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International Glaucoma Review

Volume 17-4
2016

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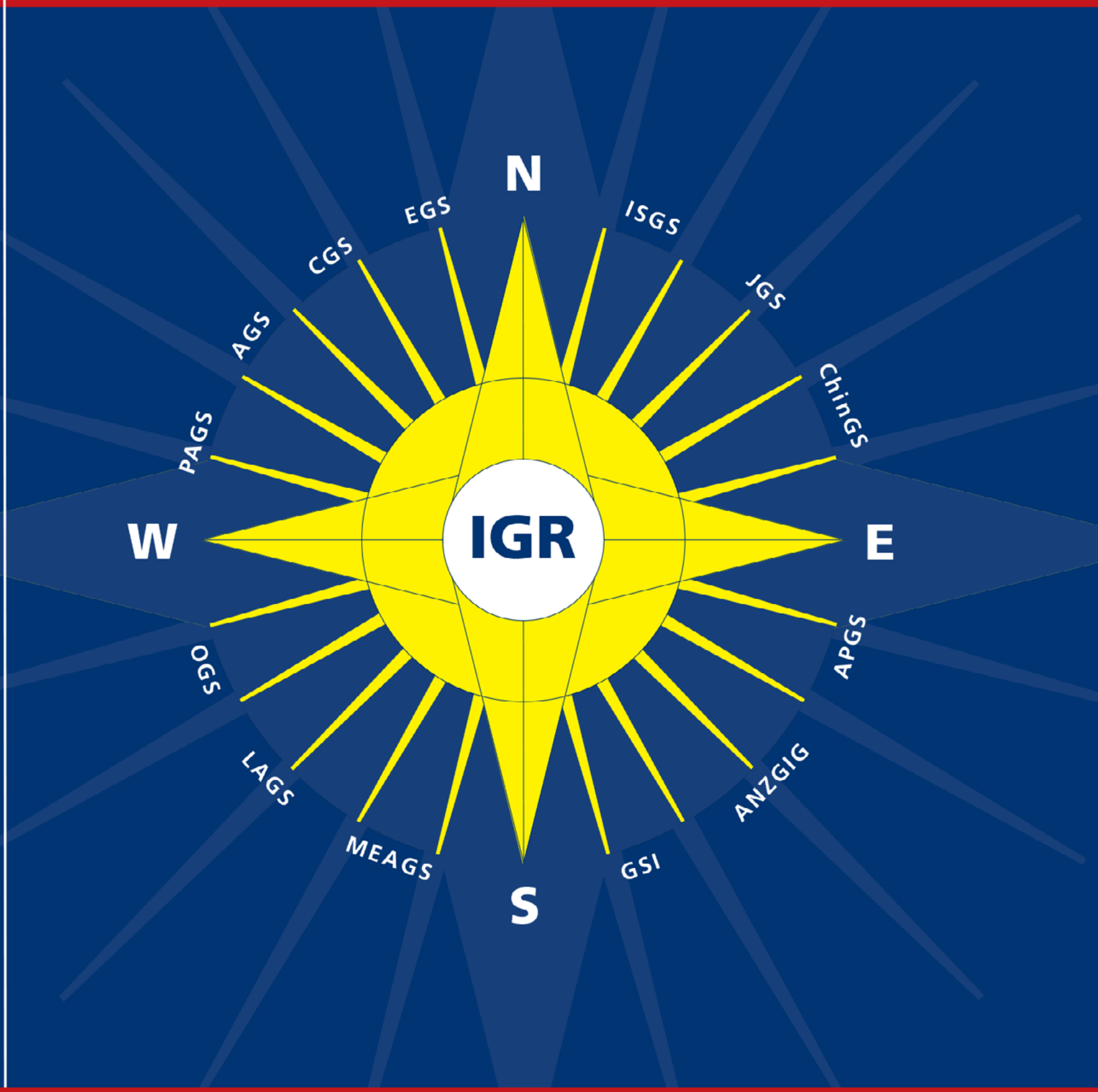

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Volume 17 no. 4

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Table of Contents

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

From the WGA Executive Office

Dear readers,

As with every issue, I am proud that once again, we are able to present expert glaucoma commentary and news from all ends in our global Glaucoma community.

IGR is delivered directly to all affiliates of our Glaucoma Society Members and Industry Members as a benefit of participation in the World Glaucoma Association. In total, the WGA database is comprised of over 12.000 individuals.

One of our educational pillars is the **World Glaucoma Congress**. The next Congress is scheduled June 28 – July 1, 2017 in Helsinki. Registration opens on October 10 and the full program will be available via our website. I wish to acknowledge the tremendous contribution of the scientific program under the guidance of Jonathan Crowston (chair) and the Program Planning Committee members. Do not miss this opportunity to visit the beautiful city of Helsinki!

Register on October 10, 2016 at www.worldglaucomacongress.com.

Via email you might receive an invitation to participate in an online survey with regards to a **needs assessment for glaucoma education** by the WGA Education Committee. We kindly ask you to complete the survey, so we are able to focus our education activities on the needs identified by the glaucoma community. If you did not receive the survey and would like to participate, please contact the WGA Executive Office and they will be happy to supply you with the information (info@worldglaucoma.org).

I hope you will enjoy this issue of IGR and would like to thank all contributors as well as our advertisers.

Robert D. Fechtner, Executive Vice President

Important Dates

OCTOBER 10, 2016

Start abstract submission and congress & hotel registration

JANUARY 30, 2017

Deadline abstract submission

MARCH 31, 2017

Early registration deadline

MAY 15, 2017

Late registration deadline

JUNE 28–JULY 1, 2017

Congress dates

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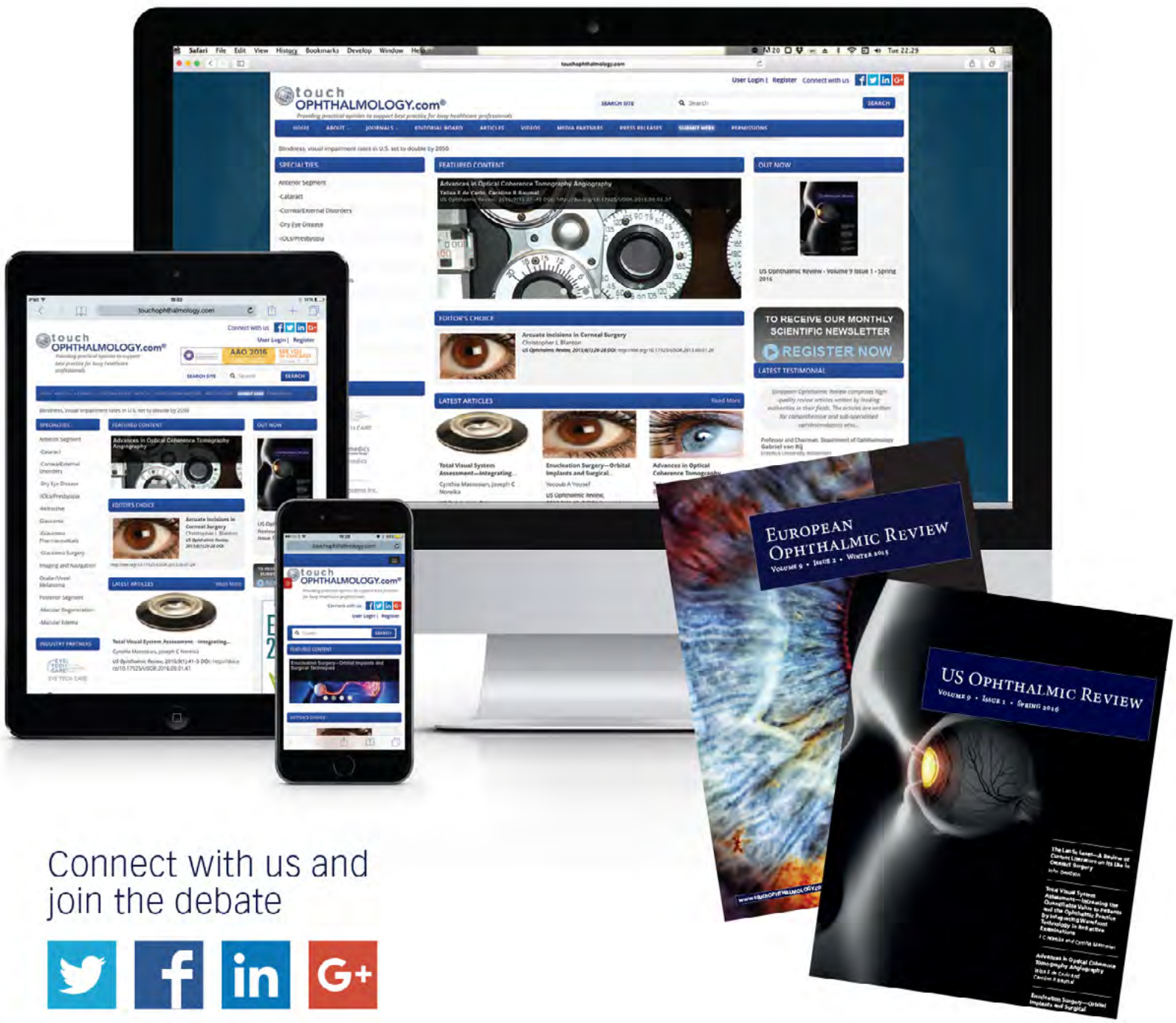

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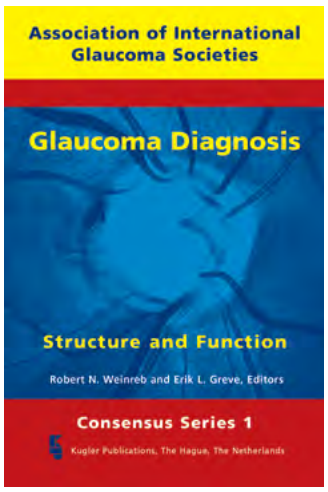
WGA Consensus Series

Robert N. Weinreb

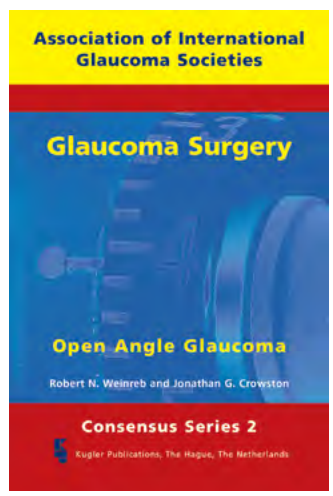
Introduction

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.



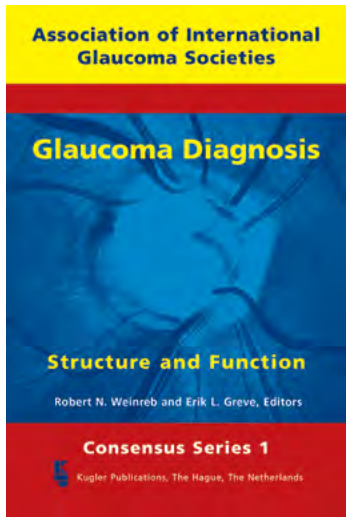
To prepare each of the consensus reports, there were several months of active discussion via the Internet by more than 100 expert members of the various consensus committees. The preliminary documents were circulated to each of the more than 70 member societies of the World Glaucoma Association, and 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 clinic acumen and knowledge of numerous and diverse practitioners and scientists can be harnessed more efficiently and effectively than ever with the contemporary inter-connected global communication. We can learn from each other by sharing, adapting and updating new information, and agreeing on the significance of the information. Linking networks of glaucoma specialists has tangible and ongoing important implications for glaucoma research, glaucoma clinical care and glaucoma education on a global basis.



Consensus 1

Glaucoma Diagnosis: Structure and Function

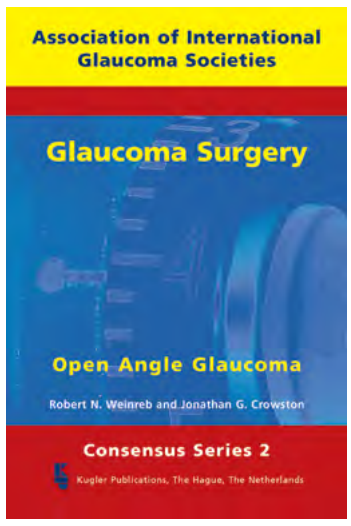


edited by: R.N. Weinreb and E.L. Greve
2004

To the best of our knowledge, the first Global WGA Consensus Meeting on 'Structure and Function in the Management of Glaucoma', held in La Jolla in November, 2003, was also the first global consensus meeting in ophthalmology. The goal was to reach an evidence-based consensus for both clinical practice and research through the use of information obtained from peer-reviewed literature describing functional and structural diagnostic testing in glaucoma. While many of the resulting consensus statements are enduring, some of the tools for clinical practice have changed.

Consensus 2

Glaucoma Surgery: Open Angle Glaucoma



edited by: R.N. Weinreb and J.G. Crowston
2005

The second Consensus Book provides valuable guidelines for surgical management and has highlighted areas where scientific evidence at present was lacking in 2005. There had been considerable interest in new surgical treatments for open angle glaucoma and some had rapidly gained acceptance in clinical practice. Although some of these modalities were promising, one always should be mindful of the need to appraise all new surgical treatments with similar rigor to that demanded of new medical treatments. This consensus in glaucoma surgery for open angle glaucoma provided valuable guidelines for surgical management and highlighted areas where scientific evidence was lacking.

Download Books

Through the courtesy of the **WGA** and **Kugler Publications**, you may now download the PDF files of Consensus 1 and 2 **free of charge** through your IGR account!

Robert N. Weinreb
Consensus Initiative Chair
World Glaucoma Association

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Your Special Attention For

Detecting IOP fluctuations in glaucoma patients
Nuyen B, Mansouri K
(abstract no. 66660)
Open Ophthalmology Journal 2016; 10: 44-55

The progress of study about endoplasmic reticulum stress in glaucoma
Hu J, Jiang B
(abstract no. 66688)
Chinese Journal of Ophthalmology 2016; 52: 231-235

Peripheral iridotomy for pigmentary glaucoma
Michelessi M, Lindsley K
(abstract no. 66803)
Cochrane Database of Systematic Reviews 2016; 2: CD005655

Cannabinoids for treatment of glaucoma
Novack GD
(abstract no. 66840)
Current Opinions in Ophthalmology 2016; 27: 146-150

Vascular and autonomic dysregulation in primary open-angle glaucoma
Pasquale LR
(abstract no. 66876)
Current Opinions in Ophthalmology 2016; 27: 94-101

Brain: The potential diagnostic and therapeutic target for glaucoma
Faiq MA, Dada R, Kumar A, Saluja D, Dada T
(abstract no. 67236)
CNS and Neurological Disorders - Drug Targets 2016; 15(7): 839-844

Where does selective laser trabeculoplasty stand now? A review
De Keyser M, De Belder M, De Belder S, De Groot V
(abstract no. 67592)
Eye and Vision (London, England) 2016; 3: 10

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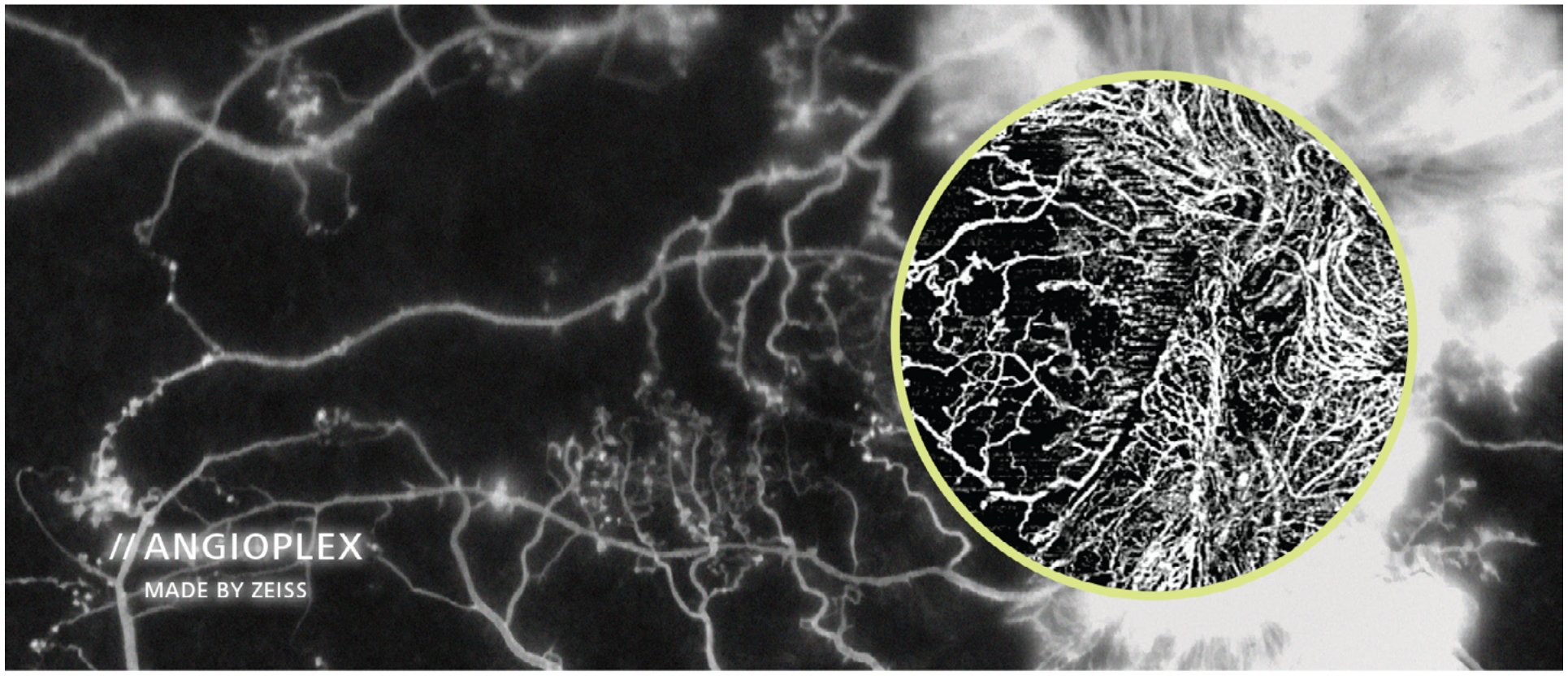

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Glaucoma Dialogue

In this section, a published manuscript of import and potential impact for discussion will be selected. It also provides a forum for manuscripts that some might judge to be controversial or where further discussion of the experimental models or data is warranted. Solicited comments of experts will be sent to the authors of a selected manuscript for a response. Both comments and responses will be published in IGR in their entirety. This should provide interesting information for our readership that is not otherwise available from the published manuscript.

Robert N. Weinreb, Chief Editor

67306 Structural and Functional Progression in the Early Manifest Glaucoma Trial, Öhnell H, Heijl A, Brenner L, Anderson H, Bengtsson B, Ophthalmology 2016; 123: 1173-1180

Comments

Comment by Chris Johnson, Iowa City, IA, USA

The Early Manifest Glaucoma Trial is one of the prominent multicenter trials in glaucoma that has had an important, meaningful impact on how eye care specialists manage and treat patients with glaucoma. In this paper, the authors have evaluated approximately eight years of follow-up results to determine the ability of functional (perimetry) and structural (optic disc photos) test procedures to detect glaucomatous progression.

The results are somewhat surprising since it has been repeatedly found over the past 150 years that structural glaucomatous deficits tend to be detected earlier and more frequently than functional losses

The findings indicated that for eyes with normal visual fields at baseline, there was no difference between structural and functional indicators of glaucomatous progression, both indicating that it occurred 15-18% of the time over the eight year period of evaluation. However, in eyes with visual field abnormalities at baseline, visual field evaluations were able to determine progression about four times greater than structural indicators (52% versus 12%). These results are useful for practitioners who manage patients with glaucoma or are at risk of developing glaucoma. The results are somewhat surprising since it has been repeatedly found over the past 150 years that structural glaucomatous deficits tend to be detected earlier and more frequently than functional losses, in spite of dramatic variations in technology and diagnostic procedures.[1]

There are several factors that should be kept in mind when assessing the conclusions from this study. The performance of a particular method of assessing progression depends on the decision rules that are used and the analysis method employed.[2] Previous investigations have demonstrated that structural and functional glaucomatous changes are not necessarily detected clinically at the same time, either structure or function can be the initial indicator of change, and that both structure and function are important factors to be monitored for proper management of glaucoma patients and glaucoma suspects.[3-6] Additionally, the recent advent of new technologies (optic disc and retinal nerve fiber layer imaging, continuous IOP monitoring and other issues) reminds us that the management of glaucoma is constantly changing and that prior evaluations of older technologies may not be relevant for more current procedures. Non-stereo optic disc photographs are but one method of evaluating structural damage, and glaucoma change probabilities is one of many approaches to the assessment of functional loss.

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4. Medeiros FA, Alencar LM, Zangwill LM, *et al.* Prediction of functional loss in glaucoma from progressive optic disc damage. Arch Ophthalmol 2009;127:1250-1256.
5. Medeiros FA, Zangwill LM, Bowd C, Mansouri K, Weinreb RN. The structure and function relationship in glaucoma: implications for detection of progression and measurement of rates of change. Invest Ophthalmol Vis Sci 2012;53:6939-6946.
6. Abe RY, Diniz-Filho A, Zangwill LM, *et al.* The relative odds of progressing by structural and functional tests in glaucoma. Invest Ophthalmol Vis Sci 2016;57:421-428.

Comment by Tae-Woo Kim, Seoul, Korea

It is common that detectable progressive structural change does not coincide temporally with the functional progression in glaucoma eyes. Ohnell *et al.* investigated the temporal relationship between detection of glaucomatous optic disc progression by fundus photography and visual field progression using the patient cohort included in Early Manifest Glaucoma Trial (EMGT).

> It is possible that the optic disc examination is not as sensitive to detect progressive change as RNFL based examination such as red-free photography or OCT RNFL thickness measurement

The optic disc progression was defined by the subjective assessment of three disc readers, who defined the progression mainly based on changes in the course of small vessels on the optic disc surface. The visual filed progression was defined using the EMGT criteria. They found that progression in the visual field was detected first more than four times as often as progression in the optic disc in eyes with manifest glaucoma. Among fellow eyes without visual field loss at baseline, progression was detected first as frequently in the optic disc as in the visual field.

It is possible that the optic disc examination is not as sensitive to detect progressive change as RNFL based examination such as red-free photography or OCT RNFL thickness measurement. This is because the axons are distributed in a widespread nature in the RNFL while they are densely packed in the optic disc. In this regard, **the current finding should not be interpreted that the visual field testing detects the glaucoma progression earlier than the structural examination**. In other words, **it is possible that structural glaucoma progression might be detected earlier than in visual field testing using an RNFL based technique**. Another factor to consider is that the ability of detecting glaucoma progression of structural and functional examination may be dependent on the stage of disease. It is generally considered that progressive structural changes are detected more commonly early in the disease, whereas functional progression is observed more commonly at later stages of the disease. These factors should be considered when interpreting the result of this study.

Comment by Chris Leung, Hong Kong, P.R. China

The Early Manifest Glaucoma Trial (EMGT) is a landmark clinical trial providing important insights into the natural history and management of open-angle glaucoma. In a recent paper, Ohnell and colleagues examined the temporal relationship between detection of optic disc progression and visual field progression in 249 glaucoma patients included in the EMGT and showed that progression in the visual field was detected first more than four times as often as progression in the optic disc in glaucomatous eyes with visual field loss at baseline.

An earlier study using the time-domain OCT has already demonstrated progressive RNFL thinning to be predictive of visual field progression in glaucoma

The ability to detect change in glaucoma depends on the precision and the reliability of the instrument for visual field or optic disc measurement and the frequency of testing. In the EMGT, **optic disc progression was determined with monoscopic fundus photographs** by three disc readers. Although optic disc photography is essential for documentation of optic disc morphology and detection of optic neuropathies in clinical practice, its reliability for change detection in glaucoma has been questioned. For example, in a study investigating the agreement among glaucoma specialists in determining progressive optic disc changes using optic disc stereophotographs in glaucoma patients, Jampel and colleagues showed a weak inter-observer agreement (Jampel *et al.*, Am J Ophthalmol 2009;147:39-44). Forty percent of cases judged to have progressed in glaucoma severity were found to have the 'worse' optic disc taken at the start of the study. In fact, Ohnell and colleagues reported that the three readers individually changed 'progression' to 'no progression' in 29 cases, 14 cases and 13 cases, respectively. Subtle changes in the neuroretinal rim and the retinal nerve fiber layer (RNFL) can be difficult to discern in optic disc photographs, which may account for the inconsistency in photo grading. The higher frequency of visual field testing in the EMGT may also contribute to the earlier detection of visual field progression compared with optic disc progression. In the EMGT, visual field testing was performed at each study visit (every three months for the first four years and then every three or six months thereafter). By contrast, monoscopic fundus photographs were obtained at baseline, three months, six months and then every six months thereafter. With different frequencies of optic disc photography and perimetry during the study period, examination of the temporal relationship between optic disc and visual field progression would be complicated. Collectively, taking consideration of the signal-to-noise ratio of the measurement of interest and the testing frequency is critical for reliable assessment of optic disc and visual field progression.

While automated white-on-white perimetry has been the standard of visual field testing for more than two decades, the technology of optic disc and RNFL imaging has advanced substantially in recent years. Fourier-domain optical coherence tomography (OCT) measurements of the optic disc and the RNFL have a higher signal-to-noise ratio for change detection compared with reader's assessment of optic disc photographs. An earlier study using the time-domain OCT has already demonstrated progressive RNFL thinning to be predictive of visual field progression in glaucoma (Sehi M, *et al.* Am J Ophthalmol 2013;155:73-82). It is conceivable that Fourier-domain OCT can outperform time-domain OCT and optic disc photography for analysis of glaucoma progression.

Response by HannaMaria Öhnell on behalf of all authors

We would like to thank Dr Weinreb and the IGR editorial board f or selecting our published work for discussion, and we appreciate that the three reviewers were willing to spend time on our paper.

Several comments emphasize that different results may have been obtained if photography had been replaced with, *e.g*., OCT. We agree with that and have discussed that in the paper stressing that our comparison is between standard automated perimetry and disc photography only. We also want to point out that OCT was not available when EMGT started in 1992. Indeed there are results suggesting that modern techniques, *e.g*., OCT, may be more sensitive for detecting structural change than disc photographs, but it is crucial to control for the amount of false positives for the different instruments and the applied criteria. Another reason to favour imaging might be the fact that identifying the minute changes in optic disc configuration that we are looking for is difficult and time-consuming. The readers are encouraged to look at the 12 randomly chosen pairs of disc photographs that were published with the paper. We believe that most will agree with our view that the observed changes are so small, that it is unrealistic that they would be regularly detected in ordinary clinical management. This is probably the reason that the earlier published results based on the EMGT Disc Photography Reading Centre indicate that less than one percent of study eyes showed disc progressed before field progression.

One reviewer remarked that it is likely that glaucomatous damage becomes visible first in structure and later in function. This may well be the case, but in our study we looked for structural and functional progression in study eyes where the vast majority had such damage at study inception. Also in the fellow eyes of these patients, 20% already had glaucomatous optic discs. If one aims to find out if structural or functional damage arises first, it would be necessary to perform a prospective study of normal appearing eyes, preferably population-based. It would require a very large study population even if one would narrow it down to those with an elevated risk. The

alternative is experimental studies where results so far indicate that the processes are parallel with a substantial inter-individual variation in what type of deterioration that is detected first (Harwerth *et al.* Invest Ophthalmol Vis Sci 1999;40:2242-2250).

One reviewer suggested that the fact that fields were obtained every three months, but disc photographs only every six months may have created a bias in favour of visual fields. This is not the case, however, as we discussed in the paper. The EMGT visual field criterion required repeated deterioration at the same test locations in three consecutive field tests. For fields the date of the last test was defined as the date for progression, while the date of the first photograph when progression could be seen was defined as the date for disc progression, creating some bias in favour of discs. Still, in the study eyes with field defects at baseline visual field progression was detected first more than four times as often as optic disc progression. In the fellow eyes, a mix of seemingly normal eyes, eyes with preperimetric glaucoma, and eyes with ocular hypertension, fields and photographs revealed progression first with the same frequency.

Our results also raised the question whether the relationship of the type of changes over the course of the disease depended on the degree of damage. This is of course generally believed to be the case. We have studied this issue in a subsequent paper which has been accepted for publication in Acta Ophthalmologica, and believe that when reading the paper our colleagues will be just as surprised at the results as we were.

Meeting Highlights

Top-Eight of the Third Asia Pacific Glaucoma Congress 2016

Chiang Mai, Thailand, July 14-16, 2016




Prin Rojanapongpun, Visanee Tantisevi, Anita Manassakorn, Rath Itthipanichpong

New findings and pathogenesis in true exfoliation syndrome

True exfoliation is characterized by peeling of the translucent membrane of the anterior lens capsule. A new classification, based on a prospective observational case series of 259 Thai patients (424 eyes) on the anterior lens capsule, was proposed. Initial capsular splits occur along the insertions of disrupted anterior zonules. It is believed that the mechanical peeling is with iris movement and aqueous flow. (Chaiwat Teekhasaenee)

Genetics of exfoliation syndrome

LOXL1 gene was found to be associated with exfoliation syndrome. The new identifying gene, CACNA1A rs4926244 on chromosome 6p was recently discovered in Genome wide association analysis (GWAS) that was performed in 9,700 exfoliation syndrome and 98,000 controls. (Mineo Ozaki)

The role of neurotrophic factors in axonal regeneration of the optic nerve

The new neurotrophic factors are: glial cell line-derived neurotrophic factor (GDNF) and its genes, neuturin (NRTN) and artemin (ARTN), and their receptors (GFRα1, 2, and 3). The most effective agent against axonal injury is ARTN and GFRα3 that will be an important factor for gene therapy in the future. (Toru Nakazawa)

Gene therapy in glaucoma

Cell culture and monkey studies showed success of gene therapy in glaucoma, in either at enhancing aqueous humor outflow by targeting the outflow pathways or at reducing the aqueous production by targeting the non-pigmented epithelium. A number of viral vectors, delivered via transcorneal injection or via micro-invasive glaucoma surgical approach through Schlemm's canal, have been shown to be superior to non-viral techniques with a longer duration and high transduction efficiency. Viral vectors carrying cytoskeleton active genes can modify the outflow pathway resulting in IOP reduction for several months in monkey models. (Paul Kaufman)

Retinal ganglion cell imaging

Retinal ganglion cell death is associated with the disturbance of axonal transport and mitochondrial dysfunction. The intravital multiphoton imaging device provides sequential time lapse of mitochondria transport in a single axon in mouse. The axonal transport is more vulnerable in older than younger mice. This imaging will be benefit to predict glaucoma progression. (Masaru Inatani)

Dendrites of the retinal ganglion cell in glaucoma

Decreases in soma size, dendritic shrinkage and loss of dendritic branches of RGC were found prior to RGC apoptosis. RGC dendrites are responsive element, unlike axons which were shown unable to regenerate after injury, modulating the RGC dendrites may be the new possibility in glaucoma treatment. (Hae-Young Lopilly Park)

Wound healing modulator in glaucoma filtering surgery

Wound healing modulation has been extensively discussed in the APGC 2016 meeting. Newer wound modulating agents based on protein such as CAT-152 (Leredelimumab), a human monoclonal antibody to Transforming Growth Factor ß2 (TGF-ß2), was described. This antibody works by decreasing TGF- ß2 induced collagen production and myofibroblast-mediated contraction. Sustain-released pharmacological agents and mechanical barrier (biodegradable collagen matrix) have been under experiment to help wound modulation in glaucoma filtering surgery and in Ahmed glaucoma implant surgery. The one-year complete success rate of Ahmed valve implantation plus collagen matrix is increased to 57% in comparison to 14% in conventional Ahmed implantation. The qualified success rate is 71% and 33% in Ahmed plus collagen matrix and Ahmed alone, respectively. (Seungsoo Rho)

Rho kinase inhibitors for glaucoma treatment

IOP lowering effect of Rho-kinase inhibitor was initially reported in 2001. Up until now, ten agents are under clinical trials. Ripasudil is one that proved effective based on phase-1-3 trials. An open label study also showed its effects on secondary glaucoma besides POAG and OHT. (Hidenobu Tanihara)

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Editor's Selection

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

Robert N. Weinreb, Chief Editor

Epidemiology

Have prevalence and incidence of glaucoma changed in a decade?

Comment by Catherine Liu, Taipei, Taiwan

67610 The prevalence and the incidence of diagnosed open-angle glaucoma and diagnosed angle-closure glaucoma: changes from 2001 to 2010, Chiu SL, Chu CL, Muo CH, Chen CL, Lan SJ, Journal of Glaucoma 2016; 25: e514-e519

Primary angle-closure glaucoma (ACG) is more visually destructive than open-angle glaucoma (OAG), and its prevalence increases exponentially with age.[1,2] Using the National Longitudinal Health Insurance Database, the authors analyzed the incidence and prevalence of OAG and ACG in one million subjects from year 2001 to 2010. They found the prevalence of **both types of glaucoma increased over the years, but OAG showed a steeper trend than ACG, making it more prevalent after the year 2005.** As well, there was a significantly decreasing trend in ACG incidence over the years; more significant in woman than in men. **The authors attributed these findings to the high prevalence of myopia and increasing number of cataract surgery in Taiwan.**

The findings may not be surprising in a society where myopia is prevalent and healthcare is accessible and inexpensive, but cautions should be exercised before we draw conclusions. Population studies found most OAG patients are unaware of this disease before study examinations,[3] and ACG also may be under-diagnosed because most cases are asymptomatic until late stage.[2] In this study, ACG might be underestimated to a greater extent than OAG because ACG is more prevalent in subjects with low socioeconomic status which is a barrier to healthcare access.[4,5] Another study limitation is uncertainty about accuracy of the diagnosis coding. Sometimes it is challenging to discriminate glaucomatous damage from myopic changes. Under such circumferences, physicians may opt for coding related to OAG, resulting in overestimation of its prevalence and incidence in populations prevalent with myopia.

ACG might be underestimated to a greater extent than OAG because ACG is more prevalent in subjects with low socioeconomic status which is a barrier to healthcare access

The fact that the authors used loose criteria for case selection may increase this possibility. Despite these limitations, the study results may reflect the reality that echo findings from another study which showed the incidence of primary ACG appeared to be decreasing after reaching a peak in the late 1990s.[6]

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Quality of Life

Impact of undiagnosed glaucoma on quality of life

Comment by George Spaeth, Philadelphia, PA, USA

67442 Mental health status and quality of life in undiagnosed glaucoma patients: A nationwide population-based study, Jung KI, Park CK, Medicine 2016; 95: e3523

Jung and Park deserve congratulations for trying to eliminate a knotty problem related to understanding the relationship between glaucoma and psychological characteristics, including self-perceived quality of life. They note that prior studies have demonstrated a poorer quality of life and more depression in those with glaucoma than those without glaucoma. But is the relationship causative? That is, does glaucoma cause the depression, or does depression cause the glaucoma?? One of the many confounding factors in such studies – as pointed out by several, including Jampel *et al.*,[1] is the possible effect of knowing one has glaucoma. Because those who know they have glaucoma are more concerned about going blind than those without glaucoma it seems reasonable to assume that this, and other fears, could cause depression. Furthermore, one of the medications used to treat glaucoma, timolol, can cause depression. These and other complicating considerations have severely limit the ability of investigators to nail down a causal relationship between glaucoma and depression or quality of life; that is, having glaucoma may not CAUSE depression or decreased quality of life, and being depressed or having a poor quality of life many not CAUSE glaucoma. Association can be very close but unrelated to causation.

> One of the medications used to treat glaucoma, timolol, can cause depression

Jung and Park had the great insight that one way this problem could be addressed was to compare those who knew they had glaucoma with those who actually had glaucoma, but did not know that they did. Brilliant. **Their study, based on data from an extensive Public Health Data base in Korea, seems to show definitely that those who do actually have glaucoma but do not know they have glaucoma have more mental health problems and a poorer quality of life than those who know they have glaucoma.** Therefore, they suggest, glaucoma can be considered to be responsible for causing those problems, or those problems can be considered responsible for causing glaucoma. They quote studies purporting to show that depression can cause heart disease by effecting inflammatory cytokines. Unfortunately, their study does not demonstrate a causative relationship between mental health problems and glaucoma, either direction.

The problem, that they did not address, is that the two populations being compared in their study – (1) those who knew they had glaucoma; and (2) those who had glaucoma but did not know it – were not comparable. Population 2, **those who did not know they had glaucoma, were significantly older, thinner, sicker (with diabetes and systemic hypertension), poorer and less educated than those who knew they had glaucoma**. Because there is evidence that those who are older are more likely to be depressed than those who are younger, it is reasonable to conclude that Jung and Park's population 2 would be expected to be more depressed and have a worse self-reported quality of life than their population 1. Depression is also believed by some to be related to general health, income and education. So it is not surprising that the older, sicker, poorer and worse educated were depressed. Did those attributes cause their glaucoma? Did the depression? Or vice versa? Who knows?

> Unfortunately, their study does not demonstrate a causative relationship between mental health problems and glaucoma, either direction

They also found that those who had been diagnosed by a doctor as having depression were not more likely to have glaucoma than those with a known diagnosis of depression.

It is not big data that will provide useful insights and facts. Big data may be revealing, but only when it is properly interpreted. Consider the generally accepted belief that those who exercise are healthier and live longer than those who do not exercise. But if one bases this conclusion on the health and longevity of a huge unselected population one could explain such an apparent causative relation by saying that those who are sick do not feel well and therefor do not exercise and die younger than those who are healthy and feel well and live longer.

Ah, "*tis a puzzlement.*"

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Anatomical Structures

Schlemm's canal

Comment by Lawrence Kagemann, Pittsburgh, PA, USA

66752 Morphological abnormalities of Schlemm's canal in primary open-angle glaucoma from the aspect of aging, Hamanaka T, Matsuda A, Sakurai T, Kumasaka T, Investigative Ophthalmology and Visual Science 2016; 57: 692-706

Visualization of the aqueous humor outflow pathway is undergoing a renaissance as new imaging technologies have enabled the first non-invasive visualization of the living functioning outflow tract in human eyes. In contrast, Hamanaka *et al.* employed standard light microscopy with immunohistochemical staining, and transmission electron microscopy to examine the distal outflow tract. In this study, the authors obtained tissue blocks from 133 patients undergoing trabeculectomy. Subjects were divided into three groups: (a) primary open-angle glaucoma (POAG) patients with a family history of POAG; (b) POAG patients without a family history of glaucoma; and (c) normal-tension glaucoma subjects. Tissue obtained during trabeculectomy was fixed, stained, and imaged, and approximately three images per sample were measured and averaged.

Visualization of the aqueous humor outflow pathway is undergoing a renaissance as new imaging technologies have enabled the first non-invasive visualization of the living functioning outflow tract in human eyes

They found that **Schlemm's canal was significantly shorter in patients with a family history of POAG compared to those without**. Staining of endothelial cells allowed accurate identification of Schlemm's canal, collector channels, and Sondermann's canals. Besides comparing Schlemm's canal morphology between groups, the authors are to be commended for the characterization of the other outflow structures of the proximal outflow pathway. **The authors observed the segmental nature of Schlemm's canal, and a recurrent presence of Sondermann's canals within the trabecular meshwork.** It is my hope that characterization of these structures concurrent with and IOP and disease data will contribute to the understanding of the complex structure-function relationship between age, disease, outflow pathway morphology, and the regulation of intraocular pressure.

Morphology/outflow and structure/function data notwithstanding, enjoy this paper for the outstanding images of outflow structures!

Bruch's membrane opening

Comment by Andrew Tatham, Edinburgh, UK

66747 Does the location of Bruch's membrane opening change over time? Longitudinal analysis using San Diego Automated Layer Segmentation Algorithm (SALSA), Belghith A, Bowd C, Medeiros FA, Hammel N, Yang Z, Weinreb RN, Zangwill LM, Investigative Ophthalmology and Visual Science 2016; 57: 675-682

In order to accurately detect glaucomatous changes using optical coherence tomography (OCT), it is important that the measurements obtained are reproducible. Improved reproducibility would enhance our ability to differentiate true progression from background noise due to measurement variability, and improve the accuracy of classification of eyes using normative databases.

It has been proposed that Bruch's membrane opening (BMO) be used as a reference landmark, from which optic nerve head parameters can be estimated. For example, the minimum rim width, which is defined as the minimum distance from BMO to the internal limiting membrane, has been shown to be useful for differentiating healthy and glaucomatous eyes. In this study, Belghith and colleagues examined whether the BMO really is a stable landmark by determining whether its location changes over time.

Improved reproducibility would enhance our ability to differentiate true progression from background noise due to measurement variability, and improve the accuracy of classification of eyes using normative databases

The study included healthy controls, patients with stable glaucoma, and patients with glaucoma and progression on visual fields or stereoscopic optic disc photographs. OCT was performed six-monthly for an average of 3.7 years. Automated software, previously developed by the group (SALSA), was used to identify the BMO in each scan.

Important findings were that the location of the BMO identified by SALSA showed good agreement with manual assessment, and most importantly, **the location of the BMO was stable over three to four years of follow-up, in both healthy and glaucomatous eyes**. In other words, change in a parameter measured relative to the BMO, such a minimum rim width, is likely to reflect genuine change, rather than change in the position of the BMO alone. This suggests that measurements using BMO as a reference are likely to be anatomically stable and useful for detecting glaucoma progression.

Although the BMO can be identified manually, advantages of SALSA are that it is automated and searches for the BMO in every B scan in an OCT volume scan, unlike manual identification of the BMO, which is limited to examination of a narrow number of radial line scans.

> Measurements using BMO as a reference are likely to be anatomically stable and useful for detecting glaucoma progression

The study had some limitations. It did not include eyes with high myopia and had a relatively short follow-up. Also, eyes with advanced glaucoma were not included. It should also be emphasized that for a small number of eyes the difference between the position of the BMO identified manually and by SALSA was relatively high, indicating the continued need to review scans for segmentation errors.

Laminar structure and field loss

Comment by Andrew Tatham, Edinburgh, UK

67171 Prelamina and lamina cribrosa in glaucoma patients with unilateral visual field loss, Kim DW, Jeoung JW, Kim YW, Girard MJ, Mari JM, Kim YK, Park KH, Kim DM, Investigative Ophthalmology and Visual Science 2016; 57: 1662-1670

Structural changes to the optic nerve head in glaucoma can be divided into prelaminar and lamina cribrosa (LC) components. Prelaminar changes include thinning due to loss of neural tissue, whereas LC changes include posterior migration and excavation beneath the anterior scleral canal associated with connective tissue remodeling. This study investigated whether patients with a glaucomatous visual field defect in one eye, but normal visual field in the other, exhibit prelaminar or LC structural changes in the perimetrically unaffected eye.

> Changes to prelaminar tissue may manifest prior to RNFL and visual changes in some individuals

Swept Source OCT was used to assess 3 parameters: (1) anterior prelaminar depth; (2) prelaminar tissue thickness; and (3) LC depth, all measured relative to a reference line at Bruch's membrane opening. The study included patients with unilateral glaucomatous visual field loss and a similar number of age-matched healthy controls.

The results of the study confirmed that glaucomatous eyes often have significant changes to the prelaminar and LC tissues. Eyes with glaucomatous visual field loss had thinner prelaminar tissue, greater anterior prelaminar depth and greater LC depth than fellow eyes and eyes of healthy subjects. However, **fellow eyes also had significantly thinner prelaminar tissue and**

greater prelaminar depth than controls, despite having normal visual fields and similar retinal nerve fiber layer (RNFL) thickness as the healthy eyes. This suggests that changes to prelaminar tissue may manifest prior to RNFL and visual changes in some individuals. In addition, **eyes with higher initial intraocular pressure (IOP) tended to have thinner prelaminar tissue, suggesting that IOP-related stress may affect prelaminar tissue early in the disease process**.

The study suggests that OCT assessment of prelaminar and LC structures may allow earlier detection of glaucoma than some currently used parameters

Of course it is important to acknowledge that this was a cross-sectional study and longitudinal studies are needed to better elucidate the temporal relationship between prelaminar, LC, RNFL and visual field changes. In addition most of the patients with glaucoma had untreated IOP of ≤ 21 mmHg. It is conceivable that the temporal relationship of glaucomatous changes may differ depending on the relative contribution of IOP-dependent and independent factors to the pathogenesis. Nevertheless, the study suggests that OCT assessment of prelaminar and LC structures may allow earlier detection of glaucoma than some currently used parameters.

Deep ONH structures in NTG

Comment by Chris Leung, Hong Kong, P.R. China

67189 Comparison of the deep optic nerve head structure between normal-tension glaucoma and nonarteritic anterior ischemic optic neuropathy, Lee EJ, Choi YJ, Kim TW, Hwang JM, PLoS ONE 2016; 11: e0150242

Lee and colleagues compared the anterior lamina cribrosa surface depth (ALCSD) and prelaminar tissue (PT) thickness among 21 non-arteritic anterior ischemic optic neuropathy (NAION) patients, 42 normal-tension glaucoma (NTG) patients and 42 healthy subjects and showed that the **ALCSD was greater and the PT thickness was smaller in NTG patients compared with NAION patients** after matching the severity of optic nerve damage between the groups. Although the results highlight the differences in the pathophysiology between NAION and glaucoma, and indicate the relevance of ALCSD and PT thickness measurements in the discrimination between NAION and NTG, the data should be interpreted with reference to the potential limitations in the study design. As most NAION patients have small optic cups, it is not surprising to observe a small ALCSD in NAION. In fact, ALCSD was not only smaller in the NAION patients (390.1 µm) compared with the NTG patients (494.2 µm), but also compared with the normal subjects (427.3 µm) although the difference was not statistically significant. Using only three horizontal

B-scans and three radial B-scans for measurements of ALCSD and PT thickness, respectively, local changes of lamina cribrosa depth and PT thickness consequential to NAION or NTG would be missed.

As most NAION patients have small optic cups, it is not surprising to observe a small ALCSD in NAION

Further, eyes with NTG had a longer axial length than the other groups and it is unclear if the differences in ALCSD and PT thickness between NAION and NTG would be explained by the difference in refractive errors (tilted optic disc configuration is not uncommon in eyes with myopia). Differentiation between glaucomatous from non-glaucomatous optic neuropathies can be challenging in clinical practice. It is hopeful that optical coherence tomography can augment the diagnostic precision for detection of different forms of optic neuropathies.

Pressures behind the lamina

Comment by Hans Peter Killer, Basel, Switzerland

67346 Intracranial pressure (ICP) and optic nerve subarachnoid space pressure (ONSP) correlation in the optic nerve chamber: the Beijing Intracranial and Intraocular Pressure (iCOP) Study, Hou R, Zhang Z, Yang D, Wang H, Chen W, Li Z, Sang J, Liu S, Cao Y, Xie X, Ren R, Zhang Y, Sabel BA, Wang N, Brain Research 2016; 1635: 201-208

Recent literature has discussed the influence of a pressure gradient between the intraocular pressure (IOP) and the pressure in the subarachnoid space (SAS) of the optic nerve on glaucoma pathogenesis. Hou *et al.* present an interesting paper on cerebrospinal fluid (CSF) pressure performed in eight healthy dogs. They report on a thorough animal model that allows for simultaneous measurement of cerebrospinal fluid (CSF) pressure in three CSF spaces: the lumbar site, intracranially and in the SAS of the optic nerve. The paper challenges the current view that CSF pressure is homogenous in all CSF spaces, *e.g.*, lumbar CSF pressure, ventricular CSF pressure (ICP) and the optic nerve sheath pressure (ONSP). In addition to the CSF pressure, the pressure in the anterior chamber was measured as well.

The paper challenges the current view that CSF pressure is homogenous in all CSF spaces

At baseline, the authors found different pressures in the different CSF spaces with the highest pressure in the anterior chamber, followed by the ventricular pressure and the lumbar pressure. The lowest pressure was found within the optic nerve sheath

(subarachnoid space). **When CSF was shunted, the ICP gradually decreased together with the optic nerve sheath pressure in a linear fashion. When the CSF pressure was further decreased to what the authors call a critical breakpoint, ICP and optic nerve sheath pressure became uncoupled and the optic nerve sheath pressure remained constant despite further ICP lowering** (ICP independent zone). This phenomenon was described as a communication arrest between the ICP and the optic nerve sheath pressure. This phenomenon was called optic nerve sheath compartmentation by other authors in previous work carried out with computed assisted cisternography.[1]

It clearly contradicts the idea of a continuous CSF pressure and flow on an experimental base

The results of this experimental study sheds light on concepts such as the translaminar pressure gradient and the optic nerve sheath compartmentation syndrome. Both concepts are thought to be involved in the pathogenesis of normal-tension glaucoma. Applying the Bernoulli equation, the pressure differences found between the single CSF spaces can help to explain the development of CSF compartmentation.

This paper is indeed especially interesting for the study of optic nerve sheath compartmentation as it clearly contradicts the idea of a continuous CSF pressure and flow on an experimental base. The experiment also renders data concerning the concept of the translaminar pressure gradient as a component of glaucomatous optic nerve damage.

I would like to congratulate the authors for this carefully performed experiment and the clear conclusions they draw form their data.

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Basic Science

Hypoxia and trabecular function

Comment by Miriam Kolko, Roskilde, Denmark

67489 Hypoxia-induced changes in DNA methylation alter RASAL1 and TGFβ1 expression in human trabecular meshwork cells, McDonnell F, Irnaten M, Clark AF, O'Brien CJ, Wallace DM, PLoS ONE 2016; 11: e0153354

Although increased intraocular pressure (IOP) is not the only cause of glaucomatous neurodegeneration, IOP-lowering drugs remain the only successful treatment option. Hence, changes in the trabecular meshwork (TM) that lead to reduced outflow is an appropriate target to investigate. Fibrosis and a hypoxic environment have been associated with changes in the TM and the present study claims that changes in DNA methylation drives fibrosis in TM cells and that DNA methylation is driven by hypoxia. In order to explore their hypothesis, TM cells were isolated from control donor eyes (NTM) as well as from glaucomatous donor eyes (GTM).

DNA methylation has increasingly been the subject of intense interest because of its recognized role in various diseases. Therefore, the particular impact on DNA methylation in TM outflow needs to be confirmed by functional studies to confirm the relevance of such in glaucoma progression

Gene and protein expressions were investigated in the two groups. Finally, NTM cells were exposed to hypoxia. The study revealed different gene expression profiles in NTM cells were compared to GTM cells with regards to profibrotic transforming growth factor (TGFβ1) and antifibrotic Ras protein activator like 1 (RASAL1), both enzymes that contribute to global DNA methylation. **Hypoxia resulted in similar changes in NTM cells as observed in GTM cells**. In this matter, induction of DNA methylation as well as DNA Methyltransferase 1, TGFβ1 and RASAL1 expression were identified in both GTM cells as well as in NTM cells after exposure to hypoxia. **The authors conclude that DNA methylation, TGFβ1 and RASAL1 appear to have an interacting relationship that may play a role in driving profibrotic disease progression in the glaucomatous TM**. Overall, the study is well performed and draws attention to fibrotic changes in the TM as a future target to lower the rate of glaucoma progression. Nevertheless, DNA methylation has increasingly been the subject of intense interest because of its recognized role in various diseases. Therefore, the particular impact on DNA methylation in TM outflow needs to be confirmed by functional studies to confirm the relevance of such in glaucoma progression.

Neuroprotection 1

Comment by Adriana DiPolo, Montreal, PQ, Canada

67595 Inhibition of the classical pathway of the complement cascade prevents early dendritic and synaptic degeneration in glaucoma, Williams PA, Tribble JR, Pepper KW, Cross SD, Morgan BP, Morgan JE, John SW, Howell GR, Molecular Neurodegeneration 2016; 11: 26

Retinal ganglion cells (RGCs) are highly compartmentalized neurons: they are endowed with dendrites, the specialized processes responsible for collecting and processing information within the retina, and with long-projecting axons that reach visual targets in the brain. RGC dendrites receive synaptic inputs from bipolar and amacrine cells, thus playing a crucial role in cell-to-cell communication and flow of visual information. It is increasingly recognized that pathological changes in RGC dendrites occur early in glaucoma and precede overt soma or axonal loss. However, the precise mechanisms triggering RGC dendritic deficits remain poorly understood.

This is an interesting and valuable study that identifies the neuroinflammatory mediator C1q as an important regulator of early dendritic and synaptic deficits in glaucoma

An intriguing observation in recent years is that the classical complement cascade, which typically plays a role during inflammation, can also contribute to the selective pruning of dendrites and synapses during central nervous system development. In this new study, Williams and colleagues tested the hypothesis that C1q, a component of the complement system, plays a role in early synapse loss and dendritic atrophy in glaucoma. The authors demonstrate that **synaptic atrophy occurs at early disease stages using two glaucoma models: DBA/2J mice and rats subjected to ocular hypertension by injection of magnetic microbeads**. Importantly, **C1q inhibition by genetic ablation or with pharmacological blockers preserved RGC dendrites and their synapses**. These data support a role for early C1q-mediated RGC dendritic pruning and synapse loss in glaucoma.

This study was carefully designed and rigorously executed. The observation that C1q contributes to dendritic alterations in different glaucoma models and species lends credibility to the findings. The authors recognize the possibility of potential regional bias using the DiOlistic labeling of dendritic arbors, a method that involves delivery of dye-coated particles to flat-mounted retinas using a gene gun system. In their favor, no apparent loss of selective RGC types was found. It will be of interest, nonetheless, to reproduce the current findings using novel genetic tools that allow visualization of RGC subtypes. Given the impressive protective effect of

C1q inhibition on RGC dendritic structure, it will be helpful to evaluate the implications of C1q blockade on RGC function. All in all, this is an interesting and valuable study that identifies the neuro-inflammatory mediator C1q as an important regulator of early dendritic and synaptic deficits in glaucoma.

Neuroprotection 2

Comment by Brad Fortune, Portland, OR, USA

67276 Axonal transport along retinal ganglion cells is grossly intact during reduced function post-injury, Fahy ET, Chrysostomou V, Abbott CJ, van Wijngaarden P, Crowston JG, Experimental Eye Research 2016; 146: 289-292

This recent brief report by Fahy *et al.* found that when young or older mice were exposed to an acute episode of elevated intraocular pressure (IOP, 50 mmHg for 30 minutes in one eye), there was no effect on axonal transport assessed five to seven days later. In their study, the investigators evaluated bulk anterograde axonal transport using bilateral intravitreal injections of fluorescently labeled cholera toxin beta (CTB) and post-mortem microscopic images of the superior colliculi obtained 48 hours after CTB injection. This assay works in C57BL/6J mice (and in pigmented rats, as had been shown previously) because > 95% of retinal ganglion cell (RGC) axons cross to synapse in the contralateral superior colliculus. Thus, the integrity of anterograde axonal transport for a given optic nerve can be compared to the fellow eye optic nerve by comparing fluorescence between the right and left superior colliculi. The investigators confirm this in a pair of control experiments in which CTB was either omitted from the injection in one eye or was injected after pre-treatment by intravitreal injection of colchicine to disrupt microtubules and axonal transport. In both cases, there was a gross asymmetry of fluorescence intensity across hemispheres of the superior colliculus. In contrast, **when young (age three months, N = 8) or older mice (18 months, N = 8) were exposed to 30 minutes of 50 mmHg in one eye, there was no defect of anterograde axonal transport evident in either group when assayed five to seven days later.** This result is interesting in the context of previous results published by this group[1] which demonstrated substantial reduction at the same time point of the electroretinogram feature known as the positive scotopic threshold response (pSTR), a signal known to depend on intact RGC function. Moreover, the results of that previous ERG study showed a clear age effect in that older mice experienced a larger decline and less recovery of the pSTR specifically after the same IOP challenge. This apparent contrast was highlighted by the authors as one of prominent findings of their newer axonal transport study: *"Impaired recovery of inner retinal function 1 week following acute IOP injury in old mice is not associated with changes in active axonal transport in RGCs at this time."* Further: *"Our results suggest that significant RGC electrical dysfunction can occur under conditions of normal axonal transport."* It should be noted, however, that **no ERG recordings were made during the present study on axonal transport, so the**

comparison is limited to historical results. Similarly, the previous ERG study did not include RGC or axon counts to document what degree, if any, of anatomical loss was associated with the marked functional deficit following this acute, sub-ischemic episode of acute IOP elevation. It is perhaps even more interesting if such functional loss occurs without any neuronal loss, nevertheless it should stimulate further exploration and explanation.

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Neuroregeneration

Comment by Derek Welsbie, Baltimore, MD, USA

66837 Transplanted neurons integrate into adult retinas and respond to light, Venugopalan P, Wang Y, Nguyen T, Huang A, Muller KJ, Goldberg JL, Nature communications 2016; 7: 10472

Neuroregenerative strategies for glaucoma and other optic neuropathies will necessarily need to tackle the issue of retinal ganglion cell (RGC) replacement. Conventional thinking has been that exogenous, intravitreally-injected RGCs would have difficulty integrating into the retina, forming appropriate connections and regenerating axons that target the correct regions of the brain. In the February 2016 issue of *Nature Communications*, Venugopalan *et al.* used cross-species transplantation of primary RGCs to demonstrate that many of these challenges can be successfully overcome.

There are still significant challenges confronting RGC transplantation

Using a technique called immunopanning, primary RGCs can be isolated from mouse retina using antibodies against the RGC surface antigen, Thy1/CD90.[1] The Goldberg lab had previously labeled primary mouse RGCs and demonstrated that these donor cells could be visualized in the immune-privileged retina of a normal host rat, up to one week after intravitreal injection.[2] In the current work, the authors more thoroughly characterize the fate of these donor cells. Looking up to one month after injection, the authors found labeled RGCs integrated into the ganglion cell layer, the majority with evidence of neurite outgrowth and some with appropriately-stratified dendritic trees in the inner plexiform layer**.** Moreover, some cells expressed synaptic markers while others even displayed the canonical RGC ON-OFF electrophysiological response when stimulated with light. Finally, the **authors found examples of donor RGCs with regenerated axons that found their way to the optic nerve head and back to visual structures in the brain.**

While certainly promising, especially as groups are developing methods to produce a source of donor *human* RGCs using embryonic stem (ES) and induced pluripotent stem (iPS) cells,[3] there are still significant challenges confronting RGC transplantation. First, only 10% of injections led to integration and even then, only 1-7% of cells survived, with far fewer actually managing to send axons back to the brain. Furthermore, while the mere presence of electrophysiological activity was exciting, the patterns were abnormal and immature-appearing. Future work will almost certainly focus on characterizing longer time points to see if further maturation occurs, augmenting the process by modulating cell death/axon regeneration pathways and establishing that transplantation is possible in diseased retinas.

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Experimental glaucoma

Comment by John Morrison, Portland, OR, USA

67161 A magnetic microbead occlusion model to induce ocular hypertension-dependent glaucoma in mice, Ito YA, Belforte N, Cueva Vargas JL, Di Polo A, Journal of Vision Exp 2016, Mar 23;(109):e53731. doi: 10.3791/537310

Understanding mechanisms of glaucomatous optic nerve damage is essential for developing new treatments to modulate axonal injury. This relies heavily on the development of reliable animal models of chronically elevated intraocular pressure (IOP). While several models have been developed for rodents over the years, injection of microbeads in the anterior chamber has gained increased popularity, due to surgical simplicity and a greater degree of success.[1,2] Samsel *et al.* subsequently modified this approach by injecting magnetic microspheres and directing them into the anterior chamber angle with a magnet to improve efficiency of aqueous outflow obstruction.[3]

While specific methods for producing this model in rats appeared in an earlier volume of this journal,[4] Ito *et al.* present a step-by-step description of producing this model in mice. They provide important details that help overcome the specific challenges presented by these small eyes, and the accompanying video nicely details specifics that are difficult to convey in words, such as microneedle construction and the injection technique.

Full documentation of the complete IOP response would further strengthen the utility of this model

The authors nicely document the IOP elevation and retinal ganglion cell and axonal effects in this model. **Although total axon counts were found to be significantly reduced three weeks after injection, there was no further reduction by six weeks, despite continued elevation of IOP.** The authors suggest that longer durations of observation may be required. However, initial IOP responses, not documented during the first few days after injection, could also be much higher than anticipated, which could lead to this initial injury, particularly in these small, more vulnerable eyes. Additionally, while IOP's are rightly carefully documented in awake animals, this is restricted to day-time measurements. Since IOP in mice is normally elevated in the dark phase of the circadian cycle,[5] outflow obstruction may result in additional, significant night-time IOP elevations. Full documentation of the complete IOP response would further strengthen the utility of this model.

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Clinical examination methods

Outflow facility

Comment by Makoto Aihara, Tokyo, Japan

67303 Measurement of outflow facility using iPerfusion, Sherwood JM, Reina-Torres E, Bertrand JA, Rowe B, Overby DR, PLoS ONE 2016; 11: e0150694

Aqueous humor dynamic is still based on the classic formula known as the Goldmann equation. So far, there are many discussions as to this formula. However, this most fundamental mechanism of IOP has not been clarified. Animal models are needed to develop this question, but big challenges are present in small eyes, especially in mouse eyes. One of the factors can be measured in aqueous dynamics, outflow facility, is still under debate in its pressure dependency.

Sherwood *et al.* developed the new device to measure mouse outflow facility incorporating an actuated pressure reservoir, thermal flow sensor, differential pressure measurement and a computer interface called *iPerfusion*™ in enucleated eyes. As a result, using several tens of B6 mice, outflow facility was best fit in the lognormal distribution and was individually different with six-fold variability.

In this study, outflow facility was well calculated based on the calibrated flow system and statistical analysis. However, there are many limitations as well discussed in the article. As mentioned, one of the issues is that this perfusion system was done in the enucleated eyes. In this incubated eyes, the episcleral venous pressure and the intraorbital pressure have been ignored. Denervation and no blood circulation are also big issues. Subchoroidal negative pressure will be definitely affected. Thus, in *in-vivo* eyes, the result will change. Hopefully, in future, these systems will contribute to clarify the aqueous dynamics in animal models. However, fundamental issues

abound. Especially, still we do not histologically know the real outflow pathway otherwise than the conventional outflow. Even in the conventional outflow, the flow may be variable in the parts of trabecular meshwork, Schlemm's canal, and collector channel. Even more, the unconventional outflow and the pressure in its unknown destinations should be investigated.

Retinal venous flow

Comment by Murray Johnstone, Seattle, WA, USA

67231 Phase and amplitude of spontaneous retinal vein pulsations: An extended constant inflow and variable outflow model, Levine DN, Bebie H, Microvascular Research 2016; 106: 67-79

Patients with glaucoma have both a lower amplitude and reduced presence of spontaneous venous pulsations. The amplitude of venous oscillations is thought to be proportional to the amplitude of the transmural driving forces and to venous capacitance. Pulse amplitudes increase when intraocular pressure (IOP) increases but other parameters may also contribute to venous pulsations.

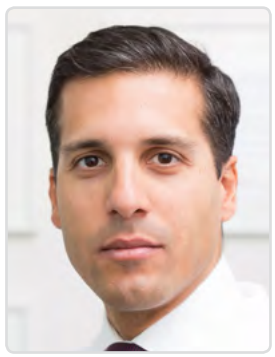
Parameters including intralaminar resistance, alterations in cerebrospinal fluid pressure (CSVP), CSFP oscillations and phase differences may also be important factors. In this study, Levin *et al.* explore the hypothesis that in chronic glaucoma the above parameters and resultant combination of forces may explain a reduction in amplitude of retinal vein oscillations.

The phase of vein and IOP oscillations predicted by CIVO has been unclear and controversial

A constant venous inflow and variable outflow (CIVO) theory has previously been used to predict spontaneous retinal vein pulsations. However, the phase of vein and IOP oscillations predicted by CIVO has been unclear and controversial. In an attempt to clarify relationships, the authors have extended the CIVO model to a larger domain that includes not only the intraocular but also the retrobulbar portion of the veins and the intervening resistance in the lamina cribrosa. This latter model posits that intraocular venous pulsations vary depending on the relative difference between means of IOP and CRVP, differences in amplitudes and differences in phase of IOP and CRVP oscillations. The authors' modeling demonstrates changes in intraocular venous pulse amplitudes that vary in response to changes in the new parameters they introduce into their model.

Model imitations include a paucity of available data related to both mean and oscillations of CSFP surrounding the optic nerve, particularly while subjects are upright. The paper nonetheless extends the conceptual framework that needs to be considered in relation to CRV pulsations. If future technologies can better define CSFP parameters *in vivo*, the author's model might prove to be useful for interpreting clinical finding in glaucoma patients.

Retrobulbar blood flow



Comment by Kaweh Mansouri, Lausanne, Switzerland

66622 Inter-device reproducibility of retrobulbar blood flow velocity measurements in healthy subjects using color Doppler imaging, Vercellin Alice CV, Cutolo CA, Dellafiore C, Lava M, Tinelli C, De Silvestri A, Calliada F, Milano G, Journal of Ultrasound 2016; 19: 125-130

The 'vascular' glaucoma theory implicates IOP-unrelated mechanisms such as reduced blood flow, suggesting that impaired regulation of ocular blood flow results in periods of relative ischemia and repeated reperfusion damage to the optic nerve. Color Doppler Imaging (CDI) can measure blood velocity but not actual blood flow. Using this device, velocity measurements have been reported for the ophthalmic, central retinal, and posterior ciliary arteries in different cohorts of glaucoma patients and healthy subjects. Most studies show impaired orbital blood flow in POAG. There are, however, important disparities including contradictory findings in between studies. The main reason, however, is the operator-dependent nature of CDI, leading to low reproducibility of measurements.[1] Furthermore, CDI is an expensive device (> $100.000) and, therefore, not readily available.

> Data from CDI studies seem to support the hypothesis whereby glaucoma is related to compromised ocular blood flow

In this small but well-designed study Vercellin *et al.* evaluate the inter-device reproducibility of two widely-used CDI devices. Two ophthalmologists and two radiologists perform CDI measurements on ten eyes of young, healthy subjects. They found unacceptably low intra-device reproducibility (0.15 < CCC < 0.37, Lin's concordance correlation coefficient), with low precision (0.18 < Pearson's r < 0.47). **Their results show that inter-device agreement is adversely and significantly affected by low precision of measurements, which in return is likely the result of high intra-subject variability**.

The issue of intra-subject and intra-observer variability can be addressed through strict acquisition protocols and training. The lack of agreement between devices, however, is harder to address. As a consequence, data from different centers using different CDI devices are not comparable. In addition, creation of normative databases become more challenging.

Despite inconsistencies, data from CDI studies seem to support the hypothesis whereby glaucoma is related to compromised ocular blood flow. However, their numerous shortcomings have discouraged a generation of researchers from entering the field of ocular blood flow and prompted them to seek safer and less uncontroversial research activities.

Enter OCT-angiography (OCT-A) with its ease of use and higher degree of repeatability and reproducibility. Although it does not measure blood flow directly (for now) and may not replace CDI (for now), OCT-A will likely increase research efforts into this field. Thanks to this technology, advances in understanding vascular factors in glaucoma are expected for the near future.

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Progression of structural and functional damage

Comment by Ki Ho Park, Seoul, South Korea

67229 Risk of visual field progression in glaucoma patients with progressive retinal nerve fiber layer thinning: A 5-year prospective study, Yu M, Lin C, Weinreb RN, Lai G, Chiu V, Leung CK, Ophthalmology 2016; 123: 1201-1210

By analysis of the serial retinal nerve fiber layer (RNFL) thickness values for 139 primary open-angle glaucoma patients followed up on for at least five years, the authors prospectively investigated whether progressive RNFL thinning can be considered to be predictive of progressive visual field (VF) loss.

Progressive RNFL thinning was determined by event analysis (Guided Progression Analysis [GPA]) and trend analysis (Trend-based Progression Analysis [TPA]) of serial registered RNFL thickness maps. VF progression was detected according to the Early Manifest Glaucoma Trial (EMGT) ('likely progression') and pointwise linear regression (PLR) criteria (^{3} three contiguous locations with sensitivity change < 0 decibels [dB]/year at $P < 0.01$).

> Progressive RNFL thinning can predict future VF progression and, therefore, can be considered to be an outcome measure in clinical trials evaluating glaucoma treatments

In the results, a total of 65 (27.1%) and 117 eyes (48.8%) showed progressive RNFL thinning based on the GPA and TPA, respectively, and 30 (12.5%) and 39 eyes (16.3%) showed VF progression per the EMGT and PLR criteria, respectively. Progressive RNFL thinning predicted the

development of VF progression: the hazard ratios (HRs) after controlling for baseline covariates were 8.44 (EMGT criteria) and 5.11 (PLR criteria) for TPA and 3.95 (EMGT criteria) and 3.81 (PLR criteria) for GPA.

This is the first paper reporting, based on a prospective study, that progressive RNFL thinning indicates increased risk of subsequent VF progression. Another strength of this paper is the fact that the progression analysis for RNFL thickness change was both event- and trend-based. The trend analysis, furthermore, detected more cases with progression and also showed higher HRs for prediction of the development of VF progression than did the event analysis.

The limitations of the study are: (1) the relatively large proportion of excluded subjects (84 patients) due to poor VF performance; (2) the shorter follow-up for normal healthy eyes (eight weeks).

Notwithstanding these limitations, the paper provides important evidence that OCT-based progression analysis of RNFL thickness – which is to say, progressive RNFL thinning – can predict future VF progression and, therefore, can be considered to be an outcome measure in clinical trials evaluating glaucoma treatments.

Glaucoma and myopia

Glaucoma diagnosis in myopic eyes

Comment by Toru Nakazawa, Miyagi-ken, Japan

67243 Diagnostic accuracy of optical coherence tomography and scanning laser tomography for identifying glaucoma in myopic eyes, Malik R, Belliveau AC, Sharpe GP, Shuba LM, Chauhan BC, Nicolela MT, Ophthalmology 2016; 123: 1181-1189

Malik *et al.* evaluated the accuracy of optical coherence tomography (OCT) and confocal scanning laser tomography (CSLT) in the diagnosis of glaucoma in myopic eyes. In Asia, where myopia is more common than in Western countries, myopia is especially important as a risk factor for normal tension glaucoma (NTG). Commonly, glaucoma is diagnosed based on a characteristic appearance of the optic nerve head (ONH), including undermining of the cup and rim thinning, and on corresponding visual field loss. In myopic eyes, however, disc appearance can vary significantly, making the diagnosis of glaucoma based on structural factors such as ONH morphology very difficult. In particular, myopic eyes have temporally tilted discs with peripapillary atrophy (PPA), confusing the interpretation of OCT topographical measurements of the ONH. In this study, the authors attempt to improve the accuracy of glaucoma diagnosis in myopic eyes with the use of new OCT-measured rim parameters. These parameters are based on Bruch's membrane opening (BMO) rather than the conventionally used optic disc margin (DM). Previously, the authors described a new parameter that measured the minimum distance

between the BMO and the internal limiting membrane, which they termed 'BMO-minimum rim width' (BMO-MRW). They found that BMO-MRW represented the amount of neuroretinal rim tissue more accurately than conventional DM-based parameters.

BMO-MRW was more sensitive than DM-RA and similar to RNFL thickness in the identification of glaucoma in myopic eyes

The primary aim of this study was to evaluate the diagnostic accuracy of BMO-MRW, DM-based rim assessments (DM-RA), based on CSLT, and RNFL thickness by comparing their ability to distinguish myopic patients with and without glaucoma. **The authors found that at a sensitivity of 90%, DM-RA had a specificity of 30%, and BMO-MRW and RNFL thickness both had a specificity of 71%**. Thus, BMO-MRW was more sensitive than DM-RA and similar to RNFL thickness in the identification of glaucoma in myopic eyes. These objective parameters offer a valuable diagnostic tool for patients with glaucoma and a myopic optic disc, and may help not only clinical research into the structure and function of the glaucomatous eye, but also follow-up care for glaucoma patients with myopia.

Glaucoma progression and myopia


Comment by Chungkwon Yoo, Seoul, Korea and Shan Lin, San Francisco, CA, USA

67575 Progression of primary open-angle glaucoma in asymmetrically myopic eyes, Song MK, Sung KR, Han S, Lee JE, Yoon JY, Park JM, Lee JY, Graefe's Archive for Clinical and Experimental Ophthalmology 2016; 254: 1331-1337

Although myopia is a well-established risk factor for development of open-angle glaucoma (OAG),[1-3] there remains controversy regarding its role in glaucoma progression.[4-7] Recent studies have negated its role as a risk factor, and some even demonstrated its protective role against progression.[5-7]

Sung and colleagues explored this issue by comparing glaucoma progression in asymmetrically myopic eyes within the same subjects. **They found no difference in glaucoma progression between the more myopic eye and the less myopic eye** in visual field (VF) or retinal nerve fiber layer analyses in their 55 patients. This corroborates the authors' earlier observations that myopia was not associated with glaucoma progression. This information may have an important clinical implication because it helps clinicians make an appropriate treatment strategy for myopic eyes with glaucoma.

By assessing asymmetrically myopic eyes of the same patient, other risk factors could be controlled. However, this study is limited by a retrospective design, relatively small sample size, and lack of treatment information. Also, the low mean untreated IOP (16.1 mmHg) suggests inclusion of predominantly normal-tension glaucoma (NTG) patients. Notably, many of the recent studies on myopia and glaucoma progression were conducted in NTG-prevalent countries.[5-7] Therefore, further studies are necessary in OAG with high IOP.

Recent studies have negated myopia's role as a risk factor, and some even demonstrated its protective role against progression

Another consideration worthy of note is the microscopic characteristics of peripapillary atrophy (PPA). Beta-zone PPA, which has been linked to glaucoma progression, can be classified into PPA+BM and PPA-BM, according to the presence of Bruch's membrane.[8,9] PPA+BM has been associated with the progression, whereas PPA-BM (γ-zone PPA) has not. In this study, more myopic eyes had a higher PPA to disc area ratio, which may be attributed to possible inclusion of more PPA-BM. It would be interesting to study whether the microscopic characteristics of PPA had any influence on the study outcomes.

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Glaucoma and systemic diseases

IOP and hyperglycemia


Comment by Lucy I. Mudie and David Friedman, Baltimore, MD, USA

67227 Increased intraocular pressure and hyperglycemic level in diabetic patients, Hymowitz MB, Chang D, Feinberg EB, Roy S, PLoS ONE 2016; 11: e0151833

The relationship between hyperglycemia, diabetes mellitus (DM) and glaucoma has been subject to scrutiny in many population based studies, as well as systematic reviews and meta-analysis. Neither the Baltimore Eye Survey nor the Rotterdam Eye Survey found an association between DM and POAG, however a recent meta-analysis reported that those with diabetes have 1.5 times the risk of glaucoma as those who do not have diabetes.[1] Hymowitz *et al.* retrospectively reviewed 114 charts of patients with non-proliferative diabetic retinopathy who did not have glaucoma. The group had poorly-controlled diabetes with a mean HbA1c above 8%. Rather than analyze the data using continuous values, the authors compared those with IOP < 14.5 to those with IOP of 14.5 mmHg or higher, and found that HbA1c was higher in those with higher IOP (9.0% versus 8.1% respectively). **Furthermore, none of those with HbA1c above 9.5% had IOP < 14.5 mmHg.**

The authors found that HbA1c was higher in those with higher IOP

The relationship between HbA1c does not appear linear, however, and at HbA1c levels lower than 9.5% the association with IOP appears minimal at best. The authors only provide a cursory analysis of the data, and details about those excluded are not provided. Furthermore, it is unclear how IOP data were handled for both eyes; was an average IOP used or did each eye of a subject individually contribute to the results? It is also unclear whether any covariates were adjusted for in this analysis.

The authors support their results with their prior mouse study showing that hyperglycemia induces changes in the extra cellular matrix of the trabecular meshwork, potentially leading to decreased outflow of aqueous humor and increased IOP. **Despite limitations, the author's finding that in this set of patients those with very high HbA1c almost never had a low IOP is intriguing and would be worth confirming.**

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Medical Treatment

Improving adherence to treatment

Comment by Anja Tuulonen, Oulu, Finland

67327 Effectiveness and cost of a personalized reminder intervention to improve adherence to glaucoma care, Pizzi LT, Tran J, Shafa A, Waisbourd M, Hark L, Murchison AP, Dai Y, Mayro EL, Haller JA, Applied health economics and health policy 2016; 14: 229-240

In the out-patient clinics of the authors, about one third of patients are lost to follow-up due to cancelling the visit without rescheduling or simply not showing up. Although the adherence to medical treatment has been relatively widely studied, little research is published on interventions increasing follow-up adherence.

Little research is published on interventions increasing follow-up adherence

This prospective study was ran at Wills Glaucoma Service during 14 months in 2012-13. Eligible patients were randomized to either usual care or intervention group. The sample size calculation was based on assumption of 50% decrease in losses of follow-up. Patients under usual care did not receive any reminders prior to the scheduled visit while the intervention group received a letter two weeks prior to the appointment and a phone call two to three days before the visit with an extra cost of US$ 11 per patient. The primary outcome measure was percentage of patients attending the planned visit. The adherence window for one-month visit was two weeks, one month for three-month visits and two months window for six-month visits. The cost analysis was conducted from the perspective of health care provider.

The results of the study indicate that a low cost reminder intervention may improve appointment adherence

The overall adherence of the 126 patients of usual care group was 69% compared to 82% in the 130 patients in the intervention group. Younger patients (< 65 years) with short interval between follow-up visits (one month), new to the service and without secondary insurance were prone to miss an appointment. **The Incremental cost-effectiveness ratio (ICER) was US$ 74 per follow-up attended.**

The results of the study indicate that a low cost reminder intervention may improve appointment adherence and encourages the care givers and patients to innovate simple reminders, *e.g.*, by implementing different cell phone applications.

PS - There is a typo in the paper of Pizzi *et al.* when they refer to number of patients with glaucoma in 2010 (page 230, ref. 3 Quigley): Quigley's estimate was 79.6 million, not 9.6 million as now written in the article.

Investigational new drugs

Comment by Fotis Topouzis, Thessaloniki, Greece

67228 A dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of 2 and 4 weeks of twice-daily ocular trabodenoson in adults with ocular hypertension or primary open-angle glaucoma, Myers JS, Sall KN, DuBiner H, Slomowitz N, McVicar W, Rich CC, Baumgartner RA, Journal of Ocular Pharmacology and Therapeutics 2016; 0:

Adenosine and its receptors seem to play a role in modulating IOP. Specifically, selective A1 receptor agonism has been shown to lower IOP. The lowering of IOP is due to increasing conventional outflow by increasing the secretion of matrix metalloproteinase-2 (MMP-2). MMP-2 digests hydrolyzed collagen type IV a major component of extracellular matrix (ECM) in the trabecular meshwork™. Trabodenoson is a highly selective adenosine mimetic targeting A1 receptor with a potential to lower IOP via a novel mechanism of action: by increasing outflow facility at the trabecular meshwork thus increasing the outflow of aqueous humor via the conventional pathway. In this multi-center, randomized, double-masked, placebo-controlled, dose-escalation Phase-2 Study, Jonathan Meyers and co-authors assess trabodenoson's safety, tolerability, and IOP lowering efficacy in subjects with ocular hypertension (OHT) or primary open-angle glaucoma (POAG).

Trabodenoson represents a potential new class of IOP lowering drug therapy with a novel mechanism of action

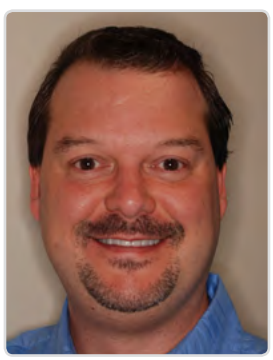
Patients received unilateral topical twice daily trabodonoson (50, 100, or 200 mcg) or placebo for 14 days, or 500 mcg trabodenoson or placebo for 28 days. Intraocular pressure (IOP) was assessed using Goldmann tonometry. **Trabodenoson was well tolerated and produced a dose-dependent IOP reduction**. IOP reduction in 500 mcg group were significantly greater than placebo at all-time points at Day 28. The Day 28 IOP lowering was significantly greater than at Day 14 indicating increased efficacy with longer treatment, and that reaching a pharmacodynamics steady state requires at least four weeks of therapy. In addition, an increase in IOP lowering efficacy was seen with increasing dose, with no apparent plateau in the dose-efficacy responses up to the highest dose tested. This suggests that higher dose could provide with

further IOP lowering. This may need to be investigated in a future trial. However, higher dose should also be evaluated for safety and tolerability. Trabodenoson represents a potential new class of IOP lowering drug therapy with a novel mechanism of action.

With the balance of ECM deposition by TM cells, and its digestion and removal by MMPs, trabodenososn's mechanism of action is very interesting and relevant to outflow pathophysiology associated with OHT and POAG. In addition, this mechanism of action may be complementary with the mechanisms of action of other classes of medications currently in use. **However, clinical evaluation in Phase 3 trials and with higher doses of trabodenoson and longer follow-up are needed.**

Surgical treatment

Post-surgery SLT



Comment by Tony Realini, Morgantown, WV, USA

66671 Selective laser trabeculoplasty in treating post-trabeculectomy advanced primary open-angle glaucoma, Zhang H, Yang Y, Xu J, Yu M, Experimental and therapeutic medicine 2016; 11: 1090-1094

Zhang and colleagues have conducted an interesting study in which Chinese subjects with POAG uncontrolled with medications following trabeculectomy underwent 360-degree SLT (using standard settings) for IOP control. Pre-treatment mean IOP was 21.3 ± 3.4 mmHg using an average of 2.8 medications. IOP at last follow-up (mean 6.3 months) was 16.2 ± 3.0 mmHg. **Nearly 80% of patients experienced a minimum 20% IOP reduction from baseline at last follow-up**. IOP reductions were achieved within one week of treatment and maintained throughout the relatively short follow-up period.

> The current study validates SLT's utility in post-trabeculectomy IOP management

Diurnal IOP variability was collapsed from 4.1 mmHg to 2.6 mmHg on average. No new safety issue were identified in this population. SLT has proven to be useful at virtually every stage of glaucoma. The treatment has been successfully applied as prophylactic therapy in ocular hypertension, as primary therapy for newly-diagnosed POAG, as adjunctive therapy with medications, and now the current study validates its utility in post-trabeculectomy IOP management.

Of all the methods we have for lowering IOP, SLT arguably has the most favorable safety profile. Considering its safety and efficacy at all stages of POAG, SLT offers the best benefit-risk profile of all our therapies for many if not most of our patients. On top of this, SLT lowers IOP throughout the 24-hour period, compresses IOP variability, requires no ongoing adherence on the patient's part, and can be safely and effectively repeated multiple times when its effect wanes. Zhang and colleagues are to be congratulated for demonstrating a novel aspect of SLT's broad applicability. **This therapy is underutilized in current clinical practice.**

Trabectome surgery

Comment by Sameh Mosaed, Irvine, CA, USA

67223 Impact of a Glaucoma Severity Index on results of trabectome surgery: Larger pressure reduction in more severe glaucoma, Loewen RT, Roy P, Parikh HA, Dang Y, Schuman JS, Loewen NA, PLoS ONE 2016; 11: e0151926

This retrospective review by Loewen *et al.* **found that patients with higher glaucoma severity scores experienced a more profound IOP reduction with trabectome surgery as compared to those in lower severity groups**. Glaucoma severity was defined with a Glaucoma Index, which was created on a scale between one to four and was based on visual field damage, number of preoperative glaucoma medications, and preoperative IOP. All groups showed similar one-year postoperative IOP of about 16 mmHg, hence the patients with the higher preoperative IOP showed a more profound IOP reduction.

These results mirror several prior published data that confirm the finding that in successful trabecular ablation patients, typical postoperative IOP is the mid-teens, regardless of preoperative IOP. This is because following trabecular ablation, IOP is dictated by the pressure in the collector channels and episcleral venous system.

> Following trabecular ablation, IOP is dictated by the pressure in the collector channels and episcleral venous system

However, this study differs from prior similar studies such that in addition to IOP alone, other glaucoma severity indicators were evaluated such as visual field and glaucoma medication burden. **While the group with the highest Glaucoma Index had the greatest IOP reduction, it also had the lowest overall success rate at the 12-month follow up (71% as compared to 90% in the lowest glaucoma index group).** This once again underscores the difficulty historically seen in controlling IOP in the sickest eyes with the most severe, refractory glaucoma.

This study has several strengths. Firstly, a very large study population of 842 subjects was included in the analysis. Secondly, the numbers in each of the four Glaucoma Index groups were balanced and robust for meaningful analysis. Only subjects undergoing trabectome were included in the study, and any simultaneous cataract extraction or other procedure were excluded from analysis. This differs significantly with other published data on angle-based surgeries where simultaneous cataract extraction confounds the results. Also, varied POAG subsets were included, and only subjects reaching a minimum postop period of one year were analyzed.

With this paper, the authors provide more evidence that the **trabectome procedure can be employed for treatment of early to refractory glaucoma with excellent result**s throughout the spectrum of disease, and that typical IOP of mid-teens can be expected regardless of preoperative IOP or disease severity.

IOP reduction in pseudophakia

Comment by Monisha Nongipur and Tin Aung, Singapore

67446 Lens position parameters as predictors of intraocular pressure reduction after cataract surgery in glaucomatous versus nonglaucomatous eyes, Coh P, Moghimi S, Chen RI, Hsu CH, Masís Solano M, Porco T, Lin SC, Investigative Ophthalmology and Visual Science 2016; 57: 2593-2599

Cataract extraction has been shown to be effective in reducing intraocular pressure (IOP); however, the responses are variable and the exact mechanisms involved in IOP lowering are not fully understood. Some of the predictors of IOP reduction after cataract surgery include higher level of pre-operative IOP, shallower anterior chambers, narrower angles and smaller anterior vault.

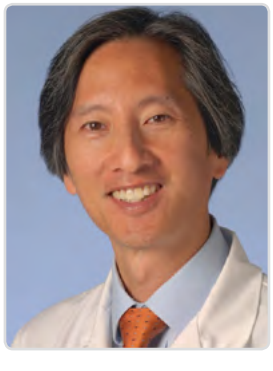
> The study suggests that lens position, an easily computed parameter, may be utilized to predict IOP response to cataract surgery

In this paper, Coh and colleagues evaluated the relationship between lens parameters and IOP reduction following cataract surgery in non-glaucomatous and eyes with primary open-angle glaucoma (POAG). **Cataract surgery resulted in 15.8% IOP lowering in the control group and 16.9% in the POAG group**. Pre-operative IOP was a significant predictor of IOP reduction in both the groups while **lens position (LP, defined as the sum of anterior chamber depth (ACD) and one-half lens thickness (LT)) was a significant predictor only in the non-glaucomatous group.** The study suggests that LP, an easily computed parameter may be utilized to predict IOP response to cataract surgery.

However, this may be contentious as the association with LP was significant in the non-glaucomatous eyes group only. Moreover, LP, computed from two axial parameters, estimates the position of the center of the lens from the cornea, and not with respect to the anterior chamber angles (unlike lens vault).

One of the limitations of the study was the inclusion of pre-operative IOP as a variable when assessing the predictors of percentage IOP reduction, as pre-operative IOP is used in the computation of percentage IOP change. It was also not clear how the authors performed the multivariate analyses since the factors significant in the univariate analysis were not adjusted for.

Combined surgery with anti-fibrotics in uveitic glaucoma



Comment by Darrell WuDunn, Indianapolis, IN, USA

67249 The influence of phacoemulsification on surgical outcomes of trabeculectomy with mitomycin-c for uveitic glaucoma, Nishizawa A, Inoue T, Ohira S, Takahashi E, Saruwatari J, Iwao K, Tanihara H, PLoS ONE 2016; 11: e0151947

Nishizawa and colleagues studied the influence of phacoemulsification on trabeculectomy MMC survival in 80 patients with uveitic glaucoma. They defined surgical success as IOP < 21 mmHg, < 18 mmHg, or < 15 mmHg with or without topical hypotensive medications. In a Cox Proportional Hazards Model analysis using phacoemulsification as a time-dependent covariate, they found that **phacoemulsification was a risk factor for failure of IOP control < 15 mmHg with or without medications**. In addition, early phacoemulsification (within one year of trabeculectomy) was associated with early failure of IOP control < 15 mmHg with or without medications.

The authors acknowledge several limitations including the retrospective nature and the small sample size. With only 24 of the 80 uveitic glaucoma patients having undergone phacoemulsification after trabeculectomy, statistical significance was only found for the most stringent IOP success criteria. The **detrimental effect of phacoemulsification on trabeculectomy survival has been well documented for primary open-angle glaucoma and this study does confirm the same effect in uveitic glaucoma**.

> Early phacoemulsification (within one year of trabeculectomy) was associated with early failure of IOP control < 15 mmHg with or without medications

However, a few additional analyses would have made this study even more useful for clinical practice. Comparing the IOP at six or 12 months post-phacoemulsification (rather than at last follow-up) to the IOP just before phacoemulsification would allow clinicians to see the direct influence of phacoemulsification on IOP. Furthermore, in the Kaplan-Meier survival analysis

comparing the 16 patients who were treated with phacoemulsification more than one year after trabeculectomy with the eight patients who were treated with phacoemulsification within one year after trabeculectomy, the start time should have been the time of the phacoemulsification rather than the time of the trabeculectomy. This would have enabled clinicians to estimate how long IOP control would be maintained after phacoemulsification and to determine whether delaying cataract surgery would prolong IOP control after phacoemulsification.

Miscellaneous

Socioeconomic factors impacting glaucoma diagnosis

Comment by Yvonne Buys, Toronto, ON, Canada

66749 Impact of socioeconomic status on the diagnosis of primary open-angle glaucoma and primary angle closure glaucoma: A nationwide population-based study in Taiwan, Ko YC, Hwang DK, Chen WT, Lee CC, Liu CJ, PLoS ONE 2016; 11: e0149698

In glaucoma the key to improve patient outcomes is early diagnosis. This can be a challenge, since in most cases glaucoma is an asymptomatic disease in the early stages. In order then to improve outcomes, **understanding patient characteristics that may influence glaucoma diagnosis** are important in order to develop strategies to target vulnerable groups. Previous studies have found that lower socioeconomic status is associated with late glaucoma diagnosis specifically for primary open-angle glaucoma (POAG). It is uncertain if lower socioeconomic status is a barrier to access to vision care or directly contributes to disease susceptibility for example through poor nutrition. The National Health Insurance Program (NHIP) in Taiwan attempts to reduce inequities to access of care by waiving fees for health services to low income individuals. An evaluation of glaucoma disease prevalence in this cohort may answer this question. In this study using data from the NHIP **the authors found that increased age and increased frequency of health care utilization were associated with glaucoma.** In addition, male gender and urbanization were associated with POAG. After adjusting for these factors lower socioeconomic status was associated with primary angle-closure glaucoma (PACG) and higher socioeconomic status was associated with POAG. To explain this finding **the authors attempt to link refractive error to socioeconomic status suggesting that low socioeconomic status is associated with lower education which in turn is associated with less myopic shift (a risk for PACG)** and higher socioeconomic status is associated with higher education and myopia (a risk for POAG). Although this explanation is possible more conclusive evidence is required to link socioeconomic status with refractive error. This study does, however, support public awareness campaigns regarding the importance of regular comprehensive visual examinations to aid in the diagnosis of glaucoma.


Comment by Erin Boese and Steve Mansberger, Portland, OR USA

66749 Impact of socioeconomic status on the diagnosis of primary open-angle glaucoma and primary angle closure glaucoma: A nationwide population-based study in Taiwan, Ko YC, Hwang DK, Chen WT, Lee CC, Liu CJ, PLoS ONE 2016; 11: e0149698

Understanding the risk factors for glaucoma is important to design effective interventions in the future. This study examines how socioeconomic status (SES) alters the diagnosis of primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG). The authors utilize the National Health Insurance Research Database (NHIRD), a national registry comprised of the 98% of Taiwan's population.

The study has the strengths of including a random selection of 1 million subjects with a detailed socio-demographic profile with equal access to healthcare (by waiving medical fees for low-income patients).

The National Health Insurance Research Database (NHIRD), a national registry comprises of the 98% of Taiwan's population

The authors found that patients with high SES were more likely to be diagnosed with POAG, while patients with lower SES were more likely to be diagnosed with PACG. The study suggests that these findings may allow more targeted approaches for screening and education.

The **authors acknowledge the discrepancy between prevalence and diagnosis of disease**, which may partially contribute to the study's relatively low rates of glaucoma. For example, POAG and PACG only occurred in 0.36% and 0.42%, respectively in subjects over 70 years, which is at least 30 times less frequent than results from prevalence studies.

This low rate of disease may be related to the definition of POAG and PACG including a diagnosis code for four or more visits per year. Only those most compliant with their visits would be considered 'glaucoma', and the study indicates that those with lower SES were less likely to utilize the health care system. A sensitivity analysis with different cut-offs for 'glaucoma' would be informative. A similar bias may occur if cataract surgery is more common in those of higher SES since they would be less likely to develop angle closure glaucoma. Interestingly, while the study focuses on how SES influences the rate of diagnosis, age was a much greater risk factor with those of older age having glaucoma at ten times the risk when compared to comparisons based on SES.

POAG and PACG only occurred in 0.36% and 0.42%, respectively in subjects over 70 years, which is at least 30 times less frequent than results from prevalence studies

While interesting, we do not anticipate the study results to significantly influence population screening because the study does not examine intervention to decrease undiagnosed glaucoma. **A potential next study could include a step-wise multivariate model to determine the most important characteristics of a population at risk for undiagnosed glaucoma using this same database (including effect of age)**. Furthermore, it would be interesting to see how these correlations hold up in other populations.

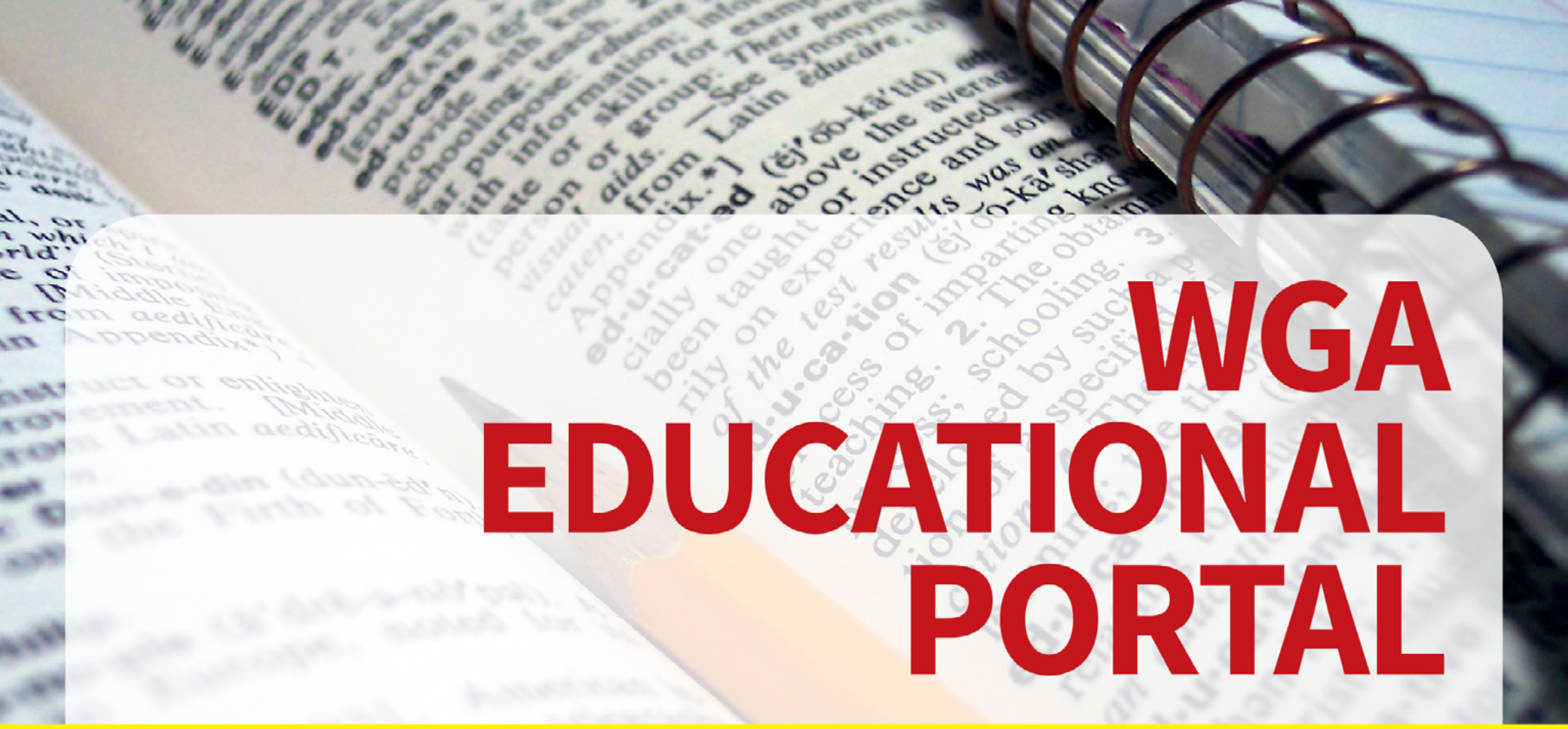
World Glaucoma Association

Diagnosis of Primary Open Angle Glaucoma

Robert N. Weinreb, David Garway-Heath, Christopher Leung,
Felipe Medeiros, Jeffrey Liebmann

Consensus Series - 10

Kugler Publications, Amsterdam, The Netherlands



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News flashes

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- ★ OCT assessment of prelaminar and LC structures may allow earlier detection of glaucoma
- ★ Challenges to the current view that CSF pressure is homogenous in all CSF spaces
- ★ The neuro-inflammatory mediator C1q as an important regulator of early dendritic and synaptic deficits in glaucoma
- ★ Progressive RNFL thinning – can predict future VF progression and, therefore, can be considered to be an outcome measure in clinical trials evaluating glaucoma treatments
- ★ Progressive RNFL thinning predicts subsequent VF progression in glaucoma patients
- ★ SLT's utility in post-trabeculectomy IOP management

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