VOLUME 21-1
2020

International Glaucoma Review

The journal of the World Glaucoma Association

Abstracts and Review of Glaucoma Literature

www.e-IGR.com

SINCE 1984

ISSN 1566-1040

Regional & International Glaucoma Societies

American Glaucoma Society

Asia-Pacific Glaucoma Society

Australia and New Zealand Glaucoma Society

Canadian Glaucoma Society

Childhood Glaucoma Research Network

Chinese Glaucoma Society

Commonwealth Independent States Glaucoma Society

European Glaucoma Society

Glaucoma Society of India

International Society for Glaucoma Surgery

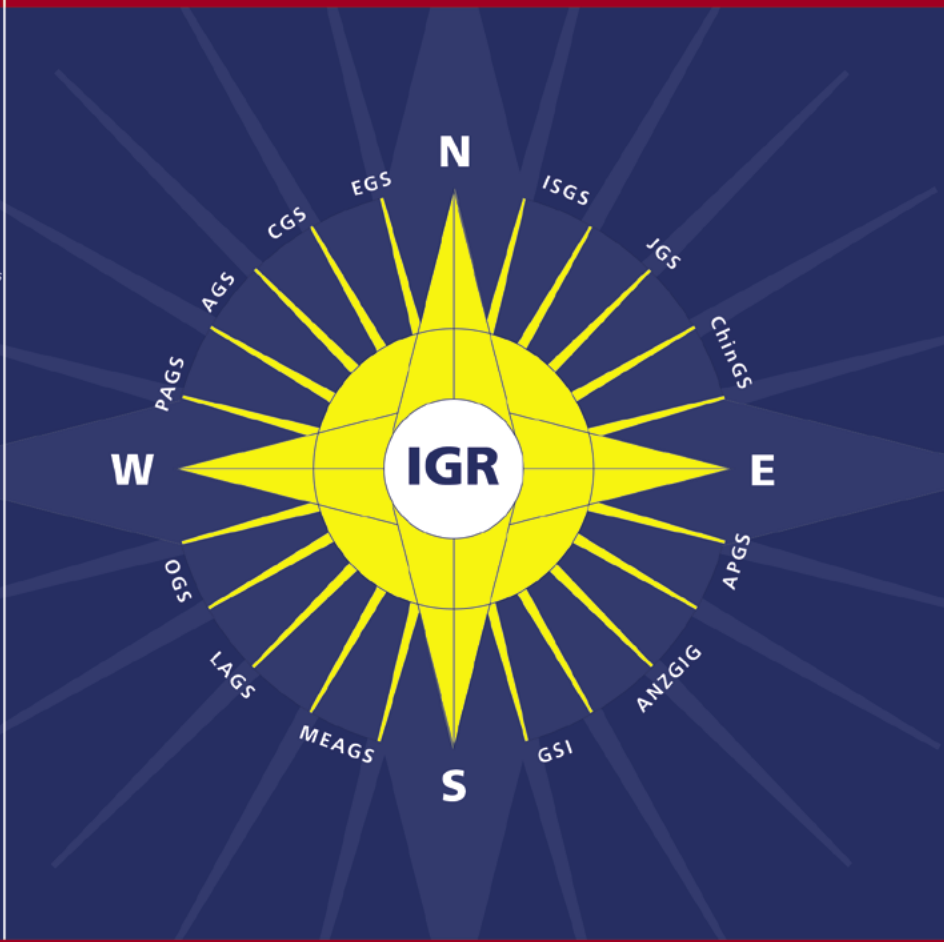
Japan Glaucoma Society

Latin American Glaucoma Society

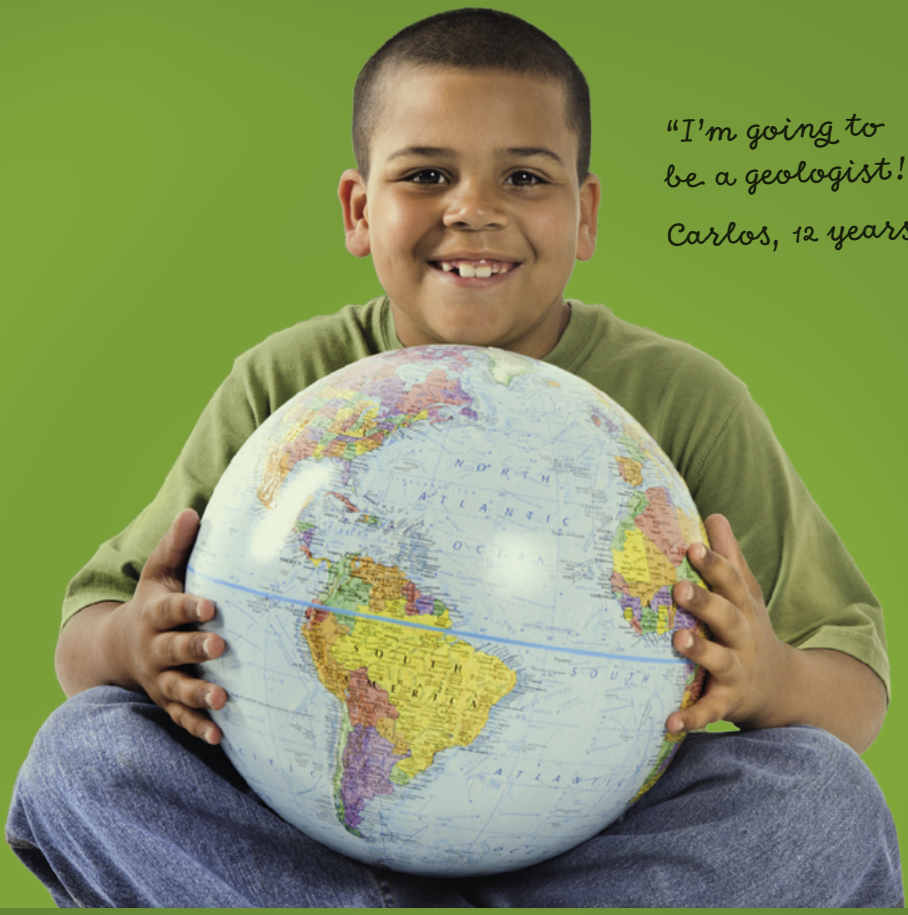
Middle East African Glaucoma Society

Optometric Glaucoma Society

Pan American Glaucoma Society



What about my future?



"I'm going to be a geologist!"

Carlos, 12 years old

OCULUS Myopia Master®

For early myopia detection and management

Myopia in children and young people is increasing worldwide. Early detection and treatment can slow or stop the progression of myopia. The new Myopia Master® combines all important parameters for myopia management in a myopia analysis software: axial length, refraction values and the central corneal radii.

Myopia management – much easier and more reliable than ever!

Click here to learn more

125 YEARS OCULUS®

ISSN 1566-1040

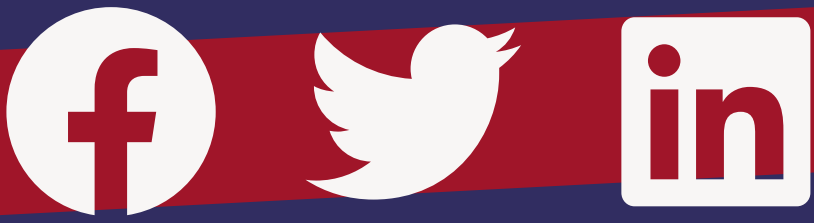
INTERNATIONAL GLAUCOMA REVIEW

A Quarterly Journal
Volume 21 no. 1

Information on the member Glaucoma Societies of the WGA can be found in the WGA Global Directory of Glaucoma Societies at www.wga.one/wga/directory-of-glaucoma-societies

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

Find us on Facebook: www.facebook.com/worldglaucoma
Find us on Twitter: www.twitter.com/WorldGlaucoma
Find us on LinkedIn: www.linkedin.com/company/world-glaucoma-association
WGA#One FAQ: www.wga.one/faq



ISSN 1566-1040

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

Published by Kugler Publications, P.O. Box 20538, 1001 NM Amsterdam, The Netherlands, on behalf of the World Glaucoma Association.
Cover design: Cees van Rutten, The Hague, The Netherlands
Typesetting: 3bergen, www.3bergen.com

WGA#One

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

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

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

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

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

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

How to activate your WGA#One profile

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

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

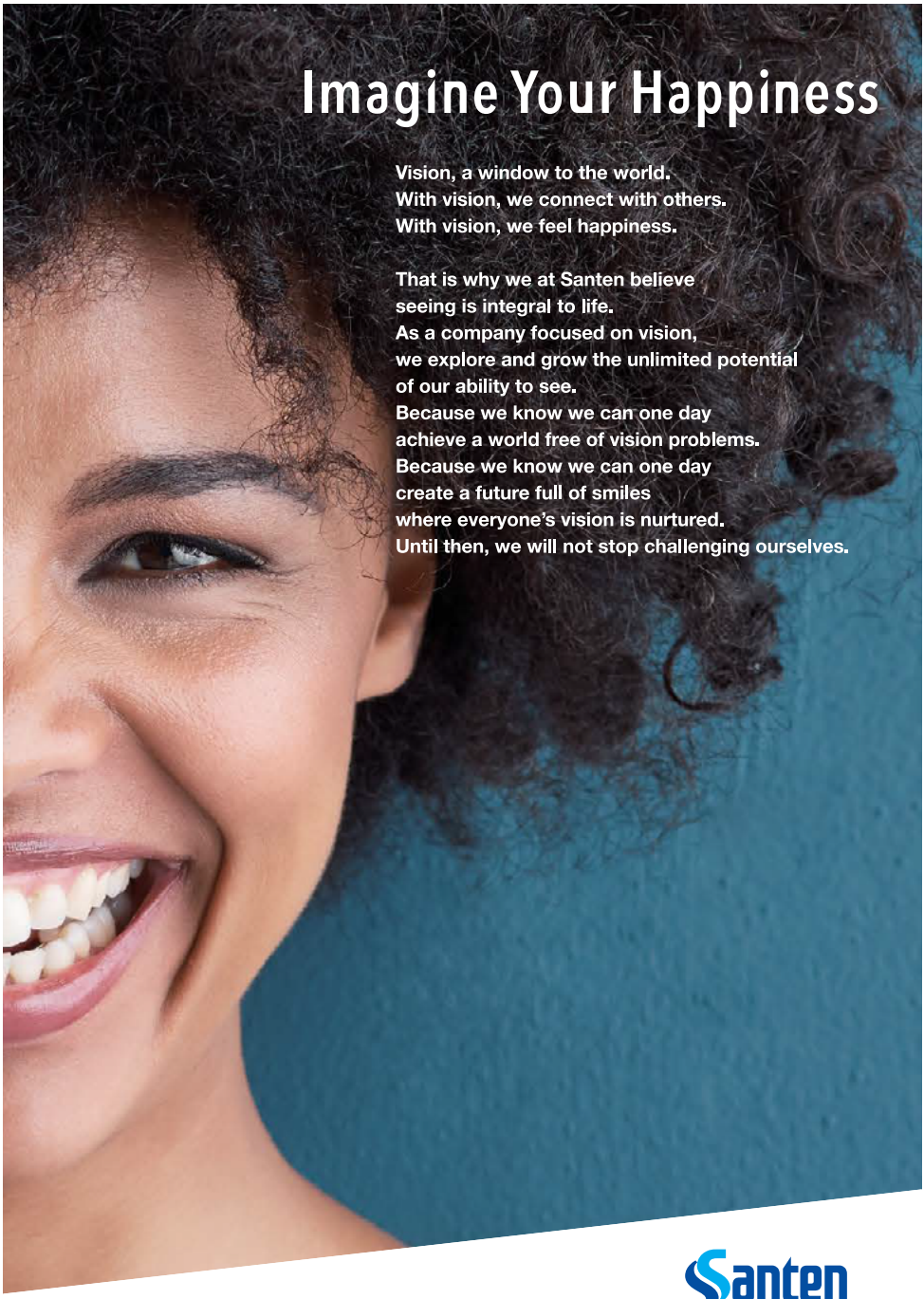

Imagine Your Happiness
Vision, a window to the world.
With vision, we connect with others.
With vision, we feel happiness.
That is why we at Santen believe
seeing is integral to life.
As a company focused on vision,
we explore and grow the unlimited potential
of our ability to see.
Because we know we can one day
achieve a world free of vision problems.
Because we know we can one day
create a future full of smiles
where everyone's vision is nurtured.
Until then, we will not stop challenging ourselves.
Santen
Imagine Your Happiness

Table of Contents

All abstracts are available online in the classified IGR searchable glaucoma database
www.e-IGR.com
The affiliations of the contributors to this issue can be found on www.e-IGR.com.

www.e-IGR.com

9th WORLD GLAUCOMA CONGRESS®

SEPTEMBER 9 - 12, 2021 KYOTO, JAPAN

worldglaucomacongress.org

NEW DATES!

Organized by:

World Glaucoma Association
The Global Glaucoma Network

Hosted by:

日本緑内障学会
Japan Glaucoma Society

e-IGR.com

IGR Searchable Glaucoma Database

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

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

Features

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

International Glaucoma Review is published as an online journal only.

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

www.e-IGR.com

From the WGA Executive Office

Dear IGR readers,

As we all adjust to the new 'normal' of the COVID-19 pandemic, the World Glaucoma Association is continuing to provide education and support to all of you who care for glaucoma patients. Under the leadership of Drs. Robert Weinreb and Fabian Lerner, the first WGA Global Webinar was held on October 10, 2020. The topic was **Glaucoma Surgery**, and there were over 9,000 live views on YouTube, the internet, and Facebook. Our next WGA Global Webinar will be on **Glaucoma Diagnostics** and take place on December 19, 2020. Please mark your calendar now for this exciting educational webinar. The start time will allow a worldwide audience to participate.

Our speakers and moderators will be some of the world's experts in glaucoma diagnostic technology.

Please join and learn, as well as participate in the discussions. If you already have a WGA#One account and are subscribed to our e-mail communications, you will receive e-mails with the details on how to join in the Webinar. Also keep an eye on our social media channels or visit the WGA website to get more information. We are looking forward to seeing you online!

WGA website: www.wga.one
WGA on Facebook: www.facebook.com/worldglaucoma
WGA on Twitter: www.twitter.com/WorldGlaucoma
WGA on LinkedIn: www.linkedin.com/company/world-glaucoma-association

World Glaucoma Association
The Global Glaucoma Network

GET TO KNOW US!

Paul Healey

Those with intellect, education and energy have the unique privilege of having the capacity to help make the world a better place. To realize this, we need like minds and organizations that facilitate achieving our common goals.

Eliminating glaucoma-related disability worldwide was the goal that first drew me to the WGA. I joined the WGA as Chair of the Associate Advisory Board a little over a decade ago after being honored with an International Clinician-Scientist award at the inaugural World Glaucoma Congress in 2005. My research background is rather diverse but is currently focused on the interaction of cell biology and genetics with epidemiology and public health. This background gave me the opportunity to help lead the 5th WGA Consensus on Glaucoma Screening and participate in all the WGA's Congresses and Consensus meetings to date.

After serving on several WGA Committees, I joined the WGA Executive Committee and Board four years ago as Treasurer. Since that time, I have been proud to have managed our most successful Southern Hemisphere Congress in Melbourne in 2019 and our most successful Congress ever in Helsinki in 2017. These successes have not only facilitated our existing initiatives such as IGR and the Consensus series, but also new expansions including an association with the Journal of Glaucoma and a heavy investment in information technology which has led to WGA#One, a worldwide online learning and communication portal for glaucoma.

Being a global organization, the WGA has global reach. There is no better example of this than World Glaucoma Week, during which the world sees thousands of events which engage the general public with our mission. We have also reached out to all our glaucoma patients, bringing them inside the WGA through the Patient Committee. After educating and motivating our patients, the best way we can help them is to ensure they have access to well-trained glaucoma doctors. While many countries are blessed with outstanding glaucoma clinicians, other areas have little opportunity for glaucoma training. The WGA has partnered with the International Council of Ophthalmology to develop the WGA-ICO Fellowship which targets key areas of need. Although in its infancy, it has already trained eight Fellows from sub-Saharan Africa, all of whom have had enormous impact on their communities. In 2019, I made the commitment on behalf of the WGA to double the number of Fellowships each cycle, allowing us to expand to other key areas of need around the world.

The true power of the WGA is the power of like minds and common goals. I am proud of my small achievements in the bigger task of eliminating glaucoma-related disability worldwide and grateful to my mentors and colleagues for their friendship and support. Every volunteer involved in the WGA started their journey with a desire to make the world a better place. If you share this desire, please volunteer to join our global family.

touch OPHTHALMOLOGY®

Practical articles
Expert interviews
News and insights

Peer reviewed | Free-to-access | Concise | Multimedia

View | Download | Subcribe
FREE

touchOPHTHALMOLOGY.com

Glaucoma Opinion


By Donald C. Hood and C. Gustavo De Moraes

Defining glaucomatous optic neuropathy using objective criteria from structural and functional testing. Iyer JV, Boland MV, Jefferys J, Quigley H. British Journal of Ophthalmology, July 2020; doi: 10.1136/bjophthalmol-2020-316237

One could debate the premise of the Iyer *et al.* study, that glaucoma research would benefit from a single definition of glaucoma. For decades, researchers have employed definitions that were the most translational for their time. Iyer et al have argued against that approach and proposed a new single definition based upon (objective) OCT and visual field (VF) results. However, let's assume as they do, that a single definition is needed and that it should be based upon objective structural and functional tests.

In their study, alternative definitions were based upon 24-2 visual field (VF) tests and OCT cube disc scans. Their best performing criterion (definition) required an abnormal circumpapillary retinal nerve fiber layer thickness (cpRNFL) in the superior or inferior quadrant of the disc and an abnormal 24-2 GHT (glaucoma hemifield test) in the corresponding hemifield.

There are at least three main problems with their approach. First, summary statistics for the 24-2 test, including the GHT, and summary statistics for the OCT disc scan, including quadrant cpRNFL thickness, can miss glaucomatous damage.[1-7] Thus, it is not surprising that their results were relatively disappointing.

It is not clear that we need a single definition of glaucoma

In particular, their data provide weak support for their best-performing definition. First, the sensitivity for eyes classified as "definite glaucoma" (DG) was only 77%. That is, about 25% of the eyes identified as DG were missed.

Second, it is likely that their definition will miss some eyes with damage to the most important retinal region, the macula,[1,2] which is not only common but also plays a major role in vision related quality of life. To test the hypothesis that macular damage is missed, we applied their 24-2 GHT criteria to data we recently published.[7] These data included 53 eyes classified as DG by the referring clinician, the same reference standard used by Iyer *et al.* The 24-2 (GHT) failed their test on two 24-2 VFs in 16 (30%) of these 53 DG

eyes. Further, when the results from 10-2 VF and OCT cube scans were examined,[7,8] their definition missed eyes with macular damage, including those with deep defects near fixation and/or diffuse damage, as expected.

Finally, their comparison of summary statistics is a suboptimal method for comparing VF and OCT data.[1,2] For example, we have developed and validated an objective and automated method[7,8] that topographically compares the abnormal regions on the 24-2 and/or 10-2 VFs to those on OCT maps. This method missed only 6 (11%) of our 53 DG eyes, as compared to over 50% based upon their criteria. Of note, although their definition aims to bring state-of-the-art technology to define glaucoma, in its current form it is not making good use of the available OCT and VF data.

In sum, it is not clear that we need a single definition of glaucoma, even if "only" for research purposes (remember the importance of translational relevance for clinical use). However, it is clear that the one proposed by Iyer *et al.* is out-of-date and suboptimal.

References

1. Hood DC, De Moraes CG. Challenges to the Common Clinical Paradigm for Diagnosis of Glaucomatous Damage With OCT and Visual Fields. Invest Ophthalmol Vis Sci. 2018;59(2):788-791.
2. Hood DC, De Moraes CG. Four Questions for Every Clinician Diagnosing and Monitoring Glaucoma. J Glaucoma. 2018;27(8):657-664.
3. De Moraes CG, Hood DC, Thenappan A, et al. 24-2 Visual Fields Miss Central Defects Shown on 10-2 Tests in Glaucoma Suspects, Ocular Hypertensives, and Early Glaucoma. Ophthalmology. 2017;124(10):1449-1456.
4. Sullivan-Mee M, Karin Tran MT, Pensyl D, Tsan G, Katiyar S. Prevalence, Features, and Severity of Glaucomatous Visual Field Loss Measured With the 10-2 Achromatic Threshold Visual Field Test. Am J Ophthalmol. 2016;168:40-51.
5. Wang DL, Raza AS, de Moraes CG, et al. Central Glaucomatous Damage of the Macula Can Be Overlooked by Conventional OCT Retinal Nerve Fiber Layer Thickness Analyses. Transl Vis Sci Technol. 2015;4(6).
6. Kim KE, Jeoung JW, Park KH, Kim DM, Kim SH. Diagnostic classification of macular ganglion cell and retinal nerve fiber layer analysis: differentiation of false-positives from glaucoma. Ophthalmology. 2015;122(3):502-510.
7. Hood DC, Tsamis E, Bommakanti N, Joiner DB, Al-Aswad LL, Blumberg DM, Cioffi GA, Liebmann JM, De Moraes CG. (2019) Structure-function agreement is better than commonly thought in eyes with early glaucoma. Invest Ophthalmol Vis Sci. 2019;60(13):4241-4248.
8. Tsamis E, Bommakanti NK, Sun A, Thakoor KA, Moraes CGD, Hood DC. An Automated Method for Assessing Topographical Structure–Function Agreement in Abnormal Glaucomatous Regions. Trans Vis Sci Tech. 2020;9(4):14-14.

www.worldglaucoma.org

Stay tuned

for the 2nd WGA Global Webinar

Mark your calendar: DECEMBER

19

2020

WGA Global Webinars
THE DIGITAL GLAUCOMA NETWORK

Organized by
World Glaucoma Association
The Global Glaucoma Network

Hosted by
Entod Pharmaceuticals
Ocular Care & Wellness Since 1977

Supported by
Allergan
an AbbVie company

Your Special Attention For

The value and caveats of interpreting small case series: Implications for patient care
Parrish RK, Chang TC, Duncan Powers SL
American Journal of Ophthalmology 2020; 211: 1-3
abstract no. 84494

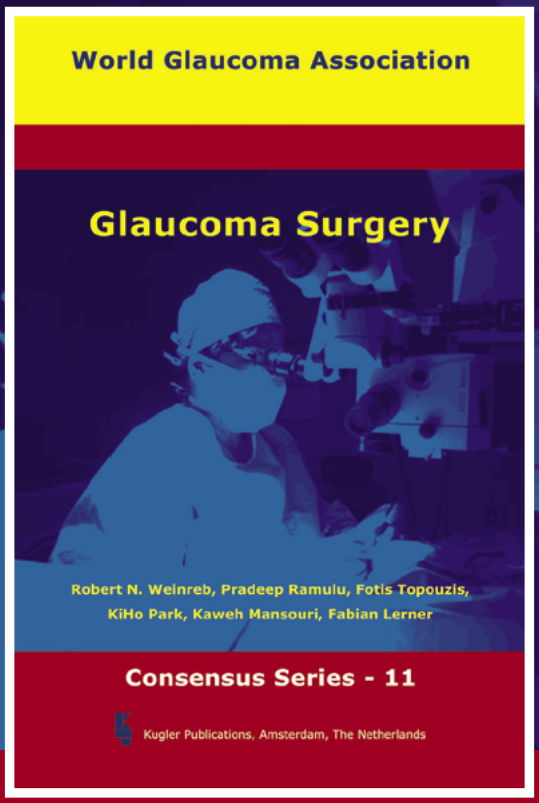
Review of non-invasive intracranial pressure measurement techniques for ophthalmology applications
Price DA, Grzybowski A, Eikenberry J, Januleviciene I, Verticchio Vercellin AC, Mathew S, Siesky B, Harris A
British Journal of Ophthalmology 2020; 104(7): 887-892
abstract no. 84504

Intra-operative optical coherence tomography in glaucoma surgery – a systematic review
Ang BCH, Lim SY, Dorairaj S
Eye 2020; 34: 168-177
abstract no. 84617

Home monitoring for glaucoma
Che Hamzah J, Daka Q, Azuara-Blanco A
Eye 2020; 34: 155-160
abstract no. 84618

OUT NOW!
WGA Consensus Series 11

Glaucoma Surgery



Order online and use discount code WGA1 to get a 10% discount at www.kuglerpublications.com

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

Pathogenesis

Eye Movements and Optic Nerve Traction

Comment by Michael Girard, Singapore

84276 Optic Nerve Traction During Adduction in Open Angle Glaucoma with Normal versus Elevated Intraocular Pressure; Demer JL, Clark RA, Suh SY, Giaconi JA, Nouri-Mahdavi K, Law SK, Bonelli L, Coleman AL, Caprioli J; Current Eye Research 2020; 45: 199-210

Recently, there has been renewed interest in the effects of eye movements on the optic nerve head (ONH) and their possible links to optic neuropathies including glaucoma. Specifically, studies that used optical coherence tomography (OCT),[1-3] finite element (FE) modelling,[4] and magnetic resonance imaging (MRI),[5] all converge to the single fact that during horizontal eye movements, the optic nerve (the 'cable' linking the eye to the brain) can exert a traction force on the eye globe to deform the ONH tissues; surprisingly these deformations can be as large (or significantly larger) than those induced by a substantial IOP elevation to 40-50 mmHg.[1]

The proposed study is one of several that aims to shed some light on whether such mechanical forces could be responsible for axonal loss in glaucoma. While a controversial topic, it could potentially explain an alternate pathway for axonal loss that is independent of intraocular pressure, and such a theory may be of high interest to explain the development of normal tension glaucoma (NTG). Specifically, in the proposed study, the authors imaged glaucoma subjects (NTG and high-tension glaucoma [HTG]) and healthy controls in both abduction and adduction using MRI. They found that in both healthy controls and glaucoma subjects, the optic nerve was straight in adduction. Furthermore, abnormal globe retraction was observed in adduction in glaucoma subjects (but not in healthy controls), which may suggest the presence of a high traction force within the optic nerve and its sheath that is transmitted to the ONH connective tissues. The authors further made 2 important observations: (1) globe retraction in glaucoma occurred regardless of the IOP level; (2) Globe retraction in glaucoma eyes was more prominent in Asians (rather than in Caucasians) – a population that is more prone to NTG.

However, it is worth mentioning that the authors would benefit from reproducing their results in much larger cohorts, as they only recruited 35 glaucoma subjects (NTG and HTG) that covered 3 ethnic groups. As wide biomechanical variations are known to exist in ocular tissues, conclusions from this study would require independent validations. The study would also benefit from additional biomechanical measurements. For instance, ONH strains (*i.e.* deformations) in adduction can be mapped from OCT images,[1] and optic nerve traction forces can be estimated using a prediction tool known as finite element modelling.[6] The use of such biomechanical metrics are important because the simple observation of a straight optic nerve does not necessarily translate to the presence of a very large traction force and/or large ONH deformations (as could occur in the presence in a soft dura and a stiff sclera).

In all, the fact that optic nerve traction could contribute to axonal loss in glaucoma is thought provoking and should not be discarded that easily. Optic nerve traction may well be the largest force that is acting on the back of the eye,[6] the implications of which could be considerable in both myopia and glaucoma. Further studies should be carried out, and they would fit nicely under a new field, named 'orbital tissue biomechanics', that remains poorly explored. Importantly, the impact of optic nerve traction does not stop here. Since a large force acts on the back of the eye, it could explain several eye disorders that currently have an unknown cause,[7] including the development of: (1) peripapillary atrophy in glaucoma and myopia; (2) staphylomas in myopia; (3) tilted discs in myopia; and (4) intrachoroidal cavitations.

References

1. Wang X, Beotra MR, Tun TA, Baskaran M, Perera SA, Aung T, Strouthidis NG, Milea D, Girard MJA. In Vivo 3-Dimensional Strain Mapping Confirms Large Optic Nerve Head Deformations Following Horizontal Eye Movements. 2016. Invest Ophthalmol Vis Sci. October 2016, Vol.57, 5825-5833. doi:10.1167/iovs.16-20560.
2. Sibony PA. Gaze evoked deformations of the peripapillary retina in papilledema and ischemic optic neuropathy. Invest Ophthalmol Vis Sci. 2016;57:4979–4987.
3. Chang MY, Shin A, Park J, et al. Deformation of optic nerve head and peripapillary tissues by horizontal duction. Am J Ophthalmol. 2016;174:85–94.

4. Wang X, Rumpel H, Lim WEH, Baskaran M, Perera SA, Nongpiur ME, Aung T, Milea D, Girard MJA. Finite Element Analysis Predicts Large Optic Nerve Head Strains During Horizontal Eye Movements. 2016. Invest Ophthalmol Vis Sci. Vol.57, 2452-2462. doi:10.1167/iovs.15-18986.
5. Demer JL. Optic nerve sheath as a novel mechanical load on the globe in ocular duction. Invest Ophthalmol Vis Sci. 2016; 57:1826–1838.
6. Wang X, Fisher LK, Milea D, Jonas JB, Girard MJA. Predictions of Optic Nerve Traction Forces and Peripapillary Tissue Stresses Following Horizontal Eye Movements. 2017. Invest Ophthalmol Vis Sci. 2017, Vol.58, 2044-2053. doi:10.1167/iovs.16-21319
7. Wang X, Rumpel H, Lim WEH, Baskaran M, Perera SA, Nongpiur ME, Aung T, Milea D, Girard MJA. Author Response: Peripapillary Suprachoroidal Cavitation, Parapapillary Gamma Zone and Optic Disc Rotation due to the Biomechanics of the Optic Nerve Dura Mater. 2016. Invest Ophthalmol Vis Sci. August 2016, Vol.57, 4374-4375

Eye Movements and Optic Nerve Traction

Comment by Ian Sigal, Pittsburgh, PA, USA

84276 Optic nerve traction during adduction in open angle glaucoma with normal versus elevated intraocular pressure; Demer JL, Clark RA, Suh SY, Giaconi JA, Nouri-Mahdavi K, Law SK, Bonelli L, Coleman AL, Caprioli J; Current Eye Research 2020; 45: 199-210

Optic nerve head tissue deformations and stresses are thought to be major contributing factors to the development and progression of glaucomatous neuropathy. These biomechanical insults are often presumed to be associated with elevated IOP. However, many patients suffer from glaucoma despite a normal IOP, and thus there are important pathogenic factors that act at normal IOP or that are independent of IOP. Over the last few years, a couple of groups, including the one led by Dr. Demer, have explored the hypothesis that eye movements, particularly adduction, can cause optic nerve tension and traction of the posterior pole. The authors hypothesize that this posterior pole traction may cause substantial insult to the tissues of the optic nerve head, and thus be an IOP-independent factor for glaucoma. This is an intriguing hypothesis that has great potential to enable a more comprehensive understanding of how the biomechanical environment within the optic nerve head is affected by intra and extraocular factors.

In this study, the authors use MRI to measure how optic nerve traction in adduction varied with factors such as race and gender, paying particular attention to the patient IOPs. The images in the manuscript are compelling. Taken together with those in previous reports, the evidence is strong that **gaze changes can cause major deformations of the optic nerve,** including straightening, and what looks like tethering and traction of the posterior globe. This is the case even in control, non-glaucomatous, eyes. The optic nerve and posterior pole deformations are large and clearly discernible, even though the resolution of patient MRIs is low compared with that of other techniques typically used to visualize the optic nerve head. The large optic nerve head deformations caused by gaze changes have also been observed using optical coherence tomography and numerical modeling. The authors also found that **in patients with open-angle glaucoma, increased adduction was associated with abnormally large globe retraction, and that this was independent of the level of IOP.** This is consistent with the authors hypothesis that optic nerve traction is an independent pathogenic factor in the neuropathy, but there are other possible explanations. For instance, altered the tissue properties, due to remodeling, as has been reported in glaucoma, could change the deformations of the optic nerve or the optic nerve head.

> Even if gaze-induced deformations are proven to cause or contribute to a neuropathy, it remains to be shown that this is a glaucomatous neuropathy

It is important to consider that it remains be demonstrated that optic nerve tethering caused by gaze changes can actually cause or contribute to the neuropathy. The observed large scale deformations of the optic nerve head are consistent with the idea, but they are not yet proof. Since tethering during adduction appears common, it would also be important to understand why only some people seem to be affected. Further, **even if gaze-induced deformations are proven to cause or contribute to a neuropathy, it remains to be shown that this is a glaucomatous neuropathy.** Of course, any neuropathy is important to the patient, and thus clinically relevant, but the mechanism does matter.

Quality of Life

Understanding the Impact of Visual Impairment

Comment by Vincent Michael Patella, Iowa City, Iowa, USA

85202 Seeing other perspectives: evaluating the use of virtual and augmented reality to simulate visual impairments (OpenVisSim); Jones PR, Somoskeöy T, Chow-Wing-Bom H, Crabb DP; NPJ digital medicine 2020; 3: 32

Jones *et al.* have evaluated the use of a binocular head mounted video display to simulate everyday difficulties caused by advanced glaucomatous visual impairment (VI). Individuals with glaucoma often report particular difficulty in locating objects in cluttered visual scenes, and also exhibit reduced mobility.[1] **The authors measured the time required for normally sighted adults to complete search and mobility tasks while wearing video goggles that simulate advanced glaucomatous visual field loss (VFL) in the superior field and, separately, the same VFL in the inferior field.** Simulated scotoma position was constantly tracked to gaze direction, and eye and head movements were used to assess individual differences in looking behaviors.

> The location of VFL can be nearly as important as the presence of the loss itself

The authors found that their simulations of VFL substantially impaired visual search capability and mobility, especially when the simulated VFL was in the inferior field, thus confirming qualitative comparisons of inferior versus superior VFL from glaucoma patients.[2] The authors also found that the difference in search time between inferior and superior VFL was 70% of the search time difference between superior VFL and normal vision, suggesting that the location of VFL can be nearly as important as the presence of the loss itself. Similarly, inferior field loss affected mobility more than superior loss. The authors also found considerable inter-individual variability in how well subjects coped with simulated VFL and that these differences were associated with systematic differences in gaze behavior.

Scotoma simulation and quantification of VI effects in terms of task completion times are not new ideas,[3] and the most important new message in this paper may be that such measurements now can be done using widely available hardware, combined with

software that the authors have made freely available online. Thus, others now can efficiently confirm the authors' findings and then move forward with their own refinements and innovations.

We wonder – as do the authors – if their device might be used to quantify VI effects on other tasks, *e.g.*, tasks that map onto each of the categories of behavior defined in the National Eye Institute's visual function questionnaire (NEI-VFQ-25).[4] Such simulations might also help architects design buildings that are more accessible to individuals with vision impairment. A widely-available simulator might lead to refinement and standardization of criteria for visual disability. It also might contribute to the development of improved coping strategies for those who have such impairments, or to assessment of the relative benefits of alternative treatment options for blinding eye disease.

Such measurements now can be done using widely available hardware, combined with software that the authors have made freely available online

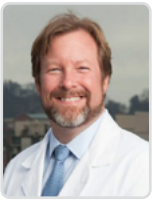
This paper has expanded my own views regarding the opportunity for further development, and perhaps even standardization of visual impairment assessments. I thank the authors for this important contribution.

References

1. Ramulu PY et al. Real-world assessment of physical activity in glaucoma using an accelerometer. Ophthalmology. 2012;119:1159-1166.
2. Crabb DP, Smith ND, Glen FC, Burton R, Garway-Heath DF. How does glaucoma look?: Patient perception of visual field loss. Ophthalmology. 2013;120:1120-1126.
3. Bertera JH. The Effect of Simulated Scotomas on Visual Search in Normal Subjects. Invest Ophthalmol Vis Sci. 1988;29(3):470-475.
4. Mangione CM, et al. Development of the 25-list-item national eye institute visual function questionnaire. Arch Ophthalmol. 2001;119:1050-1058.

Anatomical Structures

Corneal Hysteresis as a Risk Factor for Progression



Comment by Crawford Downs, Birmingham, AL, USA

84612 Relationship of corneal hysteresis and anterior lamina cribrosa displacement in glaucoma; Wong BJ, Moghimi S, Zangwill LM, Christopher M, Belghith A, Ekici E, Bowd C, Fazio MA, Girkin CA, Weinreb RN; American Journal of Ophthalmology 2020; 212: 134-143

Optic nerve head (ONH) biomechanics has been hypothesized to play an important role in the development and progression of glaucoma, but it is not well understood. The dearth of available data is due to the technical challenges involved in the measurement of ONH tissue mechanical properties (stiffness) and the complexity of the ONH and scleral geometry. Further complicating the study of ONH biomechanics is the biologic variability in the load-bearing structure, which includes geometry (regional scleral thickness, neural canal shape and size, regional laminar pore size and beam thickness, etc.), and tissue stiffness, which may change with age, pathology, extracellular matrix composition, and connective tissue remodeling. Fortunately, recent advances in OCT and other imaging technologies are leading to more accurate and comprehensive clinical assessments of ONH biomechanical behavior *in vivo*.

Wong, Weinreb and coworkers studied the association of the longitudinal change in the position of the anterior lamina cribrosa surface (ALCS, measured with OCT) to corneal hysteresis (CH), plus other factors, in 147 eyes from 96 glaucoma or glaucoma suspect patients followed for 3.5 years and 7.9 visits on average. Results show that the ALCS migrated posteriorly on average at 0.78 µm/yr. **Only 17 of the 196 eyes showed a significant ALCS posterior migration over time, while 22 eyes showed anterior migration; 74% of the eyes showed no change in ALCS position.** Choroidal thinning, a smaller IOP increase over time, and lower CH were significantly associated with posterior ALCS migration. Only 6% of eyes showed visual field progression during the study term, and so glaucoma progression was not significantly associated with ALCS migration (or CH indirectly).

This study is important because it adds weight to the available evidence that lower CH is associated with glaucoma progression, and the study shows that CH is also associated with posterior ALCS migration

This study is important because it adds weight to the available evidence that lower CH is associated with glaucoma progression, and the primary finding in the present study shows that CH is also associated with posterior ALCS migration. This study links CH to ONH morphological change and remodeling for the first time, which is thought to be one of the mechanisms underlying glaucoma pathophysiology. The authors discuss the hypothesis that CH is related to (or somehow reflects) ONH biomechanics, although most experimental evidence has not shown a relationship between anterior and posterior pole biomechanics. There is another plausible hypothesis that could explain their findings. **Experiments have shown that the cornea acts as a shock absorber of sorts and hysteresis allows the cornea to damp and absorb transient IOP fluctuations.** Hence, a lower CH would be associated with larger, more energetic transient IOP fluctuations, which may be associated with larger laminar strain fluctuations that drive greater posterior migration and remodeling of the lamina cribrosa. In this scenario, lower CH drives greater biomechanical insult to the ONH and lamina cribrosa, leading to greater axonal damage and loss. Future studies will be required to tease out the relationships that are emerging from this area of study, but the present work pushes the field further down the path to understanding the complex mechanisms underlying glaucomatous axon damage.

Corneal Hysteresis as a Risk Factor for Progression

Comment by Julian Garcia Feijoo and Frances Saenz, Madrid, Spain

84612 Relationship of corneal hysteresis and anterior lamina cribrosa displacement in glaucoma; Wong BJ, Moghimi S, Zangwill LM, Christopher M, Belghith A, Ekici E, Bowd C, Fazio MA, Girkin CA, Weinreb RN; American Journal of Ophthalmology 2020; 212: 134-143

It has been suggested that the lamina cribrosa displacement due to increased intraocular pressure (IOP) may result in the obliteration of its foramina, causing a compression of the optic nerve axons and leading to glaucomatous damage. Moreover, it has been suggested that susceptibility to lamina cribrosa displacement may be related to low corneal hysteresis (CH), which has been identified as a risk factor for glaucoma, given the anatomical continuity between the cornea, sclera and lamina cribrosa.

In this prospective observational study, the authors have **investigated the influence of baseline CH on lamina cribrosa displacement over time as determined using spectral-domain optical coherence tomography (SD-OCT).** The authors controlled for the potential confounding effects of several covariates in three multivariate models: adjusting for age, choroidal thinning, central corneal thickness (CCT), and average IOP in the first; adjusting for peak IOP, age, choroidal thinning, and CCT in the second; and adjusting for age, choroidal thinning, CCT, and IOP change during follow-up in the third. In all three models, baseline CH was significantly associated with a posterior displacement of the lamina cribrosa during follow-up. Each mmHg of lower CH was associated with 0.75 microns/year of posterior displacement (95% confidence interval (CI): 0.07-1.42) in model 1, 0.73 microns/year (95% CI: 0.06-1.39) in model 2 and 0.66 (95% CI: 0-1.32) in model 3. Lamina cribrosa displacement was also associated with choroidal thinning , but neither age, baseline CCT, or average IOP were significantly correlated with it.

> This study provides solid evidence that lower baseline CH is associated with an increase in the posterior displacement of the lamina cribrosa over time, a finding that highlights the potential role of this biomechanical parameter as an independent risk factor for glaucoma onset and progression

To sum up, this study provides solid evidence that lower baseline CH is associated with an increase in the posterior displacement of the lamina cribrosa over time, a finding that highlights the potential role of this biomechanical parameter as an independent risk factor for glaucoma onset and progression.

Corneal Hysteresis as a Risk Factor for Progression

Comment by Tony Realini, Morgantown, WV, USA

84612 Relationship of corneal hysteresis and anterior lamina cribrosa displacement in glaucoma; Wong BJ, Moghimi S, Zangwill LM, Christopher M, Belghith A, Ekici E, Bowd C, Fazio MA, Girkin CA, Weinreb RN; American Journal of Ophthalmology 2020; 212: 134-143

Wong and colleagues have conducted a prospective study to evaluate the relationship between corneal hysteresis (CH) and displacement of the anterior lamina cribrosa (ALC) over time in 147 eyes of 96 patients with glaucoma. CH was measured using the Reichert Ocular Response Analyzer at baseline, and ACL surface depth was measured using spectral domain optical coherence tomography a minimum of five times (mean 7.9) over a minimum of three (mean 3.5) years. A series of OCT images from 18 healthy subjects over the same time frame established the expected stability of ACL surface depth in the healthy state, while the mean rate of change in ACL surface depth among glaucomatous eyes was 0.78 µm/year in the posterior direction. In multivariable mixed-effects modeling, each 1 mm lower CH was associated with 0.66 µm/year of posterior ALC displacement. This is potentially a highly significant observation. More than a decade ago, several investigators (myself included) speculated that while CH's most obvious relationship to glaucoma was its effect on the accuracy of intraocular pressure (IOP) measurement, its characterization of anterior ocular biomechanical properties may reflect the nature of posterior ocular biomechanical properties. To wit, **an eye with a less viscoelastic (not easily deformable) cornea may also have a less viscoelastic (less easily deformable) lamina, which in turn may be less well able to compensate for IOP-induced structural changes**, **thereby potentially increasing the risk of axonal injury and glaucoma progression.** Several studies have established the relationship between CH and glaucoma progression risk. The study under discussion here may shed light on the mechanistic relationship between CH and progression risk.

Brain Plasticity in Glaucoma


Comment by Ji Won Bang and Kevin Chan, New York, NY, USA

85201 Altered large-scale brain functional connectivity in ocular hypertension; Giorgio A, Zhang J, Costantino F, De Stefano N, Frezzotti P; Frontiers in neuroscience 2020; 14: 146

Giorgio *et al.* investigated the structural and functional brain differences between 18 ocular hypertension (OHT) subjects and 29 normal subjects using multi-parametric magnetic resonance imaging (MRI) at 1.5 Tesla. Their findings indicated **widespread alterations in the resting-state functional connectivity (FC) of OHT subjects.** In contrast, no apparent structural brain change was detected by anatomical MRI or diffusion tensor MRI. At the intra-network level, FC decreased in key cognitive networks. Interestingly, at the inter-network level, FC between default-mode and salience networks decreased, whereas FC between primary and secondary visual networks increased. The decreased FC at both intra- and inter-network levels is in line with previous findings in patients with glaucoma, further suggesting that brain function may be affected early even in the pre-symptomatic stage. On the other hand, the increased FC between primary and secondary visual networks in OHT subjects suggests that adaptive functional reorganization may be taking place.

This pilot study provides an important evidence regarding how the brain is affected under pre-symptomatic conditions. However, several cautions should be noted when interpreting these findings. Firstly, abnormalities observed in this cross-sectional study may not be predictive of a future progression to glaucoma, given that not everyone with OHT will develop glaucoma. To address whether altered FC could serve as an early biomarker for glaucoma, longitudinal observations are necessary in the future.

To address whether altered functional connectivity could serve as an early biomarker for glaucoma, longitudinal observations are necessary

Secondly, the current study did not control for possible confounding effects of risk factors such as ethnicity, diabetes, menopause, family history of glaucoma, etc. Therefore, future studies involving larger population need to take these factors into account. Thirdly, to make the current findings clinically useful, more details should be included and exploited such as the exact intraocular pressure in each eye, how such pressure values were measured, the duration of OHT since diagnosis, etc. Future work may also include behavioral tests

and quality-of-life questionnaire to explore the functional implications of the observed FC changes. In summary, this research appears promising, but larger studies will be necessary to confirm the initial results.

Basic Science

Trabecular Meshwork Response to High IOP

Comment by Paul Kaufman, Madison, WI, USA

84633 Elevated pressure influences relative distribution of segmental regions of the trabecular meshwork; Vranka JA, Staverosky JA, Raghunathan V, Acott TS; Experimental Eye Research 2020; 190: 107888

The article by Vranka *et al.* is the latest in a long line of work emanating from the group led by Ted Acott at the Oregon University of Health & Science. Their go-to experimental model, **the perfused human organ-cultured anterior segment (HOCAS) allows measurement of conventional outflow pathway resistance and its ability to change according to the pressure challenge presented to it**, manifested by the normalized flow rate over time. Adding fluorescently-labeled amine modified 200nm red and green Fluospheres to the perfusate allows quantifiable visualization and regionalization of outflow around the entire circumference. Thus, high flow (HF), intermediate flow (MF) and low flow (LF) regions can be identified, quantified and localized.

At 8.8 mmHg in ten normal eyes, HF, MF and LF regions respectively comprised ~15%, 35% and 45% of the circumference, with little change from day one to day eight of perfusion. At 17.6 mmHg in six normal eyes, on day one, HF, MF and LF regions respectively comprised 20%, 20% and 60 % of the circumference, while on day eight the distribution was ~10%, 45% and 45%. Thus, at the higher pressure challenge, there was a larger 'redistribution' of flow over time. The data were analyzed for statistical significance by one-way ANOVA with Tukey test for multiple comparisons and using a paired *t*-test (mean of the difference in the right versus the left eye, N = 8) for the pairs of eyes that were both flowed at a continuous 1x perfusion pressure, as well as for those pairs of eyes in which one was flowed continuously at 1x pressure and the other eye from the same donor was flowed continuously at 2x pressure.

The 'take-away' message from the authors is that the conventional outflow pathway not only provides the resistance required to generate an intraocular pressure needed to maintain the shape of the globe for optical clarity, but also regionally redistributes resistance around its circumference in an attempt to maintain homeostasis when confronted with a pressure challenge. This expands the concept of the conventional outflow pathway as

a 'sentient being' with regulatory functions at a molecular/cellular level (think actomyosin contractility mediated via the rho pathway, with NO as a signaling molecule, giving us ocular hypotensive drugs like rho kinase inhibitors and nitric oxide donators) and at a more macro level.

Caveats: Despite the relatively small sample sizes / number of eyes studied, the differences found under the different conditions were statistically significant. That said however, **one must still be cautious about generalizing into a major regulatory mechanism from such a small number of eyes, with some twists and turns around the data and their interpretation**. Other complicating factors may be the old age (range 65-90 years, mean 77.6 + 3.0 yrs) and the length of time from death to stationary culture (up to 48hrs); these parameters may affect the regulatory responses being studied despite 'the anterior segments being initially placed into serum-free stationary organ culture for 5-7 days to facilitate postmortem recovery'.

Clinical Examination Methods

Corneal Thickness and IOP

Comment by Andrew Tatham, Edinburgh, UK

84094 Modified Goldmann prism intraocular pressure measurement accuracy and correlation to corneal biomechanical metrics: multicentre randomised clinical trial; McCafferty SJ, Tetrault K, McColgin A, Chue W, Levine J, Muller M; British Journal of Ophthalmology 2019; 103: 1840-1844

Although Goldmann applanation tonometry (GAT) remains the standard for measurement of intraocular pressure (IOP), readings are affected by properties of the cornea such as corneal thickness and rigidity, potentially leading to significant measurement error.[1] In March 2018, the United States Food and Drug Administration (FDA) cleared a new Correcting Applanation Tonometry Surface (CATS) prism (Intuor Technologies, Arizona) for use with Goldmann or Perkins tonometers. The CATS prism differs from a standard Goldmann tonometer prism due to the sinusoidal shaped curve of its modified applanating surface.[2] The prism is designed to partially match the curvature of the cornea, reducing force on the prism face due to corneal deformation during applanation, while also minimizing tear-film induced error.[2]

Previous studies of the CATS prism have demonstrated that it is less influenced by central corneal thickness (CCT) and corneal hysteresis (CH) than standard Goldmann prisms[3] and the CATS prism provides measurements more closely related to IOP measured using a

surgically placed intra-cameral pressure transducer.[4] The present study built on previous work by comparing IOP measurements using the CATS and standard prisms in a study including eyes with thin (< 500 µm) and thick (> 600 µm) corneas.

A calibrated Haag-Streit 900 applanation tonometer was used to measure IOP using the CATS and standard prisms in 243 eyes. IOP was measured at 180 and 90 degrees and averaged for astigmatism correction. Overall there was excellent correlation between IOP measured using the standard GAT and CATS prisms (R^2 = 0.91); however, the CATS prism reduced the slope of the relationship between IOP and CCT and the slope of the relationship between IOP and CH. Differences in paired IOP measurements were greater in eyes with high or low CCT, and in eyes with high or low CH. **Compared to the standard GAT prism, the CATS prism gave higher readings in eyes with thin corneas or low hysteresis, and lower readings in eyes with thick corneas or high hysteresis.**

CATS prism may improve the accuracy of GAT measurements, with the advantage that the CATS prism can be fitted to readily available Goldmann-type tonometers

A disadvantage of the study was that IOP was not measured using a two-person technique and though hysteresis was assessed, there was no direct comparison between IOP measurements and corneal-compensated IOP from the Ocular Response Analyzer. It would also be interesting to see a comparison between the CATS prism and dynamic contour tonometer. Nevertheless, the results provide evidence that the **CATS prism may improve the accuracy of GAT measurements, with the advantage that the CATS prism can be fitted to readily available Goldmann-type tonometers.**

References

1. Liu J, Roberts CJ. Influence of corneal biomechanical properties on intraocular pressure measurement: quantitative analysis. J Cataract Refract Surg. 2005;31(1):146-155.
2. McCafferty S, Lim G, Duncan W, Enikov E, Schwiegerling J. Goldmann Tonometer Prism with an Optimized Error Correcting Applanation Surface. Transl Vis Sci Technol. 2016;5(5):4.
3. McCafferty S, Tetrault K, McColgin A, Chue W, Levine J, Muller M. Intraocular Pressure Measurement Accuracy and Repeatability of a Modified Goldmann Prism: Multicenter Randomized Clinical Trial. Am J Ophthalmol. 2018;196:145-153.
4. McCafferty S, Levine J, Schwiegerling J, et al. Goldmann and error correcting tonometry prisms compared to intracameral pressure. BMC Ophthalmol. 2018;18.

Virtual-Reality Perimetry

Comment by Chris Johnson, Iowa City, IA , USA

84653 Validation of a head-mounted virtual reality visual field screening device; Mees L, Upadhyaya S, Kumar P, Kotawala S, Haran S, Rajasekar S, Friedman DS, Venkatesh R; Journal of Glaucoma 2020; 29: 86-91

Perimetry and visual field testing have undergone many changes throughout history, from confrontational visual field testing to the development of standardized testing and methodology with arc perimeters and tangent screens, continuing on to full hemispherical perimeter bowls that have a uniform background adaptation level and the ability to vary many properties of the test stimulus superimposed on the background. A major advance was realized approximately 40-45 years ago with the advent of automated visual field testing. Since that time, there have been many innovations that have improved the efficiency, accuracy and reliability of visual field evaluations, although it recently appears to have reached an asymptote.

As current approaches become further refined it appears that a new paradigm shift in perimetry and visual function testing is emerging

Current technological developments now make it possible to perform visual function testing on many small, portable, inexpensive devices (tablets, virtual reality headsets, smartphones, internet web sites) that allow testing to be performed in a variety of settings for population-based screening, home testing, and evaluation at eye care centers prior to examination by a practitioner. Although this new approach still needs refinement of methods and procedures, it opens up the potential for many new opportunities for providing ophthalmic services from a much broader spectrum. **The current manuscript describes the use of a virtual reality headset to perform visual field screening, and demonstrates its performance for assessing a group of healthy normal controls and glaucoma patients in comparison to results obtained using a Humphrey Field Analyzer.** The study was performed in a careful and thorough manner with excellent methodology, analysis and interpretation of results. The findings for this study were impressive and are highly similar to those that were obtained previously using a tablet-based visual field screening test in Nepal.[1] This provides additional support for the use of these approaches for performing perimetry in a variety of settings. A limitation of this study is that it is currently a screening procedure. Quantitative threshold sensitivity assessment would be more desirable. It is encouraging that in addition to this work, there are many investigators and clinical research teams that are at work in this area, quantitative

threshold sensitivity procedures are available, eye and head tracking has been incorporated into the test procedure, and new improvements are emerging at a rapid pace. Given the current activity in this area, it is clear that many colleagues see this as the wave of the future. As current approaches become further refined it appears that a new paradigm shift in perimetry and visual function testing is emerging.

Reference

1. Johnson CA, Thapa S, Kong, YXG, Robin AL. Performance of an iPad application to detect moderate and advanced visual field loss in Nepal. Am J Ophthalmol. 2017;182:147-154.

Disc Hemorrhage and Glaucoma Diagnosis

Comment by Gábor Holló, Budapest, Hungary

84619 Positive predictive value of optic disc haemorrhages for open-angle glaucoma; Hogan B, Trew C, Annoh R, Yi Loo C, Ling Tan H, Shan Tang L, Tatham AJ; Eye 2019 Nov 26. doi: 10.1038/s41433-019-0711-9. Online ahead of print.

Disc hemorrhages (DHs) occur in up to 1.4% in individuals without glaucoma, but they are more common (up to almost 18%) in glaucoma patients.[1] They can also be associated with various other conditions (*e.g.*, posterior vitreous detachment, hypertension, diabetes, and use of certain systemic medications). Thus, DHs are not specific for open-angle glaucoma. But do they represent a feature that justifies a comprehensive glaucoma assessment? This question was investigated by Hogan *et al.*, who **calculated the positive predictive value (PPV) of a DH for open-angle glaucoma in a retrospective study of 618 consecutive patients referred by community optometrists to the glaucoma service in Edinburgh**. Fifty-five patients (8.7%) had a DH (with or without other features suggesting glaucoma); in 21 patients a DH was the only reason of the referral. Twenty-nine of the DH patients were diagnosed with open-angle glaucoma (PPV 53.7%).

> An almost 24% PPV may represent an acceptable cut-off in the well-organized Scottish healthcare setting

However, the PPV was only 23.8% when patients presenting with a DH as the only feature of glaucoma were considered. For the category of DH and one additional feature of glaucoma the PPV was 55%; for DH and two additional features the PPV increased to 92.3%.

The presence of a disc hemorrhage did not increase the odds of glaucoma at the first visit. Patients with a disc hemorrhage were significantly ($P < 0.001$) older, more frequently females, had lower IOP and less features suggesting glaucoma than those without a DH.

As discussed by the authors, the translation of the results to the general clinical practice is difficult. It depends on the incidence of glaucoma in a population and the conditions offered by a health care system. They conclude that an almost 24% PPV may represent an acceptable cut-off in the well-organized Scottish healthcare setting. However, one may speculate that referring patients for glaucoma assessment because of an isolated disc hemorrhage would not be welcomed by most community health care systems in other parts of the World.

Reference

1. Razeghinejad MR, Nowroozzadeh MH. Optic disk hemorrhage in health and disease. Surv Ophthalmol. 2017;62:784-802.

Macular Vessels and Ganglion Cells

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

85134 Ganglion cell complex thickness and macular vessel density loss in primary open-angle glaucoma; Hou H, Moghimi S, Proudfoot JA, Ghahari E, Penteado RC, Bowd C, Yang D, Weinreb RN; Ophthalmology 2020; 127(8): 1043-1052

Hou and co-investigators compared the rates of change for GCC thickness measures and OCTA-derived vessel density (VD) measures in the macular region in 23 healthy eyes, 36 eyes with pre-perimetric glaucoma, and 80 POAG eyes (total of 94 subjects) who had at least three measurements available during follow-up. The average follow-up was 2.0-2.6 years with an average visit number of 3.4-3.8.

The rates of change for both thickness and OCTA parameters was higher on average in the preperimetric glaucoma group than normal subjects and in the group with established glaucoma compared with pre-perimetric glaucoma eyes. Of note, the glaucoma group consisted mostly of early glaucoma eyes (average MD: -4.2; 95% CI: -5.0 to -3.4 dB). Based on percent rates of change, they found overall higher VD rate of change in all three groups as compared to GCC thickness, which points to the possible utility of OCTA for earlier detection of structural change in the macular region.

By evaluating change rates in POAG eyes with different glaucoma severity, the investigators found that the slowest rate of GCC thinning was observed in advanced glaucoma eyes whereas the slowest rate of macular vessel density decrease was observed in mild

glaucoma eyes; the results were not provided, but were based on only five advanced eyes defined as visual field MD less than -12 dB; if confirmed they would suggest that OCTA may be a viable measure for detecting change in more advanced stages of glaucoma.

Approximately 35% of the macular scans were excluded because of poor quality. It is not clear how many OCTA scans vs. thickness scans were excluded. This is important as an unbalanced exclusion of the images (GCC vs OCTA) could lead to biased results.

The rates of change are notoriously unstable early during follow-up when a small number of datapoints are available

One has to keep in mind that the rates of change are notoriously unstable early during follow-up when a small number of datapoints are available (< 4 on average for all subgroups of this sample). For example, the loss rate of -2.5% per year for vessel density in normal subjects is evidently unsustainable during a lifetime, given the average age of 52 years in this group. The authors reported a stronger relationship between baseline visual field loss (based on MD) with VD rates of change as compared to GCC rates of change. However, the results were likely influenced by an outlier eye for both parameters and given the smaller number of eyes with advanced glaucoma, this hypothesis will have to be verified in future studies.

While the authors provide some evidence for the hypothesis that OCTA parameters could provide additional information with regard to glaucoma progression compared with GCC thickness measures, larger samples of patients with a wider range of glaucoma severity and longer follow-up are needed to definitively answer this important question.

The investigators are to be commended for uncovering another piece of the glaucoma puzzle and contributing to our understanding of the pathophysiology of change in this disease.

Artificial Intelligence


Comment by Mark Christopher and Linda Zangwill, La Jolla, CA, USA

84550 Human versus machine: Comparing a deep learning algorithm to human gradings for detecting glaucoma on fundus photographs; Jammal AA, Thompson AC, Mariottoni EB, Berchuck SI, Urata CN, Estrela T, Wakil SM, Costa VP, Medeiros FA; American Journal of Ophthalmology 2020; 211: 123-131

We are witnessing an explosion in research exploring artificial intelligence (AI) applications in clinical medicine in general and in ophthalmology in particular. It is rare that a technology has the potential to disrupt clinical practice emerges that has such a wide range of applications across virtually all clinical subspecialties. Artificial intelligence is such a technology. With such an increase in the number of publications, the quality of these publications also varies considerably which can limit the validity, generalizability and comparability of the research. To address this issue there is a recent focus on developing standards and guidelines for reporting of artificial intelligence in medical research.[1-4] One concern regarding AI studies is that it is difficult to assess the quality and validity of the label or ground truth used to train the models, which can often be subjective and variable. In Jammal *et al.*, they build on their previous work that avoided the subjective and often variable human assessment of fundus photographs as their ground truth for glaucoma. Rather, they applied a 'machine to machine (M2M)'-based approach that used objective optical coherence tomography measurements of the retinal nerve fiber layer as their reference label for training deep learning algorithms to detect glaucomatous damage from fundus photographs.[5] Their M2M approach was able to predict RNFL thickness from fundus photographs with high accuracy and thus avoid the use of subjective ground truth labelling.

> Deep learning models trained on objective labels (e.g., RNFL thickness) can be effective in glaucoma detection

In the current study, they extend this strategy to compare the ability of human graders and their M2M deep learning algorithm to detect visual field damage. Two human experts provided estimates of glaucoma likelihood (on a scale from 0 to 10) while the M2M AI method provided estimates of RNFL thickness from fundus photographs. These quantitative metrics were then used to identify perimetric glaucoma (determined by expert graders using visual field data) and compared to visual field mean deviation. A strength of this approach is that it provides the authors an additional visual field reference standard to validate their AI approach. **This study provided further confirmation that deep learning models trained on objective labels (*e.g.*, RNFL thickness) can be effective in**

glaucoma detection. Specifically, this study found that, compared to subjective graders, the performance of the objective M2M algorithm was more strongly correlated with visual field metrics, particularly in the high specificity range relevant for screening. Another strength of this study was its thorough reporting of model accuracy. The authors reported not only area under the receiver operating characteristic curves (AUC), but also partial AUC at the high specificity range (85-100%) relevant for screening and precision recall curves which can help avoid overly optimistic estimates of the model performance when the data is unbalanced (*e.g.*, unequal numbers of GON vs not GON cases).

Other concerns regarding the reporting of AI studies include providing information on how well the model will perform in other populations and on what the model is using to make its prediction (opening the black box). Estimating model generalizability on external test sets collected from diverse populations is becoming a standard for reporting AI results and was not completed in this publication. Although the authors did not include visualization strategies such as class activation maps to provide insight into model predictions, these analyses were included their original M2M publication. In future work, it will be important to understand how disease stage/severity (*e.g.*, pre-perimetric vs. perimetric) impacts M2M-based predictions, how well it performs on external datasets, and whether the objective quantitative metric provided by the M2M approach can be used to detect glaucomatous progression.

References

1. Ting DSW, Pasquale LR, Peng L, et al. Artificial intelligence and deep learning in ophthalmology. Br J Ophthalmol. 2019;103:167-175.
2. Ting DSW, Lee AY, Wong TY. An Ophthalmologist's Guide to Deciphering Studies in Artificial Intelligence. Ophthalmology. 2019;126:1475-1479.
3. Campbell JP, Lee AY, Abramoff M, et al. Reporting guidelines for artificial intelligence in medical research. Ophthalmology. 2020 (Editorial; in press).
4. Consort AI, Group S-AS. Reporting guidelines for clinical trials evaluating artificial intelligence interventions are needed. Nat Med. 2019;25:1467-1468.
5. Medeiros FA, Jammal AA, Thompson AC. From Machine to Machine: An OCT-Trained Deep Learning Algorithm for Objective Quantification of Glaucomatous Damage in Fundus Photographs. Ophthalmology. 2019;126:513-521.

Medical Treatment

The Importance of Being Adherent

Comment by Adeleh Yarmohammadi and Sally Baxter, La Jolla, CA, USA

84925 The association between medication adherence and visual field progression in the Collaborative Initial Glaucoma Treatment Study; Newman-Casey PA, Niziol LM, Gillespie BW, Janz NK, Lichter PR, Musch DC; Ophthalmology 2020; 127: 477-483

Reduced adherence to therapeutic plans remains a significant global healthcare concern in many chronic diseases, including glaucoma.[1] In this study, Newman-Casey *et al.* evaluated a spectrum of adherence among patients with glaucoma in the Collaborative Initial Glaucoma Treatment Study (CIGTS), finding a **statistically significant relationship between medication adherence and glaucomatous visual field progression among the participants randomized to the medication arm of the trial.**

Authors found that adherent patients who reported not missing any medication doses had 0.62 dB of visual field loss (ascertained by mean deviation, MD) on average over the seven years of follow-up, consistent with reported rates of age-related changes in MD.[2] In contrast, patients who reported missing doses at 1/3 of follow-up visits lost an average of 1.42 dB of MD; those who reported missing doses at 2/3 of visits lost an average of 2.23 dB. Factors associated with non-adherence were of younger age, non-married status, black race, depression, a lower degree of education, and worse baseline MD.

> This study showed a significant dose-response relationship between the extent of medication adherence and rate of glaucomatous visual field progression (p = 0.005)

This study showed a significant dose-response relationship between the extent of medication adherence and rate of glaucomatous visual field progression (p = 0.005). However, several issues require further consideration. First, the **assessment of medication adherence via self-reported data could have been confounded by overestimation of true adherence.** Patients generally overestimate their own adherence when compared to device-measured or pharmacy refill data,[3] and the rates of adherence in CIGTS participants exceeded those reported in prior studies.[4] Therefore, the magnitude of the reported association may have been underestimated.

Second, visual field progression in non-adherent patients could have been secondary to factors other than medication adherence; association does not equal causation. However, overall this study offers strong secondary analysis of clinical trial data to provide further support for the importance of evaluating patient adherence in glaucoma.

References

1. Quigley HA. 21st century glaucoma care. Eye (Lond). Published online October 10, 2018. doi:10.1038/s41433-018-0227-8 PMID: 30305707
2. Chauhan BC, Malik R, Shuba LM, Rafuse PE, Nicolela MT, Artes PH. Rates of glaucomatous visual field change in a large clinical population. Invest Ophthalmol Vis Sci. 2014;55(7):4135-4143. doi:10.1167/iovs.14-14643 PMID: 24917147
3. Friedman DS, Quigley HA, Gelb L, et al. Using pharmacy claims data to study adherence to glaucoma medications: methodology and findings of the Glaucoma Adherence and Persistency Study (GAPS). Invest Ophthalmol Vis Sci. 2007;48(11):5052-5057. doi:10.1167/iovs.07-0290 PMID: 17962457
4. Newman-Casey PA, Blachley T, Lee PP, Heisler M, Farris KB, Stein JD. Patterns of Glaucoma Medication Adherence over Four Years of Follow-Up. Ophthalmology. 2015;122(10):2010-2021. doi:10.1016/j.ophtha.2015.06.039 PMID: 26319441

The Importance of Being Adherent

Comment by Fotis Topouzis, Thessaloniki, Greece

84925 The association between medication adherence and visual field progression in the Collaborative Initial Glaucoma Treatment Study; Newman-Casey PA, Niziol LM, Gillespie BW, Janz NK, Lichter PR, Musch DC; Ophthalmology 2020; 127: 477-483

The impact of non-adherence on clinical outcomes has gained increasing attention in recent years.

The Collaborative Initial Glaucoma Treatment Study (CIGTS) was a randomized multicenter clinical trial of initial treatment with medications or trabeculectomy in which self-reported medication adherence and visual field (VF) test results were assessed over follow-up in a standardized fashion. Newman-Casey *et al.* evaluated the longitudinal relationship between medication adherence and visual field progression among participants enrolled in the medication arm of CIGTS.

Adherence to treatment was self-reported and assessed through interviews where specific question was included. Repeated interviews followed the study visits schedule while VF-tests were performed in each visit. Mean deviation over time was the main outcome measure.

Among 306 participants, 46% reported never missing a dose of medication over all available follow-up, 112 patients 37% reported missing medication at up to one third of visits, 10% reported missing medication at one third to two thirds of visits, and 7% reported missing medication at more than two thirds of visits.

An increase in the number of visits during which a patient reported a missed dose of medication was associated significantly with a decrease (worsening) in mean deviation (estimate, -0.14 dB per visit with missed dose, P = 0.0054). For subjects who reported never missing a dose of medication, the average predicted MD loss over 8 years was 0.62 dB, subjects who reported missing medication doses at one third of visits had a loss of 1.42 dB (95% CI, 1.19-3.26; P < 0.0001 and subjects who reported missing mediation doses at two thirds of visits showed a loss of 2.23 dB (95% CI, 1.19-3.26, P < 0.0001).

The CIGTS trial is one of few studies to have captured longitudinal measures of both medication adherence and visual field assessment. This longitudinal analysis demonstrated a statistically and clinically significant association between medication adherence and glaucomatous loss of visual function over eight years of follow-up. In addition**, these data display a dose-response relationship between the extent of medication adherence and glaucomatous visual field loss.**

Because adherence was self-reported the magnitude of the association between medication adherence and glaucomatous visual field progression found in this study is likely an underestimate because CIGTS participants were more likely to have overestimated their true medication adherence.

Longitudinal information on adherence and key clinical variables collected on a large number (n = 306) of people with newly diagnosed glaucoma followed up for up to eight years and uniform protocol as part of a randomized controlled clinical trial are among the strengths of this study.

On the other hand this was not a randomized controlled trial of the impact of medication adherence on visual field progression. **It is possible that the non-adherent participants showed worsening visual field loss because of factors other than medication adherence.**

Finally, like most clinical trial participants, CIGTS participants were quite adherent both to their medications and to follow-up and exhibited a fairly small amount of visual field progression. The current study likely underestimates the real world magnitude of the association between medication adherence and visual field progression.

Mitotherapy in Glaucoma

Comment by Jonathan Crowston, Singapore

84974 Neuroprotection from optic nerve injury and modulation of oxidative metabolism by transplantation of active mitochondria to the retina; Nascimento-Dos-Santos G, de-Souza-Ferreira E, Lani R, Faria CC, Araújo VG, Teixeira-Pinheiro LC, Vasconcelos T, Gonçalo T, Santiago MF, Linden R, Galina A, Petrs-Silva H; Biochimica et Biophysica Acta – Molecular Basis of Disease 2020; 1866: 165686

The authors performed an innovative set of experiments where mitochondria isolated from the livers of young Lister Hooded rats were injected intravitreally with the aim of providing neuroprotection and axonal regeneration following optic nerve crush in similar aged rats. Lysed mitochondria or saline were used for controls. Mitochondrial were seen to integrate into host axons at 24 hours and led to a short-term but not sustained alteration in respiratory capacity. Injection of intact liver mitochondria afforded a modest increase in GC survival after optic nerve crush and intriguingly lysed-mitochondria but not intact-mitochondrial promoted axonal regeneration. **Also surprising was the discovery that injected mitochondria increased a-wave (outer retina) and b-waves (mid-retina) of a full-field ERG.** Inner retina recordings were unfortunately not performed and insufficient data was provided in the main text to examine these changes in more detail and it was not evident whether transplanted mitochondria integrated into all the retinal layers.

> Accumulating evidence … is pointing to mitochondrial dysfunction playing a role in glaucoma pathogenesis.

Accumulating evidence from our laboratory and others is pointing to mitochondrial dysfunction playing a role in glaucoma pathogenesis. Mitochondria can be easily isolated and the vitreous chamber is an ideal reservoir for biologic therapies. One aspect that needs to be borne in mind is that the native mitochondria remain in the host RGCs and it is not clear how these will integrate with transplanted mitochondria. As the majority of mitochondrial proteins are derived from nuclear not mitochondria DNA, transplantation will lead to a potential mismatch between transplanted mtDNA and host nuclear DNA. This, at least theoretically, has potential for inciting variations in the OXPHOS complex subunits and their assembly, which in the longer term could lead to dysfunction or incite inflammation.

Mitotherapy in Glaucoma

Comment by Keith Martin, Melbourne, Australia

84974 Neuroprotection from optic nerve injury and modulation of oxidative metabolism by transplantation of active mitochondria to the retina; Nascimento-Dos-Santos G, de-Souza-Ferreira E, Lani R, Faria CC, Araújo VG, Teixeira-Pinheiro LC, Vasconcelos T, Gonçalo T, Santiago MF, Linden R, Galina A, Petrs-Silva H; Biochimica et Biophysica Acta - Molecular Basis of Disease 2020; 1866: 165686

There has been recent interest across a range of diseases as to whether increasing mitochondrial bulk by mitochondrial transplantation might be useful therapeutically.

Previous reports have claimed that such transplantation, either autologous or non-autologous, has been effective in myocardial ischaemia/reperfusion injury, spinal cord injury and models of Parkinson's disease.

In the study by Nascimento-dos-Santos *et al.*, **the investigators tested the effects of transplants of liver-isolated mitochondria on the survival of retinal ganglion cells and axonal outgrowth after optic nerve crush**. They interpret their findings as demonstrating that intravitreally transplanted, active mitochondria incorporate into the retina, improving its oxidative metabolism and electrophysiological activity, increasing cell survival in the ganglion cell layer at 14 days, and leading to a higher number of axons extending beyond the injury site at 28 days.

Whilst the findings are interesting, like many other studies in this field, the mechanism of the effect remains uncertain and should not be assumed to be incorporation of functional transplanted mitochondria into host cells. A more likely explanation may be related to packages of a complex assortment of genes, proteins and other factors provoking signaling responses in host cells exposed.

In the study by Nascimento-dos-Santos *et al.*, only a single retinal cell is shown with what look like stained liver mitochondria. It is hard to reconcile any downstream improvements post-injury with such a low dosage of mitochondrial uptake.

The mechanism of the effect remains uncertain and should not be assumed to be incorporation of functional transplanted mitochondria into host cells

For the respirometry of whole retinas shown in Figure 1, again the tiny dosage of introduced organelles seems inconsistent with the shown response. It is also hard to see how the a and b-wave ERG improvements in Figure 1 could be explained by mitochondrial incorporation into sufficient RGC.

The authors do use a good control in the regeneration experiments, using lysed mitochondria. Here it is interesting that this lysate showed positive effects on the axon regrowth at 14 days while the intact mitochondria showed positive effect at day 28. It is certainly conceivable that the RGC soma were getting some signal, probably a challenging one, from the lysate which encouraged the greater repair response. If so, the later response in the intact organelle injected retinas could suggest that the organelles slowly lysed in the vitreous and eventually provided the same stimulating factors later.

Thus, while the paper is interesting, there are certainly other possible explanations that may be more likely than incorporation of transplanted mitochondria into host cells.

Surgical Treatment

Selective Laser Trabeculoplasty

Comment by Miriam Kolko, Copenhagen, Denmark

84968 Real-world outcomes of selective laser trabeculoplasty in the United Kingdom; Khawaja AP, Campbell JH, Kirby N, Chandwani HS, Keyzor I, Parekh M, McNaught AI; Ophthalmology 2020; 127(6): 748-757

In the present study, **the authors assessed the efficacy of selective laser trabeculoplasty (SLT) in routine clinical care of patients with glaucoma and ocular hypertension (OHT) in the United Kingdom using real-world data collected by electronic medical records**. Moreover, the study aimed to identify factors associated with treatment success. A total of 831 patients were included and underwent SLT treatment. Whereas the recent substantial Laser in Glaucoma and ocular HyperTension (LiGHT) trial compared initial SLT with initial topical medication for treatment-naïve patients with primary open-angle glaucoma (POAG) or OHT, the present study assessed the real-world effectiveness of SLT. The authors found that patients had good effect of SLT immediately after treatment, but the effect disappeared in the majority within a year. The effect of SLT was better in patients with higher baseline IOP, but did not differ depending on the degree of glaucoma severity or with concomitant use of IOP-lowering therapy. Failure of SLT in one eye was strongly associated with failure in the fellow eye. Unexpectedly, the study found greater efficacy in patients treated with SLT by trainees compared to SLT treatment performed by more senior ophthalmologists. Although the authors do not conclude that younger ophthalmologists are more successful in performing SLT treatment, the results certainly show that SLT treatment can be performed fully at the same level by less experienced ophthalmologists in training as by experienced senior ophthalmologists. As with all retrospective studies, there is a need to be cautious with conclusions. One of the possible biases affecting the SLT outcome is the lack of knowledge about whether patients have previously had laser trabeculoplasty performed at another center. However, the large sample size in any case makes the study valuable when patients need to be informed about what to expect from SLT treatment. Over all, the authors suggest that SLT is a better treatment option for patients with OHT or high-tension POAG than for patients with normal-tension glaucoma.

Do Patients prefer MIGS?


Comment by Julian Garcia Feijoo and Lucia Perucho, Madrid, Spain

84620 Patient-reported outcomes measures and patient preferences for minimally invasive glaucoma surgical devices; Li T, Le JT, Hays RD, Cui QN, Eydelman M, Spaeth G, Tarver ME, Singh K; Eye 2020; 34: 205-210

The objective of the paper is **to summarize the progress of two projects started by the FDA to assess patient perspectives regarding MIGS devices for mild to moderate open-angle glaucoma** (OAG). One project is a questionnaire and the other one is a patient preference study to identify which outcomes matter most to them.

Questionnaire. The first phase of the questionnaire development was a physician focus group followed by patient focus groups. The information obtained from those groups, in addition to a review of the literature, was used to draft the questionnaire items.

The following categories were identified by both physicians and patients: night driving, loss of depth perception, esthetics, light sensitivity, and reading difficulties. A list of concepts deemed relevant for incorporation in the questionnaire were revised based on the 25 cognitive interviews resulting in a 52-item questionnaire. This questionnaire will be administered in a future field test with 500 or more respondents to evaluate its reliability and validity.

Patient preference study. A preference survey was drafted using 13 outcomes that patients perceived as important based on 25 one-on-one interviews.

The most important outcomes identified by the participants were 'adequate IOP control' and 'drive a car during the day' which were consistent with the ones identified in the questionnaire. Participants also expressed that the ability to perform other vision-dependent activities and maintaining visual perceptions are more important than burden of treatment.

Many of the outcomes that participants deemed as most important to them are not currently being measured consistently in MIGS studies. However, we should strive to identify those surgical techniques that meet the real expectations and needs of the patients. For this reason, studies and questionnaires such as those reported in this paper are crucial to the development of patient-oriented medicine.

Managing Drainage Device Complications-1

Comment by Leon Au, Manchester, UK

84717 EyeWatch rescue of refractory hypotony after Baerveldt Drainage Device Implantation: Description of a new technique; Elahi S, Bravetti GE, Gillmann K, Villamarin A, Meeus L, Stergiopoulos N, Mansouri K, Mermoud A; Journal of Glaucoma 2020; 29: e7-e10

Congratulations to Elahi and colleagues in describing a unique and revolutionary method in controlling chronic hypotony in Baerveldt tube (BVT) surgery. The Eyewatch device is the first truly adjustable glaucoma drainage device. The magnetically controlled compression wheel within the Eyewatch device allows external, clinic-room adjustment to the flow of the device and titration of intraocular pressure. The initial result of its efficacy as a primary tube-shunt surgery was recently published and larger multi-center study result would follow in the next year. Although not every patient undergoing glaucoma tube surgery would require the precise control of flow that the Eyewatch has to offer, the ability to potentially reduce or eliminate hypotony in tube surgery has to be described as a major surgical advancement. We have debated for years between the choice of a valved and non-valved drainage device; even with the twice-demonstrated IOP superiority of the BVT against Ahmed valve in ABC and AVB studies, many surgeons continued to champion the Ahmed based on its safety and its reduced risk of hypotony.

> The Eyewatch device is the first truly adjustable glaucoma drainage device

This case report yet again highlighted the issue with BVT and hypotony. As the author describes, many methods have been reported to combat chronic hypotony; it often starts with viscoelastic injection in the anterior chamber, followed by insertion of intralumenal stent in the anterior chamber or tying of the tube with nylon sutures. **All these interventions, in my humble opinion, can be best described as 'educated guess work'** in terms of the amount of viscoelastic required, size and length of the intraluminal stent or the tightness of the tube tie. Any subsequent IOP increase or spikes have to be cushioned with medications or laser suture lysis (hoping not to over-do it resulting in hypotony again). **Fortunately, this case report has described one of the most sensible way to titrate a non-titratable BVT, by retro-fitting an Eyewatch to it**. This allows fine control of flow in those few patients who have brittle inflow-outflow balance and hopefully finally rid of the curse of chronic hypotony. I congratulate the authors for their imaginative approach to dealing with a well-known BVT complication.

Managing Drainage Device Complications-2

Comment by Stefano Gandolfi, Parma, Italy

84816 Impact of combined XEN Gel Stent Implantation on Corneal Endothelial Cell Density: 2-Year Results; Gillmann K, Bravetti GE, Rao HL, Mermoud A, Mansouri K; Journal of Glaucoma 2019; 0:

MIGS and MIGS+ are claimed as safer than conventional ab-externo filtering surgeries. **When establishing their risk-benefit profile, the long-term impact on corneal endothelium is critical.** In fact, an ab-interno non-filtering MIGS was recently withdrawn from the market due to an abnormally increased endothelial cell loss in the mid-term.

Gillman and co-workers tackled this topic in their study, measuring corneal endothelial loss upon a combined phaco and a MIGS+ (*i.e.*, XEN gel), and comparing the data with those obtained in a group undergoing plain phacoemulsification. **In their two-year retrospective analysis, they found no significant difference in cell loss between the two study groups.** Besides, they offer further some 'food-for-thought' by dissecting selected phenotypes where the loss was somehow higher (*i.e.*, eyes undergoing multiple stent needling).

They offer some 'food-for-thought' by dissecting selected phenotypes where the loss was somehow higher (*i.e.*, eyes undergoing multiple stent needling)

According to the authors themselves, the study must be considered as a 'pilot' study, In fact, the sample size is by far underpowered (according to the expected null-hypothesis, the groups should have included approximately 450 subjects each for an 80% power), the study is retrospective and the authors counted eyes and not patients. However, their effort should be commended, having they dared to step into the difficult and dangerous path of the long-term evaluation of novel surgeries.

The 'no-risk' message, offered by this study, albeit needing further data to be fully extended to everyone, is encouraging.

Angle-Closure Glaucoma and Cataract

Comment by Augusto Azuara Blanco, Belfast, UK

84502 Phacoemulsification versus phacotrabeculectomy in primary angle-closure glaucoma with cataract: Long-term clinical outcomes; Hansapinyo L, Choy BNK, Lai JSM, Tham CC; Journal of Glaucoma 2020; 29: 15-23

In this study, the authors reviewed the medical records and pooled data from two prospective randomized controlled trials comparing two interventions for patients with PACG and cataract. The difference between trials was the IOP control (or lack of) at baseline.

The original trials reported outcomes after two-year follow-up. These trials, although relatively small, were well-designed and have been helpful to inform clinicians. In brief, combined phacotrabeculectomy with mitomycin C was found to be more effective to reduce IOP and glaucoma treatments than phacoemulsification alone. However, combined surgery was associated with more postoperative complications within five years after surgery.

Studies involving multiple surgeons are more generalizable to the community of glaucoma specialists

This paper reports five-year follow-up in the same cohort of patients. Although the study has some methodological weaknesses (retrospective design, attrition of 1/3 of the cohort) overall **the data is useful and important as it confirms the results of the initial trials.** The authors suggested that combined surgery may provide additional benefits in patients with advanced glaucoma or those suffering from side effects of glaucoma medications.

The authors mentioned that one of the limitations of the study was that surgeries were performed by different surgeons. I would not agree with this point: studies involving multiple surgeons are more generalizable to the community of glaucoma specialists, and thus I would consider it to be a strength.

Finally, I would like to congratulate the authors for conducting the original trials and reporting this long-term follow-up data. Evidence to inform clinical decisions for patients with angle-closure glaucoma is very much needed and this team is making important contributions.

Angle-Closure Glaucoma and Cataract

Comment by Benjamin Xu, Los Angeles, CA, USA

84502 Phacoemulsification versus phacotrabeculectomy in primary angle-closure glaucoma with cataract: Long-term clinical outcomes; Hansapinyo L, Choy BNK, Lai JSM, Tham CC; Journal of Glaucoma 2020; 29: 15-23

Primary angle-closure glaucoma (PACG) is a common cause of permanent vision loss worldwide.[1] The primary risk factor for PACG is closure of the anterior chamber angle, which leads to impaired aqueous humor outflow and elevated intraocular pressure (IOP). Phacoemulsification alleviates angle closure and provides more robust IOP lowering in cases of PACG than primary open-angle glaucoma (POAG). Therefore, phacoemulsification alone is a viable alternative to combined phacotrabeculectomy for up to two years in eyes with visually significant cataracts.[2,3] However, little is known about the differences in long-term outcomes between these two treatments for PACG.

This study by Hansapinya *et al.* is a follow-up to two randomized control studies comparing the outcomes of medically controlled and uncontrolled cases of PACG treated with phacoemulsification or combined phacotrabeculectomy.[2,3] The authors report that phacotrabeculectomy produces greater reduction of IOP and drop dependence but also greater numbers of post-operative complications after five years, similar to previous findings after two years. Interestingly, **fewer than 20% of patients in the phacoemulsification group required trabeculectomy after five years, which suggests that phacoemulsification alone provides adequate long-term IOP lowering in most cases of PACG**. However, it is also important to recognize that despite treatment, mean deviation (MD) on automated perimetry worsened on average in both groups, although this was not statistically significant due to limited visual field data at the five-year mark.

While this study provides valuable insight into long-term outcomes associated with phacoemulsification and phacotrabeculectomy in patients with PACG, it raises other questions. Patients with controlled PACG responded better to phacotrabeculectomy than phacoemulsification. What is the physiologic basis for this observation? Also, a wide range of IOP lowering was seen in both treatment groups. Are there clinical or biometric parameters that predict better response to one form of treatment over another? These questions present the logical next step in efforts to optimize and personalize clinical care of patients with PACG.

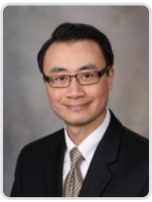
References

1. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: A systematic review and meta-analysis. Ophthalmology. 2014;121(11):2081-2090.

2. Tham CCY, Kwong YYY, Leung DYL, et al. Phacoemulsification Versus Combined Phacotrabeculectomy in Medically Controlled Chronic Angle Closure Glaucoma with Cataract. Ophthalmology. 2008;115(12).
3. Tham CCY, Kwong YYY, Leung DYL, et al. Phacoemulsification versus Combined Phacotrabeculectomy in Medically Uncontrolled Chronic Angle Closure Glaucoma with Cataracts. Ophthalmology. 2009;116(4):725-731, 731.e1-3.

Miscellaneous

IOP-Lowering through Vacuum Application



Comment by Arthur Sit, Rochester, MN, USA

84916 The effects of negative periocular pressure on intraocular pressure; Ethier CR, Yoo P, Berdahl JP; Experimental Eye Research 2020; 191: 107928

Intraocular pressure is the difference between the pressure in the eye and the pressure in the surrounding environment. In general, atmospheric pressure does not affect glaucoma, as it does not change this trans-corneal pressure: individuals living at sea level are not at higher risk of glaucoma than those living at high altitudes. However, the effects of a localized region of low pressure on the eye are less certain.

In a recent study, Ethier *et al.* investigated the effects of negative pressure goggles on IOP. The goggles generate a localized region of negative pressure around the eyes, and were modified for this study to allow pneumatonometry measurements through a latex membrane. The authors developed a lumped-parameter mathematical model to predict the effects of negative pressure on the eye and compared it with clinical measurements obtained from subjects wearing the modified goggles. **The model predicted a reduction in episcleral venous pressure and an associated decrease in IOP.** The model also predicted an increase in globe volume, associated with an initial increase in blood volume which gradually decreased as aqueous humor accumulated. The predicted results corresponded with clinical measurements of IOP performed on human subjects.

However, the results reported in this study raise significant concern about the safety of negative pressure goggles in glaucoma patients. The clinical results and the mathematical model both show that the decrease in IOP is less than the decrease in pressure applied by the goggles. With an applied negative pressure of -12.15 mmHg, only a -5.6 mmHg decrease in IOP was achieved clinically, and -6.4 mmHg predicted in the model. The authors interpret the results as showing an IOP decrease, but they defined IOP as the difference between the pressure in the eye and the surrounding room pressure (*i.e.*, where the pneumatonometer

was placed) – this does not reflect the pressure difference experienced by the eye. **Using a more conventional definition of trans-corneal pressure, the IOP was actually increased by the goggles,** by 6.55 mmHg clinically (5.6 mmHg decrease in the eye, but a 12.15 mmHg decrease just outside of the eye under the goggles). This increase in conventionally defined IOP is reflected in the model, which predicted an increase in ocular volume and would be associated with distension of ocular tissues including the scleral canal. This scleral distention may predispose patients to lamina cribrosa distention[1] and glaucoma development or progression.

> It is clear that negative pressure goggles increase trans-corneal pressure, causing ocular tissue distension, and must be considered contra-indicated in glaucoma patients

The authors hypothesize that there may be value in defining IOP with respect to atmospheric pressure instead of trans-corneal pressure. In particular, they speculate that the retrolaminar pressure may not be affected by the goggles, and hence the trans-laminar pressure difference may be reduced. While there has been interesting work suggesting a role of trans-laminar pressure difference in glaucoma pathogenesis,[2] it seems improbable that retrolaminar pressure would be unaffected by the goggles since this region resides in the orbit and not the cranial vault. Nevertheless, the effect of negative pressure goggles on this parameter is currently unknown and should be the subject of future research. In the interim, **it is clear that negative pressure goggles increase trans-corneal pressure, causing ocular tissue distension, and must be considered contra-indicated in glaucoma patients**.

References

1. Sigal IA, Yang H, Roberts MD, et al. IOP-induced lamina cribrosa deformation and scleral canal expansion: independent or related? Invest Ophthalmol Vis Sci. 2011;52:9023-9032.
2. Siaudvytyte L, Januleviciene I, Daveckaite A, et al. Literature review and meta-analysis of translaminar pressure difference in open-angle glaucoma. Eye (Lond). 2015;29:1242-1250.

Global Burden of Glaucoma

Comment by Rupert Bourne, Cambridge, UK

84714 Socioeconomic disparities in the global burden of glaucoma: an analysis of trends from 1990 to 2016; Wu J, Yu X, Ping X, Xu X, Cui Y, Yang H, Zhou J, Yin Q, Shentu X; Graefe's Archive for Clinical and Experimental Ophthalmology 2020; 258: 587-594

For readers who may not be aware of the Global Burden of Diseases, Injuries, and Risk Factors study (GBD), this is a regional and global research program of disease burden that assesses mortality and disability from major diseases, injuries, and risk factors. With its first report in 1990, it introduced the disability-adjusted life year (DALY) as a new metric to quantify disease burden to aid comparisons.[1] The authors of this paper have accessed the publicly available DALY data for glaucoma from the GBD in 2016[2] and used this to look at sex differences in age-standardized DALY rates. Additionally, the authors attempted to explore associations of glaucoma DALY burden with three covariates, socioeconomic status (Human Development Index), education (using mean Years of Education), and inequality (Gini coefficient), all measured at country level.

> GBD2019 will show a reduction in age-standardized prevalence of glaucoma blindness globally but an increase in moderate and severe vision impairment, over the past decade

Although not explained in the paper, DALYs are a composite of prevalence of vison-impairing glaucoma (derived from population-based studies of eye disease) and the disability weight associated with that severity of vision impairment. In this case, the authors have used glaucoma DALYs which are a combination of DALYs for glaucoma blindness (< 3/60) and glaucoma vision impairment (< 6/18 to 3/60). The authors report that the glaucoma burden (measured in total DALYs) had increased from 1990 to 2016. This had already been reported by the GBD [in DALYs][3] and the Vision Loss Expert Group [VLEG; in cases and crude prevalence rates][4] and would be expected given the ageing of populations. It is interesting that the increase in age-standardized DALYs (and correspondingly age-standardized prevalence) observed between 1990 and 2010 appears to have reversed in the last decade (2010-2019). **GBD 2019 (working with VLEG's more comprehensive Global Vision Database with more glaucoma data sources) will shortly report an 11% reduction in age-standardized DALY rate for glaucoma burden over the past decade.**[5] By concentrating on all DALYs due to glaucoma in this paper by Wu *et al.*, one cannot disentangle the temporal

change in differing severities of glaucomatous vision impairment. Interestingly, GBD2019 will show a reduction in age-standardized prevalence of glaucoma blindness globally but an increase in moderate and severe vision impairment, over the past decade.[5]

Despite more sources of population-based glaucoma data since 2016, the **sparsity of data still precludes precise country-specific glaucoma vision impairment prevalence rates,** which is why this is not displayed in Vision Atlas, the vision loss mapping tool hosted by the International Agency for Prevention of Blindness.[6] In spite of this country-level uncertainty, the authors then tested for relationships between glaucoma DALY rate and the aforementioned three covariates. Given that these covariates are closely related to a factor called Socio-Economic Index (a composite of education, fertility rates, and economic status) that is actually used by the GBD's statistical model to calculate DALYs, this collinearity presents the considerable risk that the analyses and conclusions drawn concerning socioeconomic disparities in glaucoma burden will be distorted.

References

1. Murray C. Quantifying the burden of disease: the technical basis for disability-adjusted life years. Bull World Health Organ. 1994;72:429-445.
2. Global Health Data Exchange. GBD results tool. http://ghdx.healthdata.org/gbd-results-tool.
3. GBD 2016 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1260-1344.
4. Bourne RR, Taylor HR, Flaxman SR, et al. Number of People Blind or Visually Impaired by Glaucoma Worldwide and in World Regions 1990-2010: A Meta-Analysis. PLoS One. 2016;11(10):e0162229.
5. Adelson JD, Bourne RRA, Briant PS, et al. Causes of blindness and vision impairment in 2020 and trends over 30 years: Evaluating the prevalence of avoidable blindness in relation to "VISION 2020: the Right to Sight". Lancet Global Health, in press.
6. International Agency for the Prevention of Blindness. Vision Atlas. http://atlas.iapb.org

www.glaucomapatients.org

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

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

Also in Spanish!

World Glaucoma Association
The Global Glaucoma Network

World Glaucoma Association
The Global Glaucoma Network

Basic Course in Glaucoma

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

Available in Chinese, Portuguese and Spanish

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.

Access Course

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.

Free access to the Journal of Glaucoma

As the official journal of the WGA, online access to the Journal of Glaucoma is provided for free to all individual members of our affiliated Glaucoma Societies, including all ophthalmologists from sub-Saharan countries and glaucoma fellows worldwide.

How to access JOG?

To access JOG, login to your WGA#One Dashboard via www.wga.one/dashboard and go to Publications.

No access? Perhaps your membership is not registered in your profile, which you can check in two easy steps:

1. At your WGA#One Dashboard check *your profile* in the tab *relationships*.
2. Is your membership not registered in your profile? Please contact the WGA Executive office at info@worldglaucoma.org.

Only after having your membership registered in your WGA#One profile, you can access JOG online for free.

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

About the Journal of Glaucoma

Journal of Glaucoma is currently the only scientific journal devoted to glaucoma that is both indexed and has an impact factor, giving the Journal a unique position in the glaucoma community. In conjunction with the World Glaucoma Association, the publisher will also be offering special rates for hard copy subscriptions. The Journal of Glaucoma boasts an impact factor of 1.661, ranking in the 3rd quartile of ranked journals in the field of ophthalmology. Accepted articles are published online ahead of print within two weeks of acceptance and published in final issues online within eight weeks. The journal website receives more than 12,000 visits per month and 20,000 page views per month.

Glaucoma Industry Members

We acknowledge the unrestricted educational grants of our industry members.

For more information about our Glaucoma Industry Members, please click below on the company names.

PLATINUM

Allergan an AbbVie company

Gold

Santen

Silver

aerie Pharmaceuticals, Inc.

GLAUKOS Transforming Glaucoma Therapy

NOVARTIS

Bronze

icare For better perception

iSTAR MEDICAL

TOMEY

SENJU

TOPCON YOUR VISION. OUR FOCUS.

News Flashes

- ★ Even if gaze-induced deformations are proven to cause or contribute to a neuropathy, it remains to be shown that this is a glaucomatous neuropathy
- ★ It is clear that negative pressure goggles increase trans-corneal pressure, causing ocular tissue distension, and must be considered contra-indicated in glaucoma patients
- ★ CATS prism may improve the accuracy of GAT measurements, with the advantage that the CATS prism can be fitted to readily available Goldmann-type tonometers
- ★ Deep learning models trained on objective labels (e.g., RNFL thickness) can be effective in glaucoma detection
- ★ The Eyewatch device is the first truly adjustable glaucoma drainage device
- ★ Studies involving multiple surgeons are more generalizable to the community of glaucoma specialists
- ★ This study showed a significant dose-response relationship between the extent of medication adherence and rate of glaucomatous visual field progression ($p = 0.005$)
- ★ GBD2019 will show a reduction in age-standardized prevalence of glaucoma blindness globally but an increase in moderate and severe vision impairment, over the past decade
- ★ To address whether altered functional connectivity could serve as an early biomarker for glaucoma, longitudinal observations are necessary
- ★ Accumulating evidence ... is pointing to mitochondrial dysfunction playing a role in glaucoma pathogenesis.
- ★ This study is important because it adds weight to the available evidence that lower CH is associated with glaucoma progression, and the study shows that CH is also associated with posterior ALCS migration
- ★ They offer some ‘food-for-thought’ by dissecting selected phenotypes where the loss was somehow higher (i.e., eyes undergoing multiple stent needling)
- ★ This study provides solid evidence that lower baseline CH is associated with an increase in the posterior displacement of the lamina cribrosa over time, a finding that highlights the potential role of this biomechanical parameter as an independent risk factor for glaucoma onset and progression
- ★ An almost 24% PPV may represent an acceptable cut-off in the well-organized Scottish healthcare setting
- ★ As current approaches become further refined it appears that a new paradigm shift in perimetry and visual function testing is emerging
- ★ The mechanism of the effect remains uncertain and should not be assumed to be incorporation of functional transplanted mitochondria into host cells
- ★ The rates of change are notoriously unstable early during follow-up when a small number of datapoints are available
- ★ Such measurements now can be done using widely available hardware, combined with software that the authors have made freely available online
- ★ The location of VFL can be nearly as important as the presence of the loss itself

www.e-IGR.com



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