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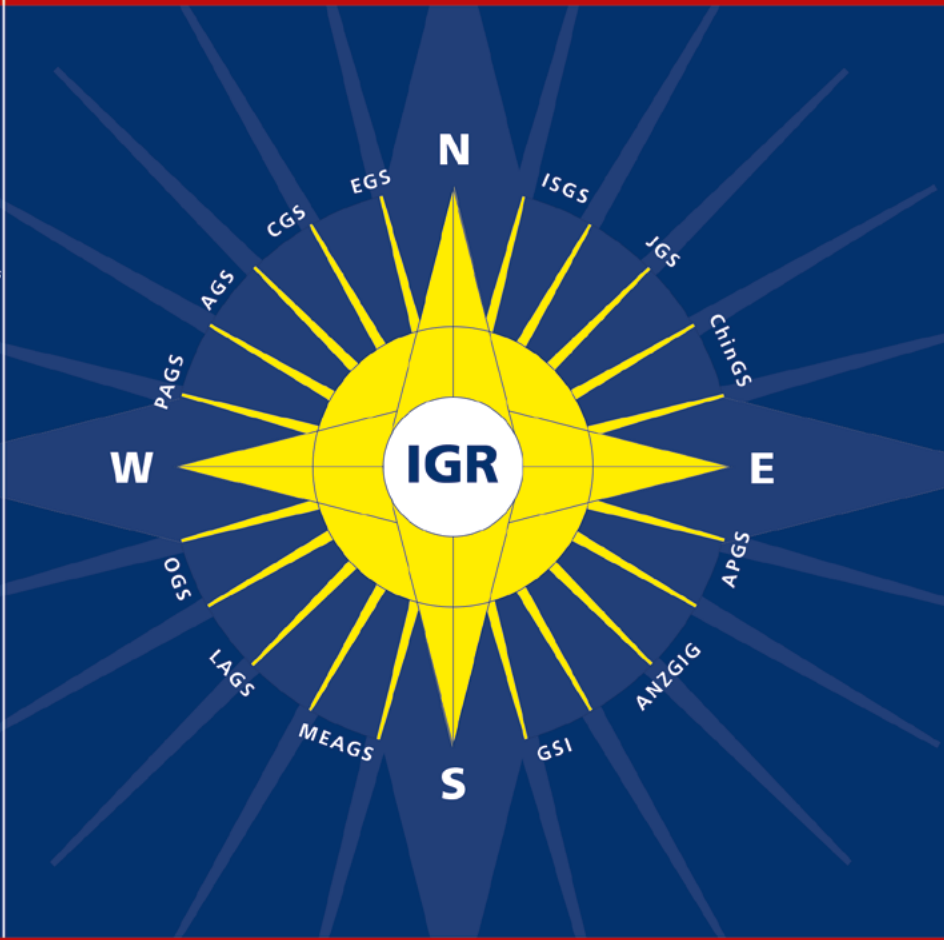

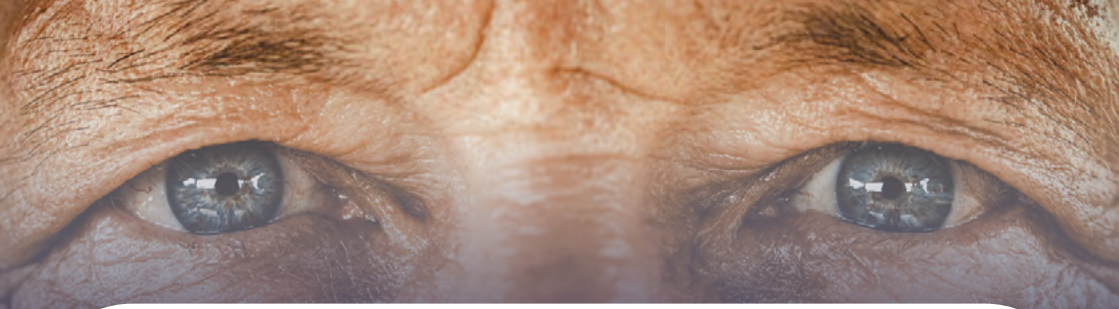

Envisioning a Better Future For Patients With Glaucoma

Glaucoma is one of the leading causes of irreversible blindness worldwide and it is a growing problem, with the number of people affected estimated to reach 111.8 million people by 2040.[1] More than 11 million people are estimated to be bilaterally blind (in both eyes) from glaucoma.[2]

Early diagnosis and treatment initiation is critical to help prevent vision loss from glaucoma, as symptoms may be hard to detect when the condition first develops.[3,4] AbbVie focuses on clinically relevant science to make a meaningful difference for patients and seeks to elevate the standard of care by addressing areas of unmet need.

With over two decades of experience researching eye diseases, Jie Shen, Ph.D., AbbVie's Vice President of Local Delivery Translational Sciences, leads a team of scientists responsible for designing and conducting studies, evaluating drug behavior in the eye, and testing promising drug candidates in early-stage clinical trials. Jie and team utilize state-of-the-art imaging modalities found in world-class clinical research institutions, digital technologies, statistical modeling, and data science to accelerate the translation of science to new medicines.

It is the people around the world living with eye conditions like glaucoma that motivate AbbVie's eye care scientists to push forward with leading-edge translational research, with the aim to deliver medicines with best-in-class outcomes to patients.

In this quest to meet patient needs, AbbVie is leveraging capabilities at its Genetic Research Center and investing in technology to accelerate and

optimize R&D, for example, identifying biomarkers that can help indicate at an early stage whether a drug may be effective. Jie also highlights the importance of AbbVie's biostatistics support, including machine learning, which can help to derive more benefit from available data in the early discovery phase.

Pursuing these goals is enabled by an eye care journey that began as Allergan over 75 years ago, bolstered today by AbbVie's legacy in complex diseases and global scale.

While eye care may seem simple, with some vision issues being solved by people wearing glasses, contact lenses, or using eye drops, the reality is what works for some does not work for others. With a background in academia and many years as a practicing ophthalmologist, Mike Robinson, M.D., AbbVie's Vice President, Clinical Development, Ophthalmology has seen firsthand the great need to elevate the standard of care and continuously improve existing options. This is why AbbVie is focused on addressing unmet needs in glaucoma.

"We continue to look for solutions in our clinical trials. Our goal has been and continues to be identifying ways to meet people where they are in their ability to preserve their vision, and our clinical trials are looking at ways to provide glaucoma patients additional options," says Mike.

AbbVie will continue to push the envelope through R&D and collaborations, to accelerate the development of better treatments for patients.

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

Registration

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

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Contact Information

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

WGA Executive Office
c/o Schipluidenlaan 4
1062 HE Amsterdam
The Netherlands
Tel: +31 20 570 9600
E-mail: info@worldglaucoma.org

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Santen

The first innovation† in the medical management of glaucoma in Europe for 25 years[4]

Welcome to a novel destination for glaucoma management[1–3]*

- Effectively lowers IOP, while targeting trabecular meshwork dysfunction[1,2,5–7]
- Complementary mechanisms of action of latanoprost and netarsudil, a ROCK inhibitor[1,5]

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50µg/ml latanoprost + 200µg/ml netarsudil, eye drops, solution

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From the WGA

Dear IGR readers,

Join us in Honolulu, Hawaii, USA from June 25–28, 2025, for the highly anticipated 11th World Glaucoma Congress—a premier gathering where global experts, leading researchers, and dedicated clinicians come together to transform the future of glaucoma care. This isn't just a congress; it's an immersive experience featuring dynamic plenary sessions, interactive workshops, live surgical demonstrations, and countless opportunities to network and collaborate on the latest breakthroughs. Discover the full program and explore the cutting-edge sessions here: worldglaucomacongress.org/program/paag/.

This year, we're thrilled to report record-breaking abstract submissions, ensuring an abundance of innovative research and fresh ideas to energize discussions and inspire new collaborations.

World Glaucoma Week—celebrated from March 9–15, 2025—captivated global attention under the banner "This Is World Glaucoma Week." The initiative united communities across continents through a vibrant mix of interactive digital campaigns, live events, and local activities designed to educate and empower. Iconic landmarks around the world lit up in green, symbolizing a unified commitment to raising awareness about glaucoma and the critical importance of early detection and treatment. Discover the exciting global activities and join the conversation here: www.worldglaucomaweek.org/activities/around-the-world/.

As a valued member of the WGA Glaucoma Societies, you enjoy exclusive benefits including complimentary IGR issues and unrestricted online access. If you haven't signed up for IGR yet, simply send your email to info@worldglaucoma.org and we'll ensure you never miss the latest insights. Your membership also grants you free access to the Journal of Glaucoma via your WGA#One account—stay up to date with pioneering research, best practices, and more by exploring past editions and signing up for alerts at www.glaucomajournal.com.

Join us on this journey of discovery, innovation, and global collaboration—together, we're shaping the future of glaucoma care.

Best wishes,

Ningli Wang, MD PhD
President
World Glaucoma Association

Kaweh Mansouri, MD MPH
Executive Vice-President
World Glaucoma Association

Get to know us!

Arthur Sit

I completed my glaucoma fellowship at the University of California San Diego, where my mentor, Dr. Robert Weinreb, introduced me to the global glaucoma community. I subsequently joined the faculty at the Mayo Clinic in Rochester, Minnesota, where I am currently Professor of Ophthalmology and Vice Chair for Research. My own research interests are focused on aqueous humor dynamics and ocular biomechanics, and the development of novel devices for their measurement.

I have been fortunate to be part of the WGA since joining the Associate Advisory Board in 2009. Since then, I have been actively involved with the WGA and currently serve as Treasurer, member of the Board of Governors and Executive Committee, and Chair the Statutes Committee.

I have been involved in numerous WGA roles and initiatives over the years. When WGA formed out of the Association of International Glaucoma Societies, I co-chaired the strategic planning process that set out the goals and direction for the organization. It has been inspiring to see these goals realized by the tireless work of everyone involved with WGA. I have also been a member of the Program Planning Committee for the World Glaucoma Congress for many years and co-chaired the committee for the congresses in 2021 and 2023. WGA is the most important organization for glaucoma education and advocacy globally. This includes the WGC (the world's premier glaucoma meeting), International Glaucoma Review, the Journal of Glaucoma (the official journal of the WGA), and all of the educational materials produced by the Education Committee. I have been delighted to play my small part in the WGA mission and ensuring that the organization remains fiscal sound. As WGA continues to expand to parts of the world that lack adequate glaucoma care, these educational efforts will undoubtedly grow in importance.

Most importantly WGA has allowed me to develop a global network of friends and colleagues. These relationships have been invaluable during my career, both personally and professionally. I think that may be the truly invaluable role of WGA – connecting people from around the world who share a passion for improving glaucoma care!

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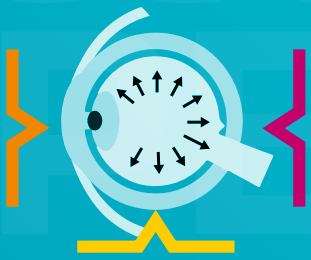

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Optic neuropathy in high myopia: Glaucoma or high myopia or both?
Zhang X, Jiang J, Kong K, Li F, Chen S, Wang P, Song Y, Lin F, Lin TPH, Zangwill LM, Ohno-Matsui K, Jonas JB, Weinreb RN, Lam DSC,
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Kolovos A, Hassall MM, Siggs OM, Souzeau E, Craig JE
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Richter GM, Takusagawa HL, Sit AJ, Rosdahl JA, Chopra V, Ou Y, Kim SJ, WuDunn D
Ophthalmology 2024; 131: 370-382
abstract no. 117928

Editor's Selection

Read Editor's Selection online

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

Join the discussion online using your WGA#One account.

Glaucoma as Cause of Blindness

Has the impact of glaucoma on global blindness changed?

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

117803 Global estimates on the number of people blind or visually impaired by glaucoma: A meta-analysis from 2000 to 2020; Eye 2024; 38: 2036-2046

Bourne et al. representing the Vision Loss Expert Group (VLEG) estimated the global and regional trends from year 2000 to 2020 of the number of persons visually impaired by glaucoma and their proportion of the total number of vision-impaired individuals through a systematic review and meta-analysis of published population studies. The estimates were age-standardized to the Global Burden of Disease standard population and 95% uncertainty intervals (UIs) were reported. Moderate or severe vision loss (MSVI) was defined as visual acuity of 6/60 or better but < 6/18 (moderate) and visual acuity of 3/60 or better but < 6/60 (severe vision loss). Blindness was defined as presenting visual acuity < 3/60.

For year 2020, the authors estimated that globally, 3.6 million (UI: 2.8-4.4) were blind and 4.14 million (UI: 3.2-5.2) had MSVI due to glaucoma. Glaucoma contributed to 8.4% of the global burden of blindness, highest contribution being noted in High income countries (26%) and North Africa and Middle East (15%) and lowest in South Asia (4.9%). Glaucoma contributed to 1.4% (UI: 1.1-1.8) of global MSVI, with Latin America and Caribbean, high-income countries and Sub-Saharan Africa regions having the highest percentages (1.9-2.0%). **The age-standardized prevalence of glaucoma blindness in population**

aged 50 years was 0.2% (UI: 0.16-0.25), the highest in Sub-Saharan Africa (0.66%). Males had higher glaucoma blindness prevalence than females across all world regions. Age-standardized prevalence of glaucoma MSVI in population aged ≥ 50 years was 0.23% (UI: 0.18-0.29).

The trend analysis shows interesting findings. **Across 2000-2020, there was reduction in age standardized prevalence of glaucoma blindness by 23.3%. However, there was an increase in age standardized prevalence of MSVI due to glaucoma by 5.9% in this period**. Regionally, Southeast Asia, East Asia and Oceania (18.4%), high-income countries (1.7%) and Sub-Saharan Africa (1.7%) showed an increase and other regions showed a decrease in glaucoma MSVI. Further, increases in MSVI due to glaucoma were higher in females (7.3%) compared to males (3.7%).

Shifts in proportion of blindness or MSVI due to glaucoma are likely to be influenced by relative changes in contributions of other non-glaucoma causes (such as cataract, corneal opacities, diabetic retinopathy) etc., but the observed trends in prevalence of glaucoma blindness and glaucoma MSVI are not likely to be influenced by these factors. The authors focus on blindness and MSVI due to glaucoma rather than overall morbidity due to glaucoma that has been previously reported.[1,4,5] The authors acknowledge that **the prevalence of glaucoma blindness and MSVI is most likely underestimated.** The most common data sources, the RAAB surveys assign the most preventable or treatable cause as primary cause to survey participants and visual fields are not assessed. There is a need for coordinated studies or development of survey methodology that can address some of the limitations of RAAB surveys in assessing glaucoma blindness. These should incorporate visual field testing to prevent misclassification of field defects as no visual impairment. The decline in age-standardized prevalence of glaucoma blindness is likely driven by improvements in health seeking resulting in early diagnosis and better management. At the same time, the increases in glaucoma MSVI prevalence that is driven by changes in certain regions demonstrate that regional gaps exist, requiring locally tailored strategies.

Glaucoma remains a serious public health issue as globally it the most common cause of irreversible blindness with over 50% of glaucoma remaining undiagnosed in developed nations reaching 95% in countries with low Human Development Index.2 Overall, the present study presents compelling evidence for prioritizing glaucoma in public health interventions.

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Anatomical Structures

Imaging ouflow pathways

Comment by Alex Huang and Ji-Hye Park, San Diego, CA, USA

118535 3D imaging of aqueous veins and surrounding sclera using a dual-wavelength photoacoustic microscopy; Ni L, Zhang W, Kim W, Warchock A, Bicket A, Wang X, Moroi SE, Argento A, Xu G; Biomedical optics express 2023; 14: 6291-6300

This research by Ni *et al*. employed dual-wavelength photoacoustic microscopy to visualize the anatomy of aqueous veins and the surrounding scleral texture in *ex-vivo* porcine and human eyes. The system's unique optical absorption properties enabled the vasculature to be imaged while avoiding more cumbersome post-processing needed for anterior segment OCT (AS-OCT). Further, dual wavelengths were used to attempt evaluation of aqueous humor outflow (AHO) pathways independent of the surrounding sclera.

Several limitations of this study must be noted. First, this approach still requires perfusion of a tracer, similar to aqueous angiography, and unlike AS-OCT. For aqueous angiography, tracers are FDA-approved for intravenous human use. In contrast, the tracer used here was a red tattoo dye, and its unique properties may have created limitations. For example, imaging was performed only after the TM was 'scratched' with a needle. It is possible that, without creating some level of ablation to the TM, the authors were unable to visualize the tracer. Second, while the 1200 nm laser setting enabled detection of collagen to provide information on the sclera, it may be an overstatement to claim that the authors fully revealed scleral texture. This is because the sclera is more than collagen and contains numerous extracellular matrix components, including different collagen subtypes, elastin fibers, proteoglycans, and glycoproteins. Moreover, as the 1200 nm laser can detect melanin, it is unclear whether underlying uveal tissue was also captured. Lastly, this approach still requires coupling. Photoacoustic imaging requires the probe to touch the eye or at least touch the eye through a coupling agent/lubricant. Translated to patient, this can get messy when imaging the entire eye and is not non-invasive/non-contact like OCT.

Ultimately, many approaches now exist to evaluate AHO pathways in both patients and experimentally in post-mortem eyes. Each has its own advantages and disadvantages. Ideally, for humans, the best method would include characteristics such as no touch/coupling agent required, no dye, rapid measurement, high resolution, and minimal image processing. No current method satisfies all these criteria, and further work is needed to achieve this goal.

Anatomical Structures

Outflow pathways in childhood glaucoma

Comment by Kaweh Mansouri, Lausanne, Switzerland

116894 Reduced aqueous humor outflow pathway arborization in childhood glaucoma eyes; Gupta S, Zhang X, Panigrahi A, Shakha , Fang R, Strohmaier CA, Zhang HF, Weinreb RN, Gupta V, Huang AS; Translational vision science & technology 2024; 13: 23

The hypothesis of this interesting paper by Gupta *et al*. is that studying abnormal aqueous humor outflow (AHO) is more straightforward in childhood glaucoma since the relationship between IOP and glaucoma is less complex than in adult forms of the disease. To do so, the authors applied aqueous angiography with indocyanine green (0.4%) to evaluate AHO patterns in five eyes with childhood glaucoma undergoing glaucoma surgery and compared these to one pediatric eye and five healthy adult eyes undergoing cataract surgery.

They found that childhood glaucoma eyes demonstrated reduced AHO pathway arborization compared to pediatric and adult eyes without glaucoma. Although childhood glaucoma and healthy adult cataract eyes showed similar AHO pathway branch lengths, childhood glaucoma eyes demonstrated significantly fewer branches and branch junctions and lower vessel densities.

For the first time, a study has demonstrated that pediatric glaucoma patients have reduced distal AHO pathways. This finding may explain why trabeculotomies (both external or internal) may be ineffective in this age group. As interesting as this finding is in itself, as so often in glaucoma, the sequence of damage remains unknown for now: whether distal AHO pathway changes are due to primary dysgenesis of the vessels or high IOP vessel collapse from lack of flow that subsequently could be rescued later.

The sequence of damage remains unknown for now: whether distal AHO pathway changes are due to primary dysgenesis of the vessels or high IOP vessel collapse from lack of flow that subsequently could be rescued later

This study is, of course, limited by a small sample size, by the fact that childhood glaucoma eyes are compared to adult cataract eyes among others. However, these limitations are to be seen in the context of a technically difficult and invasive examination

method that was performed in a vulnerable patient cohort. The authors should therefore be congratulated for this study and the light in sheds into the fundamental aspects of glaucoma.

Anatomical Structures

Fine-tuning the assessment of RNFL and disc rim

Comment by Miriam Kolko and Niklas Telinius, Copenhagen, Denmark

117105 Progressive changes in the neuroretinal rim and retinal nerve fiber layer in glaucoma: Impact of baseline values and floor effects; Tomita R, Rawlyk B, Sharpe GP, Hutchison DM, Shuba LM, Nicolela MT, Chauhan BC; Ophthalmology 2024; 131: 700-707

This study by Tomita *et al.* investigates the impact of baseline values on the detectability of structural changes in the optic nerve using optical coherence tomography (OCT).

Methods and Participants: The data originates from a longitudinal cohort study conducted at the Nova Scotia Health Eye Care Centre, which followed 97 patients with open-angle glaucoma and 42 healthy controls over a median period of seven years. Participants underwent biannual OCT imaging for a minimum of five years. Baseline minimum rim width (MRW) and peripapillary retinal nerve fiber layer thickness (RNFLT) measurements were categorized into three groups: within normal limits (WNL), borderline (BL), and outside normal limits (ONL). Linear mixed-effect models were applied to quantify global and sectoral rates of change, while the follow-up period for each participant was divided into two equal halves to examine temporal changes in progression rates.

Key Findings: Statistically significant changes in MRW and RNFLT were observed across all baseline damage categories, underscoring the value of OCT imaging even in patients with baseline values outside the normal limits. However, the magnitude of these changes diminished as baseline values decreased. Among glaucoma patients with ONL baseline MRW, 73% demonstrated measurable progression, with an average reduction of 2.74 µm/year, a rate significantly faster than the rate observed in healthy controls. Similarly, 64% of patients with ONL baseline RNFLT showed measurable changes, with an average reduction of 0.89 µm/year.

The study revealed a more pronounced floor effect in RNFLT compared to MRW. Over the follow-up period, RNFLT progression rates slowed significantly in the second half, while MRW rates remained consistent. Globally, RNFLT slopes became less negative during the latter period, indicating reduced detectability of change as RNFLT values approached the measurement floor. In contrast, MRW changes remained consistently detectable, even at

lower baseline values. These findings suggest that MRW is less affected by the floor effect, making it potentially more reliable for monitoring disease progression in advanced stages of glaucoma.

Limitations: Most participants had mild to moderate glaucoma, limiting insights into the progression patterns in more advanced stages. Additionally, while the study focused on MRW and RNFLT, it did not include macular imaging or ganglion cell complex thickness, which could provide complementary insights into glaucomatous changes. Lastly, the study did not identify a threshold for glaucomatous damage beyond which MRW or RNFLT would no longer be useful as diagnostic metrics.

Conclusion: This research underscores the importance of MRW and RNFLT as tools for monitoring glaucoma progression while highlighting notable differences in their sensitivity to baseline damage and susceptibility to floor effects. Although both parameters remain clinically valuable, MRW may offer greater reliability due to its reduced dependence on baseline values and its floor effect occurring later in the disease course. These findings support the use of OCT imaging, even for patients with baseline values outside the normal range.

Anatomical Structures

Should we rather be looking at the macula?

Comment by Jin Wook Jeoung, Seoul, South Korea

118332 Are macula or optic nerve head structures better at diagnosing glaucoma? An answer using Artificial Intelligence and wide-field optical coherence tomography; Chiang CYN, Braeu FA, Chuangsuwanich T, Tan RKY, Chua J, Schmetterer L, Thiery AH, Buist ML, Girard MJA; Translational vision science & technology 2024; 13: 5

The three-dimensional (3D) structural alterations in both the macula and optic nerve head (ONH) are critical for identifying glaucomatous damage, particularly in the earlier stages of the disease. Optical coherence tomography (OCT) has proven invaluable for diagnosing and monitoring glaucoma by capturing 3D images of these regions.[1,2] Recently, a new wide-field 3D-OCT technique has emerged, offering the advantage of simultaneously acquiring structural information from both the ONH and macula, potentially improving diagnostic accuracy.

Building on this foundation, Chiang et *al*. developed a deep-learning algorithm to automatically segment ONH and macula structures in wide-field 3D-OCT scans. This was followed by the application of a 3D convolutional neural network (3D-CNN) to classify

glaucoma and non-glaucoma eyes. The datasets utilized for classification were derived from macula scans, ONH scans, and wide-field scans, enabling a comparative analysis of diagnostic performance across these imaging modalities.

The study demonstrated that the classification algorithm achieved the highest diagnostic accuracy using wide-field scans, with an area under the curve (AUC) of 0.99 ± 0.01, compared to AUCs of 0.93 ± 0.06 for ONH scans and 0.91 ± 0.11 for macula scans. These findings provide robust evidence supporting the diagnostic superiority of wide-field OCT over localized imaging modalities.

A key strength of this study lies in its innovative integration of artificial intelligence and advanced wide-field OCT technology. The deep-learning algorithm facilitated precise segmentation and robust analysis, thereby enhancing diagnostic accuracy. Clinically, this approach holds significant potential for earlier glaucoma detection and improved management of complex cases, advancing the application of imaging technologies in routine ophthalmologic practice.

Nonetheless, several limitations warrant consideration. The cross-sectional design restricts the ability to assess the utility of wide-field OCT in monitoring glaucoma progression longitudinally. The dataset, while substantial, may not fully represent the diversity of patient demographics or glaucoma subtypes encountered in clinical practice. Moreover, the study did not evaluate the diagnostic performance of wide-field OCT in early or borderline glaucoma cases, which are critical for timely intervention. The reliance on structural imaging alone also overlooks the potential benefits of integrating functional assessments, such as visual field testing, to achieve a more comprehensive diagnostic approach.

In summary, this study highlights the promise of wide-field 3D-OCT combined with deep-learning methods for improving glaucoma diagnosis through detailed structural analysis. Future research should focus on addressing these limitations, including conducting longitudinal studies to assess the technology's value in disease monitoring, expanding datasets to enhance generalizability, and exploring the integration of functional testing.

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Basic Science

Glaucoma and metabolic dysfunction under pressure

Comment by Robert Casson, Adelaide, Australia

116853 Distinct metabolic profiles of ocular hypertensives in response to hypoxia; Langbøl M, Rovelt J, Saruhanian A, Saruhanian S, Tiedemann D, Baskaran T, Bocca C, Vohra R, Cvenkel B, Lenaers G, Kolko M; International journal of molecular sciences 2023; 25:

Langbøl *et al*. hypothesized that certain features of an individual's metabolism, in particular their response to bioenergetic stress, may contribute to the relative sensitivity/resilience of the retinal ganglion cell axons in normal tension glaucoma (NTG) and ocular hypertension (OHT), respectively. To test this, they conducted an interesting metabolomics experiment: humans with NTG, OHT, and controls were exposed to normobaric hypoxia for two hours, followed by a 30-min recovery period in normobaric normoxia; blood samples were collected at baseline, during hypoxia and in recovery. Samples were analyzed with a non-targeted metabolomics approach using liquid chromatography coupled to high-resolution mass spectrometry.

In individuals with NTG, hypoxia did not appreciably alter metabolites that were affected in controls, from which the authors infer a dysregulated metabolism in NTG. In individuals with OHT, certain metabolites involved in fatty acid biosynthesis and ketone body metabolism were upregulated, while tryptophan was downregulated. Given that tryptophan is involved in nicotinamide synthesis, one might expect downregulation to enhance axonal sensitivity;[1,2] nevertheless, the authors ascribe potential positive effects of tryptophan downregulation. The authors draw the strong conclusion that: "**the metabolomes of NTG and OHT patients are regulated differently from control subjects and show dysregulation of metabolites important for energy production.**"

The data do not support this conclusion

Untargeted metabolomics is a powerful tool, but the generated data are complex and the small sample size in each group in this study make the results difficult to interpret. **Only ten patients were included in each group and the initial principal components analysis (an 'unsupervised' statistical approach to obtain unbiased information about group separation) showed only noise**. Although the subsequent 'supervised' statistical approach using orthogonal partial to least squares-discriminant analysis had relatively high predictive scores (Q^2), this statistical method is sensitive to overfitting and

high Q^2 values can result from complicated models that fit noise rather than underlying patterns. The authors note that there were no significant differences between the groups in response to hypoxia and that no metabolites were significantly regulated in the groups when comparing levels from hypoxia to recovery.

The study motivates further research, but larger samples would be required to provide robust evidence of differential metabolic regulation in individuals with OHT and NTG.

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Basic Science

Astrocytes: what turns them from friend to foe?

Comment by David Calkins, Nashville, TN, USA

117032 A molecular switch for neuroprotective astrocyte reactivity; Cameron EG, Nahmou M, Toth AB, Heo L, Tanasa B, Dalal R, Yan W, Nallagatla P, Xia X, Hay S, Knasel C, Stiles TL, Douglas C, Atkins M, Sun C, Ashouri M, Bian M, Chang KC, Russano K, Shah S, Woodworth MB, Galvao J, Nair RV, Kapiloff MS, Goldberg JL; Nature 2024; 626: 574-582

Astrocyte glial cells play multiple functional roles throughout the central nervous system, including in the retina and optic projection. Named for their beautiful stellate appearance, astrocytes mediate critical metabolic, inflammatory, trophic, and immune interactions between neurons and their axons, vascular elements, and other glial cells, especially resident microglia. Astrocytes oscillate between different states, in a process known as reactivity. This term is not only an oversimplification, but also is associated almost entirely with pro-pathogenic processes. In fact, astrocyte phenotypes included both neurotoxic and neuroprotective states, each governed by distinct molecular signatures. Cameron *et al*. combined sophisticated analysis of astrocyte gene expression, cell culture assays, transgenic mouse modeling and demonstrates that neurotoxic vs. neuroprotective to make several important and novel discoveries stemming from the cAMP (cyclic adenosine monophosphate) signaling pathway.

> Their results shine a powerful spotlight on the innovation and utility of modulating intracellular astrocyte signaling cascades using gene therapy for patient-specific interventions tailored to key points in progression

Compartments of cAMP derived from soluble adenylyl cyclase (sAC) influence the balance between toxic vs. protective astrocyte states defined by distinct gene signatures and proliferation, which inhibits microglial activation and further astrocyte toxicity. Using a novel gene therapeutic that targets specifically optic nerve head astrocytes, the team showed that depleting cytoplasmic and increasing nuclear cAMP in astrocytes promotes retinal ganglion cell survival with nerve injury by inhibiting local microglial activity. Thus, sAC and compartmentalized cAMP define a molecular switch for inducing a protective astrocyte phenotype. Tweaking astrocyte molecular responses in glaucoma could be a critical step forward for treating optic nerve degeneration in the disease, especially for patients who progress despite efforts to manage intraocular pressure. For example,

astrocyte metabolic support of ganglion cell axons in the retina and optic nerve is important for slowing progression early in animal models of glaucoma. The approach taken in the study by Cameron *et al*. could be modified to influence astrocyte bioenergetics. Their results shine a powerful spotlight on the innovation and utility of modulating intracellular astrocyte signaling cascades using gene therapy for patient-specific interventions tailored to key points in progression.

Clinical Examination Methods

In-vivo monitoring of IOP distribution within the eye

Comment by Kaweh Mansouri, Lausanne, Switzerland

118107 Real-time in-vivo monitoring of intraocular pressure distribution in the anterior chamber and vitreous chamber for diagnosis of glaucoma; Seo H, Hong YM, Chung WG, Park W, Lee J, Kim HK, Byeon SH, Kim DW, Park JU; Science advances 2024; 10: eadk7805

> Little is known about dynamic IOP differences in the anterior and posterior chambers of the eye

Seo *et al.* developed minimally-invasive probes with pressure-sensitive transistors and used these to obtain continuous measurements of local IOP values in the anterior chamber and vitreous chamber of living rabbits. They then induced glaucoma in their animal models and compared the local IOP distribution between normal and glaucomatous eyes. They also used rebound tonometry for comparing these measurements.

They found that glaucoma induced higher IOP in the vitreous chamber than in the anterior chamber (+3.8 mmHg on average), a difference that was maintained throughout the measured range of 7-60 mmHg. Of note, the absolute difference in IOP between the vitreous chamber and the anterior chamber increased slightly in the high IOP condition (after the injection of hyaluronic acid into AC until the IOP saturation to the normal range). This absolute difference was less than 3 mmHg in the normal IOP range, but it was more than 3 mmHg in 36% of the points detected at high levels of IOP.

> Glaucoma induced higher IOP in the vitreous chamber than in the anterior chamber

Their experimental set-up is solid and maximum care was taken not to influence real IOP through the introduction of the needle-shaped sensors. Their *in-vivo* findings are also consistent with previous findings in enucleated porcine eyes. Few human studies exist that provide an insight to real-life IOP differences in human eyes. One such approach are IOP measurements with the EyeMate-SC sensor, a device which is placed within suprachoroidal space and measures IOP in the posterior chamber.

Seo *et al.*'s findings indicate that obtaining IOP measurements closer to the optic nerve may be more relevant for the diagnosis and management of glaucoma patients. It is hoped that more efforts will be invested in improving IOP measurements in the future.

Clinical Examination Methods

A virtual reality perimeter

Comment by Chris Johnson, Iowa City, IA , USA

116724 Validation of a wearable virtual reality perimeter for glaucoma staging, The NOVA Trial: Novel Virtual Reality Field Assessment; Bradley C, Ahmed IIK, Samuelson TW, Chaglasian M, Barnebey H, Radcliffe N, Bacharach J; Translational vision science & technology 2024; 13: 10

Automated perimeters that utilize a hemispheric bowl that have projected stimuli presented at different locations are a common form of visual field testing. However, they are quite expensive, require a dedicated testing room, are uncomfortable for some older patients, and require trained personnel to administer the test. As a result, portable devices for visual field testing such as tablets and virtual-reality headsets are now being developed. Alignment problems (head and eye), ambient light interference, glare, test distance consistency and other factors limit the utility of using tablets as an alternative means of performing perimetry. Virtual-reality headsets are able to overcome some of these difficulties.

There are a number of potential advantages associated with virtual-reality headsets: (1) they are portable, so testing can be performed anywhere; (2) head alignment can be maintained; (3) patients prefer testing with a virtual-reality headset; (4) virtual-reality headsets are more comfortable for testing; (5) both eyes can be tested at the same time. However, there are also disadvantages: (1) the range of intensities is smaller than for bowl perimeters; (2) older patients are not familiar with using headsets; (3) quantitative comparisons with automated bowl perimetry are still being performed; (4) there is no standard procedure for performing visual field testing with virtual-reality headsets.

This paper represents a comparison of results with a headset in comparison to the Humphrey Field Analyzer in a group of glaucoma patients and glaucoma suspects. This is admirable, but there are some difficulties associated with this investigation. (1) The test algorithm, method of determining reliability and other factors are proprietary, which basically means that one is dealing with a black box, making it difficult to assess its true performance, benefits and limitations. (2) Some of the statements are opinions that do not have evidence-based results to support them. (3) There is no indication as to how the headset was calibrated. (4) Much of the conclusions are descriptive rather than quantitative. A more comprehensive and thorough follow up study would be helpful.

What can be done to improve the clinical utility of virtual-reality headsets? When automated perimetry was first introduced, there were many manufacturers who introduced devices, most of which had different methodologies and test conditions, whereas now there are only a few that have similar procedures. It is likely that the same situation will occur for headsets. To overcome some of the current limitations, it is essential that headsets are developed with the intent of performing quantitative visual function testing. Most of the present devices utilize headsets that were originally designed for video game users that have been adapted for vision testing. This severely limits the capabilities of these instruments.

Clinical Examination Methods

Quantification of perimetric variability

Comment by Giovanni Montesano, London, UK

117840 Quantification and predictors of visual field variability in healthy, glaucoma suspect, and glaucomatous eyes using SITA-Faster; Tan JCK, Agar A, Kalloniatis M, Phu J; Ophthalmology 2024; 131: 658-666

In this study, Tan *et al.* examined the variability profile of the newest addition to the SITA strategy—SITA Faster. They performed two SITA-Faster tests per eye in a cohort of 1426 eyes of 787 patients with a mean age of 64.9 ± 12.0 years: 540 eyes with glaucoma, 753 eyes classified as glaucoma suspect and 133 eyes classified as healthy. The mean baseline MD was -1.71 ± 3.2 dB (-3.55 ± 4.0 dB in the glaucoma cohort). The mean global and pointwise variability was reported to be 2.17 ± 1.2 dB and 2.17 ± 2.9 dB respectively.

Most of their results were in line with expectations from previous literature: the pointwise variability was larger for lower sensitives and for more peripheral locations. The variability profile of SITA-Faster was noted to be similar to findings by Heijl *et al*.[1] who compared SITA-Faster, SITA-Fast and SITA-Standard in glaucoma and glaucoma-suspect patients.

Perhaps the most intriguing finding in study is the association (or rather, lack thereof) between higher false-positive (FP) error rates and a more positive test-retest difference in the MD. This resurfaces the age-old question: *are reliability indices reliable*? Most evidence, including this study, suggests, at best, a weak association between reliability indices and actual reliability of perimetric tests.[2,3] Yet, these indices continue to befuddle clinicians and harm patients, whose tests are disregarded as 'unreliable' based on flawed metrics.

This issue is only going to be exacerbated as the tests become quicker. SITA algorithms quantify FPs by using responses captured during time gaps between presentations.[4] However, shorter tests mean less time to 'listen' for false responses, leading to inaccurate – and often inflated – estimates of FPs.[5-7]

Shorter tests mean less time to 'listen' for false responses, leading to inaccurate – and often inflated – estimates of FPs

What good are faster, more frequent tests if their results are rendered unusable by arbitrary thresholds unsupported by evidence?

In summary, algorithms like SITA-Faster are proving increasingly useful in saving time and resources for individual tests, with little compromise on reliability compared to older algorithms. Our assessment of such reliability needs to evolve alongside our perimetric strategies.

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Clinical Examination Methods

Assessing RNFL damage using retinal retardance

Comment by Kazuhiro Kurokawa and Brad Fortune, Portland, OR, USA

117967 Retinal nerve fiber layer damage assessment in glaucomatous eyes using retinal retardance measured by polarization-sensitive optical coherence tomography; Parakkel RR, Wong D, Li C, Cheong J, Nongpiur ME, Chong RS, Aung T, Schmetterer L, Liu X, Chua J; Translational vision science & technology 2024; 13: 9

Advances are underway for polarimetric imaging in glaucoma

Polarimetric imaging has garnered clinical interest especially in the field of glaucoma owing to its distinct property that allows for characterizing the parallel alignment of molecules in the living ocular tissues, such as peripapillary retinal nerve fibers (pRNFs), which, were studied recently by Parakkel and colleagues. In their report, these authors quantified pRNF retardance (actually full thickness retinal retardance, a minor difference) in early, moderate and severe glaucoma (primary open-angle glaucoma, POAG) using their prototype polarization-sensitive OCT (PS-OCT) system. **One strength of their study, self-designated as a pilot study, was its relatively large sample size, including 80 healthy eyes of 49 participants comprising the control group and 90 eyes of 68 patients diagnosed with glaucoma**. They also conducted intra- and inter-visit repeatability analysis in subsets of these cohorts. The study also benefitted from a formal comparison to standard clinical SD-OCT imaging (measurement of pRNFL thickness), performed using a commercially available CIRRUS HD-OCT 6000 system. One important limitation of the study was a large difference in the age of the control groups versus the study cohort (43 ± 16 years versus 67 ± 9 years, respectively), although, post-hoc analyses included adjustments for age, gender and axial length. **Their results demonstrated excellent repeatability of retardance measured using their prototype PS-OCT system, as well as a very strong correlation between retardance and pRNFL thickness.** Both retardance and thickness provided very high levels of diagnostic accuracy,

with AUC values of 0.98 and 0.97, respectively. Retardance exhibited a slightly stronger correlation with visual field mean deviation (VF-MD) than thickness, overall, and among the sub-group of eyes with severe POAG (VF-MD values worse than -12 dB).

However, among eyes with early and moderate stage POAG, structure-function correlations were generally weaker for both retardance and thickness, and not statistically significantly different from each other. The authors argued that the stronger structure-function correlation for retardance among eyes with worse glaucoma was likely due to its reduced dependence on image segmentation accuracy, especially at the locations of larger blood vessels.

One drawback of this study was its lack of measurement of depth-resolved birefringence (a lost opportunity given the technological advance over prior clinical instruments used for measurement of retardance, *e.g.*, scanning laser polarimetry as implemented in the GDx device). Thus, the field still lacks unequivocal evidence from clinical studies that birefringence abnormalities are a harbinger of subsequent RNFL thinning in neurodegenerative diseases affecting the optic nerve, such as glaucoma, as predicted decades ago by Knighton and colleagues[1-3] and demonstrated in non-human primate experimental models of glaucoma and optic nerve injury.[4-7] In this regard, it is slightly disappointing to find that the results of this most recent study by Parakkel *et al*. reaffirm that, despite significant technological development, the diagnostic performance of PS-OCT remains similar to OCT-based RNFL thickness measures.

It is slightly disappointing to find that the results of this most recent study by Parakkel *et al*. reaffirm that, despite significant technological development, the diagnostic performance of PS-OCT remains similar to OCT-based RNFL thickness measures

However, it is quite intriguing that Parakkel *et al*. found a stronger correlation between retardance and VF-MD in the eyes with severe glaucoma. If true, this could lead to an important implication in the late stage of glaucoma along with further development of in vivo polarimetry. Future work with PS-OCT is needed to address costs and complexities while finding applications that clearly benefit patients.

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Risk Factors

Risk factors for NTG progression

Comment by Yunhan Lee and Michael Kook, Seoul, Korea

116720 Natural history and risk factors for glaucoma progression in Chinese patients with normal-tension glaucoma; Chen DF, Wang C, Si Y, Lu X, Zhou W, Huang Q, Zuo J, Cheng G, Leung DYL, Wang N, Friedman DS, Liang Y; Investigative Ophthalmology and Visual Science 2024; 65: 28

While the Collaborative Normal Tension Glaucoma Study and Early Manifest Glaucoma Trial primarily focused on non-Asian populations,[1,2] this study provides valuable insights into the progression of normal-tension glaucoma (NTG) in Chinese patients, addressing a knowledge gap regarding NTG in Asian cohorts. It complements prospective studies conducted in Japanese patients,[3] enabling comparisons of regional differences within Asia. Unlike the Japanese study, this study identifies shorter axial length (AL) and younger age as distinctive contributors to NTG progression, offering a fresh perspective on NTG pathophysiology.

Identification of shorter AL as a risk factor for NTG progression

The identification of shorter AL as a risk factor for NTG progression is noteworthy. The authors suggest that this may result from crowded optic nerve head anatomy in shorter eyes, which increases mechanical stress and susceptibility to glaucomatous damage. Conversely, longer AL may offer protection against progression by minimizing IOP fluctuations[4] and reducing mechanical strain on the lamina cribrosa. Unexpectedly, younger age was also associated with faster structural progression, in contrast to previous studies that linked older age to more rapid progression. The authors hypothesize that younger patients may lack the vascular adaptations seen in older individuals, such as elevated systolic blood pressure, which could help maintain optic nerve perfusion.

Interestingly, IOP fluctuation was not identified as a significant risk factor in this study, differing from findings in Japanese and other populations.[3] The authors propose that the higher mean IOP observed in this cohort may overshadow the effects of IOP fluctuations. This suggests that mean IOP may play a more critical role in NTG progression in populations with relatively higher baseline IOPs.

This study highlights the complex interplay of AL and age in NTG progression. Further research is needed to validate these findings and determine whether these risk factors arise from universal mechanisms or are population specific. Overall, this study makes a significant contribution to understanding NTG in Asian populations and emphasizes the importance of individualized management strategies for NTG.

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Risk Factors

Risk factors for progression of angle-closure suspect eyes

Comment by Xiulan Zhang and Deming Wang, Guangzhou, P.R. China

116739 Long-term risk and prediction of progression in primary angle closure suspect; Yuan Y, Xiong R, Wang W, Xu BY, Liao C, Yang S, Li C, Zhang J, Yin Q, Zheng Y, Friedman DS, Foster PJ, He M; JAMA ophthalmology 2024; 142: 216-223

Primary angle-closure suspect (PACS) represents an initial condition within the continuum of angle-closure diseases, which may evolve into primary angle closure (PAC) and eventually primary angle-closure glaucoma (PACG)[1]. PACS is defined by the presence of iridotrabecular contact across at least 180 degrees without elevation of intraocular pressure (IOP) or optic nerve damage.[1,2] Elucidating the progression from PACS to PAC is pivotal in clinical settings to facilitate the identification of risk factors and structural predictors, thereby enabling timely intervention strategies.[3-5]

In their 14-year longitudinal study, Yuan *et al.* examined and analyzed 377 PACS patients from the Zhongshan Angle Closure Prevention trial.[2] They discovered that during the follow-up period, 25% of the subjects advanced from PACS to PAC. Notable predictors of this progression included higher IOP, reduced anterior chamber depths, and anatomical parameters measurable via anterior segment optical coherence tomography (AS-OCT), such as the trabecular-iris space area and angle recess area. These findings underscore the importance of structural biomarkers in risk stratification and the customization of management for PACS, providing valuable guidance for the monitoring and prevention strategies in high-risk individuals.[2,6]

This study offers valuable insights into the progression from PACS to PAC, with several areas for future improvement. A more comprehensive temporal analysis of progression could yield deeper understanding of how the importance of risk factors evolves over time. Future research could also benefit from broadening the inclusion criteria to encompass eyes that have received treatment, thereby enhancing the generalizability of the results. Considering that the cohort predominantly consisted of urban Southern Chinese residents, replicating this study across a variety of demographic groups would be valuable for verifying its wider relevance. Continuing to explore these aspects is crucial for advancing our comprehension of PACS progression and improving clinical approaches for diverse patient populations.

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Glaucoma and Systemic Diseases

POAG and diabetic retinopathy

Comment by Rupert Bourne, Cambridge, UK

117110 Association of primary open-angle glaucoma with diabetic retinopathy among patients with Type 1 and Type 2 diabetes: A large global database study; Chauhan MZ, Elhusseiny AM, Kishor KS, Sanvicente CT, Ali AA, Sallam AB, Bhattacharya SK, Uwaydat SH; Ophthalmology 2024; 131: 827-835

The association between diabetes mellitus (DM) and primary open-angle glaucoma (POAG) has long been studied, with several studies reporting an increased risk of POAG in individuals with diabetes mellitus, with a prevalence around twice as high as the non-diabetic population.[1-4] IOP is an important confounder in the relationship between diabetes mellitus and POAG. There has also been a variation in the findings regarding the association between diabetes and POAG progression. In this retrospective study by Chauhan *et al*., the risk of diabetic retinopathy (DR) among those with POAG is explored, using a very large global patient database. The authors used propensity score matching (PSM) to harmonize two cohorts one of diabetics with POAG (n = 44,359) and another of diabetics without glaucoma (4,393,300), such that the two cohorts (each with 39,680 patients) could be compared for first-time onset of diabetic retinopathy, at intervals up to ten years. PSM attempts to reduce the bias due to confounding variables that could be found in an estimate of the POAG effect obtained from simply comparing outcomes among those with POAG versus those without. In this case an array of covariates included

co-morbidities, demographics, blood glucose and cholesterol, and care-seeking behaviors, were used in the PSM process. **The authors report a greater risk of proliferative diabetic retinopathy (PDR) among patients with Type 1 DM within the POAG group compared to those without glaucoma at one year (relative risk, RR, 3.0) and at ten years (RR, 7.0)** and that the elevated risk of any DR was sustained over an extended period (adjusted Hazard Ratio, 3.74; at ten years). The risk of first-time DR and PDR in Type 2 DM patients was also higher across the time period.

These findings concur with a much smaller clinical study[5] and also findings from the Danish Registry of Diabetic Retinopathy, which included almost 10,000 patients with glaucoma or ocular hypertension.[6] The authors refer to the common mechanisms associated with both DM and glaucoma such as compromised autoregulation of retinal blood flow, ischaemia, and an interesting concept whereby loss of retinal ganglion cells in POAG may disrupt 'neurovascular coupling' – a process that involves adjustment of blood flow in response to neural activity.[7] Despite limitations of selection and information bias (which are well-described), there was a significant effort by the authors to control for potential confounders, which makes it an important addition to a body of evidence that suggests eyecare providers should adjust surveillance strategies in DR screening programs when glaucoma is already known.

There was a significant effort by the authors to control for potential confounders, which makes it an important addition to a body of evidence

Additionally, DR screening programs offer the opportunity for glaucoma case-finding, which increasingly can become automated, and the heightened risk of DR in a glaucomatous diabetic flagged.

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Medical Treatment

Efficacy and safety of a fixed RKI-brimonidine combination

Comment by Kaweh Mansouri, Lausanne, Switzerland

117152 Long-term intraocular pressure-lowering efficacy and safety of ripasudil-brimonidine fixed-dose combination for glaucoma and ocular hypertension: a multicentre, open-label, phase 3 study; Tanihara H, Yamamoto T, Aihara M, Koizumi N, Fukushima A, Kawakita K, Kojima S, Nakamura T, Suganami H; Graefe's Archive for Clinical and Experimental Ophthalmology 2024; 262: 2579-2591

Tanihara *et al*. report the results of a multicenter, open-label, phase-3 study in Japanese patients with glaucoma (POAG and PEXG) or OHT, designed to evaluate the long-term (52-week) efficacy and safety of ripasudil-brimonidine fixed-dose combination (RBFC), both alone and as a concomitant medication. Previously, two phase-3 studies had demonstrated the IOP-lowering efficacy of RBFC over eight weeks and found that patients receiving RBFC had significantly greater reductions in IOP than those receiving ripasudil or brimonidine alone. Patients were assigned to one of four combination therapy cohorts, based on previous treatment(s) received: prostaglandin (PG) analogue (Cohort 1); PG analogue and beta-adrenoceptor blocker (β-blocker) (Cohort 2); PG analogue, β-blocker and carbonic anhydrase inhibitor (Cohort 3); or other/no treatment (Cohort 4), in total 179 patients.

Despite high rates of conjunctival hyperemia, ROCK inhibitors are an important addition to the glaucoma treatment armamentarium

For all cohorts, mean IOP was significantly reduced at week 52 with the changes from baseline of −2.7 to −4.1 mmHg across cohorts. Subgroup analyses showed that RBFC had stable IOP-lowering effects across patient demographics and clinical characteristics. Common adverse effects were conjunctival hyperaemia (58%), allergic conjunctivitis (18%) and blepharitis (17%), most of which were mild in severity.

This is a well-conducted and impactful study on the first topical fixed-dose combination treatment for glaucoma that combines a rho kinase (ROCK) inhibitor with an α2-agonist. It demonstrates that, despite high rates of conjunctival hyperemia, ROCK inhibitors are an important addition to the glaucoma treatment armamentarium.

Surgical Treatment

Outcomes of gonioscopy-assisted trabeculotomy

Comment by Xiulan Zhang and Zefeng Yang, Guangzhou, P.R. China

117011 Gonioscopy-assisted transluminal trabeculotomy outcomes under different levels of glaucoma severity: A multicenter, comparative study; Magacho L, Franco CGVS, I EA, Pereira ACA, Teno B, Lucena-Neto F, Faria BM, Vieira JM, Vianello MP, Kanadani FN; American Journal of Ophthalmology 2024; 264: 75-84

Gonioscopy-assisted transluminal trabeculotomy (GATT) is a minimally invasive, conjunctiva-sparing surgery, initially considered effective for mild to moderate primary open-angle glaucoma (POAG).[1] Recent evidence shows it is also safe and effective for advanced cases.[2,3] At this point, comparing GATT outcomes across different glaucoma severities can help surgeons identify its suitability for different patients.

In this multi-center retrospective study by Magacho *et al*., GATT (Phaco-GATT or GATT stand-alone) was performed on 270 eyes (90 mild, 75 moderate, 105 advanced POAG). At 12 months postoperatively, GATT reduced IOP significantly across all groups, from 18.6 mmHg (mild), 19.7 mmHg (moderate), and 21.0 mmHg (advanced) preoperatively, to around 11.9 mmHg in all groups. Relative success rates remained high (88.1% to 93.8%) in all groups. However, complete success rates declined with increasing severity (61.8% in mild, 43.8% in moderate, and 37.6% in advanced cases), even though the researchers believed that glaucoma severity is not a major variable associated with surgical success. This study addresses a common limitation of previous research that often reports average outcomes without stratifying by glaucoma severity.

GT, also called ab interno trabeculotomy, can be performed with different degrees. Previous studies comparing 120°, 240°, and 360° GT (GATT) with or without phacoemulsification cataract extraction and intraocular lens implantation (PEI) have shown similar efficacy in reducing IOP and medication use in POAG.[4-7] This suggests that 120° GT with or without PEI, which is associated with a simpler procedure and fewer complications, is sufficient for treating POAG. In juvenile-onset open-angle glaucoma (JOAG), 240° and 360°GT showed similar efficacy in IOP reduction, both superior to 120°GT (unpublished data), similar to previous study.[8] This suggests that a broader surgical range provides better results in JOAG. Therefore, larger, prospective studies, ideally RCTs, are still needed to confirm the necessity of GATT.

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Surgical Treatment

Clinical outcomes in aqueous misdirection syndrome

Comment by Luciano Quaranta, Brescia, Italy

117916 Aqueous misdirection syndrome: clinical outcomes and risk factors for treatment failure; Senthil S, Goyal S, Mohamed A, Garudadri C; Graefe's Archive for Clinical and Experimental Ophthalmology 2024; 262: 2209-2217

The study presents a detailed analysis of Aqueous Misdirection (AM) outcomes following various intraocular surgeries, with a focus on the differential impacts observed in phakic versus pseudophakic patients. The findings underscore the complexity of managing AM, particularly in the context of prior ocular surgeries, and offer valuable insights for clinical practice.

One of the key strengths of this study is its rigorous examination of treatment responses, highlighting the significantly higher success rates of iridozonulo-hyaloido-vitrectomy (IZHV) combined with Pars Plana Vitrectomy (PPV) compared to Laser Hyaloidotomy and Transscleral Cyclophotocoagulation (TSCPC). This suggests that IZHV may be a preferable intervention for patients with AM, particularly those with complex surgical histories.

Additionally, the identification of pseudophakia as a significant predictor of treatment failure for conservative management emphasizes the necessity for heighted vigilance in this patient demographic. The association of shorter axial lengths with an increased risk of treatment failure further suggests that anatomical considerations must play a central role in individualizing patient management.

The study emphasizes the critical role of early diagnosis and timely intervention, with delayed presentation correlated with poorer outcomes. This finding serves as a reminder for clinicians to prioritize prompt referral and comprehensive evaluation strategies for patients exhibiting signs of AM.

While the article presents valuable findings regarding the management and outcomes of AM in phakic and pseudophakic patients, several aspects warrant critical examination: the study includes a relatively small sample size (49 eyes from 47 patients), which may limit the generalizability of the findings.

The treatment modalities varied greatly between patients, which may introduce variability in outcomes. Without standardized treatment protocols, it becomes challenging to draw direct comparisons between the effectiveness of different interventions.

While the study reports success rates in terms of anatomical resolution and intraocular pressure (IOP) control, it lacks a comprehensive evaluation of visual outcomes and patient-reported quality of life measures. These aspects are critical in understanding the full impact of AM and its treatment on patients.

Several risk factors are evaluated, but the analysis could benefit from a more thorough consideration of confounding variables. For instance, the impact of comorbid ocular diseases or systemic conditions that could influence treatment outcomes is not adequately addressed.

While the study uses statistical comparisons to assess the efficacy of different treatments, there might be room for a different statistical model (such as multivariate analyses) that could further clarify the effect of the various factors on treatment outcomes.

As a personal comment on the topic, in my clinical practice, when I have to explain the risks/benefits of cataract or glaucoma surgery in patients with small eyes (*i.e.*, potential higher risk of AM), I always illustrate the possibility, although infrequent, not predictable and not preventable, of the onset of aqueous misdirection even after a perfectly successful surgery. I also explain the possible need for further surgery (IZHV) to solve the problem. I almost always propose an IZHV to solve the problem, as almost all other procedures analyzed in the paper have a low success rate and a higher probability of AM recurrence.[1]

In small eyes after cataract surgery, I use atropine eye drops in the first three days after surgery to prevent the onset of AM. If, upon suspension of atropine, I notice a reduction in the depth of the anterior chamber and consequent onset of myopia associated or not with an increase in IOP, I always propose an IZHV in a short time. This is because the best results, including refractive ones, are obtained only if the procedure is performed in a short time. I do not believe that the chronic use of atropine, as is still proposed by some ophthalmologists, is a current solution today.[2]

Overall, this article enriches the existing literature on anterior segment complications following ocular surgery and highlights the importance of personalized approaches to optimize patient outcomes.

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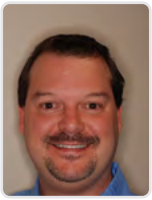
Prognostic factors
IOP variability and RGC loss



Comment by Tony Realini, Morgantown, WV, USA

118083 Association of long-term intraocular pressure variability and rate of ganglion complex thinning in patients with glaucoma; Mahmoudinezhad G, Moghimi S, Nishida T, Walker E, Latif K, Liebmann JM, Fazio MA, Girkin CA, Zangwill L, Weinreb RN; American Journal of Ophthalmology 2024; 264: 104-119

Mahmoudinezhad and colleagues have conducted a prospective cohort study in patients with glaucoma spanning the severity spectrum from early to advanced to explore the relationship between long-term intraocular pressure (IOP) variability and the rate of optical coherence tomography (OCT) ganglion cell complex (GCC) thinning over time. Study participants attended a minimum of four clinic visits with a minimum of two years of OCT follow-up. A linear mixed-effect model was utilized to investigate the association of IOP parameters (mean IOP, IOP fluctuation [the standard deviation of all IOP measurements], and IOP range [maximum minus minimum IOP]) with rates of GCC thinning. Analyses were conducted on early and moderate-advanced glaucoma subgroups. Overall, 369 eyes of 249 participants were included; 282 eyes had early glaucoma and 87 had moderate-advanced glaucoma. The mean duration of follow-up was 5.1 years. The overall mean rate of GCC change was -0.59 microns per year and was similar in both the early and moderate-advanced subgroups. In multivariable models, higher IOP fluctuation and higher IOP range were significantly associated with faster annual GCC thinning controlling for mean IOP and other cofounders. Most of what we know about the relationship between IOP variability and glaucoma progression comes from post hoc analyses of large clinical trials not designed to directly assess this important topic, and as a result, the findings of such analyses have been mixed. Also, many prior studies have utilized visual field change as the metric for disease progression, which has numerous limitations, including high test-retest variability and limited sensitivity in early disease. This study's strengths are that it was designed and conducted specifically to assess the relationship of interest, and that it relied on structural rather than functional assessment of glaucoma progression. OCT parameters are more objective than visual field parameters and are more sensitive to change early in the disease process. The clinical implications of this study are limited by a critical missing piece of the puzzle: does reducing IOP variability decrease the rate of structural glaucoma progression?

Does reducing IOP variability decrease the rate of structural glaucoma progression?

Prognostic factors

IOP variability and visual field progression

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

116979 Relationship between intraocular pressure fluctuation and visual field progression rates in the United Kingdom Glaucoma Treatment Study; Rabiolo A, Montesano G, Crabb DP, Garway-Heath DF; Ophthalmology 2024; 131: 902-913

Rabiolo *et al*. investigated the relationship between intraocular pressure (IOP) fluctuation and visual field (VF) progression in the United Kingdom Glaucoma Treatment Study (UKGTS). The study included 430 participants with at least five VF tests (213 placebo, 217 treatment). In the placebo group, the authors found that a latent variable (PC1) that captures IOP peak and mean, among others, as well Pascal ocular pulse amplitude (OPA) were associated with faster rates of VF progression. In the treatment group, only PC1 had a significant association. However, diurnal or long-term IOP fluctuations were not associated with progression in either group. **The study concluded that there was no evidence to support that either diurnal or long-term IOP fluctuation, as measured in clinical practice, are independent factors for glaucoma progression.** Other aspects of IOP, including mean IOP and peak IOP, may be more informative.

The paper presents data of a well-conducted randomized trial which helped mitigate the effects of treatment escalation on the investigated relationship between IOP and progression. This was not done as systematically in previous, related studies, therefore limiting the interpretation of their results. The authors meticulously evaluated IOP fluctuation across various timeframes, including short-term, office hours (diurnal fluctuation), and long-term (between-visit variation). This approach provides a thorough understanding of IOP fluctuation dynamics. They also employed principal component analysis (PCA) to address the issue of multicollinearity among IOP-related metrics, which was largely overlooked in previous studies. This approach ensured that the statistical analysis was not compromised by the high correlation between variables.

The study did not include nighttime/early morning IOP measurements, which could provide valuable insights into the relationship between nocturnal IOP fluctuations and glaucoma progression

Furthermore, the only relevant limitation was that the study cohort primarily consisted of treatment-naïve patients with early glaucomatous damage, mainly of European descent. This limits the generalizability of the findings to other populations, particularly those with advanced glaucoma or different racial backgrounds. Although not of major concern, the study did not include nighttime/ early morning IOP measurements, which could provide valuable insights into the relationship between nocturnal IOP fluctuations and glaucoma progression. Of course, this would have required a much more complex study design and was not the focus of the trial.

Overall, the study by Rabiolo *et al*. is a well-conducted investigation that contributes significantly to our understanding of the relationship between IOP fluctuation and glaucoma progression. The authors should be commended for their rigorous methodology, comprehensive assessment of IOP fluctuation, and efforts to minimize confounding factors.

Prognostic factors

ONH hemorrhage size and visual field progression

Comment by Stephanie Noh and Steve Mansberger, Portland, OR USA;

117171 Clinical Significance of Optic Disc Hemorrhage Size in Visual Field Progression in Glaucoma; Jeong Y, Bak E, Jang M, Ha A, Shin YI, Huh MG, Kim YK, Jeoung JW, Park KH; American Journal of Ophthalmology 2024; 263: 109-116

Disc hemorrhages (DHs) are strongly associated with the development and progression of glaucoma. While many studies report the association of glaucoma with the presence of disc hemorrhage, this study investigates the association between the size of the disc hemorrhage and risk for glaucomatous progression on visual fields. In this retrospective cohort study conducted at a tertiary center in South Korea, 250 patients with open-angle glaucoma with disc hemorrhages were followed for a minimum of five years. The main outcome measures were disc hemorrhage size and visual field progression, measured as the rate of mean deviation (MD) loss using guided progression analysis (GPA) on Humphrey visual field testing.

Subjects were divided into 'small' (< 0.049245 mm^2) versus 'large' (> 0.049245 mm^2) DH groups based on the median value. If there were multiple DHs, then the DH area was averaged. This study showed that the large DH group had statistically significant faster global MD loss rate and MD loss rate in the affected hemisphere (−0.51 ± 0.48 dB/y and −0.72 ± 0.66 dB/y, respectively), compared to the small DH group which loss rates of −0.36 ± 0.42 dB/y and −0.52 ± 0.59 dB/y (with p = .010 and .024, respectively). Notably, there

was no difference in the rate of progression between the two groups in the unaffected hemisphere. Additionally, the authors looked at factors that influenced the rate of global MD loss and found that it was significantly influenced by larger mean DH area, larger maximum DH area and worse baseline MD using multivariate analysis (p-values < .05).

Overall, the study concludes that patients with large DHs should be examined more attentively given potentially faster VF progression. The strengths of this study include the large sample size and relatively long follow-up period. Practically speaking, it may be unfeasible for clinicians to ascertain the size of a DH based on the authors' measurement protocol in daily clinical practice. In this study, there was no significant difference in the reduction of IOP between the small and large DH groups, and there did not appear to be a significant percent IOP reduction after detection of DH (mean reduction of 4.0% ± 17.0%). In future studies, it would be interesting to see if greater IOP reduction especially in cases of large DH could potentially mitigate the rate of MD loss.

Prognostic factors

Does PPA atrophy indicate glaucoma progression?

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

116870 Peripapillary atrophy area as an indicator of glaucomatous structural and functional progression; Khreish M, Schuman JS, Lee T, Ghassabi Z, Zambrano R, Hu J, Ishikawa H, Wollstein G, Lavinsky F; Translational vision science & technology 2024; 13: 1

This study investigated the relationship between peripapillary atrophy (PPA) area, measured with optical coherence tomography (OCT), and structural and functional progression in glaucoma. The study included 71 eyes from 50 subjects with open-angle glaucoma, with a mean follow-up duration of 4.4 years. The researchers found that longitudinal **changes in PPA area were significantly associated with changes in visual field parameters (mean deviation and visual field index) and structural parameters** (ganglion cell inner plexiform layer thickness), indicating that PPA area can be a useful indicator of glaucoma progression.

PPA area can be a useful indicator of glaucoma progression

A positive aspect of the study is its prospective, longitudinal design, which allowed the researchers to track changes in PPA area and other parameters over time. Many of previous studies were retrospective or just compared changes between two distinct time

points. This provides stronger evidence for the relationship between PPA area and glaucoma progression than previous studies. Additionally, the authors should be commended for their innovative methodology in measuring PPA with OCT. The utilization of OCT for PPA quantification is a significant step forward, particularly by combining en face images and b-scans, offering greater precision and reproducibility compared to traditional stereophotography. The high reproducibility achieved in this study underscores the reliability of the method and its potential for future clinical applications.

However, the study also has some limitations. **It is unclear what proportion of the sample actually had any PPA, as well as how they treated this group statistically**. It would be important to show whether there was a significant association between presence of PPA (yes vs. no) and progression, as done in previous studies. In addition, it would be worth testing for relationship between age (and aging) and PPA changes. This is important because **one alternative interpretation of the results is that PPA and progression have no cause-consequence relationship, but they could be completely independent in terms of biological effects but are simply correlated with the normal aging of the eye**.

Notwithstanding, this study provides higher level evidence for the relationship between baseline PPA, PPA changes, and glaucoma progression (on OCT and visual fields) which are invaluable for clinical management.

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- Nishani Amerasinghe (Southampton, UK) > view comments on e-igr.com
- Abdus Samad Ansari (London, UK) > view comments on e-igr.com
- Miki Atsuya (Nagoya, Japan) > view comments on e-igr.com
- Augusto Azuara Blanco (Belfast, UK) > view comments on e-igr.com
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News Flashes

- ★ The sequence of damage remains unknown for now: whether distal AHO pathway changes are due to primary dysgenesis of the vessels or high IOP vessel collapse from lack of flow that subsequently could be rescued later
- ★ Their results shine a powerful spotlight on the innovation and utility of modulating intracellular astrocyte signalling cascades using gene therapy for patient-specific interventions tailored to key points in progression
- ★ Little is known about dynamic IOP differences in the anterior and posterior chambers of the eye
- ★ Glaucoma induced higher IOP in the vitreous chamber than in the anterior chamber
- ★ Shorter tests mean less time to “listen” for false responses, leading to inaccurate—and often inflated—estimates of FPs
- ★ It is slightly disappointing to find that the results of this most recent study by Parakkel et al. reaffirm that, despite significant technological development, the diagnostic performance of PS-OCT remains similar to OCT-based RNFL thickness measures
- ★ Advances are underway for polarimetric imaging in glaucoma
- ★ Identification of shorter AL as a risk factor for NTG progression
- ★ There was a significant effort by the authors to control for potential confounders, which makes it an important addition to a body of evidence
- ★ Despite high rates of conjunctival hyperemia, ROCK inhibitors are an important addition to the glaucoma treatment armamentarium
- ★ Does reducing IOP variability decrease the rate of structural glaucoma progression?
- ★ The study did not include nighttime/ early morning IOP measurements, which could provide valuable insights into the relationship between nocturnal IOP fluctuations and glaucoma progression
- ★ PPA area can be a useful indicator of glaucoma progression

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