Volume 19-2
2018

International Glaucoma Review

The journal of the World Glaucoma Association

Abstracts and Review of Glaucoma Literature

www.e-IGR.com

SINCE 1984

ISSN 1566-1040

Regional & International Glaucoma Societies

American Glaucoma Society

Asia-Pacific Glaucoma Society

Australia and New Zealand Glaucoma Society

Canadian Glaucoma Society

Childhood Glaucoma Research Network

Chinese Glaucoma Society

Commonwealth Independent States Glaucoma Society

European Glaucoma Society

Glaucoma Society of India

International Society for Glaucoma Surgery

Japan Glaucoma Society

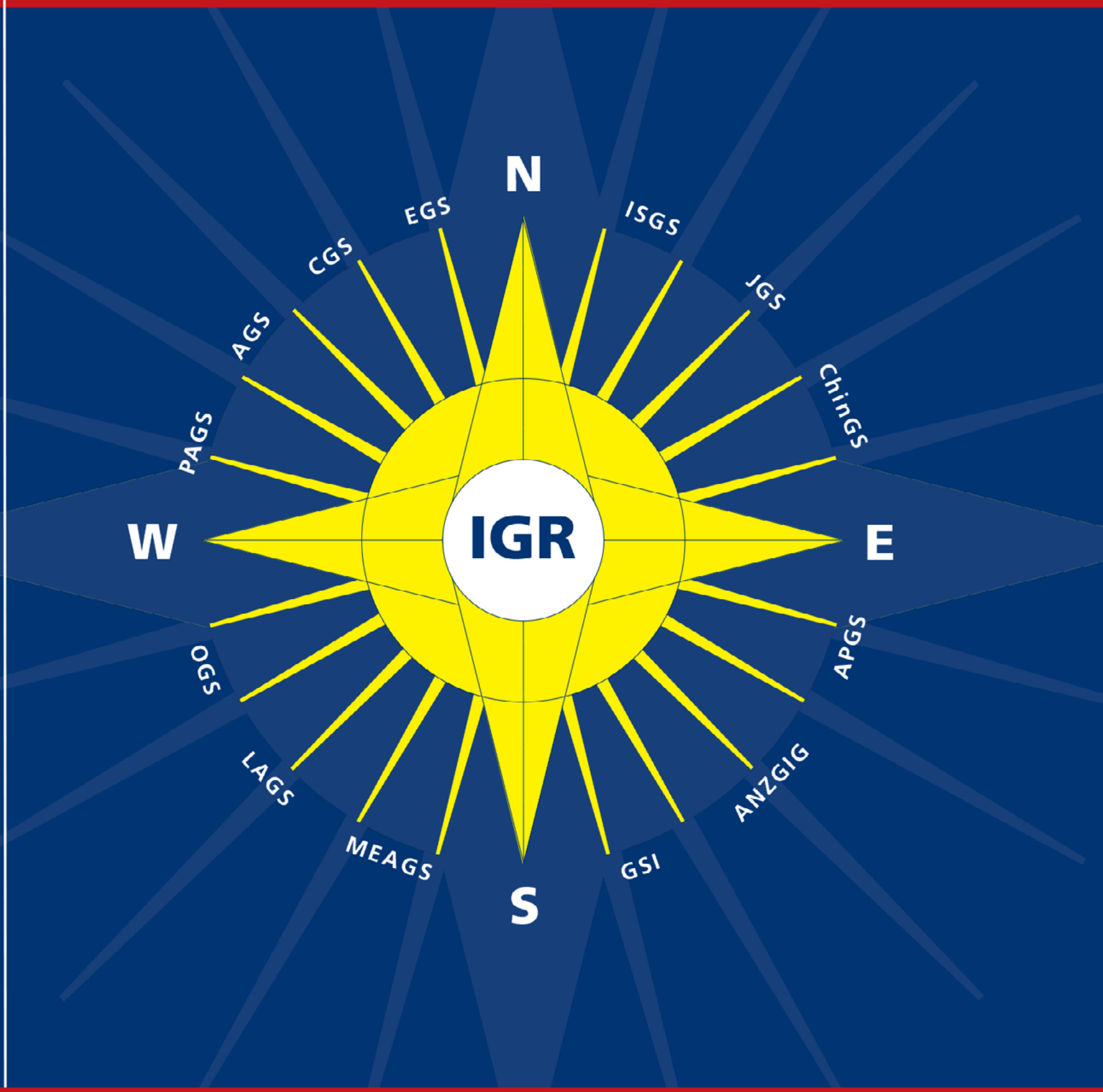
Latin American Glaucoma Society

Middle East African Glaucoma Society

Optometric Glaucoma Society

Pan American Glaucoma Society

Click here for an overview of all WGA affiliated National Glaucoma Societies



We acknowledge the unrestricted educational grants of our:

GLAUCOMA INDUSTRY MEMBERS

ASSOCIATE GLAUCOMA INDUSTRY MEMBERS

SUPPORTING GLAUCOMA INDUSTRY MEMBERS

Aeon Astron Europe B.V., Bausch + Lomb, Diopsys Inc., Ellex, EyeTechCare, Haag Streit AG, Icare Finland Oy, iSTAR Medical, Mundipharma, NeoMedix Corporation, Oculus, Optovue Inc., Reichert Technologies, Senju, Specsavers, Tomey

ISSN 1566-1040

INTERNATIONAL GLAUCOMA REVIEW

A Quarterly Journal
Volume 19 no. 2

Information on the member Glaucoma Societies of the WGA can be found in the WGA Global Directory of Glaucoma Societies at www.worldglaucoma.org

Registration

Access to IGR Online is complimentary for all members of glaucoma societies affiliated to the WGA. As of 2018, access to IGR is arranged through WGA#One; see next page for details.
Should you have any questions, please contact us at info@e-igr.com

ISSN 1566-1040

Contact Information

All correspondence on copies, supplements, content, advertising, etc. should be directed to:

WGA Executive Office
c/o Schipluidenlaan 4
1062 HE Amsterdam
The Netherlands
Tel: +31 20 679 3411
E-mail: info@worldglaucoma.org

Published by Kugler Publications, P.O. Box 20538, 1001 NM Amsterdam, The Netherlands, on behalf of the World Glaucoma Association.

Cover design: Cees van Rutten, The Hague, The Netherlands
Typesetting: 3bergen, www.3bergen.com

WGA#One

WGA#One is the name of the World Glaucoma Association's customer relationship management system. With WGA#One we are moving forward towards one platform, and hence one user profile, for all our services.

WGA#One is facilitating our communications about and access to our services, offers and initiatives. Therefore it's very important to keep your **WGA#One** profile updated. See below for details on how to activate your account for the first time.

Communicating effectively is key, and thus we extended our basic user profile with the option to activate different information preferences:

☑ **1 - Monthly newsletter**	A concise monthly digest of all WGA activities, such as congresses, publications, courses, projects, governance, scientific content, awareness activities etc. Find the archive here to get a taste: www.wga.one/wga/newsletter-archive
☑ **2 - Glaucoma awareness initiatives**	Information on awareness activities, such as World Glaucoma Week
☑ **3 - Educational & scientific content**	For example: Consensus statements/publications, International Glaucoma review, Journal of Glaucoma, recorded WGC session/enduring materials, etc.

In just a few clicks you'll be ensured to stay in touch and receive the latest news according to your own preferences. We never share your information with third parties.

Your privacy is very important to us, so please see our privacy policy at
www.wga.one/terms-and-conditions

Find us on Facebook: www.facebook.com/worldglaucoma
Find us on Twitter: www.twitter.com/WorldGlaucoma
WGA#One FAQ: www.wga.one/faq

How to activate your WGA#One profile

1. **Please visit www.wga.one/activate to activate your WGA#One profile.**
2. **Enter your email address (use the address where you are currently receiving our communications).**
3. **You will receive an email with an activation link (if not received, check your spam folder first before contacting info@worldglaucoma.org).**
4. **Click on the link, create a new password, and update your WGA#One profile.**

If none of your email addresses is found in the system you can either
contact us at info@worldglaucoma.org, or subscribe to our newsletter here:
www.wga.one/wga/subscribe-to-newsletter

touch OPHTHALMOLOGY®

Leading the Debate on the Advances in Healthcare

touch medical media

PRACTICAL ARTICLES
EXPERT INTERVIEWS
NEWS AND INSIGHTS

PEER-REVIEWED | OPEN-ACCESS
CONCISE | MULTIMEDIA

VIEW – DOWNLOAD – SUBSCRIBE
FREE

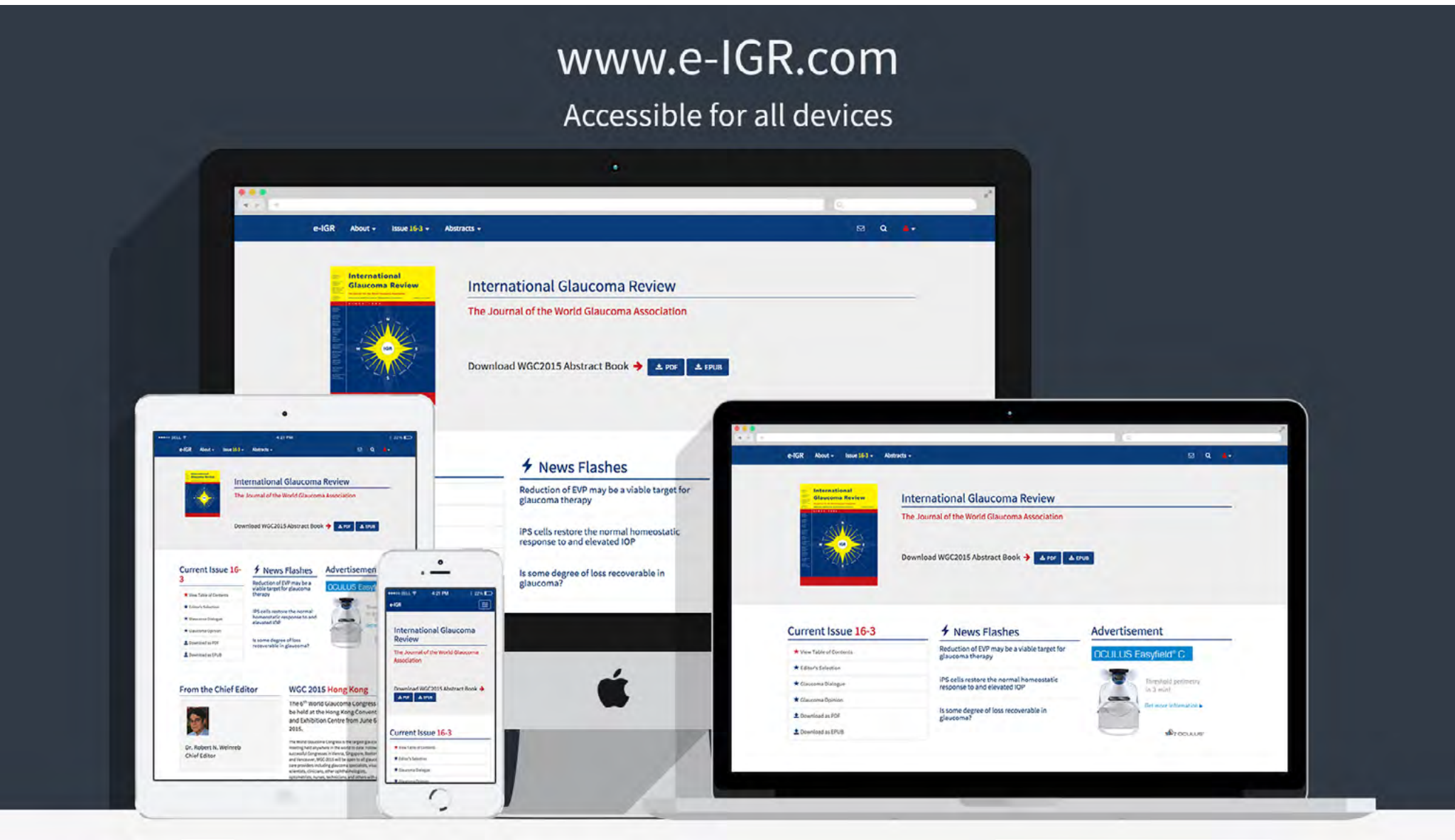
touch**OPHTHALMOLOGY**.com

Table of Contents

All abstracts are available online in the classified IGR searchable glaucoma database

www.e-IGR.com

The affiliations of the contributors to this issue can be found on www.e-IGR.com.



e-IGR.com

IGR Searchable Glaucoma Database

- Huge time saver to stay on top of the most significant glaucoma developments!
- The IGR abstract database holds **over 21,000 abstracts** related to Glaucoma, **all classified**, and some 10% commented on by leading experts.
- **Only glaucoma abstracts**: no false positives to wade through.
- Expert comments from the Editor's Selection are also **fully searchable** and linked to the abstracts.

Accessible, free of charge, to all members of WGA affiliated Glaucoma Societies

Features

- Searches in the abstracts may be limited to those abstracts that are commented on by experts.
- Limit your search or view abstracts by classification.
- Limit your search to (a range) of year(s) of publication
- Find related abstracts with one click of your mouse.
- Browse abstracts by classification, journal or author.
- Use operators to refine your queries and get better search results.

International Glaucoma Review is published as an online journal only.

If you are not yet receiving **IGR online**, we urge you go to the WGA website and supply us with your email address, so you will not miss any of the IGR content.

www.e-IGR.com

WGA Consensus Series

Robert N. Weinreb

The Glaucoma Consensus Initiative of the World Glaucoma Association is based on the idea that the collective wisdom of a group is better than the opinion of a single expert. Assembling a sufficiently large and sufficiently diverse group of glaucoma specialists and scientists provides recommendations and insights that are likely to be superior to those of a single clinician. These recommendations and insights form the foundation for the Glaucoma Consensus Reports.

To prepare each of the 10 consensus reports, there were several months of active discussion via the Internet by more than 100 expert members of the various consensus committees. The preliminary documents were circulated to each of the member societies of the World Glaucoma Association, and additional comments were solicited. Participants were asked to review the international peer-reviewed literature, with special attention to the quality of available evidence. A Consensus Meeting attended by the experts and society representatives was then conducted. Consensus points were formulated and the report revised by the Consensus Panel following these discussions.

The clinical acumen and knowledge of numerous and diverse practitioners and scientists can be harnessed more efficiently and effectively than ever with the continued enhancements of inter-connected global communication. We can learn from each other by sharing, adapting and updating new information, and then agreeing on its significance. Linking networks of glaucoma specialists has tangible and ongoing important implications for, glaucoma clinical care, research and education on a global basis.

WGA Consensus Volume 11 - Glaucoma Surgery

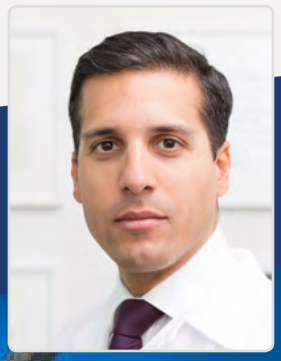
Glaucoma Surgery Consensus

Chair: Robert N. Weinreb

Co-chairs: Pradeep Ramulu, Fotis Topouzis, KiHo Park, Fabian Lerner, Kaweh Mansouri







WGA Consensus Volume 11 - Glaucoma Surgery
Melbourne Convention & Exhibition Centre (MCEC)
Tuesday March 26, 09:00 am – 06:00 pm

If you are interested to join the 11th Consensus Meeting on Glaucoma Surgery as an observer, please let us know via your WGC-2019 registration.
As a WGC-2019 delegate, attendance of the Consensus Meeting is complimentary.

From the WGA Executive Office

Dear IGR readers,

Registration and abstract submission for the **8th World Glaucoma Congress**, which takes place in Melbourne, Australia from March 27-29, 2019, is now open!

Great reason to attend WGC-2019 is the **11th Consensus Meeting on Glaucoma Surgery**, taking place just before the congress starts on Tuesday, March 26. The Glaucoma Consensus is based on an assumption that groups make better decisions than even their smartest member. If you are interested in joining the Consensus Meeting as an observer, please let us know via your WGC-2019 registration. As a WGC-2019 delegate, attendance of the Consensus Meeting is complimentary. More information about the meeting can be found online.

To conclude, we would like you to get to know the WGA Executive Office a bit better. We will introduce you to someone on our great team in each IGR. Kicking off this new feature is our Associate Executive Vice President, Kaweh Mansouri.

Please enjoy this issue of the *IGR*. You can contact our WGA Executive Office if you need any information or have questions on *IGR* or WGA-related matters (info@worldglaucoma.org).

Get to know us

Kaweh Mansouri, MD, MPH, is a Consultant Ophthalmologist at the Glaucoma Center, Montchoisi Clinic, Lausanne and an Adjoint Associate Professor at the University of Colorado, Denver.

Dr Mansouri is the Associate Executive Vice President of the World Glaucoma Association. Dr Mansouri was the first ophthalmologist to give a TEDx talk. He has been ranked twice in the Top 40 under 40 Power List by the journal *The Ophthalmologist* and has been named as a Top-50 glaucoma specialist in the world (Expertscape).

World Glaucoma Association
The Global Glaucoma Network

REGISTER NOW!

ABSTRACT DEADLINE: OCTOBER 1, 2018

WGA

8th WORLD GLAUCOMA CONGRESS

MARCH 27 – 30, 2019

MELBOURNE

www.worldglaucomacongress.org

Your Special Attention For

Glaucoma as a metabolic optic neuropathy: making the case for nicotinamide treatment in glaucoma
Williams PA, Harder JM, John SWM
Journal of Glaucoma 2017; 26: 1161-1168
abstract no. 75045

XEN Gel Implant: A new surgical approach in glaucoma
Chaudhary A, Salinas L, Guidotti J, Mermoud A, Mansouri K
Expert Review of Medical Devices 2018; 15: 47-59
abstract no. 75549

Smartphones, tele-ophthalmology, and VISION 2020
Mohammadpour M, Heidari Z, Mirghorbani M, Hashemi H
International Journal of Ophthalmology 2017; 10: 1909-1918
abstract no. 75556

Resource planning in glaucoma: A tool to evaluate glaucoma service capacity
Batra R, Sharma HE, Elaraoud I, Mohamed S
Seminars in Ophthalmology 2017; 0: 1-6
abstract no. 75619

ARVO 2019

APRIL 28 – MAY 2 | VANCOUVER, BC

Make plans to join ARVO in Vancouver!

Early Registration Opens: Oct. 15, 2018
Abstract Submissions: Oct. 15 – Nov. 30 2018

New!

ARVO.org/AM

ARVO®
The Association for Research in Vision and Ophthalmology

World Glaucoma Association
The Global Glaucoma Network

Basic Course in Glaucoma

This course consists of 4 modules that address basic aspects of glaucoma diagnosis:

GONIOSCOPY

Anton Hommer, Tanuj Dada, Pooja Shah, Talvir Sidhu

Gonioscopy is an important diagnostic test in ophthalmology to correctly diagnose and properly treat each individual patient.
In this module, you will learn about the principles of Gonioscopy, its importance, the type of lenses and classification systems.

INTRAOCULAR PRESSURE

Emily P. Jones, Robert Kinast, David Simons, Steven L. Mansberger

Intraocular pressure (IOP) is the pressure of the fluid inside the eye.

STANDARD AUTOMATED PERIMETRY

Anders Heijl, Balwantray Chauhan

Functional status in glaucoma is best evaluated with perimetry; Visual acuity is insufficient, since it usually remains normal until very late in the process of glaucomatous disease.

CLINICAL EXAMINATION OF THE OPTIC NERVE

Michael Coote, Jonathan Crowston

Examining the ONH is a key skill of ophthalmologists, optometrists and other eye care professionals.

Access Course

Now also available in Spanish!

All modules were written by world renowned experts in the field, and reviewed by members of the WGA Education Committee. They are intended for ophthalmologists and other eye-care providers.

All texts, pictures and videos were adapted to an online platform by a team of e-learning experts. This will allow you to have a pleasant learning experience. At the end of each module there is a multiple choice test that will auto correct once the exam is completed. You will also be able to download a Certificate of Completion.

The Measure of All Things

NEW

Click here

to discover more

Pentacam® AXL

Tomographer and Biometer in One Device

In the Pentacam® AXL our tried and true Pentacam® technology has become yet another bit better. Its combination of axis length measurement with anterior segment tomography requires a single measurement process to generate all the data needed for presurgical screening and IOL selection and calculation. Thanks to the TrueVision interface you can now also transmit Pentacam® data directly to your Leica microscope, saving you time, space and money as well as minimizing error sources.

!

OCULUS at the ESCRS in Vienna, booth B404

Join us at the Lunch Symposium on Saturday, 22nd Sept, 13:00 - 14:00 h

www.pentacam.com

Follow us!

OCULUS®

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. An approach to this confusing situation may be a critical selection and review of the world literature.

Robert N. Weinreb, Chief Editor

Epidemiology

Perfusion Pressure and POAG

Comment by Gustavo de Moraes, New York, NY, USA

75704 Inter-relationship between ocular perfusion pressure, blood pressure, intraocular pressure profiles and primary open-angle glaucoma: the Singapore Epidemiology of Eye Diseases study; Tham YC, Lim SH, Gupta P, Aung T, Wong TY, Cheng CY; British Journal of Ophthalmology 2018

There is growing and compelling evidence that systemic blood pressure (BP) may play a role in the pathogenesis of glaucoma. Population-based studies, randomized clinical trials, and longitudinal observational studies have shown that different BP-related parameters have a significant association with the incidence, prevalence, and progression of glaucomatous damage.

In this large population-based study (the Singapore Epidemiology of Eye Diseases Study), which included 19,587 eyes of 9,877 participants, Tham *et al.* investigated the relationship between inter-relationship between ocular perfusion pressure (OPP), intraocular pressure (IOP) profiles and primary open-angle glaucoma (POAG) in a multiethnic Asian population. This is an important study as it aims to address limitations and inconsistencies from previous studies by evaluating a larger sample and addressing issues related with how OPP, BP and IOP are analyzed in statistical

models testing their relationship with glaucoma prevalence. Another important point is that the Singapore Epidemiology of Eye Diseases Study comprises three major ethnic groups in Singapore (Malays, Indians and Chinese) that represent the majority of the Asian population.

When defining POAG based on the Society of Geographical and Epidemiological Ophthalmology criteria, the authors found a prevalence of 2.1% (213 participants), which is consistent with estimates of glaucoma prevalence in Asia. Moreover, POAG participants were older, more likely to be male, Malays and hypertensive than those without this diagnosis (all $P \leq 0.017$). Interestingly, after adjusting for a set of confounders (age, gender, ethnicity, diabetes, body mass index, smoking status and antihypertensive medication), in addition to IOP and IOP-lowering treatment, the authors found no significant association between mean arterial pressure (MAP) and diastolic blood pressure (DBP) profiles and POAG. Nonetheless, **eyes in the lowest quartile of mean OPP (MOPP, < 50 mmHg) were 1.96 times more likely to be diagnosed with POAG when compared with eyes in the highest quartile (> 61 mmHg). Similarly, eyes in the lowest quartile of diastolic OPP (DOPP, < 56 mmHg) were 1.78 times more likely to be diagnosed with POAG relative to the highest quartile (> 70 mmHg). Of note, these associations became non-significant when further adjusting for IOP-lowering treatment and IOP.** This finding suggests that the association between MOPP and DOPP and POAG may be largely the result of the use of IOP in the equation used to calculate these parameters; in other words, with regards to diastolic BP parameters, the effect of IOP may be more important than that of the mean arterial pressure or diastolic pressure alone.

On the other hand, when looking at parameters based on the systolic BP, they found that eyes with both low (< 110 mmHg) and high (> 137 mmHg) systolic OPP (SOPP) levels were significantly more likely to be diagnosed with POAG than those in the mid-range group (123-137 mmHg), even after adjusting for IOP and non-IOP-related confounders. In addition, they found that eyes of patients with low levels of systolic BP (SBP, < 124 mmHg) were 1.69 times more likely to have POAG, compared with mid-range SBP levels (138–153 mmHg). This finding suggests that, with regards to systolic BP parameters, the relationship with POAG prevalence follows a 'U'-shaped curve, reflecting higher risk among those with extreme values of SBP and SOPP, regardless of their IOP.

The authors outlined that one potential explanation for their findings was that a low SBP may indirectly compromise ocular blood supply to the ONH – more so than the DBP – causing ischaemic damage to retinal ganglion cells and initiating glaucomatous development. As a result, the authors suggested that the identification of concurrent low SBP and ocular hypertension (IOP > 21 mmHg) may potentially be a clinically-useful parameter to stratify the risk of glaucoma.

In addition to the large sample size and diverse population studied, two relevant strengths of the present study are the fact that the investigators took into account the effects of IOP and IOP-lowering as well as systemic medications. Also, by dividing the groups into nominal categories (low, mid, and high) without an assumption of linearity enabled the authors to detect a 'U'-shaped effect. This is an important message as it allows us to understand why other studies may have failed to find an association between BP parameters and glaucoma. Notwithstanding, the authors did not employ the same approach when investigating the effect of MAP and DBPP. Note, for instance, that in Tables 2 and 3 they defined the reference group as the highest quantile

for MAP, MOPP, DBP, and DOPP, but not for SBP and SOPP (for which they used the mid quantile). It would be important to describe what the results would look like had the same approach been applied across BP-related parameters.

As a limitation, the cross-sectional nature of the study and the collection of BP data at a single time-point may limit our ability to determine a causal association and the effects of circadian rhythms, respectively. Nevertheless, this is a milestone paper that provides a better understanding of the relationship between BP, IOP, and POAG prevalence in addition to cementing the need to include BP monitoring to the arsenal of tests employed in glaucoma management.[1]

References

1. De Moraes CG, Cioffi GA, Weinreb RN, Liebmann JM. New recommendations for the treatment of systemic hypertension and their potential implications for glaucoma management. J Glaucoma. 2018;27(7):567-571.

Dietary Habits and Glaucoma

Comment by David Friedman, Baltimore, MD, USA

75587 Association of dietary fatty acid intake with glaucoma in the United States; Wang YE, Tseng VL, Yu F, Caprioli J, Coleman AL; JAMA ophthalmology 2018; 136: 141-147

The authors use National Health and Nutrition Examination Survey (NHANES) data from 2005-2008 to determine if dietary fatty acid intake is associated with prevalent 'glaucoma'. Glaucoma was defined based on large grading center cup:disc ratio and abnormalities on FDT testing. Recent publications with the NHANES re-classified these diagnoses after review of optic nerve findings by glaucoma specialists, but this definition of glaucoma was not used in the analyses. Food intake was based on a food frequency questionnaire focused on recent consumption.

The authors found no association with polyunsaturated fatty acid (PUFA) intake and glaucoma diagnosis when PUFA was considered as a continuous variable. Those in the second and third quartiles of PUFA intake had a higher odds of glaucoma in a separate analysis. **Higher intake of docosohexaenoic acid (DHA) and eicosapentaenoic acid (EPA) intake were associated with lower odds of glaucoma.**

The authors cite previous work to explain the biological rationale for a possible associations, but the supporting literature is weak. For example, one cited study from Nigeria enrolled ten patients with glaucoma and eight siblings reporting associations with DHA and EPA. Possible biological explanations for the underlying protective effect are a possible impact of PUFAs on optic nerve head circulation as blood viscosity can be affected by these compounds and ganglion cell protection by higher levels of these compounds.

Overall the study supports a limited amount of previous work showing possible associations with PUFA intake and glaucoma. Many analyses were performed and it is possible that the associations were spurious. Furthermore, the associations could be related to other unmeasured factors in people with healthier diets. Nevertheless, the findings should spur researchers to confirm this finding in other populations and if so, to determine if interventions to increase DHA or EPA intake could help prevent or care for glaucoma.

Quality of Life

Assessing activity limitation in glaucoma patients

Comment by Pradeep Ramulu, Baltimore, MD, USA

75778 Objective assessment of activity limitation in glaucoma with smartphone virtual reality goggles: A pilot study; Goh RLZ, Kong YXG, McAlinden C, Liu J, Crowston JG, Skalicky SE; Translational Vision Science & Technology 2018; 7: 10

In their very nice article, Goh and colleagues examine if simulated task ability could be gauged in glaucoma patients using a virtual reality goggle system. To test this hypothesis, patients with varying degrees of glaucoma performed three series of tasks involving: (1) finding an object within a stationary scene; (2) identifying a ball moving into their field of view; and (3) identifying a dangerous situation while driving. For each test, items were graded as 'seen' or 'unseen' and then subject to Rasch analysis. **Only the object finding and moving ball tasks fit the Rasch model well, and of these two, only the object finding test became more difficult with greater VF damage**. The object finding test was also associated with glaucoma utility measures, further suggesting its validity.

The article raises the possibility that meaningful objective functional measures may be captured with a simple, low-cost set-up (the goggles employed cost only US$ 20) and might be implemented as part of routine clinical care. The authors suggest that such testing could be used to help patients understand their disability and highlight for physicians, caregivers, and patients themselves the need to address their disability, *i.e.*, through low vision rehabilitation or environmental modification. A more intriguing possibility is that in-clinic functional testing might eventually serve as an adjunct to current clinical measures. One challenge would be that age was also associated with worse performance in the study, and might also hasten functional declines more in persons with advanced damage independent of disease progression. Other time-dependent factors (*i.e.*, cognitive impairment) may also produce functional declines indistinguishable from vision-related declines. Thus, while understanding the functional status of the patient is clearly important, as with any new information, significant thought and consideration is needed to determine how it can be optimized and integrated into a clinically useful tool.

Prevention and Screening

Raising glaucoma awareness

Comment by Andrew Tatham, Edinburgh, UK

76015 The effect of a short animated educational video on knowledge among glaucoma patients; Al Owaifeer AM, Alrefaie SM, Alsawah ZM, Al Taisan AA, Mousa A, Ahmad SI; Clinical Ophthalmology 2018; 12: 805-810

Improving patients' understanding of glaucoma is likely to enhance patient engagement and improve adherence to treatment, with the potential to lead to better outcomes.[1] Possible educational interventions include nurse-led education sessions, motivational interviewing, or the provision of materials such as written materials or educational videos. Al Owaifeer and colleagues assessed the effect of a short educational video on knowledge of glaucoma among 196 adults with glaucoma in Saudi Arabia. A previously validated 11-item questionnaire was used to assess knowledge of glaucoma before and after viewing a three-minute animated educational video. The video conveyed information including the nature of glaucoma, its effect on the optic nerve and vision, the necessity of regular follow up and the importance of treatment.

Following viewing of the video there was a significant improvement in knowledge score, rising from a mean (± standard deviation) of 6 ± 3.9 (range 0 to 16) to 11.1 ± 3.2 (range 3 to 17) out of a maximum score of 17. Following intervention almost two-thirds of patients had a knowledge score of ≥ 11.[3] Factors associated with greater knowledge included younger age, male gender, higher degree of education, higher income, family history of glaucoma and residence in an urban area.

The study encouragingly demonstrates that even a short educational intervention can improve patients' understanding of their disease. However, there are limitations and the results may not be generalizable to other populations. **There was no control group and no long-term follow-up to determine if patients retained knowledge beyond the immediate post-intervention period**. There is also the possibility that patients with poorest understanding of glaucoma may have elected not to participate in the study. In addition, the study did not compare different methods of education, so it is not clear whether other interventions may have been more effective than a three-minute video. An important observation is that almost 30% of participants were illiterate, which may have made an animated video of particular value for this group. However, the most effective method of education may vary between patients meaning an individualized approach is necessary.

Finding a cost-effective educational intervention and examining its effect on disease progression is therefore an important area for further research

Although the authors did not examine the potential benefits of improving patients' knowledge of glaucoma, Friedman and colleagues' Glaucoma Adherence and Persistency Study (GAPS) previously showed that patients who do not understand the goal of glaucoma treatment have lower adherence rates.[2] This finding is not universal, however, and it has even been suggested that knowing that glaucoma is a slowly progressive disease may be associated with lower adherence to medication.[3] A 2013 Cochrane Review identified seven studies investigating the role of patient education for improving adherence, however there was insufficient evidence to recommend a particular intervention and no studies examined cost effectiveness.[4] Finding a cost-effective educational intervention and examining its effect on disease progression is therefore an important area for further research. Improved understanding of glaucoma is likely to help patients become more actively engaged in managing their disease and in making treatment decisions, helping to sustain motivation to continue treatment.4,5

References

1. Joseph A, Pasquale JR. Attributes associated with adherence to glaucoma medical therapy and its effects on glaucoma outcomes: an evidence-based review and potential strategies to improve adherence. *Semin Ophthalmol.* 2017;32:86-90.
2. Friedman DS, Hahn SR, Gelb L, *et al.* Doctor-patient communication, health-related beliefs, and adherence in glaucoma results from the Glaucoma Adherence and Persistency Study. *Ophthalmology*. 2008;115:1320-1327.
3. Hoevenaars JGMM, Schouten JSAG, van den Borne B, Beckers HJM, Webers CAB. Will improvement of knowledge lead to improvement of compliance with glaucoma medication? *Acta Ophthalmol.* 2008;86:849-855.
4. Waterman H, Evans JR, Gray TA, Henson D, Harper R. Interventions for improving adherence to ocular hypotensive therapy. *Cochrane Database Syst Rev.* 2013;30:CD006132.
5. Sleath BL, Blalock SJ, Carpenter DM, *et al.* Ophthalmologist-patient communication, self-efficacy, and glaucoma medication adherence. *Ophthalmology.* 2015;122:748-754.

Anatomical Structures

Proximal aqueous outflow pathways


Comment by Tun Wang Chang and Kaweh Mansouri, Lausanne, Switzerland

75567 Estimating outflow facility through pressure dependent pathways of the human eye; Smith DW, Gardiner BS; PLoS ONE 2017; 12: e0188769

In clinical practice, we do not know exactly how the total pressure dependent outflow changes with intraocular pressure. In this extensive paper, the authors developed and tested a new theory for pressure-dependent pathways of the eye based on the differential rates of change of IOP and the membrane reference pressure with respect to changing IOP. Prompted by the so-called equilibrium defect between the aqueous production and outflow, they explored the theory that outflow also occurs through the retinal pigmented epithelium (RPE) into the choroid. Researchers have postulated some of the theory behind complexity of the outflow system from the trabecular meshwork to the episcleral veins.

The authors developed a new theoretical model for the analysis of pressure dependent outflow from the eye and subsequently applied the equation to the animal eye, enucleated eye and *in vivo* human eyes. The theory assumes that the pressure dependent outflow is primarily due to pressure dependent changes in the driving pressure and more precise as compared to Goldman's equation and Grant's equation.

Based on their model, the authors propose three important parameters that determine pressure dependent outflow which are: (1) the hydraulic conductance for the whole eye; (2) the exponential decay constant; and (3) no-flow reference IOP. The model fits well for human subjects with IOP up to about 40 mmHg. The no-flow IOP is from zero up to 3.0 mmHg. They find that **pressure-dependent outflows are twice as large as fluorometric estimates for aqueous outflow. The reason for this discrepancy is postulated to be outflow via the RPE, possibly increased by age-related disease processes.**

This paper serves as an important milestone for future research and clinical applications of glaucoma.

Distal aqueous outflow pathways


Comment by Nils Loewen and Chao Wang, Pittsburgh, PA, USA

75468 Deep tissue analysis of distal aqueous drainage structures and contractile features; Gonzalez JM, Ko MK, Hong YK, Weigert R, Tan JCH; Scientific reports 2017; 7: 17071

Gonzalez *et al.*[1] present a smorgasbord of images of the distal outflow tract of the mouse in a total of 14 figures with up to 20 subpanels per figure. **The authors had several goals that were rather ambitious: (1) to establish 2-photon deep tissue imaging with 3D reconstruction of the imaging data; (2) to distinguish blood from lymphatic markers; and (3) to detect structures suggesting contractility.** The primary technique applied in these studies has a name that is almost as long as the list of goals: 'trans-scleral multimodal 2-photon imaging with 2-photon excitation fluorescence and second harmonic generation (2P TPEF SHG)'. 2P TPEF SHG uses deep red and near infrared light to penetrate tissue deeper than visible light used in standard confocal microscopy. It has reduced scattering which allows the fluorescent target to be well identified. The principal behind 2P TPEF SHG is that when two photons with the same frequency interact with a non-linear material they are combined in a process called second harmonic generation which generates a new photon with twice the energy of the initial photons. The difference between the exciting and the emitting light allows for easy separation of the second harmonic generation signal and a high axial and lateral resolution that is comparable to that of confocal microscopy but without having to use pinholes.

This technique is impressive and useful because it allows imaging tissues *in vivo* up to 100 to 200 microns[2] with a resolution that allows to distinguished structures several microns in size. The practically achievable depth depends on the amount of light scatter, however. A downside of 2P TPEF SHG is that fluorophores are necessary which requires either the use of transgenic animals with fluorescent proteins or *ex vivo* stains or antibodies. In contrast to confocal microscopy, that can achieve up to 365 nm resolution at 2 mm depth,[3,4] the tissue does not have to be made transparent.

If a bit overwhelming at first, **Gonzalez *et al.*'s manuscript is a treasure trove for outflow researchers that convincingly demonstrates that features are present in the distal outflow tract of the mouse that should allow it to actively contract and dilate.** Recent studies show that the distal outflow tract can indeed regulate outflow and IOP by contracting and dilating in human and porcine eyes.[5,6] Interestingly, the distal outflow tract endothelium was Prox1-positive, CD31-positive but LYVE-1-negative, giving it a signature different from blood and true lymphatic vessels. Schlemm's canal is a VEGF-C/VEGFR3-responsive lymphatic-like vessel that develops from transscleral veins and emerges together with the collector channels. While disappointing that not more lymphatic features were seen in the distal outflow tract of the mouse, they may play a more prominent role in larger primate eyes.[7] Lymphatic features in direct proximity

to these structures are already known to get activated by epibulbar glaucoma surgery where aqueous is shunted into an artificial conjunctival fluid pocket and absorbed by lymphatics.[8] Recent discoveries on prostaglandin analogs, arguably the most successful eye drops in glaucoma, showed that in addition to enhancing uveoscleral outflow, they increase contraction and propulsion of lymphatics.[9]

References

1. Tan JC, Gonzalez J, Ko MK, Masedunskas A, Weigert R, Hong Y. Contractile features of the distal aqueous drainage tract. *Invest Ophthalmol Vis Sci*. 2017;58(8):3771-3771.
2. Durr NJ, Weisspfennig CT, Holfeld BA, Ben-Yakar A. Maximum imaging depth of two-photon autofluorescence microscopy in epithelial tissues. *J Biomed Opt*. 2011;16(2):026008.
3. Waxman S, Loewen RT, Dang Y, Watkins SC, Watson AM, Loewen NA. High-resolution, three-dimensional reconstruction of the outflow tract demonstrates segmental differences in cleared eyes. *Invest Ophthalmol Vis Sci*. 2018;59(6):2371-2380.
4. Watson AM, Rose AH, Gibson GA, *et al.* Ribbon scanning confocal for high-speed high-resolution volume imaging of brain. *PLoS One*. 2017;12(7):e0180486.
5. McDonnell F, Dismuke WM, Overby DR, Stamer WD. Pharmacological regulation of outflow resistance distal to Schlemm's canal. *Am J Physiol Cell Physiol*. April 2018. doi:10.1152/ajpcell.00024.2018
6. Waxman S, Wang C, Dang Y, *et al.* Structure-function changes of the distal outflow tract in response to nitric oxide. *Preprint*. May 2018. doi:10.20944/preprints201806.0075.v1
7. Aspelund A, Tammela T, Antila S, *et al.* The Schlemm's canal is a VEGF-C/VEGFR-3-responsive lymphatic-like vessel. *J Clin Invest*. 2014;124(9):3975-3986.
8. Yu D-Y, Morgan WH, Sun X, *et al.* The critical role of the conjunctiva in glaucoma filtration surgery. *Prog Retin Eye Res*. 2009;28(5):303-328.
9. Tam ALC, Gupta N, Zhang Z, Yücel YH. Latanoprost stimulates ocular lymphatic drainage: An *in vivo* nanotracer study. *Transl Vis Sci Technol*. 2013;2(5):3.

Peripapillary choroid

Comment by Jost Jonas, Heidelberg, Germany

75572 Thin minimal rim width at Bruch's membrane opening is associated with glaucomatous paracentral visual field loss; Taniguchi EV, Paschalis EI, Li D, Nouri-Mahdavi K, Brauner SC, Greenstein SH, Turalba AV, Wiggs JL, Pasquale LR, Shen LQ; Clinical Ophthalmology 2017; 11: 2157-2167

In their study, Taniguchi and colleagues report on the association between a low minimal neuroretinal rim width at Bruch's membrane opening and glaucomatous versus peripheral paracentral visual field loss. In discussing the results, one may consider that eyes with a paracentral visual field defect have a retinal nerve fiber layer (RNFL) defect relatively close to the temporal region of the optic nerve head, since the retinal ganglion cell axons associated with a paracentral visual field loss as compared to those associated with a peripheral visual field loss enter the optic disc closer to the disc-fovea line. Since in normal eyes the RNFL is usually the thinnest and the BMO-MRW is usually the smallest in the temporal optic nerve head region as compared to any other optic nerve head region (as it was the case in 90% of the control eyes also in the present study), any additional loss in retinal nerve fiber tissue will further reduce the anyway thin BMO-MRW in that area. The question arises therefore whether it might not have been anticipated that an eye with a glaucomatous paracentral visual field defect as compared to an eye with a peripheral glaucomatous visual field defect was expected to have a thinner minimal BMO-MRW. In an eye with a peripheral glaucomatous visual field defect, the loss in RNFL occurs at a location which before onset of the optic nerve damage is relatively thick so that a local RNFL loss may reduce the BMO-MRW at that location with a primarily relatively thick RNFL while the thinnest (or minimal) BMO-MRW is still be located, and would be unchanged, in the temporal optic nerve head region. If these thoughts are valid, the association between a paracentral glaucomatous visual field defect and a low minimal BMO-MRW could be explained by the spatial structural/functional relationship and it would not necessarily be that a very low minimal BMO-MRW value is a special biomarker for a paracentral versus peripheral glaucomatous visual field defect.

Another potentially confounding factor could have been a difference between the glaucoma eyes with paracentral visual field defects and glaucoma eyes with peripheral visual field defects in the amount of the optic disc rotation around its vertical axis. **The vertical optic disc rotation increases with axial myopia and is associated with a thinning of the BMO-MRW in the temporal optic nerve head region.** The refractive error or axial length and potential differences between the glaucoma groups in these parameters have not been mentioned in the article.

Also in view of the relatively small study samples, in view of the relatively high *P*-value of 0.03 for the difference between the eyes with early paracentral visual field loss versus eyes with peripheral visual field loss, and in view of potential selection artefacts due to the hospital-based recruitment of the study participants, one may infer that additional studies may be warranted to further strengthen the conclusions drawn by the authors.

Under pressure: Lamina cribrosa

Comment by Florent Aptel, Lyon, France

75654 Association of functional loss with the biomechanical response of the optic nerve head to acute transient intraocular pressure elevations; Tun TA, Atalay E, Baskaran M, Nongpiur ME, Htoon HM, Goh D, Cheng CY, Perera SA, Aung T, Strouthidis NG, Girard MJA; JAMA ophthalmology 2018; 136: 184-192

Using SD-OCT, the authors evaluated the changes in optic nerve head morphology during IOP increase obtained with an ophthalmodynameter applied against the sclera in a large cohort of Chinese subjects with open-angle glaucoma, angle-closure glaucoma, or without glaucoma. In particular, two anatomical parameters – lamina cribosa depth and minimum rim width (MRW) – were evaluated, and the regional and global relationships with the visual field defects were calculated. They found a significant relationship between structure change in response to IOP increase and function only in open-angle glaucoma subjects: a **larger MRW reduction and larger anterior displacement of the lamina cribosa were associated with worse visual field defects.**

It would be interesting to evaluate in longitudinal studies the biomechanical response of the optic nerve head in progressing glaucoma

I think that the present study adds some valuable evidence to the growing literature about the possible role of the biomechanical response of the lamina cribosa and optic nerve head to IOP variations in the pathophysiology of open-angle glaucoma. Clearly, many studies report a different response of the lamina cribosa and optic nerve morphology during IOP increase in subjects with glaucoma compared to healthy. It should be mentioned, however, that the **studies performed to date show conflicting results about the direction and magnitude of the lamina cribosa displacement**. Some studies have rather reported a posterior movement of the lamina cribosa during IOP increase in subjects with glaucoma. Also, Quigley *et al.* have reported a smaller lamina cribosa displacement in subjects with severe glaucoma compared to

subjects with early glaucoma. Some differences in the imaging device used, in the population studied, type and stage of glaucoma, and also in the reference plane used to calculate the lamina cribosa displacement could explain the discrepancies. Particularly, it should be mentioned that the **reference structure or plane used in those studies are also likely impacted by IOP variations, and thus we do not have any invariable anatomical landmark**.

As mentioned by the authors, further studies could evaluate the diameter of the Bruch membrane or scleral canal opening during IOP increase, and correlate the opening diameter to the lamina cribosa displacement. It could be hypothesized that a large increase in opening diameter during IOP increase leads to anterior displacement, and vice-versa. Also, it could be interesting to evaluate in longitudinal studies the biomechanical response of the optic nerve head in subjects with progressing glaucoma or subjects with OHT that have developed glaucoma, compared to non-progressing glaucoma or OHT.

Computer-assisted retinal layer assessment

Comment by Paul McCann and Augusto Azuara Blanco, Belfast, UK

75979 Analysis of inner and outer retinal layers using spectral domain optical coherence tomography automated segmentation software in ocular hypertensive and glaucoma patients; Cifuentes-Canorea P, Ruiz-Medrano J, Gutierrez-Bonet R, Peña-Garcia P, Saenz-Frances F, Garcia-Feijoo J, Martinez-de-la-Casa JM; PLoS ONE 2018; 13: e0196112

Due to the high proportion of retinal ganglion cell bodies and axons concentrated in the macula, spectral domain optical coherence tomography (SD-OCT) macular parameters have received attention as potential biomarkers in the detection of early glaucoma. A meta-analysis reported that full thickness macular parameters have similar or slightly inferior diagnostic accuracy compared to circumpapillary retinal nerve fiber layer (cRNFL) parameters.[1]

However, improved technology has led to better retinal segmentation and there is now interest in the investigation of the diagnostic utility of segmented layers of the macula. Cifuentes-Canorea *et al.* investigated the diagnostic performance of Early Treatment Diabetic Retinopathy Study (ETDRS) grid sectors segmented into eight layers including the macular retinal nerve fiber layer (mRNFL), ganglion cell layer (GCL) and inner plexiform layer (IPL) using Heidelberg Spectralis. This single-center clinic-based case-control study performed in Spain included one eye of 56 normal healthy participants, 63 ocular hypertensives (OHT), 32 early primary open angle glaucoma (POAG) (MD > -6) and 42 moderate to advanced POAG (MD ≤ -6). The reference standard for POAG was determined using both structural (optic nerve head cupping or damage)

and functional (standard automated perimetry) parameters. OHT was defined as intraocular pressure (IOP) > 21 mmHg with normal optic disc and perimetry. SD-OCT was performed on all participants by one experienced operator.

Values for mRNFL, GCL and IPL showed significant differences between the four groups (Kruskal-Wallis test) therefore their potential to discriminate between early glaucoma and OHT was studied further. **The greatest areas under the curve (AUCs) to detect early POAG from OHT were reported for outer inferior sector mRNFL (0.781) and for outer temporal sector GCL (0.760) and outer temporal sector IPL (0.767) and for a combination of all three (0.807)** with a best combination of sensitivity and specificity of 0.762 and 0.719 for the combination.

> The results […] are consistent with the macula vulnerability zone (MVZ) theory and demonstrate promise for the use of macular parameters as biomarkers for the early detection of glaucoma

These results are in agreement with a study by Chien *et al.* who reported the diagnostic performance of segmented EDTRS grid sectors using Heidelberg Spectralis in 87 glaucomatous eyes and 69 normal eyes: outer inferior sector mRNFL (0.930) and outer temporal sector GCL (0.942).[2] The higher AUCs in this study are likely to be due to the comparison between glaucomatous eyes and normal eyes rather than the comparison between OHT and early glaucoma by Cifuentes-Canorea *et al.*

The results of both of these studies are consistent with the macula vulnerability zone (MVZ) theory and demonstrate promise for the use of macular parameters as biomarkers for the early detection of glaucoma.[3] Meta-analyses of studies and future studies that adopt population-based and clinical pathway designs should provide more data and aim to avoid the pitfalls of diagnostic case-control studies which tend to overestimate diagnostic accuracy. Future studies that compare diagnostic utility of segmented macular scans with cRNFL and Bruch's membrane opening minimum rim width (BMO-MRW) parameters would also be of interest.

References

1. Oddone F, Lucenteforte E, Michelessi M, Rizzo S, Donati S, Parravano M, *et al.* Macular versus retinal nerve fiber layer parameters for diagnosing manifest glaucoma: A systematic review of diagnostic accuracy studies. *Ophthalmology.* 2016;123(5):939-949.
2. Chien JL, Ghassibi MP, Patthanathamrongkasem T, *et al.* Glaucoma diagnostic capability of global and regional measurements of isolated ganglion cell layer and inner plexiform layer. *J Glaucoma.* 2017;26(3):208-215.
3. Hood DC, Raza AS, de Moraes CG V., Liebmann JM, Ritch R. Glaucomatous damage of the macula. *Prog Retin Eye Res* [Internet]. 2013;32(1):1-21.

Computer-assisted disc assessment

Comment by Gustavo de Moraes, New York, NY, USA

75568 Classification of optic disc shape in glaucoma using machine learning based on quantified ocular parameters; Omodaka K, An G, Tsuda S, Shiga Y, Takada N, Kikawa T, Takahashi H, Yokota H, Akiba M, Nakazawa T; PLoS ONE 2017; 12: e0190012

Optic disc photography is one of the most commonly used methods to document and analyze structural abnormalities due to glaucoma. Nonetheless, it is highly subjective and studies have demonstrated a moderate-to-poor agreement among graders to determine the presence of glaucomatous optic neuropathy and to detect progressive changes. With the advent of artificial intelligence (AI) and more sophisticated neural networks (NN) applied to imaging modalities, it may now be possible to improve the objectivity and repeatability of optic disc photography assessments for glaucoma management.

Omodaka *et al.* developed an AI-based algorithm for objective classification of the optic disc in patients with open-angle glaucoma (OAG) which was aided by objective, quantitative parameters obtained from ophthalmic examination instruments. In particular, they tested the ability of this algorithm to classify the optic discs of glaucomatous patients into one of the four phenotypes described by Nicolela *et al.*:[1] focal ischemic (FI), generalized enlargement (GE), myopic (MY), and senile sclerotic (SS). First, three glaucoma specialists performed the classification of optic discs of 163 eyes of 105 OAG patients; cases of disagreement were excluded. Then, they obtained 91 parameters derived from clinical data (n = 7), optic disc topography (n = 22), OCT circumpapillary retinal nerve fiber layer thickness (cpRNFLT) (n = 26), and laser speckle flowgraphy (LSFG) (n = 36). These parameters were used to develop a NN as the machine-learning classifier. The data were divided into training (n = 114 eyes) and validation (n = 49 eyes) sets which were matched from sex, age, visual field mean deviation (MD), spherical equivalent (SE), and intraocular pressure (IOP).

This study may be a useful tool in genetic studies that aim to identify markers associated with different glaucoma phenotypes

The authors found that the NN had an accuracy of 91.2% and Cohen's Kappa of 88%. The most important discriminative characteristics selected by the NN were the SE, age, average nasal rim disc ratio, average cup depth, horizontal disc angle, superior-temporal cpRNFLT, superior-quadrant cpRNFLT, maximum cup depth, and cup area. Disc-type classification by the NN matched the test data at rates of 66.7% for FI, 93.3% for GE, 83.3% for MY, and 100.0% for SS. In some cases, the NN provided ambiguous results due to overlapping phenotypes, which is expected given the subjective nature of the experts' ratings, even after excluding cases of disagreement.

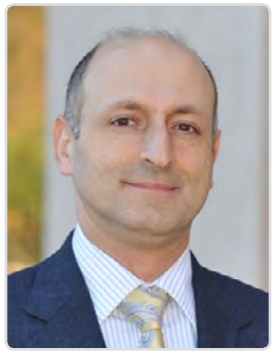
This is an important study as it describes a new technique to classify glaucomatous optic disc phenotypes in a more objective, reproducible fashion. These phenotypes have been shown to have important clinical associations, in particular a predictive value when assessing the risk of progression.[2,3] This new technique may therefore be useful in clinical practice and future studies investigating risk factors for progression. In addition, this may be a useful tool in genetic studies that aim to identify markers associated with different glaucoma phenotypes, such as IOP, disc cupping, and other optic nerve head features.

One study limitation was the small sample size of the testing set given that other AI algorithms described previously in ophthalmology were developed based upon thousands of optic discs or OCT images. NN often require a large number of images in order to extract an adequate number of training features. The fact that the investigators were able to obtain such high accuracy despite its small sample is remarkable**. One study strength that may help explain such accuracy was the inclusion of parameters beyond the optic disc photographs (*i.e.*: OCT- and LSFG-derived quantitative measurements) when developing the NN.** Future studies using AI in ophthalmology should consider a similar approach in order to optimize their diagnostic performance.

References:

1. Nicolela MT, Drance SM. Various glaucomatous optic nerve appearances: clinical correlations. *Ophthalmology.* 1996;103: 640-649.
2. Reis AS, Artes PH, Belliveau AC, *et al.* Rates of change in the visual field and optic disc in patients with distinct patterns of glaucomatous optic disc damage. *Ophthalmology.* 2012;119(2):294-303.
3. Schor KS, De Moraes CG, Teng CC, Tello C, Liebmann JM, Ritch R. Rates of visual field progression in distinct optic disc phenotypes. *Clin Exp Ophthalmol.* 2012;40(7):706-712.

Computer-assisted fundus assessment



Comment by Kouros Nouri-Mahdavi, Los Angeles, CA, USA

75175 Hybrid deep learning on single wide-field Optical Coherence Tomography scans accurately classifies glaucoma suspects; Muhammad H, Fuchs TJ, De Cuir N, De Moraes CG, Blumberg DM, Liebmann JM, Ritch R, Hood DC; Journal of Glaucoma 2017; 26: 1086-1094

Use of deep learning methods has become a hot topic in the field of Ophthalmology. Muhammad *et al.* tested a hybrid deep learning (HDL) approach for detection of eyes with definite glaucoma from healthy glaucoma suspects using a combination of a pre-trained Convolutional Neural Networks (CNNs) for feature extraction followed by a random forest model for classification.

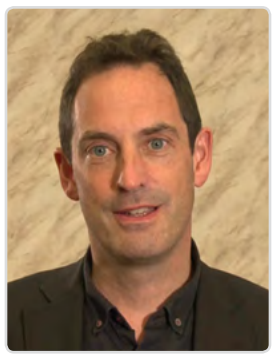
One hundred and two eyes from 130 eyes from a previous study were used to define glaucomatous vs. normal eyes. During this process, eyes that were harder to classify, *i.e.*, those that were forced-choice into glaucoma or normal groups by the expert reviewers in the original study, were excluded. The gold standard was presence or lack of glaucoma as determined by two glaucoma specialists based on 24-2 and 10-2 VFs, disc photos, patient chart information, and the single-page OCT report as previously published by Hood *et al.* containing retinal nerve fiber layer (RNFL)n and macular retinal ganglion cell/inner plexiform layer (RGC+) data. The input to HDL was a single wide-field OCT image (12x9 mm, 256 horizontal B-scans each consisting of 512 A-scans). HDL's performance was compared to that of established OCT parameters (average RNFL, quadrant and clock hour sector thickness) or 10-2 or 24-2 metrics. **Outcomes of interest** were area under the ROC curves (AUC) and model accuracy, which was seemingly the average of sensitivity and specificity values.

Overall, the HDL's performance using RNFL thickness or RNFL probability maps was excellent with an AUC of 0.970 for the RNFL thickness. The best OCT metric misclassified 13 (10%) eyes and the best 24-2 (abnormal GHT or PSD) and 10-2 VF metrics (abnormal MD, PSD, or cluster of abnormal points) misclassified 20 eyes (15%). The inadequate performance of VF metrics is not unexpected given the fact that it is not uncommon to see evidence of RNFL or RGC+ damage in the absence of clear cut evidence for VF loss.

The results are very promising since HDL could be easily incorporated in clinic and could basically elevate the performance of the average clinician to that of glaucoma experts. One has to keep in mind that the HDL's performance could have been overestimated as the controversial cases were removed from the original database. The investigators beautifully demonstrated how exploration of outliers (false positive and negative cases for the HDL classifier) could help better understand the behavior of HDLs. A limitation of this approach was the use of a *pre-trained* CNN (AlexNet). As mentioned by the investigators, further training of the CNN can be incorporated in the future iterations of HDL algorithms. Therefore, enhancing HDL's performance can be accomplished by not only better training of the neural networks but also by defining *a priori* anatomical variations and caveats that can lead to false negative or positive results.

Basic Science

A marker of retinal neuron aging?



Comment by Keith Martin, Cambridge, UK

75539 Expression of sirtuins in the retinal neurons of mice, rats, and humans; Luo H, Zhou M, Ji K, Zhuang J, Dang W, Fu S, Sun T, Zhang X; Frontiers in Aging N euroscience 2017; 9: 366

The Sirtuins (SIRT) are a class of NAD+ dependent histone deacetylases that play important roles in stress response, aging, and neurodegenerative diseases. SIRTs are involved in cell and tissue metabolism, and the dependence of Sirtuins on NAD links their enzymatic activity directly to the energy status of the cell. To date, seven Sirtuins have been identified in mammals but their distribution in the retina and response to retinal injury have not been systematically studied.

In the current study, Luo and co-workers assessed the retinal expression of Sirtuins in mice, rats, and humans and measured the expression of Sirtuins in aged and injured retinas. The authors used a variety of quantitative techniques including Real Time PCR, Western blotting and immunohistochemistry. The studies appear to have been carefully performed, although in some of the immunohistochemistry it is difficult to know how specific the labelling is and the differences reported between species are difficult to interpret.

> […] SIRT1 could be a potential therapeutic target in glaucoma

The most interesting finding was a **marked reduction of SIRT1 expression in aged retinal neurons as well as retinas injured by acute ischemia-reperfusion**. Previous studies have shown that SIRT1 plays a crucial role in age-related retinal degeneration and its activity has been studied in various animal models of neurodegenerative diseases, including Huntington's disease, Alzheimer's disease, and retinal ischemic injury. Of particular interest to glaucoma, studies have demonstrated that SIRT1 is responsible for the protective effects of resveratrol, a SIRT1 activator, against neurodegeneration and aging.

Overall, the authors have provided some nice baseline information on the retinal distribution of SIRTs that will be useful to those in the field and they have provided support for the idea that boosting SIRT1 could be a potential therapeutic target in diseases such as glaucoma.

A new gene modulating IOP

Comment by Kent Taylor, Torrance, CA, USA

75367 Systems genetics identifies a role for Cacna2d1 regulation in elevated intraocular pressure and glaucoma susceptibility; Chintalapudi SR, Maria D, Di Wang X, Bailey JNC, , , Hysi PG, Wiggs JL, Williams RW, Jablonski MM; Nature Communications 2017; 8: 1755

Chintalapudi *et al.* selected the best possible tools across both mice and humans to find a possible therapeutic for POAG. Tool #1 consisted of the BXD inbred mouse panel. This panel was generated by crossing C57BL/6J (B6) and DBA/2J (D2) mouse strains followed by successive inbreeding of strains from the second generation (F2) until each strain was homozygous at every chromosomal point, but was also a mosaic of the B6 and D2 chromosomal segments. IOP varied two fold across the panel, mapping IOP mouse chromosome 5. Tool #2 consisted of extensive bioinformatics data. The authors narrowed their list of 25 candidate genes to CACNA2D1. Tool #3 consisted of the human genome-wide association study (GWAS). The NEIGHBORHOOD consortium confirmed the association of CACNA2D1 with POAG and IOP. Tool #4 consisted of returning to the mouse as an experimental system, using histology to confirm a role for CACNA2D1 in POAG-related tissues and then turning a known affinity of pregabalin for CACNA2D1 into testing the ability of pregabalin drops to lower IOP in both B6 and D2 strains.

One critique of the paper would be that the human GWAS results for CACNA2D1 are modest considering the size of NEIGHBORHOOD, but just as different mouse strains show different IOP, perhaps additional GWAS in other ethnic groups will add to the confirmation of the role of CACNA2D1 in POAG.

The approach outlined in this paper shows the synergy possible by combining a quantitative phenotype such as IOP, a well-characterized series of mouse strains such as the BXD series, and a large human GWAS for POAG and POAG-related endophenotypes such as NEIGHBORHOOD. The paper is a model for the type of collaboration necessary to move glaucoma therapeutics rapidly forward.

Clinical Examination Methods

Telemetric IOP measurements

Comment by Crawford Downs, Birmingham, AL, USA

75299 Long-term follow-up after implantation of a telemetric intraocular pressure sensor in patients with glaucoma: a safety report; Koutsonas A, Walter P, Roessler G, Plange N; Clinical and Experimental Ophthalmology 2017; 0:

Koutsanas and colleagues published the first long-term follow-up trial on the safety of the ARGOS implantable telemetric IOP sensor in six patients. The ring-shaped sensor measures IOP using eight integrated capacitive pressure sensors and is implanted in the ciliary sulcus. A hand-held reader unit powers the implanted sensor and takes a snapshot reading of IOP, allowing for home tonometry measurements. **The device can only measure IOP at the time the reader is held up to the, which makes both frequent IOP measurement and tonometry during sleep impractical**. Despite these limitations, an accurate home tonometer that takes a non-contact IOP measurement using a sensor inside the eye would be a major advance that would likely transform clinical glaucoma management.

> The study represents a very significant accomplishment of implanting a true telemetric IOP sensor in human patients

The present study is a retrospective analysis of long-term follow-up of the safety of the ARGOS I implantable IOP sensor that was implanted in one eye of six advanced POAG patients during cataract surgery. Safety was assessed through regular clinical examinations for an average of 37.5 months after implantation (range 21-50 months) during which time an average of 1273 IOP measurements were obtained from the sensor (range 223-2884). Mild to moderate pupil distortion and iris transillumination due to pigment dispersion were common to all patients, although there were no complaints of pain or discomfort. There were no instances of pupillary block, and the implanted eye's POAG progression rate was not obviously higher than the fellow eye, although the very small sample size renders comprehensive conclusions inconclusive. IOP readings were obtained at every attempt, although these IOP measurements were subject to significant drift errors and shifts. The errors were so significant that the authors 'do not wish to suggest that the (ARGOS I) sensor reliably measures real IOP' and hence the focus of the study is device safety. Technical limitations aside, the study represents a very significant accomplishment of implanting a true telemetric IOP sensor in human patients that will allow home tonometry when the technical issues with the pressure sensors can be remedied.

Predicting visual field progression

Comment by Chris Johnson, Rochester, MN, USA

75682 Baseline 24-2 central visual field damage is predictive of global progressive field loss; Garg A, De Moraes CG, Cioffi GA, Girkin CA, Medeiros FA, Weinreb RN, Zangwill LM, Liebmann JM; American Journal of Ophthalmology 2018; 187: 92-98

There are many investigations that have reported structural damage to the macular region of glaucoma patients as revealed by Optical Coherence Tomography (OCT). However, there are a more limited number of studies that have reported central functional glaucomatous loss as determined by automated perimetry. This publication utilizes visual field data that was obtained in the African Descent and Glaucoma Evaluation Study (ADAGES) to determine whether central visual field damage in glaucoma (within the central 10 degrees) is predictive of faster global visual field loss. It is encouraging that this investigation places emphasis on careful evaluation of the central visual field in glaucoma.

The study has been conducted quite carefully and has implemented highly appropriate inclusion and exclusion criteria, statistical analyses and interpretation of results. It was found that **there was a greater amount of global visual field loss over time for the group with central visual field damage compared to the group that did not have central visual field damage at baseline**. This effect persisted when confounding variables were also taken into account. These

findings emphasize the importance of carefully assessing central macular visual field properties in glaucoma because it is a significant predictor of overall visual field loss in glaucoma. Such information is highly meaningful for effective management of glaucoma patients. Future studies should direct more effort towards central visual field evaluation.

These findings emphasize the importance of carefully assessing central macular visual field properties in glaucoma because it is a significant predictor of overall visual field loss in glaucoma

The use of a 10-2 visual field test is likely to improve the ability to quantify central visual field loss, but this places additional burdens on the stamina and attentiveness of the patient and the effective management of a busy glaucoma clinical practice. However, it has been reported that adding just two additional central test locations to the 24-2 test can greatly improve the ability to detect macular visual field deficits in glaucoma.[1] Also, given that there are structural and other differences between individuals of African descent and European origins, it would be beneficial in the future to determine whether there are any variations in the importance of central visual field loss for these two groups.

Reference

1. Chen S, McKendrick AM, Turpin A. Choosing two points to add to the 24-2 pattern to better describe macular visual field damage due to glaucoma. *Br J Ophthalmol.* 2015;99(9):1236-1239.

Detecting visual field progression

Comment by Murray Fingeret, Brooklyn, NY, USA and Mike Patella, Santa Rosa, CA, USA

75703 SITA-Standard perimetry has better performance than FDT2 matrix perimetry for detecting glaucomatous progression; Wall M, Johnson CA, Zamba KD; British Journal of Ophthalmology 2018; 0:

The authors compared the abilities of FDT Matrix threshold perimetry and Humphrey SITA Standard to identify glaucomatous progression. **Using their own progression analysis, the authors concluded that the Matrix at best performed similarly to the HFA and was probably slightly inferior in identifying glaucomatous progression**. We believe that their analysis was suboptimal and that better methods are available and can be applied to their data.

Matrix was designed to test different visual processes than those assessed by HFA. The two devices also have different dynamic ranges.[1] Despite these differences, the authors converted the data from one device to be comparable to the other, prior to assessing how well each device detected progression. This data conversion was not only unnecessary, it also threatens their basic conclusions, to the extent that the data conversion cannot ever be exact.[2]

Fortunately, methods exist to determine the number of statistically significant progression events that each device is capable of detecting, based only upon measurement variability and dynamic range.[3] This approach avoids having to resort to inherently inexact data conversion formulas and also avoids adoption of an arbitrary rate of progression as a surrogate for statistically significant progression events. For example, Jampel found that Standard Automated Perimetry (SAP) Mean Deviation (MD) values could be analyzed to detect 7.5 statistically significant progression steps, while optic nerve rim area and cup shape measurement made with an imaging device could detect 5.7 and 2.3 steps respectively.

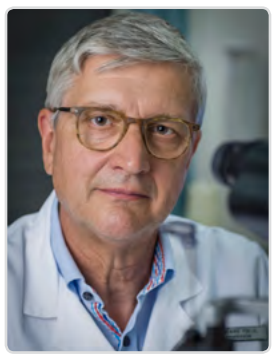
Jampel's method encourages us to dream. What if we could measure 30 or even 50 progression steps between normal and blind? How might glaucoma management improve? Couldn't we quickly sort out which glaucoma suspects actually *are* progressing and which ones are not?

We invite the authors to have another go at analyzing their data and getting to the bottom of the very important question that they have posed.

References

1. Artes PH, Hutchison DM, Nicolela MT, LeBlanc RP, Chauhan BC. Threshold and variability properties of matrix frequency-doubling technology and standard automated perimetry in glaucoma. *IOVS.* 2005;46(7):2451-2457.
2. Fredette MJ, Giguère A, Anderson DR, Budenz DL, McSoley J. Comparison of Matrix with Humphrey Field Analyzer II with SITA. *Optom Vis Sci.* 2015;92(5)527-536.
3. Jampel HD, Vitale S, Ding Y, *et al.* Test-retest variability in structural and functional parameters of glaucoma damage in the glaucoma imaging longitudinal study. *J Glaucoma*. 2006;15(2):152-157.

Better instruction leads to more reliable fields



Comment by Anders Heijl, Malmo, Sweden

75548 Impact of different visual field instruction strategies on reliability indices; Rao A, Sarangi SP, Padhy D, Raj N, Das G; Seminars in Ophthalmology 2017; 0: 1-7

Rao and co-workers undertook an unusual and interesting study – the influence of different strategies of instructing patients before performing standard computerized perimetry. They compared three different: an oral instruction, a video instruction and a combination of both in 90 field-naïve patients. The instructions before the first test were all very ambitious compared to what I believe constitutes the average clinical standard. Thus, the authors spent five minutes for the oral instructions with a very comprehensive list of 15 items, and similarly for the video presentation.

There were few statistically significant differences in the results among the three groups, but there was a **clear tendency for better reliability, as expressed by lower FN and FP rates in patients with severe or end-stage field loss (MD worse than -12dB), who had received both verbal and video instructions.** The relatively small sample size limits the conclusions, but is also a factor that might have masked other differences between the three approaches.

The main importance of this paper is that it highlights the importance of giving proper instructions to all patients who undergo computerized visual field testing for the first time. During my whole career, I have heard complaints that many patients cannot undergo standard automated perimetry. This, in my opinion, is totally wrong. Our experience from EMGT is that almost 100% of patients can do SAP, if really well instructed and supervised before and during the first one or two tests.

Our experience from EMGT is that almost 100% of patients can do SAP, if really well instructed and supervised

I would love to see the differences in results obtained in patients instructed in any of the three ambitious ways that Rao *et al.* used, and a normal sloppy instruction of the type that I feel that we have all seen far too often.

Retinal vessel density in POAG

Comment by David Greenfield, Miami, FL, USA

75362 Peripapillary and macular vessel density in patients with primary open-angle glaucoma and unilateral visual field loss; Yarmohammadi A, Zangwill LM, Manalastas PIC, Fuller NJ, Diniz-Filho A, Saunders LJ, Suh MH, Hasenstab K, Weinreb RN; Ophthalmology 2018; 125: 578-587

Optical coherence tomography-angiography (OCT-A) is a non-invasive imaging technology that has facilitated visualization and measurement of the capillary networks in different layers of the retina. A variety of spectral domain and swept source OCT technologies are commercially available that enable calculation of superficial and deep vascular plexus measurements. Vessel density calculations within the optic disc, peripapillary retina, and macula have been shown to be associated with glaucomatous structural damage and visual field loss.

In the present cross-sectional study, Yarmohammadi and colleagues used OCT-A to compare the retinal microvasculature of 33 patients with primary open-angle glaucoma (POAG) with unilateral visual field (VF) loss to 33 healthy eyes. Study participants underwent VF testing, spectral-domain OCT measurements of the circumpapillary RNFL (cpRNFL) and macular ganglion cell complex (mGCC), and OCT-A imaging (Avanti AngioVue; Optovue, Inc, Fremont, CA) of the circumpapillary vessel density (cpVD), parafoveal vessel density (pfVD), and the vessel density of the whole image scanned (wiVD). Eyes were stratified into three categories: (1) healthy eyes; (2) POAG eyes with perimetric loss; and (3) perimetrically unaffected eyes of POAG patients. **Unaffected eyes of POAG patients had significantly thinner structural parameters (macula GCC and RNFL) and capillary density (cpVD and pfVD) compared to healthy eyes**, and the wiVD parameter had the highest discriminating power.

> The fundamental question remains whether reductions in vascular density represent the so-called chicken or the egg

Key questions remain unanswered: (1) Will longitudinal OCT-A studies provide useful information regarding the underlying pathogenesis of glaucoma; (2) Do changes in capillary density precede or follow structural damage to the RGCs and their axons; (3) Is OCT-A useful for predicting or identifying progression; and (4) which vascular networks are most relevant in glaucomatous eyes, and is there a 'floor effect' in eyes with severe damage. Additionally, logistical hurdles must be overcome to reduce projection artifacts caused by large vessels and motion artifact caused by lengthy image acquisition times, reduce segmentation error, and improve the signal-to-noise ratio.

This well designed study provides important information. Changes in capillary density represent a surrogate for blood flow and these results suggest a potentially useful role for OCT-A in glaucoma monitoring. The fundamental question remains whether reductions in vascular density represent the so-called chicken or the egg. Longitudinal studies are currently underway and data will be forthcoming.

Refractive Errors and Glaucoma

Glaucoma progression in myopes

Comment by Zeynep Ozturker, Istanbul, Turkey

75544 Impact of optic disc hemorrhage on subsequent glaucoma progression in mild-to-moderate myopia; Ha A, Kim YK, Jeoung JW, Park KH; PLoS ONE 2017; 12: e0189706

Ha *et al.* performed a retrospective comparative study to evaluate the myopic patients' clinical disc hemorrhage implications for glaucoma progression. This paper provides the first evaluation of glaucomatous progression related to optic disc hemorrhage in myopic patients.

They enrolled 59 eyes of myopic open-angle glaucoma patients with disc hemorrhage (DH) and 59 eyes of patients without DH matched for age, axial length and visual field (VF) mean deviation. Only IOP stable, early glaucoma patients were included in the study. Three blinded observers reviewed each patient's optic disc photographs and visual field tests to assess structural and functional progression. **They found that the structural glaucoma progression was significantly greater in the DH group than in the non-DH group (p = 0.001). The two groups did not significantly differ in terms of functional progression (p = 0.79).**

As glaucoma diagnosis relies on progressive optic nerve damage and corresponding visual field loss, there are challenges due to the difficult assessment of optic nerve features in myopic eyes with regard to glaucoma.[1] Although the association between myopia and glaucoma is suggested, there are difficulties in differentiating between glaucomatous changes, particularly in the early stages of the disease, and normal myopia. Myopia may influence VF progression due to optic disc shape alterations.[2] Additionally, myopic visual field defects can be progressive even without glaucoma, which makes interpretation of the study's finding difficult.[3]

Optic disc hemorrhage in glaucoma has clinical value for disease progression. However, we still do not fully understand the impact of DH if it represents an ongoing progression or indicates a future progression. As the authors rightly point out, glaucomatous progression was evaluated only after the occurrence of DH, and deterioration before the event was not assessed in the study. Most studies in the literature focus on VF changes after DH and functional loss before their onset is rarely reported. A longitudinal analysis of visual field before and after the DH would help

better understand whether a correlation exists between DH and future progression. In addition, indicating spatial consistency between the disc hemorrhage and the progressive damage to the optic nerve would be suggestive for a stronger connection between the two entities.

Further prospective studies, with standardized progression criteria are needed to validate optic disc hemorrhage as a prognostic sign for progression in myopic glaucoma.

References

1. Chang RT, Singh K. Myopia and glaucoma: Diagnostic and therapeutic challenges. *Curr Opin Ophthalmol.* 2013;24:96-101.
2. Sawada Y, Hangai M, Ishikawa M, Yoshitomi T. Association of myopic deformation of optic disc with visual field progression in paired eyes with open-angle glaucoma. Bhattacharya S, ed. *PLoS ONE*. 2017;12(1):e0170733.
3. Ohno-Matsui K, Shimada N, Yasuzumi K, *et al.* Long-term development of significant visual field defects in highly myopic eyes. *Am J Ophthalmol.* 2011;152:256-265.

Clinical Forms of Glaucoma

ON subarachnoid space in normal pressure glaucoma

Comment by Hanspeter Killer, Basel, Switzerland

75531 Measurement and associations of the optic nerve subarachnoid space in normal tension and primary open-angle glaucoma; Liu H, Yang D, Ma T, Shi W, Zhu Q, Kang J, Wang N; American Journal of Ophthalmology 2018; 186: 128-137

Liu *et al.* present an interesting and well researched paper on the optic nerve sheath diameter (ONSD) in 40 patients with normal tension glaucoma, 42 patients with primary open-angle glaucoma (POAG) and a control group of 45 healthy subjects.

Applying B-scan ultrasound they measured the smallest ONSD in the NTG group. Taking the ONSD as a surrogate for intracranial pressure (ICP) they concluded that NTG patients must have the lowest ICP and therefore the largest translaminar pressure gradient (TLP) gradient.

These findings contrast the measurements reported in two studies performed in Caucasian patients.[1,2] The study of Pinto also applied B-scan ultrasound and did not find a significant difference between the ONSD of 46 NTG patients, 61 POAG patients and 42 healthy controls. Jaggi *et al.* measured the ONSD with computed tomography in 17 patients with NTG and compared them to 17 age and sex matched controls without optic nerve and intracranial disease.[2] This study found significantly larger ONSD in the NTG group.

There are several possibilities that could explain the differences in these studies:

1. There might be a discrepancy between the methods. Giger *et al.*[3] compared the results of ONSD measurement between CT, MRI and ultrasound. They found a high correlation between CT and MRI while comparability between ultrasound and computed tomography or magnetic resonance tomography seemed to be less reliable.
2. The ONSD is dependent on the position of the globe and therefore is variable.[4]
3. A genetic difference in the two populations. This might affect the sheath compliance and the optic canal diameter.[5]
4. Jaggi *et al.* included mostly late stage NTG patients that developed optic nerve sheath compartmentalization as demonstrated by cisternography. Compartmentation might have led to an accumulation of lytic peptides such as metalloproteinases that could have changed the sheath compliance.
5. The anatomy of the orbit of Asians might be different compared to Caucasian. This could influence the pressure in the orbit around the optic nerve. A higher intraorbital pressure could affect the optic nerve sheath diameter.

NTG remains a conundrum with many possible pathophysiological mechanisms. It's time for a large multicenter study including Chinese and Caucasian patients examined with a standard protocol. I am looking forward to such a combined effort to get more answers about the pathophysiology of NTG.

References

1. Abegão Pinto L, Vandewalle E, Pronk A, Stalmans I. Intraocular pressure correlates with optic nerve sheath diameter in patients with normal tension glaucoma. *Graefes Arch Clin Exp Ophthalmol.* 2012;250(7):1075-1080.
2. Jaggi GP, Miller NR, Flammer J, Weinreb RN, Remonda L, Killer HE. Optic nerve sheath diameter in normal-tension glaucoma patients. *Br J Ophthalmol.* 2012;96(1):53-56.
3. Giger-Tobler C, Eisenack J, Holzmann D, *et al.* Measurement of Optic Nerve Sheath Diameter: Differences between Methods? A Pilot Study. *Kling Monbl Augenheilkd.* 2015;232(4):467-470.
4. Gans MS, Byrne SF, Glaser JS. Standardized A-scan echography in optic nerve disease. *Arch Ophthalmol.* 1987;105(9):1232-1236.
5. Pircher A, Montali M, Berberat J, Remonda L, Killer HE. The optic canal: A bottleneck for cerebrospinal fluid dynamics in normal-tension glaucoma? *Front Neurol.* 2017;23;8:47.

Risk Factors in Glaucoma

Lurking in the night: Blood pressure dips and glaucoma

Comment by John Liu, La Jolla, CA, USA

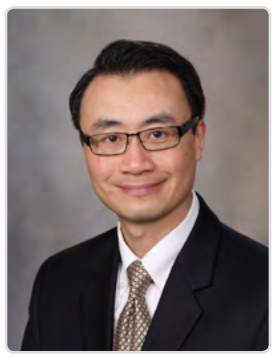
75672 Glaucomatous optic neuropathy associated with nocturnal dip in blood pressure: Findings from the Maracaibo Aging Study; Melgarejo JD, Lee JH, Petitto M, Yépez JB, Murati FA, Jin Z, Chávez CA, Pirela RV, Calmón GE, Lee W, Johnson MP, Mena LJ, Al-Aswad LA, Terwilliger JD, Allikmets R, Maestre GE, De Moraes CG; Ophthalmology 2018; 0:

Like any vital organ, the eye receives its daily nutrition from blood circulation by a physiological force called perfusion pressure. Ocular perfusion pressure is set by local arterial pressure minus the resistance to perfusion. The resistance to perfusion is closely related to local venous pressure and intraocular pressure. Previous studies employing 24-hour ambulatory blood pressure monitor have indicated that nocturnal hypotension in systemic blood pressure is a significant risk factor for glaucoma. In this cross-sectional study of 26 Hispanic individuals with glaucomatous optic neuropathy and 67 Hispanic individuals with healthy eyes, the authors evaluated major parameters of 24-hour ambulatory blood pressure associated with glaucomatous optic neuropathy, as these subjects no recorded elevated office-hour intraocular pressure (< 22 mmHg). **The authors concluded that the link between optic neuropathy and the extreme dipping status (> 20%) of systemic blood pressure at night from individual daytime level is much stronger than the links with other blood pressure parameters such as the nocturnal systolic and diastolic blood pressure levels**. This new discovery affirms the concept that **pathogenesis of open-angle glaucoma in regard to pressure forces in the eye should be evaluated individually for each patient instead of using an arbitrarily chosen number of simple or average pressure level within the 24-hour time period.** Results from the current study also suggest that useful information may be obtained by studying the links between glaucomatous optic neuropathy and the parameters of 24-hour intraocular pressure. There are reports that a significant number of glaucoma patients with normal office-hour intraocular pressure actually show an elevation of intraocular pressure at night more than the average magnitude of increase in healthy persons.

> Pathogenesis of open-angle glaucoma in regard to pressure forces in the eye should be evaluated individually for each patient instead of using an arbitrarily chosen number of simple or average pressure level within the 24-hour time period

Technological advances in recent years have made monitoring 24-hour intraocular pressure possible under the ambulatory condition. A combination of 24-hour ambulatory monitoring blood pressure and intraocular pressure will probably provide even more insights for patients with unexplainable glaucomatous optic neuropathy.

IOP variation and glaucoma



Comment by Arthur Sit, Rochester, MN, USA

75758 Variation in intraocular pressure and the risk of developing open-angle glaucoma: The Los Angeles Latino Eye Study; Jiang X, Torres M, Varma R,; American Journal of Ophthalmology 2018; 188: 51-59

Fluctuations in intraocular pressure (IOP) have long been suggested as potential risk factors for the development of glaucoma. However, the availability of longitudinal data to study this issue has been limited, and the reported results have been contradictory.[1-3] Jaing *et al.* report on the relationship between IOP variability and the risk for developing open angle glaucoma among the participants of the Los Angeles Latino Eye Study (LALES), a cross-sectional, population-based study with a follow-up study after four years.

A total of 3666 individuals without glaucoma at baseline were included. IOP was measured a total of six times: three times within minutes at baseline, and three times within minutes at the four-year follow-up exam. Open angle glaucoma was diagnosed based on optic disc appearance on stereoscopic fundus photographs and/or characteristic visual field changes. Mean, maximum, standard deviation, and range of IOP were calculated, and univariate and multivariate logistic regression models were used to assess the association between these variables and the risk of glaucoma.

> This study provides further evidence that IOP variability contributes to the risk of developing glaucoma, and this effect appears to be more important in patients with low mean IOP

The authors reported that glaucoma occurred in 73 of the study participants. Both standard deviation and range of IOP were found to be significant risk factors for the development of glaucoma, even after adjustment for mean IOP. However, in the multivariate model only maximum IOP remained a significant independent predictor of glaucoma, while mean, standard deviation and range dropped out. A subgroup analysis was also performed to differentiate participants with low and high IOP. **For participants with mean IOP < 15 mmHg, maximum, standard**

deviation and range of IOP were all associated with higher risk of glaucoma but mean IOP was not. For patients with mean IOP of > 15 mmHg, mean and maximum IOP were associated with the development of glaucoma while standard deviation and range were not.

This study provides further evidence that IOP variability contributes to the risk of developing glaucoma, and this effect appears to be more important in patients with low mean IOP. What is remarkable about the results from this study is that IOP variation was detected as a risk factor for glaucoma based on only six IOP measurements at two time points for each patient. However, this may be a reflection of the large sample size rather than the predictive ability of a small number of individual IOP measurements. One potential confounder in this study is that the measures of IOP variability included both short and long-term variations. While the authors demonstrated that inter-visit variability provided a greater contribution than intra-visit variability, it is not clear which of these two types of variations may be more predictive of glaucoma development. Fully understanding the role of IOP variations in glaucoma development and progression will likely require technology to continuously monitor IOP over extended time periods.

References

1. Bengtsson B, Bengtsson B, Leske MC, Hyman L, *et al.* Fluctuation of intraocular pressure and glaucoma progression in the early manifest glaucoma trial. *Ophthalmology*. 2007;114(2):205-209.
2. Caprioli J, Coleman AL. Intraocular pressure fluctuation a risk factor for visual field progression at low intraocular pressures in the advanced glaucoma intervention study. *Ophthalmology*. 2008;115(7):1123-1129.
3. Musch DC, Gillespie BW, Niziol LM, Lichter PR, Varma R; CIGTS Study Group. Intraocular pressure control and long-term visual field loss in the Collaborative Initial Glaucoma Treatment Study. *Ophthalmology*. 2011;118(9):1766-1773.

Corneal hysteresis as a predictor for glaucoma

Comment by Steve Mansberger, Portland, OR, USA

75661 A Prospective longitudinal study to investigate corneal hysteresis as a risk factor for predicting development of glaucoma; Susanna CN, Diniz-Filho A, Daga FB, Susanna BN, Zhu F, Ogata NG, Medeiros FA; American Journal of Ophthalmology 2018; 187: 148-152

Studies evaluating glaucoma risk factors help predict and prevent visual impairment from glaucoma. This study by Susanna and colleagues investigates the role of corneal hysteresis (CH) as a risk factor for the development of glaucoma. The study includes 287 eyes of 199 patients suspected of having glaucoma with a follow-up time of 3.9 ± 1.8 years.

The study found that lower CH was associated with the development of repeatable visual field defects (a pattern standard deviation (PSD) with P < .05 or a Glaucoma Hemifield Test result outside normal limits) in a univariate (9.5 ± 1.5 mm Hg vs 10.2 ± 2.0 mm Hg; P = .012), and multivariate model including age, intraocular pressure (IOP), central corneal thickness, PSD, and treatment (hazard ratio = 1.20; 95% CI: 1.01–1.42; P = .040). Overall, this suggests that **CH is an independent risk factor for development of glaucoma even when including central corneal thickness (CCT) as a known risk factor.**

The study does not fully explain the model building procedure for the multivariable statistical model such as a stepwise entering of variables, or entering all eligible variables using the enter function. This may alter the final multivariable model. Previous studies suggest that CH is correlated with both IOP and CCT, while other studies only show a correlation with CCT. A correlation matrix would have been informative to determine whether IOP and CCT were associated with CH, and whether this is the explanation for those factors becoming not statistically significant in a multivariable model with CH. The model building procedure should explain why it used PSD as an explanatory variable when PSD is part of the definition of repeatable visual field loss (see above). It would also be helpful to know whether a model would have similar or worse explanatory power using IOP and CCT, which are more commonly used clinically.

We clearly need more information regarding the contribution of CH to our understanding of glaucoma pathophysiology and risk of glaucoma progression

Previous studies have shown this contribution of CH to glaucoma using retrospective and prospective studies in glaucoma patients. Susanna and colleagues should be congratulated for adding to this evidence by showing explanatory results of CH in glaucoma suspects. While research has suggested an association of CH with biomechanical stress and strain of the eye, we clearly need more information regarding the contribution of CH to our understanding of glaucoma pathophysiology and risk of glaucoma progression.

Medical Treatment

Rho-kinase Phase 3 trials

Comment by Robert Feldman, Houston, TX, USA

75444 Two Phase 3 clinical trials comparing the safety and efficacy of netarsudil to timolol in patients with elevated intraocular pressure: Rho Kinase Elevated IOP treatment Trial 1 and 2 (ROCKET-1 and ROCKET-2); Serle JB, Katz LJ, McLaurin E, Heah T, Ramirez-Davis N, Usner DW, Novack GD, Kopczynski CC,; American Journal of Ophthalmology 2018; 186: 116-127

Rho kinase (ROCK) inhibitors are a new class of topical medications for elevated IOP. ROCK inhibitors lower IOP by increasing aqueous outflow through the trabecular meshwork. ROCK inhibitors decrease cellular contraction and rigidity and synthesis of fibrotic extracellular matrix proteins.[1] Serle *et al.* describe two studies, with the purpose of evaluating the safety and efficacy of netasrsudil 0.02% ophthalmic solution, a ROCK inhibitor and norepinephrine transporter inhibitor, in open-angle glaucoma and ocular hypertension.

These 2 studies were double-masked, randomized, non-inferiority clinical trials, Rho Kinase Elevated IOP Treatment Trial 1 and 2 (ROCKET-1 and ROCKET-2). These studies included 1167 patients randomized to receive netarsudil 0.02% qd, timolol bid, and netarsudil 0.02% bid (ROCKET-2 only) and described three-month results. **Netasurdil treatment resulted in a clinically significant IOP reduction from baseline (**P **< 0.001) and was non-inferior to timolol in both trials where maximum baseline IOP was < 25 mmHg.** Conjunctival hyperemia was the most frequent reported adverse event (incidence of 50-53% with netarsudil qd, 59% with netarsudil bid, and 8-10% with timolol bid), with conjunctival hemorrhage and cornea verticillata also reported frequently. Conjunctival hyperemia and hemorrhage were expected as ROCK inhibitors dilate the vasculature.[1] As netarsudil bid resulted in a greater incidence of adverse events and higher patient discontinuation rate (30% vs 10-12% qd dosing), the authors suggest that the optimal dosing regimen is qd in the evening.

ROCK inhibitors are an effective new addition to glaucoma therapy. Their unique mechanism of increasing aqueous outflow through the trabecular pathway is mechanistically additive to our other available treatments.

Reference

1. Rao PV, Pattabiraman PP, Kopczynski C. Role of the Rho GTPase/Rho kinase signalling pathway in pathogenesis and treatment of glaucoma: Bench to bedside research. *Exp Eye Res.* 2017;158:23-32.

Surgical Treatment

XEN Gel: with or without phaco?

Comment by Sameh Mosaed, Irvine, CA, USA

75591 Prospective Evaluation of standalone XEN gel implant and combined phacoemulsification-XEN gel implant surgery: 1-year results; Mansouri K, Guidotti J, Rao HL, Ouabas A, D'Alessandro E, Roy S, Mermoud A; Journal of Glaucoma 2018; 27: 140-147

The study by Kaweh Mansouri and colleagues compared XEN alone (40 eyes) vs. XEN + cataract surgery (109 eyes) in a predominantly white population with mostly mild to moderate open-angle glaucoma. All patients received XEN with 45-micron internal diameter, and mitomycin was applied intraoperatively in all cases. The primary outcome was IOP reduction greater or equal to 20% at one year post-op. Overall, 62.1% of the patients achieved this goal, with the mean IOP decreased from 20.0 ± 7.1 mmHg to 13.9 ± 4.3 mmHg. At one year, the median IOP reduction was 40% in the XEN alone group and 22.9% in the XEN+ CE group, although this difference was not statistically significant. **There was no difference between the XEN-alone and XEN+CE in terms of success rate, regardless of whether that success was defined as complete or qualified**. These success rates ranged in the upper 50s for complete success, and low 70s for qualified success. The adverse event rates in this study were in the < 5% range which was somewhat lower than most of the other available studies.

This study confirmed what had been shown in other smaller studies, that:

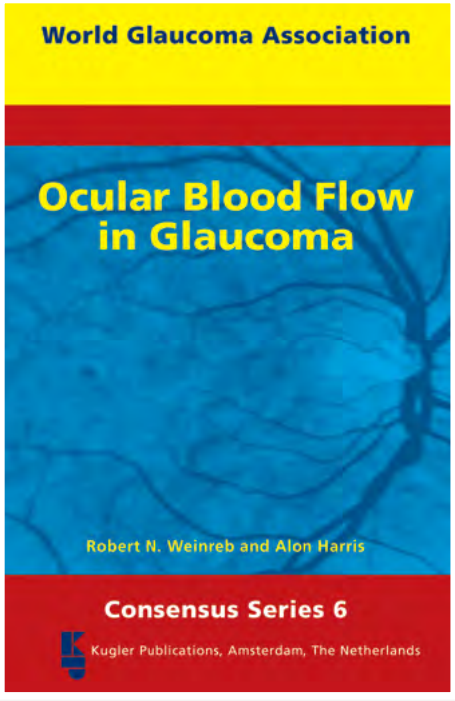
1. XEN stent can lower IOP to a slightly greater extent than what had been seen in some of the MIGS devices at one-year postop; and
2. concomitant cataract surgery does not seem to confer significant additional IOP reduction than what the XEN stent alone could accomplish.

> XEN […] seems to work a bit better than most MIGS, but that comes at the price of a bleb-reliant procedure with more involved postoperative care

This study had a few limitations. Firstly, it did not specify how patients were divided into the XEN alone vs. XEN + cataract surgery. This decision did not seem to stem from visual acuity, since the preoperative best corrected visual acuity was similar between the groups. Secondly, needling was not considered an adverse event, even though this necessitated another trip the OR. Thirdly, the preoperative IOP was not washed out, which made the results difficult to compare with other studies that used washed-out IOP for baseline. Nevertheless, this study demonstrated

that XEN occupies a unique space in the glaucoma surgical armamentarium. It seems to work a bit better than most MIGS, but that comes at the price of a bleb-reliant procedure with more involved postoperative care.

Consensus 6 - Ocular Blood Flow in Glaucoma



edited by: R.N. Weinreb and A. Harris
2009

“Obtaining consensus on the relationship of blood flow to glaucoma was a daunting task. So much has been studied and written, but how much do we really know? As with the previous WGA consensuses, the Glaucoma Blood Flow consensus is based on the published literature and expert opinion.

Although consensus does not replace and is not a surrogate for scientific investigation, it does provide considerable value, especially when the desired evidence is lacking. The goal of this consensus was to establish a foundation for ocular blood flow research of glaucoma and the best practice for its testing in clinical practice. Identification of those areas for which we have little evidence and, therefore, need additional research was a high priority. We hope that this consensus will serve as a benchmark of our understanding, and that it will be revised and improved with the emergence of new evidence.”

Table of contents

Consensus 6 Summary Consensus Points 2009

ANATOMY AND PHYSIOLOGY

- Blood supply to the retinal nerve fiber layer invariably comes from the central retinal artery and, when present, from the cilioretinal artery(ies).
  Comment: There are no anastomotic connections between the arteries, which function as end-vessels even though the capillaries are a continuous bed.
- Blood supply to the prelaminar and laminar portion of the optic nerve head comes from branches of the short posterior ciliary arteries.
  Comment: These often form an incomplete vascular ring around the optic nerve head ('Vascular ring of Zinn and Haller'), before giving off branches into the tissue of the optic nerve head located inside of the peripapillary scleral ring of Elschnig. These vessels feature an anastomotic blood supply.
- Retinal vessels are not fenestrated and are not innervated. Since they lack a continuous tunica musculosa, the retinal 'arteries', except for the main central retinal vessel trunk, are anatomically arterioles.
  Comment: These anatomical features may have implications for understanding how blood flow is regulated in this vascular bed.
- It is unclear whether the branches of the posterior ciliary artery that feed the intrascleral portion of the optic nerve are innervated and/or fenestrated.
  Comment: Such knowledge is essential to understand how the intrascleral papillary tissue responds to various insults, including abnormally high IOP.
- Branches of the short posterior ciliary arteries supply the choroidal vasculature. The majority of total ocular blood volume and flow (~80-90%) is derived from the choroidal vascular. The capillaries are among the largest in the body and are fenestrated. The arteries that feed them are innervated.
  Comment: These features have important implications for how the choroidal vasculature is regulated. It has remained unclear whether there is a clinically relevant anastomotic blood exchange between the choroidal vasculature bed and the vascular system of the ciliary body, which is fed by the two long posterior ciliary arteries and the 7 anterior ciliary arteries.
- The central retinal vein drains all blood from the entire retina and the optic nerve head.
  Comment: Upon contact-free ophthalmoscopy, a spontaneous pulsation of the central retinal vein can be detected in ~80 to 90% of normal eyes. Since the central retinal vein passes through the optic nerve and then through the cerebrospinal fluid space before piercing through the optic nerve meninges in the orbit, the blood pressure in the central retinal vein should be at least as high as the cerebrospinal fluid pressure within the optic nerve meninges in the orbit plus a (hypothetical) trans-lamina cribrosa outflow resistance.
- Blood flow to the optic nerve and retina is dominated primarily by myogenic and metabolic regulation. The blood flow to the choroid is believed to be primarily regulated mainly by hormonal and neuronal mechanisms. The extent of autoregulation in the choroid is not known.
  Comment: Ocular vascular autoregulation maintains adequate blood flow that provides nutrients and oxygen, as well as adequate tissue turgor, to ocular structures in the face of changing metabolic needs and altered ocular perfusion pressure. Such functions are all designed to allow sharp vision at all times.

CLINICAL MEASUREMENT OF OCULAR BLOOD FLOW

- Color Doppler imaging of the ophthalmic artery, central retinal artery and posterior ciliary arteries measures blood flow velocity noninvasively and calculates resistive index.
  Comment: Color Doppler imaging does not measure flow.
  Comment: With careful interpretation, color Doppler imaging measures blood flow velocity and vascular resistivity in the retrobulbar blood vessels. The exact relationship between vascular resistivity index and resistance is not fully understood.
  Comment: The measurements with one color Doppler instrument are not necessarily compatible with those of another.
- Scanning laser Doppler flowmetry measures velocity, volume and flow limited to the retinal microcirculation and the optic nerve head.
  Comment: There is a lack of standardization for analysis, and flow is limited to arbitrary units of measure.
  Comment: The depth of the measurements is not known and may not be comparable among subjects.
- The retinal vessel analyzer provides a dynamic assessment of retinal vessel diameters of branch retinal arterioles and venules.
  Comment: The retinal vessel analyzer does not evaluate either velocity or blood flow.
  Comment: At the current time, vessels with a diameter of 90 micrometers or larger are measured.
- The relationship between ocular pulse amplitude and total blood flow to the eye and, specifically, to the optic nerve is uncertain.
- Laser speckle flowgraphy provides 2-dimensional in vivo measurements of blood velocity in the optic nerve head and subfoveal choroid.
  Comment: Measurements in human eyes of the retina and iris have been problematic.
  Comment: Measurement with laser speckle flowgraphy is not clearly understood.
- Digital scanning laser ophthalmoscope angiography allows direct visualization of retinal and choroidal microvasculature.
  Comment: Various aspects of observed blood flow parameters and filling characteristics can be quantified, including retinal velocity and circulation times with fluorescein dye, and relative regional choroidal filling delays with indocyanine green dye.
  Comment: At the current time, scanning laser ophthalmoscope angiography requires an intravenous dye injection.
- By combining bidirectional laser Doppler velocimetry with simultaneous measures of retinal vessel diameter and centerline blood velocity, it is possible to calculate retinal blood flow in absolute units.
  Comment: These measurements require clear optical media and pupil dilation.
  Comment: The method is limited to vessels greater than 60 micrometers.
- Doppler Fourier Domain Optical Coherence Tomography provides rapid measurements of volumetric flow rate, velocity, and cross-sectional area in branch retinal vessels.
  Comment: At the current time, the method is limited to vessels greater than 60 micrometers and there are limited data.
- Retinal oximetry is a non-invasive measurement of oxygen saturation.
  Comment: At the current time, there are limited data. The method is limited to retinal vessels greater than 60 micrometers. It may be applicable also to the optic nerve head..
- At the present time, there is no single method for measuring all aspects of ocular blood flow and its regulation in glaucoma.

Comment: A comprehensive approach, ideally implemented in a single device, may be required to assess the relevant pathophysiology of glaucoma.

CLINICAL RELEVANCE OF OCULAR BLOOD FLOW (OBF) MEASUREMENTS INCLUDING EFFECTS OF GENERAL MEDICATIONS OR SPECIFIC GLAUCOMA TREATMENT

- Blood pressure (BP) is positively correlated with IOP.
- It is unclear whether the level of BP is a risk factor for having or progressing open-angle glaucoma (OAG) in an individual patient.
  Comment: It has been hypothesized that low blood pressure is a risk factor for patients with abnormal autoregulation.
- Lower ocular perfusion pressure (OPP = BP – IOP) is a risk factor for primary OAG.
- OBF parameters measured with various methods are impaired in OAG, especially in NTG, compared with healthy subjects.
  Comment: Reduction of OBF with aging has been confirmed by various methods.
  Comment: The optic nerve head blood flow may be reduced during the nocturnal period.
- Vascular dysregulation may contribute to the pathogenesis of glaucoma, more likely in people with lower intraocular pressure.
- Certain drugs, even when formulated in an eye drop, may have an impact on ocular blood flow and its regulation.
  Comment: The impact of eye drop related changes in ocular blood flow on the development and progression of glaucoma is unknown.
  Comment: Some data support increased blood flow and the enhancement of ocular blood flow regulation with carbonic anhydrase inhibitors. These appear to exceed what one would expect from their ocular hypotensive effect alone.
- Some systemic medications may have an impact on ocular blood flow and its regulation.
  Comment: The impact of systemic medications altering ocular blood flow on the development of glaucoma and the progression of glaucoma is unknown.
  Comment: Classes of systemic medications with agents that have been reported to increase ocular blood flow include calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor inhibitors, carbonic-anhydrase inhibitors, phospodiesterase-5 inhibitors.
- The association between diabetes and cardiovascular diseases with OAG still remains unclear.

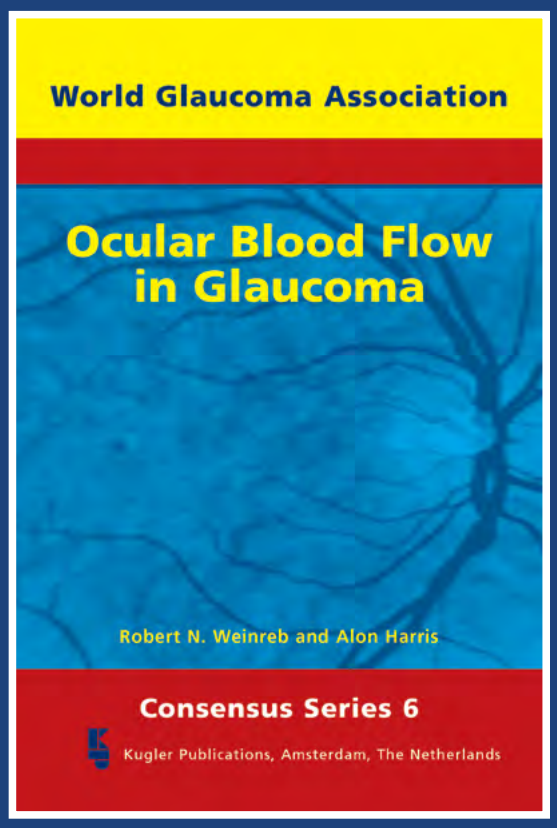
SHOULD MEASUREMENTS OF OCULAR BLOOD FLOW BE IMPLEMENTED INTO CLINICAL PRACTICE?

- Measurements of ocular blood flow are currently research tools for the study of glaucoma.
  Comment: Assessing ocular blood flow has been of interest to clinicians and scientists over several decades, and sophisticated diagnostics directed at measuring ocular perfusion have emerged.
  Comment: Before deciding whether to implement measurements of blood flow into clinical practice for glaucoma management, however, these measurements need to be critically assessed in clinical studies.
- Although there is an association between measurements of ocular blood flow and glaucoma progression, a causal relationship has not been established.
- There are insufficient data to support the measurement of ocular blood flow for clinical decision making in glaucoma practice.
  Comment: Prior studies of ocular blood flow in glaucoma have varied considerably in their methodologies, numbers of patients, and study design pertaining to design, conduct and analysis.

- Evidence that measurement of blood flow leads to better clinical outcomes for the glaucoma patient is lacking.
- There is no evidence that altering blood pressure changes the course of glaucoma.

WHAT DO WE STILL NEED TO KNOW?

- Clinical studies are essential to establish the clinical application of ocular blood flow measurements in glaucoma.
  Comment: Appropriately designed studies utilizing standardized measurement techniques are needed to ascertain the relationships among ocular blood flow, metabolism and glaucoma progression.
  Comment: Future studies should ascertain the relationship between blood pressure and glaucoma.
- The physiology of ocular blood flow regulation needs to be elucidated. Laboratory studies designed to detect molecular and cellular mechanisms in vitro and in vivo that support the presence of ischemia are needed.
  Comment: Experimental research is needed to elicit the existence and role of hypoxia/ischemia in relevant glaucoma models.
- Longitudinal studies are necessary to confirm whether blood flow abnormalities precede visual field defects and correlate with their severity.
- The hypothesis should be tested that treatment of OPP, rather than IOP alone, is beneficial in glaucoma.
- There is a need to determine at what levels IOP and OPP increase the risk for the onset and/or progression of glaucoma for an individual eye.
- The clinical outcome of ocular blood flow fluctuation, perfusion pressure and their impact on glaucoma needs to be investigated.
  Comment: The contribution of the blood flow within the entire central visual pathway is unknown and still needs to be determined.
- A normative database for ocular blood flow measurements that can be used in research and clinical practice should be established.



Download Book at: www.wga.one/wga/consensus-downloads

Through the courtesy of the WGA and Kugler Publications, you may now download the PDF file of Consensus 6 **free of charge** through your WGA#One account. Consensus 1–5 have previously been made available through IGR and are now also accessible through your WGA#One account.

Robert N. Weinreb
Consensus Initiative Chair
World Glaucoma Association

www.e-IGR.com

News flashes

★ We clearly need more information regarding the contribution of CH to our understanding of glaucoma pathophysiology and risk of glaucoma progression

★ The fundamental question remains whether reductions in vascular density represent the so-called chicken or the egg

★ These findings emphasize the importance of carefully assessing central macular visual field properties in glaucoma because it is a significant predictor of overall visual field loss in glaucoma

★ XEN […] seems to work a bit better than most MIGS, but that comes at the price of a bleb-reliant procedure with more involved postoperative care

★ It would be interesting to evaluate in longitudinal studies the biomechanical response of the optic nerve head in progressing glaucoma

★ Finding a cost-effective educational intervention and examining its effect on disease progression is therefore an important area for further research

★ […] SIRT1 could be a potential therapeutic target in glaucoma

Published by the World Glaucoma Association in collaboration with
Kugler Publications, Amsterdam, The Netherlands