quite feasible."

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Dr Quigley did not indicate any proprietary interest relevant to the subject matter.

Quest for data increases debate over anti-VEGF therapy approach

Arguments can be made both for, against treating high-risk eyes

By Cheryl Guttman Krader;

Reviewed by Dr Charles C. Wykoff

Dr Wykoff

The threshold for initiating anti-VEGF therapy for an eye with diabetic retinopathy (DR) without diabetic macular edema (DME) is currently a matter of debate, and reasonable arguments can be made both in favour and against treating high-risk eyes with moderately severe to severe high-risk nonproliferative disease (NPDR).

More insight on this issue is expected to be forthcoming as data accumulate from prospective studies and are used to develop prognostic deep-learning algorithms.

In addition to considering interventional management of eyes with NPDR on an individualised basis, ophthalmologists would do well to concentrate on strategies that will bring more patients with diabetes in for ophthalmic care, said Charles C. Wykoff, MD, PhD, at the 2019 meeting of the American Academy of Ophthalmology.

"I do believe there is a signal that some patients with high-risk NPDR benefit from earlier intervention with anti-VEGF therapy," said Dr Wykoff, director of research, Retina Consultants of Houston and the Greater Houston Retina Research Foundation (GHRRF), and deputy chairman of Ophthalmology, Blanton Eye Institute, Houston Methodist Hospital, Houston, TX, USA. "The problem we face is identifying who these patients are."

Dr Wycoff pointed out that while additional information is gathered, there are additional challenges to be faced.

"I think a greater challenge than whether or not we should treat patients with NPDR without DME is simply to get these patients to undergo the recommended retinal screening exams," he said. "Unfortunately, a minority of patients with diabetes in the United States today are coming in for screening before they develop visual problems. We can do better."

Existing guidance

The current AAO Preferred Practice Pattern for DR, which was last updated in 2017, states that for severe NPDR, panretinal photocoagulation or intravitreal anti-VEGF therapy can be considered sometimes. Thus, the guidelines suggest individualising therapy decisions rather than providing specific direction on a population basis.

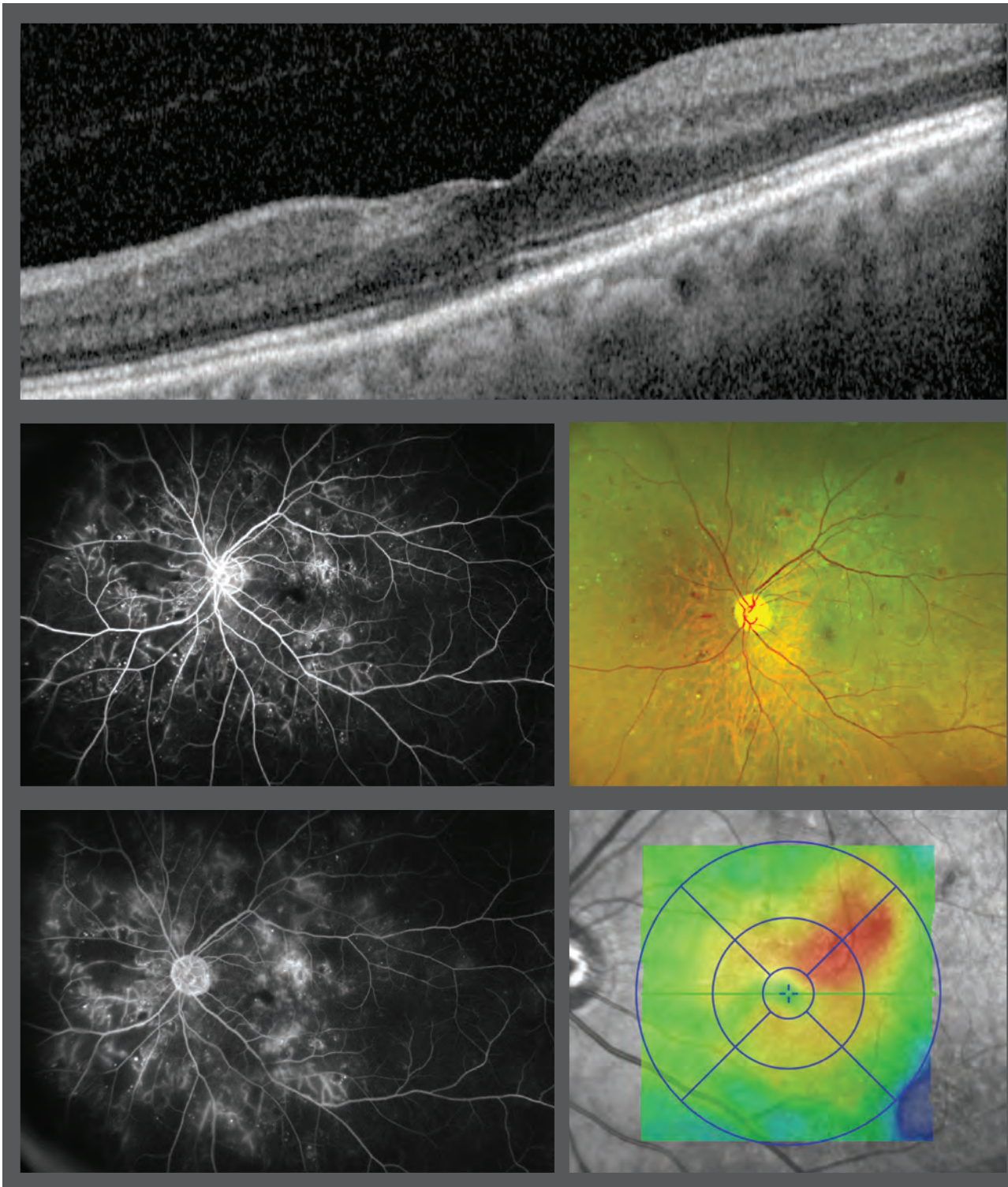
A role for anti-VEGF therapy in the treatment of high-risk NPDR derives from data collected in the DME registration trials for anti-VEGF agents. Data from studies of aflibercept (Eylea, Regeneron) and ranibizumab (Lucentis, Genentech) showed that with regular injections, approximately one-third of eyes with centre-involved DME (CI-DME), vision loss and DR, had a ≥two-step improvement in their Diabetic Retinopathy Severity Scale (DRSS) score. Stratification showed that eyes with moderate to severe NPDR (DRSS score of 47 to 53) were particularly likely to benefit with the DRSS improvement relative to those with mild disease or PDr

Because of such data, two large and rigorously designed Phase III trials were initiated to investigate the safety and efficacy of aflibercept treatment for moderately severe to severe NPDR in patients with good baseline vision. DRCR.net Protocol W, which is fully enrolled with 322 participants that have clinically-diagnosed severe NPDR without DME and VA ≥20/25, is comparing sham treatment and intravitreal aflibercept 2 mg × two monthly injections and then every 16 weeks (Q16W) for 2 years, then treatment as needed for 2 years. Results from the primary endpoint are not anticipated for about 2 years, Dr Wykoff said.

Primary outcome data are available from PANORAMA that randomly assigned 402 patients

IN SHORT

- ***The threshold for treatment with an anti-VEGF agent for diabetic retinopathy without diabetic macular edema is controversial. Two Phase III studies are now investigating aflibercept for moderately severe to severe nonproliferative diabetic retinopathy in patients with good vision.***



(FIGURE 1) Images from a 72-year-old male with type II diabetes mellitus (HbA1c 9.4, BCVA 20/25, CRT 305 microns, DRSS 53) show no CI-DME and extensive areas of retinal non-perfusion on wide-field fluorescein angiography.
(Images courtesy of Dr. Wykoff)

with moderately severe to severe NPDR without DME and VA ≥20/40 to sham injection, aflibercept 2 mg Q16W (following four loading doses), or aflibercept 2 mg Q8W (following five loading doses).

Baseline data showed that enrolled patients had excellent vision (mean visula acuity 20/25) with normal central retinal thickness in these eyes without DME. Most eyes were asymptomatic

The primary endpoint analysed the proportion of eyes with a ≥two-step improvement in DRSS at weeks 24 and 52, and the results showed a highly statistically significant difference favouring both the aflibercept Q16W and Q8W groups versus sham treatment at 52 weeks. (65% and 80% versus 15%, respectively).

A secondary endpoint analysis showed vision was generally stable in all groups. At 1 year, the aflibercept groups had a mean gain of approximately 1.5 letters and patients in the sham injection arm gained an average of 0.3 letters.

According to Dr Wykoff, the patients in PANORAMA started with excellent vision, and so there was no reason to expect that they would have gained vision.

"For the most part, the primary issue for these patients is that they are able to see well and maintain their vision," he said. "What their fundus photographs look like is of secondary concern to most patients."

Considering such clinically relevant endpoints, Dr Wykoff suggested that the most interesting finding from the 1-year data collected in PANORAMA comes from the prespecified safety analysis looking at the development of PDR and CI-DME, clinical endpoints that physicians and patients would prefer to avoid.

This meaningful secondary analysis showed the rate of progression to PDR or CI-DME, was significantly lower in the aflibercept Q16W and Q8W arms compared with sham (11% and 10% versus 41%, respectively).

"The benefit of aflibercept Q8W and Q16W represents a relative reduction in each of these categories of about 70–85%," Dr Wykoff said.

Dr Wykoff pointed out that researchers know they can take eyes that have many haemorrhages and turn them into eyes with fewer haemorrhages.

"The question of whether that affects long-term outcome and/or treatment burden is still being studied, and sets up a theoretical debate between those who believe this data is paradigm shifting and those who think it is important data but at this time does not change practice pattern," he said.

Pros versus cons

Dr Wykoff identified several arguments favoring both sides of the debate.

The idea that anti-VEGF treatment is paradigm shifting is supported by the data that shows earlier treatment significantly decreases the probability of developing PDR or CI-DME, both of which can be used as indications to initiate treatment.

Second, there is evidence from studies of anti-VEGF therapy for CI-DME with vision loss and for exudative age-related macular degeneration that earlier treatment initiation is associated with a better long-term outcome and perhaps a reduced treatment burden over the long-term.

In addition, and perhaps most interesting according to Dr Wykoff's perspective, it is known that anti-VEGF treatment can slow the development and progression of retinal nonperfusion, which is believed to be the core vascular pathology underlying Dr

There are population-based data indicating that NPDR without DME is associated with reduced visual function and quality of life.

Recent data from the IRIS registry show that, in the era when anti-VEGF and laser treatment are readily available, severe NPDR in addition to PDR predict rates of vision loss and blindness that are higher than in eyes with earlier stages of Dr

> 'The benefit of aflibercept Q8W and Q16W represents a relative reduction in each of these categories of about 70–85%.'
>
> – Dr Charles C. Wykoff

In comparison, those who believe that the data from PANORAMA is interesting but do not support widespread use of anti-VEGF treatments for high-risk NPDR without DME at this time can point to the fact that 59% of sham eyes did not develop PDR or CI-DME. Therefore, routine treatment would result in patients receiving injections that may not be required.

Second, intravitreal injections do carry risks.

Third, there are no data at this time to show that anti-VEGF treatment initiated before an eye develops early PDR or DME improves long-term functional outcomes or reduced treatment burden.

Finally, there is a need for longer-term data on compliance with treatment and durability of the benefit.

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This article is was adapted from Dr Wycoff's presentation at the 2019 meeting of the American Academy of Ophthalmology. Dr Wykoff is a consultant for and performs research in collaboration with companies that market anti-VEGF therapies.

Biweekly anti-VEGF targeted as potential wet AMD treatment

Support for prospective investigation of biweekly dosing for refractory nAMD

By Cheryl Guttman Krader;

Reviewed by Dr Eric W. Schneider

Dr Schneider

Biweekly anti-VEGF dosing is a potential option for treating neovascular age-related macular degeneration (nAMD) that is refractory to chronic monthly injections, according to Eric W. Schneider, MD.

Dr Schneider's statement was based on a retrospective case series of 18 patients that found significant reduction in refractory intraretinal and subretinal fluid along with improvement in visual acuity after receipt of five biweekly doses. The gains achieved with biweekly dosing were reduced but not completely eliminated after patients returned to standard of care monthly dosing. No serious ocular or systemic safety events were noted during the study period.

"Our ability to make any definitive conclusions about the safety and efficacy of biweekly dosing to treat refractory nAMD is limited by the study design. It is a small, retrospective analysis utilising various combinations of different anti-VEGF agents and biweekly dosing regimens," said Dr Schneider, private practice, Tennessee Retina, Nashville, TN, USA.

> 'One approach is to increase the monthly dose of the anti-VEGF agent.'
>
> – Dr Eric W. Schneider

"The results are encouraging, however, and have led us to initiate a prospective study (TRISTAR) investigating biweekly aflibercept (Eylea, Regeneron) in a similarly refractory patient population," he added. "The study is currently fully enrolled with 22 patients with the last patient's last visit expected in November."

Dr Schneider noted that the study was an outgrowth of frustration with his inability to completely dry the macula in a subset of patients with nAMD. Despite aggressive monthly anti-VEGF therapy, persistent intra- and subretinal fluid remains a common challenge in treating patients with nAMD.

"We see evidence of this in our real-world clinical practices as well as in major clinical trials with all of the available anti-VEGF agents," he said.

Dr Schneider pointed out that there are limited options to escalate therapy in this refractory population.

"One approach is to increase the monthly dose of the anti-VEGF agent," he explained. "This has been looked at in prospective fashion in several trials with mixed results. A second approach is to increase the frequency of dosing, an approach for which there is limited data available in the literature."

For the current study, patients were identified through a billing record search for those diagnosed with exudative AMD having more than ten claims for intravitreal injections over a 12-month period. The study included only patients with refractory nAMD receiving at least five consecutive biweekly (12–21 days) anti-VEGF injections with 2-week follow-up visits after the fifth biweekly injection, and a minimum of 12 months of follow-up after starting biweekly therapy.

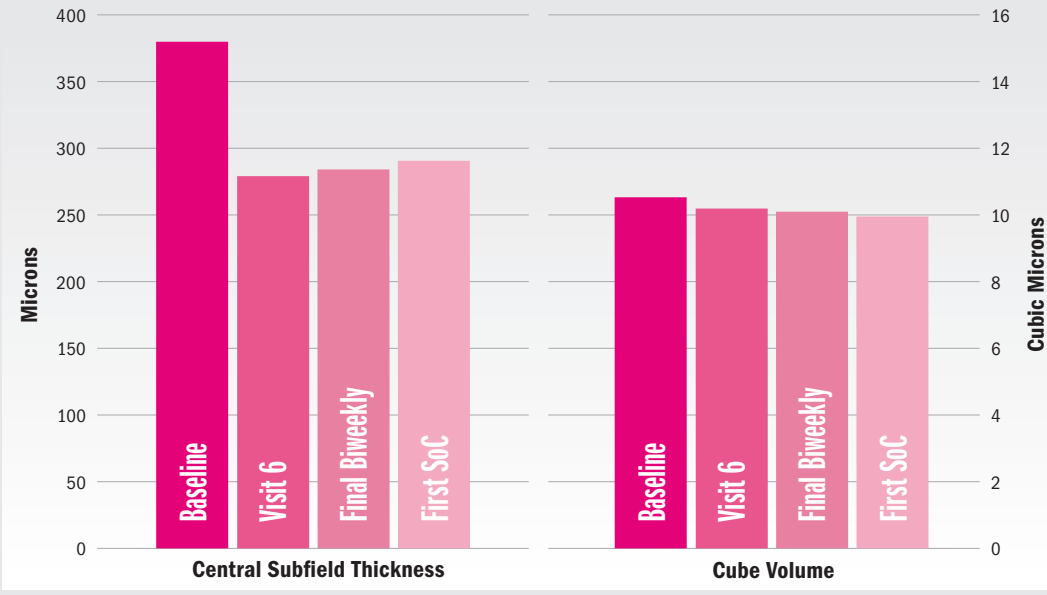
For purposes of the study, refractory disease was defined as persistent intra-/subretinal fluid on spectral domain OCT after at least six consecutive monthly (28–35 days) anti-VEGF injections.

The primary outcome looked at changes in BCVA and multiple OCT-based anatomic metrics from baseline to the sixth visit, which was 2 weeks after the fifth biweekly injection.

Secondary endpoints evaluated changes when patients had their final biweekly visit and their first standard-of-care visit, which was defined as the first

IN SHORT

- ***Research finds a reduction in refractory intraretinal and subretinal fluid along with improvement in visual acuity after receipt of five biweekly doses.***



*Significant decrease versus baseline (paired *t*-test).

(FIGURE 1) A retrospective case series of 18 patients found significant reduction in refractory intraretinal and subretinal fluid along with improvement in visual acuity after five biweekly doses. *(Data courtesy of Dr Schneider)*

visit at least 4 weeks after a prior injection.

The 18 patients who were included in the study had received standard anti-VEGF dosing for a mean of 35.4 months prior to beginning biweekly treatment. Approximately three-fourths of the patients had been treated with a combination of ranibizumab and aflibercept; only 5.6% had received standard dosing with bevacizumab monotherapy.

Mean Snellen BCVA at baseline was 20/82, mean central foveal thickness was 333.6 µm, 28% of patients had intraretinal fluid, and subretinal fluid was present in 89% of eyes.

The mean number of biweekly injections for the group was 18.1 and the treatments were given at a mean interval of 16.5 days.

A single patient (5%) received treatment with a single anti-VEGF agent whereas the rest received various combinations of ranibizumab (Lucentis, Genentech), aflibercept, and bevacizumab (Avastin, Genentech).

The analysis of anatomic outcomes showed statistically significant improvement in central subfield thickness (CST) and cube volume at the primary outcome visit and at the final biweekly visit. The improvement in CST was not sustained at the first standard of care visit.

"About 35% of patients achieved complete resolution of subretinal fluid during biweekly dosing, although this effect waned somewhat upon return to standard of care dosing and the impact of biweekly dosing on the resolution of intraretinal fluid was less notable," Dr Schneider reported.

Visual acuity also improved significantly at the primary outcome visit (sixth visit), reaching a mean of 20/51, but it worsened to 20/65 at the final biweekly visit and was 20/67 at the first standard of care visit. About 70% of patients maintained or gained vision and the majority gained at least one line of vision at all three assessments.

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This article is adapted from Dr Schneider's presentation at the 2019 meeting of the American Society of Retina Specialists. Dr Schneider is a consultant to and receives research grants from Regeneron.

Making the ROP diagnosis: Technology versus humans

Artificial intelligence may hold promise in recognising retinopathy of prematurity

By Rachael Zimlich;

Reviewed by Dr Michael F. Chiang

Although nothing may ever totally replace the healing hands of a good physician, a new study reveals that artificial intelligence (AI) outperformed several ophthalmology specialists in diagnosing a potentially blinding disease that affects premature infants.

Michael F. Chiang, MD, a professor of Ophthalmology and Medical Informatics and Clinical Epidemiology at the Oregon Health and Science University (OHSU) School of Medicine, Portland, OR, USA, and a paediatric ophthalmologist at the Elks Children's Eye Clinic, OHSU Casey Eye Institute, Portland, and co-author of the report, said the study shows that AI may hold promise in aiding the diagnosis of retinopathy of prematurity (ROP) in babies.

"Computer and information technologies are dramatically changing the practice of medicine, and require that people from different clinical and scientific backgrounds work together," he said.

The study evaluated 5,511 retinal photographs using a new diagnostic algorithm with five-fold cross-validation.[1] The algorithm achieved 91% accuracy, outperforming six of eight ROP specialists.

ROP develops when abnormal blood vessels grow and spread through the retina, and begin to leak and detach, scarring the retina and displacing it, according to the National Institutes of Health (NIH). A common cause of vision loss in childhood, roughly half of the 28,000 children born each year in this population type are affected. Although some cases are mild and require no intervention, about 1,500 of infants born with ROP require medical treatment and 400–600 infants become legally blind.

ROP is treated based on the presence of "plus disease," a dilation and tortuosity of retinal vessels. Clinical diagnosis of this disease is subjective and variable, notes the report, and the goal of the study was to determine whether technology could aid in developing improved diagnostic tools.

ROP is traditionally diagnosed through an examination using dilation of the eyes and indirect ophthalmoscope in neonatal intensive care units (NICUs).

IN SHORT

- ***A recent study reveals how diagnostic algorithms may achieve 91% accuracy, outperforming retinopathy of prematurity specialists.***

"This is time intensive and logistically difficult for ophthalmologists, neonatologists, and NICU staff," Dr Chiang said. "Because of these challenges, telemedicine has become increasingly popular as an alternative method for ROP diagnosis in which retinal photographs are taken—often by NICU nurses—and transmitted securely to a remote ophthalmologist for diagnosis."

The study demonstrates that computer-based diagnosis of "plus disease" had comparable or better diagnostic accuracy compared with a group of eight clinicians. Of the 5,511 retinal photographs examined, 82.3% were found to be normal, 14.6% were classified as pre-plus disease, and 3.1% were diagnosed as plus disease—results superior to those of human experts examining the patients.

"I hope computer-based tools like this will eventually improve the quality and delivery of ROP care," Dr Chiang said. "This study is an example of how these tools can help provide diagnostic advice to ophthalmologists and neonatologists—and ultimately, improve the quality of care for babies at risk for ROP."

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Dr Chiang did not indicate any proprietary interest in the subject matter.

Study recommends vigilant eye screenings in JIA disease

JIA patients encouraged to adhere to examination schedule

By Lisette Hilton;

Reviewed by Dr Karen N. Watanabe Duffy

The clear message to paediatricians from a recent prospective study looking at new onset uveitis risk in juvenile idiopathic arthritis (JIA) is to encourage patients and families to get the recommended eye exams, even when patients do not have ocular or joint symptoms.[1]

JIA is the most common paediatric rheumatic disease and uveitis is one of its most frequent and potentially devastating extra-articular manifestations with complications that can compromise eyesight, according to the article's senior author, Karen N. Watanabe Duffy, MD, FRCPC, a rheumatologist in the Division of Rheumatology, Department of Pediatrics, at the Children's Hospital of Eastern Ontario (CHEO), Ottawa, Ontario, Canada.

"JIA-uveitis is most often asymptomatic, and those who are at highest risk for uveitis are younger children who are diagnosed with JIA before the age of 7 years and those with a positive antinuclear antibody (ANA). Children with JIA should have screening eye examinations for at least 5 years after JIA diagnosis," said Dr Watanabe Duffy, who is also associate professor of paediatrics, University of Ottawa, Canada.

JIA and uveitis

The prevalence of JIA is about 1–4 for every 1000 children,[1] and when JIA-associated uveitis does occur in these patients, more than half will develop vision-threatening complications.

Early detection and vigilant screening are essential to reduce ocular complications, including blindness, Dr Watanabe Duffy writes.

Key points from the study

Dr Watanabe Duffy and colleagues studied data from the Research in Arthritis in Canadian Children Emphasizing Outcomes (ReACCh-Out) inception cohort, including 1183 patients enrolled within 6 months of their JIA diagnosis. The researchers report 87 of those patients, who were followed for up to 5 years, developed new-onset uveitis post-enrollment.

The researchers found the incidence of new-onset uveitis was 2.8% each year in the first 5 years after diagnosis. Whereas the annual incidence fell slightly from the first through fifth year post-JIA diagnosis, incidence was still 2.1% in the fifth year.

Notably, JIA subtype and female sex were not independent predictors for JIA-related uveitis. Rather, being aged younger than 7 years at JIA diagnosis and having positive ANA were independent predictors, according to the paper published in *Arthritis Care and Research*.

> 'This article is the first to demonstrate the yearly incidence of uveitis, highlighting the importance of vigilance in screening.'
>
> – Dr AnneMarie C. Brescia

"This article is the first to demonstrate the yearly incidence of uveitis, highlighting the importance of vigilance in screening. [It's] important to note, although we concentrate on the younger patient, the oldest patient was 18.4 years at uveitis diagnosis. So, although less likely, uveitis can still appear in older children," according to AnneMarie C. Brescia, MD, FAAP, FACR, chief of paediatric rheumatology at Nemours/Alfred I duPont Hospital for Children, Wilmington, DE, USA. Dr Brescia is not an author on the paper.

Although paediatric rheumatologists make it a point to encourage JIA patients to get recommended ophthalmology screenings, it's often not enough to

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- ***A prospective study highlights the importance of vigilance in screening for new-onset uveitis after a diagnosis of juvenile idiopathic arthritis.***

get families and patients to comply, according to Sheila T. Angeles-Han, MD, MSC, associate professor of paediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA.

What paediatricians need to know

Families might not understand the urgency of going for regular screenings when their children don't have symptoms and aren't suffering. The demand on families can be substantial, said Dr Angeles-Han, whose research focus is in uveitis associated with JIA, but she is not an author of the paper featured here.

> 'Some patients think that because their arthritis is well controlled, they don't need to continue with their eye screenings with ophthalmology, but the arthritis and uveitis activity don't parallel each other.'
>
> - *Dr Sheila T. Angeles-Han*

"Children who are at highest risk for uveitis need regular ophthalmology screening every 3 months for several years. [Because] they often have no symptoms, the best way to screen is through a slit-lamp examination. The frequent visits can be a burden for families, but that's the only way to detect eye inflammation unless the child has developed eye complications. By then, the damage from uveitis has occurred. You want to detect the uveitis before you get complications," Dr Angeles-Han said. "[Because] these children are regularly seen by their paediatricians with whom they have a close relationship, I think it's important that paediatricians emphasise the importance of screening, as well."

For how often those visits should occur according to risk, paediatricians can refer to "Ophthalmologic examinations in children with juvenile rheumatoid arthritis" published in 2006 in *Pediatrics*.[2]

They can also refer to the "Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative," in an open-access paper[3] published August 2018 in the *Annals of the Rheumatic Diseases*.

"Ongoing monitoring by the paediatrician is crucial to ensure that patients undergo eye examinations on a recommended and ongoing basis according to contemporary and audited screening protocols," Dr Watanabe Duffy writes.

Dr Angeles-Han said paediatricians should note that JIA patients need the screenings even when their arthritis is inactive or well controlled.

"Some patients think that because their arthritis is well controlled, they don't need to continue with their eye screenings with ophthalmology, but the arthritis and uveitis activity don't parallel each other. You can have arthritis that's in remission or inactive and still develop the uveitis," Dr Angeles-Han said.

Paediatricians should also note that ophthalmologists might treat JIA-associated uveitis with systemic immunosuppressive medicines when topical medicines are insufficient or result in adverse effects, such as glaucoma or cataracts, according to Dr Brescia.

"Kids with JIA who are not on immunosuppressive medications can get all the vaccines," according to Dr Brescia. "Kids with JIA on systemic immunosuppressive medicines should not get the live virus vaccines."

Uveitis risk and JIA treatment

Medications used to treat arthritis, including methotrexate and some of the tumour necrosis factor (TNF) inhibitors, are also used to treat uveitis, according to Dr Angeles-Han. Research is showing that being on these medications for JIA may change whether a child will develop uveitis, she said.

However, children with JIA who are in the process of tapering and stopping systemic immunosuppressive therapy after a period of remission are at risk for developing new-onset uveitis, according to Dr Watanabe Duffy.

"It is recommended that those who discontinue such treatment should have screening eye examinations every 3 months for 1 year," Dr Watanabe Duffy writes.

The researchers note that a limitation of the study was that it was only for 5 years.

"It would be important to determine what the risk is after that 5-year period," Dr Angeles-Han said.

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Triage in ocular emergencies: What clinicians need to know

How paediatricians can quickly assess need for referral to an ophthalmologist

By Mary Beth Nierengarten;

Reviewed by Dr Donny Suh

Dr Suh

Dr Shah

Five minutes. That's how long it takes to do a basic eye exam to determine how urgent an ocular problem is and the appropriate approach for treatment. It is an exam that every paediatrician, paediatric emergency medicine physician, and other frontline clinicians need to know when presented with a child with an ocular problem, particularly those who present to the emergency department (ED).

"The first person to see the child in case of an eye emergency can be of enormous value in preventing and treating the eye injury and subsequent visual loss," said Donny Suh, MD, FAAP, chief of Pediatric Ophthalmology and Adult Strabismus, Children's Hospital and University of Nebraska Medical Center, Omaha, Nebraska, USA.

As a paediatric ophthalmologist, Dr Suh typically is not the first person to see an eye injury in a child and relies on the diagnostic and clinical skills of paediatricians and other frontline clinicians to know when an eye injury warrants referral to an ophthalmologist.

To help paediatricians and other frontline clinicians better understand when such a referral is needed, and how timely that referral needs to be, Dr Suh provided some basic information about how to diagnose and triage a child who presents to the ED with an eye injury.

Dr Suh was joined in the discussion by Binita R. Shah, MD, FAAP, Distinguished Teaching Professor of Emergency Medicine and Pediatrics, State University of New York (SUNY) Downstate Medical Center, Brooklyn, NY, USA, who spoke from the perspective of paediatric emergency medicine physician. They presented a number of case studies (see examples in Table 1) on how to diagnose a given eye problem and, importantly, how to triage the patient based on the urgency of the injury.

Both Dr Suh and Dr Shah provide a practical step-by-step approach to evaluate and manage the paediatric ocular injuries resulting from trauma, infections, and tumours.

Five questions in 5 minutes: what to ask

Dr Suh began by talking about the importance of the simple 5-minute eye test that consists of five eye exams that every clinician needs to know (Table 2).

According to Dr Shah, these eye exams are well known to physicians and are a part of their medical training. For children who arrive in the ED with an eye injury, using this 5-minute test is critical to appropriately triage the child based on the urgency of the condition.

> 'The first person to see the child in case of an eye emergency can be of enormous value in preventing and treating the eye injury and subsequent visual loss.'
>
> – Dr Donny Suh

"This is very important," said Dr Shah. "Within 5 minutes, you can do five essential eye examinations that will enable you to figure out if the patient has an emergency problem, an urgent problem, or a routine problem."

For a child who has an injury that is considered an emergency (immediate) or one that is considered urgent (can wait to be evaluated/treated within 24–48 hours), a paediatric ophthalmologist should

IN SHORT

- ***When a child presents with an eye injury, frontline clinicians should implement this 5-minute eye exam to quickly recognise what treatment is warranted and when to refer to an ophthalmologist.***

Table 1. Presenting symptoms, diagnosis and take-home message

PRESENTING SYMPTOMS	DIAGNOSIS	TAKE-HOME MESSAGE
PATIENT 1 Previously healthy infant presents with periorbital skin rash.	Ocular herpes simplex viral infection (HSV)	■ May present with recurrent ocular infections. ■ Topical corticosteroids by themselves are contraindicated. ■ HSV keratitis is a major cause of blindness. ■ If patient has history of HSV keratitis, always check fluorescein test and then refer, if the test is positive.
PATIENT 2 Adolescent with history of dry eyes presents with intense eye pain, excessive tearing, and foreign body sensation in the eye.	Corneal abrasion	■ Never dispense topical anaesthetic for continued use. ■ Use frequent antibiotic ointment. ■ Consider cycloplegic agent. ■ Systemic analgesics. ■ No patching needed in most cases.
PATIENT 3 An 11-month-old infant presents with anaemia and weight loss.	Neuroblastoma	■ Most common metastatic tumour of the orbit (about 20% of patients with neuroblastoma). ■ Red flag: “racoon eyes” without history of trauma.
PATIENT 4 Adolescent male hit in the eye with a ball in the gym; now complains of eye pain and somnolence.	Hyphema	■ Without history of trauma, exclude underlying disease such as coagulopathy or sickle cell disease. ■ Management includes bed rest, head elevation, avoiding sports, using an eye shield (not patch), acetaminophen for pain (avoid ibuprofen); admit to hospital if home situation is unreliable.
PATIENT 5 A 6-year-old boy with history of rhinorrhea, cough for 12 days, and temperature of 104°F; not able to open his eye.	Orbital cellulitis	■ Recognise cardinal signs of orbital cellulitis (proptosis with globe displacement, impaired ocular motility, loss of visual acuity, ophthalmoplegia). ■ Hospitalisation and emergent consultations with ophthalmologist and otolaryngologist. ■ Begin treatment with IV antibiotics with very close monitoring; some patients may need surgical intervention.
PATIENT 6 Child accidently splashes the eye with an unknown solution.	Chemical injury	■ Initial treatment is irrigation, checking the pH, followed by more irrigation. ■ Timing of initial irrigation is key. ■ Preventive injury: counsel parents about safety locks for laundry detergent and household cleaning products.
PATIENT 7 Adolescent male presents with blurry vision and eye pain after a forceful blow to the eye.	Ruptured globe	■ Stop further manipulation of the eye! ■ Immediate consult needed. ■ IV antibiotics. ■ Tetanus. ■ Pain control/antiemetic. ■ Do not patch. ■ Do not remove FB that perforates the globe. ■ Protect the eye.
PATIENT 8 A 2-year-old previously healthy child incidentally noted to have white reflex of the eye (leukocoria).	Retinoblastoma	■ Presence of bilateral red reflexes suggests absence of cataracts or other intraocular pathology. ■ Abnormal red reflex: almost always concerning.
PATIENT 9 Infant admitted for bronchiolitis with chest radiograph showing incidental finding of bilateral rib fractures.	Abusive head trauma (shaken baby/impact syndrome) • Retinal haemorrhages • Acute subdural haematoma • Metaphyseal chip fractures • No external signs of trauma	■ Typically, numerous retinal haemorrhages, extensive, and involving multiple layers of the retina. ■ Diffuse retinal haemorrhages in macula and periphery. ■ Seen in 75–90% of cases. ■ Abuse NOT excluded if no indication of haemorrhages.

Abbreviations: FB, foreign body; IV, intravenous.
From Shah and Suh (2018).

be included to either confirm the diagnosis and/or manage treatment.

The rest of the discussion was devoted to presenting case studies to illustrate how a paediatrician, paediatric emergency physician, or other frontline clinician would approach a child presenting with given symptoms by first using the 5-minute exam and then deciding on the appropriate triage.

> 'Within 5 minutes, you can do 5 essential eye examinations that will enable you to figure out if the patient has an emergency problem, an urgent problem, or a routine problem.'
>
> - Dr Donny Suh

Case studies

A number of case studies were presented to illustrate the diagnostic and triage approach to each. Dr Shah opened each case study by describing the presenting symptoms of a child, giving the audience time to weigh in (online using an app downloaded onto their smartphones, iPads, and other devices) on the diagnosis and/or initial treatment, and then discussing the correct answer.

"As the focus of our [discussion] was on ocular emergencies [related to either acute injuries, infections, or tumours], every case study included the need for an ophthalmologist," said Dr Shah, adding that each case study required referral to an ophthalmologist either for confirmation of the diagnosis or referral for treatment.

Summary

It is important for paediatricians, paediatric emergency room physicians, and other frontline clinicians to implement a 5-minute eye exam when presented with a child with an eye injury to quickly recognise whether the injury warrants emergency attention, urgent attention, or is routine. Referral to a paediatric ophthalmologist is warranted for most emergency and urgent cases.

Table 2. Five essential eye exams in 5 minutes

	DETAILS	TRIAGE
1 VISUAL ACUITY	■ Patch the eye for accurate vision testing. ■ Do a physical exam.	■ If vision is poor, consider it urgent or emergent. ■ If patient has only light or no light perception, it is an emergency.
2 PUPIL	■ Signs of intraocular damage: eye swelling with no view of the pupil. ■ Suspected corneal abnormality: fluorescein stain with topical anaesthetic or saline, moistened fluorescein strip, or fluorescein (orange colour); fluoresces yellow-green when exposed to blue light.	■ If pupil abnormalities noted, refer to eye specialist.
3 EXTERNAL EXAM	■ Pull eyelid with history of trauma, foreign body, or lid laceration.	■ This is an urgent situation.
4 MOTILITY	■ Double vision: warning sign indicating a possible blowout fracture.	■ This is an emergency situation.
5 FUNDUS EXAM	■ Attempt to look at the fundus if possible. Look for signs of optic nerve swelling.	■ Depending on what the fundus exam shows, the patient would need either emergency or urgent evaluation, e.g., retinal haemorrhages in an infant indicate abusive head trauma. This is an urgent situation.

From Shah and Suh (2018).

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Vivior's visual monitor objectively measures behavioural data

Vivior introduces its visual monitor, a novel wearable device that designed to objectively measure patients' behavioural data prior to vision correction interventions. The system collects daily activity data from patients, processes the data in the cloud and the patient's lifestyle patterns using machine-learning algorithms.

Our objective behavioural data support ophthalmic surgeons to provide personalised solutions to their customers and patients, said the company in a prepared statement.

At this autumn's meeting of the European Society of Cataract and Refractive Surgeons, attendees were able to try out the monitor to experience first-hand the effect of having objective behavioural data. In an instructional course, healthcare professionals also learned about the benefits of data-driven decision processes.

Prof. Michael Mrochen, chairman of the Board of Directors, explains: "With this launch event, we start the success story of Vivior in cataract refractive surgery to ensure the best possible outcomes for patients and surgeons."

Arthur Cummings, chairman of the Medical Advisory Board, adds: "Imagine having everything you need to select the most appropriate lens design for your patient, all based on objective data."

For more information, go to www.vivior.com

Oculus licenses predictive algorithm developed by BHVI

BHVI and Oculus announced an agreement that will see Oculus incorporate BHVI's algorithms for tracking and estimating refractive error into its Myopia Master ophthalmic instruments developed for the myopia management.

The device combines all the important measurement methods of myopia management: axial length, refraction values, and the central corneal radii, according to Oculus.

"This license agreement is another example of the cutting-edge technologies that BHVI is engaged in. BHVI literally 'wrote the book' on myopia when its seminal research paper Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050 was published in 2016. Our agreement with Oculus will see our research translated into more instruments that ... can [be used] to manage myopia, globally," said Yvette Waddell, BHVI's CEO.

"Using large and expansive datasets generated on our own and in collaboration with our research partners across the globe, the team at BHVI is continually engaged in expanding the state of knowledge as well as bringing solutions to reverse the rising myopia epidemic. We are delighted for the opportunity to work together with leading ophthalmic industry such as Oculus to translate some of this knowledge," said Prof. Padmaja Sankaridurg, head of myopia programme at BHVI.

"Through working with and incorporating BHVI's unique technology into our Myopia Master suite of offerings, we can continue to deliver world class instruments to our clients," said Christian Kirchhübel, chief executive officer of Oculus.

For more information, go to www.bhvi.org

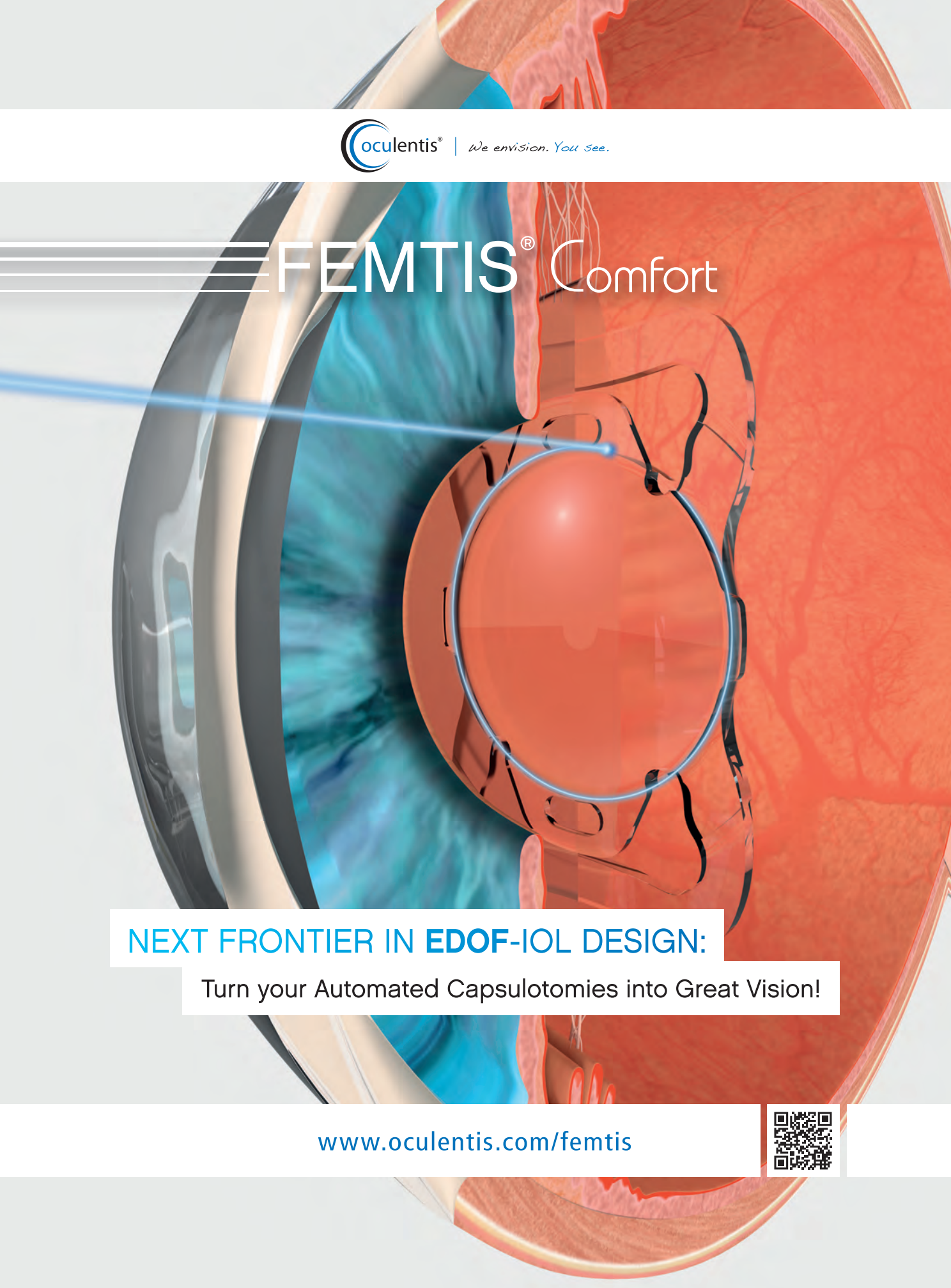
Ziemer debuts Aquariuz ablation laser for refractive

Ziemer Ophthalmic Systems AG presents its new Aquariuz ablation laser. The compact, solid-state ablation laser for refractive surgery is based on the latest technological improvements and can be easily integrated with Ziemer's femtosecond lasers (FEMTO LDV Z-Models) and diagnostic devices (GALILEI G-Models).

"The progression toward a refractive suite is a logical and consistent step toward the future. We have further developed the basic idea of the FEMTO LDV line with the Aquariuz to provide a perfectly complementary system. The surgeon thus has one complete refractive platform as a comprehensive solution for his or her current needs and a reliable companion into the future," said President and CEO Frank Ziemer.

The Aquariuz is neither CE marked nor FDA cleared and therefore not commercially available in the United States and in all other countries.

For more information, go to www.ziemergroup.com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