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International Glaucoma Review

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2015

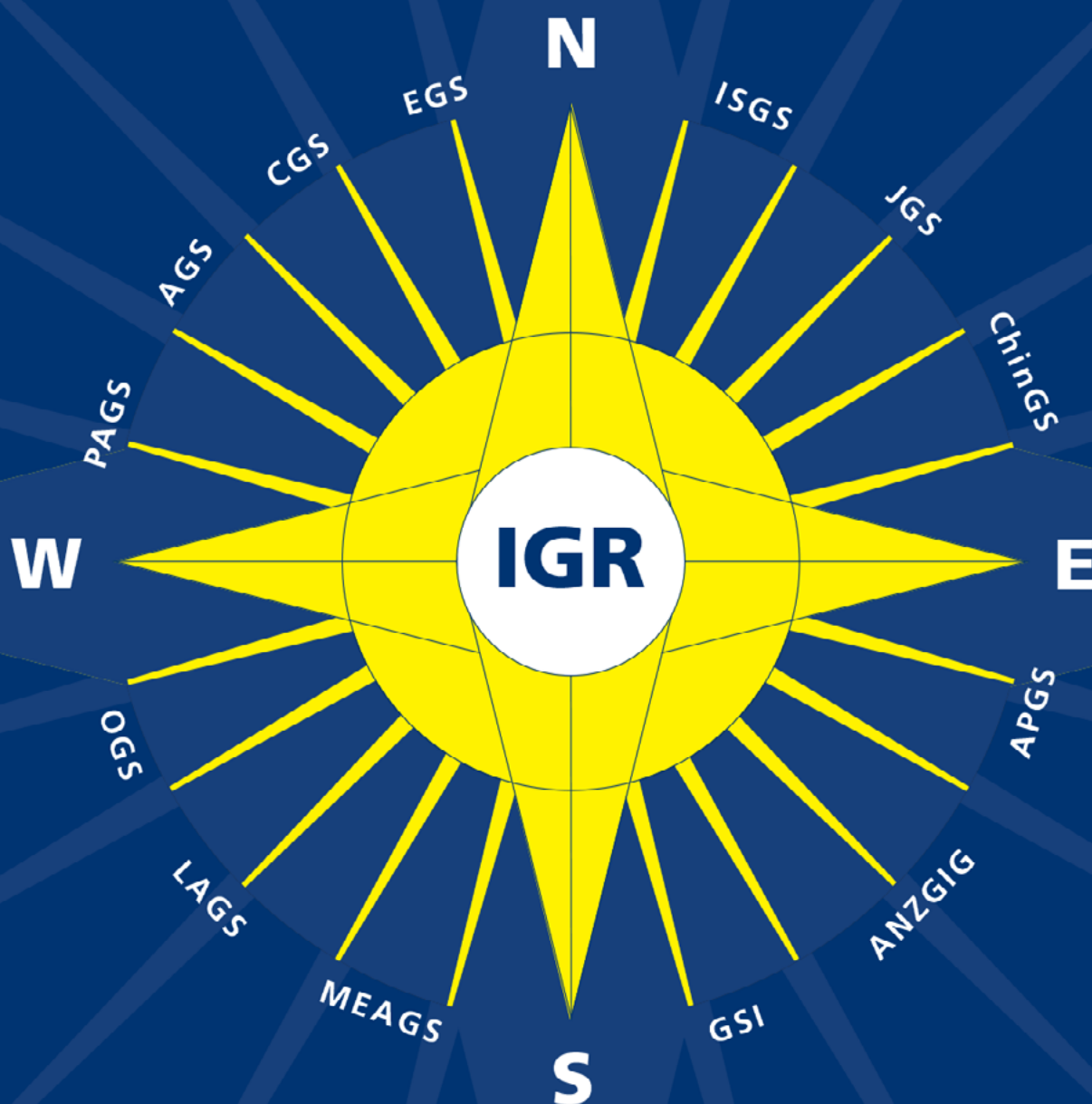
The journal of the World Glaucoma Association

Abstracts and Review of Glaucoma Literature

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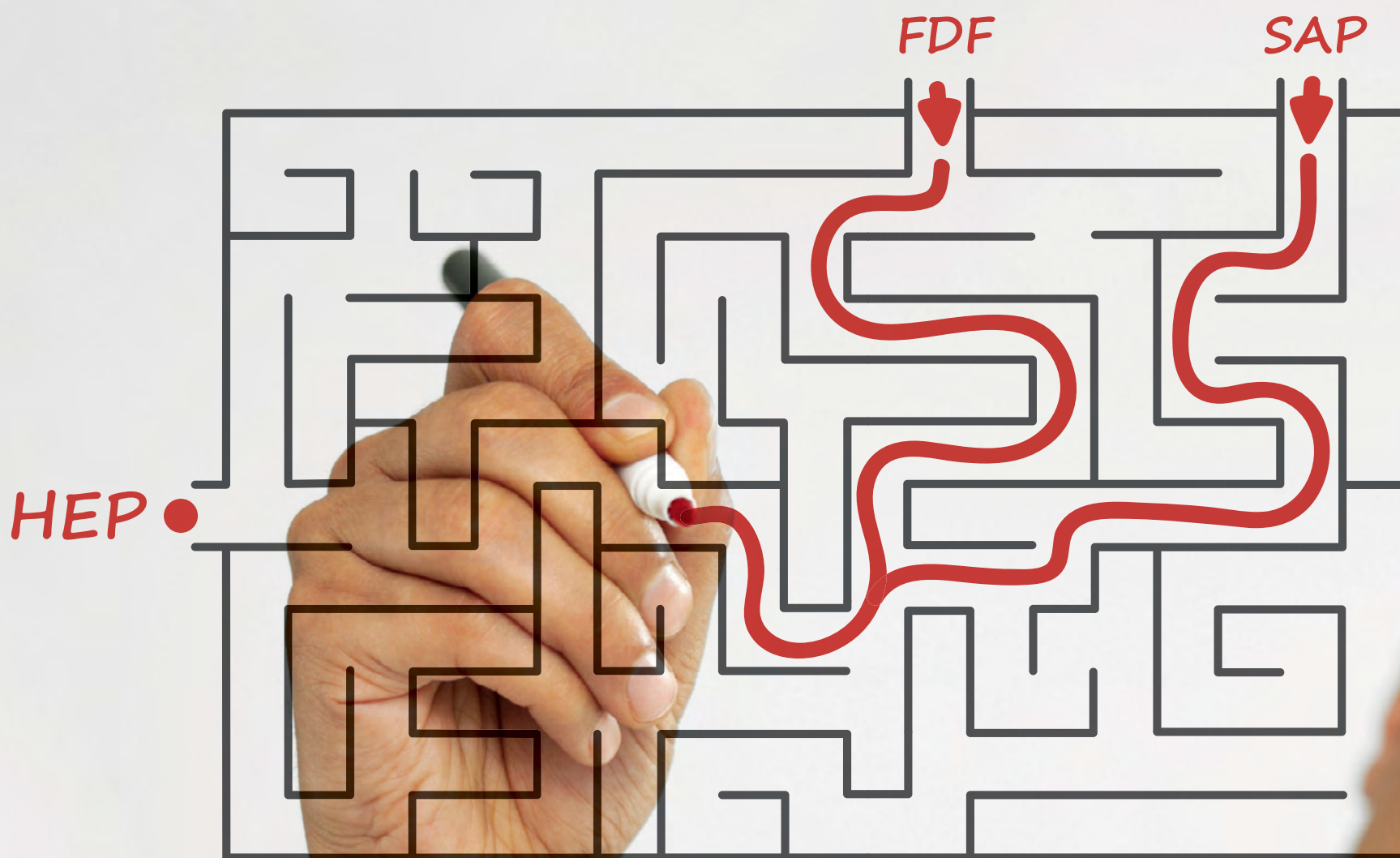
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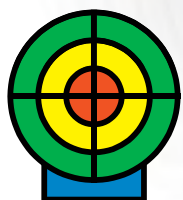
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Volume 16 no. 4



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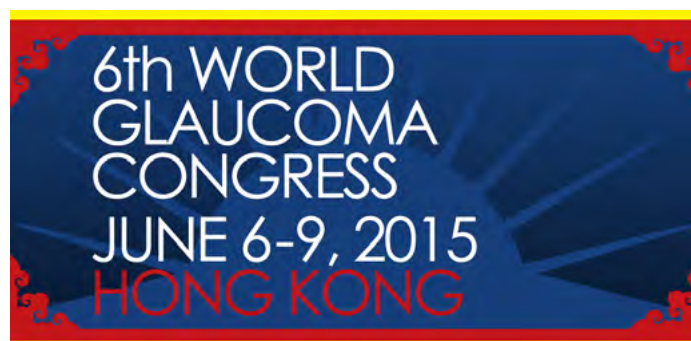
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Table of Contents

From the WGA Executive Office , by Robert D. Fechtner	5
Your Special Attention For	7
Meeting Highlights:	
• Top-Five of the Second National Glaucoma Congress of Serbia	9
• Top-Nine of the WGC-2015 Presidents Symposium	10
• Top-Eleven of the 18 th South African Glaucoma Conference	12
Editors Selection , with contributions by Tin Aung, Anjali Bhorade, Michael Boland, Don Budenz, Jonathan Crowston, David Friedman, Steven Gedde, Franz Grehn, Henry Jampel, Jin Wook Jeoung, Chris Johnson, Jost Jonas, Paul Kaufman, Rachel Kuchtey, Simon Law, Shan Lin, John Liu, Kaweh Mansouri, Keith Martin, Marisse Masis, Darryl Overby, Ki Ho Park, Andrew Tatham, Carol Toris, Sameer Trikha, Tony Realini, Tina Wong	16



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WORLD GLAUCOMA WEEK 2016

March 6–12, 2016



We have started preparations for World Glaucoma Week 2016 so keep an eye on our website or follow us via facebook or twitter!

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From the WGA Executive Office

Did you attend the 6th World Glaucoma Congress, held early June in Hong Kong? In this new issue of IGR you will find a report by the Program Planning Committee co-chairs to inform you about some of the sessions, particularly the Presidential Symposium on Glaucoma Innovation and Opportunities, which presented the state of the art in glaucoma. This highly informative symposium has been recorded and is now available via the [WGA website](#).

Another highlight during the 6th WGC-2015 was the symposium entitled 'Tackling Glaucoma in Sub-Saharan Africa' which signals the launch of a new WGA project on glaucoma care in Africa. In this issue of IGR you will find summaries of the different presentations during this symposium. Via future issues of IGR we will be updating you regarding our plans. In the meantime, do inform us on names of colleagues working in Africa via Mariska van der Veen at the WGA Executive Office (vanderveen@worldglaucoma.org), as we are starting to create a mailing list.

Did you already explore the WGA Educational Portal, which provides you with all recorded sessions of the 5th WGC-2013? WGC-2015 participants are now also able to view captured sessions of the 6th WGC in Hong Kong. If you did not attend the congress access to these WGC-2015 symposiums is available for a small fee. For more information please visit www.worldglaucoma.org.

Save the dates!

Please do not forget to mark your agenda with the following important dates:

- World Glaucoma Week 2016: March 6-12, 2016
- 7th World Glaucoma Congress: June 28-July 2, 2017

I hope you enjoy this issue of IGR. Please let me know your thoughts regarding our efforts in this and all WGA initiatives. You can reach me at Fechtner@worldglaucoma.com. You can also contact our WGA Executive Office at info@worldglaucoma.org if you need any information or have questions on IGR or WGA related matters. I look forward to hearing from you.



Professor Dr. Robert D. Fechtner, Executive Vice President



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Glial cell interactions and glaucoma

Chong RS, Martin KR

(abstract no. 600850)

Current Opinions in Ophthalmology 2015; 26: 73-77

Exfoliation syndrome: a disease with an environmental component

Dewundara S, Pasquale LR

(abstract no. 602850)

Current Opinions in Ophthalmology 2015; 26: 78-81

Corneal hysteresis and its relevance to glaucoma

Deol M, Taylor DA, Radcliffe NM

(abstract no. 603120)

Current Opinions in Ophthalmology 2015; 26: 96-102

Mechanism and management of angle closure in uveitis

Sng CC, Barton K

(abstract no. 603130)

Current Opinions in Ophthalmology 2015; 26: 121-127

Sustained drug release by contact lenses for glaucoma treatment – a review

Carvalho IM, Marques CS, Oliveira RS, Coelho PB, Costa PC, Ferreira DC

(abstract no. 603230)

Journal of Controlled Release 2015; 202: 76-82

Facts and myths of cerebrospinal fluid pressure for the physiology of the eye

Jonas JB, Wang N, Yang D, Ritch R, Panda-Jonas S

(abstract no. 603320)

Progress in Retinal and Eye Research 2015; 46: 67-83

Association between glaucoma and obstructive sleep apnea syndrome: a meta-analysis and systematic review

Shi Y, Liu P, Guan J, Lu Y, Su K

(abstract no. 605120)

PLoS ONE 2015; 10: e0115625

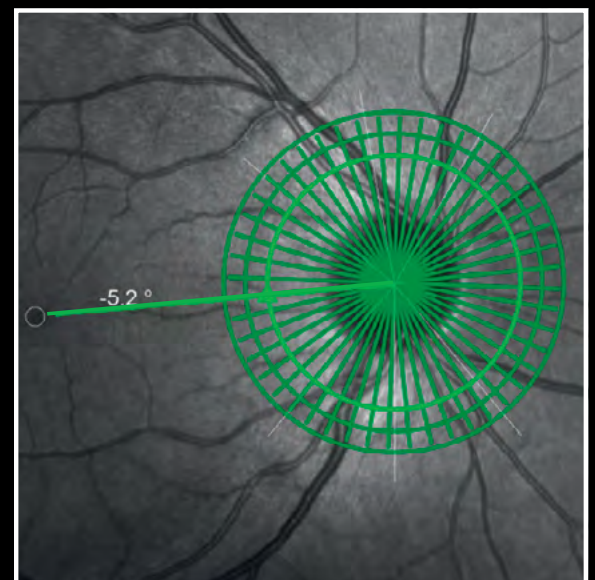
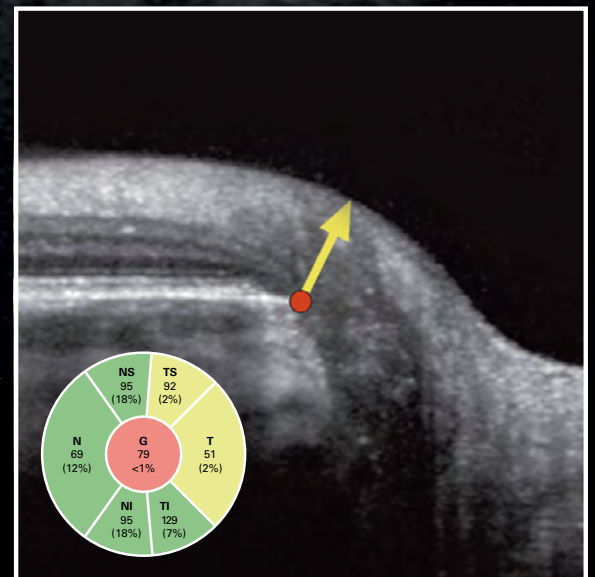
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Meeting Highlights

Top-Five of the Second National Glaucoma Congress of Serbia Kopaonik, Serbia, May 15-16, 2015



Predrag Jovanovic, Nis, Serbia

- Implantation in one eye of two ex-press implants with two different operations in a patient with advanced, refractory primary open-angle glaucoma. (B. Anguelov, Sofia, Bulgaria)
- Importance of Guidelines in diagnosis and treatment of glaucoma patients (EGS 2014). (Predrag Jovanovic, Nis, Serbia)
- Changes in ocular pulse amplitude and retrobulbar hemodynamics in dipper and non-dipper normal-tension glaucoma patients. (Ivan Marjanovic *et al.*, Belgrade, Serbia)
- Registration of patients with diagnosed glaucoma in Serbia. Registration of patients is an organized system for collecting clinical data with the aim of evaluation and results analysis in a population affected by a certain condition/disease. The purpose of registration is to enable assessment of the glaucoma burden, monitoring of the disease, calculation of the number of years of patients' inability, tracking of medical expenses, health care and prevention planning. It consists of glaucoma cases that are systematically and continuously collected, analyzed and interpreted in electronic form, signed patients' consents and personal data protection. (Lidija Magarasevic, Belgrade, Serbia)
- Incidence of secondary glaucoma after vitreoretinal surgery. Early or late IOP increase as vitreoretinal surgery complication occurs after buckling and VPP procedures. Secondary glaucoma is due to pupillary block (phacic, pseudophakic, aphakic) or trabecular meshwork inflammation/infiltration by emulsified silicone oil. In 274 VPP cases (80.6% without retinotomy, 15.6% retinotomy 180, 3.8% retinotomy 360), secondary glaucoma occurs in 84 (30.7%), in the first 48 h in 34 (40%) of patients. In thirty patients (36%) IOP was controlled by one medication, 34 (40%) had combined therapy, 20 (24%) underwent silicone oil evacuation surgically. (Marija Radenkovic *et al.*, Nis, Serbia)

Top-Nine of the WGC-2015 Presidents Symposium

Hong Kong, June 6, 2015



S. Fabian Lerner, Buenos Aires, Argentina

An outstanding symposium co-chaired by **Tin Aung**, **Robert Fechtner**, **Franz Grehn** and **Jeffrey Liebmann** was presented following the Opening Ceremony of the WGC in Hong Kong. This event, entitled: *Glaucoma Innovations and Opportunities*, addressed several aspects of the present and future of glaucoma diagnosis and management.

- **Adriana Di Polo (Montreal)** talked on **The RGC and its microenvironment: What we know and what we need to know**. The RGCs live within a rich and complex environment, which is a key factor to their survival, and there is an important interaction between ganglion cells and other cells, particularly astrocytes and microglia, in this microenvironment. Glial cells may play a role in the pathophysiology of the disease. Could modulation of glia have an effect in glaucoma? A possible neuro-inflammatory component on glaucoma was suggested.
- **Jost Jonas (Mannheim)** presented **Is the lamina cribrosa the site of glaucoma damage and what can we do about it?** The lamina cribrosa is the limit between two pressure compartments: the IOP and the cerebrospinal fluid pressure (CSFP) sections. It gets thinner in glaucoma and, thus, the gradient of pressure across the lamina increases. The lamina gets thinner also in high myopia in which there is a stretching of the optic nerve, and this may be a risk factor for the higher prevalence of the disease among high myopes, usually with an axial length of more than 26.5 mm. Dr Jonas also discussed the different zones of parapapillary atrophy and their possible association with glaucoma; as well as the possible role of a low CSFP in the disease.
- **Tin Aung (Singapore)** presented **Glaucoma genetics: recent advances and future directions**. Dr Aung presented the list of genes found by GWAS. He also discussed the work of the International Glaucoma Genetic Consortium that looks at quantitative traits in OAG. Genes have been discovered for optic disc size, central corneal thickness and IOP. Using GWAS, genes for ACG were also discovered. Moving into new technologies may allow finding new genes, mechanisms of action of the genes, what targets are involved and possibly new therapies.
- **Keith Martin (Cambridge)** talked on **Applying regenerative medicine techniques and technology tomorrow**. Dr Martin began his talk by stating that we are living the era of regenerative medicine. Particularly in glaucoma, experiments are trying to replace ganglion cells with its different types and connections, and these are particularly difficult cells to replace. A possible and short to medium-term approach is to use stem cells methods and protective factors to protect the ganglion cells against pressure-induced injury. Axonal regeneration is feasible. However several questions remain including, how to guide axons to the correct place, how are we going to prevent ongoing regeneration, and how much regeneration will we need to get

functional recovery. Can we engineer a retina? Regenerative medicine is coming to the eye. Is already happening with RPE cells and photoreceptors may follow. Tissue engineering advances very fast. Work is being done to protect injured cells and regenerate new ones. Function recovery is still a big challenge.

- **Kazuhisa Sugiyama (Kanazawa)** presented **Integrating RGC counts and optic nerve structure and function measures to improve care**. Dr. Sugiyama presented simultaneous evaluation of structure and function point by point. Correlation between structure and function points is moderate and depends on the stage of the disease. OCT structure analysis is useful in early stages and visual field function in more advanced stages. RGC counts may be important in all stages of the disease.

- **Robert N. Weinreb (La Jolla)** talked on **Personalizing IOP**. The concept of measuring 24-hour IOP will transform medical therapy and surgical therapy and reduce glaucomatous blindness. Currently we manage glaucoma with single IOP measurements, however, IOP fluctuates very rapidly and is not consistent from day to day. IOP is highest at night in two thirds of individuals, while aqueous inflow is lowest at the same time, and uveoscleral outflow also decreases at night compensating for the reduce inflow. Together with the increased episcleral venous pressure at night, the IOP is increased at night. Drugs may be seen as those that decrease IOP during 24 hours and increase perfusion pressure (PGAs and carbonic anhydrase inhibitor and alpha agonists). Laser trabeculoplasty and trabeculectomy are effective throughout the 24-hour day. Continuous 24-hour IOP measurements may be temporary or permanent. Treatments will be individualized based on an individual's 24 hour of IOP profile.

- **Glaucoma surgery of tomorrow: beyond IOP** was presented by **Tarek Shaarawy**. Current available operations reduce IOP, which is the primary endpoint for glaucoma surgery. We still rely on four mechanisms to do this: filter into the subconjunctival space, enhance filtration through the conventional outflow, use the suprachoroidal space, or reduce production by cyclodestruction. Each of these four strategies can be addressed *ab interno* or *ab externo*. There are still unmet needs, including safety, visual outcomes as well as health economics. Safety is not as good as needed yet. New 'bleb-less' devices or modalities are being used and also the suprachoroidal space is explored as a new approach for glaucoma surgery. Visual outcomes need to be improved, and health economics taken into consideration.

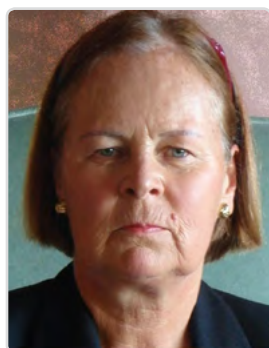
- **Neeru Gupta** presented **Using technology to mitigate glaucoma disability and improve the lives of our patients today and tomorrow**. Electronic Medical Records and Ocular Risk Calculators are available now. New technologies, available in our smartphones, might be able to help us determine progression. There is a need to peer review of new 'eye apps' to allow them to become standard. Also this is an opportunity for low-income areas. The future is mobile. Assisted technology is becoming mobile. Some of the technologies going on in the retina field may be transferable to glaucoma. Virtual reality technology may help glaucoma patients with their balance. For every one-dollar invested to prevent blindness there are four dollars in economic benefits generated. The technology exists. We need education and programs. The future of glaucoma is at the palm of our hands.

- **Roy Wilson** finished the symposium with **The consequences of longevity: implications for glaucoma surveillance and management in the 21st century**. Increased longevity has some consequences, including the decline of economic growth, and the increase in health care expenditures. There is considerable research trying to slow down the aging process at the cellular level.

The prevalence of glaucoma increases with increase of age in any population. As life expectancy increases, this has consequences in the actual management of a patient and the possibility of visual disability during lifetime. The increase in glaucoma will be a challenge in developing economy countries. We have to think about adjusting our current treatment strategies. More aggressive IOP lowering may be needed earlier in the disease.

Top-Eleven of the 18th South African Glaucoma Conference

Zimbali-Kwazulu Natal, South Africa, May 29-31, 2015



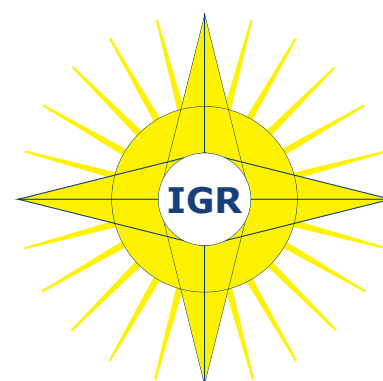
Ellen Ancker, Cape Town, South Africa

-
- RF of developing glaucoma with a positive family is eight to ten-fold higher.
 - Thirteen percent of patients with OH develop glaucoma in seven years, not everyone with OH develops glaucoma.
 - The 'glaucoma Zone' is 70 years and above due to increased vascular insufficiency, neuronal vulnerability. Evidence of mitochondrial dysfunction with glaucoma.
 - Even at normal IOP levels, the ON is probably under stress.
 - IOP is dynamic with many pressure spikes per hour.
 - It can take two to five years to detect RoP, 11 VFs over a two-year period are necessary to detect the trend.
 - Patient question: can I do anything else? Yes, diet increase in vegetables, obesity is associated with glaucoma, coffee is a RF above five cups, marijuana lowers IOP, exercise: a ten-km race lowers IOP by 37%. ([Jonathan G. Crowston, Sydney, Australia](#))
 - ONH evaluation: do not miss NFL loss, haemorrhage, do not underestimate c/d ratio, 90% of temporal arteritis have got rim loss, glaucoma with triangular optic atrophy think of mitochondrial dysfunction.
 - Do not miss OSD with glaucoma patients, 60% have symptoms in one eye, 38% were on single medication, treat with antihistamine and lubricants.
 - Wound Healing: Needling with MMC: 42% need a redo, minimize conjunctivitis and inflammation with Acular and FML, MMC for all trabeculectomies, do not wait for IOP to rise before acting! When bleb needling: gonio prior! at slitlamp/OR. Determine site, well anaesthetized injection with 30/27 gauge needle, pass through tenon's barrier, 5FU/ MMC/Avastin.
 - With PEX, do cataract extraction early to reduce IOP; with OH look for PEX. Medicinal cannabis is less effective than glaucoma drugs. Recognizing patterns of IOP circadian rhythms may better assist in choosing the most appropriate therapy. ([Grant McLaren, Johannesburg, SA](#))
-

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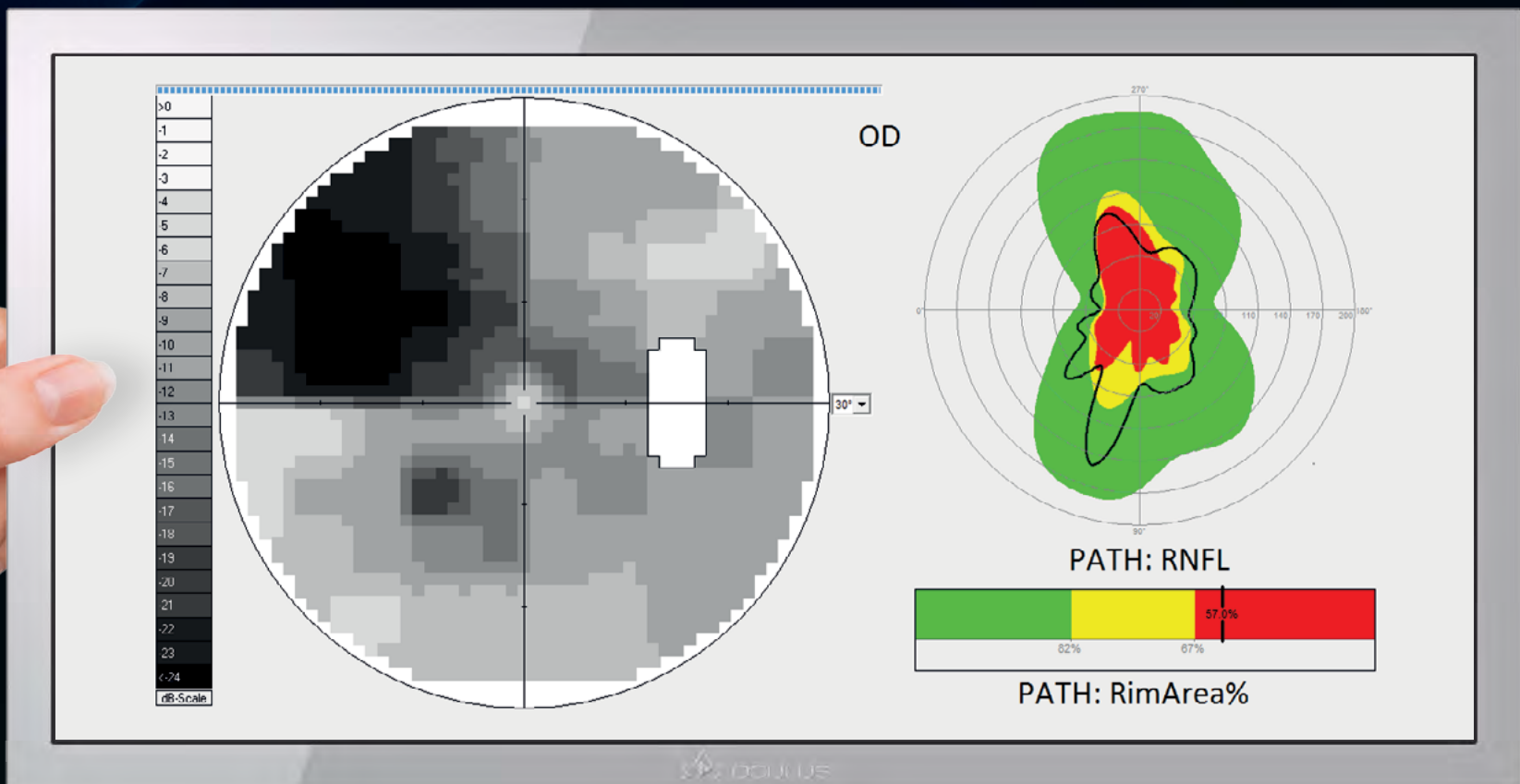
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Editor's Selection

With the multitude and variety of publications it seems almost impossible for the ophthalmologist to intelligently read all the relevant subspecialty literature. Even the dedicated glaucomatologist may have difficulty to absorb 1200+ yearly publications concerning his/her favorite subject. A solution to this confusing situation may be a critical selection and review of the world literature.



Robert N. Weinreb, Chief Editor

Quality of Life

Impact of retinal damage on Quality of Life



Comment by **Shan Lin** and **Marisse Masis**, San Francisco, CA, USA

60235 Association between progressive retinal nerve fiber layer loss and longitudinal change in quality of life in glaucoma, Gracitelli CP, Abe RY, Tatham AJ, Rosen PN, Zangwill LM, Boer ER, Weinreb RN, Medeiros FA, JAMA ophthalmology 2015; 133: 384-390

The ultimate goal in glaucoma management should be the maintenance of a person's quality of life. Visual acuity and visual fields are not the only factors that need to be taken into consideration when evaluating the real visual functionality of a glaucoma patient. Daily activities of glaucoma patients could be affected even in the absence of a clearly diagnosed scotoma. Peripheral scattered vision loss, dark adaptation, glare and difficulty with outdoor mobility are pathological findings that could be present even in early stages of the disease and these outcomes are difficult to detect by standard automated perimetry.

To assess and detect concrete changes in the patient, visual functionality despite adjustment for visual field progression is a very interesting step towards new clinical considerations

It is well known that measuring the rate of change in RNFL thickness is a helpful tool, mainly in early stages, for observing and managing patients with glaucoma.¹ **In this observational cohort study of 260 eyes of 130 patients, the authors evaluated the relationship between rates of retinal nerve fiber layer (RNFL) loss and longitudinal changes in quality of life in glaucoma.** Using a non-specific quality of life scale for glaucoma, the authors show a strong association with binocular RNFL loss and decrease in the quality of life. They report that **a one- μ m-per-year loss in binocular RNFL thickness corresponded to a change of 1.1 units per year in the NEI VFQ-25 scores, even after adjustment for the degree of visual field loss** as measured by standard perimetry and statistical modeling.

There have been a number of attempts to develop quality of life scales for glaucoma. Many of the instruments specific for glaucoma assess symptoms of glaucoma and effects on activities, but do not include assessment of the importance of such impacts for the individual². Also vision specific instruments, such as the NEI VFQ-25, might leave out of the equation more specific evaluation of glare, peripheral vision, outdoor mobility and contrast. Although this instrument is not specific for glaucoma, it is likely the best existing validated tool for visual function assessment.

Although this was a longitudinal study, the follow-up time was relatively short and more evidence should be added in the future to confirm the findings.

As mentioned by the authors, there is no previous study describing the association between progressive RNFL loss and changes in quality of life. To assess and detect concrete changes in the patient, visual functionality despite adjustment for visual field progression is a very interesting step towards new clinical considerations when diagnosing and making therapeutic decisions.

Reference

1. Leung CK, Cheung CY, Weinreb RN, et al. Evaluation of retinal nerve fiber layer progression in glaucoma: a study on optical coherence tomography guided progression analysis. *Invest Ophthalmol Vis Sci*. 2010;51(1):217-222.
2. Nelson P, Aspinall P, O'Brien C. Patients' perception of visual impairment in glaucoma: a pilot study. *Br J Ophthalmol*. 1999; 83:546–552.

Visual Impairment

Vision loss and reading ability



Comment by **Anjali Bhorade**, St Louis, MO, USA

60588 Severity of vision loss interacts with word-specific features to impact out-loud reading in glaucoma, Mathews PM, Rubin GS, McCloskey M, Salek S, Ramulu PY, Investigative Ophthalmology and Visual Science 2015; 56: 1537-1545

Reading is a critical vision-related skill essential for many daily activities. In prior studies, glaucoma patients had a slower overall reading rate compared to controls, however, the underlying mechanisms were not explored.^{1,2} Ramulu and colleagues conducted a study analyzing word-specific features that may contribute to reading difficulty in glaucoma patients.

In this cross-sectional study, **63 glaucoma patients with bilateral visual field loss (average mean deviation of -8.9 decibels and 20/40 visual acuity of the better eye) and 57 glaucoma suspects were recorded while reading a standardized reading test.** Masked evaluators analyzed word specific features associated with reading. Increased difficulty with length, frequency, and location of words as well as lexical errors was associated with increased glaucoma severity (*i.e.*, decreased contrast sensitivity or increased visual field loss).

Measuring contrast sensitivity in the clinic may provide useful clinical information regarding the function of our glaucoma patients

An interesting finding was that **contrast sensitivity had a greater impact on reading than visual field loss in glaucoma patients.** These findings challenge the traditional thought that glaucoma is a disease of peripheral vision, and that central-vision tasks, such as reading, are not affected until later in the disease.

These findings challenge the traditional thought that glaucoma is a disease of peripheral vision, and that central-vision tasks, such as reading, are not affected until later in the disease.

Strengths of this study include the standardized reading test, masked evaluators, and analysis of multiple components of reading. Some limitations include the lack of evaluation of reading comprehension and strategies used by patients to compensate for their visual field loss while reading. In addition, the **glaucoma group was significantly older than the control group** and age-related factors not fully evaluated in this study may contribute to reading difficulty.

This study provides critical information on reading that can be implemented in evidenced-based training programs and assistive devices to improve the reading skills of glaucoma patients. These results also emphasize the importance of contrast sensitivity on visual function. **Measuring contrast sensitivity in the clinic may provide useful clinical information regarding the function of our glaucoma patients.**

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2. Ishii M, Seki M, Harigai R, Abe H, Fukuchi T. Reading performance in patients with glaucoma evaluated using the MNREAD charts. *Jap J Ophthalmol*. 2013;57:474-474.



Comment by **David Friedman**, Baltimore, MD, USA

60354 Severity of vision loss interacts with word-specific features to impact out-loud reading in glaucoma, Mathews PM, Rubin GS, McCloskey M, Salek S, Ramulu PY, *Investigative Ophthalmology and Visual Science* 2015; 56(3): 1537-1545

Reading is slower and more difficult for individuals with glaucoma. Matthews and colleagues, in an attempt to help develop better methods for reading rehabilitation in glaucoma patients, assessed what text factors led to greater reading difficulty. In order to determine this, the investigators had those with glaucoma and control subjects read standardized text (fifth grade level) out loud. The researchers abstracted voice recordings to identify how long it took to say each word and how long the intervals were between words. Visual acuity and contrast sensitivity (CS) were measured binocularly. Those with glaucoma were on average four years older than controls, but otherwise were similar, and those with glaucoma had an average mean deviation in the better-eye visual field of 8.9 dB. Words that were longer required more time to read and reading longer words also increased the interval before the next word. Similarly, words at the end of a line of text required longer to read and the interval to the next word was also longer.

One simple approach suggested by the authors would be to instruct glaucoma patients to read in landscape mode to reduce the number of line shifts in text

Those with glaucoma took longer to say words (both short and long words) and had a longer delay before saying the next word. There was a substantial increase in the delay between ending the last word of a line and starting the first word on the next line. CS was more strongly correlated with reading findings than visual field although both were associated. Using CS as

a reflection of glaucoma severity, the length of time needed to read was substantially longer with worsening CS (*i.e.*, they interacted). Those with increasing degrees of loss of CS had even greater difficulty with words that were longer, relatively uncommon, and those at the end of a line of text. Also, mispronunciation or misidentification of words was increasingly common among those with more severe glaucoma. Word length interacted the most strongly with CS and reading speed.

This work required incredible attention to detail and precise measurement and the authors are to be commended. They have made an important contribution to our understanding of the impact of glaucoma on reading and the findings will be useful for those designing systems to improve reading despite loss of CS in glaucoma. One simple approach suggested by the authors would be to instruct glaucoma patients to read in landscape mode to reduce the number of line shifts in text. Other innovations could also be incorporated into reading devices. The authors note that vision loss from glaucoma currently cannot be reversed, but disability from that loss can be reduced.



Anatomical Structures

Myopic disc appearance



Comment by **Simon Law**, Los Angeles, CA, USA

59842 Novel screening method for glaucomatous eyes with myopic tilted discs: the crescent moon sign, Kim MJ, Kim SH, Hwang YH, Park KH, Kim TW, Kim DM, JAMA Ophthalmology 2014; 132: 1407-1413

Myopia is the most common human eye disorder in the world, and high myopia is a risk factor for glaucoma. A myopic optic disc is notoriously difficult to be differentiated from a glaucomatous disc because of its atypical size and shape. Even with the current digital imaging technology, evaluation of myopic disc encounters many imaging artifacts.

Although the reported specificity and sensitivity seem impressive, it is important to understand that the predictive value depends on the disease prevalence

In this cross-sectional study, Kim and associates evaluated the diagnostic ability of the crescent moon (CM) sign for the detection of glaucomatous eyes with myopic tilted discs. CM sign is defined by the neural rim of the superior or inferior quadrant as not connected curvilinearly to that of the temporal quadrant. Schematically, it is defined by the tangential line, which is drawn along the inner curvature of the neural rim margin meeting the disc margin, extending in the direction opposite to the macula. **This method was found to have a high specificity and sensitivity (91% and 83%, respectively), and compared favorable to the ISNT rule.** ISNT rim pattern was described by Jonas *et al.* in the 80's to describe the normal neural rim profile in eyes with discernable rim and has since been applied clinically.

Although the authors rightfully included patients with glaucoma confirmed by RNFL and visual field defect and disease progression, certain selection bias may be unavoidable. **The sensitivity and specificity will undoubtedly be high if the diagnostic method used for case inclusion and the one to be studied are similar.** Indeed, in myopic tilted discs, the nasal and temporal rims are often difficult to be evaluated due to crowding of the vessels in the nasal rim and temporal sloping of the rim, leaving only the superior and inferior rims for evaluation. In addition, the performance of this test in those eyes with earlier stages of glaucoma is unknown.

Although the reported specificity and sensitivity seem impressive, it is important to understand that the predictive value depends on the disease prevalence. For example, in a busy clinical practice where one thousand patients with myopic tilted discs were evaluated for glaucoma

annually and assuming the prevalence of glaucoma is 5% in patients with myopic tilted disc, 50 of the one thousand patients have glaucoma, and 950 patients do not have glaucoma. A test of 91% sensitivity and 83% specificity will diagnose glaucoma in 45 glaucoma patients (true positives) and 161 patients without glaucoma (false positives). That is, in 100 myopic tilted disc patients with CM sign, about 22 have glaucoma and the rest are normal. Of course, the exact prevalence of glaucoma in this group of patients is unknown.

Even with these limitations, the authors should be commended for proposing such a very practical method that can be applied qualitatively or schematically to evaluate the superior and inferior rims of myopic tilted discs. This screening method underscores the importance and usefulness of stereoscopic evaluation of the optic disc.



Comment by **Jin Wook Jeoung** and **Ki Ho Park**, Seoul, South Korea

60256 Is myopic optic disc appearance a risk factor for rapid progression in medically treated glaucomatous eyes with confirmed visual field progression?, Lee JR, Kim S, Lee JY, Back S, Lee KS, Kook MS, Journal of Glaucoma 2015; e-pub ahead of print

Many studies have confirmed the strong association between myopia and glaucoma. Population-based studies have established myopia as a risk factor for development of glaucoma.¹ Controversy remains, however, with respect to the question of whether or not myopia is an independent risk factor for glaucoma progression.

Lee *et al.* examined myopic glaucomatous eyes with documented visual field (VF) progression to determine the velocities of both global and regional VF progression. The velocity of VF progression in these patients was compared with that in the non-myopic group. Their main findings were similar VF progression rates globally and regionally, after controlling for clinical factors related to VF progression.

The proposed mechanism of myopia as a risk factor for glaucoma progression is the structural weakness of the optic nerve head and thinning of the lamina cribrosa and/or surrounding sclera resulting from globe elongation. According to this theoretic framework, myopia-related structural changes might make the optic nerve more susceptible to intraocular pressure (IOP)-related strain. Such structural changes, however, probably cease to pose a threat of further damage once the progressive thinning and tilting become stabilized. The authors suggest, therefore, that **myopic disc change may not be an independent risk factor for rapid VF progression in progressive glaucomatous eyes.**

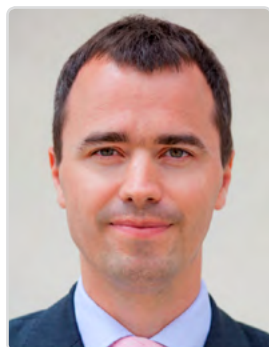
There are several limitations to this study. First, due to the inherent nature of the retrospective design, it lacked a non-treatment control group as well as any target IOP setting standardization. If the patients are truly progressing, it remained unclear whether progression was due primarily

to myopia or glaucoma. Also, in myopic glaucoma patients, the role of IOP lowering treatment and the correct target IOP ranges should be further elucidated. It would be interesting to know if prospective controlled studies can make the present data more relevant.

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Lamina Cribrosa in Normal Pressure Glaucoma



Comment by **Andrew Tatham**, Edinburgh, UK

60790 3D Evaluation of the Lamina Cribrosa with Swept-Source Optical Coherence Tomography in Normal Tension Glaucoma, Omodaka K, Horii T, Takahashi S, Kikawa T, Matsumoto A, Shiga Y, Maruyama K, Yuasa T, Akiba M, Nakazawa T, *PLoS ONE* 2015; 10: e0122347

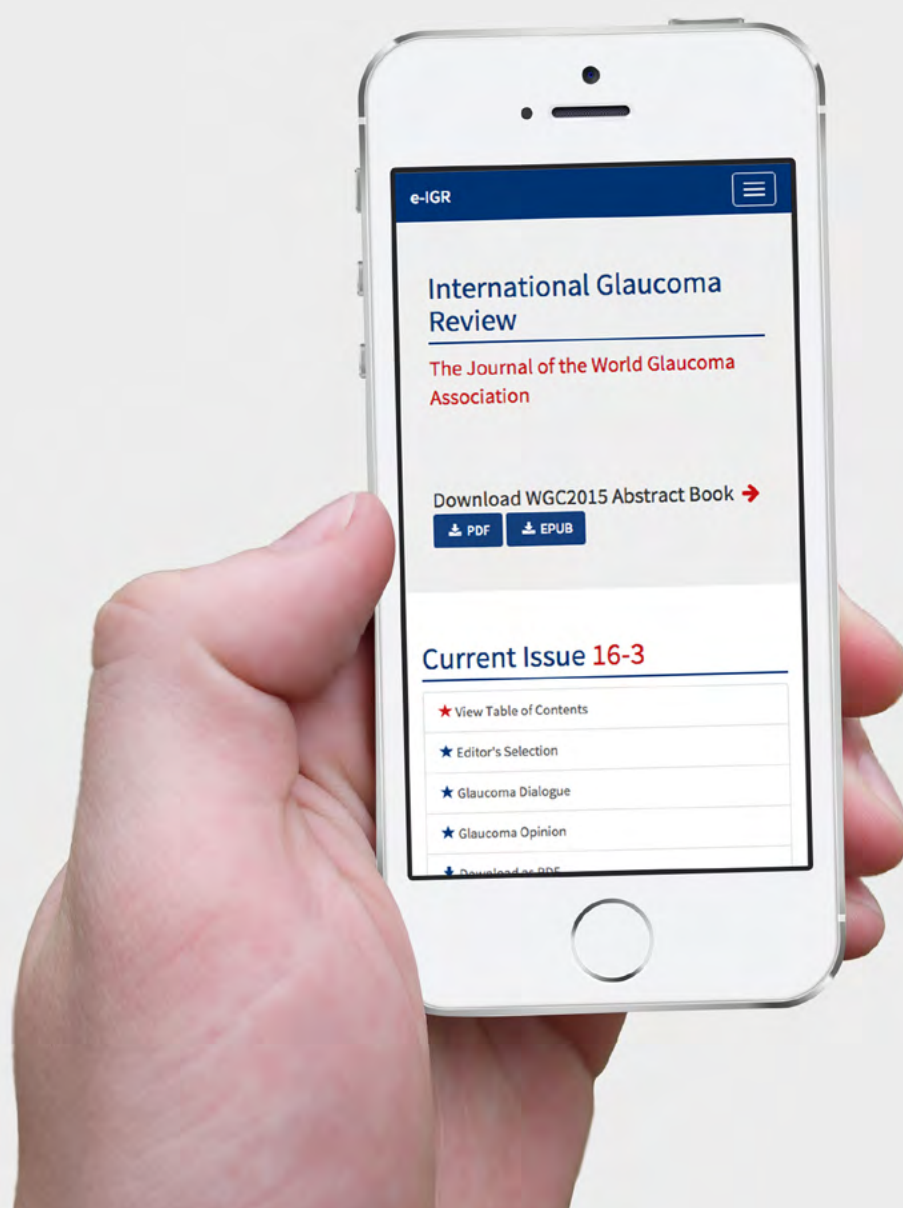
Imaging of the lamina cribrosa (LC), the putative site of glaucomatous retinal ganglion cell damage, has become a hot topic for glaucoma research, in part due to innovations such as enhanced depth imaging and swept source OCT (SS-OCT). Previous studies have demonstrated glaucomatous eyes to have LC defects including disinsertion, thinning and focal defects, but even with new OCT technologies, accurately identifying the posterior border of the LC, especially beneath the neuroretinal rim, is challenging.

Omodaka *et al.* describe a new approach to LC imaging using SS-OCT. Software was developed that enabled generation of LC thickness maps similar to retinal nerve fiber layer (RNFL) thickness maps currently used in clinical practice. The software allowed simultaneous visualization of various depth en-face and corresponding B-scan LC images. En-face OCT slices were serially examined and the anterior and posterior borders of the LC identified as the first slices where lamina pores were no longer visible. Computer generated three-dimensional models of the LC were derived and from these color-coded maps of LC thickness generated.

The software was used to examine 54 Japanese subjects, including 18 controls, 18 with pre-perimetric glaucoma and 18 defined by the authors as having normal-tension glaucoma (NTG). Measurements of average LC thickness were highly reproducible and thinner LC was significantly correlated with thinner circumpapillary RNFL thickness and worse perimetric mean deviation. **Eyes with NTG had the thinnest LC, followed by those with pre-perimetric glaucoma, and then controls.**

Although the study included only small numbers of patients, the ability to better examine LC thickness offers the opportunity for further study of LC characteristics as possible risk factors for glaucoma. It should be emphasized though that the **software does not overcome the problem of visualization of the entire LC as visualization was still impeded by shadows from blood vessels and the neuroretinal rim.** This was partially overcome by manually marking reliably measured regions, however this step made the process more labor intensive, resulting an average processing time of 40 minutes per eye. Because of this the software is unfortunately not yet ready for use on a large scale.

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Basic Science

Trabecular molecular biology



Comment by **Rachel Kuchtey**, Nashville, TN, USA

60729 Mapping molecular differences and extracellular matrix gene expression in segmental outflow pathways of the human ocular trabecular meshwork, Vranka JA, Bradley JM, Yang YF, Keller KE, Acott TS, PLoS ONE 2015; 10: e0122483

Although intraocular pressure (IOP) reduction remains the only proven therapeutic approach in treating glaucoma patients, and despite the fact that the pathological site of IOP dysregulation, namely trabecular meshwork (TM) and Schlemm's canal, has been known for many decades, no anti-glaucoma medications directly target the diseased region. This is largely due to the lack of understanding of aqueous humor outflow regulation.

The evidence of complexity of segmental flow of aqueous humor in the TM is beautifully presented in the study

Segmental flow of aqueous humor, characterized by high and low flow regions within the TM is a well-known phenomenon, however, neither the significance of this observation nor the underlying mechanisms is known. In this study, **Vranka and co-workers rigorously tested different fluorescently labeled microspheres to define different flow regions of TM using well-established human anterior segment organ culture.** With robust methods, **the investigators not only confirmed segmental flow of aqueous humor in the TM, they also elegantly demonstrated such pattern on both a macro- and micro-scale.** The labeling system also allowed the authors to investigate the distribution of collector channels in the high and low flow regions. Interestingly, no differential distribution was seen. **Using quantitative PCR arrays, the authors reported a number of extracellular matrix genes differentially expressed in the high and low flow regions of the TM.** Although some differential protein levels in different regions were evident, matrix metalloproteinase (MMP) proteolytic enzyme activity was similar in high and low flow regions. The authors speculate this finding was largely due to the fact they used non-specific MMP substrate for the assay. The evidence of complexity of segmental flow of aqueous humor in the TM is beautifully presented in the study. However, the clinical significance of the findings remains elusive. Would targeting the specific region with specific flow pattern, either with pharmacological agents or surgical approach, be the future treatment of lowering IOP?

Schlemm's endothelial cells



Comment by **Darryl Overby**, Tucson, AZ, USA

60132 Finite element analysis of the pressure-induced deformation of Schlemm's canal endothelial cells, Vargas-Pinto R, Lai J, Gong H, Ethier CR, Johnson M, Biomechanics and modeling in mechanobiology 2014; 14(4): 851-863

The endothelium of Schlemm's canal (SC) serves a dual role. On one hand, SC endothelium must be conductive enough to allow aqueous humor to cross the endothelium, enter SC and drain from the eye. On the other hand, SC endothelium must be resistive enough to prevent blood or serum proteins from entering the anterior chamber from the episcleral veins, thereby maintaining the blood-aqueous barrier (BAB). To satisfy these divergent roles, SC endothelium must function as a one-way valve that opens in the direction of outflow, but closes to oppose retrograde flow. This one-way valve function appears to be regulated by the biomechanics of SC cells. Prior work from this same group has identified that the biomechanical stiffness of SC cells increases in glaucoma, which could potentially disrupt SC valve function, impede outflow and elevate IOP.

To understand how SC cell biomechanics influences outflow physiology, **Rocio Vargas-Pinto and colleagues use computer modeling to demonstrate how SC cells deform in response to a transendothelial pressure drop as occurs *in vivo***. This is relevant because SC cell deformation is thought to trigger the formation of micron-sized transendothelial openings (pores), the presumed site where aqueous crosses SC endothelium when draining from the eye. This mechanism allows SC cells to localize pore formation to sites of sufficient filtration demand, while maintaining relatively low porosity elsewhere so as to preserve the BAB. **Vargas-Pinto et al. convincingly demonstrate that the cortical cytoskeleton bears most of the biomechanical load acting on SC cells such that increasing cortical stiffness or thickness allows SC cells to support greater loads.** When prescribing values of cell stiffness measured in vitro, however, SC cells were able to support only a fraction of the pressure drop across the outflow pathway. This important result suggests that the majority of the pressure drop may not lie across SC cells themselves, but elsewhere in the outflow pathway, presumably across the extracellular matrix underlying SC endothelium. Alternatively, SC cells in vivo may be considerably well adapted to withstand even greater loads than predicted by computer simulations, presumably on account of increased cell or cortical stiffness or specialized cell-cell or cell-matrix attachments.

This elegant bioengineering study brings to light several questions that are fundamental to the pathogenesis of ocular hypertension in glaucoma. Namely, what is the stiffness of SC cells *in vivo*? What is the biomechanical mechanism of pore formation? What is responsible for elevated SC cell stiffness in glaucoma? Ultimately, this work points to a new therapy to improve aqueous humor outflow and lower IOP by targeting SC cell stiffness, but the success of such a therapy

depends on understanding the intricate coupling between outflow and SC cell biomechanics. The excellent work by Vargas-Pinto and colleagues describes this coupling and brings us closer to realizing the dream of a conventional outflow drug that targets the root pathology of ocular hypertension in open-angle glaucoma.

Neuroprotection



Comment by **Jost Jonas**, Heidelberg, Germany

60369 Hydrostatic pressure does not cause detectable changes in survival of human retinal ganglion cells, Osborne A, Aldarwesh A, Rhodes JD, Broadway DC, Everitt C, Sanderson J, PLoS ONE 2015; 10: e0115591

In this study, Osborne and colleagues found that **directly applied hydrostatic pressure within a range of ten to 100 mmHg, in contrast to simulated ischemia, had no detectable impact on the survival of retinal ganglion cells and on stress-signaling in human organotypic retinal cultures.** This result might have been anticipated since **it is not the absolute pressure within the intravitreal cavity but the trans-lamina cribrosa pressure difference which may be the main pressure-related parameter for the development of glaucomatous optic neuropathy.**

The intraocular pressure is not a parameter of absolute pressure but just describes the trans-corneal pressure difference

Consequently, deep-sea diving to a depth of 100 m does not cause an acute glaucoma attack although the absolute pressure in the eye (as well as in the cerebrospinal fluid space) is approximately 11 times higher than atmospheric. Conversely, climbing Mt. Everest with an air pressure of roughly only 50% of the air pressure at sea level does not cure glaucoma, although the absolute pressure in the eye (as well as in the cerebrospinal fluid space) is approximately 50% of the normal values. NB: The intraocular pressure is not a parameter of absolute pressure, but just describes the trans-corneal pressure difference.

Clinical Examination Methods

Trabecular OCT



Comment by **Sameer Trikha** and **Tin Aung**, Singapore, Singapore

60496 Morphometry of the trabecular meshwork in vivo in a healthy population using fourier-domain optical coherence tomography, Fernández-Vigo JI, García-Feijoo J, Martínez-de-la-Casa JM, García-Bella J, Fernández-Vigo JA, Investigative Ophthalmology and Visual Science 2015; 56: 1782-1788

Glaucoma is associated with a reduction in aqueous humor outflow through the trabecular meshwork (TM) causing a rise in intraocular pressure. Whilst a number of mechanisms have been postulated to account for a reduction in functionality of the TM, physiological and anatomical studies of TM *in vivo*, and across different populations, are lacking. **Fernandez-Vigo and colleagues describe a large cross-sectional study identifying the morphology of the TM *in vivo*, using the Fourier Domain RTVue.** Interestingly, **they found that the length of TM varied largely (range 275-800 microns)** with less range for TM area and volume across subjects. The TM was found to be marginally thicker in men than in women ($p = 0.046$), but no differences were found in TM length or area. Furthermore, no correlations were identified between the TM parameters and axial length, age, sex, IOP or spherical refractive error. The study is particularly interesting as it is one of the first to be conducted in Caucasians. Fourier domain OCT, conducted *in vivo*, potentially heralds a new era in anterior chamber angle imaging. These devices offer high resolution and speed of image processing. Knowledge of TM morphology may be of relevance in the context of aiding surgical procedures such as angle surgery for glaucoma. **TM analysis using OCT devices also opens up the possibility of 'dynamic' assessment of the TM after minimally invasive glaucoma surgery (MIGS),** or following the use of medications such as prostaglandin analogues.

Telemetric tonometry



Comment by **John Liu**, La Jolla, California, USA

60318 Implantation of a novel telemetric intraocular pressure sensor in patients with glaucoma (ARGOS study): 1-year results, Koutsonas A, Walter P, Roessler G, Plange N, Investigative Ophthalmology and Visual Science 2015; 56: 1063-1069

Recent advances in wireless technology have provided opportunities for developing sophisticated medical devices for monitoring intraocular pressure (IOP), the most significant risk factor for glaucoma. **Koutsonas *et al.* reported their early experience in a clinical trial of an implantable wireless IOP sensor. The trial enrolled six patients (aged 70-76 years) with cataract and primary open-angle glaucoma. Toward the end of cataract surgery, a ring-shaped telemetric IOP sensor was implanted in the ciliary sulcus. The authors reported the tolerability of this sensor in detail as well as IOP data selected throughout the first postsurgical year. As anticipated, temporary adverse events occurred due to the implanted sensor.**

Comparison of IOP readings obtained between the external IOP reader and the standard Goldmann tonometer showed that the correlation of these two sets of IOP readings was short of what we hoped for

However, **there was no adverse impact on vision at the one-year checkup except some narrowing of the anterior chamber angle.** Measurements of IOP were performed during office visits and also by the patients at home using an external IOP reader. Comparison of IOP readings obtained between the external IOP reader and the standard Goldmann tonometer during the office checkups was shown. By visual inspection of IOP data, the correlation of these two sets of IOP readings was short of what we hoped for. **A side-by-side evaluation indicated that the IOP difference was larger than the clinically acceptable IOP accuracy when using the Goldmann tonometer (two to three mmHg). Also, there was a critical lack of consistency in the IOP difference between the two measuring devices.**

The report brings us good news that **this implantable IOP sensor seems to be well-tolerated up to one year.** The associated medical risk is not high. While a longer follow-up is certainly warranted for these six patients, recruitment of more subjects for similar clinical trial will not be inappropriate. Unfortunately, this device does not have the accuracy as hoped. One may argue that inaccuracy can be overcome if IOP consistency exists and *in vivo* calibration can be done. Unlike a contact lens based IOP sensor, a permanent implanted IOP sensor should have a high consistency of determining IOP in practice.

What causes the inconsistency of this IOP sensor is uncertain and should be investigated. Patients who have the implanted IOP sensor can easily collect data at home for a study of IOP consistency, for example the well-defined postural IOP difference and the diurnal IOP curve. It is possible the authors are already proceeding with this research project. There will be plenty of IOP data to study, which is part of the goal for developing this IOP monitoring device in the first place.



Comment by **Tony Realini**, Morgantown, West Virginia, USA

60367 Automated Detection and Quantification of Circadian Eye Blinks Using a Contact Lens Sensor, Gisler C, Ridi A, Hennebert J, Weinreb RN, Mansouri K, Translational vision science & technology 2015; 4: 4

Gisler and colleagues have conducted an innovative blink detection study utilizing the Triggerfish contact lens system (CLS) that has a number of potentially useful applications. The CLS infers IOP based on changes in corneal curvature detected by a strain gauge embedded in a contact lens. The device samples IOP nearly continuously, obtaining 300 measurements over a 30-second period (10 Hz) every five minutes, and is typically worn for up to 24 hours per session. The device output is a graph in arbitrary units (notably not mmHg) that represents a semi-quantitative circadian IOP curve. There is noise in the system – most notably blinks, which can raise IOP significantly and frequently albeit transiently. **These investigators have developed an automated algorithm to detect the IOP peaks attributable to blinks that is highly accurate when compared to simultaneous video recordings of a subset of subjects. The immediate application of this algorithm is the ability to clean up the CLS output by filtering out the blinks and better illustrating the background IOP variability that occurs during CLS wear.** Other potential applications include determination of blink rate in disease states in which blink rate is known to be relevant, as in some neurological or psychiatric conditions. One caveat with this latter use is that the device itself resides on the cornea and has a modest discomfort factor that may induce blink rates different from unperturbed resting blink rates. There remain many unanswered questions regarding the clinical significance of circadian IOP variation and the emergence of tools such as the Triggerfish CLS will afford us the opportunity to address these going forward. The authors are to be commended on taking the next step toward a better signal-to-noise ratio with this device.

Stimulus size and visual field reliability



Comment by **Don Budenz**, Chapel Hill, NC, USA

60796 The effect of stimulus size on the reliable stimulus range of perimetry, Gardiner SK, Demirel S, Goren D, Mansberger SL, Swanson WH, Translational Vision Science & Technology 2015; 4: 10

Following glaucoma patients for progression who have moderate severe disease presents a dilemma for the clinician. These patients are the ones most likely to go blind and surgical intervention is frequently considered to halt or slow worsening and preserve vision. Yet tools that are very helpful in diagnosing glaucoma and glaucoma progression at the early stages of glaucoma have limited usefulness at later stages due to the 'floor effect' of measuring retinal nerve fiber layer thickness using optical coherence tomography, detecting small changes in optic nerve cupping or rim thickness using stereoscopic disc photography, and measuring the visual field reliably. The study by Gardiner *et al.* **compares the sensitivities of Size III and Size V stimuli in four moderate to severely depressed locations of the visual field** in 35 subjects with glaucoma.

The clinical importance of this is that patients can be followed for a longer period of time with a Size V stimulus compared to a Size III stimulus, perhaps years longer

They found that neither stimulus size had adequate reliability below the 15-19 dB range and that the Size V stimulus was no more useful in this range than a Size III stimulus. However, they did find that **increased stimulus size results in better sensitivity measurements**, suggesting that the dynamic range measurable with a Size V stimulus is wider than with a Size III stimulus. The clinical importance of this is that patients can be followed for a longer period of time with a Size V stimulus compared to a Size III stimulus, perhaps years longer.

The improved sensitivity and dynamic range of the Size V stimulus may be due to recruitment of adjacent, less affected areas of the receptive field being tested. The authors review several possibilities for improving visual field testing algorithms based on their results. These include changing all automated perimetry to Size V, increasing to a Size V stimulus automatically within a test when sensitivities with the Size III stimulus is below the reliable range, or **following patients with a Size III stimulus until most of the thresholds are below a reliable range and then changing to all Size V stimuli in future tests**. Until there is evidence that one of these strategies is superior to another, the third option seems like the best strategy for now.

Perimetric visual field pattern and early defect screening



Comment by **Chris Johnson**, Iowa City, IA , USA

60424 Modifying the conventional visual field test pattern to improve the detection of early glaucomatous defects in the central 10°; Ehrlich AC, Raza AS, Ritch R, Hood DC, Translational Vision Science & Technology 2014; 3: 6

It has been reported by many laboratories that there is structural damage to the macula in glaucoma patients and glaucoma suspects based on optical coherence tomography (OCT) measurements.¹ Dr. Hood and his associates have previously reported that there are functional visual field deficits that occur due to the macular damage in glaucoma patients and suspects.¹⁻³

Adding macular test points to the 24-2 pattern improved the ability to detect functional losses associated with glaucoma

While the six-degree spacing of test points for the conventional 24-2 visual field test pattern does not properly evaluate the macula, it can be appropriately tested with the 10-2 pattern with a two-degree spacing between points within the central ten degrees of vision. However, administering both the 24-2 and 10-2 test patterns for both eyes can be quite time consuming and exhausting for the patient, and can be difficult to perform in a busy clinic. **The present study was designed to evaluate the benefit of adding either four (two per superior and inferior hemifield) or 16 (eight per superior and inferior hemifield) test points to the 24-2 test pattern as a means of detecting macular functional abnormalities in glaucoma.**

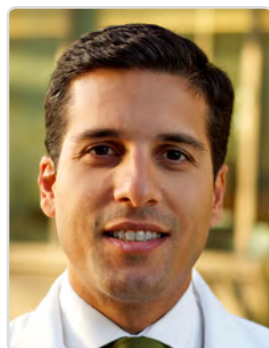
The investigation was performed on 144 eyes of 144 glaucoma patients with early damage, and was performed in a careful, well-constructed manner. **Adding macular test points to the 24-2 pattern improved the ability to detect functional losses associated with glaucoma**, which has important clinical and quality of life implications. Generalization of this finding to other clinics could help refine the arrangement and number of additional macular test locations, and assist in determining the clinical utility of this procedure.

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Clinical Forms of Glaucoma

Circadian IOP and blood-flow rhythms



Comment by **Kaweh Mansouri**, Geneva, Switzerland

59909 The circadian changes of intraocular pressure and ocular perfusion pressure after tafluprost compared with travoprost in normal-tension glaucoma, Shin J, Lee JW, Choi BS, Yun EY, Jung JH, Kim EA, Caprioli J, Journal of Ocular Pharmacology and Therapeutics 2014; 30: 803-809

The Low-pressure Glaucoma Treatment Study showed that a lower mean ocular perfusion pressure (OPP) was associated with progression in patients with normal tension glaucoma (NTG). Despite a plethora of data comparing different prostaglandin analog (PGA) drops to each other, 24-h data on OPP-effects are scarce. **Shin *et al.* compare the circadian efficacy profile of tafluprost, a newer member of the PGA family, to travoprost.** Using a randomized crossover design, 24-h IOP and OPP data are presented from 41 NTG patients. A limitation of the study is the absence of data on corneal thickness changes after therapy and the potential confounding effect of IOP measurements between the two drugs.

The authors show that both medications were effective in lowering IOP and increasing OPP throughout the day and night. However, travoprost showed greater efficacy than tafluprost in the 10 AM to 8 PM period. The reasons for this difference are unknown but the authors speculate that the three fluorine atoms of travoprost (vs. two for tafluprost) may offer greater metabolic stability and bioavailability and translate into the observed diurnal difference.

Is that difference of any clinical relevance? Unfortunately, no data are available regarding the chronobiological effects of IOP on glaucoma progression. Are there specific moments of the day when IOP-lowering is more beneficial than others? Should we individualize the timing of drop application instead of the current rigid schedules? Answering these questions requires prospective therapeutic studies using continuous 24-h IOP monitoring.

Glaucoma progression in myopic eyes



Comment by **Marisse Masis** and **Shan Lin**, San Francisco, CA, USA

60495 Effect of myopia on the progression of primary open-angle glaucoma, Lee JY, Sung KR, Han S, Na JH, Investigative Ophthalmology and Visual Science 2015; 56: 1775-1781

The authors of this **retrospective study describe the role of myopia in glaucoma progression in a Korean population**. A total of 369 eyes were classified into non-myopic, mild to moderate (0 to -6 diopters) and highly myopic (< -6 diopters) according to the level of spherical equivalent.

To determine progression they used optic disc and red-free RNFL photographs, Cirrus HD OCT optic nerve analysis and serial Humphrey visual field data. After performing univariate and multivariate Cox proportional hazard models they concluded that **no levels of myopia were associated with glaucoma progression and that high myopia might be a protective factor for optic disc/RNFL progression.**

The clinical diagnosis in patients with myopia is often difficult; bigger optic disc size, tilting and peripapillary atrophy are some of the findings that could overlap with glaucoma features in a myopic eye. The follow-up of the myopic patient is a challenge as well, since the most commonly used structural parameters are often altered because of the abnormal anatomic findings and the progression analyses are usually based on normal subject databases. Also visual field defects have been previously described in myopic subjects without glaucoma. All of these factors make the documentation of progression even more difficult.¹

Evidence suggests that highly myopic eyes are different in structure from non-myopic or mildly myopic eyes, and may be at higher risk for glaucomatous damage and progression of VF loss in POAG patients.²

In 2008, a retrospective study of a Taiwanese population that included 515 eyes concluded that after five years of follow up, POAG patients with myopia greater than -6 D had greater progression of VF loss.³

Whether myopic eyes are more susceptible to glaucomatous damage is still debatable. As the authors suggest, **a possible interpretation for the results could be that a lower progression detection rate was found when using the structural criteria or due mistaken glaucoma diagnosis secondary to the optic nerve characteristics.**

Further prospective studies, with standardized progression criteria and including the axial length as a confounding factor in the statistical analysis are needed to validate high myopia as a protective factor for glaucoma progression.

Nonetheless, this article opens an interesting discussion about the role of myopia in glaucoma that may lead to new research avenues.

The follow-up of the myopic patient is a challenge since the most commonly used structural parameters are often altered because of the abnormal anatomic findings and the progression analyses are usually based on normal subject databases.

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Medical Treatment

Investigational drugs



Comment by **Paul Kaufman**, Madison, WI, USA

60077 Intra-ocular pressure-lowering effects of a Rho kinase inhibitor, ripasudil (K-115), over 24 hours in primary open-angle glaucoma and ocular hypertension: a randomized, open-label, cross-over study, Tanihara H, Inoue T, Yamamoto T, Kuwayama Y, Abe H, Suganami H, Araie M, Acta Ophthalmologica 2015; 93(4): e254-260

This paper is of interest only because it **reports on the first-in-class commercially available rho kinase inhibitor**. Much has been written about this class of drugs, and need not be repeated here. This particular iteration **is an effective ocular hypotensive, albeit not as effective as our other major first-line drugs, i.e., prostaglandin F2a agonists and B2-adrenergic antagonists**. Its additivity to these other agents would be of interest, as of course will its long-term efficacy and tolerability and adherence profile, both in Japan and elsewhere. Of note, the references are nearly all to Japanese work. Our Japanese colleagues have indeed done a lot in this arena, but so have many others in the arenas of the underlying relevant basic and translational science and clinical development. **This should by no means be viewed as a 'Japanese' class of drugs.**



Comment by **Carol Toris**, Cleveland, OH, USA

60621 Effect of AR-13324 on episcleral venous pressure in Dutch Belted Rabbits, Kiel JW, Kopczynski CC, Journal of Ocular Pharmacology and Therapeutics 2015; 31: 146-151

The report by Kiel and Kopczynski is a rare study that specifically investigated alteration in episcleral venous pressure (EVP) as a means to lower intraocular pressure (IOP). The drug of interest was AR-13324, a combined rho-associated protein kinase (ROCK) inhibitor and norepinephrine transporter (NET) inhibitor. EVP was thought to decrease with drug treatment via its NET inhibition. However, the experimental design could not eliminate a contribution from the ROCK

inhibition. AR-13324 was administered to Dutch belted rabbits for two days and the carefully controlled methods by Kiel were used to measure EVP, IOP, arterial pressure, carotid blood flow and heart rate. **Compared to baseline or vehicle treatment, the drug decreased EVP and IOP without affecting the cardiovascular parameters.** It was concluded that EVP is an important, but not sole contributor to the IOP reduction by AR-13324 in this animal model.

The methods by Kiel are technically challenging and cannot be used in awake animals or humans. Unfortunately, available noninvasive methods are subjective and highly variable. Often, in studies of aqueous humor dynamics, EVP is not measured but rather assumed to be unchanged by the experimental manipulation. The interaction of blood flow, vascular resistances, arteriovenous anastomoses, and muscular veins is so complex that it becomes difficult to assume anything regarding a drug effect on episcleral veins. Both vasodilators and vasoconstrictors have been reported to decrease EVP. Clearly, studies of aqueous humor dynamics are incomplete without assessing the pressure in these veins. Kiel's study reminds us of this point. Improved methods are sorely needed to make accurate EVP assessment more obtainable.

A secondary finding of the Kiel study is that Dutch belted rabbits have normal IOPs in the high range (30 mmHg or more) yet they do not suffer from glaucoma. The arterial pressure in these animals is relatively high making the ocular perfusion pressure high which apparently is protective in these animals. This supports the idea that **ocular perfusion pressure may be a more important risk factor for glaucoma than IOP alone.**



Comment by **Tina Wong**, Singapore

60083 A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study, Weinreb RN, Ong T, Scassellati Sforzolini B, Vittitow JL, Singh K, Kaufman PL, British Journal of Ophthalmology 2015; 99(6): 738-745

Prostaglandin analogues, introduced over two decades ago are now the most prescribed glaucoma drug worldwide. The search for a new class of drug for IOP lowering that can match or supersede the indomitable prostaglandin analogue family continues. Latanoprostene is one such competitor. This new molecule possesses dual action which once cleaved, into a prostaglandin F_{2α} receptor agonist and nitric oxide donating moiety, which reduces the IOP by increasing uveoscleral pathway outflow and reducing resistance to outflow through relaxation of the trabecular meshwork/Schlemm's canal inner wall respectively.

In this study, the VOYAGER investigators not only identified the most effective concentration of Latanoprostene (0.024%) but also reported a greater IOP lowering of an average of 1.2 mmHg compared to Latanoprost alone. In terms of safety, Latanoprostene had numerically higher

incidence of adverse events compared to Latanoprost, the most significant was the report of pain on drop instillation. Safety remains paramount.

My immediate thought on Latanoprostene is whether it is claiming to be a new drug or a fixed combination drug. If it is the latter, with an additional one mmHg lowering, there does not appear to any advantage over the much more effective fixed combination monotherapies that can achieve IOP lowering of several mmHg. But with the concern of systemic effects of beta blockers in some susceptible patients, it would be beneficial to develop dual acting formulations that contain another drug class. So **it remains to be seen whether the IOP lowering effect from the NO moiety in Latanoprostene can be further enhanced to really give a convincing IOP lowering that competes with existing drugs.**

Perhaps this additional function can be isolated to produce a new drug class of its own. For this would be the most exciting news in glaucoma drug development.

Drug delivery



Comment by **Tina Wong**, Singapore

60294 Nanosponge-mediated drug delivery lowers intraocular pressure, Lambert WS, Carlson BJ, van der Ende AE, Shih G, Dobish JN, Calkins DJ, Harth E, Translational Vision Science & Technology 2015; 4: 1

Development of drug delivery systems for ophthalmology, particularly for glaucoma and fibroproliferative retinal disorders is a fast growing area of research.

Here the authors report on a proof of concept evaluation of their nanosponge delivery system for the extended release of brimonidine, travaprost in a mouse model of raised intraocular pressure. First of all, the description is rather misleading in that the nanoparticles described are not actually sponges, which one would think of. Instead the 'sponges' are biodegradable cross-linked particles that are injected intravitreally. This route of delivery of the brimonidine or travaprost would appear to be unnecessarily invasive for clinical use in glaucoma.

The authors show that IOP lowering effect for the brimonidine nanosponges was sustained for longer, 30 days with the larger 700 nm nanosponge compared to the 400nm version, which showed IOP lowering for 18 days. This is not surprising since the amount of drug loading is higher in the larger nanosponges. Similar effect of size was reported with the travoprost nanosponges.

A practical challenge in the use of such a delivery system would be the effect of size of the injected particles into the vitreous cavity. There is no mention of whether these nanosponge particles aggregate upon injection, an important factor to consider. Patients may experience

visual disturbances from the opaque particles floating inside and particle aggregation may exacerbate this. So size and transparency are considerations to take when it comes to designing drug delivery systems for intravitreal injection. The authors also evaluated the nanosponge delivery system as a potential carrier for drugs and active biological molecules for vitreoretinal disorders such as age related macular degeneration. It seems to be a better fit for this delivery system to be applied for AMD.

The nanosponge delivery will ensure that the drug effectively reaches the target tissue, the retina. As to its application for glaucoma, it seems to be a less attractive approach compared to other systems being developed in this area. The target tissues in glaucoma remain in the anterior segment and it therefore seems logical to have a delivery platform placing the active drug closest to the site of action, namely the trabecular meshwork and ciliary body. Perhaps with this in mind, the nanosponge delivery system could provide a more effective and sustained IOP lowering than it currently does.

Dietary supplements



Comment by **Jonathan Crowston**, Melbourne, Australia

60639 Protection of injured retinal ganglion cell dendrites and unfolded protein response resolution after long-term dietary resveratrol, Lindsey JD, Duong-Polk KX, Hammond D, Leung CK, Weinreb RN, *Neurobiology of Aging* 2015; 36(5): 1969-1981

Resveratrol, a polyphenol present in red wine and peanuts has long been thought to have anti-ageing effects and is thought to contribute to the 'French Paradox'; the lower than expected rates of coronary heart disease in the French population, despite a tasty but somewhat saturated fat-laden diet.

Resveratrol, a polyphenol present in red wine and peanuts has long been thought to have anti-ageing effects and is thought to contribute to the 'French Paradox'

James Lindsey and colleagues investigated **whether resveratrol confers protection in retinal ganglion cells of older mice, after optic nerve crush injury**. They fed a cohort of transgenic mice (Thy-1-YFP, which have fluorescent retinal ganglion cells) a diet supplemented with resveratrol starting from one month of age. Unilateral optic nerve crush was induced at 12 months of age and subsequent alterations in RGC dendrite architecture was followed over time, using *in-vivo* fluorescent imaging, which generated some impressive pictures.

Mice fed the resveratrol diet had slower rates of dendrite shortening, delayed loss of dendrite complexity and complete dendrite loss compared to mice of equivalent age, but fed on a resveratrol-free diet. Interestingly, sub-analysis of different RGC subtypes (identified on the basis of dendrite morphology) suggested that some but not all RGC types were protected. Protection, as expected from such a significant injury was only temporary with substantial loss of RGCs in all groups by four weeks.

To investigate possible mechanisms as to how resveratrol may be protecting RGCs, the authors chose to look at proteins of unfolded protein response, these are thought to protect endoplasmic reticulum in times of cellular stress. Resveratrol did alter expression of three UPR proteins (BiP, CHOP and XBP-1) but **further work is required to determine whether these changes are key to conferring protection through resveratrol or merely associated changes.**

Resveratrol has received much attention over recent years as a candidate agent for delaying age-related morbidity and mortality. This work provides an exciting insight into the possibility that it may have a direct impact on protecting retinal ganglion cells from injury.



Comment by **Keith Martin**, Cambridge, UK

60189 A two-year follow-up of oral antioxidant supplementation in primary open-angle glaucoma: an open-label, randomized, controlled trial, Garcia-Medina JJ, Garcia-Medina M, Garrido-Fernandez P, Galvan-Espinosa J, Garcia-Maturana C, Zanon-Moreno V, Pinazo-Duran MD, *Acta Ophthalmologica* 2014; e-pub ahead of print

Mixed supplements containing antioxidants, vitamins and minerals have been shown to reduce progression in a subset of patients with age-related macular degeneration in the AREDS studies. In an open label, randomized controlled trials of 117 eyes of 117 patients with mild or moderate POAG, Garcia-Medina *et al.* explored whether similar preparations could influence structural and functional measures of glaucoma progression over two years of follow-up.

Patients were randomised to receive either daily oral supplementation with ICAPS R (n = 26), OFTAN MACULA (n = 28), or no treatment (n = 63). Humphrey 24-2 perimetry and FD-OCT scans were performed every six months for two years. **No statistically significant differences were found on any structural or functional measure between treated and control groups, nor was there any difference in IOP control.**

The study is of interest, not least because of a number of contradictory studies in the literature concerning the effects of antioxidants in glaucoma. Although the groups were quite small, the authors estimated they had 80% power to detect a difference in perimetric mean deviation of 0.6dB over two years between treated and control groups. Another limitation was that patients were not masked to their treatment which could potentially affect their attitude to, and thus performance of, automated visual field tests.

Nevertheless, the study suggests that there is unlikely to be a large effect of oral antioxidant supplementation with or without omega-3 fatty acids in the population studied. Given the bias in published literature towards clinical studies with positive finding, and the consequent risk that the literature is skewed as a result, it is good to see carefully performed studies with negative findings being published prominently. **Strong negative findings are arguably at least as important as positive results in aiding future clinical treatment decisions.**

Persistency of topical treatment



Comment by **Michael Boland**, Baltimore, MD, USA

59872 Persistence of topical glaucoma medication: a nationwide population-based cohort study in Taiwan, Hwang DK, Liu CJ, Pu CY, Chou YJ, Chou P, JAMA ophthalmology 2014; 132: 1446-1452

This retrospective study of persistence with glaucoma medications is an important contribution in that it is based on data from a national health system (Taiwan). This fact helps to alleviate concerns about potential bias in prior studies which were limited to health insurance programs that covered only particular groups within an overall population.

At least two of the findings from this work are consistent with prior studies – those **patients on treatment for a longer time and those taking prostaglandins are more likely to be refilling their medications**. In addition, there are two novel findings reported: that the sex of the treating physician is important (patients with female physicians were more likely to be persistent) and that patients with a higher continuity of care are more likely to be persistent. Both of these warrant further study as potential avenues to improve persistence.

Patients with female physicians were more likely to be persistent

As with all such studies based on claims data, the measures used are a few steps removed from the actual taking of the medication by the patient. It is also true that it is difficult to determine from claims data just how long a particular prescription should last due to differences in bottle sizes, differences in drop size delivered, differences in patient accuracy, and the fact that one cannot tell whether one or two eyes are being treated. On the other hand, this study does not suffer from the problem of patients moving from one health plan to another during the period of analysis as is the case with commercial claims data.

This study is now one of many demonstrating that adherence and persistence with glaucoma medications is fair to poor in most settings. Investigators interested in this topic should turn their attention to determining the difference (or not) in the rates of glaucoma worsening in these populations.

Surgical Treatment

Pediatric glaucoma



Comment by **Franz Grehn**, Würzburg, Germany

60800 Comparison of 360-degree versus traditional trabeculotomy in pediatric glaucoma, Lim ME, Neely DE, Wang J, Haider KM, Smith HA, Plager DA, Journal of AAPOS 2015; 19: 145-149

Pediatric glaucoma has always been a challenging therapeutic issue as it needs specific surgery at a very early age in a rare disease. Although most of the cases are being treated in tertiary care centers, the low frequency of these surgical procedures have made innovative changes in surgical techniques difficult. Hitherto, goniotomy and traditional trabeculotomy were the two procedures used in most centers, as these operations aim at opening the malformed trabecular meshwork as the primary site of outflow resistance.

Three hundred-sixty-degree trabeculotomy is a logical approach that opens up the complete circumference of the malformed trabecular meshwork. It has been performed by a few centers since its introduction in 1960 using a suture for trabeculotomy. However, the visibility of the suture during probing of Schlemm's canal is limited and specific serious complications by misdirection of the suture may occur. The introduction of an illuminated catheter as used for canaloplasty has now facilitated the technique and many pediatric glaucoma surgeons have adopted this technique.

360-degree trabeculotomy is a logical approach that opens up the complete circumference of the malformed trabecular meshwork

The present paper compares 77 eyes treated with traditional trabeculotomy to 14 eyes treated with 360-degree catheter trabeculotomy in a non-randomized comparison of the two techniques. The success criteria was absence of additional surgery at the one-year follow-up. In the traditional trabeculotomies, 37 of 77 eyes completed the one-year follow-up (IOP 17.05 ± 5.92 mmHg) and the success rate as defined above was 58.44% (all eyes). In the 360-degree trabeculotomy group, seven of 14 eyes completed the one-year follow up (IOP 11.00 ± 2.31 mmHg) and the success rate as defined above was 85.71% (all eyes). In three eyes, 360-degree trabeculotomy was attempted but could not be completed due to a block along the circumference of Schlemm's canal. These eyes received a partial catheter cut-down trabeculotomy or a traditional trabeculotomy. Two of them were failures and required additional surgery.

If the results relating to primary congenital glaucoma only (PCG) were analyzed separately, all 11 PCG eyes treated with 360-degree trabeculotomy were successful (100%) but only 32 of 58 PCG eyes treated with traditional trabeculotomy were successful (55,17%). The circumferential

introduction of the catheter was possible in all PCG glaucoma eyes.

The rate of additional medication at one-year follow-up was approx. 0.5 in either technique for all eyes, and 0.2 (360-degree trabeculotomy) and 0.3 (traditional trabeculotomy) in the PCG only group, respectively.

The comparison of the two techniques results in a better outcome after 360-degree illuminated catheter trabeculotomy, in particular in primary congenital glaucoma. However, due to the non-randomized design of this comparison and the unequal number of eyes in the compared groups (five times more traditional trabeculotomies), **the favorable results of 360-degree trabeculotomy must be considered still somewhat preliminary**. Another challenge is the fact that three eyes (non PCG eyes) could not be probed circumferentially, but were not counted as failures of the 360-degree trabeculotomy group. In contrast, they were included into the traditional trabeculotomy group. If one includes these three eyes as failures into the 360-degree trabeculotomy group (as they were intended to receive 360-degree trabeculotomy), five out of 17 eyes were failures (29.41%) in an intention-to-treat analysis, although one eye was successful as a traditional trabeculotomy. This critical view underlines the authors' comments that 360-degree trabeculotomy is particularly successful in primary congenital glaucoma but still has some challenges in secondary pediatric glaucoma.

This paper is a very valuable contribution to the increasing experience with 360-degree catheter trabeculotomy and supports the results of other studies showing high efficacy of 360-degree trabeculotomy when compared to goniotomy or combined MMC trabeculotomy/trabeculectomy.

Complications



Comment by **Steven Gedde**, Miami, FL, USA

60596 Trabeculectomy-related complications in Olmsted County, Minnesota, 1985 through 2010, Olayanju JA, Hassan MB, Hodge DO, Khanna CL, JAMA Ophthalmology 2015; 133(5): 574-580

Olayanju and colleagues provide a retrospective review of trabeculectomy-related complications in Olmsted County, Minnesota from 1985 to 2010. **The study includes 460 eyes of 334 patients with a mean follow-up of 7.7 years, and it represents the longest population-based study assessing the long-term risks associated with glaucoma filtering surgery. The 20-year cumulative probability of early and late complications was 19.7% and 26.0%, respectively.** The cumulative chance of vision-threatening complications during 20 years was 2.0% for blebitis and 5.0% for endophthalmitis. The authors noted a lower rate of early complications, and a similar rate of late complications compared with other published reports.

Difficulties arise when attempting to compare results across various studies, given differences in study populations, losses to follow-up, definitions of trabeculectomy complications, and

methods used to assess for postoperative complications. The homogenous population of white patients in this study is not representative of the general population of glaucoma patients. **Retrospective case series like this one generally report lower complication rates than prospective studies.** Surgical complications may be overlooked unless attention is specifically directed toward their detection. Moreover, complications may not be documented in the medical record even when observed, especially if they are believed to be insignificant.

The authors are to be congratulated for adding important information to the medical literature about the risks of glaucoma filtering surgery. The study highlights the importance of educating patients about the presenting symptoms of bleb-related infections and the need for timely ophthalmic attention should they develop. The search continues for a glaucoma procedure as effective as trabeculectomy in lowering intraocular pressure, but provides a more favorable safety profile with a lower risk of vision-threatening complications.



Comment by **Henry Jampel**, Baltimore, MD, USA

60609 Long-term bleb-related infections after trabeculectomy: incidence, risk factors, and influence of bleb revision, Kim EA, Law SK, Coleman AL, Nouri-Mahdavi K, Giaconi JA, Yu F, Lee JW, Caprioli J, American Journal of Ophthalmology 2015; 159(6): 1082-1091

Kim *et al.* report a **retrospective analysis of a large case series of late trabeculectomy-related infections at a single academic center** in the United States. The rationale for the undertaking of such labor-intensive research (almost 2000 eyes operated on over a 20-year period!) is the realization of the importance of this often devastating complication and the hope that by understanding its risk factors we can reduce its occurrence.

An increased incidence in juvenile and pigmentary glaucoma is puzzling

Their work nicely complements older publications on the risk factors for bleb-related infection,^{1,2} recent publications from our group,^{3,4} as well as the ongoing work from the Japanese Collaborative Bleb-Related Infection Incidence and Treatment Study Group.⁵

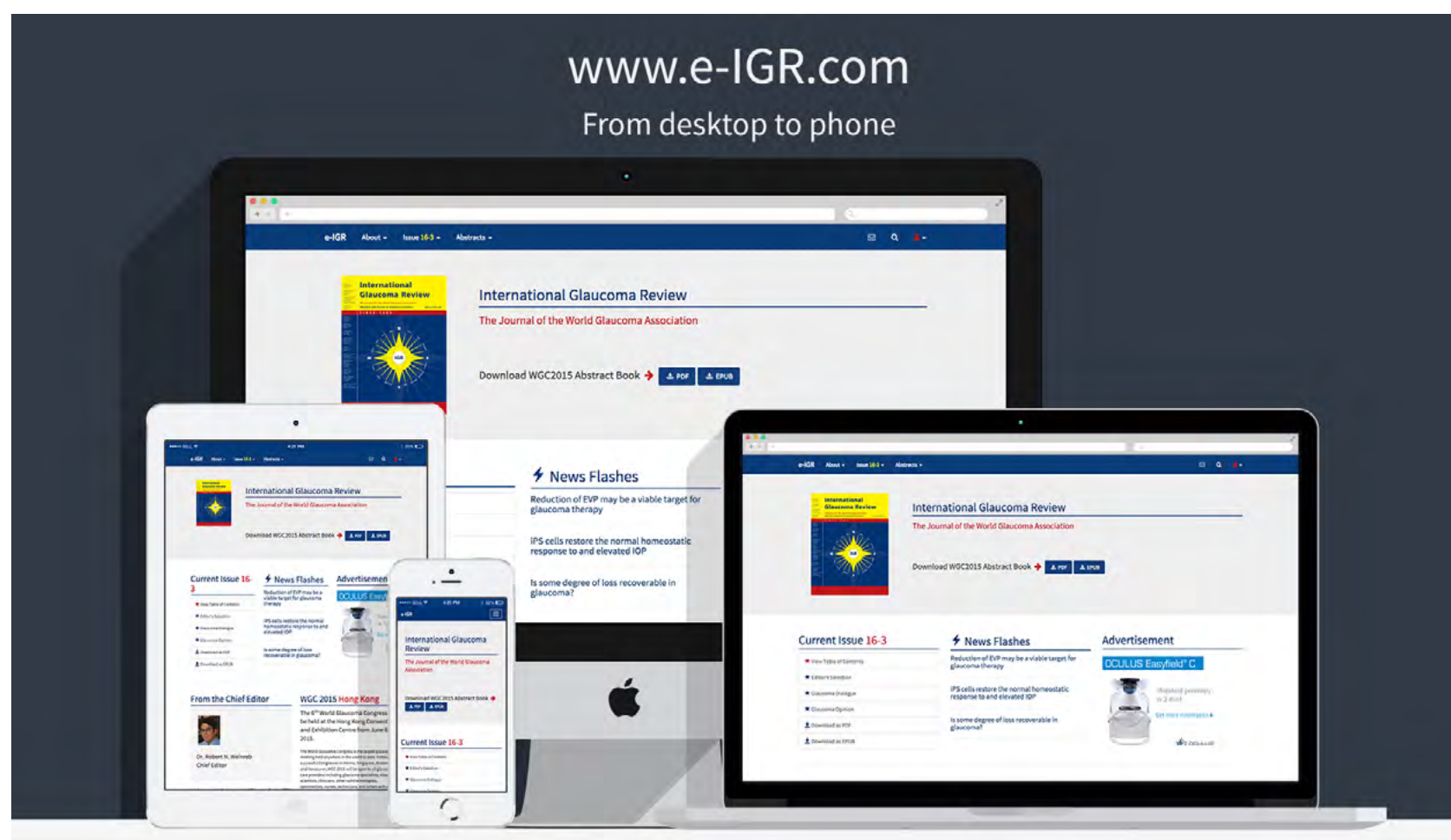
The authors' analysis is appropriate and thorough, but is limited by the inherent shortcomings of a retrospective chart review. **Particularly frustrating, but totally predictable, is that incomplete and imprecise information on bleb morphology precludes this likely important parameter from being analyzed.** They confirm many previously known risk factors, and add a few more. An increased risk with punctal plugs is plausible, due to stagnation of tears on the ocular surface, but an increased incidence in juvenile and pigmentary glaucoma is puzzling. **An important finding of this work is that eyes that underwent surgical revision when risk factors were present had a lower likelihood of infection than eyes that did not.**

Elimination of the risk of infection is one of the principal reasons we so greatly desire an effective micro-invasive glaucoma operation

Only a few risk factors are modifiable, so education of the patient to recognize early signs and symptoms and report them immediately may be the best way to reduce the devastating sequelae of infection. However, because susceptibility to infection is an inherent property of trabeculectomy, we will continue to see infections as long as we perform it. Elimination of the risk of infection is one of the principal reasons we so greatly desire an effective micro-invasive glaucoma operation.

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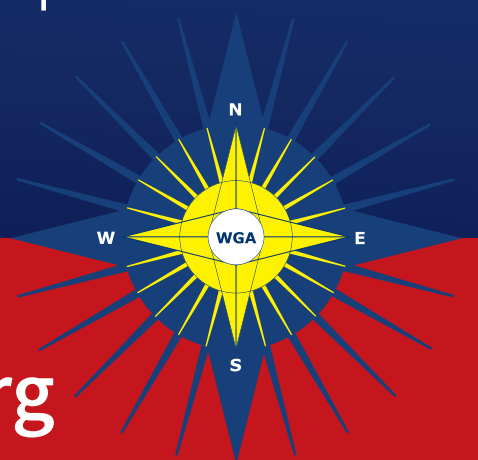
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