VOLUME 19-4
2019

International Glaucoma Review

The journal of the World Glaucoma Association

Abstracts and Review of Glaucoma Literature

www.e-IGR.com

SINCE 1984

ISSN 1566-1040

Regional & International Glaucoma Societies

American Glaucoma Society

Asia-Pacific Glaucoma Society

Australia and New Zealand Glaucoma Society

Canadian Glaucoma Society

Childhood Glaucoma Research Network

Chinese Glaucoma Society

Commonwealth Independent States Glaucoma Society

European Glaucoma Society

Glaucoma Society of India

International Society for Glaucoma Surgery

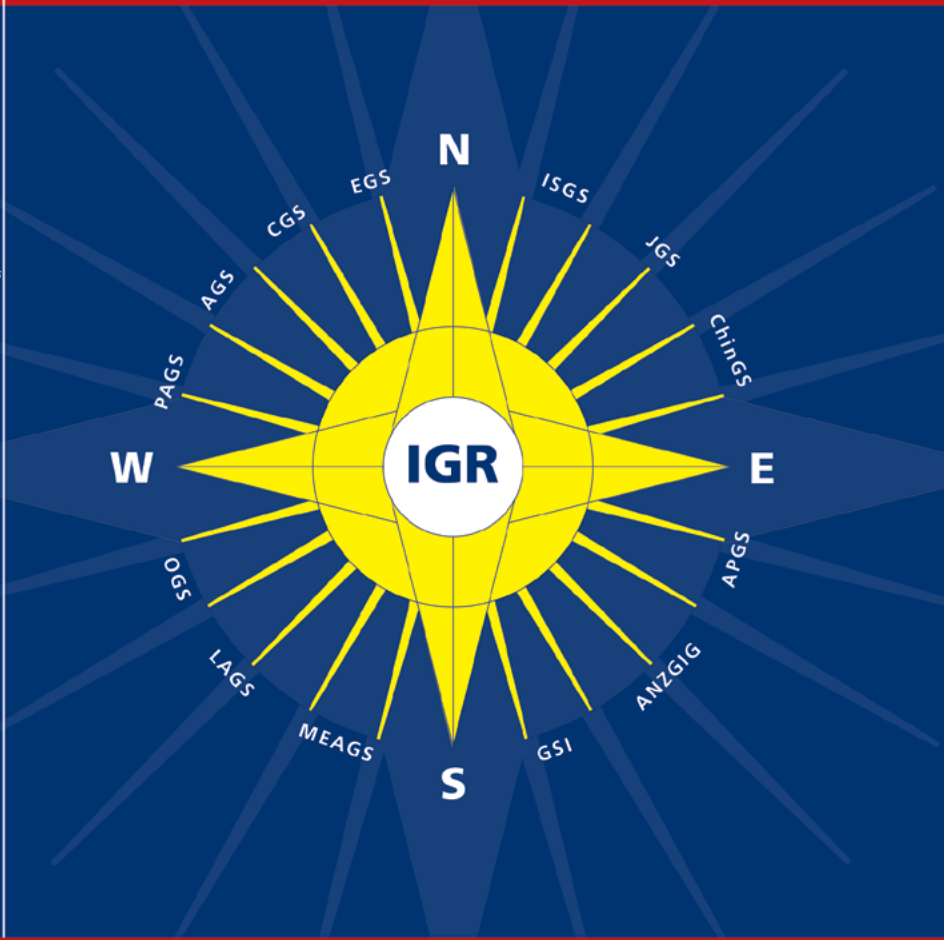
Japan Glaucoma Society

Latin American Glaucoma Society

Middle East African Glaucoma Society

Optometric Glaucoma Society

Pan American Glaucoma Society



SPARKtacular
features in one device

Click here to learn more

OCULUS Smartfield: Fast, Small, Affordable

A complete perimeter with a small footprint

SAVE TIME
SPARK strategy for threshold perimetry in 3 minutes

SAVE SPACE
Compact size, low space requirement

SAVE MONEY
Low price, high performance

www.sparktacular-visual-field.com

Follow us!

OCULUS®

ISSN 1566-1040

INTERNATIONAL GLAUCOMA REVIEW

A Quarterly Journal
Volume 19 no. 4

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

Registration

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

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

ISSN 1566-1040

Contact Information

All correspondence on copies, supplements, content, advertising, etc. should be directed to:
WGA Executive Office
c/o Schipluidenlaan 4
1062 HE Amsterdam
The Netherlands
Tel: +31 20 570 9600
E-mail: info@worldglaucoma.org

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

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

WGA#One

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

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

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

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

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

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

How to activate your WGA#One profile

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

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

THE ONLY
COMPLETE OCT SYSTEM
IN THE WORLD

AL
BIOMETRY
OCT

T
OCT CORNEAL
TOPOGRAPHY

A
ANTERIOR
WIDE

RA
ANGIO OCT

D
GLAUCOMA
ANALYSIS
GCL & RNFL

FULL AUTO

The World's first OCT Biometry | The World's fastest OCT | The World's first OCT Topography

OPTOPOL
technology

manufacturer of the first in the world Spectral Domain OCT

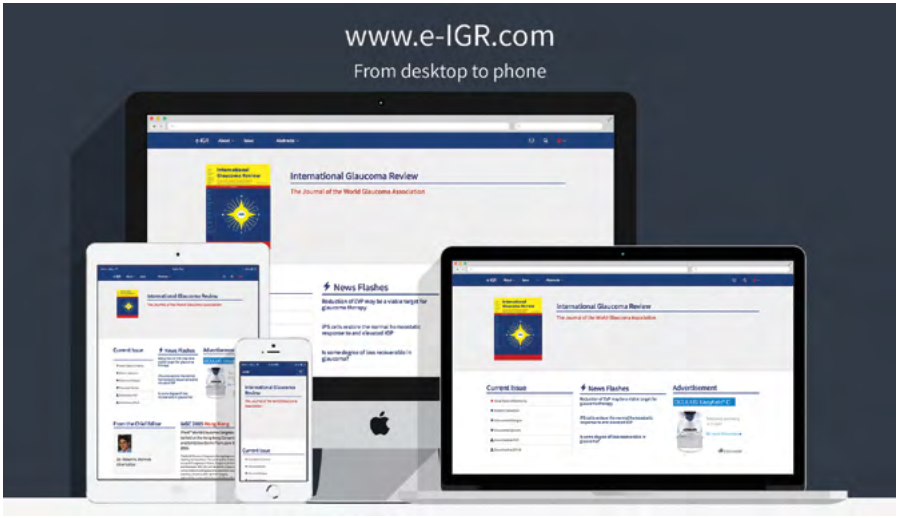
optopol.com

Table of Contents

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

www.e-IGR.com

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



From the WGA Executive Office

Dear IGR readers,

With the 8th World Glaucoma Congress just around the corner, the WGA Executive Office is fully focused on the final preparations. We are coordinating all the WGA committee meetings, finalizing the content for the congress app and fine-tuning the 11th Consensus Meeting on Surgery: we truly start to feel excited. Be welcome and join us in Melbourne from March 27-30 for an educational, entertaining and collegial congress!

During WGC-2019 we offer all our delegates a complementary printed edition of the IGR 19-4. At the time of the congress, you can pick up your free printed edition at the WGA Networking Area.

Please make sure to download the WGA app, in which you will find all information related to WGC you will need during your stay in Melbourne. Find out which sessions are running, and which are up next, find your way through the convention centre effortlessly using the floor plans, explore your virtual congress bag and find useful information about Melbourne.

This edition, it is time for us to give extra credit and a big thank you for all her hard work to Mariska van der Veen, who has been the Executive General Manager of the World Glaucoma Association for over twelve years now.

If you do not yet receive an e-mail notification when a new issue of IGR is published, please pass by the WGA Networking Area during the congress. We are happy to assist you with updating or creating your WGA#One account.

World Glaucoma Association
The Global Glaucoma Network

We hope you enjoy reading this issue of the IGR and wish you a wonderful time in Melbourne. You can contact our WGA Executive Office (info@worldglaucoma.org) if you need any information or have questions on IGR or WGA-related matters.

Shan Lin
Executive Vice President

Get to know us!

Mariska van der Veen, WGA Executive General Manager, is pleased to have worked for the WGA Executive Office for the past 12 years. Working as an associate executive was unknown to Mariska, when she first started working for the WGA in 2006 after being a professional congress organizer for many years. During the first years, she really invested in getting to know all stakeholders, of course the Glaucoma Society members, board & committee members but also the industry representatives.

Over the past years, a lot has changed, especially the number of volunteers actively involved in the association, which results in the many projects that have been initiated, like the online course program, the patient education website, the fellowship program, IGR, 8 World Glaucoma Congresses, 10 consensus meetings & publications, as well as the 1000's of activities for World Glaucoma Week.

World Glaucoma Association
The Global Glaucoma Network

The WGA could not do all of this without this splendid support of glaucoma specialists and industry members from all over world. Thank you all for making this possible! Looking forward to meeting you at the 8th World Glaucoma Congress in Melbourne or at another future occasion!

touch OPHTHALMOLOGY®

Leading the Debate on the Advances in Healthcare

touch medical media®

PRACTICAL ARTICLES
EXPERT INTERVIEWS
NEWS AND INSIGHTS

PEER-REVIEWED | OPEN-ACCESS
CONCISE | MULTIMEDIA

VIEW – DOWNLOAD – SUBSCRIBE
FREE
touch**OPHTHALMOLOGY**.com

IGR Reviewers volume 19

The International Glaucoma Review would like to thank the following reviewers for their contribution to volume 19

Makoto Aihara (Japan)

Wallace Alward (USA)

Florent Aptel (France)

Tin Aung (Singapore)

Augusto Azuara Blanco (UK)

Eytan Blumenthal (Israel)

Rupert Bourne (UK)

Tanuj Dada (India)

Gustavo de Moraes (USA)

Crawford Downs, Director (USA)

Ross Ethier (USA)

Massimo Fazio, Birmingham (USA)

Robert Fechtner (USA)

Robert Feldman (USA)

Murray Fingeret (USA)

David Friedman (USA)

Aakriti G Garg (USA)

Ivan Goldberg (Australia)

David Greenfield (USA)

Vivek Gupta (India)

Alon Harris (USA)

Anders Heijl (Sweden)

Esther Hoffman (Germany)

Alex Huang (USA)

Jin Wook Jeoung (South Korea)

Chris Johnson, Iowa City (USA)

Jost Jonas (Germany)

Paul Kaufman (USA)

Hanspeter Killer (Switzerland)

Tae-Woo Kim (South Korea)

George Lambrou (Greece)

Shan Lin (USA)

John Liu (USA)

Catherine Liu (Taiwan)

Nils Loewen (USA)

Eugene A. Lowry (USA)

Steve Mansberger (USA)

Kaweh Mansouri (Switzerland)

Keith Martin (Australia)

Jose-Maria Martinez de la Casa (Spain)

Paul McCann (UK)

Neha Midha (India)

Stefano Miglior (Italy)

Sameh Mosaed (USA)

Kouros Nouri-Mahdavi (USA)

Zeynep Ozturker,

Paul Palmberg, Miami (USA)

Ki Ho Park (South Korea)

Louis Pasquale (USA)

Vincent Michael Patella (USA)

Claudio Perez, San Francisco (USA)

Zia Pradhan (India)

Luciano Quaranta (Italy)

Pradeep Ramulu (USA)

Harsha Rao (India)

Prin Rojanapongpun (Thailand)

Luca Rossetti (Italy)

Leopold Schmetterer (Singapore)

Arthur Sit (USA)

Ernst Tamm (Germany)

James Tan (USA)

Andrew Tatham (UK)

Kent Taylor (USA)

Fotis Topouzis (Greece)

Eranga Vithana (Singapore)

Ningli Wang (P.R. China)

Tsing-Hong Wang (Taiwan)

Tun Wang Chang,

Derek Welsbie (USA)

Zhang Ye (P.R. China)

Linda Zangwill (USA)

Ze Zhang (USA)

WGA Consensus Volume 11 - Glaucoma Surgery

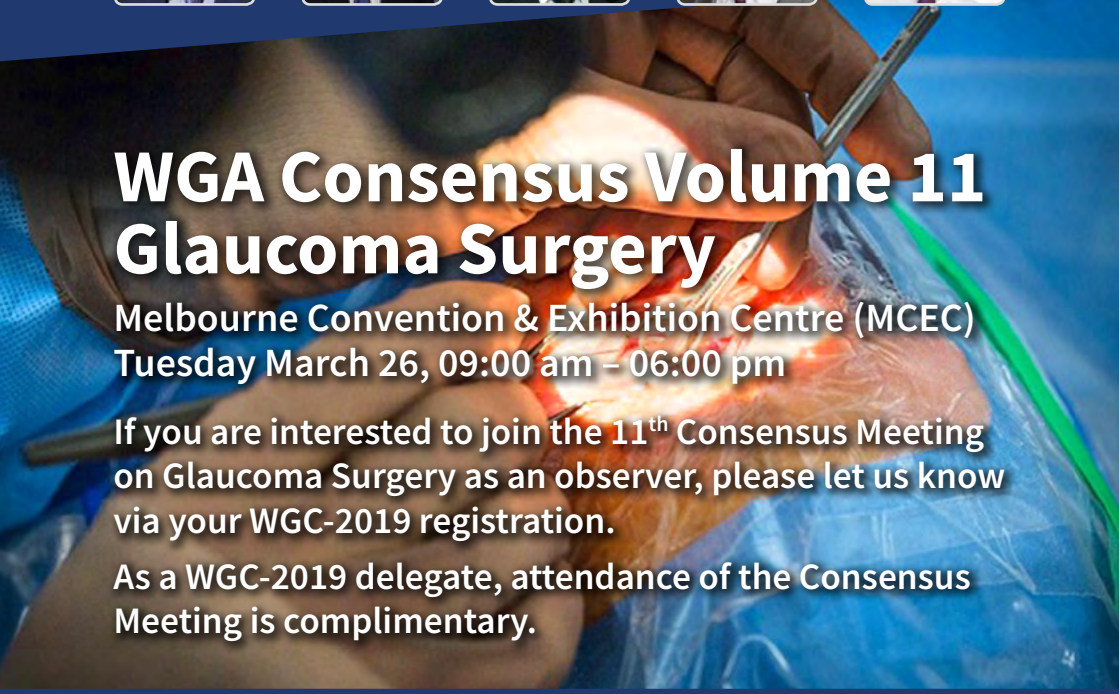
Glaucoma Surgery Consensus

Chair: Robert N. Weinreb

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







WGA Consensus Volume 11 Glaucoma Surgery

Melbourne Convention & Exhibition Centre (MCEC)
Tuesday March 26, 09:00 am – 06:00 pm

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

As a WGC-2019 delegate, attendance of the Consensus Meeting is complimentary.

WGA Consensus Series

Robert N. Weinreb

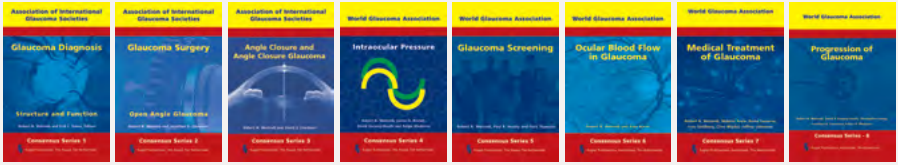
The Glaucoma Consensus Initiative of the World Glaucoma Association is based on the idea that the collective wisdom of a group is better than the opinion of a single expert. Assembling a sufficiently large and sufficiently diverse group of glaucoma specialists and scientists provides recommendations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

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

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

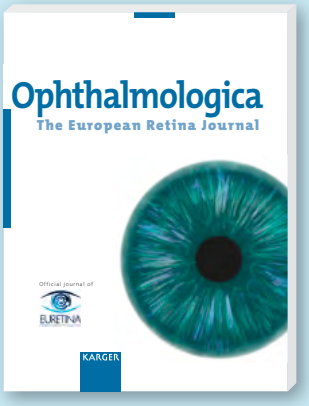
See all complimentary available WGA Consensus volumes through WGA#One

www.wga.one/wga/consensus-downloads



Karger Journals in

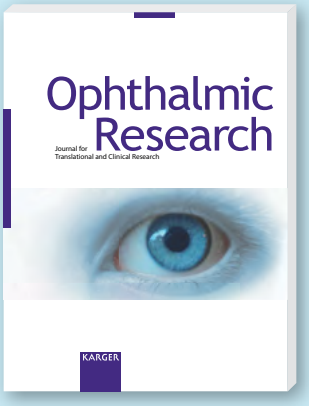
Ophthalmology



Clinical research in ophthalmology with special focus on management of retina and vitreous diseases

Editor
Sebastian Wolf, Bern

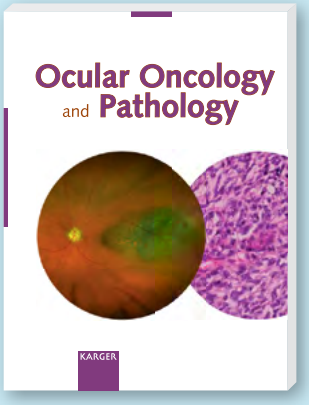
www.karger.com/oph



Vision in focus

Editor
José Cunha-Vaz, Coimbra

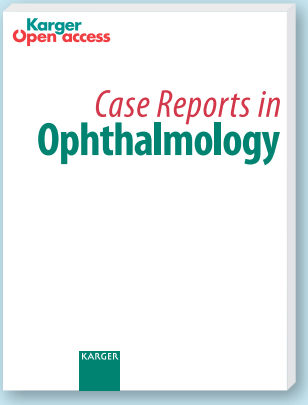
www.karger.com/ore



Your source for clinical and basic research in ophthalmology with special focus on oncology and pathology

Editors
Arun D. Singh, Cleveland, Ohio
Hans E. Grossniklaus, Atlanta, Ga.

www.karger.com/oop



The first ophthalmology journal dedicated exclusively to case reports

Editor
Anat Loewenstein, Tel Aviv

www.karger.com/cop

Please visit our website for further information:
www.karger.com/ophthalmology

KARGER
Medical and Scientific Publishers

19110_a

Your Special Attention For

Neuroprotection in glaucoma: recent advances and clinical translation
Guymer C, Wood JP, Chidlow G, Casson RJ
Clinical and Experimental Ophthalmology 2018; DOI:10.1111/ceo.13336
abstract no. 77930

Real-time imaging of retinal ganglion cell apoptosis
Yap TE, Donna P, Almonte MT, Cordeiro MF
Cells 2018; 7(6): pii: E60.
abstract no. 77950

Intracranial pressure and glaucoma: Is there a new therapeutic perspective on the horizon?
Wostyn P, Van Dam D, De Deyn PP
Medical Hypotheses 2018; 118: 98-102
abstract no. 78164

Comparison of visual field point-wise event-based and global trend-based analysis for detecting glaucomatous progression
Wu Z, Medeiros FA
Translational vision science & technology 2018; 7: 20
abstract no. 78287

SOE 2019

European Society of Ophthalmology

13-16 JUNE 2019, NICE, FRANCE

Register NOW!

A TRULY COMPREHENSIVE OPHTHALMOLOGY MEETING FOR ALL OPHTHALMOLOGISTS

SEE YOU IN NICE

www.SOE2019.org

Looking forward to the World Glaucoma Congress in Melbourne

The World Glaucoma Association looks forward to welcoming ophthalmologists and allied health professionals to the World Glaucoma Congress 2019, which will take place from March 27-30, 2019 in Melbourne.

The scientific program comprises a stimulating mix of symposiums, courses, posters and rapid-fire presentations covering topics from the basic science and genetics of glaucoma, to the latest developments in medical and surgical management of glaucoma.

Emerging new topics will include: potential applications of artificial intelligence to glaucoma management, the role of the mitochondria in glaucoma pathogenesis, and the use of large data sets in glaucoma research. Symposiums and courses will provide an update on the latest results from laser and surgical treatment trials, practical tips on glaucoma surgery, and the impact of glaucoma on patients/challenges of providing a service in different global settings. There will be debates on angle closure, normal-tension glaucoma, pediatric glaucoma and imaging.

In parallel to these sessions there will be opportunities to take part in a poster walk with leading glaucoma experts, and participate in surgical wet lab training.

A globally diverse faculty of experts in glaucoma research and clinical practice will come together to share their knowledge and insight in what promises to be an exciting and interesting meeting.

Winifred Nolan
Chair Program Planning Committee WGC-2019

World Glaucoma Association
The Global Glaucoma Network

8th WORLD GLAUCOMA CONGRESS
MARCH 27 – 30, 2019
MELBOURNE

www.glaucomapatients.org

A brand new website brought to you by the World Glaucoma Association. At this website, you will find out who is at risk, what are the symptoms, and how glaucoma can be treated. Our aim is to offer information about glaucoma, using easy accessible language in a user-friendly platform. We sincerely hope you will find useful information about glaucoma here.

You will learn what are the exams used for glaucoma diagnosis and follow-up, get useful information on how to best perform in such exams and how frequent they should be repeated. There are also some considerations about glaucoma and driving, how to treat it during pregnancy, and if glaucoma patients can undergo refractive surgery. Finally, some advice on how to live with this disease and how relatives can help the glaucoma patient.

World Glaucoma Association
The Global Glaucoma Network

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

Glaucoma and Diabetes Mellitus

Comment by Eugene A. Lowry and Steve Mansberger, Portland, OR, USA

77861 Increased risk of open-angle glaucoma among patients with diabetes mellitus: a 10-year follow-up nationwide cohort study, Rim TH, Lee SY, Bae HW, Seong GJ, Kim SS, Kim CY, Acta Ophthalmologica 2018; 96(8): e1025-e1030

The authors investigate the incidence of open-angle glaucoma within a subpopulation from Korean national insurance data who have diabetes compared to a non-diabetic control group. Patients with diabetes are match 1:1 to non-diabetic patients controlling for basic demographic and clinical variables. Over ten years of follow-up from 2004 through 2013, **the authors find a small but significant increased incidence of open-angle glaucoma in patients with diabetes** (20/10,000 person years) compared with controls (17/10,000 person years), with a corresponding hazard ratio of 1.19. This increased risk was seen across age and sex groups.

The authors use a robust definition of glaucoma, requiring ICD codes in combination with billing for visual fields and topical therapy. They validate this definition with a manual review of 200 charts from two hospitals, with 188 patients (94%) have the diagnosis confirmed on chart review. Interestingly, the majority (152 patients, 78%) had normal-tension glaucoma, which may affect the generalizability of the study.

A major challenge of using insurance data sets to look at associations between diabetes and open-angle glaucoma is detection bias. Though patients with diabetes were matched to controls on the number of medical visits, the authors did not match on number of visits to eye care providers or number of dilated eye exams. Given practice guidelines, it is reasonable to wonder whether diabetic patients may have had more frequent dilated eye examinations than their matched controls with corresponding bias towards increased detection rates.

The association between diabetes with incidence and progression of open-angle glaucoma remains controversial

Overall, the association between diabetes with incidence and progression of open-angle glaucoma remains controversial both in the direct effect of diabetes and impacts of systemic diabetic medications. Further studies, including a burgeoning literature on peripapillary vasculature, may help the mechanisms of any possible association and guide future clinical care.

Quality of Life

Quality of Life Impact in Early Glaucoma - II

Comment by George Lambrou, Greece

78204 Macular damage, as determined by structure-function staging, is associated with worse vision-related quality of life in early glaucoma, Garg A, Hood DC, Pensec N, Liebmann JM, Blumberg DM, American Journal of Ophthalmology 2018; 194: 88-94

How does macular damage impact quality of life in early glaucoma? Traditionally glaucomatologists have focused on arcuate functional loss, assuming that central vision was minimally affected by the disease and that quality of life would therefore depend essentially on mid-peripheral visual field defects. However, **macular damage is becoming increasingly recognized as a common disease feature and may have significant implications on vision-related quality of life (VRQoL)**

It is those implications that Garg *et al.* sought to investigate, by exploring the relationship between the NEI Visual Function Questionnaire (NEI-VFQ25) and macular damage in both eyes of 44 patients with early POAG (i.e. with 24-2 MD better than -6dB). Macular damage was defined as the concomitant presence of corresponding structural (SD-OCT) and functional (VF) defects in the central 8°. Of the 44 patients, 12 had bilateral, 15 had unilateral and 17 had no macular damage.

The authors found a strong association between calibrated NEI-VFQ25 scores and the presence of macular damage. Although significant in both cases, this association was much stronger with macular damage in the worse than in the better eye ("better" and "worse" defined by the 24-2 Mean Defect), while the concomitant presence of peripheral field loss improved the correlation only marginally. Interestingly, the presence or absence of peripheral field loss in eyes without macular damage seemed uncorrelated to VRQoL. Additionally, there seemed to be no difference in QoL scores between eyes with "diffuse" and "focal" macular damage

> Macular damage is not uncommon, even in early glaucoma, and is much more impactful on VRQoL than peripheral damage

What are the take-home messages of this study? First, macular damage is not uncommon, even in early glaucoma, and is much more impactful on VRQoL than peripheral damage, which is the focus and main driver of disease management today. Second, diffuse visual field damage – often dismissed as dry eye or cataract – impacts VRQoL in a similar manner

to focal loss and should be evaluated through combined VF and OCT assessment. Finally, that macular damage in the worse eye may contribute more to VRQoL deterioration than currently believed.

Overall, the authors' findings suggest that macular damage should be evaluated in patients with early glaucoma and possibly prompt a more aggressive treatment in order to alleviate the impact of the condition on their quality of life.

Anatomical Structures

Posterior Pole Vascularization and Structural Progression

Comment by Andrew Tatham, Edinburgh, UK

77939 Macular and optic nerve head vessel density and progressive retinal nerve fiber layer loss in glaucoma, Moghimi S, Zangwill LM, Penteado RC, Hasenstab K, Ghahari E, Hou H, Christopher M, Yarmohammadi A, Manalastas PIC, Shoji T, Bowd C, Weinreb RN, Ophthalmology 2018; 125: 1720-1728

OCT angiography (OCTA) provides a method for non-invasive imaging of the microvasculature of the optic nerve head and retina. Several studies using OCTA have shown patients with glaucoma have reduced peripapillary and macular vessel density,[1-3] with vessel density frequently reported to have similar ability to differentiate healthy and glaucomatous eyes compared to retinal nerve fibre layer (RNFL) thickness.[1,2] **These and other studies support the theory that impaired ocular blood flow is associated with the development and progression of glaucoma.**

Moghimi and colleagues take a step beyond these cross-sectional analyses and report the results of the first study to examine the relationship between baseline OCTA measurements and subsequent rates of change in RNFL thickness over time. This is an important study as it is the first to show low vessel density is a risk factor for glaucoma progression. Eighty-three patients with mild to moderate glaucoma were followed for an average of over two years, with OCT circumpapillary RNFL and macular ganglion cell inner plexiform layer (mGCIPL) measurements obtained semi-annually. Baseline OCTA measurements included macular whole image vessel density (m-wiVD) and optic nerve head whole image vessel density (onh-wiVD).

The main finding of the study was that eyes with lower baseline macular and optic nerve head vessel density had significantly faster rates of loss of RNFL during follow-up compared to eyes with higher vessel density. The overall average rate of RNFL loss was -1.07 µm/year, however, rates of loss were 0.11 µm/year and 0.06 µm/year faster for each 1% lower baseline m-wiVD and onh-wiVD respectively.

> Eyes with lower baseline macular and optic nerve head vessel density had significantly faster rates of loss of RNFL during follow-up compared to eyes with higher vessel density

The association between lower vessel density and faster rates of RNFL loss was present even when accounting for potential cofounders known to affect rates of progression, including age, intraocular pressure, central corneal thickness, and disease severity at baseline. **Vessel density also provided additional predictive value compared to conventional structural measurements such as baseline RNFL and mGCIPL thickness.** This suggests that impaired optic nerve head and retinal perfusion may lead to faster rates of retinal ganglion cell loss in glaucoma, however, it is possible that vascular dropout may occur due to reduced metabolic demands of already dysfunctional retinal ganglion cells.

Determining a patient's risk of progression is essential to inform decisions regarding monitoring intervals and appropriate treatment, however risk assessment remains challenging. This study shows measurements of vessel density using OCTA may improve our ability to assess to risk. OCTA also has the potential to improve our understanding of glaucoma pathogenesis and better explore the role of ocular blood flow in glaucoma.

Further work is needed to elucidate the relationship between vessel density and structural measurements across different severities of disease and to determine the dynamic range of vessel density.

References

1. Yarmohammadi A, Zangwill LM, Diniz-Filho A, et al. Optical Coherence Tomography Angiography Vessel Density in Healthy, Glaucoma Suspect, and Glaucoma Eyes. Invest Ophthalmol Vis Sci. 2016;57:451-459.
2. Chen HS, Liu CH, Wu WC, et al. Optical coherence tomography angiography of the superficial microvasculature in the macular and peripapillary areas in glaucomatous and healthy eyes. Invest Ophthalmol Vis Sci. 2017;58:3637-3645.
3. Rao HL, Pradhan ZS, Weinreb RN, et al. A comparison of the diagnostic ability of vessel density and structural measurements of optical coherence tomography in primary open-angle glaucoma. PLoS One. 2017;12(3):e0173930.

Laminar Curvature and Functional Progression

Comment by Florent Aptel, Lyon, France

78012 Baseline lamina cribrosa curvature and subsequent visual field progression rate in primary open-angle glaucoma, Ha A, Kim TJ, Girard MJA, Mari JM, Kim YK, Park KH, Jeoung JW, Ophthalmology 2018; 125(12): 1898-1906

Ha *et al.* investigated the relationship between the posterior bowing of the lamina cribosa – in subjects with early POAG medically treated – and the subsequent risk and rate of visual field progression. They used swept-source OCT to investigate the optic nerve head anatomy, and the main parameters used to perform the statistical analysis were derived from the geometric distance between the anterior laminar insertion and the mean position of the anterior laminar surface (called lamina cribosa curvature index, LCCI). Assessment of the visual field progression was performed using a linear regression of the MD against time.

One hundred and one eyes were analyzed. It should be mentioned that about 20% of the OCT scans were not analyzed because of poor image quality. The baseline MD was −3.8 ± 3.4 dB and the mean rate of progression −0.18 ± 0.33 dB/year over a 3.6 ± 0.8-years period.

Among all the demographic, clinical and anatomical parameters included in the univariate and multivariate analysis, **only the mean adjusted LCCI was significantly associated to a higher rate of visual field progression.** It should be noted that the mean IOP, IOP fluctuations, and baseline MD were not significantly associated to the rate of visual field progression.

I think that this study performed in a large cohort of subjects and using careful evaluations of the lamina cribosa anatomy adds some evidences of the potential role of the lamina cribosa biomechanics in the glaucoma pathophysiology. It particularly emphasizes the importance of the lamina cribosa curvature and posterior bowing.

> This study emphasizes the importance of the lamina cribosa curvature and posterior bowing

Surprisingly, the untreated and treated IOP were not associated to the rate of visual field progression. It should be noted that the study was conducted in Asia, and most of the subjects likely had normal-tension glaucoma (the authors mentioned that the mean pretreatment IOP was 16.2 ± 4.3 mmHg in the discussion). Of course, it will be interesting to duplicate such analysis in other ethnicities and also subjects with high tension glaucoma. It is possible that the respective role of the IOP level and lamina cribosa curvature would have been different.

Neuroretinal Rim Assessment after Trabeculectomy

Comment by Massimo Fazio, Birmingham, AL, USA

78205 Structural reversal of disc cupping after trabeculectomy alters bruch membrane opening-based parameters to assess neuroretinal rim, Gietzelt C, Lemke J, Schaub F, Hermann MM, Dietlein TS, Cursiefen C, Enders P, Heindl LM, American Journal of Ophthalmology 2018; 194: 143-152

This retrospective study quantified longitudinal changes in Bruch membrane opening minimum rim width and area (MRW and MRA, as defined by Gardiner *et al.*[1]) as measured by a Spectralis SD-OCT following trabeculectomy with mitomycin C at three, six, and 12 months.

The primary finding of this study was that MRW and MRA significantly increased post trab at three months (p = 0.012), at six months (p = 0.007), and at 12 months (p=0.010). Importantly, RNFL thickness remained stable between baseline and follow-up at three, six, and 12 months and showed a moderate loss after 18 months (p = 0.021) of follow-up. No statistically significant changes in global visual field after trab were observed.

By now, it has been investigated by many whether structural changes of the optic nerve head (ONH) following IOP reduction by trabeculectomy are associated with betterments in the visual field function. **This study confirms that, once again,[2,3] structural changes of the ONH following trabeculectomy are correlated with the magnitude of change in IOP but not with visual function.**

Of particular interest in this study is that RNFL thickness was not affected by IOP reduction, while MRA was. The authors do not stretch their discussion to try to provide a possible explanation of this observation.

MRA is an interesting novel parameter that attempts to provide a surrogate measure for the number of axons entering the optic nerve head. It has been shown to be better correlated to RNFL thickness than rim area measured by confocal scanning laser ophthalmoscopy (CSLO).[1] The area depicted by MRA is inclusive of both neural tissue (axons) and non-neural tissue (primarily vasculature). The fraction of volume described as vasculature is mainly constituted by blood. Blood, being a fluid, provides no resistance to the mechanical deformations induced by IOP. Consequentially, under varying IOP, vascular tissue in the ONH deforms more than the surrounding tissue, as recently quantified by Fazio *et al.*[4] While reduction in mechanical stretching following trabeculectomy of the rim tissues[5] would certainly contribute to the sensitivity of rim morphology to IOP, because of the weak resistance to compression of vascular tissue, one would wonder if findings like in this study of changes in MRA or MRW following IOP reduction are a consequence of deformations in the vasculature tissue first of anything else.

Deformations of the ONH vascular tissue under varying IOP has been scarcely investigated. Novel mechanistic models[6] postulate that vasculature compression under increasing IOP may be a primary factor determining blood-flow autoregulation and provide a plausible explanation to otherwise controversial findings on changes in hemoregulation following trab.[7,8]

The contribution of vasculature anatomy to ONH morphologic changes with IOP and glaucoma progression is currently poorly understood. The rise of OCT-angiography, with its ability to separate structural from vascular tissue, will certainly facilitate an explanation to findings like those proposed by this study.

References

1. Gardiner SK, Ren R, Yang H, et al. A method to estimate the amount of neuroretinal rim tissue in glaucoma: comparison with current methods for measuring rim area. Am J Ophthalmol. 2014;157(3):540-9 e1-2.
2. Waisbourd M, Ahmed OM, Molineaux J, et al. Reversible structural and functional changes after intraocular pressure reduction in patients with glaucoma. Graefes Arch Clin Exp Ophthalmol 2016;254(6):1159-1166.
3. Kiessling D, Christ H, Gietzelt C, et al. Impact of ab-interno trabeculectomy on Bruch's membrane opening-based morphometry of the optic nerve head for glaucoma progression analysis. Graefe's Arch Clin Exp Ophthalmol. 2018. doi: 10.1007/s00417-018-4187-2.
4. Fazio MA, Clark ME, Bruno L, Girkin CA. In vivo optic nerve head mechanical response to intraocular and cerebrospinal fluid pressure: imaging protocol and quantification method. Scientific Reports. 2018;8(1):12639.
5. Girard MJA, Beotra MR, Chin KS, et al. In Vivo 3-Dimensional Strain Mapping of the Optic Nerve Head Following Intraocular Pressure Lowering by Trabeculectomy. Ophthalmology. 2016;123(6):1190-1200.
6. Guidoboni G, Harris A, Cassani S, et al. Intraocular Pressure, Blood Pressure, and Retinal Blood Flow Autoregulation: A Mathematical Model to Clarify Their Relationship and Clinical Relevance. Investigative Ophthalmology & Visual Science. 2014;55(7):4105-4118.
7. Trible JR, Sergott RC, Spaeth GL Trabeculectomy is associated with retrobulbar hemodynamic changes. A color Doppler analysis. Ophthalmology. 1994;101:340-351.
8. Cantor LB. The effect of trabeculectomy on ocular hemodynamics. Trans Am Ophthalmol Soc. 2001;99:241-252.

Basic Science

GWAS and Glaucoma - II

Comment by Tin Aung and Eranga Vithana, Singapore

78212 Genome-wide association study of intraocular pressure uncovers new pathways to glaucoma, MacGregor S, Ong JS, An J, Han X, Zhou T, Siggs OM, Law MH, Souzeau E, Sharma S, Lynn DJ, Beesley J, Sheldrick B, Mills RA, Landers J, Ruddle JB, Graham SL, Healey PR, White AJR, Casson RJ, Best S, Grigg JR, Goldberg I, Powell JE, Whiteman DC, Radford-Smi, Nature Genetics 2018; 50: 1067-1071

Genetic factors behind a complex disease such as primary open-angle glaucoma (POAG) can be resolved by the analysis of quantitative traits, or endophenotypes, that are associated with the disease such as intra ocular pressure (IOP) or vertical cup-to-disc ratio (VCDR). These traits are heritable and primarily state-independent, *i.e.*, they manifest in the individuals regardless of the disease state but the disease risk is correlated genetically with the endophenotype.[1] By identifying the genes that govern these quantitative traits, it is possible to unravel the genetic determinants that confer individual susceptibility to POAG. Khawaja and Colleagues proved this point unequivocally in one of the largest Genome-wide Association Studies (GWAS) conducted to date on IOP, which included 139,555 European participants, the majority of whom were derived from the UK Bio Bank (n = 103,382). They identified a remarkable 112 genomic loci associated with IOP, 68 of which are novel. In addition, 48 of the loci were nominally associated with glaucoma, with 14 of the loci being significant at a Bonferroni-corrected threshold, highlighting the high genetic correlation between IOP and glaucoma. The data in this study was replicated and corroborated by another, which was published back to back in the same issue of Nature Genetics.[2]

Several important insights were brought forth by this study that may be of clinical significance

Several important insights were brought forth by the Khawaja study that may be of clinical significance. **Several of the IOP loci discovered supported an important role for angiopoietin receptor tyrosine kinase (ANG-TEK) signaling in IOP regulation**. Functional validation of these genes in appropriate model systems would indicate if ANG-TEK signaling would be a good therapeutic target for POAG. Indicating that risk stratification for POAG would also be a possible reality in the future, the regression-based POAG-prediction model built using the 123 significant SNPs along with age and sex predicted a substantial portion of POAG cases in two independent cohorts. Area under the receiver operating

characteristic curve (AUROC) of 0.76 and 0.74 were observed in US NEIGHBORHOOD study participants and in independent glaucoma cases from the UK Biobank, respectively. In future additional SNPs and other clinical risk factors could be added to further improve discriminatory power (AUC) of these genetic prediction models. Certainly, there are more variants to be found for IOP.

> The SNPs discovered in this study collectively explained between 17%-19% of the IOP variance

The SNPs discovered in this study collectively explained between 17%-19% of the IOP variance, indicating that GWAS has not yet reached its limit in identifying genetic loci for IOP given the estimated heritability of IOP at 55%.[3] Expanding the sample size would identify more loci, albeit of increasingly low effect sizes. One of the limitations of this study is the fact that genetic data was derived from only Caucasian samples, excluding individuals of Asian and African ancestry. This questions the transferability of this data to the other races. Recent studies have found that **POAG genetic susceptibility alleles associated in Caucasians appear to play a greatly reduced role in populations of African ancestry**, indicating the need for separate studies.[4] Nevertheless, findings in this study bring close the translation of the genetic findings to clinical prediction and diagnosis and now direct the research community towards the more challenging task of functional validation and assessment of clinical utility of these risk variants.

> This study brings closer the translation of the genetic findings to clinical prediction and diagnosis

References

1. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 2003;160:636-645.
2. MacGregor S, Ong JS, An J, et al. Genome-wide association study of intraocular pressure uncovers new pathways to glaucoma. Nat Genet. 2018;50(8):1067-1071. doi: 10.1038/s41588-018-0176-y. Epub 2018 Jul 27. PubMed PMID: 30054594.
3. Sanfilippo PG, Hewitt AW, Hammond CJ, Mackey DA. The heritability of ocular traits. Surv. Ophthalmol. 2010;55:561-583.
4. Liu Y, Hauser MA, Akafo SK, et al. Investigation of known genetic risk factors for primary open-angle glaucoma in two populations of African ancestry. Invest Ophthalmol Vis Sci. 2013;54(9):6248-6254.

Systemic Biomarkers of Glaucoma


Comment by Tanuj Dada and Vivek Gupta, New Delhi, India

78259 Bone lead levels and risk of incident primary open-angle glaucoma: The VA Normative Aging Study, Wang W, Moroi S, Bakulski K, Mukherjee B, Weisskopf MG, Schaumberg D, Sparrow D, Vokonas PS, Hu H, Park SK, Environmental health perspectives 2018; 126: 087002

Wang *et al.* report the association between risk of POAG and lead exposure (which leads to oxidative stress) using bone lead as a biomarker of cumulative lead dose (tibia lead) or an endogenous source of stored lead (patella lead). The study examined a prospective cohort of 634 men without glaucoma who had tibia and patella K X-ray fluorescence lead measurements between 1991 and 1999 and standard ocular evaluations by optometrists until end of 2014. Forty-four incident cases of POAG were identified by the end of follow-up (incidence rate = 74 per 10,000 person-years; median follow-up = 10:6 y) and a **ten-fold increases in patella lead and tibia lead were associated with HRs of 5.06 (95% CI: 1.61, 15.88, p = 0:005) and 3.07 (95% CI: 0.94, 10.0, p = 0:06), respectively**. This study provides the first longitudinal evidence that increased levels of bone lead may be an important risk factor for POAG.

> This study provides the first longitudinal evidence that increased levels of bone lead may be an important risk factor for POAG

The major limitations of the study are the nonspecific criteria for diagnosis of glaucoma and the diagnosis not being confirmed by glaucoma specialists. Glaucoma (POAG) was diagnosed by optometrists in participants who showed any one of the following characteristics: (a) either eye having a CDR ≥ 0.7; (b) the difference of two eyes' CDRs ≥ 0:2; (c) any eye's CDR ≥ 0:6, with either disc hemorrhage or visual field defect; or (d) vision loss due to nerve fiber layer loss. This could have led to an overestimation of glaucoma with incorporation of false positive results based on large cup disc ratio's (physiological cupping) and nerve fiber layer loss due to causes of optic atrophy other than glaucoma. Longitudinal evaluation with serial photographs of the optic nerve and evaluation by expert ophthalmologists to detect structural changes were missing. Additionally, the IOP levels after follow-up were not included. It would have been useful if the investigators documented IOP values during follow-up and produced evidence for elevation of IOP attributed to lead toxicity which subsequently caused the development of glaucoma. Furthermore, eyes which were later diagnosed as POAG had much higher rates of ocular hypertension at baseline as compared to those who did not develop glaucoma (18.2 vs 2.2%) and this raises a possibility that all

subjects were not free of glaucoma at baseline evaluation. Data on impact of lead toxicity on other systems which may seriously impact quality of life and also impact glaucoma such as central/peripheral nervous system, cardiovascular, gastrointestinal, renal, haematological, etcetera, and blood levels of lead to categorize severity of health risk at baseline/follow-up were also not incorporated.

Nevertheless, the manuscript presents a valuable addition to published literature and underscores the importance of evaluating POAG patients (especially with occupational exposure) for lead toxicity.

Models of Glaucoma

A new Murine Model of Glaucoma

Comment by Makoto Aihara, Tokyo, Japan

78021 A murine glaucoma model induced by rapid *in vivo* photopolymerization of hyaluronic acid glycidyl methacrylate, Guo C, Qu X, Rangaswamy N, Leehy B, Xiang C, Rice D, Prasanna G, PLoS ONE 2018; 13: e0196529

Guo C. *et al.* developed a new ocular hypertension mouse model by impeding the outflow pathway in a controllable manner using a photopolymerizable biomatrix and a subsequent UVA light flash. A number of methods have previously been developed with the goal of producing ocular hypertension in rodents. However, an ideal model mimicking clinical glaucoma has been a big challenge. The new method in this paper looks simple to perform, with a high success rate. **The IOP elevation is mild and sustained compared to the previous models, and RGC loss and optic nerve degeneration were observed**. The ability to use OCT imaging is another significant advantage because continual examination is required to evaluate the glaucomatous progression in the animal model. This suggests that severe cataract or pupillary contraction may not be present in this model.

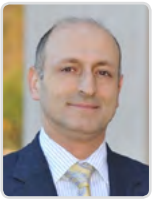
> This model is not suitable for screening of IOP-lowering therapies that target the conventional outflow pathway

While not specified in the paper, I hope that this procedure does not induce a severe inflammatory response or transient IOP elevation immediately after the procedure, which may affect the cellular reaction or the blood circulation of the retina or optic nerve. A potential limitation (as mentioned in the discussion) is that rodents lacks a stiff lamina cribrosa, in contrast to monkeys and humans, and the structural changes in mouse optic nerve may be induced by a different mechanism compared to the animals with a load-bearing lamina cribrosa. In addition, this model is produced by anatomically obstructing the angle.

Thus, it is not suitable for screening of IOP-lowering therapies that target the conventional outflow pathway. However, the advantages of this new procedure may outweigh the negative aspects and can be useful as a mouse ocular hypertension model.

Clinical Examination Methods

Retinal Layers in Glaucoma



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

78008 Diagnostic accuracy of macular ganglion cell-inner plexiform layer thickness for glaucoma detection in a population-based study: Comparison with optic nerve head imaging parameters, Koh V, Tham YC, Cheung CY, Mani B, Wong TY, Aung T, Cheng CY, PLoS ONE 2018; 13: e0199134

Koh *et al.* compared the diagnostic performance of macular and optic disc OCT parameters as measured with Cirrus HD-OCT to that of HRT3 for detection of glaucoma in the Singapore Chinese Eye study. The study provides us with important information regarding performance of the OCT or HRT3 in a population-based setting. There is a concern that case-control studies using patients and normal subjects enrolled in clinics could overestimate performance of diagnostic devices due to potential selection and/or ascertainment bias. **The investigators found that the vertical cup-to-disc ratio (and inferior quadrant RNFL thickness) derived from SD-OCT performed better (AUC = 0.94) than the best macular GCIPL measure (minimal GCIPL, AUC = 0.89) or HRT3's vertical CDR (AUC = 0.86) based on area under ROC curves or sensitivity at 85% specificity (sensitivities of 89%, 61%, and 65%, respectively).**

> There is a concern that case-control studies using patients and normal subjects enrolled in clinics could overestimate performance of diagnostic devices due to potential selection and/or ascertainment bias

The results are encouraging and confirm the potential role of SD-OCT optic disc/RNFL measures for glaucoma screening or detection of glaucoma under other settings. It is not unexpected to see OCT-derived CDR or RNFL thickness measures outperform macular parameters for detection of glaucoma as the former measures are better reflective of the entire RGC complement of an eye than macular measures. However, the results should be interpreted taking into account of a few caveats. It seems that diagnosis of glaucoma, or lack thereof, was established in real-time by clinical examination of the optic disc by a single clinician and therefore, one cannot rule out possible ascertainment bias that could

have actually diluted the performance of OCT measures. The mean deviation of the glaucoma group was about –9 dB and therefore, the glaucoma subgroup had moderate disease on average. This could, conversely, have led to a more optimistic impression of OCT or HRT3's performance. The average axial length was 23.9 mm in both glaucoma and normal groups, on the low side for an Asian population, and thus limiting the generalizability of the findings to myopic individuals. It would have been interesting to see the proportion of eyes detected by each of the best-performing measures in a Venn diagram to see how complementary the corresponding information would be. Also, an ROC curve for a linear combination of the best-performing parameters from each modality would have been very useful to confirm or refute the utility of using combined parameters from different diagnostic domains.

I would like to commend the authors for providing much needed data to better clarify the potential utility of OCT devices for screening in real-world setting.

Retinal Vasculature in Glaucoma

Comment by Alex Huang, Los Angeles, CA, USA

78032 Pilot study assessing the structural changes in posttrabecular aqueous humor outflow pathway after trabecular meshwork surgery using swept-source optical coherence tomography, Yoshikawa M, Akagi T, Uji A, Nakanishi H, Kameda T, Suda K, Ikeda HO, Tsujikawa A, PLoS ONE 2018; 13: e0199739

In this paper, the authors compared post-trabecular aqueous humor outflow (AHO) pathway anatomy using anterior segment swept-source optical coherence tomography before and after minimally invasive glaucoma surgeries (MIGS). The authors reconstructed a 3-D representation of distal-AHO pathways using methods they previously developed. The constructs were compared qualitatively as pathways as being 'increased,' 'non-significantly changed,' or 'decreased' after surgery. Quantitatively, AHO pathways were measured from the collector channel to episcleral vein when the entire pathway was observable. After successful MIGS and IOP lowering, all of the qualitative outcomes were seen. **There was no significant difference in AHO pathway area before (3155 ± 1633 pixels) and after (3212 ± 1684 pixels; $p = 0.50$) surgery**.

The immediate impression was that there was no consistent structural association between distal AHO pathway anatomy (qualitatively or quantitatively) and IOP reduction. The authors noted considerable prior AHO structural and tracer-based research, spurned in large part by MIGS. Put together, the only consistent conclusion has been that the AHO biological system is much more complex than originally appreciated.

The immediate impression was that there was no consistent structural association between distal AHO pathway anatomy (qualitatively or quantitatively) and IOP reduction

The TM has long been held to be the main source of AHO resistance. In this case, the observations in this report are not surprising. TM was ablated, IOP was lowered, and thus the distal outflow pathways did not have to change. However, we simultaneously know that distal AHO can change. Phase-sensitive OCT,[1] muscarinic agonists, and laser trabeculoplasty have shown distal AHO pathway structural alterations. Aqueous angiography has shown the ability of the eye to dynamically increase and decrease AHO.[2,3] Thus, the overall 'no-change' in this paper was unlikely because distal AHO pathways simply did not change but instead because the eye was responding differently to different circumstances ('increased,' 'decreased', etc.). There was no 'net' change. Potential reasons for various ocular responses would be to prevent blood reflux into the eye or to maintain stable IOP for stable optics.

Ultimately, this paper showed that distal AHO anatomy *change* did not predict MIGS outcomes. What remains to be seen is whether pre-operative characteristics (structural or flow-based) can predict MIGS outcomes.

Ultimately, this paper showed that distal AHO anatomy *change* did not predict MIGS outcomes

References

1. Li P, Reif R, Zhi Z, et al. Phase-sensitive optical coherence tomography characterization of pulse-induced trabecular meshwork displacement in ex vivo nonhuman primate eyes. J Biomed Opt 2012;17(7):076026.
2. Huang AS, Li M, Yang D, et al. Aqueous Angiography in Living Nonhuman Primates Shows Segmental, Pulsatile, and Dynamic Angiographic Aqueous Humor Outflow. Ophthalmology 2017;124(6):793-803.
3. Huang AS, Camp A, Xu BY, et al. Aqueous Angiography: Aqueous Humor Outflow Imaging in Live Human Subjects. Ophthalmology 2017; 124(8):1249-1251.

Forms of Glaucoma

Carbs and Glaucoma

Comment by Louis Pasquale, New York, NY, USA

77892 Carbohydrate ingestion induces differential autonomic dysregulation in normal-tension glaucoma and primary open-angle glaucoma, Cao L, Graham SL, Pilowsky PM, PLoS ONE 2018; 13: e0198432

This paper explores the role of autonomic dysfunction in primary open-angle glaucoma (POAG, n = 18), normal tension glaucoma (NTG, n = 19) and 36 age-matched controls. The exact IOP profile of the glaucoma patients was not provided. All patients fasted overnight and the following morning they underwent continuous electrocardiogram and measures of finger blood pressure while lying down. These measures were repeated after five minutes of passive standing. Subsequently, they consumed a 600 kilocalorie, carbohydrate-rich meal. This was followed by repeat physiological measures in both the supine and standing position at 30-minute intervals over a two-hour period. In this experimental paradigm, the effect of two perturbations are assessed: passive positional change and a vasovagal response whereby a meal induces a shift in blood flow to the gut.

A major concern is that a myriad of derived outcomes are generated and numerous comparisons between these outcomes are made. While the authors recognize this issue, I do not believe they fully correct for the multiple comparison problem that this work presents

In addition to heart rate and blood pressure, the investigators derive the spectral power of the variability of these parameters at low frequency and high frequency bands to assess the intrinsic sympathovagal function of the heart. A major concern is that a myriad of derived outcomes are generated and numerous comparisons between these outcomes are made. While the authors recognize this issue, I do not believe they fully correct for the multiple comparison problem that this work presents. With that said, I would highlight the following outcome. **Thirty minutes after the meal, the mean arterial pressure decreased in POAG versus control subjects by approximately ten mmHg both in the supine and standing position.** This did not happen in the NTG group. The authors suggest this postprandial hypotensive response represents a form of autonomic failure after an

essential normal activity that might de-stabilize ocular perfusion and contribute to optic nerve degeneration in POAG. The subject of dynamic autonomic function in POAG most certainly deserves further study.

> The authors suggest this postprandial hypotensive response represents a form of autonomic failure after an essential normal activity that might de-stabilize ocular perfusion and contribute to optic nerve degeneration in POAG

Surgical Treatment

Trends in Glaucoma Surgery

Comment by Rupert Bourne, Cambridge, UK

78029 Trends in Glaucoma Surgical Procedures in Portugal: A 16-Year Nationwide Study (2000-2015), Barbosa-Breda J, Gonçalves-Pinho M, Santos JV, Rocha-Sousa A, Abegão-Pinto L, Stalmans I, Freitas A, Journal of Glaucoma 2018; 27: 682-686

In this paper, Barbosa-Breda *et al.* report a retrospective database analysis of inpatient and surgical outpatients' episodes of all public hospitals in mainland Portugal, in order to model the change in types of glaucoma surgery conducted between 2000 and 2015. Although this does not reflect the full panorama of glaucoma surgery in the country, given that a quarter of all ophthalmic procedures are carried out in private facilities, this does give an interesting overview of practice patterns in a European country which can be compared with similar studies over different time periods in other countries. A previous study has shown that in 2015, 2.2% of the total Portuguese population were taking at least one ocular hypotensive eye drop medication, which gives context to this country's burden of known glaucoma/treated ocular hypertension.[1] Other European and high-income countries such as the UK,[2] the Netherlands,[3] Canada[4] and the USA[5] noted a reduction in trabeculectomies in the mid-1990s to mid-2000s with the advent of prostaglandins. In several countries there followed a later upsurge, for example in the UK between 2005 and 2009.[6]

> This does give an interesting overview of practice patterns in a European country which can be compared with similar studies over different time periods in other countries

The authors note that the all-surgery glaucoma surgical rate is increasing as one would expect in an ageing population yet for trabeculectomies there was a relatively stable rate observed in Portugal (7/100,000) between 2000 and 2015. Interestingly, the average age of patients undergoing glaucoma surgery was approximately 67 years throughout this time period, suggesting that Portuguese ophthalmologists have been consistent in offering surgery relatively early in a patient's period of care. The authors comment that with older patients, ophthalmologists may favor augmenting topical treatment or offering laser on account of a shorter life expectancy and more in the way of comorbidities. **Cyclophotoablation rates increased over the time period with a steep increase in 2015 (accounting for 16% of the glaucoma surgical procedures undertaken), possibly reflecting its use across a wider range of glaucoma severities than in the past**.

References

1. Sousa DC, Leal I, Nascimento N, et al. Use of ocular hypotensive medications in Portugal: PEM study: a cross-sectional nation-wide analysis. J Glaucoma. 2017;2:571-576.
2. Keenan TDL, Wotton CJ, Goldacre MJ. Recent trends in the rate of trabeculectomy in England. Eye. 2011;25:1243-1245.
3. van der Valk R, Schouten JS, Webers CA, Beckers HJ, van Amelsvoort LG, Schouten HJ et al. The impact of a nationwide introduction of new drugs and a treatment protocol for glaucoma on the number of glaucoma surgeries. J Glaucoma 2005;14(3):239-242.
4. Rachmiel R, Trope GE, Chipman ML, Gouws P, Buys YM. Effect of medical therapy on glaucoma filtration surgery rates in Ontario. Arch Ophthalmol 2006;124(10):1472-1477.
5. Strutton DR, Walt JG. Trends in glaucoma surgery before and after the introduction of new topical glaucoma pharmacotherapies. J Glaucoma 2004;13(3):221-226.
6. Tatham A, Sarodia U. Trends in the rate of trabeculectomy. Eye (London, England). 2010;24:1532-1533.

Baerveldt Implant and Endothelial Cell Loss

Comment by Robert Feldman, Houston, TX, USA

78195 Prospective cohort study of corneal endothelial cell loss after Baerveldt glaucoma implantation, Iwasaki K, Arimura S, Takihara Y, Takamura Y, Inatani M, PLoS ONE 2018; 13: e0201342

Aqueous shunt surgery is an increasingly prevalent treatment option for glaucoma. Decrease in endothelial cell density (ECD) is a serious and unfortunately common complication of this procedure. Iwasaki *et al.* describe a prospective study evaluating changes in ECD after Baerveldt glaucoma implantation with tube insertion in the anterior chamber versus the pars plana. The study also analyzed whether tube position affected ECD with anterior segment optical coherence tomography (ASOCT).

This study included 59 eyes with Baerveldt glaucoma implantation, with the tube inserted in the anterior chamber in 45 eyes and the pars plana in 14 eyes. Included patients were 20 years of age or older and had a diagnosis of refractory glaucoma. Eyes where the primary surgery was a Baerveldt implant, with a previous aqueous shunt, or with congenital glaucoma were excluded. Baerveldt implants with a 350-mm^2 plate were used. ECD was calculated overall, in the central cornea, and for the quadrants where the tube was inserted and contralateral to the tube. ASOCT was used to image the tube at one month postoperatively, with tube-cornea distance and tube-cornea angle calculated by the instrument's software.

Forty-one eyes had adequate corneal ECD measurements from all follow-up visits. ECD overall decreased significantly from baseline at three months (5.2%), six months (6.4%), and 12 months (9.2%) after surgery, with decreases in the tube insertion quadrant at all postoperative visits and at six months and 12 months postoperatively in the central and contralateral to the tube quadrants. In 32 eyes with anterior chamber tube insertion, corneal ECD decreased significantly from baseline in the tube insertion quadrant at 3 months (9.6%), six months (10.7%), and 12 months (9.2%) postoperatively. ECD at the central cornea decreased significantly at six months (7.2%) and 12 months (12.1%) postoperatively; contralateral cornea ECD decreased significantly at only 12 months (10.3%) postoperatively. **Eyes with pars plana tube insertion had no decrease in ECD density at any corneal areas postoperatively**.

ASOCT analysis found that the **tube-cornea angle was negatively correlated with the decrease in ECD at the tube insertion quadrant and central cornea** only. No correlation was found with tube-cornea distance and ECD decrease. Multivariate analysis showed that exfoliation glaucoma and narrow tube-cornea angle were associated with severe ECD decrease.

This study analyzes the relationship between ECD decrease and Baerveldt implantation with tubes in the anterior chamber and pars plana prospectively. It is a good start at determining the risk factors for this complication.

Outcomes of a Schlemm Microstent Implantation

Comment by Nils Loewen, Pittsburgh, PA, USA

78011 A Schlemm canal Microstent for intraocular pressure reduction in primary open-angle glaucoma and cataract: The HORIZON Study, Samuelson TW, Chang DF, Marquis R, Flowers B, Lim KS, Ahmed IIK, Jampel HD, Aung T, Crandall AS, Singh K, Ophthalmology 2018; 0:

In this randomized controlled study, Samuelson *et al.* followed 556 patients for 24 months and compared IOP and medication after Hydrus implantation (Ivantis, Inc, Irvine, CA) combined with cataract surgery versus cataract surgery alone. The Hydrus is made out of nitinol, nickel-titanium alloy, and has a length of 8 mm[1] spanning about 76°. Like the iStent (Glaukos, San Clemente, CA) made of titanium, it is implanted through viscoelastic under direct gonioscopic visualization. The study had an adequate sample size and was rigorously designed.

The differences between both groups were surprisingly small: Hydrus patients had a 2.2 mmHg larger IOP reduction than control patients (Hydrus: −7.6 ± 4.1 mmHg (mean ± standard deviation, SD), control: −5.3 ± 3.9 mmHg control). 19.5% more Hydrus than control patients had a more than 20% IOP reduction (Hydrus: 77.3%, control: 57.8%). Similarly, the Hydrus reduced medications by 0.4 more than the control (Hydrus: 1.7 ± 0.9 to 0.3 ± 0.8, control 1.7 ± 0.9 to 0.7 ± 0.9). The results are strikingly similar to the seminal iStent study,[2] in which 18% more iStent eyes achieved an IOP reduction of more than 20% compared to controls.

> The results are strikingly similar to the seminal iStent study, in which 18% more iStent eyes achieved an IOP reduction of more than 20% compared to controls

In this Hydrus study, patients had an IOP of about 18 mmHg prior to and 25 mmHg after washout. One can compute this as an IOP reduction to 18 mmHg (Hydrus) and to 20 mmHg (controls).

Cataract surgery can cause an IOP drop on its own.[3] Interestingly, **such a trabeculoplasty-like effect is not present in MIGS procedures that ablate the TM**, like the Trabectome (Neomedix Inc., Tustin, CA).[4,5]

Because Schlemm's canal has septations that hinder circumferential flow, a single opening (*e.g.*, iStent) provides access to approximately 60° of outflow channels.[6] The Hydrus would be predicted to achieve access to nearly 120° when disrupting Schlemm's canal septations 60° apart. It is interesting that the Hydrus does not appear to be fundamentally better than the iStent despite this advantage. Recent reports found a biofilm buildup[7] and fibrosis[8] that occlude the lumen of the iStent. This might explain the declining efficacy compared to TM ablation as observed in a study using *Exact Matching*[9] and also affect the Hydrus.

References

1. Shareef S, Fea A, Ahmed IIK. The Hydrus Micro-stent. In: Samples JR, Ahmed IIK (eds.), Surgical Innovations in Glaucoma, pp. 171-174. Springer, New York, 2014.
2. Samuelson TW, et al. Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. Ophthalmology. 2011;118:459-467.
3. Mansberger SL, et al. Reduction in intraocular pressure after cataract extraction: the Ocular Hypertension Treatment Study. Ophthalmology. 2012;119:1826-1831.
4. Neiweem AE, Bussel II, Schuman JS, Brown EN, Loewen NA. Glaucoma Surgery Calculator: Limited Additive Effect of Phacoemulsification on Intraocular Pressure in Ab Interno Trabeculectomy. PLoS One. 2016;11, e0153585.
5. Parikh HA, Bussel II, Schuman JS, Brown EN, Loewen, N. A. Coarsened Exact Matching of Phaco-Trabectome to Trabectome in Phakic Patients: Lack of Additional Pressure Reduction from Phacoemulsification. PLoS One. 2016;11, e0149384.
6. Rosenquist R, Epstein D, Melamed S, Johnson M, Grant, WM. Outflow resistance of enucleated human eyes at two different perfusion pressures and different extents of trabeculotomy. Curr Eye Res. 1989;8:1233-1240.
7. Shah M, Campos-Möller X, Werner L, Mamalis N, Ahmed IIK. Midterm failure of combined phacoemulsification with trabecular microbypass stenting: Clinicopathological analysis. J Cataract Refract Surg. 2018;44:654-657.
8. Capitena Young CE, et al. Histopathologic Examination of Trabecular Meshwork Changes After Trabecular Bypass Stent Implantation. J Glaucoma. 2018;27:606-609.
9. Esfandiari H, et al. Two-year data comparison of ab interno trabeculectomy and trabecular bypass stenting using Exact Matching. J Cataract Refract Surg. 2018; doi:10.20944/preprints201811.0109.v1

Ethnic Differences in Trabectome Outcomes

Comment by Sameh Mosaed, Irvine, CA, USA

78271 Ab interno trabeculectomy with Trabectome: outcomes in African American versus Caucasian patients, Nazarali SA, Damji KF, Canadian Journal of Ophthalmology 2018; 53: 361-364

In this prospective case-control study, 82 African-American patients were compared with 82 Caucasian patients who underwent ab-interno trabeculectomy with the Trabectome over an eight-year period. The data were collected from the Trabectome database, representing the results from dozens of different Trabectome surgeons from US and international centers. Nearest-neighbor matching was used to match data by glaucoma type, age, and baseline IOP. All subjects had at least 12 months followup. Thirty-four percent of the cases in both groups were comprised of combined Trabectome+ phaco cases, where 66% were Trabectome alone cases.

The authors found that there were no statistical differences in the outcomes between the two groups in terms of IOP, number of medications, or complication rates. IOP was reduced from 21.2 mmHg in both groups to 16.1 mmHg in the African-American group and 15.7 mmHg in the Caucasian group.

African-American patients are known to have poorer outcomes with incisional glaucoma surgery as compared with Caucasian patients as supported by decades of evidence in the literature. This is true for trabeculectomy, as well as for tube shunt implantation, ex-PRESS glaucoma filtration devices, and canaloplasty. The basis of these race-based differences are thought to be related to more robust wound-healing responses in patients of African descent. However, little data exists on the outcomes of angle-based surgeries in this population, which may be affected less by wound-healing responses than conjunctival or tenon-based procedures. Late postoperative scarring can result in PAS formation and closure of the trabecular-bypass cleft created by the Trabectome, however, it appears more likely that downstream outflow resistance is the limiting factor in cases of failed TM bypass procedures. The data from this study suggests that race does not significantly reduce the success rate or IOP reduction seen in patients from African descent, implying that postoperative wound healing plays a diminished role in outcomes of TM bypass surgery.

The limitations of the study include use of the multi-center database which can lead to incomplete data collection and lack of a controlled protocol for degrees of ablation, postoperative medication usage, and variability in surgeon technique. Nevertheless, this study provides some confidence that TM bypass procedures may rely less on post-operative wound healing and may level the proverbial playing field among races for surgical success.

References

1. The Advanced Glaucoma Intervention Study (AGIS): 4. Comparison of treatment outcomes within race: Seven-year results. Ophthalmology. 1998;105:1146-1164.
2. The Advanced Glaucoma Intervention Study (AGIS): 9. Comparison of glaucoma outcomes in black and white patients within treatment groups. Am J Ophthalmol. 2001;132:311-320.
3. Freedman J, Ferri S. Long-term comparison using Ex-Press glaucoma shunt in black and white patients. Can J Ophthalmol. 2014;49:200-204.
4. Gedde SJ, Schiffman JC, Feuer WJ, et al. Treatment outcomes in the Tube Versus Trabeculectomy (TVT) study after five years of follow-up. Am J Ophthalmol. 2012;153:789-803.
5. Ishida K, Netland PA. Ahmed Glaucoma Valve implantation in African American and white patients. Arch Ophthalmol. 2006;124:800-806.
6. Taubenslag KJ1, Kammer JA. Outcomes Disparities between Black and White Populations in the Surgical Management of Glaucoma. Semin Ophthalmol. 2016;31(4):385-393.

Reporting Surgical Harm

Comment by Luca Rossetti, Milan, Italy

78208 Reporting harm in glaucoma surgical trials: Systematic review and a consensus-derived new classification system, Sii S, Barton K, Pasquale LR, Yamamoto T, King AJ, Azuara-Blanco A, American Journal of Ophthalmology 2018; 194: 153-162

Assessment of safety of surgical procedures can be as important as efficacy evaluation. A comprehensive list of complications is mandatory in a surgical trial report although not sufficiently informative if not coupled with a quantification of harm severity. For example, general surgery trials usually adopt a standardized classification of severity to quantify degree of surgical harm. Are the standards of harm reporting for glaucoma surgical trials adequate to help ophthalmologists in the choice of a surgical procedure? This topic was the objective of a recently published meta-analysis. As a result of the systematic review, one further goal of the study was the development of a classification system for reporting surgical complications severity through a Delphi consensus approach.

This meta-analysis included 47 glaucoma surgery trials focusing on outcomes of trabeculectomy and aqueous shunts published in English approximately in the last decade. The authors found that the quality of harm reporting was generally poor – using the CONSORT checklist for reporting of harm – and none of the studies used a validated instrument to report severity of adverse events. Criteria that were infrequently reported included withdrawals owing to harm, subgroup analyses for harm, absolute risk of harm, severity of

adverse events, definition and analysis of harm. And the few trials reporting the severity of complications did not use a standardized method for classification. To provide a standardized instrument to report harm according to severity, 43 glaucoma experts from the US, Asia-Pacific countries and Europe participated in a Delphi survey. All complications of glaucoma surgery were reviewed and graded according to a 1 to 10 severity scale and substantial consensus was achieved. Although with some limitations, *e.g.*, results from a Delphi survey are not necessarily valid and in this case need to be validated with the patients' perspective, the proposed classification system of severity based on expert consensus might help to better compare risks and benefit of different surgical procedures for glaucoma.

Miscellaneous

Strategies to Compensate for Visual Field Impairment

Comment by Pradeep Ramulu, Baltimore, MD, USA

78199 Glaucoma-related differences in gaze behavior when negotiating obstacles, Lajoie K, Miller AB, Strath RA, Neima DR, Marigold DS, Translational vision science & technology 2018; 7: 10

In a very nice set of experiments, Lajoie and colleagues examine how glaucoma patients with significant VF damage (better-eye MD =-9 dB) and a slightly younger control group with normal vision navigate a customizable obstacle course. Using a sophisticated set-up, the authors compare how quickly individuals move through the course, how often they contact obstacles they were asked to avoid and, merging head-mounted eye-tracker data with head-mounted video camera data, where they direct their gaze during the mobility task. Both groups were asked to walk the course under normal (undistracted) conditions and also while counting backwards by 3's or while completing a visual search task. For both the distracted and undistracted conditions, **glaucoma patients walked slower than controls and were more likely to contact an obstacle**. For both groups, gait speed slowed and the number of obstacle contacts increased with distraction. Glaucoma patients also differed from controls with regards to where they set their gaze while navigating the course. Specifically, **glaucoma patients directed their gaze more proximal to where they were, and also directed their gaze towards obstacles more than controls**. Given that the gaze changes in the glaucoma group did not enable normal walking speeds, and occurred in the context of more obstacle contacts, the authors argue that they were not adaptive, and may be maladaptive. For example, fixating on closer locations makes it harder to route-plan, making overall walking speed slower. It may also result in sharper, more frequent turns, resulting in more collisions. Likewise, fixating on an obstacle may not help avoid the obstacle, as our natural tendency is to move in the direction we look. We hope the authors follow up on this work to determine if altering the gaze patterns of glaucoma patients can prevent falls, and result in safer, more confident glaucoma patients.

ARVO 2019

APRIL 28 – MAY 2 | VANCOUVER, BC

There's still time!

Make plans to join ARVO in Vancouver.

ARVO.org/AM

ARVO®
The Association for Research in Vision and Ophthalmology

World Glaucoma Association
The Global Glaucoma Network

Basic Course in Glaucoma

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

GONIOSCOPY

Anton Hommer, Tanuj Dada, Pooja Shah, Talvir Sidhu

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

INTRAOCULAR PRESSURE

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

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

Now also available in Spanish!

STANDARD AUTOMATED PERIMETRY

Anders Heijl, Balwantray Chauhan

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

CLINICAL EXAMINATION OF THE OPTIC NERVE

Michael Coote, Jonathan Crowston

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

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

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

Journal of Glaucoma & WGA

It is with great pleasure that we announce that the Journal of Glaucoma (JOG) has become the official journal of the World Glaucoma Association (WGA)!

This collaboration joins together the world's premier journal for glaucoma research and the largest international society for glaucoma, representing over 11,000 members and 89 glaucoma societies from around the world.

Free access for members of WGA affiliated Glaucoma Societies

As the official journal of the WGA, online access to the *Journal of Glaucoma* is now provided **for free** to all individual members of our affiliated Glaucoma Societies, including all ophthalmologists from sub-Saharan countries and glaucoma fellows worldwide. This free access has been made possible through generous support from two of our industry partners, **Allergan** and **Novartis**. Access is provided via the personal profile page of every individual member via the WGA#One platform.

Please visit www.wga.one/wga/journal-of-glaucoma to find out how you are able to access JOG via the WGA#One platform.

In case you are a member of one of our affiliated Glaucoma Societies, but not yet registered in WGA#One, please complete the contact from on the WGA homepage and contact your regional or local Glaucoma Society to notify WGA about your membership via info@worldglaucoma.org. Only after their confirmation we are able to connect you.

If you are not affiliated to any Glaucoma Society yet, but are interested, please contact your local or regional glaucoma society for membership opportunities. An overview of all WGA affiliated Glaucoma Societies can be found in the WGA Directory.

Journal of Glaucoma

Journal of Glaucoma is currently the only scientific journal devoted to glaucoma that is both indexed and has an impact factor, giving the Journal a unique position in the glaucoma community. In conjunction with the World Glaucoma Association, the publisher will also be offering special rates for hard copy subscriptions.

Journal of Glaucoma has had considerable success in 2017, with a rising impact factor (2.263, representing an 8% increase from 2015), increasing submissions (>660), and decreased times from acceptance to online publication (2 weeks) and print (< 3 months).

Journal of Glaucoma now ranks among the fastest growing journals and is a leader in publication turn-around time.

Free access to *Journal of Glaucoma* (JOG) online is only available when you are logged into your WGA#One account!.

GREEN = Go get your eyes tested for Glaucoma Save Your Sight!

World Glaucoma Week

March 8–14, 2020

www.worldglaucomaweek.org

worldglaucomaweek | worldglaucomaweek | #GlaucomaWeek

e-IGR.com

IGR Searchable Glaucoma Database

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

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

Features

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

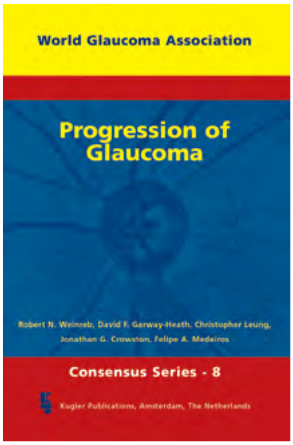
International Glaucoma Review is published as an online journal only.

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

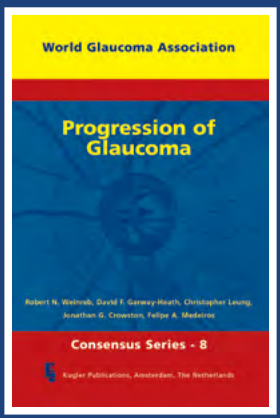
www.e-IGR.com

Consensus 8 - Progression of Glaucoma

Edited by: R.N. Weinreb, D.F. Garway-Heath, C. Leung, J.G. Crowston and F.A. Medeiros
2011



The goal of this consensus is to provide a foundation for identifying progression of glaucoma and how it can be best done in clinical practice. Identification of those areas for which we have little evidence and, therefore, the need for additional research always is a high priority.



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

Through the courtesy of the WGA and Kugler Publications, you may now download the PDF file of Consensus 8 **free of charge** through your WGA#One account. Consensus 1–7 have previously been made available through IGR and are now also accessible through your WGA#One account.

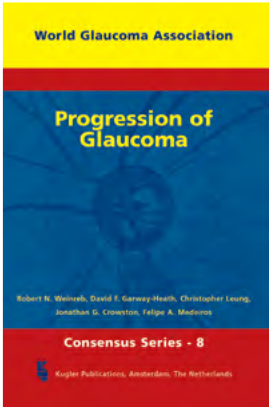
Robert N. Weinreb
Consensus Initiative Chair
World Glaucoma Association

Consensus 8 - Table of contents

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

Through the courtesy of the WGA and Kugler Publications, you may now download the PDF file of Consensus 8 **free of charge** through your WGA#One account. Consensus 1–7 have previously been made available through IGR and are now also accessible through your WGA#One account.

Robert N. Weinreb
Consensus Initiative Chair
World Glaucoma Association



SUMMARY CONSENSUS POINTS

Section 1 – Visual function progression

1. Standard white-on-white automated perimetry (SAP), with a fixed testing matrix covering at least the central 24 degrees, is preferred for measuring progression in eyes with glaucomatous VF loss.
   Comment: more research is needed into the use of alternative measures of visual function (FDP, resolution perimetry, motion perimetry and others) to detect glaucomatous progression, before any of these can be considered alternatives to SAP for measuring progression.
   Comment: It is possible for glaucomatous optic neuropathy to progress structurally in the absence of functional progression and vice-versa.
2. Perform sufficient examinations to detect change.
   Comment: decisions on progression should not be made by comparing only the most recent field with the one before.
   Comment: suspected progression should be confirmed by repeating the field.

Baseline data collection (no previous VFs available) – first two years

3. In clinical practice, at least two reliable VFs is optimal in the first six months.
   Comment: In clinical scenarios, where the lifetime risk of visual disability is high, such as those who already have advanced damage, three baseline VFs may be necessary.
   Comment: A good baseline of reliable VFs is essential to be able to monitor for progression.
   Comment: Unless there are obvious learning effects, high false-positive errors, rim artifacts, or other obvious artifacts, examinations should not be removed from the analyses.
4. At least two further VFs should be performed within the next 18 months.
5. VF testing should be repeated sooner than scheduled if possible progression is identified on the basis of an 'event' analysis.
   Comment: In patients at risk of visual disability, performing six VFs in the first two years enables the clinician to rule out rapid progression (2 dB/year or worse) and establishes an ideal set of baseline data.
   Comment: the identification of possible progression may be on the basis of an 'event' criterion such as the Glaucoma Progression Analysis (in the Humphrey perimeter software) or 'Nonparametric Progression Analysis'.
6. Establish a new baseline after a significant therapeutic intervention (*e.g.*, surgery).
   Comment: the new baseline can be the last fields that defined the previous progression 'event'.

Follow-up data collection (after the initial two years)

7. The frequency of follow-up VFs should be based on the risk of clinically significant progression (based on extent of damage and life expectancy).
8. In low and moderate risk patients, subsequent VF frequency should be one VF per year (unless there is a long follow-up) and, as a rule, repeated sooner if possible. Progression is identified on the basis of an 'event' analysis, or if other clinical observations are suggestive of possible progression or increased risk of progression.

Comment: relevant clinical observations include structural progression (clinically noted or measured by imaging), a splinter hemorrhage, or inadequate IOP control.

9. In high risk patients, subsequent VF frequency should be two VFs per year and repeated sooner if possible progression is identified on the basis of an 'event' analysis, or if other clinical observations are suggestive of progression or increased risk of progression.
   Comment: following confirmed progression (by an 'event'), the frequency of testing should be based on the estimated rate of progression, risk factors and other clinical indicators of progression, stage of disease and life expectancy.
   Comment: patients who have been stable for a long period, or who are progressing so slowly as to be at little risk for reaching disabling levels of field loss, and other clinical parameters indicate low risk of progression, may have VF testing less frequently than 1 VF per year.

Visual field progression may be analyzed by either 'event-' or 'trend-'based methods

Event analysis: is change from baseline greater than a predefined threshold; the threshold is based on test retest variability (according to level of damage).

Trend analysis: determines the rate of change over time; the significance is determined by the variability of the measurement and the magnitude of change.

10. Both event and trend analyses are needed, largely for different time points in the follow-up during clinical care.
11. In general, event-based methods are used early in the follow-up, when few VFs are available for serial analysis.
    Comment: progression by an event criterion usually requires confirmation on at least two further occasions to be sufficiently sure that progression has truly occurred.
    Comment: confirmation of progression should usually be made on a separate occasion (patients have 'off days').
    Comment: When interpreting VF progression that is confirmed by an 'event' method, the clinician should look at:
    - the baseline fields, to ensure they are reliable and appropriate for the analysis;
    - the estimated rate of progression and the confidence of the estimate;
    - the severity of the visual loss in terms of impending impairment;
    - the risk factors for progression.
12. In general, rate-based analyses are used later in the follow-up, when a greater number of VFs is available over a sufficient period of time to measure the rate of progression.
    Comment: a rate of progression in the first two years is a rough estimate (wide range of possible rates around the central estimate); in most patients it takes longer to obtain a reliable estimate of the rate of progression.
    Comment: trend (regression) analysis provides an estimate of the rate of progression and a measure of the reliability of the estimate; the reliability of the estimate is judged from the confidence limit.
    Comment: clinicians should consider other clinical measures of progression and risk of progression when interpreting this information (these data provide the 'prior probability' for progression).
13. When progression is identified, the clinician should ensure that the progression is consistent with glaucoma and not related to some other cause.

Measure the rate of visual field progression

14. Clinicians should aim to measure the rate of VF progression.
    Comment: Estimating the rate of progression is invaluable for guiding therapeutic decisions and estimating the likelihood of visual impairment during the patient's lifetime.
15. In the absence of significant changes in therapy, the rate of progression of suitable global indices (MD or VFI, but not PSD or LV) is linear in treated glaucoma eyes, except at the most advanced stages.
16. As a linear model for progression is acceptable, trends may be extrapolated to predict future loss if there is no change in therapy, over appropriate intervals.
17. Both local and global metrics are needed for assessment of progression.
    Comment: Rates are most often measured on 'global' parameters, such as mean deviation, mean defect or visual field index. However, focal progression (such as paracentral) may be missed by a global index.
18. Total Deviation based methods are more sensitive to cataract than Pattern Deviation based methods. However, by eliminating or reducing the component of diffuse visual field loss, Pattern Deviation based methods may underestimate progression rates.
19. Use available software support.
    Comment: Subjective judgment of VF print-outs is unreliable and agreement among clinicians is poor. Statistical analysis, either in the perimeter software or stand-alone software, is advantageous to reliably identify and measure progressive VF change.

Pay attention to examination quality

20. Examinations of poor quality will likely lead to an erroneous assessment of progression.
    Comment: The most important factors to reduce test variability are a proper explanation of the test to the patient, appropriate instrument setup and 1:1 monitoring of the patient by a trained technician.
21. Do not rely automatically on the VF reliability indices.
    Comment: The VF reliability indices may be unreliable! The most useful index is the 'False Positive' rate; values greater than 15% likely represent a less reliable performance; values less than 15% do not guarantee reliability.

The technician is the best judge to exam quality.

22. If unreliable tests require repeating, the patient should be carefully reinstructed.

Use the same threshold test

23. Clinicians should select their preferred perimetry technology, test pattern, and thresholding strategy for the baseline tests and stick with the same test throughout the follow up.
    Comment: any analysis of progression can only be performed if a compatible threshold algorithm and test pattern is used.
24. In advanced glaucoma, smaller angular size SAP testing grids, *e.g.*, HFA 10-2 may be of value in a minority of patients.
    Comment: Kinetic perimetry and SAP with larger targets (*e.g.*, size V) may also be useful.

Comment: The advantages of a change in test pattern (*e.g.*, from a 24-2 to a 10-2 grid) should also be weighed against the disadvantages for progression analysis by commercial software.

Clinical trials

25. Event analyses aim to identify a statistically significant difference between study arms and not necessarily a clinically significant difference.
    Comment: As glaucoma is a chronic progressive disease and progression is generally linear, small amounts of progression that reach statistical significance become larger, clinically significant amounts of progression if there is no additional therapy.
26. Rate analyses of VF indices are an appropriate statistical approach to identify differences between treatment groups.
    Comment: Rate analysis methods have been used often in trials for other chronic progressive diseases, such as dementia.
27. Difference in the progression 'event' criterion applied in the various clinical trials limits comparison of the incidence of progression determined in those trials.
    Comment: Comparison of groups in different clinical trials is also hampered by mismatch of subjects with regard to stage of glaucoma, quality of visual field exams, and other traits.

Research needs

1. The development of 'event' criteria for progression based on individual patient test-retest variability.
2. There is a need to *compare event-based endpoints* and *rate of progression outcomes* in a data set with data acquired with appropriate frequency and test intervals with respect to clinical trials.
3. Further research is needed into the added value of smaller angular size test grids, and different size stimuli, *e.g.*, size V, in advanced glaucoma.
4. Determine appropriate dynamic ranges of stimulus contrasts for size III, and develop new stimuli with larger dynamic ranges of appropriate stimulus contrasts.
5. Improve the interface between perimetrist and device, and between patient and device.
6. Identify, or develop, stimulus types (*e.g.*, FDT) and test algorithms which provide optimal information content for progression analysis in children and adults who have difficulty performing a reliable SAP test.
7. Develop alternate methods for selecting stimulus locations in order to avoid extensive testing of blind areas and to focus on areas of interest.
8. Further assess the benefits of using prior threshold as a starting point in a follow-up test (or if threshold is < 0 dB previously, confirmation at that point that a 0 dB stimulus is not seen is sufficient).
9. Determine the optimal frequency and timing of tests for individual patients.
10. Use of good mathematical modeling.
11. Develop better approaches to identify learning effects.
12. Identify the appropriate test and frequency of testing for patients with progressive glaucomatous optic neuropathy and SAP within normal limits.

Section 2 – Structure

2.1 Technologies for measurement of optic disc and retinal nerve fiber layer (RNFL) parameters

1. Serial optic disc stereo-photography and RNFL photography are valuable and enduring methods for monitoring structural progression.
   Comment: Stereoscopic clinical examination of optic disc and RNFL may be useful to detect change in comparison with a baseline photograph.
   Comment: Subjective estimates of cup/disc ratio only detect large changes in cupping and are insufficient for monitoring structural changes.
2. Color fundus photography is the preferred imaging modality to identify disc hemorrhages and parapapillary atrophy.
   Comment: Disc hemorrhages and beta-zone PPA are known risk factors for glaucoma progression.
3. Changes in beta-zone parapapillary atrophy can signal glaucoma progression.
   Comment: Methods for evaluating changes in PPA require further validation and include fundus photography, CLSO, and SDOCT.
4. Several imaging instruments, including confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography objectively provide reproducible measurements and quantitative assessment of the optic disc and RNFL change.
   Comment: The detection of glaucoma progression by comparing sketches or descriptions of cup disc ratio in the clinical chart is generally not suitable for an early detection of progression and may be replaced by imaging techniques and/or optic disc photography.
   Comment: Imaging instruments provide progression detection analyses that can determine whether change is greater than the measurement variability of an individual eye.
5. There are several structural components of longitudinal change detection that likely contribute to the variability of measurements.
   Comment: These include variation in clinical disc margin visibility, intersession variation and accuracy of segmentation algorithms, variation in vascular blood volume and reference plane anatomy, and longitudinal image registration.
6. Image quality can influence our ability to detect structural change.
   Comment: Automated quality indices vary by instrument and are often proprietary with little information available about how they are constructed.
   Comment: Poor quality images can lead to either false positive or false negative results.
   Comment: For patient management decisions, clinicians should review the quality of images included in glaucomatous progression assessment.
7. More than one good quality baseline image facilitates progression analysis.
   Comment: Some instruments automatically acquire several baseline images during one imaging session.

2.2 Reproducibility of digital imaging instruments

1. Measurement variability influences the ability of any device to detect progression.

Comment: There is a wide range of reproducibility estimates in the literature for SLP, CSLO, and OCT. Although studies of comparisons of instruments within the same patient populations are limited, these techniques likely provide data of similar reproducibility.
Comment: Overall, SDOCT has better reproducibility than TDOCT.

2. There is a lack of consensus in the literature as to whether reproducibility changes across disease severity and this may vary across measured anatomic structures and techniques.

2.3 How to detect and measure structural change?

1. Event and trend based analyses are both useful for change detection.
   Comment: These analyses do not always concur.
2. It is important to estimate the rate of structural progression for clinical management decisions.
   Comment: The rates of change obtained from measurements from optic disc, RNFL and macular parameters may vary from each other.
3. Quantitative assessment of optic disc and retinal nerve fibre layer (RNFL) with imaging instruments is useful and complementary for change detection.
   Comment: Data are limited on whether macular measurements may be useful for change detection.
4. Differences in technologies and scan protocols could influence the detection of progression even when the same structure is measured.
5. There is no clear consensus on which instruments or parameters are optimal to detect structural progression. As technologies evolve, new instruments and parameters which are clinically useful will emerge.

2.4. How to define clinically significant structural change?

1. Interpretation of statistically significant change should take into account test-re-test variability and knowledge on the magnitude of age-related change in healthy individuals.
2. Knowledge of age-related change in healthy individuals should preferably come from actual longitudinal data and not extrapolation from crosssectional data.
3. A statistically significant change in a structural parameter such as rim area or nerve fiber layer thickness is a relevant change, however, it may not be clinically meaningful. The latter also should take into account the age and stage of the disease as well as an assessment of risk factors present.
   Comment: Currently, we have the tools to measure statistically significant change, however, to date we do not know how to fully assess the clinical importance of this change.

2.5 Issues in clinical practice

1. The optimal frequency of imaging tests is unknown.
   Comment: It depends on the severity of the disease and on the expected speed of progression.
2. In longitudinal studies investigating optic disc and RNFL progression in glaucoma, imaging tests have been performed once a year to three times a year.

3. The same structural measures (*e.g.* RNFL thickness) obtained with different instruments from the same manufacturer or the same technology from different instrument manufacturers (*i.e.*, spectral domain OCT) are not necessarily interchangeable for progression assessment.
4. Structural assessment of change is a valid method for detection of glaucomatous progression in a clinical trial.
   Comment: structural change has been shown to be predictive of future functional loss in glaucoma.

Section 3 – Structure and function

1. Both optic nerve structure and function should be evaluated for detection of glaucomatous progression.
2. Currently, no specific test can be regarded as the perfect reference standard for detection of glaucomatous structural and/or functional progression.
3. Progression detected by functional means will not always be corroborated using structural tests, and vice-versa.
   Comment: This is due to the imperfect nature of testing analysis, individual variability, and the structure-function relationship.
4. The use of standard automated perimetry as the sole method for detection of change may result in failure to detect or underestimate progression in eyes with early glaucomatous damage.
   Comment: In glaucoma suspect or ocular hypertensive eyes with initially normal achromatic perimetry, a change in optic nerve structure (*e.g.*, optic topography, retinal nerve fiber layer, optic disc hemorrhage, or parapapillary atrophy) may occur before perimetric change.
5. In general, detection of progression is more difficult in eyes with advanced disease.
   Comment: In eyes with advanced visual field damage, alternative perimetric strategies (*i.e.*, larger stimulus, macular strategies, kinetic perimetry, etc.) may need to be employed.
6. A statistically significant change in structure and/or function (which takes age and variability into account) is not always clinically relevant.
   Comment: Its clinical relevance for patient management must take into account other risk factors and lifetime risk of visual disability.
7. Progressive structural changes are often but not always predictive of future development or progression of functional deficits in glaucoma.
   Comment: The predictive strength depends on the method used to assess structural/functional change.
8. Corroboration of glaucomatous progression through the use of more than one test may provide more effective and more rapid detection of glaucomatous progression than repeated confirmation of change using a single modality.
   Comment: Examples of corroborative change include structure-function (*e.g.*, a structural change of the optic nerve and a spatially consistent functional change).
9. In order to increase the likelihood of detecting progression, test results should be of sufficient quality and appropriate quantity to provide meaningful information.
   Comment: While adjunctive testing can help clinical decision making, the use of multiple modalities of testing, at the expense of quality and appropriate frequency and quantity, should be avoided.

10. Life expectancy should be considered when evaluating the clinical relevance of a structural and/or functional change in glaucoma.
11. Structural and/or functional testing should be conducted throughout the duration of the disease.

Section 4 – Risk factors

1. Risk factors for glaucoma progression should be ascertained in all patients with glaucoma or suspected of being at increased risk of glaucoma.
2. Clinical risk factor assessment in glaucoma serves two roles. It provides (a) prognostic information; and (b) a basis for disease management.
   Comment: While proof of causality is desirable, the pragmatic nature of clinical medicine allows the use of risk factors of varying evidence quality and even clinical signs to be used in clinical management.
3. The use of risk factors in clinical management should take into account: (a) the strength of the risk factor for disease progression; and (b) the practicality and potential harm of reducing that risk factor.
4. Ocular hypertension is itself a strong risk factor for glaucoma, with rates of progression depending on the presence or absence of other risk factors.
   Comment: Accounting for these risk factors is critical to clinical decision making in the management of OHT patients.
   Comment: Risk factor assessment in OHT helps determine an individual's need for IOP lowering medication and also informs on the frequency of follow up.
5. Risk calculators provide a means for quantifying risk of glaucoma progression in appropriate individuals with similar baseline characteristics to those present in the study.
   Comment: The utility of these risk calculators in clinical practice still needs to be determined.
6. Higher mean IOP is a strong risk factor for glaucoma progression.
   Comment: More studies are needed to evaluate the role of other IOP parameters as risk factors for glaucoma progression.
7. A thinner central cornea is a risk factor for progression in patients with higher baseline IOP.
8. The presence of pseudo-exfoliation syndrome is an independent risk factor for progression.
9. The presence of a disc haemorrhage, older age, and lower ocular perfusion pressure are risk factors for progression.
   Comment: The relationship between low blood pressure and risk of progression is complex.
10. While estimates of risk of progression for individual patients based on completed large clinical trials are available, the use of such estimates varies considerably in clinical practice.
11. There is greater information available regarding the importance of risk factors for progression from early to moderate disease than from moderate to severe disease.
    Comment: Few adequately powered studies have prospectively assessed the risk factors for blindness from glaucomatous disease.
12. The relative importance of risk factors for progression may vary depending upon the stage of glaucomatous disease.

Comment: Some risk factors that do not appear to be important predictors of progression from early to moderate glaucoma may be relatively more important in predicting progression from moderate to severe disease and vice versa.

13. Studies that longitudinally assess risk factors for functional vision loss and blindness from glaucomatous disease are needed.

Section 5 – Glaucoma and its impact on patient function

1. Standard measures for assessing glaucoma include measures of optic nerve structure and function including cup/disc ratios, thickness of the retinal nerve fiber layer and ganglion cell layer, white on white visual fields, blue on yellow visual fields, and intraocular pressure. While these measures provide an assessment of the eye, they are surrogates for how the patient is functioning. Both PROs and functional tests provide important information in addition to standard tests on the impact of glaucoma on the patient.
2. It was previously believed that only advanced glaucoma damage has an impact on the patient ability to function. However, more recent cross-sectional clinic-based and population-based studies have demonstrated that early glaucomatous visual field loss has an impact on the patients' ability to function as assessed by patient reported outcome measures and functional tests.
3. Future studies are needed to explore the relationship between PROs and functional measures and glaucoma progression.
4. Numerous instruments and tests have been used for assessing PROs and functional measures in research settings. However, there is no consensus on a single PRO or functional measure (or set of PROs or functional measures) for clinical practice. There is a need to create simpler PROs and functional tests which can easily be reproduced in a wide variety of settings.

Robert N. Weinreb.

We acknowledge the unrestricted educational grants of our:

GLAUCOMA INDUSTRY MEMBERS

Alcon® Allergan NOVARTIS

ASSOCIATE GLAUCOMA INDUSTRY MEMBERS

aerie Pharmaceuticals, Inc. GLAUKOS Changing Perspectives HEIDELBERG ENGINEERING

Santen TOPCON ZEISS

SUPPORTING GLAUCOMA INDUSTRY MEMBERS

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

The Global Glaucoma Network

The Journal of the World Glaucoma Association

www.e-IGR.com

NEWS FLASHES

- ★ Increased levels of bone lead may be an important risk factor for POAG
- ★ Case-control studies using clinic patients may overestimate performance of diagnostic devices
- ★ No consistent structural association between distal AHO pathway anatomy and IOP reduction
- ★ Distal AHO anatomy does not predict MIGS outcomes
- ★ Postprandial hypotensive response might de-stabilize ocular perfusion and contribute to optic nerve degeneration in POAG
- ★ The association between diabetes with incidence and progression of open-angle glaucoma remains controversial
- ★ Macular damage in glaucoma is much more impactful on VRQoL than peripheral damage
- ★ Eyes with lower baseline macular and optic nerve head vessel density had significantly faster rates of loss of RNFL during follow-up
- ★ SNPs can explain between 17%-19% of the IOP variance

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