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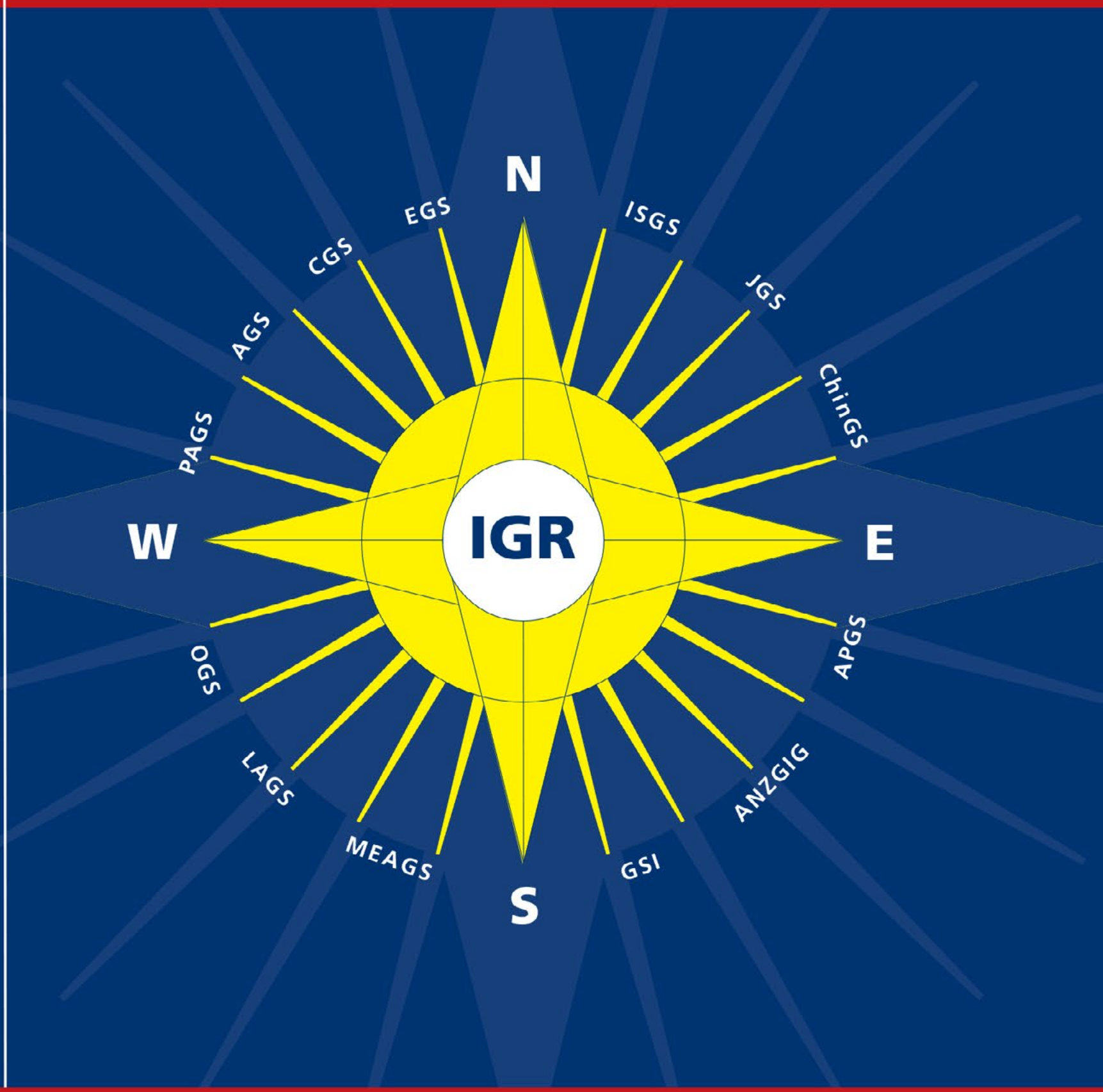

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Robert N. Weinreb

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WGA Consensus Volume 11 - Glaucoma Surgery

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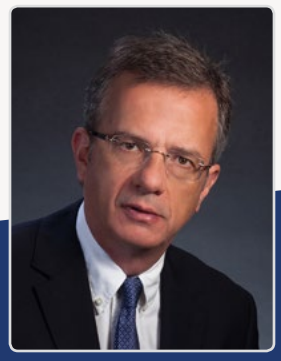


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From the WGA Executive Office

Dear IGR readers,

With less than four months before the start of the next World Glaucoma Congress, the Executive Office is full of activity. Final preparations for the program, logistical challenges and promotional efforts via multiple channels. For a sneak preview of the program, please click here.

The regular registration deadline for WGC-2019 is also fast approaching. Register today for the World Glaucoma Congress 2019 and save!

WGA stays committed to giving young ophthalmologists from Sub-Saharan Africa the opportunity to expand knowledge and skills in several subspecialties in ophthalmology. That is why we continue with the Fellowship program for 2019: attendance of WGC-2019 in Melbourne, Australia, and three months of training at an Australian institute: Royal Victorian Eye and Ear Hospital (Melbourne), Westmead Hospital (Sydney), Lion's Eye Institute/Royal Perth (Perth), Flinders Hospital (Adelaide) or Sydney Eye Hospital (Sydney). More information on the 2019 Fellows can be found online at the WGA website.

In the previous issue of *IGR* we introduced a new column: 'Get to know the WGA Executive Office' to introduce you to members of our team. In this issue we provide you with a short bio of Shan Lin, the current Executive Vice President of the WGA.

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

Shan Lin
Executive Vice President

Get to know us

Shan Lin, MD, is Research Director at the Glaucoma Center of San Francisco. He is former Director of the Glaucoma Service at the University of California, San Francisco, and the Zuckerberg San Francisco General Hospital. He is an author of over 220 peer-reviewed publications. His past leadership positions include Chair of the American Glaucoma Society's Patient Care Committee, Chair of the Glaucoma Section of the Ophthalmic Technology Assessment Committee of the American Academy of Ophthalmology, Chair of the American Glaucoma Society's Document Review Subcommittee, and President, Vice President and Program Chair of the Pacific Coast Oto-Ophthalmological Society (PCOOS). His past honors include the Heed Fellowship Award, the American Glaucoma Society and The Glaucoma Foundation's Clinician-Scientist Awards, and the Mid-Career Award by the AGS. He has also been funded as a Principal Investigator by the National Institute of Health, including as a PI for the Ocular Hypertension Treatment Study (OHTS) study. He has been selected annually for 'Best Doctors' in the U.S. since 2009. He is currently on the editorial boards for the *American Journal of Ophthalmology*, *Journal of Glaucoma*, and AJO Case Reports.

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Glaucoma Opinion

Challenges with deep learning in glaucoma

Leopold Schmetterer

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Introduction

Imaging is an essential part of glaucoma care. In the recent years, optical coherence tomography has to a large degree replaced earlier technologies such as fundus photography or scanning laser ophthalmoscopy, due to its unprecedented resolution, three-dimensional representation of tissue and good reproducibility. From images either semantic features defined by human experts (*e.g.*, fiber bundle defects, optic disc hemorrhages, cup/disc ratio at the slitlamp) or agonistic features defined by equations (ganglion cell complex, nerve fiber layer thickness, minimum rim width) are extracted. Semantic features may provide good specificity; however, they depend on the level of experience, differ between different experts and are often time consuming to obtain. Agonistic features may have limited specificity, but usually have little inter-observer variability. Different agonistic features can in principle be combined, thereby offering improved diagnostic performance.

Some agonistic features related to the disease process, such as loss of retinal ganglion cells and their axons, are part of standard diagnosis in glaucoma. Other characteristic features, such as optic nerve head morphology or vascular changes, are not considered, although this information is present in OCT images. Machine learning approaches use agonistic features with a black-box approach, and not based on mathematical description or modeling. Importantly, such an approach can also include non-imaging features such as visual field data, intraocular pressure and anatomical factors such as eye length. Glaucoma is a good candidate for machine learning approaches because of the poorly understood pathogenesis[1] and the complex structure-function relationship (Malik *et al.* 2012).[2] Moreover, OCT is an imaging modality that acquires tissue characteristics with almost histological resolution.

The concept of deep learning

More than 10 million OCT retinal scans are obtained annually providing an enormous amount of data that cannot be categorized by human graders. Machine-based classification is now the aim of many research groups and diagnostic performance has improved rapidly. In 2012, a

Convolutional Neural Network (CNN) was, for the first time, capable to defeat human graders in the ImageNet challenge,[3] a large visual database designed for use in visual object recognition software research. Since then, the performance of new machine learning-based systems has continuously improved. **Computer vision, referring to machine-based image analysis seeks to automate tasks that human visual systems can do including classification, detection, segmentation, and image enhancement**. CNNs are algorithms used to solve computer vision tasks under the umbrella term Artificial Intelligence (AI). Machine learning is a subclass of AI and refers to the ability of learning without being programmed for specific models or equations; humans define imaging features and statistical analysis is used for classification. Deep learning (DL) on the other hand learns by itself which features are most suitable for classifying the data. The basis of most deep learning approaches is the Artificial Neural Network (ANN) that mimics biological neural networks including neurons, dendrites and axons. The first layer of an ANN is the input layer where the image data are entered (Fig. 1). The dendrites are assigned a random number at initialization and each input is multiplied by this random number. The results are then summed for each neuron and passed to the next layer until the final result is obtained in the output neuron. Increasing the number of layers usually improves the performance of the ANN, but increases the need for more input data.

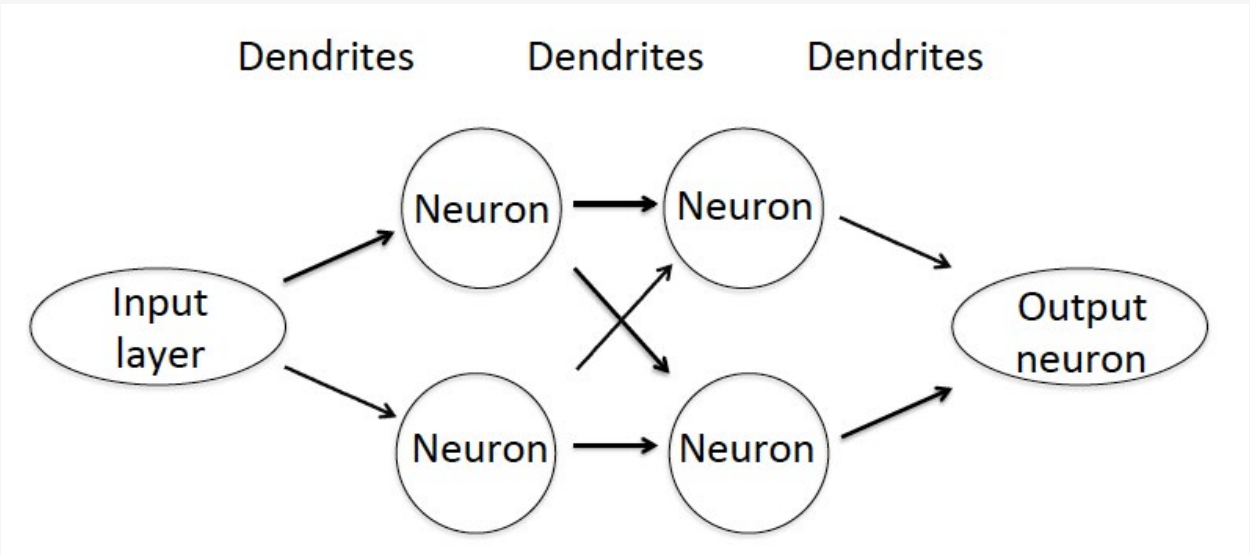

Fig. 1. Schematic illustration of a simple artificial neural network (ANN) with two layers. Whereas ANNs that are used for AI-based solutions in image analysis are more complex and use more layers the working principle still remains the same.

Problems of deep learning in glaucoma

The number of images required for DL approaches highly depends on the complexity of the network and the degrees of freedom. For optimal performance, it is considered that at least 100,000 images are required at the input layer, which is called training dataset. In this training data*set all* stages of the disease and healthy control subjects are included. The outcome of the network depends on the quality of the images and careful phenotyping. It is desirable to achieve a balance between different stages of the disease. Lack of late stage patients is a common problem in the training datasets. In case of over-fitting of data there is a risk that the performance in the validation dataset is not as good as in the training dataset. To which degree networks trained with data from one ethnicity can also be used in populations consisting of other ethnicities is largely unknown. It is also unknown whether it is critical if the training dataset contains OCT images as obtained from only one specific machine.

Until now, AI-based approaches in medical care are narrow and are focused on one specific task. In performing this task, the network may be superior to humans for instance in estimating the risk of having glaucoma based on fundus photographs just as Goldmann tonometry is more accurate than palpation in measuring intraocular pressure. As such, performance may not be mixed up with competence. The many factors that are assessed by the physician during a patient examination include general appearance of the subject, presence of concomitant disease and estimation of patient's adherence to medication are not within the scope of the ANN. Also, when novel imaging modalities become available that either provide better resolution, molecular contrast or functional tissue properties, previously trained networks become useless. Again, the network provides performance for one specific task in classifying images, but not competence in ocular imaging.

Implementing AI-based solutions in glaucoma care has several practical hurdles. The current system of reimbursement does not include machine-based image classification. Hence, there will be a continuous re-distribution of money within the health care system when machine learning solutions will be implemented. Related to this issue is the question who will assume liability in case of incorrect classification. If not all images are finally re-evaluated by human graders, it seems reasonable that the maker of the network will be responsible. This risk will be reflected in the retail price of the AI product. Economic considerations may also lead to different solutions depending on local insurance systems and the clinical needs in each country.

The cost issue is closely related to the application of AI-based systems. As mentioned above, such applications need to follow a well-defined task. Such tasks may include segmentation of OCT images,[4] de-noising of OCT images,[5] glaucoma diagnosis or progression analysis.[6] In terms of diagnosis, the major problem is that OCT provides good performance for late-stage disease, but not for early stage disease.[7] Whereas this might be improved with AI-based networks over classical approaches such a retinal nerve fiber layer thickness or ganglion cell mapping, the large number of false positives still remains a problem. A potential solution may be to use of AI systems that provide high sensitivity followed by human over-reading to increase specificity.

Before using AI-based systems, approval by the local authorities such as FDA or EMA will be required. The required performance for such solutions in glaucoma still needs to be defined. Whereas using machine learning for segmentation or de-noising of OCT images may be easily accepted, basing diagnosis or progression analysis on AI approaches is more critical. Clearly, clinical outcome studies comparing AI-based treatment decisions with classical approaches will increase the general acceptance. Whereas the current use of OCT in glaucoma care is easily comprehensible, AI-based solutions are black-box systems. This is a paradigm change, because the physician will not be able to decide whether a certain categorization is due to changes in retinal nerve fibers, retinal ganglion cells or other posterior pole structures. At the end of the day, however, it will be patient acceptance that decides when and to which degree AI-based solutions will be implemented into clinical practice.

Outlook

AI-based classification of glaucoma is still in its very early stages. Preliminary data are promising even when relying only on fundus photographs.[8] ANNs will not replace soon physicians for diagnosing glaucoma. AI-based solutions will, however, become part of glaucoma care in the near future and may bring us closer to the goal of cost-effective population-based glaucoma

screening. Roy Amara from Institute for the Future (Palo Alto, CA) stated: 'We tend to overestimate the effect of a technology in the short run and underestimate the effect in the long run.' This appears to be very true for AI in glaucoma and other ophthalmic diseases.

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

Robert N. Weinreb, Chief Editor

Epidemiology

Incidence of angle closure in China

Comment by Ningli Wang and Zhang Ye, Beijing, China

77130 Ten-year incidence of primary angle closure in elderly Chinese: the Liwan Eye Study; Wang L, Huang W, Huang S, Zhang J, Guo X, Friedman DS, Foster PJ, He M; British Journal of Ophthalmology 2018; 0:

This is a nice and important article. The authors reported the ten-year incidence of all forms of primary angle closure (PAC) defined by ISGEO including primary angle closure suspect (PACS), PAC and primary angle-closure glaucoma (PACG) and their risk factors in an urban Chinese population aged 50 years and older. Participants with baseline angle closure or bilateral cataract surgery during the ten-year period were excluded. Occludable angle had invisible posterior pigmented trabecular meshwork for 270° or more in static gonioscopy.

As the authors point out, this is the first population-based study evaluating the incidence of PAC among elderly Chinese people.[1]

With data obtained from 620 participants, the ten-year incidence of PAC was found to be 20.5%, including 16.9%, 2.4% and 1.1% with incident PACS, PAC and PACG in either eye, respectively. The incidence of PAC (2.05% annually) was much higher than that those reported in an Indian

population (0.7% annually) aged 40 years and older and in a Greenland Inuit population (1.6% annually), but lower than that in a Mongolian population aged 50 years or older (3.4% versus 2.56% annually) using the same diagnostic standard . This finding supports the notion that East Asians have a higher risk of primary angle closure.

The risk factors for incident PAC were greater baseline lens thickness (LT), shallower anterior chamber depth (ACD) and narrower angle width. Also, a higher incidence was observed in women and in older people. These results are consistent with previous cross-sectional and other longitudinal studies.[2-5]

Another interesting finding of this study is that none of the ACD, LT and axial length from baseline showed an acceptable sensitivity and specificity in predicting incident PAC spectrum or determining who requires more intensive monitoring.

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Quality of Life

Are glaucoma patients more sensitive to extreme luminance?

Comment by Eytan Blumenthal, Haifa, Israel

76662 Visual complaints of patients with glaucoma and controls under optimal and extreme luminance conditions; Bierings RAJM, van Sonderen FLP, Jansonius NM; Acta Ophthalmologica 2018; 96: 288-294

Beirings *et al.* from the Netherlands studied visual complaints of glaucoma patients vs. controls in both optimal as well as challenging lighting conditions, defined as: ideal, low, high, sudden decrease & sudden increase in the level of lighting. This was a questionnaire study based on the subjective reporting of patients, while their spouses/neighbors served as controls. A high (81%) response rate was achieved. The percentage of subjects with complaints were (for glaucoma/normal, respectively): optimal lighting: 4/0, low lighting: 48/6, high: 22/1, sudden decrease: 32/1, sudden increase: 25/3; all comparisons were statistically significant. Complaints were highly correlated with the severity of the glaucoma, as judged by the visual field mean deviation. It may be concluded that **for a glaucoma patient the most disturbing lighting environment, from worst to best, would be: low light, sudden decrease, sudden increase, high lighting and finally optimal.**

The authors conclude that even early glaucoma patients reported complaints in non-ideal lighting conditions, more so in the dark, leading them to conclude that early glaucoma might not be an asymptomatic disease.

Early glaucoma might not be an asymptomatic disease

Drawbacks of this study include the subjective, questionnaire, nature of the study and the fact that patients and controls were not tested under standardized conditions. **Knowing one's diagnosis might have introduced some bias into the study.** One take-home message might be that even an early glaucoma patient with normal visual acuity and only mild VF changes might, contrary to the current dogma, not be asymptomatic under less than ideal lighting conditions.

Which visual function affects glaucoma patients most?

Comment by George Lambrou, Strasbourg, France

76940 Predicting visual disability in glaucoma with combinations of vision measures; Lin S, Mihailovic A, West SK, Johnson CA, Friedman DS, Kong X, Ramulu PY; Translational vision science & technology 2018; 7: 22

Why is it that we diagnose so many patients with significant perimetric damage and they are surprised to find out that their vision is so much affected without them experiencing any noticeable visual disability? Is it just that perceptive mechanisms in the brain are so efficient in compensating for field loss? Or is it that perimetry is not the most relevant vision measure to assess disability? In which case, what are the best measures to predict visual disability in glaucoma?

This is the question that Lin *et al.* have sought to address, by comparing the outcomes of seven visual measures with the patient-reported Glaucoma Quality of Life (GQL-15) score in 150 glaucoma patients. More specifically, they analyzed integrated (binocular) visual field sensitivity, visual acuity, contrast sensitivity (CS), area under the log CS function, color vision, stereo-acuity and visual acuity with noise. As prior work indicates that the correlation between single visual measures and patient-reported disability is moderate at best, they explored (a) the correlation between the individual measures and (b) whether a combination of several measures (a 'multi-dimensional visual space') would provide a better predictor of visual disability.

Their reported results are that indeed the investigated visual measures do correlate with each other, supporting the concept of such a space, but that the contributions of each measure to the GQL-15 score is variable: the highest contributing function was CS, while integrated visual fields came third, after visual acuity with noise. Modelling various combinations of visual measures showed that two-measure models were the best in predicting visual disability, provided that CS was one of the two measures.

The authors recognize that the study may have been limited by the patient sample being representative of their institution's glaucoma clinic patients but not of the wider glaucoma population, by the exclusive use of functional and not structural parameters like OCT and by the use of the GCL-15 scale, which is mostly mobility-focused. **Nevertheless, it provides significant insights in the visual mechanisms underlying disability in glaucoma patients and suggesting a more prominent role of contrast sensitivity, alongside visual fields in its assessment and prediction.**

Quality of life after glaucoma treatment

Comment by Pradeep Ramulu, Baltimore, MD, USA

76554 Factors associated with health-related quality of life in medically and surgically treated patients with glaucoma; Khanna CL, Leske DA, Holmes JM; JAMA ophthalmology 2018; 136: 348-355

A growing literature has explored the numerous ways that glaucoma impacts patients' quality of life, and Khanna and colleagues advance this body of work by comparing quality of life measures, including specific measures designed to evaluate various aspects of quality of life from adult strabismus, across glaucoma patients who've undergone distinct forms of IOP-lowering treatment: medical treatment, trabeculectomy, and glaucoma drainage device (GDD) implantation. When evaluating quality of life using the Adult Strabismus-20 questionnaire, patients in the GDD group reported worse self-perception and interactions scores as compared to both medically treated patients and patients having received trabeculectomy. No differences in scores were noted between for domains in the NEI-VFQ questionnaire, nor were any differences noted for any questionnaire domain when comparing patients in the trabeculectomy and medical therapy groups.

This work extends on the authors' previous work from the same cohort showing a significantly higher percentage of diplopia in patients having previously undergoing GDD implantation as compared to medically-treated and trabeculectomy patients. However, it is important to note that the observed differences in self-perception and interactions in the GDD group were found *independent* of patients' self-reported diplopia. Thus, **the observed quality of life difficulties may not be a direct result of the diplopia produced with GDD implantation**. Of note, patients who received both trabeculectomy and GDD implantation were considered in the GDD group. Thus, it is possible that patients in the GDD group were worse off simply because of the number of prior eye surgeries, and the consequences of multiple surgeries in the eye (ptosis, chronic injection, pain/discomfort, *etc.*) Nonetheless, the article highlights some of the difficulties encountered by patients having undergone GDD implantation, although **more work is needed to determine if these troubles are directly the result of GDD implantation, or rather a reflection of having undergone multiple surgeries.**

Anatomical Structures

Microvascular dropout and peripapillary atrophy

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

76968 Deep-layer microvasculature dropout by optical coherence tomography angiography and microstructure of parapapillary atrophy; Suh MH, Zangwill LM, Manalastas PIC, Belghith A, Yarmohammadi A, Akagi T, Diniz-Filho A, Saunders L, Weinreb RN; Investigative Ophthalmology and Visual Science 2018; 59: 1995-2004

Beta parapapillary atrophy (PPA) is the area adjacent to the clinically delineated optic disc margin where the retinal pigment epithelium (RPE) is absent and hence the underlying sclera and large choroidal vessels are visible. Enhanced-depth OCT imaging allows detailed visualization of the parapapillary region and has shown that the Bruch's membrane (BM) may be present in only part of this region. Therefore, the region of beta-PPA has been divided into gamma-PPA (defined as an area adjacent to the disc border which is devoid of RPE and BM) and beta-PPA$_{+BM}$ (defined as an area with intact BM, but no RPE).[1]

Complete loss of choriocapillaris in localized regions of PPA, called deep-layer or choroidal microvasculature dropout (CMvD), is a relatively novel finding observed on the choroidal OCTA slabs of glaucoma eyes

The development of OCT angiography (OCTA) has allowed imaging of vasculature in the PPA. Complete loss of choriocapillaris in localized regions of PPA, called deep-layer or choroidal microvasculature dropout (CMvD), is a relatively novel finding observed on the choroidal OCTA slabs of glaucoma eyes.[2,3] CMvD has been shown to be a true choroidal perfusion defect using indocyanine green angiography.[4] A few recent studies have explored the associations of CMvD in POAG eyes and have reported that CMvD was more frequently seen in glaucoma eyes with greater severity of structural and functional damage,[2,5,6] focal lamina cribrosa defects[2] and disc hemorrhage (DH).[7] The study by Park *et al.* also reported an association between CMvD and progressive retinal nerve fiber layer thinning in POAG eyes with DH.[7] This may mean that CMvD is a marker for glaucoma progression.

Suh *et al.* recently evaluated the association between CMvD and the microstructure of the beta-PPA.[8] POAG eyes were divided into two groups based on the microstructure of βPPA; one group with γPPA and the other with intact BM (βPPA+BM). The groups were matched for glaucoma severity as determined by visual field loss. It was found that **CMvD was more frequently**

(p = 0.004) seen in eyes with γPPA (75.7%) compared to eyes with βPPA_{+BM} (40.8%). Logistic regression analysis also showed that CMvD was significantly associated with the presence and larger width of γPPA, but not with βPPA_{+BM}.[8]

This is an interesting result, but not in complete agreement with the findings of previous studies. An OCT study has shown that γPPA is associated with older age, high myopia and the absence of glaucoma.[1] γPPA has also been associated with a slower rate of glaucoma progression.[9,10] In contrast, previous OCTA studies have shown that CMvD was associated with more advanced glaucoma and glaucoma progression.[2,5-7] Therefore, there is need for a better understanding of the complex association between γPPA and CMvD, and the role of the optic nerve head border tissues in the pathogenesis of glaucoma.

There is need for a better understanding of the complex association between γPPA and CMvD, and the role of the optic nerve head border tissues in the pathogenesis of glaucoma

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Detecting macular damage in glaucoma

Comment by Andrew Tatham, Edinburgh, UK

76858 Evaluation of a region-of-interest approach for detecting progressive glaucomatous macular damage on Optical Coherence Tomography; Wu Z, Weng DSD, Thenappan A, Ritch R, Hood DC; Translational vision science & technology 2018; 7: 14

There is growing appreciation of the importance of macular imaging in glaucoma, with several studies showing macular changes are common, even in early disease, and that glaucoma may be missed if retinal nerve fibre layer (RNFL) analysis is used alone.[1,2] Macular changes and central vision are also of particular importance for daily function and vision-related quality of life. At present, detection of glaucoma progression is overly reliant on global indices, which fail to take account of localized changes and prior knowledge of patterns of glaucomatous damage. Wu and colleagues hypothesized that accuracy of detection of progression could be improved by evaluating changes in regions of observed or suspected glaucomatous damage, using a region(s)-of-interest (ROI) approach.[3]

At present, detection of glaucoma progression is overly reliant on global indices, which fail to take account of localized changes and prior knowledge of patterns of glaucomatous damage

The study compared two methods of identifying ROIs; (1) an automatic approach, which considered ROIs those with significantly lower ganglion cell complex (GCC) thickness compared to normative limits, exceeding a prespecified area (288 um^2); and (2) a manual approach, where ROIs for each eye were determined manually using the full wealth of OCT images, including an *en-face* projection image, macular RNFL and GCC thickness plots, and thickness deviation probability plots. ROI approaches were compared to the more common method of progression analysis; change in global macular GCC thickness.

One of the most important aspects of detecting progression is the ability to differentiate true change from the noise of test-retest variability. The ideal method needs a high signal to noise ratio (SNR)4 and so SNR was chosen as the primary outcome for comparison of approaches. SNR was determined by examining test-retest differences in each ROI and calculating region-specific estimates of variability. Region-specific age-related rates of change in GCC thickness were also calculated using a cohort of healthy eyes. As ROIs are unique to each eye, region-specific estimates of variability and age-related change had to be calculated individually.

The study's central finding was that the manual ROI method had a significantly more negative SNR (-1.03 y^{-1}) than the automated ROI (-0.91 y^{-1}) and global GCC thickness (-0.90 y^{-1}) methods. A more negative SNR indicates a greater extent of GCC thickness loss relative to age-related change and measurement variability, and therefore the manual ROI was the best method of detecting longitudinal change in macular GCC, with automated ROI and global GCC thickness analysis performing similarly.

Although the study did not evaluate the clinical implications of the different approaches and was limited by use of within session estimates of variability, which are likely to be lower than between-session estimates, it nevertheless demonstrates that detection of progression can be improved by evaluating change in regions of observed or suspected glaucomatous macular damage or 'regions of interest'. The manual approach of identifying ROIs is likely to have been superior to automated identification of ROIs as it was based on careful qualitative evaluation of all the available information from the OCT images. The automated method of ROI identification may have failed to detect regions of genuine damage that remained statistically within normative limits or regions of damage not meeting the predefine minimum area. Although manual definition of regions of interest performed best it has the disadvantage of being more time consuming than automated identification, it is, however, possible that automated methods may be improved using alternative definitions of abnormality.

The study provides further evidence of the importance of qualitative evaluation of OCT images and suggests that trend or event-based analyses of macular GCC are more likely to be effective if performed in regions of observed or suspected glaucomatous macular damage.

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Basic Science

Oxidative stress in the ONH

Comment by Makoto Aihara, Tokyo, Japan

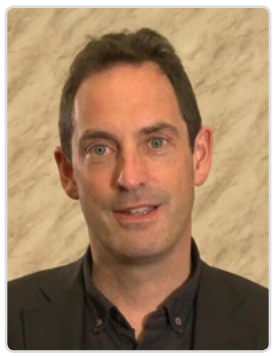
76536 Elevated intracellular cAMP exacerbates vulnerability to oxidative stress in optic nerve head astrocytes; Shim MS, Kim KY, Bu JH, Nam HS, Jeong SW, Park TL, Ellisman MH, Weinreb RN, Ju WK; Cell Death and Disease 2018; 9: 285

It is shown that cAMP/PKA pathway activation exacerbates ONH astrocyte dysfunction induced by oxidative stress. Suppression of cAMP/PKA activation rescues astrocyte dysfunction via AKT phosphorylation. Oxidative stress itself tended to decrease cAMP/PKA activation to protect astrocyte. In addition, elevated cAMP is shown to enhance TNFalpha from astrocyte, leading to astrocyte dysfunction and axon damage. Taken together, **modulation of cAMP/PKA pathway may be effective to protect ONH astrocytes and axons.** Thus, the authors suggest that inhibition of this pathway is one of the targets for glaucoma therapy.

Inhibition of the cAMP/PKA pathway may be effective to protect ONH astrocytes and axons

The involvement of this pathway in ONH is a complicated but interesting story. This result is fully supported by the in vitro assays in detail. In the *in vivo* study on astrocyte dysfunction, the DBA2J glaucoma model was used, and degenerative astrocyte and axon loss in ONH were shown by SBEM images. In POAG, pressure stress at ONH promotes lamina deformation leading to a reduction in axoplasmic flow and capillary blood flow. **Thus, oxidative stress-induced ONH astrocyte dysfunction may accelerate RGC axon damage**. Although modulation of cAMP may be partially effective to suppress ONH astrocyte dysfunction, lowering the IOP remains the first line of treatment. The pathogenesis of ONH deformation is complicated. In addition to oxidative stress, the effect of shear stress on cAMP/PKA signaling should be examined in ONH astrocyte. Investigating how to modulate the cAMP/PKA pathway in a glaucoma model would be the next step. Needless to say, determining the timing of modulation and the methods of drug delivery is also important.

Neuroprotection



Comment by Keith Martin, Cambridge, UK

77097 Structural and functional rescue of chronic metabolically stressed optic nerves through respiration; Harun-Or-Rashid M, Pappenhagen N, Palmer PG, Smith MA, Gevorgyan V, Wilson GN, Crish SD, Inman DM; Journal of Neuroscience 2018; 38: 5122-5139

The importance of metabolic stress as a contributing factor to retinal ganglion cell (RGC) loss in optic nerve diseases such as glaucoma has been highlighted in numerous recent studies. **A key question is whether energy substrate availability or mitochondrial dysfunction contributes to the energy compromise observed in glaucoma.**

The current study adds to a growing body of literature on the potential benefits of dietary modification

To test this idea, Harun-Or-Rashid and co-workers placed DBA/2J mice (which develop a form of pigmentary glaucoma as they age) and control mice on a ketogenic diet composed primarily of fat in order to promote mitochondrial biogenesis and compel mitochondrial respiration through utilization of ketone bodies rather than glucose. **They found that eight weeks of the diet generated increased numbers of mitochondria, improved energy availability, reduced glial hypertrophy and protected RGC and their axons from degeneration**.

The experiments appear to have been carefully performed and it is of interest that similar metabolic changes were also observed in a microbead model of glaucoma as well as in the DBA/2J mice. In previous studies by other groups, caloric restriction by alternate day fasting has been shown to improve RGC survival and function in a mouse model of normal tension glaucoma. Ketogenic diets have also been shown to reduce neurodegeneration in models of Alzheimer's disease. The current study therefore adds to a growing body of literature on the potential benefits of dietary modification in animal models of glaucoma and the results of future human clinical trials are awaited with interest.

Clinical Examination Methods

Detecting progression

Comment by Vincent Michael Patella, Santa Rosa, CA, USA

76870 Event-based analysis of visual field change can miss fast glaucoma progression detected by a combined structure and function index; Zhang C, Tatham AJ, Daga FB, Jammal AA, Medeiros FA; Graefe's Archive for Clinical and Experimental Ophthalmology 2018; 256: 1227-1234

Zhang and colleagues followed 135 eyes of 97 glaucoma patients for an average of 3.5 years to compare glaucoma progression as identified by a perimetric event analysis (Humphrey GPA) to progression events based upon rates of progression as estimated a) by OCT measures of RNFL thickness and b) by an index (RGC Index) combining standard automated perimetry (SAP) and OCT RNFL measurements. For RNFL thickness and RGC Index, eyes were deemed to have progressed if the slope was statistically significant ($P < 0.05$) and faster than average age-related loss, as determined from a group of 50 healthy eyes followed for an average of 1.9 years.

At baseline, median MD of the glaucoma eyes was -2.80 dB (IQR -4.76 to -1.26). **Twenty-one eyes progressed by the RGC index but not by GPA, whereas only five eyes showed progression on GPA that was not detected with the RGC index. Eighteen eyes progressed by the RGC index but not by SDOCT, whereas eight eyes progressed by SDOCT but not RGC index**. None of the healthy eyes showed perimetric progression on GPA.

The authors concluded that many glaucomatous eyes that were not found to be progressing by perimetric event analysis may actually have had fast rates of progression as detected by a combined index of structure and function.

This paper nicely demonstrates the advantages of analyses that combine data from complementary sources

Comments

1. This paper nicely demonstrates the advantages of analyses that combine data from complementary sources. Based upon the MD range cited above, most patients in this study had early glaucoma, which is exactly where OCT can contribute best in an OCT-Perimetry combined analysis. More importantly, the RGC index standardizes and simplifies the identification of glaucomatous progression based upon OCT & SAP.

2. Unfortunately, the compared metrics were not specificity matched, and without specificity matching, the sensitivities of diagnostic methods cannot be precisely compared, as authors from this group have recently affirmed.[1] However, we do see that GPA found zero progression events in 50 healthy controls, and RGC measurements showed nearly zero overlap between normal aging in the controls and the glaucoma eyes it found to progress. Thus, both methods appear to be operating at high specificities in this particular cohort. Therefore, I believe that the RGC Index would have been shown to be more sensitive than GPA, even at matched specificities. But we cannot use this paper to say by how much.
3. More generally, defining a rate of progression to be *excessive* when it simply exceeds average normal aging rates, as has been done in this study, may produce insufficient specificity in everyday clinical use. Instead, perhaps progression rates should only be considered to be outside normal limits when they exceed, *e.g.*, the fastest 5% of observed normal aging rates, which would be consistent with our treatment of other diagnostic metrics.
4. Regardless, this is timely and important work, and the idea of combination analysis, be it perimetry plus OCT – or simply complementary combinations of, e.g., OCT metrics2 – cries out for practical clinical implementation.

Defining a rate of progression to be *excessive* when it simply exceeds average normal aging rates, as has been done in this study, may produce insufficient specificity in everyday clinical use

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Nailfold capillaroscopy

Comment by Alon Harris, Indianapolis, IN,USA

77007 Resting nailfold capillary blood flow in primary open-angle glaucoma; Cousins CC, Chou JC, Greenstein SH, Brauner SC, Shen LQ, Turalba AV, Houlihan P, Ritch R, Wiggs JL, Knepper PA, Pasquale LR; British Journal of Ophthalmology 2018; 0:

Vascular dysfunction in glaucoma has been well documented in a generalized sense, but consensus regarding the specificity of biomarkers and their ability to predict glaucoma status remains elusive. Distinguishing a primary perfusion deficit from a secondary reduction of blood

flow due to intraocular pressure (IOP) and/or localized tissue loss is a critical consideration in determining the influence of vascular dysfunction on a person's overall risk for the development and progression of glaucoma.

A significant strength of the current study is the identification of altered hemodynamics in glaucomatous optic neuropathy that was independent of covariates such as IOP, blood pressure, pulse and/or ocular tissue loss

Cousins *et al.* present evidence of systemic vascular dysfunction as a predictor for glaucomatous status. Utilizing a modality originating over 25 years ago as presented by Gasser and Flammer, the authors identified reduced resting nailfold capillary blood flow in persons with primary open-angle glaucoma compared to healthy controls. Specifically **they found that every picolitre per second increase in resting nailfold blood flow was associated with a 6% (95% CI 0.92 to 0.96) reduced odds of POAG ($p < 0.0001$)**. A significant strength of the current study is the identification of altered hemodynamics in glaucomatous optic neuropathy that was independent of covariates such as IOP, blood pressure, pulse and/or ocular tissue loss. The author's data builds upon the previous findings of Gasser and Flammer who identified reduced blood flow velocity in normal tension glaucoma patients that was especially evident following a cold provocation. However, a weakness of the current, as well as historical, studies is the cross sectional design which limits the ability to determine the influence on glaucoma progression. Another limitation is the lack of a modality to directly measure ocular blood flow, such as optical coherence tomography angiography, which might help confirm if nailfold flow reductions correspond to optic nerve perfusion reductions in glaucoma subjects. In summary, the authors present important novel data confirming systemic vascular dysfunction in glaucoma independent of traditional clinical covariates. However, it is important to stress the need for large sample longitudinal studies to confirm the utility of vascular biomarkers in determining not only glaucoma disease status, but also predicting disease progression.

OCT-A and macular region OCT

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

77216 Optical Coherence Tomography Angiography compared with Optical Coherence Tomography Macular measurements for detection of glaucoma; Wan KH, Lam AKN, Leung CK; JAMA ophthalmology 2018; 0:

OCT has been widely used to detect glaucomatous structural damage in the parapapillary and macular region. OCT angiography (OCT-A) visualizes the capillary networks in different layers of the retina. Studies have shown that the vessel density as measure by OCT-A is decreased in glaucomatous eyes compared to healthy eyes. This opens the possibility that OCT-A can be used as a tool to diagnose glaucoma. Wan *et al.* compared the diagnostic performance for detection of glaucoma and the structure-function association between that inner macular vessel density and inner macular thickness. At 90% specificity, the sensitivity of mean inner macular thicknesses for detection of glaucoma was greater than that of mean inner macular vessel densities. In addition, the strength of the structure-function association was stronger for mean inner macular thickness than mean inner macular vessel density. **Another noteworthy finding is that 102 and 19 participants were excluded due to poor quality OCT-A and OCT images, respectively.** The result of this study contrasts with previous studies which showed a higher or similar diagnostic performance of the inner macular thickness compared with the inner macular vessel density for detection of glaucoma.[1-3] The reason of the discrepancy is not clear. One possible source is the application of customized software in this study to standardize the macular area and the macular layers with exclusion of the fovea to compare the diagnostic performance between inner macular vessel density and inner macular thickness, while previous studies used the default setting to define the macular area and layers. Based on the current data and considering the higher frequency of poor quality image for OCT-A, it can be regarded that OCT-A does not have a distinct advantage over OCT for diagnosing glaucoma in its current version.

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Forms of Glaucoma

Low perfusion pressure and NTG progression risk

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

76600 Low nocturnal diastolic ocular perfusion pressure as a risk factor for NTG progression: a 5-year prospective study; Raman P, Suliman NB, Zahari M, Kook M, Ramli N; Eye 2018; 0:

Raman *et al.* investigated the predictive value of simultaneous 24-hour intraocular pressure (IOP) and blood pressure (BP) monitoring on visual field progression in normal-tension glaucoma (NTG) patients followed for a minimum of five years. They defined NTG based upon the presence of manifest glaucoma, open angles, and all IOP measurements prior to 24-hour monitoring not exceeding 21 mmHg during office-hours with Goldmann applanation tonometry.

Before coming to the sleep lab, patients underwent a wash-out period and the 24-hour curves were performed on no anti-glaucoma medications. This was done to rule out IOP peaks and misclassification of NTG. IOP and BP measurements were performed every two hours – in the sitting position during the diurnal period and in the supine position during the nocturnal period. Anti-glaucoma medications were re-started after the curves and continued (sometimes modified) during follow-up. In addition, they classified severity based upon the AGIS criteria and defined visual field progression using the modified Anderson criteria as a function of baseline severity. Survival analyses with Kaplan-Meier curves and Cox proportional hazards regression were used to test the association between BP and IOP parameters and an event-based visual field progression endpoint during follow-up.

They found that 35% of patients progressed over the study period with an average mean sensitivity slope of −0.70 ± 1.1 dB/year. In the multivariable analysis, the main predictor of visual field progression was nocturnal diastolic ocular perfusion pressure, which was defined as the difference between the mean diastolic BP and the mean IOP during sleep. **Interestingly, they also found that eyes with central field visual field defects at baseline had a 3.5 higher risk of progression than those without it.** The main finding, however, was that **the cumulative probability of non-progression was 38% at 60 months in patients with diastolic ocular perfusion pressure < 35 mmHg and 88% in those with DOPP > 43.7 mmHg, which translates to a 2.3-fold higher risk among those with lower perfusion** (P = 0.01).

The study adds to the current evidence of a strong association between BP, particularly nocturnal BP dips, and glaucoma progression

The study was well-designed and included a very rich database, as many previous studies did not include simultaneous 24-hour IOP and BP monitoring at baseline. Moreover, other studies did not follow all patients for such a long period (five years). The study adds to the current evidence of a strong association between BP, particularly nocturnal BP dips, and glaucoma progression.

One limitation, however, is that the **24-hour IOP monitoring was done after wash-out, thus we cannot infer whether the ocular perfusion estimates reflect the actual perfusion status over the course of follow-up on anti-glaucoma treatment.** Therefore, the actual ocular perfusion pressure estimates were likely higher (*i.e.*: not as severe) than what the study reported during the five years patients were treated. Nonetheless, the study provides compelling evidence that patients with NTG may benefit from 24-hour BP monitoring.

Another interesting finding was the lack of association between BP treatment and visual field progression. Studies have shown that certain types of drugs – and sometimes excessive treatment – could be detrimental to glaucoma patients. Testing or confirming this hypothesis is challenging, however, as studies often lack information on duration of treatment and treatment changes during follow-up. One suggestion to the authors would be to investigate the interaction between drug classes and BP parameters and their association with visual field progression.

The authors should be congratulated for their study and for helping elucidate the relationship between BP, IOP, and glaucoma progression. We now have overwhelming evidence to support future clinical trials testing the hypothesis that BP could be a new modifiable risk factor in glaucoma.

OCT-A in myopia-associated glaucoma

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

76868 Association of myopia with peripapillary perfused capillary density in patients with glaucoma: An Optical Coherence Tomography Angiography Study; Suwan Y, Fard MA, Geyman LS, Tantraworasin A, Chui TY, Rosen RB, Ritch R; JAMA ophthalmology 2018; 136: 507-513

Individuals with myopia are at an increased risk of developing primary open-angle glaucoma (POAG). Because of the anatomic traits of myopic eyes, characteristic features of glaucoma seen in these eyes differ from glaucomatous features of non-myopic eyes. **Axial elongation of the eye causes a temporal shift of the superior and inferior arcuate RNFL bundles as well as the major retinal vessels**.[1,2] Therefore, it may be hypothesized that the pattern of retinal vasculature, as assessed by OCT angiography (OCTA), may also be different in glaucoma patients with myopia compared to those without myopia.

In a recent OCTA study, Suwan *et al.* have examined the peripapillary perfused capillary density (PCD) in 87 myopes with glaucoma (M+G+), 93 non-myopes with glaucoma (M-G+), 17 myopes without glaucoma (M+G-) and 51 non-myopes without glaucoma (M-G-).[3] For the purpose of the study, myopes were defined as those with a spherical equivalent of less than -3.0 D. **Since most of the participants in the study were over the age of 60 years, their refraction may have been influenced by lenticular changes or pseudophakia,** the details of which are not provided by the authors. Hence, definition of myopia based on axial length might have been more appropriate.

The results showed mean global PCD demonstrated a progressive decrease from the M^-G^- group (41.0%), to the M^+G^- group (38.4%), to the M^-G^+ group (31.9%), to the M^+G^+ group (28.2%; all $P < 0.001$).[3] A similar pattern was seen in the sectoral PCD measurements. The results also showed that the reduction in peripapillary PCD was greater due to glaucoma compared to myopia. **The authors concluded that the simultaneous presence of myopia and glaucoma results in a level of microvascular attenuation greater than is observed with either pathology alone.**

Multiple factors can influence the PCD measurements of OCTA. A previous study has shown that signal strength index of the OCTA scans can affect PCD measurements.[4] In addition, topical anti-glaucoma medications may also affect the OCTA measurements. The results would have been more robust had the authors accounted for all these confounders in their study.

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Glaucoma post-corneal-transplantation


Comment by Tanuj Dada and Neha Midha, New Delhi, India

77105 Risk of glaucoma surgery after corneal transplant surgery in medicare patients; Zheng C, Yu F, Tseng VL, Lum F, Coleman AL; American Journal of Ophthalmology 2018; 0:

In a retrospective (2010-2013) cohort study, Zheng *et al.* evaluated a 5% random sample of medicare beneficiaries aged 65 years or above and reported on risk of glaucoma surgery within one year of corneal transplant surgery (CTS) from 3098 patient files (1310 had baseline Glaucoma – 42%). This included 1919 endothelial keratoplasties (EK), 1012 penetrating keratoplasties (PK) and less than 50 lamellar keratoplasties (ALK) and Keratoprosthesis (KPro) procedures. Rates of glaucoma surgery within one year of any CTS ranged from 6.1% to 9.4% in the corneal transplant groups, without statistically significant differences among groups. However, 10.0% of patients with pre-existing glaucoma required glaucoma surgery following any transplant surgery, compared with 5.3% of patients without preexisting glaucoma. This included 12.4% of PK patients with pre-existing glaucoma compared with 2.8% of PK patients without pre-existing glaucoma.

The three major conclusions from the paper were that (I) **the rates of glaucoma surgery are significantly higher in patients undergoing CTS** as compared to those who do not; (II) there were no significant difference in one year rates of glaucoma surgery between different types of cornea transplant procedures; and (III) pre-existing glaucoma overall increased the chances of glaucoma surgery by two-fold after any CTS and especially after penetrating keraptoplasty (2.8% vs 12.4%, $p < 0.01$) in patients aged more than 65 years.

Although the study reports no difference in rates of glaucoma surgery in eyes undergoing PK/EK versus LK and KPro, the data set for the latter two is quite small and may not be an accurate estimation. One would expect a higher incidence of glaucoma in eyes with KPro, however, eyes which underwent a combined tube with KPro were not included in the analysis. Another issue is that the incidence of glaucoma increases over time and the results are only reported for glaucoma surgery within 12 months of the corneal procedure. A major limitation of the study was that due to problems in coding with ICD9, **it was not possible to ascertain that glaucoma surgery was performed in the eye with corneal transplant or the fellow eye.** There was also no information on eyes undergoing diode laser/endo-cytophotocoagulation which are often performed in eyes with poor visual potential after corneal transplant procedures.

Despite these limitations, the study provides important information on the rates of glaucoma surgery after corneal transplant procedures, and highlights the importance of pre-existing glaucoma as a risk factor for post keratoplasty glaucoma, as well as the need for long-term follow-up with IOP checks and optic disc evaluation in all eyes undergoing any form of corneal transplant surgery.

Diabetes and POAG progression

Comment by Louis Pasquale, New York, NY, USA

76505 Progression of primary open-angle glaucoma in diabetic and nondiabetic patients; Hou H, Shoji T, Zangwill LM, Moghimi S, Saunders LJ, Hasenstab K, Ghahari E, Manalastas PIC, Akagi T, Christopher M, Penteado RC, Weinreb RN; American Journal of Ophthalmology 2018; 189: 1-9

The relation between type-2 diabetes (T2D) and glaucoma-related traits remains controversial. The authors analyzed structural and functional progression in primary open glaucoma (POAG) patients stratified by T2D status in the Diagnostic Innovations in Glaucoma Study cohort. In univariate analysis, **the global retinal nerve fiber loss on Spectral Domain Ocular Coherence Tomography was 0.40 microns/year in the POAG/T2D+ group versus 0.83 microns/year in the POAG/T2D- group (p = 0.01). The difference in the temporal superior quadrant loss (0.33 microns/year vs 1.34 microns/year for the POAG/T2D+ and POAG/T2D- groups, respectively; p = 0.001) was more impressive and would survive conservative corrections for the multiple comparisons of all parameters that were assessed**. The authors report that the differences in structural progression remained significant after correction for age, sex, race, mean IOP during follow-up, baseline mean deviation and hypertension. While a similar trend was found in the visual field parameters, the differences were not statistically significant. Mean follow-up in both groups was comparable: 6.2 years versus 5.6 years in the POAG/T2D+ and POAG/T2D- groups, respectively.

Almost every T2D patient had both eyes enrolled (55 eyes of 32 patients) compared to 142 eyes of 111 patients without T2D. T2D is a systemic disease that would affect both eyes of each patient. Thus, the results from the eyes in the T2D arm are highly correlated with one another and this could have a major impact on study outcome. The study would benefit from having only one eye from each arm enrolled.

71.9% of T2D patients were using metformin. Thus, the geroprotective effect of this drug[1] and not T2D itself, could be mediating the results reported here

Notably, T2D was not associated with more rapid structural progression in this study. *As the authors point out, 71.9% of T2D patients were using metformin. Thus, the geroprotective effect of this drug*[1] *and not T2D itself, could be mediating the results reported here*. More work is needed to explore the relation between T2D and glaucoma-related traits.

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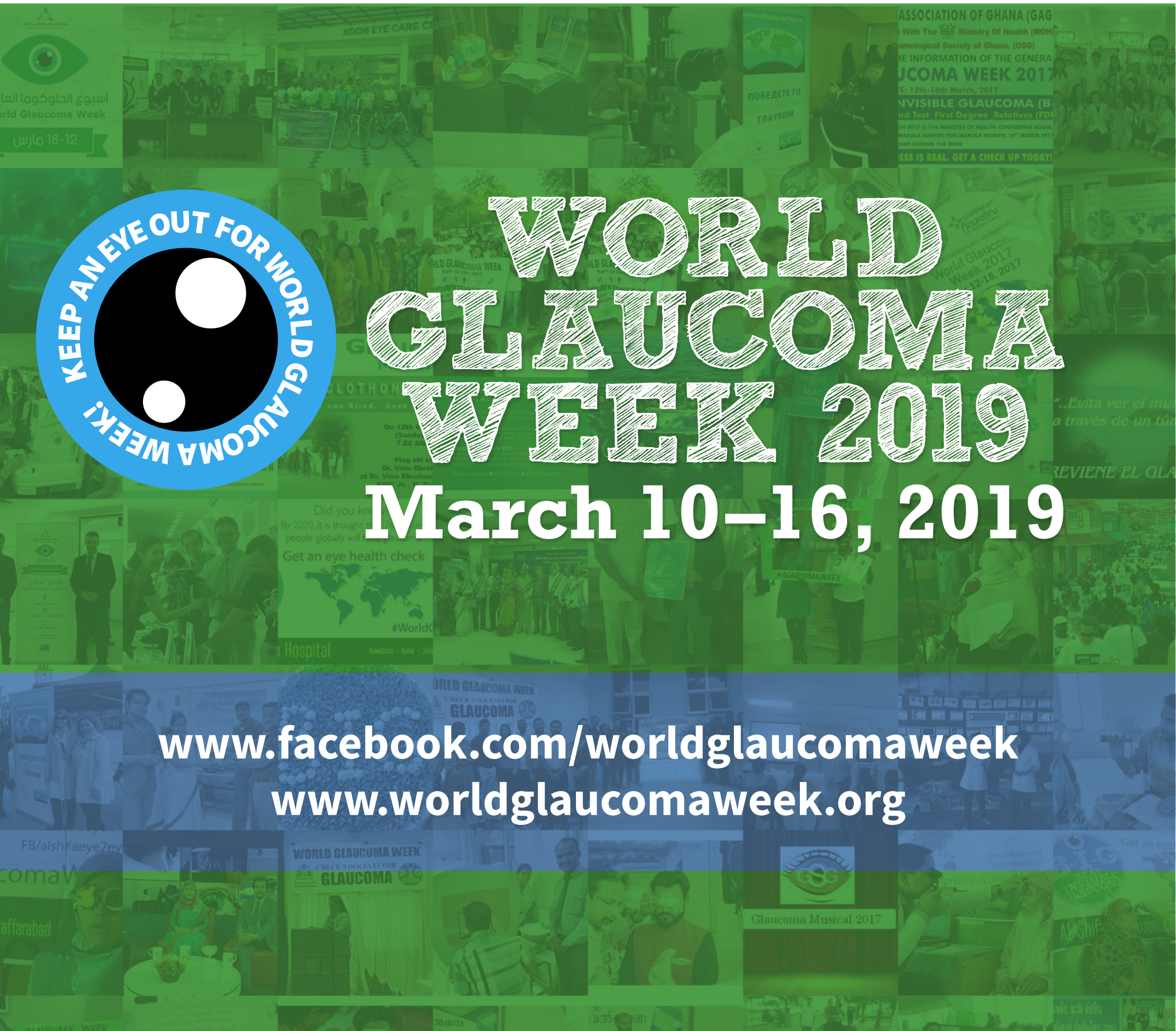

Medical Treatment

Regulating outflow resistance post-Schlemm

Comment by Fotis Topouzis, Thessaloniki, Greece

76886 Pharmacological regulation of outflow resistance distal to Schlemm's canal; McDonnell F, Dismuke WM, Overby DR, Stamer WD; American Journal of Physiology and Cell Physiology 2018; 315: C44-C51

McDonnell and colleagues examined the effect of a potent vasodilator, nitric oxide (NO), and its physiological antagonist, endothelin-1 (ET-1), on the regulation of outflow resistance in the distal regions of the conventional outflow pathway.

Human and porcine anterior segments were perfused in organ culture under constant flow conditions, while intrachamber pressure was continually monitored.

In human anterior segments, 100 nM ET-1 significantly decreased distal outflow facility from 0.49 ± 0.26 to 0.31 ± 0.18(mean ± SD) µl-min-1 mmHg, P < 0.01. Perfusion with 100 µ M diethylenetriamine-NO in the presence of 1n M ET-1 immediately reversed ET-1 effects, significantly increasing distal outflow facility to 0.54 ± 0.35 µ1 min $^{-1}$ mmHg, P = 0.01. Similar results were obtained in porcine anterior segment experiments. The data show a dynamic range of resistance generation by distal vessels in both the human and porcine conventional outflow pathways.

The majority of current daily pharmacological treatments do not target the conventional outflow, but rather target the production of aqueous humor by the ciliary body or drainage through the unconventional outflow pathway. Current glaucoma treatments that target the conventional outflow pathway are often destructive, involve applying laser energy to the Trabecular Meshwork (TM) tissues or surgical removal/bypass of the TM and inner wall of Schlemm's Canal.

This study provides data on the outflow resistance of the conventional pathway and specifically of the distal vasculature, including collector channels, aqueous veins, and intrascleral venous plexus.

Increasing knowledge in distal conventional outflow resistance would be very valuable. **Potential treatment development targeting distal conventional outflow would provide an innovative approach in glaucoma management.**

Preventing ocular surface disease in prostaglandin-treated patients

Comment by Esther Hoffman, Mainz, Germany

77008 Effect of a punctal plug on ocular surface disease in patients using topical prostaglandin analogues: a randomized controlled trial; Sherwin JC, Ratnarajan G, Elahi B, Bilkiewicz-Pawelec A, Salmon JF; Clinical and Experimental Ophthalmology 2018; 0:

It is well known that antiglaucomatous eye drops – whether they are with or without preservatives – may influence ocular surface integrity tremendously. Many glaucoma patients complain dryness, hyperemia and foreign body sensation while using their eye drops.

Sherwin and colleagues performed a randomized clinical trial and included 60 patients under prostaglandin antiglaucomatous therapy of whom 48 participated in the trial. Punctal plugs were applied in one eye (inferior punctum), leaving the fellow eye as control. The following parameters were observed over a period of six weeks: Ocular surface disease index (OSDI- questionnaire), tear-film breakup time (TF-BUT), Oxford Cornea score, tear osmolarity and intraocular pressure were compared at baseline and six weeks by masked investigators. The results showed that the objective and subjective parameters improved over time.

A small but statistically significant influence on IOP values was measured between eyes that received punctal plugs (lower IOP) and eyes that received no plugs (higher IOP).

Although the study had a small sample size and the effects between the two eyes were possibly not clinically significant, there is, however, an association between occlusion of punctums and better objective and subjective status of ocular surface disease.

Patient acceptance of sustained-release glaucoma medications

Comment by Steve Mansberger, Portland, OR USA

76539 Patient acceptance of sustained glaucoma treatment strategies; Varadaraj V, Kahook MY, Ramulu PY, Pitha IF; Journal of Glaucoma 2018; 27: 328-335

Varadaraj and colleagues surveyed patient acceptance of sustained delivery of ocular hypotensive therapies. Sustained delivery may be an important method to treat glaucoma considering poor adherence with ocular hypotensive eye drop medications.[1] Yet, there is a paucity of information on patient acceptance of sustained therapies currently undergoing investigation. The researchers administered electronic surveys to 163 participants from two sites: Johns Hopkins University (JHU) and University of Colorado. **The majority of participants would accept sustained-delivery therapies [contact lenses (59%), ring inserts (51%), punctal plugs (57%) or subconjunctival injections (52%)] in order to avoid surgery. They found similar acceptance if sustained therapies were deemed more effective than drops (range 47% to 56%), and lower acceptance when they would reduce or eliminate drops (range 23% to 42%). Patients most often preferred contact lenses and punctal plugs.**

The study did not evaluate the association between severity of glaucoma and acceptance of sustained therapy. One could theorize that those patients needing surgery would be more likely to accept a sustained therapy. Because the study was located at tertiary referral centers, the authors suggest that the study populations may not be representative of all glaucoma patients. Interestingly, the study found differences in acceptance rates between study sites (Colorado participants were less likely (0.48 times the odds, p = .01 in multivariable model)) of JHU participants to accepting sustained delivery therapy. Examining this difference may uncover differences in severity of glaucoma, different practice patterns, or acceptability of 'usual' vs. 'new' treatments. Overall, this study suggests that sustained delivery of glaucoma medications may be an accepted treatment in the majority of glaucoma patients if it was more effective than drops or helped them avoid surgery.

Sustained delivery of glaucoma medications may be an accepted treatment in the majority of glaucoma patients if it was more effective than drops or helped them avoid surgery

Surgical Treatment

Goniotomy-assisted trabeculotomy

Comment by Sameh Mosaed, Irvine, CA, USA

76848 Gonioscopy-assisted transluminal trabeculotomy: An ab interno circumferential trabeculotomy: 24 months follow-up; Grover DS, Smith O, Fellman RL, Godfrey DG, Gupta A, Montes de Oca I, Feuer WJ; Journal of Glaucoma 2018; 27: 393-401

In the May 2018 issue of *Journal of Glaucoma,* Grover *et al.* published the 24-month results of the GATT procedure in their article entitled, 'Gonioscopy-assisted Transluminal Trabeculotomy: 24 Months Follow Up.' This is a follow-up to the 2014 study published in *Ophthalmology* that presented the initial results of the procedure, and includes data from patients in that publication, but also includes additional subjects and longer-term follow-up. This is a retrospective chart review of 198 patients who had at least 18-month follow-up data, with most achieving 24-month follow-up. The authors provide data for the entire group, as well as for six subcategories: POAG with no prior CE, POAG combined with CE/IOL, POAG with prior CE/IOL, secondary open-angle glaucoma (SOAG) with no prior CE, SOAG combined with CE/IOL, SOAG with prior CE/IOL. The POAG group had a 9.2 mmHg reduction in IOP, representing a 37.3% reduction from baseline. The SOAG group had a 14.1 mmHg reduction in IOP, representing a 49.8% reduction from baseline. **Of all the groups, the pseudophakic POAG group had the highest proportion of failure. This was thought to be the result of having a higher proportion of advanced glaucoma patients in this group, with lower target IOP, resulting in more re-operations for IOP control.** As a result, the authors suggest considering an alternative treatment if the HVF MD is worse than -15 dB. **This finding that patients with more advanced glaucoma tended to do substantially worse with GATT when compared to patients with mild to moderate glaucoma is postulated to result from downstream collector channel and intrascleral plexus sclerosis in these advanced POAG patients.** This finding is somewhat contradictory to some studies published on other trabecular bypass procedures, such as a recent study by SF Ahmed *et al.* showing that IOP reduction and overall success following Trabectome was relatively similar in advanced cases as compared to early disease. However, comparisons between these studies are impossible to draw, given the retrospective nature and variable reporting standards. Larger controlled, prospective studies on trabecular bypass procedures will help elucidate patient populations that benefit most from these interventions.

The authors report that hyphema was the most common complication, occurring at a rate of about 30% within the first week, with nearly all cases resolving by 30 days post op. The evolution of the surgical technique and decision-making resulting from the author's initial experience include:

leaving a modest amount of viscoelastic in the anterior chamber to reduce large hyphema from hypotony, and considering the inability to discontinue anticoagulants as a contraindication to GATT.

One key issue that Grover *et al.* touch upon in this paper is that when the GATT is performed using a thermally-blunted 5-0 prolene suture, the cost of the suture is only 5$. This is in stark contrast to the other trabecular bypass procedures where implants or required disposables cost several hundreds of dollars per case. In a strained global healthcare delivery environment, development and optimization of such a low-risk, inexpensive surgical option such as the GATT is imperative, and these results are highly encouraging.

Development and optimization of such a low-risk, inexpensive surgical option such as the GATT is imperative, and these results are highly encouraging

Effect of Mitomycin C on corneal endothelial cell loss

Comment by Jose-Maria Martinez de la Casa, Madrid, Spain

76854 Comparison of mean corneal endothelial cell loss after trabeculectomy with and without Mitomycin C; Shaheer M, Amjad A, Ahmed N; Journal of the College of Physicians and Surgeons Pakistan 2018; 28: 301-303

Trabeculectomy has been the gold-standard surgery for glaucoma since the mid-20th century. Its results have been improved by the use of antimetabolites, especially Mitomycin C (MMC). However, MMC has been linked to multiple adverse effects including the decreases in endothelial cellularity.

MMC has been linked to multiple adverse effects including the decreases in endothelial cellularity

In this article, Shaheer *et al.* studied the endothelial cell loss produced by the use of MMC as an adjuvant to trabeculectomy in a prospective and randomized study. They compared two groups of 30 patients each with primary open-angle glaucoma who underwent a trabeculectomy for the first time. In one of the groups, MMC was used and in the other one not. The conclusion of the study was that the use of **MMC produced a three times higher endothelial cell loss 283**

(66.50) vs 72.50 (19.25) cel / mm^2 (p < 0.001). This loss represented a decrease of 12.4% in the MMC group and 3.2% in the control group, without the authors specifying when the measurements were made along the postoperative period.

These results are in line with previous studies[1-3]. Sihota *et al.*[1] studied three groups of patients who were operated on trabeculectomy. They found that the endothelial cell loss was 3.73% (2.73) in the group without MMC and 13.9% (4.7) and 14.5% (7.8) in the MMC groups 0.2 mg/ml and 0.4 mg/ml respectively. Storr Paulsen *et al.*[2] found a decrease of 9.5% and 10% at 3 and 12 months after surgery, showing that the cytotoxic effect of MMC on the endothelium is limited to the moment of surgery and the immediate post-partum without a progressive loss later.

The use of MMC should therefore be extremely careful both in concentration and exposure time and always trying to minimize the passage of it to the anterior chamber to avoid its cytotoxic effects on the endothelium.[4]

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Can ARBs inhibit fibrosis?

Comment by Ernst Tamm, Regensburg, Germany

76926 Inhibitory effects of angiotensin II receptor blockade on human tenon fibroblast migration and reactive oxygen species production in cell culture; Kim D, Pattamatta U, Kelly E, Healey PR, Carnt N, Zoellner H, White AJR; Translational vision science & technology 2018; 7: 20

There is considerable evidence showing that the renin angiotensin system (RAS) is not limited to its endocrine physiologic role controlling blood pressure, electrolytes, and fluid homeostasis. In addition, it plays an important role in wound healing, fibrosis, and inflammation.

Renin angiotensin system plays an important role in wound healing, fibrosis, and inflammation

The principal effector of the RAS, angiotensin II, acts mainly via the angiotensin receptor 1 (AT1R). Kim an coworkers followed up on the hypothesis that the RAS is involved in postoperative wound healing in the human eye, and that its blockade may modulate fibroblast activity in the context of postoperative wound healing in glaucoma filtration surgery. The authors investigated the effects of angiotensin receptor blockade on the migration of human Tenon fibroblasts (HTF), using Irbesartan, an angiotensin II receptor type 1 (AT1R) blocker (ARB) as a potential antifibrotic agent in glaucoma filtration surgery. In HTF cell cultures **Irbesartan inhibited HTF migration by 50% to 70% compared to controls**. Irbesartan reduced cell numbers by 50%. Conversely, angiotensin II increased cell numbers up to four-fold while retaining cell viability. All in all, the findings are in line with previous studies showing that **Losartan, the first approved AT1R blocker attenuates scar formation after trabeculectomy and that Olmesartan, another angiotensin receptor blocker (ARB), also inhibits fibroblast proliferation.** This elegant study clearly suggests a potential therapeutic strategy using AT1R blocker after filtration surgery, an approach that is certainly worthwhile to pursue. Having said this, it should be taken into account that the study is currently limited in its nature as it is only based on cell culture experiments. Clearly, wound healing after trabeculectomy is a process that is under the influence of a multitude of factors including not only HTF but also cells of the immune system, factors released from aqueous humor or blood vessels and many more. The next logical step is now to bring those culture experiments to an experimental level that investigates the effects of Irbesartan in the living eye.

The next logical step is now to bring those culture experiments to an experimental level that investigates the effects of Irbesartan in the living eye

Miscellaneous

Digital technology, online resources and treatment adherence

Comment by Ivan Goldberg, Sydney, NSW, Australia

76984 Access to and experiences with e-health technology among glaucoma patients and their relationship with medication adherence; Newman-Casey PA, Killeen OJ, Renner M, Robin AL, Lee P, Heisler M; Telemedicine Journal and E-Health: the Official Journal of the American Telemedicine Association 2018; 0:

'As online health information becomes common, it is important to assess patients' access to and experiences with online resources,' state Dr Newman-Casey and co-workers as they set out to determine glaucoma patient use of internet information strategies and to test whether or not such usage links with medication adherence.

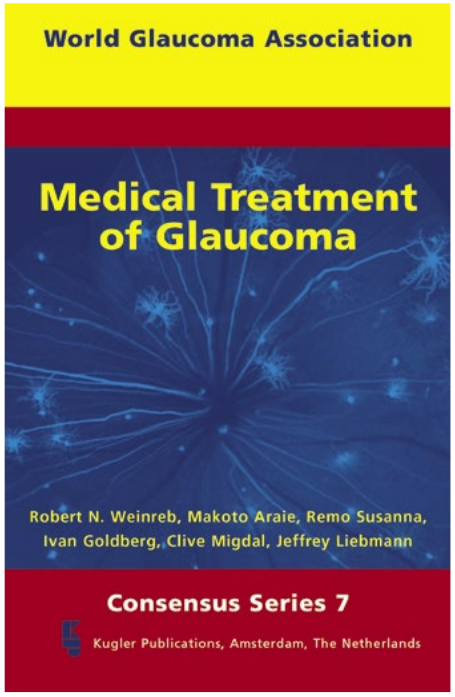
In this prospective survey, the authors recruited 164 glaucoma patients prescribed at least one topical medication from two glaucoma clinics (in Ann Arbor, Michigan and Baltimore, Maryland). Patients completed a questionnaire that covered demographics (age, sex, location, level of education), disease characteristics (duration of glaucoma treatment, number of glaucoma medications, number of other chronic medical conditions as well as subjective assessment of overall health and vision status), self-reported adherence to their glaucoma treatment and technology usage (access to the internet at home, frequency and usage of the internet, use of a smart phone along with use of technology to access glaucoma information or at least interest in such access).

With a mean age of 66 years, results from this glaucoma patient cohort included: 26% self-reported non-adherence, older patients were more likely to be adherent and there was no demonstrated association between technology use and adherence. Unsurprisingly, older patients were less likely to access the internet or to use cell phones and were less likely to wish to receive information about glaucoma via emails, text messages or through the internet. Of particular interest, **those patients who self-reported poorer adherence were more likely to have had a negative experience the last time they had searched for glaucoma resources on-line and/or to have been confused by the material accessed.** Reported too was the lack of *emotional* support patients received if and when they used internet access.

An increasing proportion of glaucoma patients wish to expand their understanding of their condition online but yet are not being guided by their ophthalmologists to helpful, worthwhile and quality internet resources

While accepting their study's limitations (self-reported, patient cohort a convenience sample, absence of chart verification or determination of glaucoma severity), the authors note an increasing proportion of glaucoma patients wish to expand their understanding of their condition on-line and yet are not being guided by their treating ophthalmologists to helpful, worthwhile and quality internet resources. They stress the opportunity awaiting us all to continue to develop and to guide our patients towards such sites.

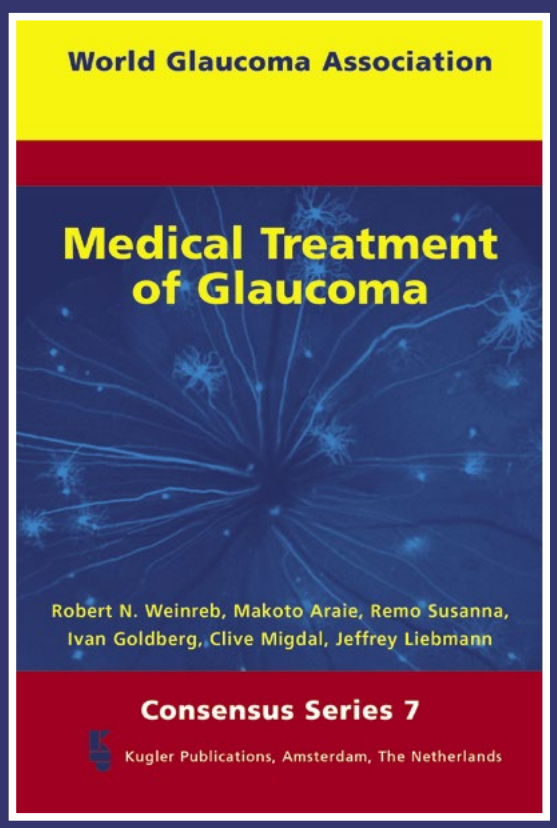
Consensus 7 - Medical Treatment of Glaucoma



edited by: R.N. Weinreb, M. Araie, R. Susanna Jr, I. Goldberg, C. Migdal and J. Liebmann
2010

Medical Treatment of Glaucoma is the topic of the seventh World Glaucoma Association Consensus. Medical treatment of glaucoma continues to be at the core of glaucoma management. Hence, the results of this report will have broad and significant impact on glaucoma research and clinical practice.

The global faculty, consisting of leading authorities on the clinical and scientific aspects of medical management, met in Fort Lauderdale on May 1, 2010 to discuss the reports and refine the consensus statements.



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Robert N. Weinreb
Consensus Initiative Chair
World Glaucoma Association

Consensus 7 - Table of contents

SUMMARY CONSENSUS POINTS - 2010

Section 1 – Visual function progression

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

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

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

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

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

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

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

Event analysis: is change from baseline greater than a predefined threshold; the threshold is based on test retest variability (according to level of damage).
Trend analysis: determines the rate of change over time; the significance is determined by the variability of the measurement and the magnitude of change.

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

Measure the rate of visual field progression

14. Clinicians should aim to measure the rate of VF progression.
    Comment: Estimating the rate of progression is invaluable for guiding therapeutic decisions and estimating the likelihood of visual impairment during the patient's lifetime.

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

Pay attention to examination quality

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

Use the same threshold test

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

Clinical trials

25. Event analyses aim to identify a statistically significant difference between study arms and not necessarily a clinically significant difference.
    Comment: As glaucoma is a chronic progressive disease and progression is generally linear, small amounts of progression that reach statistical significance become larger, clinically significant amounts of progression if there is no additional therapy.
26. Rate analyses of VF indices are an appropriate statistical approach to identify differences between treatment groups.

Comment: Rate analysis methods have been used often in trials for other chronic progressive diseases, such as dementia.

27. Difference in the progression 'event' criterion applied in the various clinical trials limits comparison of the incidence of progression determined in those trials.
    Comment: Comparison of groups in different clinical trials is also hampered by mismatch of subjects with regard to stage of glaucoma, quality of visual field exams, and other traits.

Research needs

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

Section 2 – Structure

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

1. Serial optic disc stereo-photography and RNFL photography are valuable and enduring methods for monitoring structural progression.
   Comment: Stereoscopic clinical examination of optic disc and RNFL may be useful to detect change in comparison with a baseline photograph.
   Comment: Subjective estimates of cup/disc ratio only detect large changes in cupping and are insufficient for monitoring structural changes.
2. Color fundus photography is the preferred imaging modality to identify disc hemorrhages and parapapillary atrophy.
   Comment: Disc hemorrhages and beta-zone PPA are known risk factors for glaucoma progression.
3. Changes in beta-zone parapapillary atrophy can signal glaucoma progression.

Comment: Methods for evaluating changes in PPA require further validation and include fundus photography, CLSO, and SDOCT.

4. Several imaging instruments, including confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography objectively provide reproducible measurements and quantitative assessment of the optic disc and RNFL change.
   Comment: The detection of glaucoma progression by comparing sketches or descriptions of cup disc ratio in the clinical chart is generally not suitable for an early detection of progression and may be replaced by imaging techniques and/or optic disc photography.
   Comment: Imaging instruments provide progression detection analyses that can determine whether change is greater than the measurement variability of an individual eye.
5. There are several structural components of longitudinal change detection that likely contribute to the variability of measurements.
   Comment: These include variation in clinical disc margin visibility, intersession variation and accuracy of segmentation algorithms, variation in vascular blood volume and reference plane anatomy, and longitudinal image registration.
6. Image quality can influence our ability to detect structural change.
   Comment: Automated quality indices vary by instrument and are often proprietary with little information available about how they are constructed.
   Comment: Poor quality images can lead to either false positive or false negative results.
   Comment: For patient management decisions, clinicians should review the quality of images included in glaucomatous progression assessment.
7. More than one good quality baseline image facilitates progression analysis.
   Comment: Some instruments automatically acquire several baseline images during one imaging session.

2.2 Reproducibility of digital imaging instruments

1. Measurement variability influences the ability of any device to detect progression.
   Comment: There is a wide range of reproducibility estimates in the literature for SLP, CSLO, and OCT. Although studies of comparisons of instruments within the same patient populations are limited, these techniques likely provide data of similar reproducibility.
   Comment: Overall, SDOCT has better reproducibility than TDOCT.
2. There is a lack of consensus in the literature as to whether reproducibility changes across disease severity and this may vary across measured anatomic structures and techniques.

2.3 How to detect and measure structural change?

1. Event and trend based analyses are both useful for change detection.
   Comment: These analyses do not always concur.
2. It is important to estimate the rate of structural progression for clinical management decisions.
   Comment: The rates of change obtained from measurements from optic disc, RNFL and macular parameters may vary from each other.
3. Quantitative assessment of optic disc and retinal nerve fibre layer (RNFL) with imaging instruments is useful and complementary for change detection.
   Comment: Data are limited on whether macular measurements may be useful for change detection.
4. Differences in technologies and scan protocols could influence the detection of progression even when the same structure is measured.

5. There is no clear consensus on which instruments or parameters are optimal to detect structural progression. As technologies evolve, new instruments and parameters which are clinically useful will emerge.

2.4. How to define clinically significant structural change?

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

2.5 Issues in clinical practice

1. The optimal frequency of imaging tests is unknown.
   Comment: It depends on the severity of the disease and on the expected speed of progression.
2. In longitudinal studies investigating optic disc and RNFL progression in glaucoma, imaging tests have been performed once a year to three times a year.
3. The same structural measures (*e.g.* RNFL thickness) obtained with different instruments from the same manufacturer or the same technology from different instrument manufacturers (*i.e.*, spectral domain OCT) are not necessarily interchangeable for progression assessment.
4. Structural assessment of change is a valid method for detection of glaucomatous progression in a clinical trial.
   Comment: structural change has been shown to be predictive of future functional loss in glaucoma.

Section 3 – Structure and function

1. Both optic nerve structure and function should be evaluated for detection of glaucomatous progression.
2. Currently, no specific test can be regarded as the perfect reference standard for detection of glaucomatous structural and/or functional progression.
3. Progression detected by functional means will not always be corroborated using structural tests, and vice-versa.
   Comment: This is due to the imperfect nature of testing analysis, individual variability, and the structure-function relationship.
4. The use of standard automated perimetry as the sole method for detection of change may result in failure to detect or underestimate progression in eyes with early glaucomatous damage.
   Comment: In glaucoma suspect or ocular hypertensive eyes with initially normal achromatic perimetry, a change in optic nerve structure (*e.g.*, optic topography, retinal nerve fiber layer, optic disc hemorrhage, or parapapillary atrophy) may occur before perimetric change.
5. In general, detection of progression is more difficult in eyes with advanced disease.
   Comment: In eyes with advanced visual field damage, alternative perimetric strategies (*i.e.*, larger stimulus, macular strategies, kinetic perimetry, etc.) may need to be employed.

6. A statistically significant change in structure and/or function (which takes age and variability into account) is not always clinically relevant.
   Comment: Its clinical relevance for patient management must take into account other risk factors and lifetime risk of visual disability.
7. Progressive structural changes are often but not always predictive of future development or progression of functional deficits in glaucoma.
   Comment: The predictive strength depends on the method used to assess structural/functional change.
8. Corroboration of glaucomatous progression through the use of more than one test may provide more effective and more rapid detection of glaucomatous progression than repeated confirmation of change using a single modality.
   Comment: Examples of corroborative change include structure-function (*e.g.*, a structural change of the optic nerve and a spatially consistent functional change).
9. In order to increase the likelihood of detecting progression, test results should be of sufficient quality and appropriate quantity to provide meaningful information.
   Comment: While adjunctive testing can help clinical decision making, the use of multiple modalities of testing, at the expense of quality and appropriate frequency and quantity, should be avoided.
10. Life expectancy should be considered when evaluating the clinical relevance of a structural and/or functional change in glaucoma.
11. Structural and/or functional testing should be conducted throughout the duration of the disease.

Section 4 – Risk factors

1. Risk factors for glaucoma progression should be ascertained in all patients with glaucoma or suspected of being at increased risk of glaucoma.
2. Clinical risk factor assessment in glaucoma serves two roles. It provides (a) prognostic information; and (b) a basis for disease management.
   Comment: While proof of causality is desirable, the pragmatic nature of clinical medicine allows the use of risk factors of varying evidence quality and even clinical signs to be used in clinical management.
3. The use of risk factors in clinical management should take into account: (a) the strength of the risk factor for disease progression; and (b) the practicality and potential harm of reducing that risk factor.
4. Ocular hypertension is itself a strong risk factor for glaucoma, with rates of progression depending on the presence or absence of other risk factors.
   Comment: Accounting for these risk factors is critical to clinical decision making in the management of OHT patients.
   Comment: Risk factor assessment in OHT helps determine an individual's need for IOP lowering medication and also informs on the frequency of follow up.
5. Risk calculators provide a means for quantifying risk of glaucoma progression in appropriate individuals with similar baseline characteristics to those present in the study.
   Comment: The utility of these risk calculators in clinical practice still needs to be determined.
6. Higher mean IOP is a strong risk factor for glaucoma progression.
   Comment: More studies are needed to evaluate the role of other IOP parameters as risk factors for glaucoma progression.

7. A thinner central cornea is a risk factor for progression in patients with higher baseline IOP.
8. The presence of pseudo-exfoliation syndrome is an independent risk factor for progression.
9. The presence of a disc haemorrhage, older age, and lower ocular perfusion pressure are risk factors for progression.
   Comment: The relationship between low blood pressure and risk of progression is complex.
10. While estimates of risk of progression for individual patients based on completed large clinical trials are available, the use of such estimates varies considerably in clinical practice.
11. There is greater information available regarding the importance of risk factors for progression from early to moderate disease than from moderate to severe disease.
    Comment: Few adequately powered studies have prospectively assessed the risk factors for blindness from glaucomatous disease.
12. The relative importance of risk factors for progression may vary depending upon the stage of glaucomatous disease.
    Comment: Some risk factors that do not appear to be important predictors of progression from early to moderate glaucoma may be relatively more important in predicting progression from moderate to severe disease and vice versa.
13. Studies that longitudinally assess risk factors for functional vision loss and blindness from glaucomatous disease are needed.

Section 5 – Glaucoma and its impact on patient function

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

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News Flashes

- ★ Altered hemodynamics in glaucomatous optic neuropathy are independent of covariates such as IOP, blood pressure, pulse and/or ocular tissue loss
- ★ Defining a rate of progression to be excessive when it simply exceeds average normal aging rates may produce insufficient specificity in clinical use
- ★ The geroprotective effect of this metformin may be protective against glaucoma.
- ★ Sustained delivery of glaucoma medications may become an accepted treatment
- ★ Early glaucoma might not be an asymptomatic disease
- ★ Detection of glaucoma progression is overly reliant on global indices
- ★ An increasing proportion of glaucoma patients wish to expand their understanding of their condition online but yet are not being guided by their ophthalmologists to helpful, worthwhile and quality internet resources

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