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International Glaucoma Review

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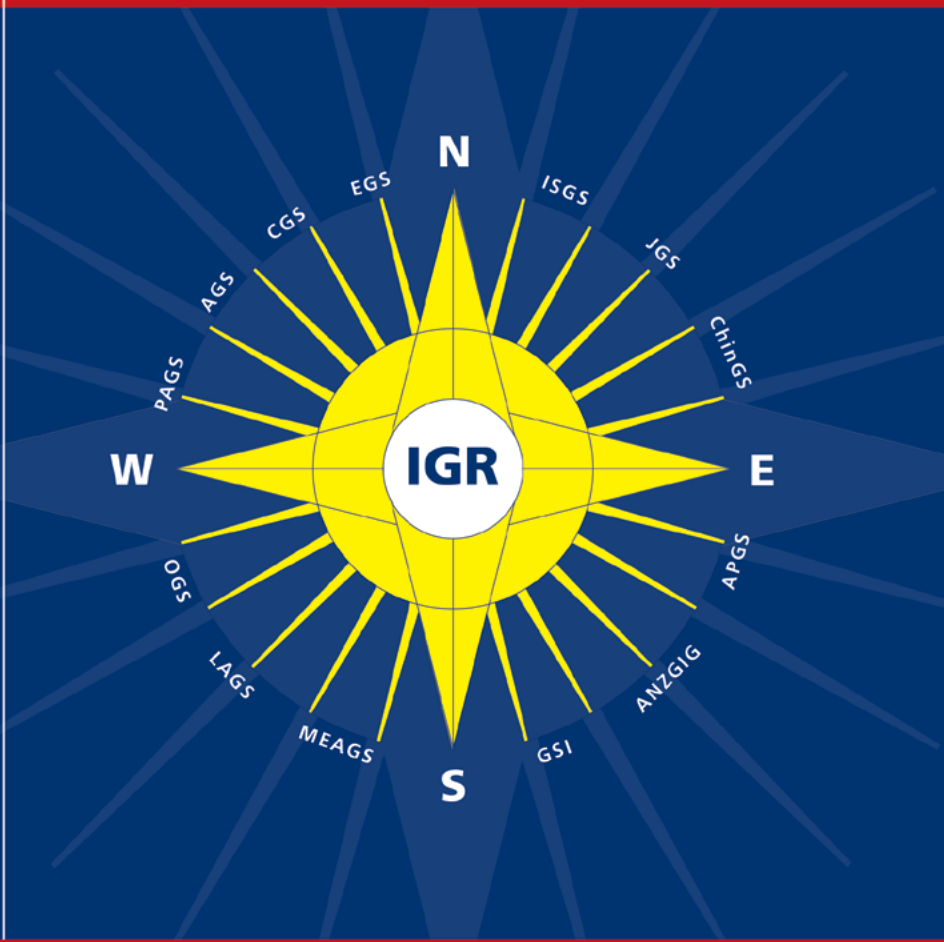

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INTERNATIONAL GLAUCOMA REVIEW

A Quarterly Journal
Volume 19 no. 1

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

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Contact Information

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

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

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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.

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4. **Click on the link, create a new password, and update your WGA#One profile.**

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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.

www.wga.one/wga/basic-course-in-glaucoma

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.

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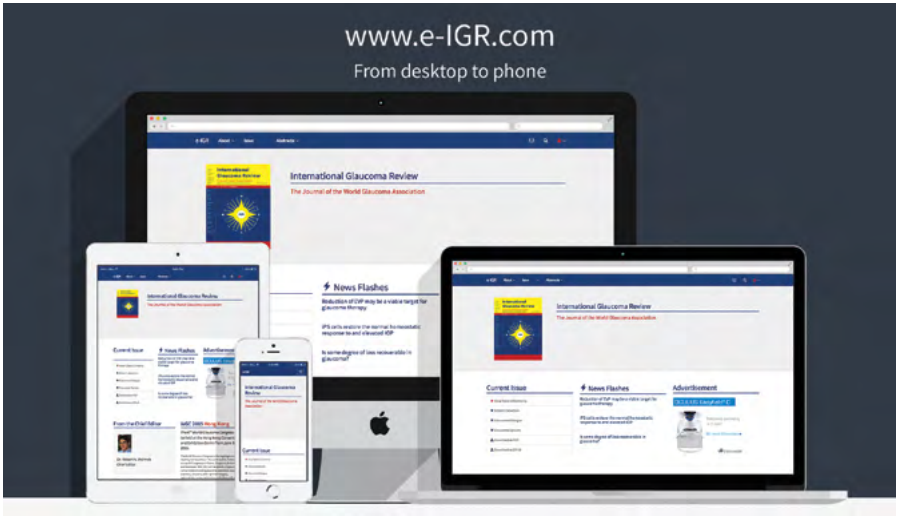
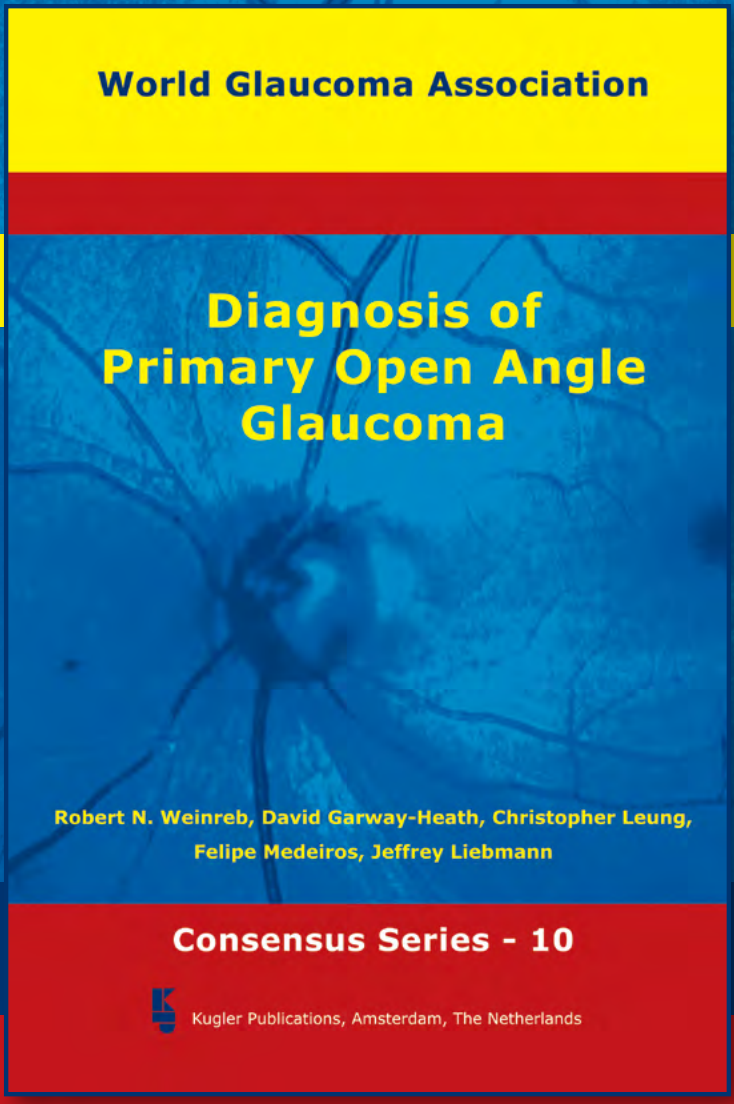
All abstracts are available online in the classified IGR searchable glaucoma database

www.e-IGR.com

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





CONSENSUS SERIES 10

Diagnosis of Primary Open Angle Glaucoma

From the WGA Executive Office

Dear IGR readers,

I would like to introduce myself to you. My name is Shan Lin and I started my role as Executive Vice President as of January 1 of this year. Besides my activities for the World Glaucoma Association, I work as a glaucoma specialist and research director at the Glaucoma Consultants of San Francisco.

Looking back at the beginning of this year, it was great to see so much commitment and activity with regard to **World Glaucoma Week**, which took place from March 11-17. With over 750 activities submitted to the WGW world map, it clearly showed how many people around the world are assisting us in creating more glaucoma awareness. And of course, this number of events only represents the tip of the iceberg, as many more events were organized! Thank you for your support! See www.worldglaucomaweek.org.

In only one month, the abstract submission and congress & hotel registration for the **8th World Glaucoma Congress 2019** will start. This time, the WGC is going down under. The Congress will take place at the Melbourne Convention & Exhibition Centre (MCEC) Australia from March 27-30, 2019. Make sure to mark your calendar for June 1, 2018 and register as soon as possible. See www. worldglaucomacongress.org.

I also would like to direct your attention to the **WGA Basic Course in Glaucoma**. This course has been online for a few months. We have received very positive feedback from our initial users, based on a recent survey. One of the participants said: "the tips given have enabled me to become a better clinician by applying those tips in my practice". See page 4 for details.

If you haven't accessed the Basic Course in Glaucoma yet, you can find the course on our website. All modules are now also available in Spanish (next to the English tab) and soon to be in Portuguese and Chinese.

Another important milestone will be the launch of the **WGA Patient Education website**, which is planned to be ready within the next few weeks. Please watch your mailbox!

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

Enjoy this issue of IGR!

Shan Lin, WGA Executive Vice President

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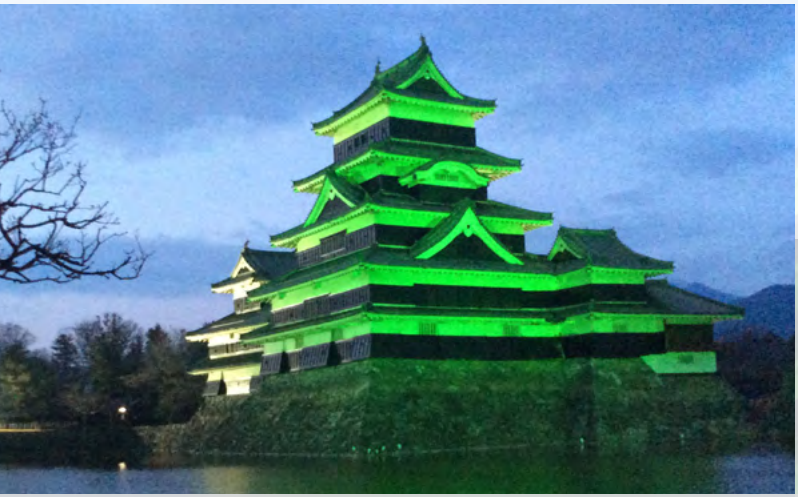
World Glaucoma Week 2018: a great success!

World Glaucoma Week 2018 was a great success, all over the world many activities were organized to raise awareness about Glaucoma. We want to thank all of you that have been a part in this year's **World Glaucoma Week** and are already looking forward to next year. In the meantime, read about activities that were organized this year and get inspired for next year!

World Glaucoma Week 2018 - Stories



JAPAN

The **Japanese Glaucoma Society (JGS)** is raising the bar each year with even more public building being illuminated in green. This campaign was started in 2015 with five landmarks lit up in this first year. Since this campaign was designated an official public awareness program of JGS in 2016, the number of participated sites increased to 44 sites in 2017, and to a stunning 68 sites this year.

Why is green the color of choice for our campaign?

Remo Susanna Jr. explains: "The word glaucoma originates from the ancient Greek word '*glaucos*', meaning 'blue-green haze'. In Germany, they refer to glaucoma as '*Grüne Star*' (Green Stare) and in Japan it literally means '*green intraocular morbidity*'".

Green is also associated with progress, showing that the ways to avoid blindness are open and depend on us all; on actions patients can take, and progress doctors and scientists can make in finding a cure.

MOLDAVIA

Remember that picture with the special **WGW2017 BIG** campaign shirts from last year that drew a lot of attention and served as an inspiration around the world for old school copy and paste actions?

This year, the institute of Emergency Medicine, Ophthalmology department, Chisinau, Republic of Moldova wore green scarfs during the entire **World Glaucoma Week** and green ribbons were handed out to all patients, while also organizing public educational and screening events.

BARBADOS

On Barbados free screenings were offered by many participating ophthalmology and optometry practices for people who had not been tested for glaucoma before. The goal: make sure that people get their eyes tested for glaucoma!

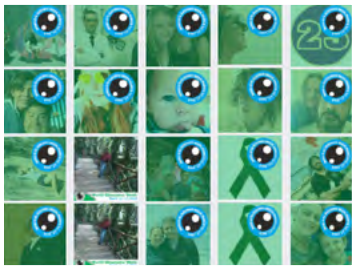
Their camera frame was quite an eyecatcher!

THAILAND

This year, Nuttamon Srisamran from Bangkok, Thailand and her team set up a free screening event with glaucoma education. A badge was created following the WGW-2018 logo for the participants and related healthcare personnel. A great awareness activity and maybe we will see more badges next year.

FACEBOOK CAMERA EFFECTS

There were two camera effects available through our Facebook page.



www.facebook.com/worldglaucomaweek

This is just an arbitrary selection from all the create stories and initiatives that were organized. Want to see more?

- Check out our community on Facebook www.facebook.com/pg/worldglaucomaweek/community
- check the news stream on the World Glaucoma Week website www.worldglaucomaweek.org.
- See the World Map for an impressive overview www.wgweek.net/activities/around-the-world

Want to tell us your story?

Connect on Facebook, or send us an email at info@wgweek.net

Activate your WGA#One profile (see page 3), or subscribe to our newsletter (www.wga.one/wga/subscribe-to-newsletter) if you wish to receive updates for World Glaucoma Week.

www.worldglaucomaweek.org

WORLD GLAUCOMA WEEK 2019

March 10–16, 2019

We have started preparations for World Glaucoma Week 2019 so keep an eye on our website and follow us via facebook!

KEEP AN EYE OUT FOR WORLD GLAUCOMA WEEK!

www.facebook.com/worldglaucomaweek
www.worldglaucomaweek.org

Your Special Attention For

Normal tension glaucoma management: a survey of contemporary practice
Symes RJ, Mikelberg FS
Canadian Journal of Ophthalmology 2017; 52: 361-365
abstract no. 74081

Mitochondrial dynamics, transport, and quality control: A bottleneck for retinal ganglion cell viability in optic neuropathies
Ito YA, Di Polo A
Mitochondrion 2017; 36: 186-192
abstract no. 74304

Structural and functional imaging of aqueous humour outflow: a review
Huang AS, Francis BA, Weinreb RN
Clinical and Experimental Ophthalmology 2017;
abstract no. 74355

Hypothyroidism as a risk factor for open angle glaucoma: A systematic review and meta-analysis
Wang S, Liu Y, Zheng G
PLoS ONE 2017; 12: e0186634
abstract no. 74679

A Novel Uveolymphatic Drainage Pathway-Possible New Target for Glaucoma Treatment
Tomczyk-Socha M, Turno-Kręcicka A
Lymphatic research and biology 2017; 15: 360-363
abstract no. 74696

MARK YOUR CALENDAR!

JUNE 1 - Start Abstract submission, congress & hotel registration

WGA

8th WORLD GLAUCOMA CONGRESS

MARCH 27 – 30, 2019

MELBOURNE

www.worldglaucomacongress.org

Education Committee Highlights WGC-2017

The Education Committee of the World Glaucoma Association has highlighted several WGC-2017 sessions from the Educational Portal, one of which is discussed below.

From among the many high quality videos online, the committee selects for these Highlights that are of broad interest and significantly advance knowledge or provide new concepts or approaches that extend our understanding. The highlighted sessions are available free-of-charge.

Activate your **WGA#One** account to receive further releases of WGC-2017 content and much more – see page 3 for details.

Presidential Symposium: Exfoliation Syndrome – The first century

Chair(s): Tin Aung (Singapore);
Robert Ritch (United States);
Anja Tuulonen (Finland);
Hannu Uusitalo (Finland);

This Symposium addressed the 100th anniversary of the discovery of Exfoliation Syndrome (XFS) by John Lindberg.

- Introduction to the Presidential Symposium - Robert Ritch (United States)
- 100 Years of exfoliation syndrome. John Lindberg and his legacy - Ahti Tarkkanen (Finland)
- Genetics of exfoliation syndrome - Tin Aung (Singapore)
- Etiology and pathophysiology of exfoliation syndrome - Ursula Schlötzer-Schrehardt (Germany)
- Environmental determinants in exfoliation syndrome - Louis Pasquale (United States)
- Complex cataract surgery in exfoliation syndrome- avoiding trouble - Ike Ahmed (Canada)
- Rapamycin and Other Potential Drugs Targeting Exfoliation Syndrome - Najam Sharif (United States)

Robert Ritch, in the first talk, gave an excellent perspective of the evolution of knowledge about exfoliation syndrome and its current understanding as an ocular manifestation of a systemic disease. He also presented XFS as a potential preventable or curable disorder with many scientists from different areas doing research related to XFS.

Ahti Tarkkanen gave a wonderful portrait of John Lindberg and his research on XFS. He also remarked the growing interest on XFS in the medical literature, and the challenges we face with exfoliation syndrome and exfoliation glaucoma.

Tin Aung talked about the genetics of XFS, the discovery of LOXL1, and some new discoveries, including rare variants with protective effects in some populations. He described his collaborative studies with Japanese colleagues and the Worldwide XFS Consortium that lead to the discovery of the CACNA1A gene. Dr. Aung also described his latest discoveries including 5 new loci for XFS with samples for all around the world, and talked about the possibility of using this knowledge to develop new treatments for XFS.

Louis Pasquale talked about environmental determinants of XFS. He described latitude possibly being a risk factor for the development of XFS, and climatic factors and time spent outdoors, may be important as well. Dr. Pasquale gave a fascinating explanation about UV exposure to the eyes in different parts of the world. He also mentioned other factors, including cold, low folate, coffee consumption and others.

Ursula Schlötzer-Schrehardt addressed the etiology and pathophysiology of XFS. She talked about the exfoliation material, how is formed, and aggregates. Molecular mechanisms are yet not fully developed. She described this syndrome as a stress-induced fibrosis, with inflammatory and other processes. The genomics era was marked by the discovery of 7 genes involved in XFS. The role of LOXL1 and other genes in forming or aggregating the exfoliation material, as well as in other mechanisms, was also discussed.

Naj Sharif talked about the current and future approaches to treatment of XFS. He discussed targeting genes or gene products in treatment. For example using TGFbeta receptor antagonists, as well as autophagy stimulators. He also talked about the need for cell lines and animal models of the disease.

Ike Ahmed talked about avoiding trouble in cataract surgery in XFS. He talked about intra and post-operative complications that may occur. How to predict zonular instability and the use of capsular tension rings and capsular retractors. The manage of late in-the-bag IOL dislocations. His presentation was illustrated with many outstanding videos.

WGA Consensus Series

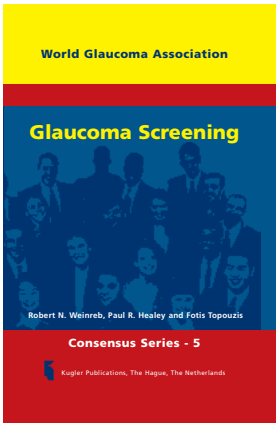
Robert N. Weinreb

Introduction

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

To prepare each of the 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.



Consensus Series 5

Glaucoma Screening

From the preface

This was the fifth WGA Consensus Meeting. As with other consensus topics, the discussion and conclusions of Glaucoma Screening, the subject for the 2008 consensus, had a broad impact.

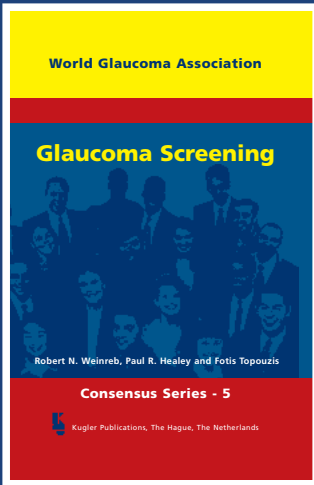
The global faculty, consisting of leading authorities on various aspects of glaucoma screening, met in Fort Lauderdale on April 26, 2008 to discuss the reports and refine the consensus statements. The Consensus Panel also met at that time, as well as electronically during the subsequent four weeks.

Obtaining consensus on how best to conduct glaucoma screening was quite a challenge, especially since the epidemiology and testing paradigms are so different for open-angle and angle-closure glaucoma. As with the previous WGA consensuses, the Glaucoma Screening consensus was based on the published literature and expert experience. The goal of this consensus was to establish the best practice for glaucoma screening, as well as to identify those areas for which we have little evidence and, therefore, need additional research.

We hope that this consensus will serve as a benchmark of our understanding, and that it will be revised and improved with the emergence of new evidence.

Robert N. Weinreb
Paul R. Healey
Fotis Topouzis
Anne Coleman
Ningli Wang

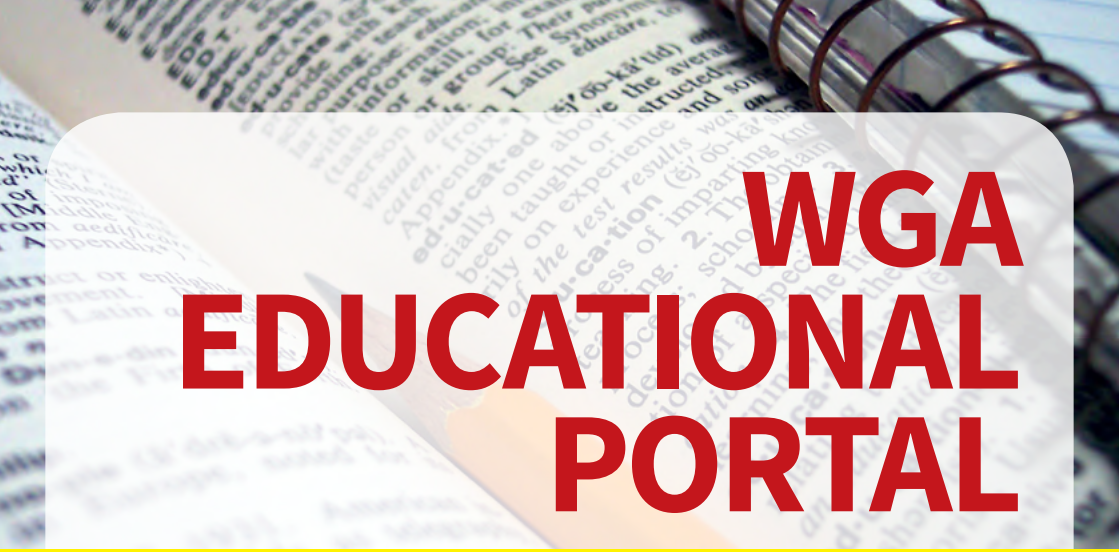
Consensus Series 5 - Table of contents



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

Through the courtesy of the **WGA** and **Kugler Publications**, you may now download the PDF files of Consensus 3 and 4 **free of charge** through your WGA#One account. Consensus 1 and 2 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



WGA EDUCATIONAL PORTAL

Getting the knowledge you want anytime, anywhere!

The World Glaucoma Association aspires in becoming the most important source of education for ophthalmologists and other healthcare providers related to glaucoma. In becoming a knowledge platform, the association offers access to the Educational Portal that includes recorded sessions from past World Glaucoma Congresses.

Watch the recorded sessions of our past congresses via www.wga.one/wga/educational-portal.

WGC-2015 and **WGC-2013** content is freely available for all. The sessions recorded during the 7th World Glaucoma Congress in Helsinki (**WGC-2017**) are only available for registered participants; content will also be circulated on a monthly basis via the WGA newsletters.

Please do not miss this opportunity of online glaucoma top education and visit the WGA Educational Portal!

Forgot your login details? Contact us at info@worldglaucoma.org.

www.worldglaucoma.org

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

Quality of Life

Reading Speed in Glaucoma

Comment by Pradeep Ramulu, Baltimore, MD, USA

74764 Slow Reading in Glaucoma: Is it due to the Shrinking Visual Span in Central Vision?; Kwon M, Liu R, Patel BN, Girkin C; Investigative Ophthalmology and Visual Science 2017; 58: 5810-5818

Kwon and colleagues compare reading speeds in a group of control and POAG patients, asking which vision measures are most relevant to reading speed. The Flash Card Reading test, in which patients read short 4-line sentences on a computer screen was used to evaluate reading. In regression analyses including multiple visual predictors (acuity, contrast, stereoacuity, visual field), **size of the visual span was the only significant predictor of reading speed.** Size of the visual span, measured by briefly flashing 13 letters spanning 10° of visual field to patients and asking them to identify as many letters as possible, was significantly smaller in glaucoma patients, who recognized two letters fewer than controls. This article recalls the fundamental findings of Gordon Legge in his Psychophysics of Reading series, which demonstrated that low vision patients have more trouble reading because they recognize fewer letters with each fixation because their contrast and acuity fall off more precipitously. Kwon's work suggests this same phenomenon obtains in persons with glaucoma and explains their difficulties reading. One study limitation is that models without reading span as a predictor were not presented, so the additional value

of this measure is unclear. Also, the importance of visual span may have been artificially inflated as a result of the large number of regression covariates used in a sample of only 38 patients. Finally, the reading task presented short simple text which was read out loud, which may not relate to the more common scenario of silently reading more complex material over longer durations. Nonetheless, the article is a wonderful description of the importance of visual span with regards to reading in glaucoma, and furthers the concept that glaucoma Is not purely a disease of the peripheral visual field, but also has strong effects on tasks of central vision.

Prevention and Screening

An iPad App to Detect Visual Field Loss

Comment by Ivan Goldberg, Sydney, Australia

74230 Performance of an iPad Application to Detect Moderate and Advanced Visual Field Loss in Nepal; Johnson CA, Thapa S, George Kong YX, Robin AL; American Journal of Ophthalmology 2017; 182: 147-154

As the authors point out, visual field loss from glaucoma is progressive and irreversible and mostly asymptomatic till advanced; this results in the appalling 50 - 60% non-detection rate in developed societies, rising to over 90% in developing communities. Early detection is vital if glaucomatous visual disability is to be minimized, or eliminated.

Community screening has not proved viable unless the screened population is "enriched" (*e.g.* family members of diagnosed persons) and/or other eye or even other health issues are included. Attempts to improve early detection with opportunistic screening have been disappointing.

Hence efforts abound to use technological advances to improve screening: use of smart-phone-captured images of optic discs with telemedicine-assisted remote assessment and use of e-tablets to measure visual sensitivity. Johnson *et al.* describe a new, free, down-loadable App to do just this - Visual Fields Easy (VFE).

Their setting was the famous Tilganga Eye Center in Kathmandu; their method, to test 210 normal, 183 glaucoma and 18 diabetic retinopathy eyes with the new App and to compare results with those from the 24-2 Humphrey SITA Standard for 373 of those eyes. **Missed locations with the VFE correlated reasonably with the Humphrey Mean Deviation (MD, r = 0.79), particularly for those eyes with MD less than -6D (moderate-to-advanced damage).** A raised false positive response rate was thought contributory to poorer VFE results with mild damage.

Believing that better control of eye-to-iPad distance along with monitoring of fixation, reduction in the number of tested points (currently 96, with a testing time too long at over 3 minutes), finding a way for participants to avoid touching the screen (producing smudges) and re-testing missed points, the authors believe will overcome many challenges.

Refinements like these would enable more effective screening, and offer home tonometry for treated glaucoma sufferers, thereby enhancing quality of care. We keenly await these advances.

Basic Science

Gene Expression and Sex

Comment by Louis Pasquale, Boston, MA, USA

74657 Retinal gene expression responses to aging are sexually divergent; Du M, Mangold CA, Bixler GV, Brucklacher RM, Masser DR, Stout MB, Elliott MH, Freeman WM; Molecular Vision 2017; 23: 707-717

Age and sex significantly influence the risk for developing glaucoma and other age-related blinding conditions, such as age-related macular degeneration, yet pathophysiology of eye aging is not well understood.[1]

> Pathophysiology of eye aging is not well understood

Likewise, it is not known if an aging process differs between men and women. As an age-related neurodegeneration, primary open-angle glaucoma (POAG) is also considered accelerated optic nerve aging because the glaucomatous optic nerve shares both immunohistochemical and clinical characteristics, similar to aging. Evidently, they both exhibit reactive products from an oxidative stress[2] and a characteristic pattern of neuroretinal rim loss in the inferotemporal region.[3] In addition, the risk of POAG in women is affected not only by chronological age, but also by advancing reproductive age and lifetime exposure to estrogens.[4] Recognized the critical effects of the biological sex on aging eye conditions, such as POAG and retinal diseases, Du *et al.* investigated sex differences in aging. By comparing retinal gene expression responses in female and male C57BL/6JN mice, aged 3 and 24 months, they demonstrated retinal sex differences throughout a mouse lifespan. Notably, while common gene expression exists, as anticipated, the gene expression responses to aging indeed predominantly differ between male and female mice. They further hypothesized that the sexually divergent gene expression throughout life is likely the effects of sex hormones on the retina. Specifically, sex hormones could potentially affect cell function and gene regulation through estrogen, androgen, and non-estrogen

receptors within the retina and the retinal pigment epithelium. **This observed sexually divergent gene expression responses to aging certainly warrants further investigations.** Most importantly, these findings highlight an urgent need to include both sexes in pre-clinical and clinical research. **Considering both sexes in aging research will subsequently lead to better understanding of likely interactions between the effects of age and sex on various age-related blinding conditions.**

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1. Vajaranant TS, Pasquale LR. Estrogen deficiency accelerates aging of the optic nerve. *Menopause (New York, N.Y.* Aug 2012;19(8):942-947.
2. Tezel G, Luo C, Yang X. Accelerated aging in glaucoma: immunohistochemical assessment of advanced glycation end products in the human retina and optic nerve head. *Investigative ophthalmology & visual science.* Mar 2007;48(3):1201-1211.
3. See JL, Nicolela MT, Chauhan BC. Rates of neuroretinal rim and peripapillary atrophy area change: a comparative study of glaucoma patients and normal controls. *Ophthalmology.* May 2009;116(5):840-847.
4. Pasquale LR, Rosner BA, Hankinson SE, Kang JH. Attributes of female reproductive aging and their relation to primary open-angle glaucoma: a prospective study. *Journal of glaucoma.* Oct-Nov 2007;16(7):598-605.

Pathophysiology

Comment by Paul Kaufman, Madison, WI, USA

74403 Impaired angiopoietin/Tie2 signaling compromises Schlemm's canal integrity and induces glaucoma; Kim J, Park DY, Bae H, Park DY, Kim D, Lee CK, Song S, Chung TY, Lim DH, Kubota Y, Hong YK, He Y, Augustin HG, Oliver G, Koh GY; Journal of Clinical Investigation 2017; 127: 3877-3896

This long and complex paper[1] in the Journal of Clinical Investigation from September 2017 is a challenging read, especially for those not well-versed in mouse genetics. Nonetheless, the experimental crosses are logically and clearly designed, the structural and functional data are clear and are correctly interpreted, and the findings and conclusions are eye opening. One must remember, of course that these are mice, not monkeys or humans, and time is measured in weeks, not years and decades. That said, the authors demonstrate convincingly that signaling between angiopoietin (Angpt) and the Angpt receptor Tie2, which is critical for Schlemm's canal (SC) formation, is also indispensable for maintaining SC integrity during adulthood.

Signaling between angiopoietin (Angpt) and the Angpt receptor Tie2, which is critical for Schlemm's canal (SC) formation, is also indispensable for maintaining SC integrity during adulthood

Deletion of *Angpt1/Angpt2* or *Tie2* in adult mice severely impaired SC integrity and transcytosis, leading to elevated IOP, retinal neuron damage, and impairment of retinal ganglion cell function, all hallmarks of POAG in humans. SC integrity is maintained by interconnected and coordinated functions of Angpt-Tie2 signaling, aqueous humor outflow (AHO), and Prox1 activity. These functions diminish in the SC during aging, leading to impaired SC structural integrity and transcytosis. Tie2 reactivation using a Tie2 agonistic antibody rescued the POAG phenotype in *Angpt1/Angpt2*-deficient mice and rejuvenated the SC in aged mice. The authors conclude that the Angpt-Tie 2 system is essential for SC integrity, and that the impairment of this system underlies POAG-associated pathogenesis, supporting the possibility that Tie2 agonists could be a therapeutic option for glaucoma in humans.

The authors did not discuss the pitfalls of extrapolating directly from mice to humans, and there is a long, long drive between this paper and a therapeutic intervention of any sort. Nonetheless, some of these genetic linkages are seen in some primary congenital glaucoma patients and families, giving credence at least to the development story, so stay tuned for the follow-ups to this stellar tour-de-force work.

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1. Kim J, Park D-Y, Bae H, Park DY, Kim D, Lee C-k, Song S, Chung T-Y, Lim DH, Kubota Y, Hong Y-K, He Y, Augustin HG, Oliver G, and Koh GY: Impaired angiopoietin/Tie2 signaling compromises Schlemm's canal integrity and induces glaucoma. J Clin Invest. 2017;127(10):3877–3896.https://doi.org/10.1172/JCI94668

Trace Elements in the Aqueous


Comment by Claudio Perez and Shan Lin, San Francisco, CA, USA

74802 Levels of aqueous humor trace elements in patients with open-angle glaucoma; Hohberger B, Chaudhri MA, Michalke B, Lucio M, Nowomiejska K, Schlötzer-Schrehardt U, Grieb P, Rejdak R, Jünemann AGM; Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements (GMS) 2018; 45: 150-155

Glaucoma is an optic neuropathy in which the most validated and treatable risk factor is the elevated intraocular pressure (IOP). Nevertheless, the etiology of glaucoma is multifactorial, with several possible concomitant factors including vascular changes and oxidative stress. Priors studies had suggested that oxidative stress and free radical accumulation may harm the trabecular meshwork resulting in an increased IOP[1] and also harm to the retinal ganglion cells, with resultant cell death that leads to optic nerve damage characteristic of glaucoma.[2] Data from a population-based study had suggested that body levels of trace metals could be involved in the pathogenesis of glaucoma, specifically that lower blood manganese levels or higher serum mercury and ferritin levels are associated with greater odds of glaucoma.[3]

Therefore, evaluating levels of trace elements in the aqueous humor of glaucomatous patients should provide further information related to this potential avenue of etiology. The cross-sectional study performed by Hohberger B, *et al.* evaluated the aqueous humor levels of cadmium, iron, manganese, cobalt, copper and zinc in patients with primary open angle glaucoma (POAG, n=12), pseudoexfoliation glaucoma (PEXG, n=10) and cataract patients as controls (n=11). The authors found significantly higher aqueous humor levels of zinc in POAG and PEXG patients compared to controls. They conclude that zinc may be related to glaucoma pathogenesis in general, as matrix metalloproteinases are zinc-containing enzymes and play a possible role in glaucoma pathogenesis.

> Matrix metalloproteinases are zinc-containing enzymes and play a possible role in glaucoma pathogenesis

Also, they found **significantly lower aqueous humor levels of iron in PEXG patients compared to POAG and controls.** Although this study has some design issues, including the relatively small number of eyes in each group and a high variability of results within each group, the findings are of significant interest and provide an excellent starting point for further investigation.

As with other cross sectional studies, it cannot be concluded that zinc or iron levels are a cause or consequence of glaucoma. For example, increased zinc can block copper absorption and cause iron and copper imbalance, and these are elements essential for neural development and immune system. On the other hand, increased zinc could be a compensation mechanism to increase the neutralization of free radicals that are higher in glaucoma.[4,5] Future studies can also concurrently measure element concentrations in the serum as well as the aqueous humor. For example blood-aqueous barrier defects have been described in PEXG,[6] and therefore increased levels of elements in aqueous humor could be a reflect of increased elements concentration in blood.

As with other cross sectional studies, it cannot be concluded that zinc or iron levels are a cause or consequence of glaucoma

In conclusion, this study suggests that understanding the concentration changes in trace elements in aqueous humor may lead us to further elucidate glaucoma pathophysiology. It encourages future prospective studies into the role of trace elements in this blinding disease.

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Neuroprotection

Comment by Derek Welsbie, La Jolla, CA, USA

74614 Neuroprotective Effects of Human Mesenchymal Stem Cells and Platelet-Derived Growth Factor on Human Retinal Ganglion Cells; Osborne A, Sanderson J, Martin KR; Stem Cells 2018; 36: 65-78

Mesenchymal stem cells (MSCs) are the stem cells found in bone marrow and are responsible for producing cartilage, adipose and bone tissue. While these stem cells lack the capacity to regenerate retinal ganglion cells (RGCs), multiple groups have demonstrated that intravitreal injection of MSCs can prevent RGC loss in rodent models of optic neuropathy. Keith Martin's group at University of Cambridge has previously shown that one mechanism of the neuroprotection involves the secretion of platelet-derived growth factor (PDGF) by MSCs. In this article, Osborne *et al.* test whether MSCs and/or PDGF confer a similar protection upon human retinas. To study human RGC cell death, the authors took advantage of an explant model in which retinas were isolated from human donor eyes. After being cultured ex vivo for one week, multiple retinal cells, including RGCs, undergo cell death. As in the rodent model, **treatment of human retinal explants with PDGF reduced RGC loss and was associated with the activation of various pro-survival pathways,** including Akt and ERK.

> Together these results suggest that MSCs are likely producing other soluble neuroprotective factors, in addition to PDGF

Interestingly, **coculture with MSCs had a more robust neuroprotective phenotype than PDGF treatment and the effect of MSCs was not blocked by inhibition of PDGF.** Together these results suggest that MSCs are likely producing other soluble neuroprotective factors, in addition to PDGF. In order to evaluate the safety of this approach, the authors looked at glial/microglial activation and found that both PDGF and MSC coculture induced neuroinflammation. Future work will almost certainly focus on identifying the other neuroprotective agents produced by MSCs and on anti-inflammatory strategies that might permit the use of MSCs therapeutically.

Effects of IOP on Cognitive Function in Rats

Comment by Luciano Quaranta, Brescia, Italy

74344 High intraocular pressure produces learning and memory impairments in rats; Yuan Y, Chen Z, Li L, Li X, Xia Q, Zhang H, Duan Q, Zhao Y; Brain Research 2017; 1675: 78-86

The results of the present study show that **high IOP impaired learning and memory in ocular hypertension model in rats and concurrently increased β-amyloid (Aβ) and phospho-tau expression in the hippocampus** by altering the activation of different kinase and phosphatase proteins in the hippocampus. This study provides novel suggestion for the relationship between high IOP and hippocampal alterations, especially in the context of learning and memory.

There is evidence suggesting that glaucoma also affects other components of the visual pathway. Glaucomatous neuronal death occurs in the retina, optic nerve, lateral geniculate nucleus (LGN), and the visual cortex. Neuropathologic examination revealed marked degenerative changes, including neuron shrinkage and loss in the LGN, which was accompanied by reactive astrogliosis or glial activation.[4] Magnetic resonance (MR) techniques are well suited for evaluating the brain changes *in vivo*. Moreover, studies have demonstrated decreases in LGN volume[25]and visual cortex thickness. Functional MR showed decreased response in the visual cortex after stimulation of the glaucomatous eye. Therefore, these mechanisms are similar to those first described in neuro-degenerative diseases, which comprise a heterogeneous group of disorders with clinical and pathologic diversity, including Alzheimer's disease (AD), Parkinson's disease, and amyotrophic lateral sclerosis.

The clinical and pathologic relationship between AD and glaucoma remains obscure

Other investigations on chronic glaucoma model in rhesus monkeys, have shown that distribution of AD-like pathology along the visual pathway occurred in an ascending order without being observed in cognitive areas, particularly the Hyppocampus, indicates that IOP elevation may produce damage to the glaucomatous central visual system via axonal and synaptic changes.

No consensus has been established regarding whether clinical correlations between the two diseases might be due to shared risk factors or the influence of one disorder on the other, and different mechanisms may trigger the biomolecular processes leading to cell death in these diseases. These observations raise the intriguing possibility that

underlying AD-like pathology contributes to the visual impairment due to glaucoma. Studying these pathologies may result in a paradigm shift in the management of ocular diseases. It has been shown that targeting different components of the β-amyloid formation and aggregation pathway can reduce glaucomatous retinal ganglion cells apoptosis *in vivo* and, therefore, raises the possibility of using neuroprotective mechanisms to combat glaucoma.

The clinical and pathologic relationship between AD and glaucoma remains obscure.

Clinical Examination Methods: IOP

Self-tonometry

Comment by Kaweh Mansouri, Lausanne, Switzerland

74284 Measurement of Intraocular Pressure by Patients With Glaucoma; Pronin S, Brown L, Megaw R, Tatham AJ; JAMA ophthalmology 2017; 135: 1-7

Glaucoma specialists are in the constant pursuit of more IOP data for improved patient management. This study investigated the ability of patients to perform self-tonometry using the rebound tonometer (iCare HOME) in a consecutive cohort of 100 glaucoma patients with a mean age of 67.5 years.

> Patient-obtained IOP measurements were reproducible and similar to physician-obtained ones

The authors found that patient-obtained IOP measurements were reproducible and similar to physician-obtained ones with an intraclass coefficient of 0.9. However, despite training by the study staff, not all patients were able to obtain accurate measurements: **27% of patients had values that deviated by more than 5 mmHg from the investigators' measurements** and were therefore not included in the analysis. Patients were also given a short questionnaire about their acceptability of self-tonometry. Overall, 71% of patients believed the device was easy to use with 92% stating good comfort. Importantly, a similar proportion were willing to use the device again in future. In contrast, only 56% of measurements were within 5 mmHg of Goldmann applanation tonometry, a lower number than found in previous studies.

This study shows that a majority of patients were able and happy to use self-tonometry. It took an average of 20 minutes to teach patients to use the device. Given the potantial benefits of home-tonometry, this may be time well spent. This study was conducted at the investigators' office and did not evaluate actual home tonometry. Longitudinal data are

necessary to study the continued interest and ability of patients to obtain home measurements over the long term and how the data would influence adherence with medications and other glaucoma outcomes. In the meantime, physicians are encouraged to make use of this technology and health systems to provide funding for it.

Clinical Examination Methods: Function

Relation Between Reliability Index and Sensitivity

Comment by Andrew Tatham, Edinburgh, UK

74300 The Effect of Testing Reliability on Visual Field Sensitivity in Normal Eyes: The Singapore Chinese Eye Study; Tan NYQ, Tham YC, Koh V, Nguyen DQ, Cheung CY, Aung T, Wong TY, Cheng CY; Ophthalmology 2018; 125: 15-21

Standard automated perimetry, in common with other psychophysical tests, is profoundly influenced by reliability of performance. Reliability can be quantified using indices such as false negatives (FNs), false positives (FPs) and fixation losses (FLs), with cut-off values used to differentiate reliable and unreliable tests aiming to balance reliability with the risk of excluding too many tests.[1] The current manufacturer guideline for the Humphrey Field Analyzer recommends a reliability limit of 20% FLs and 15% FPs.[2]

Tan and colleagues emphasize that **setting reliability cut-offs is oversimplistic and introduces a false dichotomy between "reliable" and "unreliable".** Reliability actually falls along a continuum and even unreliable visual fields may contain useful information. By discarding unreliable tests, one reduces the number of available tests, and potentially reduces power to detect progression. This study quantified the effects of reliability indices on mean deviation (MD) and pattern standard deviation (PSD).

A total of 1,828 visual field tests from 830 healthy participants were included in this cross-sectional study, with regression analysis used to examine the relationship between reliability indices and MD and PSD. A higher rate of FNs was associated with lower MD and higher PSD, whereas a higher rate of FPs was associated with higher MD and lower PSD. The relationship was non-linear, with a greater effect on global indices observed with higher rates of error. MD decreased by 1.15 dB per 5% increase in FNs when FNs were ≥15% but decreased by only 0.71 dB when the FN rate was <15%. MD increased by 1.26 dB per 5% increase in FPs when FPs were ≥15%, compared a 0.65 dB increase when FPs were <15%. A similar relationship was observed between FPs and FNs and PSD. Although FLs are the most common reason for poor reliability[3], they had no significant effect on MD and only a small effect on PSD, perhaps due to averaging of regions of falsely high or low sensitivity resulting in little overall effect.

The current recommendation to disregard FNs from reliability assessment does not mean that FNs should not be considered when estimating progression rates

The study provides insight into the effect of unreliable responses on MD and PSD which may allow clinicians to better estimate rates of progression. Even low levels of FNs or FPs had a significant impact on MD and PSD meaning it may be important to consider the effect of reliability indices on MD when calculating rates of progression. Furthermore, the current recommendation to disregard FNs from reliability assessment[2] does not mean that FNs should not be considered when estimating progression rates. FNs had a similar (though inverse) effect on global indices as FPs. Patients with glaucoma are well known to have higher FN rates due to inability to see the catch trial stimuli, however if FN rates affect MD and PSD this may need to be taken into account in progression analysis. Further research is needed as the study was limited to including only healthy subjects and it is possible that the relationship between reliability and global indices may differ in eyes with established visual field defects. For example, although FLs were not strongly associated with global indices in healthy subjects, others have reported higher FLs to decrease PSD and increase MD in patients with glaucoma.[4]

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Visual Field Progression

Comment by Rupert Bourne, Cambridge, UK

74502 Tolerable rates of visual field progression in a population-based sample of patients with glaucoma; Salonikiou A, Founti P, Kilintzis V, Antoniadis A, Anastasopoulos E, Pappas T, Raptou A, Topouzis F; British Journal of Ophthalmology 2017;

This report by Salonikiou *et al.* tests a metric described as 'maximum tolerable rate of progression to avoid visual impairment' (maxTRoP_VI) and a similar metric for blindness (maxTRoP_BL) that may be applied to patients with open-angle glaucoma (OAG). This is an interesting concept and fits with the objective of glaucoma treatment to maintain lifelong preservation of visual function and related quality of life. **Using data from a population-based cross-sectional study of 5000 randomly selected people aged 60+ years in an urban area of northern Greece (The Thessaloniki Eye Study), the authors were able to obtain visual field data for 123 study participants with Open Angle Glaucoma, OAG).** A strength of using population-based data is that the risk of selection bias is reduced which may occur when using clinical trial data and convenience samples of clinic-based patients which are not representative of the natural history of all persons affected by OAG in a population (half or more of those identified in population based studies being unaware they have OAG).

Using a statistical model that requires age, sex and MD of the visual field at presentation as input values, each participant's life expectancy was calculated based on life expectancy tables. Their software tool then calculated the maxTRoP_VI and maxTRoP_BL, which are essentially the rates of progression which would not lead to visual impairment and blindness, respectively, until the very end of each participant's expected lifetime.

There have been relatively few attempts to model visual field progression using cross-sectional data. Notably Broman *et al.* developed a model that calculates OAG incidence from age-specific prevalence using cross-sectional survey data to estimate the average rate of progression for an individual with OAG,[1] based on an approach suggested by Leske *et al.*[2] Since OAG does not spontaneously disappear and produces either stable or worsening damage, the increment in prevalence at each succeeding age in a cross sectional study is a measure of the number of new cases added (incidence). Broman *et al.* modeled OAG visual field progression using age-specific damage data from nine large population-based studies, (392 subjects in the European dataset). They were able to estimate the proportion of all OAG patients expected to become bilaterally blind (30 dB MD loss in both worse and better eye. By contrast, this study by Salonikiou *et al.* does not describe the equation that underlies the calculator and therefore it is unclear as to how rates of progression were calculated in this rather smaller sample of Europeans with OAG. While Broman *et al.* used a threshold of vision function that is much more severe (30dB MD loss), Salonikiou

et al. additionally used the thresholds of -14dB and -12dB in better or worse eyes. Mean Deviation, a summary measure of visual field damage, is likely to encompass a much wider range of disability when these less severe thresholds are reached, than when considering a 'blindness' cut-off, and therefore one has to be cautious in conflating 'visual impairment' defined by an MD threshold with 'visual impairment' defined by a visual acuity threshold, a more common usage of the term (*e.g.* as defined by the World Health Organisation).

Salonikiou *et al.* report that 70% of those with OAG would become visually impaired (Using −12 dB as threshold for visual impairment) at rates of progression as slow as −1 dB/year. More than 70% would have a maximum tolerable rate of progression to avoid blindness during their expected lifetime of slower than −2 dB/year. The authors therefore argue that being complacent about an eye that appears to have a slower rate of progression may not be appropriate. Certainly their findings do not contradict the importance of excluding a rate of progression of−2 dB/year, as was recommended by Chauhan *et al.*[3] Although there are clearly limitations in this approach that assumes linearity of the rate of change in the visual field over time and the issue of ocular co-pathology that may affect the visual field, these findings do raise an interesting discussion about how best to individualize our approach to measuring progression and the need to find better more practical tools.

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Home monitoring

Comment by Robert Fechtner, Newark, NJ, USA

74061 Can Home Monitoring Allow Earlier Detection of Rapid Visual Field Progression in Glaucoma?; Anderson AJ, Bedggood PA, George Kong YX, Martin KR, Vingrys AJ; Ophthalmology 2017; 124: 1735-1742

Glaucoma progression, as measured by visual field testing, is a statistical event. A few fundamental principles are used to determine statistically significant change in the visual field. The first step is to establish a baseline. Then we need to know intra-test variability. And finally, we must determine and confirm that a test point or points are statistically significantly different from the baseline taking into consideration the variability. In a model where visual fields are tested once or twice yearly this can take several years. Even using the strategy of pointwise linear regression it requires several field tests to determine significant change over time.

For patients with "slow" glaucoma this may be acceptable. However, for patients with rapidly progressing glaucoma substantial vision might be lost over the period of time it takes to establish a sufficient number of fields required for statistical analysis. The authors raise the intriguing idea that frequent home testing might allow detection of progression over a much shorter period of time than office testing. A tablet-based perimeter (Melbourne Rapid Fields) can be used for self-testing at home. As an exploratory study, the authors used simulation methods to quantify benefits that might be expected from using frequent home monitoring. Subjects performed supervised tablet testing on two occasions two months apart to establish inter-test variability. Two in-office scenarios were simulated (six monthly and yearly testing.) Three home monitoring scenarios were simulated (weekly, fortnightly, and monthly testing).

It took 2.5 years to achieve a sensitivity of 0.8 in the model of six monthly testing in the clinic. In contrast, home monitoring on a weekly basis achieved 0.8 sensitivity after only 0.9 years (at 46 weeks.) The weekly home testing model achieved specificity of 0.9 by 12 weeks.

In this simulation of tablet based home monitoring of visual fields, the results suggest that this technology could lead to earlier detection (and intervention) for rapidly progressing patients. The authors caution that the baseline testing upon which these simulations were created was conducted under controlled conditions and that prospective clinical trial is warranted. These simulations strongly suggest that frequent home monitoring is likely to improve our ability to detect rapid progression of glaucoma even with imperfect compliance. The cost benefits of home monitoring remain to be determined.

An Application of the Amsler Grid in Glaucoma

Comment by Pradeep Ramulu, Baltimore, MD, USA

74472 Assessment of patient perception of glaucomatous visual field loss and its association with disease severity using Amsler grid; Fujitani K, Su D, Ghassibi MP, Simonson JL, Liebmann JM, Ritch R, Park SC; PLoS ONE 2017; 12: e0184230

Fujitani and colleagues examine how often, and in what terms, patients with visual field damage on a 10-2 test describe difficulties when looking at an Amsler grid. **Over 80% of patients noticed some form of abnormality, using a variety of terms to describe what they noticed.** Patients' words to describe their observations were then grouped into three categories: missing/white, blurry/gray, or black. Some patients also used a combination of these terms, particularly when they had more severe damage. Of note, the least common term used was "black" (<5%), while the most common terms used were missing/white (50%). The specific terms used varied across the spectrum of disease severity, with the patients describing a black scotoma having a higher degree of visual field damage (median 10-2 MD below -20 dB), while those describing either missing/white or blurry/gray regions having more modest levels of damage (median 10-2 MD just below -10 dB).

> What most patient see is not reflected in the gray scale print out from visual field machines or in online depictions of what glaucoma looks like

The article highlights several important points, primarily that what most patient see is not reflected in the gray scale print out from visual field machines or in online depictions of what glaucoma looks like, including pictures shown on prominent websites such as that of the National Eye Institute. A limitation of the work is that the descriptions used to report perceptions from an Amsler grid may not reflect the words used to describe complex real-world scenes in which adjacent objects have more subtle differences in contrast. Additionally, the words or phrases that patients volunteer to describe their perceptions may not be those that most accurately and specifically capture glaucoma-related symptoms. Further research in this important area is needed to help clinicians improve in the art of determining if a patient has become visually symptomatic from glaucoma and in distinguishing visual symptoms due to glaucoma from symptoms of other ocular conditions.

Clinical Examination Methods: OCT

Early Glaucoma Detection

Comment by Jin Wook Jeoung, Seoul, South Korea

74140 Vertical Macular Asymmetry Measures Derived From SD-OCT for Detection of Early Glaucoma; Sharifipour F, Morales E, Lee JW, Giaconi J, Afifi AA, Yu F, Caprioli J, Nouri-Mahdavi K; Investigative Ophthalmology and Visual Science 2017; 58: 4310â€“4317

The distribution of retinal ganglion cell axons and cell bodies is highly symmetric between the superior and inferior hemi-field of the retina in normal eyes.[1] It is well known that glaucomatous visual field loss is commonly asymmetric across the horizontal meridian.[2,3] Likewise, glaucomatous changes of the retinal layers are often asymmetric between the upper and lower hemifields, especially in the early stages of glaucoma.[4]

Sharifipour *et al.*[5] tested the hypothesis that biomarkers of vertical macular thickness asymmetry based on ganglion cell-inner plexiform layer (GCIPL) measurements can improve discrimination of early glaucoma from normal subjects. This study demonstrated **that macular vertical thickness asymmetry measures did not perform better than sectoral or minimum GCIPL thickness for detection of early glaucoma.** A combination of sectoral GCIPL thickness and the best local vertical asymmetry parameter significantly improved the diagnostic performance of macular images.

The asymmetry analysis in this study was based on the following assumptions: 1) inter-hemispheric anatomic symmetry is preserved in normal healthy eye; 2) glaucoma often shows asymmetric features at initial diagnosis and during progression. From this background, the authors propose a novel and simple index, termed as 'asymmetry index', for quantitative evaluation of vertical macular asymmetry.

Some points need to be considered when interpreting the results of this study. First, temporal raphe varies among individuals, which highlights the importance of customized algorithm to increase its glaucoma diagnostic performance and clinical utility. Second, considering the current macular OCT images were not precisely designed to measure vertical asymmetry across the horizontal raphe, further studies would be needed using higher resolution OCT images and automated algorithms for measuring global and local macular asymmetry. It would be interesting to know if further examinations including various stages of glaucoma can make the present data more relevant.

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Structure-Function Relationship

Comment by Tae-Woo Kim, Bundang-gu, Seongnam, Korea

74353 Structure-Function Relationships in Perimetric Glaucoma: Comparison of Minimum-Rim Width and Retinal Nerve Fiber Layer Parameters; Amini N, Daneshvar R, Sharifipour F, Romero P, Henry S, Caprioli J, Nouri-Mahdavi K; Investigative Ophthalmology and Visual Science 2017; 58: 4623-4631

Structural assessment is widely used to diagnose and monitor the disease in glaucoma. Minimum rim width estimated from the Bruch membrane opening (BMO-MRW) has been proposed as an alternative structural measure. This parameter is theoretically robust due to its independence of any arbitrary reference planes and geometrically precise nature than 'cup' or 'rim' measurement based on an operator-defined disc margin. However, it is controversial whether the BMO-MRW thickness is superior to peripapillary RNFL for detection of early glaucoma or with regard to structure-function relationships in the real world.

> Structure–function relationships were somewhat weaker with BMO-MRW parameters compared with pRNFL thickness in eyes with perimetric glaucoma

Amini *et al.* reported that structure–function relationships were somewhat weaker with BMO-MRW parameters compared with pRNFL thickness in eyes with perimetric glaucoma. In addition, the relationship was not significantly increased even after normalization of the BMO-MRW according to average BMO circumference. If a structural parameter which has a good structure-function relationship particularly in advanced disease, using that parameter can extend the useful range of structural measurements in glaucoma. The result of

the study suggests that the BMO-MRW is not such a parameter normalization of BMO-MRW based on BMO area, did not significantly change the SF relationships. While this finding may suggest that BMO-MRW is not significantly influenced by the BMO circumference, this could be attributed to the limited number of eyes with extreme BMO measurements in their study. Therefore, it is likely prudent to consider such corrections in eyes in which the BMO size significantly deviates from the average values of the SD-OCT normative database.

Clinical Examination Methods: Blood Flow

Factors affecting Ocular Blood Flow

Comment by James Tan, Los Angeles, CA, USA

74076 The effects of antioxidants on ocular blood flow in patients with glaucoma; Harris A, Gross J, Moore N, Do T, Huang A, Gama W, Siesky B; Acta Ophthalmologica 2017; 0:

This paper reports ocular blood flow findings in open angle glaucoma (OAG) patients receiving a fixed dietary supplement containing vitamins (C, E, B6, B12, folate), minerals (magnesium), and agents considered to be heart-healthy (omega-3 fatty acid, flaxseed oil) and to have antioxidant properties (gingko bilobaextract, bilberry fruit extract, taurine, alpha lipoic acid, N-acetylcysteine, grape seed extract). The hypothesis was that dietary supplementation with this 'optic nerve formula' would have a beneficial effect on ocular hemodynamic parameters of retinal and retrobulbar blood flow. The study design was a randomized, double blind, placebo-controlled, cross-over study of 45 subjects with OAG.

After treatment with the dietary supplement for a month, peak systolic and end diastolic velocity of blood flow in retrobulbar vessels were significantly higher compared with placebo controls based on non-invasive measurements (*e.g.*, ultrasound and laser Doppler flowmetry). An accompanying reduction in vascular resistance was seen in central retinal and short posterior ciliary arteries in the treated group. Mean blood flow in superior and inferior temporal retinal arteries and recruitment of retinal capillaries was also higher in the treated group ($p<0.05$ for all significant differences). Daytime IOP and ocular perfusion pressure readings were found to be similar between the groups. The hemodynamic findings were captured following a relatively long period (1 month) of using the supplements.

Whether the hemodynamic observations are accompanied by functional and structural differences are further important questions to answer, especially in the context of progressive glaucoma

These observations are in line with previous reports of lower blood volume, flow and velocity in regions of the neuroretinal rim, temporal peripapillary retina and retrobulbar vessels in OAG (and normal tension glaucoma) patients compared with normal controls. The present study did not define OAG by IOP level. Concurrent use of glaucoma and other systemic medications in both groups may have confounded hemodynamic observations, although randomization is expected to have minimized this effect. In future studies it would be interesting to know if non-glaucomatous eyes show similar responses to those reported for OAG eyes. Whether the hemodynamic observations are accompanied by functional and structural differences are further important questions to answer, especially in the context of progressive glaucoma.

Macular OCT-A in Glaucoma

Comment by Zia Pradhan and Harsha Rao, Narayana Nethralaya, Bangalore, India

74446 Quantitative optical coherence tomography angiography of macular vascular structure and foveal avascular zone in glaucoma; Choi J, Kwon J, Shin JW, Lee J, Lee S, Kook MS; PLoS ONE 2017; 12: e0184948

There is a rapidly growing body of knowledge examining the diagnostic value of optical coherence tomography angiography (OCTA) in glaucoma. Vessel density, the percentage area occupied by the large vessels and microvasculature in a particular region, is the most common parameter quantified on the OCTA scans. While most studies reported good diagnostic value of peripapillary vessel density in glaucoma,[1,2] the same for macular vessel density was poor.[3,4] In a recent study, **Choi *et al*[5] determined a few new parameters of the foveal avascular zone (FAZ) on OCTA, namely the FAZ size, perimeter, and circularity index, and evaluated their diagnostic ability in glaucoma.**

> While most studies reported good diagnostic value of peripapillary vessel density in glaucoma,the same for macular vessel density was poor

The FAZ circularity index, which is a measure of the compactness of shape relative to a circle, graded as 1.0 for a perfect circle and a value closer to 0 for an irregular shape, was found to have an area under the receiver operating characteristic curve (AUC) of 0.905; this was similar to the AUC of peripapillary retinal nerve fiber layer (RNFL) thickness (0.969) and macular ganglion cell-inner plexiform layer thickness (0.948). In addition to this study, a few others have reported that the diagnostic value of macular vessel density measured

beyond the central 3 mm zone was greater than that measured within the central 3 mm zone (as done in most previous studies).[6,7] These results highlight that a lot remains to be explored in the field of macular imaging with OCTA in glaucoma.

The clinical usefulness of imaging the macular vasculature in glaucoma is likely to be limited since the geriatric macula is affected by several other diseases (age-related macular degeneration, diabetic retinopathy, etc)

Despite these interesting findings, the clinical usefulness of imaging the macular vasculature in glaucoma is likely to be limited since the geriatric macula is affected by several other diseases (age-related macular degeneration, diabetic retinopathy, etc). Additionally, systemic diseases, such as diabetes mellitus and hypertension, are known to affect the macular vessels on OCTA in the absence of any clinically detectable retinal changes.[8] Therefore, currently RNFL thickness remains the most useful parameter in glaucoma imaging. However, these new findings with OCTA will help us better understand the pathogenesis of glaucomatous macular damage.

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Clinical Examination Methods: other

Measuring Elasticity in Vivo

Comment by Ross Ethier, Atlanta, GA, USA

74266 In Vivo Noninvasive Measurement of Young's Modulus of Elasticity in Human Eyes: A Feasibility Study; Sit AJ, Lin SC, Kazemi A, McLaren JW, Pruet CM, Zhang X; Journal of Glaucoma 2017; 26: 967-973

Sit and coworkers describe the application of ultrasound surface wave elastography to measure the stiffness (Young's modulus, or E) of the cornea in ostensibly normal volunteers. The motivation for this proof-of-concept study is a body of evidence that the stiffness of ocular tissues, particularly the peripapillary sclera and lamina cribrosa, modulate the effects of intraocular pressure on the sensitive cells of the optic nerve head and can thus influence glaucoma risk in individual patients. Although many techniques exist for measuring tissue stiffness in a laboratory setting, clinical measurements are more challenging. The technique used here is clever: a small mechanical probe was placed on the closed eyelid and vibrated to cause tiny displacement waves to propagate laterally in the cornea, which were then imaged using a standard ultrasound system. Finally, the wave speed was obtained by image analysis and a theoretical model was used to infer corneal E from wave speeds. **E was correlated with IOP measured by GAT, as expected, but not with age, central corneal thickness, and axial length, although this lack of correlation was possibly due to the small cohort (20 eyes in 10 subjects).** Advantages of the technique include its relatively simplicity, non-invasive nature, and rapidity. Importantly, E is a direct measure of inherent tissue properties, which is attractive compared to systems such as the Ocular Response Analyzer that produce biomechanical outcome measures that are harder to interpret.

E is a direct measure of inherent tissue properties, which is attractive compared to systems such as the Ocular Response Analyzer that produce biomechanical outcome measures that are harder to interpret

Drawbacks include the assumptions required in the theoretical model used to infer E: these include simplifications of the tissue geometry and neglect of several complex tissue properties (anisotropy and viscoelasticity). The authors wish to now extend the approach to measure stiffness of posterior ocular tissues – this will be more challenging, possibly due to imaging issues and also because the above-mentioned assumptions of the theoretical model become less correct near the optic nerve head. If further validated, this technique would provide a much-needed tool for interrogating posterior ocular tissue biomechanical properties.

Refractive Errors

High Myopia and Glaucoma

Comment by Tsing-Hong Wang, Taipei, Taiwan

74798 Intraocular Pressure and Glaucomatous Optic Neuropathy in High Myopia; Jonas JB, Nagaoka N, Fang YX, Weber P, Ohno-Matsui K; Investigative Ophthalmology and Visual Science 2017; 58: 5897-5906

The authors conducted a hospital-based study in a third referral myopia clinic and demonstrated that higher prevalence of GON was correlated with higher IOP in eyes with an axial length of < 27.4 mm. However, **in highly myopic eyes (axial length > 27.5 mm), the frequency of GON was not correlated with IOP.**

Diagnosing glaucoma in a highly myopic eye is never an easy job. Many other reasons besides glaucoma can produce various visual filed defects in highly myopic eyes. OCT images also can't provide a clear distinction between a normal optic nerve and GON in the majority of highly myopic eyes. The authors made the diagnosis of GON by observing the ophthalmoscopic appearance of the optic nerve head. The neuroretinal rim had to have a clearly glaucoma-like appearance, either in the form of marked rim notches touching the disc border or in the form of an advanced loss of neuroretinal rim with an optic cup extending to the disc border for a large sector of the optic nerve head. This definition of GON may underestimate the prevalence of GON.

IOP was one of the main outcome parameters, but the study participants were enrolled into the study based on their myopia, while glaucoma was not a reason for attending the hospital. Therefore, some IOP related parameters such as IOP diurnal variation, blood pressure, and central corneal thickness were not assessed in the present retrospective study. The glaucomatous group as compared to the nonglaucomatous group had a significantly higher prevalence of IOP-lowering therapy, and this could also explain the lack of a difference in IOP between both groups.

If the observation of a missing association between IOP and GON in the highly myopic group in the present study population is valid, this may be due to the anatomic particularities of the high myopia optic nerve heads, such as thinning of the lamina cribrosa and a steeper translamina cribrosa pressure. It is possible that the influence on the glaucoma progression of these optic nerve features far outweigh that of IOP. Another reason could be that highly myopic glaucomatous eyes have a markedly lower IOP threshold to develop optic nerve damage, and a target IOP of much lower than the mid-teens might be necessary to prevent the development of GON in the highly myopic eyes.

Clinical Forms of Glaucoma

Relative Afferent Pupillary Defect in NTG

Comment by Ki Ho Park, Seoul, South Korea

74629 Patients With Normal Tension Glaucoma Have Relative Sparing of the Relative Afferent Pupillary Defect Compared to Those With Open Angle Glaucoma and Elevated Intraocular Pressure; Lawlor M, Quartilho A, Bunce C, Nathwani N, Dowse E, Kamal D, Gazzard G; Investigative Ophthalmology and Visual Science 2017; 58: 5237-5241

This is very pioneering and interesting paper. The authors investigated whether there is relative sparing of pupil function in glaucoma patients with normal pressures compared with those with high pressures. The relative afferent pupillary defect (RAPD) was quantified with the RAPDx device in 68 patients with primary open-angle glaucoma (POAG), of which 38 had normal IOPs on all-day phasing before treatment (never >21 mm Hg), with confirmed progression of glaucomatous optic neuropathy (NTG), and 30 had glaucomatous optic neuropathy associated with elevated intraocular pressures (>25 mm Hg; HP-POAG).

The difference in slope between NTG and HP-POAG was evaluated on plots of RAPD magnitude against difference in HVF MD and of RAPD magnitude against difference in RNFL thickness. The authors found that, with regard to the difference in MD, **the slope for patients with NTG was flatter than that for those with HP-POAG,** which means that patients with NTG have a lesser RAPD for a given level of inter-eye difference of HVF MD, as compared with patients with high IOPs. From the results, the authors hypothesized that damage to intrinsically photosensitive retinal ganglion cells (ipRGCs) differs between NTG and HP-POAG and that their data supports the theory that mitochondrial optic neuropathies have a role in NTG, as ipRGC is known to be spared in the mitochondrial optic neuropathies.

There is limitation to this study. There was no matching of disease severity between the two groups, or in any case, there was no discussion of matching in the manuscript. Actually, the MD of the left and right eyes in NTG were -8 and -7.5 dB, respectively, while those in HP-POAG were -4.7 and 5.6 dB, respectively. Further, the RNFL thickness difference between both eyes was smaller in NTG (0.6 um) than in HP-POAG (3.8 um), even though the statistical significance was not provided. So, there is a possibility that the lesser RAPD in the NTG group was at least partially affected by the inter-group disease-severity and structural-damage differences between both eyes.

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However, this paper raised the important issue that mitochondrial neuropathy might have a role in NTG, and it provided quantitative evidence in the form of plots comparing pupillary response and functional and structural optic nerve damage. Further study on mitochondrial gene sequencing and the relationship with pupil function in those or similar subgroups of patients would be in order.

Childhood Glaucoma Suspects


Comment by Ze Zhang and Wallace Alward, Iowa City, IA, USA

74465 Clinical management outcomes of childhood glaucoma suspects; Greenberg MB, Osigian CJ, Cavuoto KM, Chang TC; PLoS ONE 2017; 12: e0185546

Greenberg *et al.* reported a succinct retrospective series of outcomes of childhood glaucoma suspects with 39+/- 34 months of follow-up from a single large tertiary referral center.

They found that **up to 25% of children with 2 or more episodes of elevated IOP above 21 may develop glaucoma.** The authors found no significant difference in gender, family history, or baseline central corneal thickness between those who developed glaucoma and those who did not. There was a trend for higher IOPs in those who developed glaucoma.

The authors are among the first to start filling a gap in the literature regarding the characteristics of childhood glaucoma suspects for conversion to glaucoma. While many trials have examined risk factors for glaucoma and the clinical course of glaucoma suspects in the adult population, similar knowledge specific to the pediatric population is sparse.

In this study of childhood glaucoma suspects, **only 50% of those who developed glaucoma had an elevated IOP greater than 21 mmHg at baseline.** Of the 44.4% of patients who demonstrated 2 or more episodes of elevated IOP, 25.6% developed glaucoma with a mean follow up of 2.8 years.

While many trials have examined risk factors for glaucoma and the clinical course of glaucoma suspects in the adult population, similar knowledge specific to the pediatric population is sparse

The manuscript brings up important considerations in the long-term management of pediatric glaucoma suspects. The results show that long-term follow up is very important. Absence of family history of glaucoma, normal baseline IOP, and normal CCT do not preclude the development of glaucoma over the long run. It may be that risk factors for glaucoma in pediatric patients differ from those of the adult population.

The retrospective design and the single tertiary referral center for patient cohort limits the generalizability of the results. The study does highlights the need for a prospective longitudinal multi-centered study examining the clinical outcomes and incidence of childhood glaucoma to better elucidate risk factors for glaucoma development in the pediatric population.

OCT-A in POAG and NTG

Comment by Linda Zangwill, La Jolla, CA, USA

74388 Optical coherence tomography angiography of the peripapillary capillaries in primary open-angle and normal-tension glaucoma; Igarashi R, Ochiai S, Sakaue Y, Suetake A, Iikawa R, Togano T, Miyamoto F, Miyamoto D, Fukuchi T; PLoS ONE 2017; 12: e0184301

Optical coherence tomography angiography (OCTA) has facilitated the visualization of retinal vascular architecture of the optic nerve head and macula. The ability to visualize the vascular system at different layers of the retina has immediate benefit for characterizing and monitoring various retinal diseases including diabetic retinopathy, age-related macular degeneration, and retinal vascular occlusions. The advantages of utilizing OCTA for detecting and monitoring glaucoma compared to standard measures such as retinal nerve fiber layer thickness (RNFLT) is less clear and is the topic of numerous investigations. Igarashi and colleagues[1] assessed the relationship between the vascular architecture of the radial peripapillary capillaries (RPC) and severity of visual field damage in a relatively small study of 20 open angle glaucoma and 32 normal tension glaucoma with moderate to advanced disease. The investigators evaluated RNFL thickness and flow density (more commonly known as vessel density) along with 2 new metrics: the disappearance angle of the RPCs, and the angle of the retinal nerve fiber layer (RNFL) defect. **They found that flow density and the disappearance angle of the RPC was independently associated with visual field mean deviation.** Igarashi's results confirm numerous other reports that vascular dropout of the RPCs measured by vessel density is positively associated with severity of glaucomatous visual field damage.[2-4]

Although not highlighted in the discussion, **the investigators also found that both RNFL defect angle and RNFL thickness are more strongly associated with visual field MD and PSD than the OCTA metrics, particularly in the normal tension group.** In addition, the authors conclude that flow density and the disappearance angle of the RPCS were significantly and independently correlated with glaucoma functional and structural damage; however no multivariable analysis was completed to determine whether these parameters were independently associated with severity of glaucoma when other measures, such as RNFL thickness were included in the model. The authors also suggest that "progression

of glaucoma may be predicted by the disappearance angle of the RPC"; such statements should be reserved for inference from longitudinal studies as cross-sectional studies cannot directly inform on prediction or progression of disease.

The question remains whether the visualization and quantitation of retinal vasculature will provide additional information that will change glaucoma clinical decision making when RNFL thickness and ganglion cell layer measurements are already available to the clinician

The high-resolution visualization of perfused retinal vasculature provided by OCTA has already begun to improve our understanding the role of the retinal vascular system in the pathophysiology of glaucoma. The question remains whether the visualization and quantitation of retinal vasculature will provide additional information that will change glaucoma clinical decision making when RNFL thickness and ganglion cell layer measurements are already available to the clinician. Longitudinal studies are needed to answer this important question.

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Intracranial Pressure in NTG

Comment by Ningli Wang, Beijing, China

74728 Normal-Tension Glaucoma Has Normal Intracranial Pressure: A Prospective Study of Intracranial Pressure and Intraocular Pressure in Different Body Positions; Lindén C, Qvarlander S, Jóhannesson G, Johansson E, Östlund F, Malm J, Eklund A; Ophthalmology 2017;

Lindén *et al.*[1] presented a prospective study on intracranial pressure (ICP) and intraocular pressure (IOP) in different body positions, and demonstrated that there was no evidence of reduced ICP in normal tension glaucoma (NTG) patients as compared with healthy controls, either in supine or in upright position. The conclusion of their study differed from that of the previous studies by Berdahl *et al.*[2] and our team.[3] The discrepancy could be the result of synergy of several possible causes:

In prior studies by Berdahl *et al.*[2] and Ren *et al.*[3], all NTG patients underwent 24-hour IOP monitoring to make sure their IOP ≤ 21mmHg. However, some NTG patients in Lindén *et al.*'s study had occasional IOP up to 24mmHg, and they did not mention whether the 24-hour IOP monitoring was performed. There is possibility that hypertension glaucoma patients were included in the NTG group, which may influence the final results.

Moreover, previous study has already revealed an average ICP of 12.5mmHg among healthy population.[4] However, ICP in the control group reported in this study is only 11.3mmHg. The lower ICP in the control group may have contributed to the lower TLCPD in this study.

Additionally, it has been reported that blood pressure and body mass index (BMI) have positive correlation with ICP[4], hence, the higher ICP in the NTG group could be well-explained by the higher blood pressure and BMI in this study. In comparison, the blood pressure and BMI of the NTG patients in Chinese population were relatively low[3], which may be attributable to the racial difference.

Considering that current studies in this field have small sample sizes, differ in the methodology and were conducted among population of different ethnic groups, an international cooperative study among different ethnic groups with a standard protocol should be carried out to clarify the contribution of each factors to the study results.

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Surgical Treatment of NTG

Comment by Robert Feldman, Houston, TX, USA

74241 Effect of trabeculectomy on visual field progression in Japanese progressive normal-tension glaucoma with intraocular pressure < 15 mmHg; Naito T, Fujiwara M, Miki T, Araki R, Fujiwara A, Shiode Y, Morizane Y, Nagayama M, Shiraga F; PLoS ONE 2017; 12: e0184096

Naito *et al.* Effect of trabeculectomy on visual field progression in Japanese progressive normal-tension glaucoma with intraocular pressure < 15 mmHg.

Normal tension glaucoma (NTG) occurs when glaucomatous optic nerve damage is present with IOP in the "normal" range. It is the most common form of glaucoma in Japan, with a prevalence rate of 3.6%. Treatment for NTG is medication to lower IOP, with surgical intervention to further lower IOP if progression continues. The purpose of this study was to determine the efficacy of lowering IOP by trabeculectomy in decreasing the slope of mean deviation (MD) in patients with IOP < 15 mmHg.

The authors retrospectively reviewed records of 17 cases of NTG who had undergone trabeculectomy with mitomycin-C for progressive NTG with medically controlled IOP < 15 mmHg, 5 reliable visual field tests both pre- and postoperatively, and > 2 years follow-up. Cases where cataract surgery was done in conjunction with trabeculectomy or previous cataract surgery were included. Postoperative IOP was significantly lowered (mean reduction 5.8 mmHg, 41.7%) from preoperative IOP. In eyes with single-digit postoperative IOP, 91.7% showed improvement in MD slope, while only 20% with postoperative IOP > 10 mmHg showed MD slope improvement. Three eyes had decline in visual acuity > 0.1 logMAR units, and all 3 had hypotony maculopathy. Preoperative MD slope that could predict 50% improvement in postoperative MD slope was -0.91 dB/year. The group showing no improvement in MD slope had a significantly higher postoperative IOP, lower mean rate of IOP reduction, and used more IOP-lowering medications after surgery.

The authors concluded that achieving single-digit IOP by trabeculectomy results in slowing visual field progression in NTG patients. They cautioned that IOP < 7 mmHg could result in visual acuity decline. As with small retrospective studies, the usual limitations apply.

Additionally, visual field testing was not consistent, with some patients followed with a 30-2 test and others with a 10-2 test. Even though both groups showed delays in glaucoma progression, the two slope changes are not comparable.

Macular Choroidal Thickness in Pseudoexfoliation


Comment by Aakriti Garg and Gustavo de Moraes, New York, NY, USA

74825 Comparison of macular choroidal thickness in patients with pseudoexfoliation syndrome to normal control subjects with enhanced depth SD-OCT imagingl; Moghimi S, Mazloumi M, Johari MK, Fard MA, Chen R, Weinreb R, Nouri-Mahdavi K; Journal of current ophthalmology 2017; 29: 258-263

Pseudoexfoliation syndrome is an important risk factor for the development of secondary open angle glaucoma and is associated with faster progression to advanced disease.[1]

Moghimi and colleagues sought to investigate the structural features of the macular choroid in patients with pseudoexfoliation syndrome.[2] This cross-sectional study included 32 non-glaucomatous pseudoexfoliation patients with 29 normal controls who underwent enhanced depth imaging spectral domain optical coherence tomography (EDI SD-OCT). This technique captures high resolution images of posterior segment structures, including the choroid and lamina cribrosa.

There was a significant difference between the pseudoexfoliation syndrome group and the normal controls in choroidal volume, central subfield choroidal thickness, inner superior and inner nasal choroidal rings of the EDTDRS grid. However, **after adjustment for age, sex, and axial length, these differences were non-significant and macular choroidal thickness and RNFL thickness were similar between groups.** Interestingly, although differences in sex, mean axial length and mean age were non-significant (p-values = 0.10, 0.43, 0.52, respectively), they blunt the differences detected in the two groups' choroidal measures in the univariable analysis. The current report agrees with other studies in not finding an independent association between macular choroidal thinning and glaucoma risk factors and/or glaucomatous loss.[3-7]

> The current report agrees with other studies in not finding an independent association between macular choroidal thinning and glaucoma risk factors and/or glaucomatous loss

Additionally, there was a significant negative correlation between age and central subfield choroidal thickness and choroidal volume in the control group, although such an association was not found in pseudoexfoliation syndrome. The association between increasing age and decreasing choroidal thickness is well established,[8] therefore it is interesting that this finding was not seen in pseudoexfoliation syndrome group. One possible explanation, as brought up by the authors, is that pseudoexfoliation may have some influence on the effect of aging on choroidal thickness, which resulted in a non-significant relationship between choroidal thickness and age. We also believe this could have been the result of the study selection process, as eyes with pseudoexfoliation syndrome, which is associated with aging, were probably more homogenous in their age distribution. Additionally, pseudoexofoliation syndrome may be associated with accelerated aging of the ocular tissues, which may lead to a thinner choroid independent of the duration of the disease.

Pseudoexofoliation syndrome may be associated with accelerated aging of the ocular tissues, which may lead to a thinner choroid independent of the duration of the disease

Increasing the size of the study and control group is advisable. Additionally, despite excellent agreement between observers, the report did not mention if the measurements were made by observers who were masked to the diagnosis.

In summary, the macular choroidal thickness is thinner in eyes with pseudoexofoliation syndrome (without glaucoma) compared to healthy controls. However, this difference was influenced by confounders such as age, axial length, and sex, resulting in non-significant differences between groups.

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Medical Treatment

Travoprost vs. Timolol in Pediatric Glaucoma

Comment by Stefano Miglior, Milan, Italy

74332 A 3-month safety and efficacy study of travoprost 0.004% ophthalmic solution compared with timolol in pediatric patients with glaucoma or ocular hypertension; Dixon ER, Landry T, Venkataraman S, Gustafson N, Salem C, Bradfield Y, Aljasim LA, Feldman R; Journal of AAPOS 2017; 21: 370-374.e1

Management of pediatric glaucoma is particularly challenging and, despite being primarily surgical, medical treatment is widely used and significant. However, medical therapy is limited due to the possibility of systemic adverse events and to the lack of robust scientific evidence concerning both safety and efficacy.

In this paper the authors report the results of a double masked, randomized, prospectictively planned clinical trial comparing travoprost 0.004% with timolol 0.25% or 0.5% (depending on the agegroups) in pediatric patients with glaucoma or ocular hypertension.

The study is well executed clinically, considering the high degree of difficulty associated with acquiring accurate IOP measurements (which may require the need of sedation or anesthesia) in infants and young children. The only major concern is the single day wash out from previous medications, which likely affected accurate baseline IOP measurements. While some children were without therapy, a higher number were on medical treatment including beta-blockers, PG analogues and carbonic anhydrase inhibitors, and in some cases two medications. A minor concern is the 3 month follow up period which is insufficient to allow long-term evaluation of the study drugs.

The results show that travoprost 0.004% and timolol had no statistically significant differences (non inferiority) at the 3 month time point both in terms of efficacy (about 5-6 mmHg reduction from baseline, either in the Intention to Treat or in the Per Protocol analyses) and in terms of safety (with no relevant side effects or systemic events closely related to the studied drugs).

The results of this study represent the first data on safety and efficacy of a PG analogue (namely travoprost 0.004%) from a double blind prospectively planned randomized clinical trial in pediatric patients

The results of this study represent the first data on safety and efficacy of a PG analogue (namely travoprost 0.004%) from a double blind prospectively planned randomized clinical trial in pediatric patients. Their impact on daily practice is scientifically and clinically relevant, and should help clinicians in better manage pediatric glaucoma.

Ocular Surface Disease

Comment by Paul Palmberg, Miami, FL, USA

74615 Use of Topical Cannabinomimetic Palmitoylethanolamide in Ocular Surface Disease Associated with Antiglaucoma Medications; Di Zazzo A, Roberti G, Mashaghi A, Abud TB, Pavese D, Bonini S; Journal of Ocular Pharmacology and Therapeutics 2017; 33: 670-677

The authors report the results of a pilot study, described as an open label, single masked, randomized trial of the effect of adding DeFluxa drops (containing palmitoylethanolamide) bid for 30 days to usual topical glaucoma therapy to see if the signs of ocular surface inflammatory disease would be improved. The rationale for the study was sound, as palmitoylethanolamide, a natural substance in the brain, has known anti-inflammatory actions (inhibits inducible nictric oxide synthase, inducible cyclooxygenase, and cytokines IL-1b, PGE2, and TNF-a by inhibiting the transcription of nuclear factor NFkb), and analgesic effect (by stimulation of peroxisome proliferator-activated receptor [PPAR]a and indirectly by cannabinoid receptor CB1).

Palmitoylethanolamide, a natural substance in the brain, has known anti-inflammatory actions

The results reported were small, but **statistically significant improvements in tear production (Schirmer score), tear film stability (tear break up time) and hyperemia score.** The control group was given preservative free hyaluronic acid drops to use, with the implication that it served as a vehicle control. In neither group did the addition of study drops affect IOP control.

There were aspects of the study that were not clearly defined, most importantly what "single masked" meant. Were the subjects or the evaluators masked? That is critical to the validity of the study as the measurements used were subject to some bias. Were the subjects "assigned" to the treatment groups, as stated in one place, or "randomized", a word mentioned only in a table? What were the glaucoma medications being used, since prostaglandin analogs, alpha-2 agonists, and preservatives would be expected to have different mechanisms of promoting hyperemia and ocular surface disorder.

Despite the limitations of this small pilot study, the results do suggest that a larger and longer placebo controlled, double masked trials should be performed in subjects with ocular surface inflammatory disease using specific classes of glaucoma drops.

Piezo-electric Eyedrop Microdosing

Comment by Eytan Blumenthal, Jerusalem, Israel

74692 High-precision piezo-ejection ocular microdosing: Phase II study on local and systemic effects of topical phenylephrine; Ianchulev T, Weinreb R, Tsai JC, Lin S, Pasquale LR; Therapeutic delivery 2018; 9: 17-27

Eye drops are the time-honored way we deliver topically applied medications to the eye. While cheap, simple and readily available, several limitations and disadvantages include the use of far more active ingredient than needed, systemic absorption of medication that escapes through the nasolacrimal tract and absorbed by the nasal mucosa, and spillage of excessive drops down the periocular skin. Additional limitations include limited compliance (eye-drops often do not drop into the eye), occasionally multiple drops are required to complete the task, and a proportion of elderly patients unable to self-administer their drops.

Ianchulev *et al.* present a phase II clinical trial evaluating a novel microdosing system based on piezo-ejection of a small volume of spray aimed at the cornea. An electronic device sprays a micro-dose of the desired medication onto the eye as the patient fixates on an LED targeting light. Very accurate volumes can be ejected, in this study 8 microliter, one quarter the volume of the drop used in the control arm of the study. The medication chosen for this trial was phenylephrine, chosen as both the clinical effect (dilation of the pupil), systemic effect (pulse rate and blood pressure) as well as its concentration in the blood can all be readily and objectively evaluated.

This clinical trial concludes that a device spraying topical medication directly onto the cornea in minute volumes, much smaller than the volume of an eyedrop, can achieve similar clinical efficacy, with significantly lower plasma concentrations. Eight microliters of phenylephrine 10% delivered via this novel piezo-ejection technique outperformed

the same amount of active ingredient delivered as 2.5% drop of quadruple volume. When compared to a 10% conventional drop containing 4-times the active ingredient, similar efficacy resulted, but with significantly higher plasma concentrations suggesting higher systemic absorption.

The authors conclude that beyond reducing systemic and allergic side effects, this novel approach may benefit compliance, the ability to monitor compliance objectively, as well as eHealth communication between patient and physician. This novel delivery system also may benefit treatment with rare and expensive drugs, nanoparticles and perhaps one day also stem-cell and gene-therapy.

Surgical Treatment

Placement of Iridotomy

Comment by Prin Rojana-Pongpun, Bangkok, Thailand

74729 Comparison of New Visual Disturbances after Superior versus Nasal/Temporal Laser Peripheral Iridotomy: A Prospective Randomized Trial; Srinivasan K, Zebardast N, Krishnamurthy P, Abdul Kader M, Raman GV, Rajendrababu S, Venkatesh R, Ramulu PY; Ophthalmology 2017; 0:

Laser peripheral iridotomy (LPI) is widely practice with favorable risk/benefit ratio. Yet, it may produce undesirable complications like dysphotopsia that could be quite disabling without any real benefit to those relatively healthy angle closure suspect subjects (PACS). So, it is the physician's responsibility to avoid any known visual disturbances. As there were some conflicting evidence on where to perform LPI and its relation to post-LPI dysphotopsia, Srinivasan *et al.* investigated this with a larger scale, well powered study in a RCT fashion. Based on Srinivasan,[1] LPI location either superior, nasal or temporal was not associated with statistically significant differences in new visual disturbances. However, their results contradict another randomized, prospective, single-masked, paired-eye comparative study of Vera *et al.*[2] which found that temporal LPI was less likely to result in linear dysphotopsia compared with superior placement. Why the differences?

Different study design, subject type and technique detail will definitely dictate the different outcomes and side effects of LPI. There could several missing parts of information specifically the followings:

a. Dynamic lid margin and LPI location: Placing LPI near the lid margin, with good tear meniscus, has been considered an important factor for linear dysphotopsia in Spaeth[3] and Vera[2] studies. However, none of these studies ever designed to study dynamic lid position and LPI location in relation to dysphotopsia. Srinivasan[1] also did not report

information on post-laser location of LPI in relation to lid margin. Although study protocol stated 'completely clear from lid margin', it is hard to know whether how many final locations are at any lid margin and any correlation to new dysphotopsia.

b. Size and exact peripheral location of LPI: a large enough size at a more central location may induce stronger straylight through crystalline lens equatorial area while the very far peripheral temporal location will less likely produce any focused rays of light on the retina. Superior LPI is usually more central location as well as in the area of thicker iris and needing more laser energy. This reflects well in the study showing significant higher total laser energy needed at superior location (59.1 mJ vs. 45.1 mJ with $p<0.001$). If both superior and temporal LPI were performed in a more central iris location, both would produce nearly the same frequency of dysphotopsia. But if temporal LPI was performed in the far periphery while superior LPI was performed naturally more central, the dysphotopsia rate could be different. Srinivasan reported 12.3% of all patients with new-onset of 1 or more dysphotopsia symptoms. There is no detailed information on the dimension of LPI performed by 4 different participating centers. It is not known whether the incidence of dysphotopsia was evenly distributed or skewed. The exact description of LPI in term of size and how peripheral it is made is also needed to understand the different outcome.

c. Data collection and follow-up: Dysphotopsia is subjective and could be variable. Assessment at 2 weeks could be different from a longer follow-up. Questionnaire distribution and data collection process can obtain different results. Self-report symptoms vs direct questioning will provide different outcomes.

d. Study population: Which category of angle closure cases compose into the study subjects will dictate the outcome. It is known that primary angle closure spectrum ranges from primary angle closure suspect (PACS), primary angle closure (PAC) and primary angle closure glaucoma (PACG). The outcome of LPI in preventing IOP rise varies from >90% success in PACS to <10% success in PACG. Likewise, the complications could be quite different from almost nil to corneal decompensation. This could partly explain why the outcomes of different studies looking for dysphotopsia were different or even contradictory. There were 16.4-17.5% of PAC or PACG in Srinivasan study. Besides, all subjects are south Asian population which is quite different from Vera that has only 34.9% of the same south Asian population.

The study does confirm the safety of LPI and remind us that it can lead to dysphotopsia. It also confirms that LPI can be performed in either superior or temporal/nasal location. It is the physician responsibility to avoid placement of LPI near the lid margin while choosing the best location that requires least laser energy to minimize any complications from LPI.

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Zonular Instability in ACG

Comment by Catherine Liu, Taipei, Taiwan

74391 Factors Associated With Zonular Instability During Cataract Surgery in Eyes With Acute Angle Closure Attack; Kwon J, Sung KR; American Journal of Ophthalmology 2017; 183: 118-124

Eyes with zonular instability (ZI) usually manifests itself as phacodonesis at slit-lamp biomicroscopy, but a large lens held in a limited space between iris and vitreous body may obscure this sign. Out of fear of exacerbating pupillary block with high intraocular pressure following pharmacological mydriasis in eyes with a history of acute angle closure (AAC), displacement or tilt of the lens indicating the presence of ZI could be missed preoperatively.

The authors are to be commended for conducting this retrospective case-control study which first reports **preoperative factors associated with ZI in AAC eyes, including less hyperopic spherical equivalent, longer axial length, and higher lens volt as detected with AS-OCT.** Of note is that among the 10 eyes with ZI, the diseased eyes had significantly shallower anterior chamber (AC) and higher lens volt than their fellow eyes. Although the difference did not reach statistical significance after Bonferroni correction, probably due to small sample size, these findings support the conventional teaching that asymmetric AC depth between the two eyes of one subject indicates the presence of zonular weakness.

It is regretful that cases with lens subluxation not detected at the clinic but noted in the surgical theater after pupil dilation were excluded from this study. This group of eyes are those very likely to benefit from the study findings as surgeons can prepare well preoperatively for them. In addition, being a retrospective study, possibly involving more than one surgeon, which defined cases with or without ZI based on medical records (whether single-piece IOL was placed in-the-bag or capsule tension ring was inserted, etc.), the possibility of listing some cases with iatrogenic zonular damage which occurred during operation in the ZI (+) group and misclassifying cases with mild zonular weakness in the ZI (-) group could not be ruled out.

Biomarkers of Fibrosis

Comment by Esther Hoffman, Mainz, Germany

74514 Genotype-Phenotype Associations of IL6 and PRG4 With Conjunctival Fibrosis After Glaucoma Surgery; Yu-Wai-Man C, Tagalakis AD, Meng J, Bouremel Y, Lee RMH, Virasami A, Hart SL, Khaw PT; JAMA ophthalmology 2017; 135: 1147-1155

Success of glaucoma filtration surgery depends on the amount of fibrosis developing at the surgical site. **The prevention of scarring of the surgical opening allowing filtration from the anterior chamber into the subconjunctival space is the big challenge in filtering surgery.**

The process of wound healing starts immediately after injury to the conjunctiva. During this phase of consecutive steps inflammatory cytokines such as interleukin 6 (IL6) play a major role in the formation of fibrosis. Furthermore, the glycoprotein proteoglycan 4 (PRG4) has been detected at the ocular surface and might be protective and stabilisators after an injury of the conjunctiva.

Yu-Wai-Man and co-authors performed a cross-sectional study and included 42 glaucoma patients. Of these, 28 had undergone glaucoma surgery and 14 patients had no previous glaucoma surgery. Patients with glaucoma surgery showed conjunctival fibrosis and bleb appearance was assessed by using the Moorfields Bleb Grading System.

The purpose of this study was to evaluate whether IL6 and PRG4 are potential biomarker of conjunctival fibrosis after filtering glaucoma surgery. Conjunctival biopsies were collected from both study groups and fibrotic fibroblast and non-fibrotic fibroblast primary cell lines were established. The authors found an upregulation of IL6 gene in the fibrotic cell lines and a downregulation of PRG4 in the same cell lines.

> Upregulation of IL6 gene in the fibrotic cell lines and a downregulation of PRG4

Further studies might show whether these biomarkers may provide sensitive and reproducible information about disease severity and the amount of conjunctival scarring afte glaucoma surgery and furthermore, whether targeting these biomarkers may improve outcome and long-term survival of the bleb.

Pharmacoeconomics

Changing Therapies Costs More Childhood Glaucoma Suspects

Comment by Rupert Bourne, Cambridge, UK

74248 Changing Initial Glaucoma Medical Therapy Increases Healthcare Resource Utilization; Trese MGJ, Lewis AW, Blachley TS, Stein JD, Moroi SE; Journal of Ocular Pharmacology and Therapeutics 2017; 33: 591-597

Large claims databases offer the opportunity to generate large datasets of information on practice patterns. This paper involves a claims based model to evaluate how frequently 15,000 USA-based patients with newly diagnosed Open Angle Glaucoma (OAG) or Ocular Hypertension (OHT) started on either a topical beta-blocker (BB) or prostaglandin analogue (PGA) underwent a change in their index therapy within 12 months of starting the medication, and the costs incurred to the healthcare provider (between 2001-2012). To be included, the enrollee had to have been continuously enrolled in the plan for 3 years before the patient's index prescription (what the authors called the 'look back period') of either a topical BB (19% of enrollees) or PGA (81%). The eligible enrollees were then divided into 2 groups based upon their index prescription (topical BB or topical PGA). The outcome measure within these 2 groups was a change in the index therapy (addition of another class of ocular hypotensive, a change in medication, cessation of all therapy, or glaucoma surgery) within 12 months after starting either of these medications. Multivariable logistic regression analysis was used to explore whether the odds of continuing initial treatment were associated with age, sex, race/ethnicity, education level, household income, or region of residence. **A higher proportion of those started on BBs (39%) had a change in therapy within 12 months of initiating therapy compared to the PGA group (29%).** Those requiring a change in therapy were understandably seen more often and accrued more in median charges than those who did not require a change in their initial therapy. **Older patients and those with higher income were less likely to have their initial therapy changed.** Latinos and those of African-American race/ethnicity were associated with a higher likelihood of a medication change. Clearly changing medications and more frequent office visits are major contributors to the annual cost of treatment for glaucoma patients, yet the absence of clinical information in this study makes any attempt to explain the difference in findings between these two treatment groups entirely speculative. It is also impossible to really draw conclusions regarding the reasons why lower income groups and certain racial groups were at higher risk of a medication change as the reason for the change is unknown. As we know there could be a myriad of reasons ranging from practice policy, adverse events, advent of evidence that favoured PGAs, and use of generics, all of which may have changed considerably over an 11 year time period. Or indeed a

'trial-and-error approach' which the authors conclude to be the reason why a substantial proportion of patients require a change in therapy within a year. To my mind, **this is a good example of how analysis of 'big data' can at first glance look attractive with the lure of thousands of patient datasets, yet the absence of key variables, in this case, clinical information, makes it very difficult to derive meaningful outcomes.**

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NEWS FLASHES

- ★ Palmitoylethanolamide, a natural substance in the brain, has known anti-inflammatory actions
- ★ Upregulation of IL6 gene in the fibrotic cell lines and a downregulation of PRG4
- ★ Pathophysiology of eye aging is not well understood
- ★ The clinical and pathologic relationship between AD and glaucoma remains obscure
- ★ Patient-obtained IOP measurements were reproducible and similar to physician-obtained ones.
- ★ While many trials have examined risk factors for glaucoma and the clinical course of glaucoma suspects in the adult population, similar knowledge specific to the pediatric population is sparse
- ★ The current report agrees with other studies in not finding an independent association between macular choroidal thinning and glaucoma risk factors and/or glaucomatous loss
- ★ Pseudoexofoliation syndrome may be associated with accelerated aging of the ocular tissues, which may lead to a thinner choroid independent of the duration of the disease
- ★ Matrix metalloproteinases are zinc-containing enzymes and play a possible role in glaucoma pathogenesis.
- ★ As with other cross sectional studies, it cannot be concluded that zinc or iron levels are a cause or consequence of glaucoma
- ★ The results of this study represent the first data on safety and efficacy of a PG analogue (namely travoprost 0.004%) from a double blind prospectively planned randomized clinical trial in pediatric patients
- ★ What most patient see is not reflected in the gray scale print out from visual field machines or in online depictions of what glaucoma looks like
- ★ While most studies reported good diagnostic value of peripapillary vessel density in glaucoma,the same for macular vessel density was poor
- ★ The clinical usefulness of imaging the macular vasculature in glaucoma is likely to be limited since the geriatric macula is affected by several other diseases (age-related macular degeneration, diabetic retinopathy, etc).
- ★ Together these results suggest that MSCs are likely producing other soluble neuroprotective factors, in addition to PDGF
- ★ Detecting and monitoring glaucoma compared to standard measures such as retinal nerve fiber layer thickness (RNFLT) is less clear
- ★ The question remains whether the visualization and quantitation of retinal vasculature will provide additional information that will change glaucoma clinical decision making when RNFL thickness and ganglion cell layer measurements are already available to the clinician
- ★ There is a possibility that the lesser RAPD in the NTG group was at least partially affected by the inter-group disease-severity and structural-damage differences between both eyes.

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