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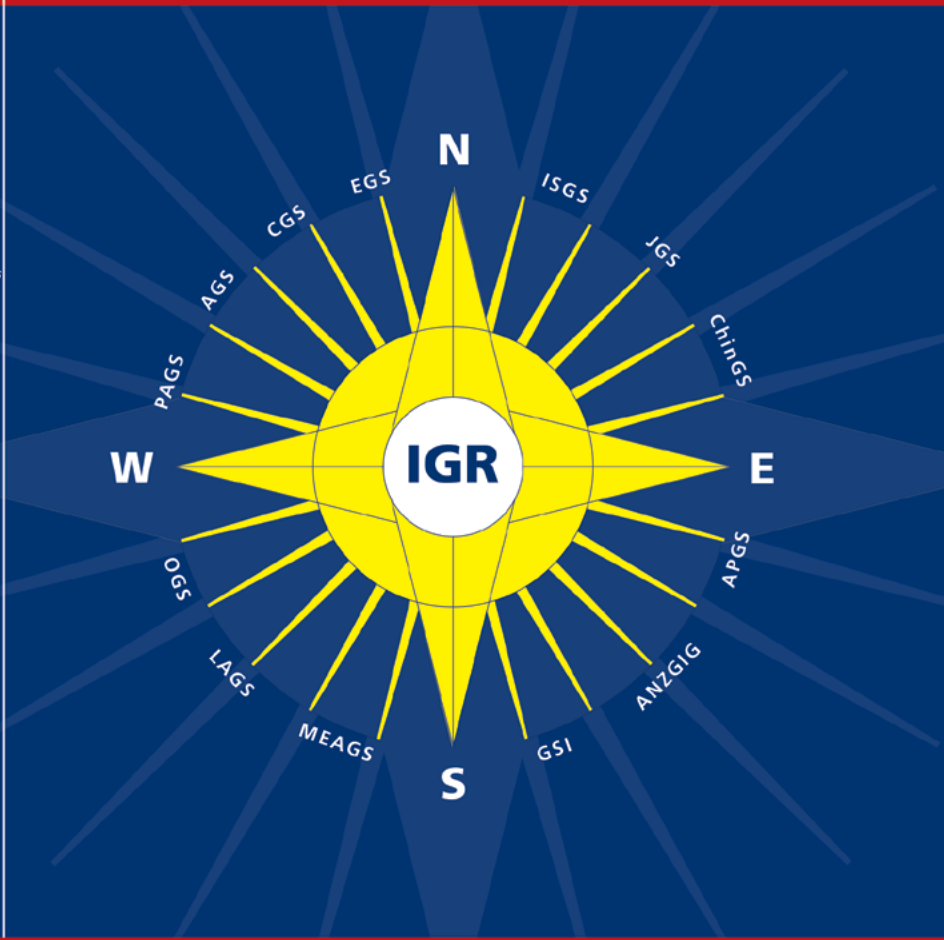

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The 8th World Glaucoma Congress was held from March 27–30, 2019 in Melbourne, Australia

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We welcomed over **2000 ophthalmologists** and allied health professionals from more than **90 different countries**.

The scientific program was a stimulating mix of symposiums, courses, workshops, wetlabs, rapid fire sessions and poster walks covering topics from the basic science and genetics of glaucoma, to the **latest developments** in medical and surgical management of glaucoma.

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We look forward to welcoming you for the next edition, taking place March 24-27, 2021 in Kyoto Japan!

WGA

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From the WGA Executive Office

Dear IGR readers,

We wish to express a special THANK YOU! to all those who contributed to the 8th World Glaucoma Congress! We welcomed over 2000 ophthalmologists and allied health professionals from more than 90 different countries to our biennial congress in Melbourne this year, as well as over 300 patients and family members who attended the Patient Symposium. The scientific program was a stimulating mix of symposia, courses, workshops, wet labs, rapid-fire sessions, and poster walks covering topics from the basic science and genetics of glaucoma to the latest developments in medical and surgical management of glaucoma. Keep a close watch on your inbox for your personal log-in details to check the captured content on the WGA Educational Portal.

The location of WGC-2021 was presented during WGC-2019 by Makoto Aihara, Chair of the Local Organizing Committee. The 9th World Glaucoma Congress will take place from March 24-27, 2021, in Kyoto, Japan. Mark your calendar for WGC-2021, and we hope we can welcome all of you to Kyoto with its rich culture, beautiful temples, and unique culinary scene.

Neeru Gupta (Canada) was recommended for President-Elect 2020-2021 (including renewal of term) to the General Assembly. Moreover, three new governors who will serve a three-year (renewable) term on the Board were presented: Xinghuai Sun (China), Nkiru Kizor-Akaraiwe (Nigeria), and Pradeep Ramulu (USA). Finally, Robert Fechtner (USA) has been recommended to join the WGA Audit Committee as a member. The nominations were made according to the Statutes and Regulations, presented to the Board of Governors and presented for a vote to the General Assembly. All were unanimously approved.

In this edition, we introduce you to Irene Koomans. Irene took over the responsibilities of Mariska van der Veen as the Executive General Manager of the World Glaucoma Association. We wish Irene the best of luck in her new role.

We hope you enjoy reading this first issue of the IGR's 20th volume. You can contact our WGA Executive Office(info@worldglaucoma.org) if you need any information or have questions on IGR or WGA-related matters.

WGA Executive Office

Get to know us!

At WGC-2019 in Melbourne, we said goodbye to Mariska van der Veen who advanced to a new, exciting position at MCI, and welcomed a new WGA Executive General Manager: Irene Koomans.

Having been involved with the WGA as Committee Liaison for the past two years, she has already gained valuable insights in the organization, its core purpose, values and goals.

She's joining the WGA as Executive General Manager at an exciting time with new developments such as 'Meet the Experts' Webinars and the possibility for Patient Organizations to join the WGA, as well as projects that have made their mark and continue to grow, including the Global Outreach Fellowship Program and Online Education Courses for ophthalmologists and patients.

World Glaucoma Association
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Irene brings over ten years of international project management to the WGA and looks forward to helping eliminate glaucoma-related disability worldwide, together with all our dedicated glaucoma specialists and industry members.

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WGA Consensus Series

Robert N. Weinreb

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

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

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

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Your Special Attention For

The current status of glaucoma and glaucoma care in Sub-Saharan Africa
Kyari F, Adekoya B, Abdull MM, Mohammed AS, Garba F
Asia-Pacific Journal of Ophthalmology (Philadelphia, Pa.) 2018; 7: 375-386
Abstract no. 79080

Recent advances in genetically modified animal models of glaucoma and their roles in drug repositioning
Harada C, Kimura A, Guo X, Namekata K, Harada T
British Journal of Ophthalmology 2019; 103: 161-166
Abstract no. 79146

Caffeine and the eye
Yoon JJ, Danesh-Meyer HV
Survey of Ophthalmology 2019; 64: 334-344
Abstract no. 79147

Prevalence of normal-tension glaucoma in the Chinese population: A systematic review and meta-analysis
Zhao J, Solano MM, Oldenburg CE, Liu T, Wang Y, Wang N, Lin SC
American Journal of Ophthalmology 2019; 199: 101-110
Abstract no. 79174

Nutritional supplementation in the treatment of glaucoma: A systematic review
Loskutova E, O'Brien C, Loskutov I, Loughman J
Survey of Ophthalmology 2019; 64: 195-216
Abstract no. 79255

Editor's Selection

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

Robert N. Weinreb, Chief Editor

Epidemiology

Glaucoma and dementia

Comment by Mitchell Lawlor and Paul Healey, Sydney, NSW, Australia

79027 Association of retinal neurodegeneration on optical coherence tomography with dementia: A population-based study; Mutlu U, Colijn JM, Ikram MA, Bonnemaijer PWM, Licher S, Wolters FJ, Tiemeier H, Koudstaal PJ, Klaver CCW, Ikram MK; JAMA Neurology 2018; 75: 1256-1263

With the ongoing development of a range of treatments for dementia, there is a strong imperative to develop non-invasive methods of assessing surrogate endpoints of disease. With the eye as a visible part of the CNS, ocular OCT is a natural candidate. This paper reports a subgroup of the population-based Rotterdam Study investigating outcomes across a diverse range of conditions. The aim was to investigate the association between OCT parameters and prevalent and incident dementia in a population-based study.

A large number of the total cohort were excluded from the analysis; there were relatively large exclusions for those who did not have an OCT or had ungradable imaging; exclusions for ocular comorbidities including retinal changes, glaucoma, high myopia, and optic nerve pathology; and for systemic reasons including history of stroke or other neurological

conditions. Of the 7918 eligible patients, the analysis was performed on 3289 patients (42%) for the optic nerve head parameters, and 2998 patients (38%) for the macula inner retinal layer (38%).

Large exclusions may increase data quality and precision of patient phenotype, but they introduce a potential for bias that may alter the outcomes of analysis. The excluded were in fact significantly different from the included based on age, diastolic BP, use of blood pressure lowering medications, presence of diabetes mellitus, cholesterol parameters, current smoking status and education status.

An association between Ganglion Cell-Inner Plexiform layer thickness and prevalent dementia was reported. However, **the result was borderline at a p = 0.05 level** in a simplified model and non-significant in the full model at this level. The longitudinal analysis was based on a very small number of individuals who developed new dementia throughout the study period. A thinner retinal nerve fiber layer at baseline was associated with increased risk of developing dementia over the study period (adjusted HR, 1.43 [95% CI, 1.15-1.78]) with a $p < 0.001$. This was only found with the retinal nerve fiber layer, not with other inner retinal layers.

The prevalence data has to be interpreted with some caution given the large number of exclusions and the p value. While a p value cut-off of 0.05 is fine for a small clinical study, it is rather too generous for a study of 3000 subjects. Borderline significance at this level suggest at least a great deal of noise in the data signal and at most a chance finding. The longitudinal data has a more appropriate p value and a good rate of follow-up, making these exclusions are less relevant. There does appear to be an association between a thinner retinal nerve fiber layer at baseline and developing dementia, but this would need to be confirmed in larger, appropriately designed studies.

Borderline significance at this level suggest at least a great deal of noise in the data signal and at most a chance finding

The eye is a part of the CNS and so it remains very plausible that OCT can inform on CNS disease, however, further studies will be required to clarify more precisely the nature of that information.

Quality of Life

When does disability appear?

Comment by Pradeep Ramulu, Baltimore, MD, USA

78887 What is the amount of visual field loss associated with disability in glaucoma?; Jammal AA, Ogata NG, Daga FB, Abe RY, Costa VP, Medeiros FA; American Journal of Ophthalmology 2019; 197: 45-52

What level of visual impairment is required to cause disability? Typically, this question has been answered by relating disease severity to disability measures, or simply by using convenient numerical cut-offs. Jammal and colleagues take a different approach: they used latent class analysis (LCA) on NEI-VFQ questionnaire data from 263 individuals and found their analysis supported a separation of these individuals into two groups. The quality of this separation, judged by model fit indices, was high. It should be noted that LCA does not have a preconceived notion about how it creates groups; it simply creates groups with individuals as similar to each other as possible with regards to their pattern of questionnaire responses.

These two groups created differed primarily with regards to their vision, with one group demonstrating more better-eye (MD = -6.0 vs. -2.5 dB) and worse-eye (MD = -13.4 vs. -6.1 dB) VF damage, and also worse VA (logMAR of 0.05 vs. -0.02). The two groups also differed with regards to their age, with the older group showing greater VF damage. The authors label these groups as disabled and non-disabled, though the trait described by LCA is latent (hidden), such that the groups may differ by the amount of disability, the pattern of disability, or both. To this point, the amount of VF damage overlapped substantially across the two groups, with several eyes in the group labeled as disabled showing little VF damage, and several eyes in the group labeled as non-disabled showing significant VF damage. Thus, while it is very intriguing that responders could be separated into groups so well, **further work is required to clarify exactly what separated these groups, whether these groups can be used to classify disability in glaucoma, and whether similar groupings would have been noted in a population with more advanced glaucoma patients.**

Anatomical Structures

Anterior segment microvasculature

Comment by Benjamin Xu, Los Angeles, CA, USA

78498 Conjunctival and intrascleral vasculatures assessed using anterior segment optical coherence tomography angiography in normal eyes; Akagi T, Uji A, Huang AS, Weinreb RN, Yamada T, Miyata M, Kameda T, Ikeda HO, Tsujikawa A; American Journal of Ophthalmology 2018; 196: 1-9

Extraocular blood vessels of the conjunctiva and sclera are readily accessible sources of information regarding systemic and ocular disease processes. Superficial conjunctival vasculature is affected by systemic diseases, such as diabetes and hypertension. Deep episcleral and intrascleral vasculature comprise the distal portions of the conventional aqueous humor outflow (AHO) pathway, which may reflect anatomical abnormalities associated with ocular hypertension and glaucomatous optic neuropathy. Therefore, ophthalmologists could benefit from new non-invasive methods to assess and quantify the state of these extraocular blood vessels.

This study by Akagi and colleagues proposes an innovative application of anterior segment optical coherence tomography angiography (AS-OCTA) for visualizing superficial conjunctival and deep episcleral and intrascleral vasculature. The authors imaged ten young, healthy subjects on a commercially available OCTA device. Extraocular blood vessels were segregated into superficial (0-200 um depth) and deep (200-100 um depth) layers using manufacturer-provided segmentation algorithms. Qualitatively, the superficial vessels resembled vasculature delineated by fluorescein angiography and the deep vessels resembled vasculature delineated by aqueous angiography with indocyanine green (ICG). Quantitative **AS-OCTA measurements of vessel density and other vessel properties demonstrated modest and significant inter-quadrant differences in the superficial and deep layers,** respectively.

> Non-invasive imaging of distal AHO pathways could provide valuable insight into the relationship between the dynamics of extraocular blood flow and effectiveness of IOP lowering treatments

Non-invasive imaging of distal AHO pathways could provide valuable insight into the relationship between the dynamics of extraocular blood flow and effectiveness of IOP lowering treatments, including eye drops, laser, and surgery. This information could

also be valuable for operative planning prior to minimally invasive glaucoma surgery (MIGS). However, it is important to acknowledge limitations associated with the proposed method. AHO channels are only detectable on AS-OCTA when they contain red blood cells, which means that Schlemm's Canal and the collector channels normally cannot be visualized. However, the relationship between flow in different segments of the AHO pathway is incompletely understood. In addition, it is unclear what proportion of deep vessels are involved in venous outflow as opposed to aqueous outflow. Therefore, additional work is needed before the long-term clinical value of AS-OCTA can be determined.

Schlemm's canal

Comment by Alex Huang, Los Angeles, CA, USA

78884 Schlemm's canal measured by optical coherence tomography and correlation study in a healthy Caucasian child population; Fernández-Vigo JI, Kudsieh B, De-Pablo-GÓmez-de-Liaño L, Almorín-Fernández-Vigo I, Fernández-Vigo C, García-Feijóo J, Fernández-Vigo Já; Acta Ophthalmologica 2019; 97: 493-498

In this paper, the authors evaluate oft studied anterior segment optical coherence tomography (AS-OCT) endpoints in a frequently unstudied population, children. Using Fourier-domain AS-OCT, cross-sectional acquisition of angle images were obtained from 290 healthy Caucasian subjects (10.7 ± 3.4 average years of age) in the nasal/temporal quadrants of the eyes. Angle, Schlemm's canal (SC), and trabecular meshwork measurements were made and compared temporal vs. nasal, between eyes, and across age. The results showed that SC measurements were only possible in ~70% of eyes due to poor image quality per the authors. **Intra- and inter-reproducibility of capable measurements were performed showing good intra-class correlation coefficients ~0.94**. Quantitative measurement did not differ much between eyes and between the nasal/temporal quadrants of each eye. However, multivariate analyses did yield a statistically significant positive correlation between age and SC size ($p \leq 0.041$).

> Anterior segment OCT is limited by the lack of a reference function where OCT can be performed in the same location across visits

The primary limitation of this paper was that only one image per quadrant was analyzed for each quadrant. This makes analyses difficult given known segmental aqueous hour outflow (AHO) patterns seen in aqueous angiographic studies[1,2] and in

structural evaluation of AHO pathways in adults.[3] Further, anterior segment OCT is limited by the lack of a reference function where OCT can be performed in the same location across visits. In a cross-sectional study this is not critical, but this is a key future challenge.

Ultimately, **the key finding was the positive relationship between SC size and age**. Potential explanations include passive change to SC as the eye grows and changes to SC size that is somehow connected to age-related AHO alterations. As the authors mentioned, they did not have IOP to add to their results. The next steps could be longitudinal evaluation of SC size with age to confirm findings here which ultimately would be best accomplished with an AS-OCT reference function.

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Macular structure and function

Comment by Andrew Tatham, Edinburgh, UK

79073 Improving visual field examination of the macula using structural information; Montesano G, Rossetti LM, Allegrini D, Romano MR, Crabb DP; Translational Vision Science & Technology 2018; 7: 36

There is growing interest in developing methods to combine information from structural and functional tests to improve the assessment of glaucoma progression and a potential technique is to use information from OCT to individualize automated perimetry testing strategies.[1,2] **A major advance in automated perimetry was the introduction of Bayesian algorithms such as the Swedish Interactive Threshold Algorithm (SITA),** which reduce test time, with minimal to no loss in accuracy, by estimating thresholds using prior knowledge concerning the distribution of sensitivity at each test point, modified according to individual test responses. In this study, Montesano and colleagues investigated whether information from OCT could be used as an additional 'prior' to improve visual field testing in the macula.

Thirty patients with glaucoma and 20 healthy controls performed a 10-2 visual field using a fundus perimeter equipped with scanning laser ophthalmoscopy tracking (Compass, CenterVue, Padua, Italy). Participants were tested using the standard 10-2 Zippy Estimation by Sequential Testing (ZEST) strategy and an independent validation group of 20 patients with glaucoma had high precision testing of eight visual field locations using a full-threshold strategy. Macular OCT was used to estimate ganglion cell density for corresponding visual field test points using a previously described model,[3] accounting for lateral displacement of ganglion cells, and these estimates were used to construct a structure-function model. Logistic regression was employed to determine the probability of a stimulus being seen or not seen based on age, local ganglion cell density, eccentricity and stimulus intensity. A series of 'probability of seeing curves', which incorporated information from OCT, were then constructed and these were used to modify the ZEST visual field strategy by altering the starting prior distribution on a point by point basis depending on estimates of ganglion cell density. The structural-ZEST algorithm was then validated using simulations based on data obtained from the independent group of glaucoma patients.

Important findings were that the novel structural-**ZEST algorithm led to a 13% reduction in the number of stimulus presentations in reliable simulated subjects and a 14% reduction in those with higher (≥ 20%) false positive or false negative** rates. This likely means that test time could be significantly reduced by using information from OCT to modify the 10-2 visual test algorithm. The simulation also suggested improved precision when measurements from OCT were taken into account. The structural-ZEST algorithm was less susceptible to higher levels of error, as shown by mean absolute error rates 10.6% less for structural-ZEST compared to ZEST when there was a 30% false-positive rate, and 18.3% less when there was a 30% false-negative rate. Structural-ZEST therefore seemed particularly beneficial in patients with less reliable visual fields.

Structural-ZEST therefore seemed particularly beneficial in patients with less reliable visual fields

Overall, the study provides further evidence that combining information from tests of structure and function is likely to improve the sensitivity for detection of glaucoma and glaucoma progression and more specifically that information from OCT can be used to improve visual field test strategies. **A major strength of the study was the use of a fundus perimeter to improve fixation stability**, but further work is needed to evaluate the model in real patients.

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Lamina cribrosa

Comment by Min Hee Suh, Busan, South Korea

79287 Visualization of the lamina cribrosa microvasculature in normal and glaucomatous eyes: A swept-source optical coherence tomography angiography study; Numa S, Akagi T, Uji A, Suda K, Nakanishi H, Kameda T, Ikeda HO, Tsujikawa A; Journal of Glaucoma 2018; 27: 1032-1035

Lamina cribrosa (LC) is known to be a putative site of retinal ganglion cell axonal injury. Moreover, there is increasing evidence that morphological changes of the LC including focal LC defect and increased LC curvature may be associated with the impaired optic nerve head (ONH) microvasculature in glaucoma due to the recent advent of optical coherence tomography (OCT-A) that enables visualization of the superficial and deep-layer microvasculature.[1-4] Particularly, assessment of the microvasculature within the LC is essential in understanding the direct relationship between the mechanical and vascular changes of the ONH.[2-4]

OCTA is still an evolving technology and these results highlight the fact that there is a need for consensus on the method that is best suited for quantification

Numa and Akagi *et al.* nicely demonstrated that Swept source (SS)-OCT angiography system, multiple image averaging, and a projection resolved algorithm enabled enhanced visualization of the microvasculature within the LC. They showed that OCT-A signals are present in lamina beams, not in lamina pores and that glaucomatous eyes had lower signal than normal eyes. Averaging of multiple OCT-A images enhanced the image quality. In addition, the projection removal technique allowed removing artifacts of the superficial vessels thus provided more accurate information of the deep ONH microvasculature.

However, caution is needed in assessing the microvasculature within the LC. Firstly, the current projection removal technique is not perfect. Residual projection of the large vessels is still observed in the enface OCT-A image of this article (Figs. 1G and 2G). On the other hand, the true vasculature located in the prelaminar tissue can be removed. Further enhancement of the analytics for the user-defined artifact removal is required. Secondly, assessment of the LC microvasculature is problematic in a considerable number of eyes due to shadowing by a neuroretinal rim and large retinal vessels.

Despite these limitations, **this study has its clinical importance by introducing up-to-date OCT-A technique in visualizing the LC microvasculature.** Ongoing innovation on the OCT-A analytics may help us better understand the pathogenic role of the LC vasculature in the development and progression of glaucoma.

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Basic Science

Corneal effects of prostaglandins

Comment by Cynthia Roberts, Columbus, OH, USA

78821 Experimental evaluation of travoprost-induced changes in biomechanical behavior of ex-vivo rabbit corneas; Zheng X, Wang Y, Zhao Y, Cao S, Zhu R, Huang W, Yu A, Huang J, Wang Q, Wang J, Bao F, Elsheikh A; Current Eye Research 2018; 1-6 (e-pub ahead of print)

This is a critically important study for any clinician in measuring intraocular pressure (IOP) while treating patients with prostaglandins analogs (PGA). IOP is the load that generates stress on the cornea. It can easily be seen in Figure 3 (see the original article) that as IOP and the associated stress increases, the elastic modulus (tangent slope) also increases and the cornea exhibits stiffer behavior at higher IOP. Therefore, it is quite difficult to separate the effect of lowering IOP with PGA treatment from the effect on the intrinsic corneal properties, when both reduce the stiffness response. This study removes the confounding effect of IOP and focuses strictly on the change in the material properties of the cornea in a well-conducted, careful investigation.

From a clinical perspective, the pre-treatment cornea would be at a point on the control group curve with open circles on the left in Figure 3, at a specific IOP. Post-treatment, the cornea would move down the curve as IOP is lowered, and also jump to the curve on right due to the change in corneal properties. This has a profound effect on any tonometer technology that is affected by corneal properties, including Goldmann Applanation tonometry (GAT),[1] the most common tonometer in the world. In other words, GAT underestimates the IOP with PGA treatment, and overestimates the amount of IOP lowering that has occurred.

Clarification of the clinically available biomechanical parameters is offered, including corneal hysteresis (CH) and corneal resistance factor (CRF) from the Ocular Response Analyzer, as well as deformation amplitude (DA) from the Corvis ST. The authors state that CRF is a measure of corneal stiffness, which is not completely accurate. CRF is an empirically derived parameter designed for maximum correlation with central corneal thickness (CCT). However, it is a function of both the loading and unloading applanation pressures, so it is also influenced by viscoelasticity. Unlike CH which is a simple difference between the two applanation pressures, CRF is weighted more heavily by the loading applanation pressure so it has a stronger relationship to the elastic response. Fundamentally, though, it remains a viscoelastic parameter. In addition, the authors state that DA is a measure of corneal stiffness, which is a bit misleading. The strongest influence on DA is IOP, with corneal stiffness having a much smaller influence than IOP. The paper referenced[2] did not show a reduction in DA with PGA treatment, but was a cross-sectional study comparing long-term PGA use against both normal controls and newly diagnosed glaucoma. They did not study the response to newly-initiated PGA treatment. In addition, the authors cited

inconsistent results with regard to CH after PGA treatment. The only cited paper[3] that showed a decrease in CH was not a study of prostaglandin naïve subjects, but a cessation of PGA treatment where corneal biomechanical effects had already occurred. Other papers cited showed an increase in CH with initial prostaglandin treatment, combined with a reduction in IOP, and were consistent in reported response.

GAT underestimates the IOP with PGA treatment, and overestimates the amount of lOP lowering that has occurred

An example of the artifact produced using GAT in combination with PGA treatment is with a patient seen in The Ohio State University clinic with GAT of 11 mmHg in both eyes after treatment with PGA's. Yet, the left eye had rapidly progressive visual field loss and the right eye was stable. However, when measured with other technologies including the PASCAL Dynamic Contour Tonometer (OD: 16.0 mmHg; OS: 17.5 mmHg), both eyes had higher pressure than measured with GAT and the IOP in the left eye was greater than the IOP in the right eye, consistent with the field loss. The Corvis ST confirmed visually the left eye had greater IOP than the right eye, as shown in the overlapped deformation images of both eyes in Figure 1. The deformation amplitude in the left eye was visibly less than in the right eye, which means the left eye had greater resistance to deformation with higher pressure than the right. This was not recognized by GAT. Figure 2 shows the associated visual fields.[4]

Fig. 1. Overlapped single frames extracted from Corvis ST videos from the left eye, pseudo-colored red, and the right eye, pseudocolored blue, both at highest concavity or maximum displacement. The smaller displacement of the left eye means the IOP is higher than the right, consistent with visual fields in Figure 2.

It is important for glaucoma specialists to ask themselves if IOP is an appropriate target when using PGA's for treatment, or in comparing IOP-lowering medications in clinical trials. If PGAs reduce IOP as well as induce artifact which causes underestimation of IOP due to a reduction in corneal stiffness, comparisons with other medications are confounded. At best, **a tonometer technology other than applanation, including GAT, should be used to estimate IOP if PGAs are used for treatment or in clinical trials.**

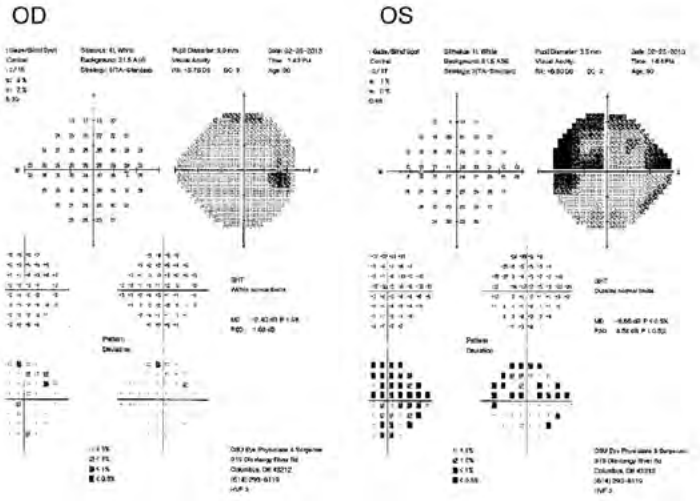

Fig. 2. Visual fields of patient shown in Figure 1.

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Immunobiology and neurodegeneration

Comment by Derek Welsbie, La Jolla, CA, USA

78502 Commensal microflora-induced T cell responses mediate progressive neurodegeneration in glaucoma; Chen H, Cho KS, Vu THK, Shen CH, Kaur M, Chen G, Mathew R, McHam ML, Fazelat A, Lashkari K, Au NPB, Tse JKY, Li Y, Yu H, Yang L, Stein-Streilein J, Ma CHE, Woolf CJ, Whary MT, Jager MJ, Fox JG, Chen J, Chen DF; Nature Communications 2018; 9: 3209

Nearly 30 years ago, Martin Wax and colleagues noted that glaucoma patients have an increased prevalence of circulating autoantibodies compared to controls (*see* Wax, 2011 for a comprehensive review).[1] However, it was unclear whether these autoantibodies arose secondary to the injury of retinal ganglion cells (RGCs) or whether autoimmunity played a primary role in glaucoma pathophysiology. In this paper, Chen *et al.* address this question using the mouse microbead glaucoma model. They transiently raise intraocular pressure (IOP) in mice and produce a gradual loss of RGCs that continues even after the return to baseline IOP. When they examine these retinas after two weeks, they observe an infiltration with CD4+ TH1 cells, some of which seem to be specific for heat shock protein 27 (HSP27). To test whether this immune response is causally involved in the RGC degeneration, the authors repeat the experimental glaucoma model in mice deficient in T and/or B cells and find that the loss of T cells attenuates the late, progressive RGC loss, but has little effect on the initial RGC loss. Moreover, they can reconstitute the immune system of these mice with T cells from mice that have been immunized with HSP27 (but *without* experimental glaucoma) and restore the RGC degeneration, suggesting that **anti-HSP immunity is involved in the late phase of RGC degeneration**. Finally, using two different glaucoma models, the authors show that mice reared in germ-free conditions (without gut microflora) have markedly attenuated RGC loss. The authors conclude that IOP elevations might compromise the immune privilege status of the retina and allow T cells that have been primed by exposure to gut bacterial HSPs to respond to the HSP27 autoantigen in RGCs (*i.e.*, molecular mimicry) and trigger a chronic neurodegeneration.

There is little-to-no data in the literature confirming the presence of lymphocytes in tissue specimens from glaucoma patients

While potentially exciting, both glaucoma models used in this paper have relatively robust IOP increases that have been shown to cause pan-retinal injury[2,3] so it will be interesting to see the contribution of the autoimmune mechanism at more modest IOP elevations. Also, while immunoglobulins have been detected in retinas from glaucoma patients and these authors themselves demonstrate anti-HSP antibodies in some glaucoma patients, there

is **little-to-no data in the literature confirming the presence of lymphocytes in tissue specimens from glaucoma patients so the relevance to the clinical disease is still an open question.** Nonetheless, the work has provided a key insight into RGC loss in mouse models of glaucoma.

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Clinical Examination Methods

Visual field progression

Comment by Gustavo de Moraes, New York, NY, USA and Carina Torres Sanvicente, Atlanta, GA, USA

78474 Association between rates of visual field progression and intraocular pressure measurements obtained by different tonometers; Susanna BN, Ogata NG, Daga FB, Susanna CN, Diniz-Filho A, Medeiros FA; Ophthalmology 2019; 126: 49-54

Goldmann applanation tonometry (GAT) is the gold standard for intraocular pressure (IOP) measurement,[1] which remains the only known modifiable risk factor for glaucoma progression.[2]examined every 3 months for up to 11 years. METHODS: Cox proportional hazard analyses, expressed by hazard ratios (HRs Still, a considerable proportion of patients will have progressive disease despite presenting IOP measurements that are compatible with a clinically-defined target.[3]eyes were randomly assigned to one of two sequences of glaucoma surgery, one beginning with argon laser trabeculoplasty and the other trabeculectomy. In the present article we examine the relationship between intraocular pressure and progression of visual field damage over 6 or more years of follow-up. In the first analysis, designated Predictive Analysis, we categorize 738 eyes into three groups based on intraocular pressure determinations over the first three 6-month follow-up visits. In the second analysis, designated Associative Analysis, we categorize 586 eyes into four groups based on the percent of 6-month visits over the first 6 follow-up years in which eyes presented with intraocular pressure less than 18 mm Hg. The outcome measure in both analyses is change from baseline in follow-up visual field defect score (range, 0 to 20 units Therefore, the search for parameters that could further explain glaucoma progression is a topic of much relevance in the field.

Previous reports suggest that corneal biomechanical properties could possibly function as a confounder of applanation tonometry readings and could partly explain glaucoma progression unrelated to IOP.[4] In a prospective observational cohort study, Susanna *et al.* investigated the associations between IOP measurements obtained by different tonometric methods and rates of visual field change over time.[5] The tonometric measurements investigated were: GAT IOP (Haag-Streit International, Köniz, Switzerland), corneal-compensated IOP (IOPcc) yielded by the Ocular Response Analyzer (ORA, Reichert, Inc., Depew, NY), and ICare Rebound Tonometer IOP (RBT, Tiolat, Oy, Helsinki, Finland). The authors hypothesized that an IOP assessment able to account for corneal biomechanical properties would be more strongly correlated with visual field outcomes.

The three tonometric methods were applied in a randomized sequence in follow-up visits of 125 patients with primary open-angle glaucoma. All participants had at least four reliable visual field tests over a mean of 2.4 ± 0.6 years. The average baseline visual field mean deviation (MD) was -3.7 ± 5.5 dB. There was a statistically significant association between the readings from all the studied tonometers and rates of visual field change, which remained significant after adjusting for central corneal thickness, corneal hysteresis, and demographic factors. However, the **ORA IOPcc had the strongest correlation with the rate of MD change (R^2 = 24.5%), which was statistically higher than correlations observed with GAT (R^2 = 11.1%) and RBT (R^2 = 5.8%) IOP readings**. Even though RBT had the weakest correlation with the rate of visual field change, it was not significantly different from GAT IOP.

The authors not only sought to validate different tonometric methods, but also applied strong methodology to investigate how their readings correlated with functional outcomes based on a well-founded hypothesis, which led to findings with important clinical implications.

Some of the limitations of the study resemble those commonly encountered in the clinical setting, such as difficulty to account for the effects of IOP reduction, pre-treatment IOP, and IOP diurnal fluctuation. Nonetheless, these limitations were largely overcome by the fact that the same eyes were tested with the three tonometers and thus shared the same sequence of visual field tests. Noteworthy is that the ORA measurements were the result of the average of three measurements, whereas the other methods were measured only once per visit, which may have contributed, at least in part, to the stronger correlation between ORA IOPcc and rates of visual field change. It would have been interesting to investigate how a single IOPcc measurement correlated with visual field progression in comparison to the single GAT IOP assessment. Notwithstanding, the techniques for measuring IOP in this study followed the recommendations from the manufacturers of each tonometer and, more importantly, resembled those employed in clinical practice, thus supporting the generalizability of their findings.

Further studies on how the different tonometers perform with regard to functional outcomes with extended follow-up, stratification by glaucoma severity, and inclusion of different types of glaucoma (*e.g.,* normal tension) will provide valuable information on the expected trajectory of disease progression, and possibly, introduce new tools to improve clinical decision making and definition of IOP targets in clinical practice.

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Perimetric algorithms – 1

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

79200 A new SITA perimetric threshold testing algorithm: Construction and a multicenter clinical study; Heijl A, Patella VM, Chong LX, Iwase A, Leung CK, Tuulonen A, Lee GC, Callan T, Bengtsson B; American Journal of Ophthalmology 2019; 198: 154-165

Heijl and colleagues are to be commended for a very well-designed study that aims to validate an important addition to the Humphrey Field Analyzer's tool box, a new perimetric testing strategy called SITA Faster (SFR) that leads to a 30% reduction in VF testing time, compared with SITA Fast (SF), without a significant increase in measurement variability. There has been a paucity of innovations in the field of perimetry over the last two decades since the introduction of SITA strategy. In the meantime, measuring rates of change in glaucoma has become a topic of interest in both research and clinical settings; as a corollary, more frequent perimetric testing, especially in the first couple of years after diagnosing glaucoma, has been proposed in the hopes of estimating the rates of change more accurately. Although SITA standard (SS) represented a huge improvement in VF testing time, it can take an average of five to seven minutes to carry out in one eye.

The SFR strategy implements seven modifications of the SITA strategy to shorten the test. **The main changes involve modifications to the staircase strategy, stimulus timing and starting threshold at primary points, along with elimination of blind spot and false negative catch trials.** In this study, Heijl and colleagues, compared SFR to SF and

SS in a group of 126 patients with suspected or definitive glaucoma of varying severity who had the same battery of three tests at two separate sessions. Most of the reported outcome measures were similar among all the testing strategies, other than slightly better VFI, on average, on SFR and SF tests compared with SS. Also, the SS strategy tended to flag about 1.1 (± 3.8) more point at p < 1% level on the PD plot. The investigators did not report whether the performance of the SFR strategy varied as a function of eccentricity, but it is reassuring that the measurement variability did not change as a function of the baseline threshold.

SITA Faster (SFR) that leads to a 30% reduction in VF testing time, compared with SITA Fast (SF), without a significant increase in measurement variability

Overall, the results are promising and given the very short testing time (75 ± 31 seconds) with SFR, I predict that many clinicians will adopt the SFR as the strategy of choice in all patients. In the meantime, I would consider using this strategy in patients who have difficulty in performing well with the SS or SF strategy, the elderly, and young patients with short attention span.

Perimetric algorithms – 2

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

78327 Improving spatial resolution and test times of visual field testing using ARREST; Turpin A, Morgan WH, McKendrick AM; Translational Vision Science & Technology 2018; 7: 35

The authors present computer perimetric simulation results of a white Goldmann Size III variant of the *ZEST* Bayesian thresholding procedure, called *ARREST (Australian Reduced Range Extended Spatial Test*). *ARREST* censors threshold testing at test points where the algorithm has already found that sensitivity is < 17dB. Time thus saved is used to examine additional test point locations near the detected defect. In computer simulations comparing their method to ZEST, **ARREST used 25% to 40% fewer test presentations, while showing sensitivity to detect visual field progression that was similar to that of ZEST**.

These simulation findings are consistent with the work of Gardiner and colleagues,[1,2] confirming that censoring SAP testing below approximately 19 dB may save testing time without impairing detection of visual field progression. How best to use resulting time

savings remains an open question. Time savings might be used as the authors suggest, to provide higher spatial definition in areas adjacent to detected loss. Alternatively, savings might be used to test more carefully for macular field loss,[3,4] or to simply shorten testing time in the hope of achieving improved clinical compliance with currently recommended visual field testing frequencies.

As the authors note, we also have good evidence that perimetric progression detection can be significantly improved simply by using test stimuli that are larger than Size III,[5] and by progressively increasing step size as scotomas deepen.[6,7] Thus, censoring might be beneficially combined with use of larger stimuli and variable step size. It is well past time for us all to work decisively toward the development of practical and widely-available visual field testing strategies that hasten and simplify detection of progressive visual field loss.

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Fiber layer measurements at various sites

Comment by Gábor Holló, Budapest, Hungary

79196 Macular versus nerve fiber layer versus optic nerve head imaging for diagnosing glaucoma at different stages of the disease: Multicenter Italian Glaucoma Imaging Study; Michelessi M, Riva I, Martini E, Figus M, Frezzotti P, Agnifili L, Manni G, Quaranta L, Miglior S, Posarelli C, Fazio S, Oddone F; Acta Ophthalmologica 2019; 97: e207-e215

In addition to the peripapillary retinal nerve fiber layer thickness (RNFLT), various parameters including macular retinal thickness and minimum rim width (MRW) have become available on the Spectralis OCT system for glaucoma assessment. In the Multicenter Italian Glaucoma Imaging Study, Michelessi *et al.* address an important issue for Spectralis OCT users: which parameter perform the best to separate healthy eyes from open-angle glaucomatous eyes. The study population comprised 197 glaucoma eyes and 83 normal eyes (one eye per participant) which were classified according to the result of reliable Humphrey 24-2 visual field tests. Glaucoma suspects and preperimetric glaucoma eyes were not

included. **The average MRW showed the best diagnostic performance (AUC 0.968; sensitivity at > 90% specificity 92.4%), followed by the average RNFLT (AUC 0.939; sensitivity at > 90% specificity 84.77%), and then central macular thickness (AUC ≤ 0.918; sensitivity at > 90% specificity ≤ 81.73).** For the separation of early glaucoma eyes from the normal eyes average MRW (AUC 0.956) and average RNFLT (AUC 0.929) performed similarly and significantly better than central macular thickness parameters (AUC ≤ 0.874). It is also interesting that AUCs of the MRW sectors were not statistically inferior to that of average MRW. These results suggest that average and sector MRW are particularly useful new diagnostic parameters of the Spectralis OCT. They perform similarly to average RNFLT and considerably better than any macular thickness parameter of the same OCT system.

Structural disease progression

Comment by Andrew Tatham, Edinburgh, UK

78995 Serial combined wide-field optical coherence tomography maps for detection of early glaucomatous structural progression; Lee WJ, Kim TJ, Kim YK, Jeoung JW, Park KH; JAMA ophthalmology 2018; 136: 1121-1127

Optical coherence tomography (OCT) measurements of the retinal nerve fiber layer (RNFL) are widely used to assess for progressive changes in glaucoma, and there is growing realization of the importance of also detecting progressive macular changes.[1] Commercial OCT devices are beginning to offer wide-field imaging capabilities that allow results from RNFL and macular imaging to be combined. In this study, Lee and colleagues examined the ability of wide-field OCT maps, which include circumpapillary RNFL (cpRNFL) and macular ganglion cell-inner plexiform layer (mGCIPL) measurements, to detect progression in early glaucoma.

Ninety-four eyes with an average visual field mean deviation of -1.9 dB were imaged using the Cirrus HD-OCT. Wide-field images were generated from a montage of 200 x 200 pixel optic disc and macular cube scans. Progression on OCT was determined using the Cirrus HD-OCT guided progression analysis (GPA) event analysis and by two masked observers examining serial sets of wide-field OCT thickness and deviation maps. Progression was defined as appearance of a new RNFL defect (or deviated pixels) or an increase in depth or width of an existing defect (or deviated pixels).

Over an average follow-up of almost five years, 50% of eyes progressed on serial stereo disc or red-free fundus photographs. Eyes progressing on photographs had significantly faster rates of change in cpRNFL (-1.65 versus -0.61 µm/year) and mGCIPL (-0.91 versus -0.27 µm/year) and a significantly greater proportion of eyes progressing on photographs were also noted to have progressed on cpRNFL GPA (83.0% versus 15.2%, $P < 0.001$) and

mGCIPL GPA (66% versus 6.4%, P < 0.001). The combined wide-field OCT maps had similar sensitivities and specificities compared to RNFL and mGCIPL GPA (*e.g.*, 83% sensitivity and 95.7% specificity for wide-field OCT deviation map compared to 83% sensitivity and 84.8% specificity for cpRNFL GPA).

Although combined wide-field OCT maps had similar ability to detect progression as GPA software, wide-field images have potential advantages over isolated parapapillary and macular measures**. By allowing evaluation of both regions in a single image it is easier to observe the pattern of progressive change; deepening and widening of defects can be seen more easily, and the spatial relationship between RNFL and macular thinning and visual field loss is more apparent.** Recent studies have indicated macular measurements may be of particular value in advanced glaucoma and therefore wide-field images may also allow improved detection of progression through a wider spectrum of disease severity.[2]

Disadvantages of the study included that the wide-field images were obtained by merging two separate scans which led to errors in alignment necessitating almost 5% of paired scans to be excluded. In addition, the reference standard of progressive changes on photographs is likely to be more closely correlated with changes in cpRNFL than mGCIPL and may be less sensitive at detecting change than OCT.

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Clinical Examination Methods

Retinal vessel density

Comment by Harsha Rao, Narayana Nethralaya, Bangalore, India

79201 Comparison of methods to quantify macular and peripapillary vessel density in optical coherence tomography angiography; Rabiolo A, Gelormini F, Sacconi R, Cicinelli MV, Triolo G, Bettin P, Nouri-Mahdavi K, Bandello F, Querques G; PLoS ONE 2018; 13: e0205773

OCTA is a relatively recent, non-invasive, dye-less imaging modality that enables visualization of the vasculature of the retina, optic nerve head and the choroid. Delineation of the vasculature is achieved using algorithms that evaluate variability produced by moving columns of blood in sequentially acquired OCT B-scans. Each OCTA manufacturer has their own proprietary algorithms to delineate vasculature. The most popular vascular parameter quantified on the OCTA scan is the 'vessel density'. Vessel density is the percentage of angio-cube occupied by vessels.

> Patients were recruited from all other the world, and thus results are generalizable to the worldwide pediatric population

Previous studies have used multiple thresholding methods to binarize the OCTA image and measure the vessel density from the exported raw image; some of them being fixed cut-off method, dynamic cutoff method, Image J methods, etc. Rabiolo and colleagues examined the agreement in macular (superficial and deep capillary plexus) and peripapillary (radial capillary plexus) vessel density measurements among seven such binarization methods. Their study included 44 eyes of 27 healthy subjects, 44 eyes of 31 subjects with diabetic retinopathy (DR) and 44 eyes of 26 subjects with POAG. They found that the agreement between the different binarization methods was poor with substantial systemic, non-constant biases evident between most tested methods. For example, the mean difference in peripapillary vessel density was as low as 1.4 between two methods to as high as 9.6 between two other methods. The range of 95% LoA between any two methods of peripapillary vessel density measurement was as low as 2.2 to as high as 28.8. The authors concluded that the vessel density measurements calculated with different methods are not interchangeable and longitudinal monitoring of vessel density in diseases such as DR and POAG should be carried out with the same method. The authors also compared the diagnostic ability of the vessel density measurements derived from these methods in DR and POAG separately and found that no one method was better than the others.

Previous studies have shown that the OCTA vessel density measurements are dependent on the device, angio-cube size, image averaging and signal strength. This study by Rabiolo *et al.* shows that the vessel density values are also dependent on the post-processing method used. In spite of its popularity, OCTA is still an evolving technology and these results highlight the fact that there is a need for consensus on the method that is best suited for quantification.

Forms of Glaucoma

Ocular hypertension

Comment by Luciano Quaranta, Pavia, Italy

78941 A long-term safety study of Latanoprost in pediatric patients with glaucoma and ocular hypertension: A prospective cohort study; Younus M, Schachar RA, Zhang M, Sultan MB, Tressler CS, Huang K, Xu W, Klein M, Platt RW, Mukherjee N, Haenel E, Freedman SF; American Journal of Ophthalmology 2018; 196: 101-111

This is the first large-scale study analyzing the long-term safety of latanoprost in a pediatric cohort affected by a mixed variety of glaucoma and ocular hypertension.

As stated by the authors, latanoprost showed an acceptable safety profile over the three-year follow-up provided by the study. The most important aspect of the study is that patients were recruited from all other the world, and thus results are generalizable to the worldwide pediatric population.

From a clinical point of view, latanoprost and other prostaglandin analogues are commonly used for the treatment of childhood glaucoma, so their good tolerability and efficacy are not surprising for the clinician.[1-3]

What is unfortunately limited from this real world study is a safety analysis in patients affected by glaucoma at a younger age (*i.e.*, < five years), even if other studies have demonstrated an excellent safety profile in pediatric glaucoma patients.[3]

Surprisingly, in spite of the good safety profile of latanoprost, the IOP was unchanged from baseline (mean change, 0.1 ± 4.48 mmHg). This could be due to the heterogeneity of the studied cohort.

> These physiological parameters significantly vary over a 24-hour period with postural and diurnal variation unaccounted for in the current study

In contrast, in a recent prospective study, latanoprost was shown to be effective in a long-term follow-up (three-year) in selected patients affected by primary pediatric glaucoma who underwent a single surgical procedure.[4] The efficacy of pharmacological treatment was inversely related to central corneal thickness at the time of surgery, and the age at the time of surgery. Similar to Younus *et al.*, the safety was excellent and none of the patients withdrew due to adverse events.

I would like to applaud the authors for their important contribution to our knowledge of pediatric glaucoma and its treatment. Future research from this group will hopefully provide complete safety and efficacy profiles for latanoprost and other prostaglandin analogues in patients affected by pediatric glaucoma with longer term follow-up.

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Normal-tension glaucoma

Comment by Alon Harris, Indianapolis, IN,USA

78478 Blood pressure and heart rate variability in primary open-angle glaucoma and normal tension glaucoma; Lindemann F, Kuerten D, Koch E, Fuest M, Fischer C, Voss A, Plange N; Current Eye Research 2018; 43: 1507-1513

The reduction of intraocular pressure (IOP) remains the only currently proven and approved method to arrest the onset and progression of glaucoma. However, the complex and multifactorial nature of the disease allows for many individuals to suffer glaucomatous vision loss despite low initial IOP and/or significantly reduced IOP via medical intervention. Vascular contributions to the disease process are fairly well established with ocular perfusion pressure (defined as 2/3 mean arterial pressure – IOP) being recognized as an independent risk factor for the disease.[1] Determining individual risk often involves careful consideration of IOP, age, race, gender, and other cofounders such as systemic vascular health.

These physiological parameters significantly vary over a 24-hour period with postural and diurnal variation unaccounted for in the current study

Lindemann and colleagues present novel data on blood pressure (BP) and heart rate variability patterns in 37 patients with (high pressure) primary open-angle glaucoma (POAG), 27 patients with normal-tension glaucoma (NTG), and 87 control subjects. Under resting conditions, continuous BP and heart rate were simultaneously recorded over 30 min with time series of heart rate, systolic blood pressure and diastolic blood pressure analyzed utilizing univariate linear (time domain, frequency domain), non-linear (symbolic dynamics), and bivariate (joint symbolic dynamics) indices. The authors identified **12 significantly different parameters between POAG patients and controls**, however they found a full **80 parameters that were significantly different between NTG patients and controls**. **The data showed a much higher sensitivity (82% at a specificity of 87%) for NTG patients compared to high pressure POAG suggesting impaired patterns of autonomic cardiovascular regulation in glaucoma, especially within NTG patients**.

The use of continuous monitoring (30 min) to examine systemic differences in vascular health is unique and a strength of the current study as is the inclusion of both high and low pressure glaucoma patients to elicit differences in risk profiles. Conversely, a limitation is the absence of a direct ocular blood flow modality such as optical coherence angiography, which may have shown how these systemic vascular disturbances influence perfusion to the retina and optic nerve head. It is also important to acknowledge that these physiological parameters significantly vary over a 24-hour period with postural and diurnal variation unaccounted for in the current study.

Our understanding of glaucoma and vascular involvement in the disease process continues to evolve. Moving forward, the inclusion of novel biomarkers to understand overall glaucoma risk, especially if possible through non-invasive monitoring of vascular health, may provide improvements to individual diagnosis, disease management, and vision preservation.

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Medical Treatment

Fellow eye treatment

Comment by Tony Realini, Morgantown, WV, USA

78984 Association of fellow eye with study eye disease trajectories and need for fellow eye treatment in Collaborative Initial Glaucoma Treatment Study (CIGTS) Participants; Niziol LM, Gillespie BW, Musch DC; JAMA Ophthalmology 2018; 136: 1149-1156

The landmark Collaborative Initial Glaucoma Treatment Study (CIGTS) demonstrated that while surgery lowers intraocular pressure (IOP) more than medications in eyes with primary open-angle glaucoma (POAG), both treatment modalities confer similar protection against future progression. In CIGTS, data from one study eye of 607 POAG patients were analyzed. In a recent report by Niziol and colleagues, clinical outcomes in non-study fellow eyes have been described, as have correlations of clinical course between study and non-study fellow eyes over seven years of follow-up. Perhaps intuitively, **the clinical course of between study and non-study fellow-eye pairs – as measured by the slope of visual field mean deviation over time – was highly correlated (r = 0.73) when both eyes have POAG and receive treatment**. Less intuitive is the observation that fewer than half of individuals (47.9%) required treatment in the non-study eye at enrollment: essentially, more than half of CIGTS participants had unilateral POAG at study entry. Further, **nearly one-third of participants (31.8%) did not require treatment for POAG in the non-study eye over a seven-year follow-up period**. This finding is unlikely to be shaped by the restrictive eligibility criteria defining POAG for study entry, as the current analysis pertains to the clinical decision to treat or not treat the non-study eyes and not to its meeting the study criteria for POAG diagnosis. This finding – that half of POAG patients effectively have unilateral disease at diagnosis and one-third will remain unilateral for > seven years – is contrary to conventional wisdom and worthy of further investigation. One potential ramification of this observation pertains to the pathogenesis of POAG. While the genetic basis of POAG is all but certain, the underlying genetic mechanisms leading to the disease remain incompletely characterized. The fellow-eye discordance of POAG described in this analysis suggests that eye-level (rather than or in addition to individual-level) factors may play an important role in the development of POAG in at-risk individuals.

Pilocarpine and prostaglandins

Comment by Kaweh Mansouri, Lausanne, Switzerland

78946 The diurnal and nocturnal effects of pilocarpine on intraocular pressure in patients receiving prostaglandin analog monotherapy; Seibold LK, Wagner BD, Lynch AM, Kahook MY; Journal of Ocular Pharmacology and Therapeutics 2018; 34: 590-595

In recent years, increased attention has been directed to the circadian effects of glaucoma medications. While prostaglandin analogues (PGA) and, to a lesser degree, carbonic anhydrase inhibitors (CAI) have been shown to have a sustained IOP-lowering effect at nighttime, beta-blockers and alpha-sympathomimetics do not. Pilocarpine is one of the oldest glaucoma medications, but has been largely abandoned for glaucoma therapy due to its unfavorable safety profile, the necessity of four times daily applications, and modest efficacy. Scarce data were available on its 24-h efficacy.

In this interesting and potentially impactful paper, Seibold *et al.* studied the 24-h IOP effects of four times daily pilocarpine 2% as an add-on to PGA therapy. Twenty-seven patients with ocular hypertension and open-angle glaucoma were housed in a sleep laboratory for 24 hours. IOP and ocular perfusion pressure (OPP) were measured in the habitual body positions.

The investigators found that pilocarpine could lower IOP significantly in patients on PGA monotherapy throughout the 24-h cycle, while there was no effect on OPP.

Important questions remain unanswered: Which would be the optimal sequence of pilocarpine instillation, before or after PGA? What would be the effect of pilocarpine in patients on more than PGA monotherapy? What would be the effect of previous SLT on pilocarpine (this study is probably underpowered to answer this)?

More intense medical therapy leads to lower IOP

These findings may potentially herald a new era for pilocarpine in glaucoma treatment. As we move towards better monitoring of IOP over the full circadian cycle, treatments to lower nighttime IOP will be sought. It can be argued that a once-daily dose of pilocarpine (bedtime) would eliminate most of this drugs' unpleasant side effects.

Mono- vs. multi-therapy

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

78343 Initial intraocular pressure reduction by mono- versus multi-therapy in patients with open-angle glaucoma: results from the Glaucoma Intensive Treatment Study; Lindén C, Heijl A, JÓhannesson G, Aspberg J, Andersson Geimer S, Bengtsson B; Acta Ophthalmologica 2018; 96: 567-572

Linden *et al.*[1] compared the effect intraocular pressure (IOP)-lowering between newly diagnosed glaucoma patients treated with mono- versus multi-therapy regimens in a randomized clinical trial. The mono-therapy group (N = 118 patients) received any one of three classes of glaucoma drops commercially-available in Sweden, while the multi-therapy group (N = 122) received three different classes (one fixed combination plus a third class) followed by laser trabeculoplasty (LTP, either selective or argon laser trabeculoplasty). Of note, all eyes had early-to-moderate visual field loss at baseline (visual field index > 65%) and all levels of untreated IOP at study entrance were allowed. The present analysis is part of a larger study goal of assessing whether immediate, more intense treatment or conventional, stepwise treatment would result in better functional and quality-of-life outcomes in the long run in patients newly diagnosed with glaucoma.

> To successfully decrease visual disability due to glaucoma worldwide, treatment options in glaucoma need to become more affordable

The first main finding was that, after one month, both the absolute and percentage IOP reduction were dependent upon the baseline IOP levels – with higher baseline measurements resulting in greater reduction – which is consistent with what has been described in a number of studies investigating different types of IOP-lowering interventions. Nonetheless, this effect was more pronounced in the intense (multi-therapy) eyes: for each mmHg higher baseline IOP, these eyes experienced a 0.84 mmHg IOP reduction compared to 0.56 mmHg in the mono-therapy eyes.

Secondly, **despite similar median baseline IOP prior to initiation of treatment (median= 24 mmHg in both groups), the multi-therapy group experienced a median pressure reduction 6 mmHg greater than the mono-therapy group** (final median IOP = 12 and 18 mmHg, respectively, P < 0.001).

Finally, and perhaps the most relevant finding, **multi-therapy enabled achieving pressures lower than several different target IOPs in a greater proportion of patients than mono-therapy**. For instance, while an IOP < 18 mmHg was achieved in 49% of eyes in the

mono-therapy group, multi-therapy achieved the same target in 92% of eyes. This finding was also true regardless of the baseline IOP. For instance, while an IOP < 14 mmHg was achieved in 34% of eyes whose baseline IOP was < 21 mmHg in the mono-therapy group, that number was 92% in the multi-therapy group.

Although it appears intuitive that more intense medical therapy leads to lower IOP, this is the first report to provide quantitative estimates in a randomized trial. It would have been valuable had the authors also described how the two groups compared in terms of quality-of-life measurements given that IOP drops can adversely affect these estimates due to topical or systemic effects,[2] even after short periods of follow-up. This will hopefully be addressed in a follow-up publication by the investigators in this database. Although the benefits of multi-therapy were clear after one month, more compelling information will be available in the long-term analysis. Adherence is one major confounder as patients tend to be less compliant when treated with more complex regimens.[3]

Of course, the long-term effects on visual function and the cost-benefit analyses will be crucial to help clinicians decide whether the new treatment paradigm – which recommends an immediate, intense multi-therapy regimen – should be considered at least in some patients with newly diagnosed glaucoma. The authors should be congratulated for the design of this clinical trial and the novel information to be added to the literature.

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Surgical Treatment

What laser after SLT?

Comment by Tony Realini, Morgantown, WV, USA

78815 Selective laser trabeculoplasty versus argon laser trabeculoplasty in glaucoma patients treated previously with 360°; selective laser trabeculoplasty: a randomized, single-blind, equivalence clinical trial; Hutnik C, Crichton A, Ford B, Nicolela M, Shuba L, Birt C, Sogbesan E, Damji KF, Dorey M, Saheb H, Klar N, Guo H, Hodge W; Ophthalmology 2019; 126: 223-232

Hutnik and colleagues have conducted a prospective, randomized trial in which medically-uncontrolled eyes with POAG previously treated with 360° selective laser trabeculoplasty (SLT) underwent subsequent repeat SLT or argon laser trabeculoplasty (ALT) (each 180°) to determine whether there were differences in intraocular pressure (IOP) reduction between these two modalities in this setting. The results of the study demonstrated that **both laser platforms delivered approximately 3 mmHg IOP reduction from baseline at Month 12. The authors note that this magnitude of effect is approximately 50% of the reported effect for first SLT in prior studies**, and they conclude that this observation 'implies strongly that although initial SLT may produce no histologic changes to the TM, there is likely some change nevertheless because the second SLT is not as effective as the first.' In fact, this conclusion may be entirely wrong, as their findings can be easily explained by a methodological error in their study design. **They utilize change from baseline in IOP as their measure of repeat SLT efficacy. The problem with this approach is that the baseline for repeat SLT is not the same as the baseline for first SLT.** A simple clinical scenario makes this clear.

Consider a patient with newly diagnosed POAG and IOP of 24 mmHg whose target IOP is a 25% reduction (18 mmHg) and who undergoes initial SLT and achieves IOP of 16 mmHg (an 8-mmHg, 33% reduction). Over time, the SLT effect begins to wear off and IOP drifts up to 20 mmHg, which is above target. SLT is repeated, and IOP of 16 mmHg is regained. Virtually everyone would consider that repeat SLT was as effective as first SLT in that both achieved the same post-laser IOP level, even though repeat SLT only lowered IOP 4 mmHg, which is half the change from baseline observed with initial SLT. This is the problem with using change from baseline for evaluation of repeat SLT: because we do not let first SLT wear off completely (*i.e.*, we do not let IOP return to pretreatment levels) before retreating, second SLT's baseline is necessarily lower than initial SLT's baseline, so the magnitude of change from baseline will always be smaller with repeat SLT. Future studies of repeat SLT should consider re-attainment of IOP delivered by initial SLT as the optimal metric of repeat SLT success.

Pharmacoeconomics

Costs of early vs. late laser and surgery

Comment by Gauti Jóhannesson, Umeå, Sweden

79286 A worldwide price comparison of glaucoma medications, laser trabeculoplasty, and trabeculectomy surgery; Zhao PY, Rahmathullah R, Stagg BC, Almobarak F, Edward DP, Robin AL, Stein JD; JAMA ophthalmology 2018; 136: 1271-1279

The global prevalence of glaucoma is expected to increase substantially in the future and will possibly affect over 110 million people worldwide by 2040, with most glaucoma patients residing in developing countries.[1] Thus, the cost of glaucoma treatment becomes increasingly important in relationship to the household income in these countries.

This study highlights this important relationship by investigating the cost of glaucoma medications, laser trabeculoplasty (LTP) and trabeculectomy in 38 countries worldwide relative to median annual household income (MA-HHI). The included countries represent almost two thirds of the global population and include both developed and developing countries.

The authors found an extensive difference between countries where costs of topical treatment, LTP and trabeculectomy were ≥ 2.5% of MA-HHI in 41%-78% of developed countries, but 65%-95% in developing countries. Of the treatments investigated, timolol seemed to be a viable option for glaucoma patients all over the world. However, the authors also highlight that although costly initially, surgery may be a good option for glaucoma patients in developing countries due to the high long-term cost of medications.

Comparing costs of glaucoma treatments between countries is an important task, but there are several limitations and confounding factors that need to be considered. These include the existence of national health care insurance in some countries, difficulties in obtaining reliable information on costs, surgery related costs and patients adherence.

This is the first study to compare costs of glaucoma treatment in a global perspective. Overall, it shows that the cost of glaucoma treatment represents too large a proportion of median annual household income for patients in many countries. The results emphasize that, in order to successfully decrease visual disability due to glaucoma worldwide, treatment options in glaucoma need to become more affordable.

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Miscellaneous

Artificial Intelligence aided Glaucoma Diagnosis

Comment by Naama Hammel and Sonia Phene, Mountain View, CA, USA

79224 Using deep learning and transfer learning to accurately diagnose early-onset glaucoma from macular optical coherence tomography images; Asaoka R, Murata H, Hirasawa K, Fujino Y, Matsuura M, Miki A, Kanamoto T, Ikeda Y, Mori K, Iwase A, Shoji N, Inoue K, Yamagami J, Araie M; American Journal of Ophthalmology 2019; 198: 136-145

Deep learning algorithms have been applied to produce highly accurate systems that can detect various eye conditions from fundus images,[1,2] as well as optical coherence tomography (OCT) scans.[3,4] Both clinically and in research settings, OCT measurements of the inner layers of the retina (including the ganglion cell layer) are used to quantify glaucomatous damage of the macula – damage that may detectable via OCT in the early stages of the disease.[5]

> In the setting of sufficient data, DLSs are more accurate than more classical techniques

Asaoka and colleagues developed a deep learning system (DLS) to distinguish early-onset glaucoma from normal eyes using macular OCT scans. **Their main finding was that a DLS that uses an 8 x 8 grid macular retinal nerve fiber layer (RNFL) thickness and ganglion cell complex (GCC) layer thickness from OCT can achieve an area under receiving-operating characteristic curve (AUC) of 93.0%**. They further validated that the DLS performed better than two traditional machine learning techniques, the support vector machine and the random forest. These findings validate a generally-accepted sentiment in the machine learning community[6] for medical imaging: in the setting of sufficient data, DLSs are more accurate than more classical techniques.

The major limitations of the study are the size of the data set and the exclusion of difficult cases. A paper describing a DLS for the detection of DR from fundus photos found that the minimum number of images required for development was over 50,000.[1] Asaoka and colleagues had a 'pre-training' data set of 4,316 OCTs, while the test set consisted of only 114 patients with early open-angle glaucoma and 82 normal patients. Thus, we postulate that the DLS developed by the authors could potentially be improved further with additional training data. In addition, the authors excluded difficult images, such as ones with

tilted discs, from the training and test sets. Because such images are not uncommon in routine clinical workflows, exclusion criteria such as this may limit the ability to extrapolate the model's performance to the general clinical setting.

To conclude, Asaoka *et al.* have made solid initial steps to applying DLS to OCTs, which contain crucial information for diagnosing and managing glaucoma. Additional work will be needed to further validate their findings on larger datasets of a clinically diverse patient population and breadth of images.

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- ★ To successfully decrease visual disability due to glaucoma world-wide, treatment options in glaucoma need to become more affordable

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