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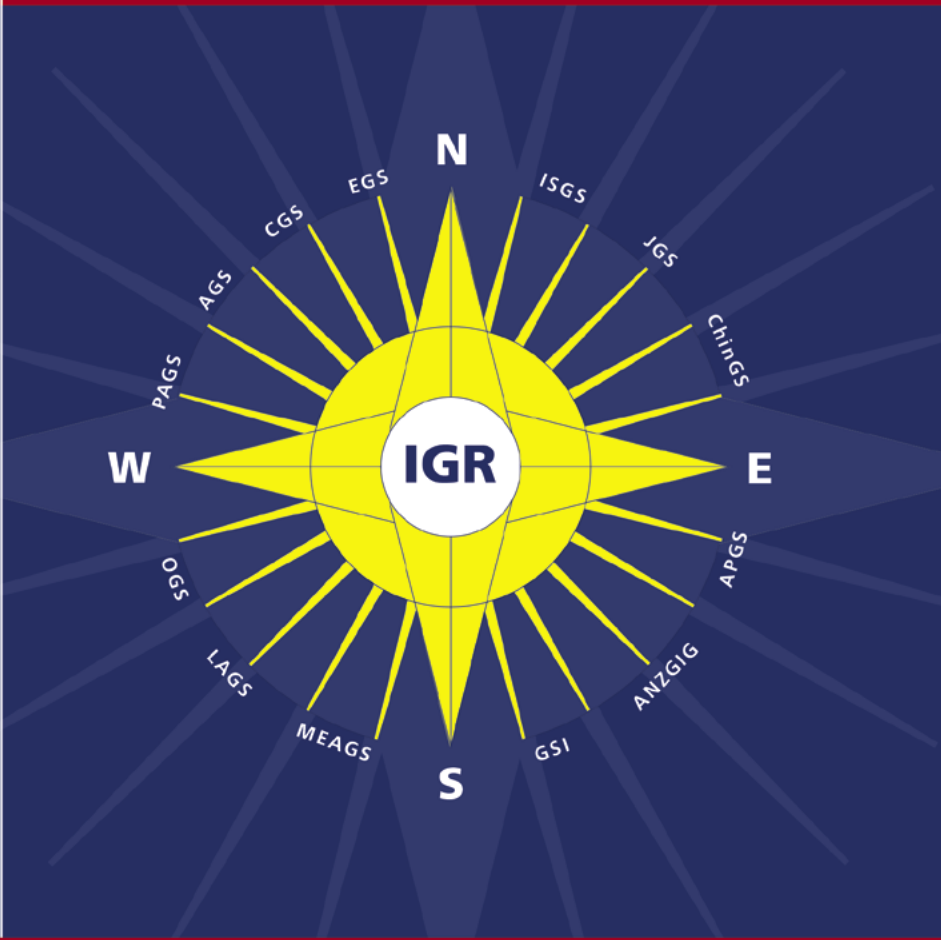

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From the WGA Executive Office

Dear IGR readers,

We hope that this issue of *IGR* finds all of you, your families, and your staff staying healthy and safe during this COVID-19 pandemic. These past several months have been a very difficult and challenging period for all the world. The leadership of the World Glaucoma Association has been closely monitoring the spread of the virus and its impact on our members. The WGA administrative team consisting of Irene Koomans (Executive General Manager) and Marije de Graaf (Operations Manager) have remained working full-time to serve our membership. We are committed to providing you resources related to the COVID-19 epidemic as well as educational materials to keep you up-to-date on the latest in glaucoma diagnosis and management.

We encourage you to utilize extra free time from the quarantine to access these valuable sources of information via your WGA#One Dashboard and our social media channels on Facebook, Twitter, and LinkedIn. We recently created a video for WGA members composed of messages from our WGA leadership – distributed via our social media channels and on our website – giving recommendations addressing issues ranging from patient care to self-care during these tough times. This effort was coordinated by Dr. Ziad Khoueir (Member, Associate Advisory Board of the WGA) and Dr. Pradeep Ramulu (Chair, Education Committee of the WGA).

Furthermore, we continue to provide new educational resources for our members including the latest video presentations of the *Journal of Glaucoma* Paper of the Month. In the March 2020 edition, we featured Dr. Kaweh Mansouri who reported the results of his recent publication on the impact of cataract surgery combined with XEN gel stent implantation on corneal endothelial cell density (two-year results) (J Glaucoma. 2020;29(3):155-160. doi: 10.1097/IJG.0000000000001430.). WGA members can also access the hundreds of recorded talks from 64 sessions at the recent World Glaucoma Congress meeting in Melbourne (2019). The sessions include diagnostic and therapeutic symposia and courses; basic science symposia; industry-focused breakfast symposia; and member society symposia from all major continents around the world. In addition, presentations from prior WGC symposia can be accessed from the WGA#One website.

We also welcome you to brush up on your glaucoma knowledge with our Basic Course in Glaucoma and the Continued Education in Glaucoma modules, developed by world renowned experts. The Basic Course in Glaucoma is available to take in English, Spanish, Portuguese, and Chinese. The modules in Continued Education in Glaucoma are for now only available in English. Our current modules include Ocular Hypertension (Kay Lam and Ivan Goldberg), OCT in Glaucoma (Gus de Moraes, Harsha Rao, and Don Hood), Tips to Maximize Adherence (Parul Ichhpujani), How to Approach the Failed Bleb (C Henein, Y Bouremel, and PT Khaw), and Managing Complications of Post-surgical Hypotony (Ricardo Abe and Vital Costa).

We invite you to keep up with the very latest publications in glaucoma during the COVID-19 epidemic, as WGA members have access to the Journal of Glaucoma (official publication for the WGA) as well as the International Glaucoma Review online. In addition, the detailed outlines for the WGA Consensus meetings are accessible at the WGA#One website. The latest Consensus meeting took place in conjunction with the WGC 2019 in Melbourne with the focus being on Glaucoma Surgery. Covered topics included laser trabeculoplasty, minimally invasive glaucoma surgeries (MIGS), filtering surgery complications, and cyclodestructive procedures.

We sincerely hope that all of you will be able to join us for the next World Glaucoma Congress meeting in 2021, to get the most up-to-date information on glaucoma care for your patients, and to catch up with your friends and colleagues around the world. The meeting was originally scheduled for March 24-27, 2021, to take place in Kyoto, Japan. However, due to concerns that COVID-19 may persist through the summer and re-emerge in another wave of infections in the winter of 2020-2021, we have postponed the meeting till the latter half of 2021. Our main concern is for the health and safety of our members. As a member of the WGA, you will receive an update with the specifics of the meeting in the near future. The Program Planning Committee, led by Drs. Tina Wong and Arthur Sit, have already laid the foundation for a wonderful program encompassing the latest developments in the diagnostics, management, and basic science of glaucoma care. Moreover, there will be special programs such as the popular Rapid Fire sessions to allow you to test your knowledge of glaucoma.

We thank you for your continued dedication to the care of your glaucoma patients as well as for your support of the World Glaucoma Association and the *International Glaucoma Review.* Please stay safe and healthy as we all adapt to these new challenges!

World Glaucoma Association

The Global Glaucoma Network

GET TO KNOW US!

Keith Martin

I joined the Associate Advisory Board of WGA in 2007 as one of a band of young(ish) clinician scientists keen to get more involved in the organization and help it move forward into the future. I was appointed to the Executive Committee in 2009 as Treasurer and I was honoured to serve as President of WGA in 2019-2020.

I was Professor and Head of Ophthalmology at the University of Cambridge until 2019 when I moved to Australia to become Director of the Centre for Eye Research Australia and Head of Ophthalmology at the University of Melbourne. My research is focused on understanding the mechanisms of retinal ganglion cell death in glaucoma and developing new treatment approaches to protect and regenerate the optic nerve.

I have been involved in many WGA projects over the years, including helping to organize most of the World Glaucoma Congresses that have been held to date. It has been wonderful to see the WGA develop and grow over the years into an organization which I think now performs a vital function in our glaucoma community. I am proud that WGA has organized some of the best glaucoma meetings ever held worldwide, but also between congresses is delivering high quality education (including IGR and Journal of Glaucoma) and innovative programs such as our WGA/ICO Glaucoma Fellowships for emerging leaders in our field from sub-Saharan Africa, to name just a few examples.

WGA has helped me develop a network of friends and colleagues around the world that I hope will last a lifetime. I look forward to seeing the organization continue to thrive well into the future despite challenges present and future!

In Memoriam Franz Werner Fankhauser

The ophthalmological community has lost one of the most important 'giants' of the last century, Franz Fankhauser. Modern glaucoma management was initiated by him with his research and interventions in the field of automated perimetry and laser.

Franz Werner Fankhauser was born on the 7th September 1924 in Thun (Switzerland) and passed away on the 27th of April 2020 in Berne.

Franz Fankhauser started his training in 1954 at the University Eye Clinic in Berne, headed by Hans Goldmann, the inventor of manual Goldmann Perimetry in 1946. Under his mentorship Fankhauser completed his residency in ophthalmology in 1958. To elaborate his surgical skills, he went for two years to the Department of Ophthalmology at the Medical College in Ludhiana, in the Indian state of Punjab. At that time already, clinical ophthalmology was very relevant to him as well.
With the support of Hans Goldmann (intellectual) and the 'Swiss Grant' of the National Institute of Health (financial) Fankhauser worked after his stay in India as a research fellow at the Department of Ophthalmology, Washington University, St. Louis, led by Bernhard Becker. At this time, he was supported by his wife Verena, working there as well, as a technician. Coming back to Berne, Fankhauser worked again with and for Goldmann. Despite, or more likely because of many intense and controversial discussions with Goldmann, Fankhauser was able to develop the first automated perimeter, the Octopus 201, with the physicist Jürg Spahr and the support of Interzeag (later Haag-Streit) in 1974. One of the essential benefits compared to other perimetry systems was the target to evaluate the visual field by determination of the differential light sensitivity threshold. Another benefit was the Octopus Fixation Control, which automatically eliminates fixation loss from the visual field testing.

But Fankhauser was not only focused on visual field testing and diagnostics.
By using his (and Walter Lotmar's) new optical concept of 60-diopter three-mirror contact lens photocoagulation (and observation) a significant progress was achieved compared to the previous direct ophthalmoscope using photocoagulation with Xenon lamp, developed

by Meyer-Schwickerath. Later on, various laser systems where used (Ruby, Argon, and finally the Nd:Yag laser by LASAG Medical Company). Many different applications especially for the Q-switched Nd:YAG laser were developed, iris, chamber angle, vitreous, posterior capsule, and cyclodestructive procedures. Of course these many different laser applications resulted in the development of many new contact lenses as well.

Because of the fact that my father was a well-connected ophthalmologist, I had the opportunity to meet his famous colleagues from childhood on in our house or other places. For example, when visiting Goldmann in the early 1970s, in his wonderful house above the Lago Maggiore, I did not realize what genius I met.
Just after finishing my study in medicine in the late 80s, I was sent as a young 'doctor' by my father to his friend Franz in Berne for a few weeks. There I stayed at the apartment of Franz Fankhauser in the old city center. I never felt so 'incapable' as in those days and during late evening's discussions with Franz. Whether it was about physics, mathematics or medicine, I recognized that the title of a 'doctor' does not mean too much. But Franz never pointed out my ignorance, instead he was happy to carry me through the challenges in medicine and research with his encyclopedic knowledge and gentle character.
Franz incited me to glaucoma in the Eye Clinic Lindenhof-Hospital and under the famous contemporary art collection in his apartment, together with his second wife Sylwia Kwasniewska (an excellent scientist and supporter of Franz). He installed in me, that there is so much to do in this exiting field in diagnosis and therapy and even more: the unknown fundamentals of this disease, that I knew from that time on, this was going to be my medical future.
Franz Fankhauser, a scientist, who was always looking behind the limits, had a great skill to detect, inspire and promote numerous scientists from other fields, such as engineers, physicists, mathematicians, opticians, micro-morphologists, anatomists and others.

Among the many awards and prizes Franz Fankhauser received I just want to mention: 1982 Marcel-Benoist-Preis, 1984 Dr. med. h.c. Basel, 1988 Helmholtz-medal, 1994 Karl-Wessely-medal, 1996 v. Graefe medal.
He has published more than 300 scientific papers, many of them together with his wife Sylwia.

In 2003 Josef Flammer created the Fankhauser medal and lecture, awarded by the University of Basel.
Franz Fankhauser is survived by his wife Sylwia and his son Franz Fankhauser, an ophthalmologist as well.

Franz, we will miss you.

Tony Hommer, Vienna, Austria

(Written with the support of Franz Fankhauser Jr. and Baldur Gloor)

Literature

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World Glaucoma Week

#glaucomaweek was a success!

Throwback to World Glaucoma Week

Thank you to all who showed their support during World Glaucoma Week. With your continuous collaborative efforts, we have confidence that we will improve the current state of glaucoma diagnosis and early treatment worldwide. Have a look at some of the best moments captured on social media by browsing the official hashtag #glaucomaweek on Facebook, Twitter or Instagram.

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Glaucoma Dialogue

Comments on:

Review of hygiene and disinfection
Recommendations for outpatient glaucoma care: A COVID era update

Shabto JM, De Moraes CG, Cioffi GA, Liebmann JM
Journal of Glaucoma: June 2020 - Volume 29 - Issue 6 - p 409-416
DOI: 10.1097/IJG.0000000000001540

READ ARCTICLE

Comment by Ningli Wang and Chunyan Qiao, Beijing, China

Currently, the world is faced with severe challenges brought by COVID-19, and healthcare workers are at the frontline of this war against the pandemic.

Our study, published in *Ophthalmology*[1], found that the overall incidence of symptomatic COVID-19 among eye professionals across Wuhan's ten hospitals was 2.52% at the early stage of the COVID-19 outbreak, similar to the incidence among other subspecialties health workers. Ophthalmologists face a similar risk compared with healthcare workers of other subspecialties. **Adequate personal protective equipment (PPE), hygiene and disinfection, are important in preventing disease transmission.**

Clinical practice in most Chinese hospitals has returned to normal now, including our own. We limited the number of registered appointments to avoid congestion in our hospital. Except forurgent cases, all outpatients are required to make an appointment in advance. In our department, the daily number of outpatients is about half of the pre-COVID-19 number.

Many extra protective measures became regular practices. These include protection for healthcare workers, environment disinfection and screening patients. Most of them are the same as the recommendations in this article, and many of them are mandatory in our hospital.

Every healthcare worker must wear PPE during practice, including medical surgical masks, gloves and protective goggles. The additional disposable protective gown and N95 mask are required for emergency service. Strict hand disinfection (wash hands with soap or alcohol sanitizer) after examination and treatment of each patient should be performed. Most doctors use cotton swabs to avoid direct contact with patient's eyes. Social (physical) distancing of one meter is also required, but is difficult to achieve in times of crowding.

A protective breath shield (self-made of used CT or X-ray film) is set up in front of every slit-lamp microscope to prevent splash of patient's secretions. The equipment touched by patients, such as mandibular rest, frontal rest and armrest of slit-lamp microscope are disinfected after examination of each patient. The ophthalmic instruments in contact with a patient's conjunctiva are fully and effectively disinfected before and after each examination to avoid cross-infection. The windows of consulting rooms are opened regularly to ventilate and let in fresh air every day, and the consulting room and corridor are disinfected twice a day.

Patients and accompanying persons are asked to wear masks in the hospital. Taking temperature is the first and mandatory step before they enter the hospital. The history is asked, particularly for travel, can be checked by personal smart phone before they enter the consulting room. Suspected COVID-19 cases are referred and reported as soon as possible.

For outpatient glaucoma care, in order to avoid close contact, we adopt alternative examination methods such as choosing hand-held indirect lenses before slit lamp, or fundus camera. Optical coherence tomography (OCT) for fundus examination is used instead of direct ophthalmoscopy, anterior segment optical coherence tomography (AS-OCT) for chamber angles examination instead of gonioscopy, and iCare for the measurement of intraocular pressure. We stopped using contact tonometry, and non-contact tonometry is still used in many Chinese hospital departments, including our own. Non-contact tonometers are placed in a well-ventilated room and disinfected with 75% alcohol after examination of each patient.

These practices have been implemented in our hospital since the outbreak of COVID-19. To date, neither staff nor faculty have been infected by SARS-CoV-2. In our experience, adequate PPE, strict hygiene and disinfection are necessary to limit exposure and transmission of infection in outpatient glaucoma clinics during the current COVID-19 pandemic.

Reference

1. Symptomatic COVID-19 in Eye Professionals in Wuhan, China; Qiao, Chunyan et al.; Ophthalmology, Volume 0, Issue 0; DOI: https://doi.org/10.1016/j.ophtha.2020.04.026

Comment by Luciano Quaranta, Pavia, Italy

I am living and practicing in Brescia and Pavia, two of the most affected towns in Italy by COVID-19, and for this reason I face the problem daily.

Life has changed for all of us, and also our way of visiting patients. The hygiene and disinfection of ophthalmological instruments (slit lamps, lenses, tonometers, OCT, Visual Field Analyzers…) needs to be particularly accurate and safe now.

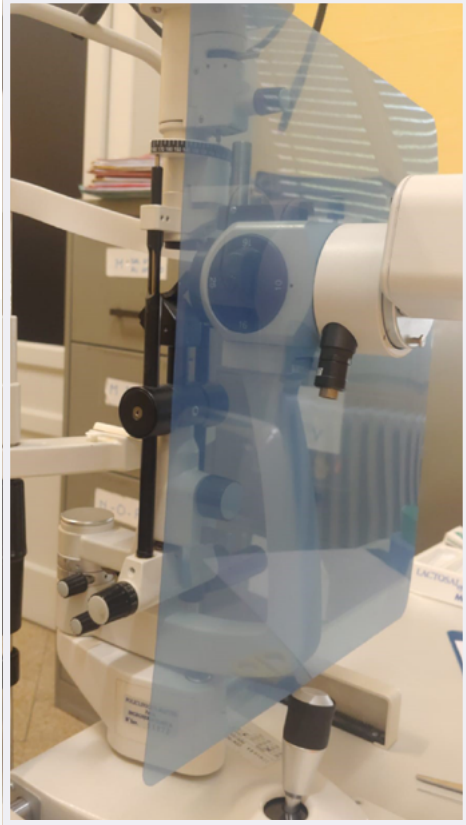

Fig. 1.
Slit lamp breath shield: x-ray film (11 x 13 inches).

For these reasons I think this paper gives extremely useful information for our practice.

I draw inspiration from this article to illustrate the situation in Northern Italy.

In order to avoid gatherings of patients in the waiting rooms, we have rescheduled all the appointments. We are visiting only urgent and non-deferrable glaucoma patients. At present, we are able to visit no more than two patients per hour (in the pre-COVID era we had a schedule of one patient every 15/20 minutes for routine glaucoma follow-up visits).

The majority of the suggestions proposed in the paper are almost similar to the ones I have applied in my outpatient practice at the University of Pavia, and in my private practice in Brescia.

During the pandemic lockdown (March 9-May 4) I faced the problem to continue to visit patients recently operated by filtering surgeries, and to give reassurances to glaucoma patients who needed to be operated in the near future. For this reason, special caution had to be taken when visiting patients to avoid contamination. For added security, we decided to perform applanation tonometry by single-use, disposable tonometer prisms.

Due to the shortage of breath shields for the slit lamps, we have adapted x-ray films for protection (Fig. 1).

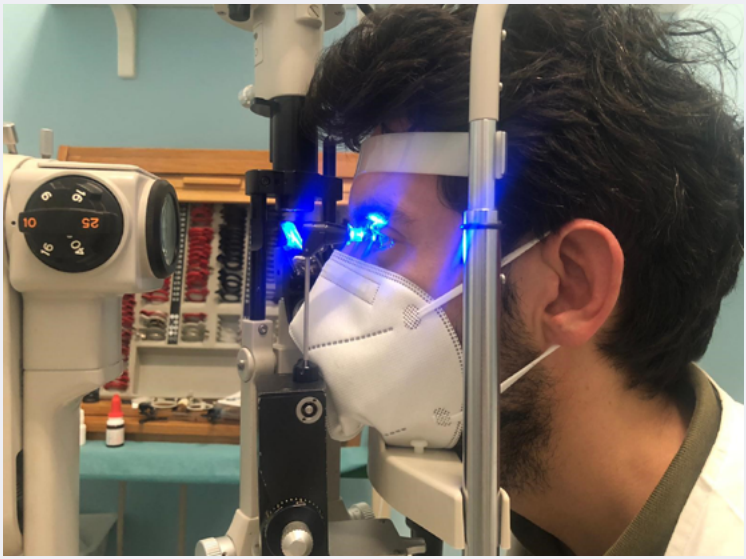

Fig. 2. Tonometer rod – mask contact.

Furthermore, I would like to add a simple personal observation related to the use of a mask.

In Northern Italy, patients frequently wear FFP masks in different shapes. Particular attention should be paid in order to avoid contact between the mask and the metal rod of the tonometer, in some cases preventing the approach of the prism to the cornea, but in other cases resulting in abnormal values of the IOP (Fig. 2). My personal suggestion is to recommend to patients to wear a surgical mask during an ophthalmological visit, or at least during IOP measuring.

I hope a cure for this disease will be found soon.


Comment by Poemen Chan and Clement Tham, Hong Kong, P.R. China

Anecdotal reports have suggested that the virus could also be transmitted by aerosol contact with conjunctiva.[2] The proximity between ophthalmologists and patients during ophthalmic examination and the use of ophthalmic equipment (which could be a potential source of transmission if disinfection procedures are not performed properly), pose an infectious risk to eye care professionals and other patients in outpatient clinic.

This paper by Shabto *et al*. summarized a set of recommendations for the disinfection of instruments and devices that are commonly used in glaucoma practice. The precautions could be divided into two different categories: (1) disinfection of the waiting room and patient rooms; and (2) disinfection of equipment and other instruments. The first aims to minimize the risk of transmission via contact with contaminated surfaces or objects; hourly cleaning of waiting rooms, restrooms, exam lanes, and office furniture is recommended. This should be done with appropriate disinfectant agents (*e.g*., diluted household bleach with > 1000 ppm sodium hypochlorite, 70% alcohol solution and common EPA-registered household disinfectants). Careful disinfection of equipment is important in order to prevent viral transmission via contaminated devices, which could become a potential vector of transmission if proper disinfection precautions are not taken.

The authors also tabulated the cleaning and disinfection instruction from manufacturers of other instruments including visual field analyzer, optical coherence tomography (OCT) machinery, tonometers and lenses. Non-contact tonometry is not recommended because previous study demonstrated the formation of micro-aerosol on most eyes during air-puff tonometry.[3] Single-use disposable instruments could be considered instead of instruments that are frequently handled either in direct contact (*e.g*., applanation tonometer prism) or are used in proximity to the eye (*e.g*., hand-held indirect lens). They also pointed out that the perimeter bowl of the visual field analyzer could be an important source of respiratory droplet accumulation, since SARS-CoV-2 can remain viable up to 72 hours after application on different types of surfaces (more stable on plastic and stainless steel than on copper and cardboard).[4] It may be difficult to disinfect instruments such as the visual field analyzer. Therefore, routine investigation that involves these types of instruments should be deferred.

Indeed, apart from ensuring environmental control, infection control measures during the COVID-19 pandemic should also aim at minimizing cross-infection within the hospital, as well as providing adequate support and protection to hospital staff. For instance, our hospital has reduced 40% of the outpatient attendance and elective surgery, as well as 90% of the general anesthesia procedures. All patients are screened for fever, travel history, contact and cluster history, and COVID-19-related symptoms before they enter

the hospital. To support the hospital staff, we also ensure provision of adequate personal protective equipment (PPE) and clear guidelines on the level of PEE needed for different clinical situation. Other supportive measures include provision of work uniforms, easy access to alcohol-based hand rub, setting up new lunch areas, implementing a self-monitoring and reporting system, as well as regular updates and communication via an online education system.[5]

Eye care professionals are at high risk of acquiring COVID-19. Hygiene and disinfection precautions should be taken seriously, given that the pandemic has reached a scale that total eradication is unlikely and future recurrence of outbreak is possible.

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Comment by Brandon J. Wong, Los Angeles, CA, USA

In this timely review article, Shabto and coworkers describe disinfection practices relevant to the glaucoma clinic during the present COVID-19 pandemic, specifically practices concerning the clinic environment and commonly used equipment and instruments. The authors provide a comprehensive review of the varying manufacturer recommendations for disinfection of non-contact ancillary testing, such as perimetry and optical coherence tomography, and testing involving direct patient contact, such as applanation tonometry and gonioscopy. **Clinicians and staff should be familiar and attentive to the proper disinfection practices of the clinic and equipment, especially as clinics reactivate and patient volumes increase.** While different institutions may be at various stages of reactivation, our hospital-based academic glaucoma clinics are now re-opening with a limited clinic capacity to comply with local and state guidelines. Our approach to re-opening clinics includes adhering to all manufacturer recommendations for instrument disinfection as well as other environmental and engineering control measures.

We have converted to the use of disposable tonometer prisms which obviates the need to disinfect reusable tonometer tips and are transitioning to single use lenses for gonioscopy and laser procedures, such as laser peripheral iridotomy and selective laser trabeculoplasty. Anecdotally, we have not had issues with the lens quality or visualization for these procedures.

Since the publication of this article, Zeiss has updated its recommended cleaning guidelines for the Humphrey Visual Field Analyzer to incorporate updated information regarding the perimeter's ventilation and guidance on how to clean the bowl, if deemed necessary. The HFA2, HFA2-i, and HFA3 perimeters have fans which circulate and exchange air in the bowl, and the HFA2-i, and HFA3 perimeters continuously push air out of the bowl and past the patient while the machine is powered on.[1] It is not known if viral particles or respiratory droplets that accumulate on the bowl could potentially be aerosolized due to this fan mechanism. The updated Zeiss guidelines recommend the use of 70% isopropyl alcohol and a fine misting sprayer to sanitize the bowl surface if necessary.[2] Importantly, the alcohol must dry (approximately 5-10 minutes) prior to the next test. For patients requiring perimetry, our clinic practice is to have all patients wear surgical masks for the duration of the test. Routine N95 masks for patients appears impractical given that the physical size of most N95 masks interferes with proper placement of the trial lens. The visual field technician in the room also wears a surgical mask, or N95 mask, if available. While Shabto and co-workers recommend deferring 'routine' perimetry, the risks and benefits of perimetry must be weighed with the individual patient and the stage of disease in mind, particularly if there is concern for disease progression.

In addition to clinic modifications for in-person visits, our institution has also actively moved to telemedicine visits to limit physical interactions between individuals. We are exploring 'testing-only' visits in which patients come for all ancillary testing with a technician (including an intraocular pressure check) with a subsequent follow-up telemedicine visit by the clinician. Satellite clinics may also employ drive-through intraocular pressure checks for certain high-risk patients or for those unwilling or unable to come for in-person visits. These drive-through visits could potentially incorporate even more clinical testing in the future, such as virtual reality visual field testing.

> The pandemic has created the opportunity for our specialty to advance new and innovative methods of health care delivery and accelerate research into making glaucoma care safer, more convenient, and more accessible to our patients than ever before

While increased attention and adherence to proper disinfection practices are critical to mitigating risk of acquiring COVID-19, successful strategies will incorporate these and other clinic environmental controls in an integrated approach to make the delivery of glaucoma care safer. Prior to COVID-19, thriving glaucoma clinics relied upon significant patient volumes, arrays of imaging and testing, and circuitous clinic throughput with multiple, in-person, interactions to function. We cannot anticipate a return to that clinic model any time soon. Nonetheless, the pandemic has created the opportunity for our

specialty to advance new and innovative methods of health care delivery and accelerate research into making glaucoma care safer, more convenient, and more accessible to our patients than ever before. The glaucoma clinic of the future will, and must, be different.

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Comment by Rahat Husain and Tin Aung, Singapore

The authors adopted a ‘common sense’ approach early on in the Covid-19 pandemic, such as using eye shields on slit lamps, and minimizing conversation between the patient and doctor while using the slit lamp. Whilst waiting for more robust data on how to reduce infection risk, many units around the world including our own, introduced such measures.

The possibility that bowl perimeter visual field testing (such as the Humphrey Visual Field analyzer) may be a particularly insidious source for infection spread was an immediate concern for glaucoma departments. Certainly, the postponing of such investigations, as the authors have suggested, will eliminate this risk but is not a sustainable solution. The advice on cleaning of the perimeter is welcome although cleaning of machines between patients will undoubtedly have an effect on the throughput of patients. Presently, there are no data to advise how long we should wait between patients, as droplets may persist in the relatively enclosed area of the bowl. Staff cleaning the equipment will need to wear gowns, gloves and appropriate masks, perhaps N95 or similar. These measures may have financial implications for clinic running costs.

As regards to measurement of intraocular pressure (IOP) using the Goldmann Applanation Tonometer (GAT), the risk of Creutzfeldt-Jakob prion transmission led some clinics to adopt the use of disposable tonometer tips for all patients. The Icare tonometer is a reliable instrument that minimizes contact between patient and practitioner and has

a disposable tip. The ease of use and size of the instrument make it an attractive alternative to both slit lamp mounted GAT and Non-Contact Tonometry, with the added bonus of being the least likely of the three options to transmit the COVID virus.

In our department in Singapore, the cleaning of equipment is undertaken by the nurses and cleaning staff using various chemicals depending on the area to be cleaned. All slit lamps/investigation machines are cleaned after every patient using alcohol wipes. The Goldmann Applanation Tonometers are cleaned with hydrogen peroxide solution. From our experience, the cleaning of the inside of the Humphrey Visual Field analyzer with 70% isopropyl alcohol in water causes staining of the bowl and hence may cause problems with the testing. Omitting testing is a short-term solution but eventually physicians will want to restart and this could be a real problem.

As the world adapts to the 'new normal' with the risk of recurrent epidemics breaking out and asymptomatic reservoirs of infection in the community, the approach to limiting disease spread needs to be holistic. The disinfecting guide in this article is essential but continuous adherence may be difficult once lockdowns are eased. As congested centralized specialist outpatient clinics for eye patients with long waiting times, multiple assessment stations and close contacts between patients and healthcare providers, may lead to an increase in COVID-19 infections, we need to think of new models of care to reduce this risk. Outsourcing of investigations in several locations in the community combined with telemedicine is one way of achieving this aim, whilst maintaining good, appropriate quality of care for glaucoma.

Comment by Pradeep Ramulu, Baltimore, MD, USA

We thank Shabto, De Moraes, Cioffi, and Liebmann for offering a timely and informative review of formal disinfection recommendations for equipment used in the glaucoma exam, and for describing how they have changed their clinic in the COVID-19 era. No doubt, this is an issue all of our readers have been dealing with. Here, we highlight some of the authors' ideas that others may not have considered, expand upon areas of potential controversy, and discuss some suggestions the authors may well be implementing, but did not mention. We offer advice with the caveat that infection rates differ by region and time, and it remains important to adhere to regulations from the governments, medical bodies, and local institutions where you work. Another important caveat is many recommendations involve balancing cost and burden with an unquantifiable benefit in safety; until further knowledge is gained, we must 'first, do no harm' and err on the side of safety.

With regards to keeping the office safe, the authors highlight the need for frequent (hourly) cleaning of waiting areas, and also other areas including check-in kiosks, doorknobs, and bathrooms. As a way to decrease time spent in the clinic, they suggest collecting any payments on-line instead of in person. We are also reviewing medications and changes in vision/symptoms one to two days before the visit and scheduling all follow-ups by phone, lowering time spent with technicians and allowing quicker exits. The authors are limiting patients to one companion to lessen the number of patients in the waiting room; Johns Hopkins is limiting companions altogether except when necessary (poor mobility, limited cognition). In cases where difficult decisions must be made, patients can call their family/friend so they may join discussions by speaker phone.

We highly recommend readers review the official manufacturer recommendations for cleaning glaucoma-related equipment detailed in the manuscript tables. These thorough tables cover products by multiple manufacturers, describe the agents suitable for disinfection, the company-recommended frequency of disinfection, and provide links to the product manuals. Notably, products are covered which we may not often think about how best/often to clean, including non-Goldmann tonometers (iCare, Tono-Pen) and lenses (gonioscopy, ophthalmoscopy, laser). While these recommendations predate COVID-19, it is important that they are now followed with greater diligence.

Two pieces of glaucoma equipment deserve special mention based on their design and critical importance to decision-making. Regarding applanation tonometry, the authors make no firm recommendations. Prior systematic reviews and review articles on the topic are referenced, as is a recent paper demonstrating detectable COVID-19 RNA in the tears of 2/38 eyes, including 2/12 eyes with ocular findings, but none of the 26 eyes without ocular findings (chemosis, hyperemia, epiphora). A second study in 17 COVID-19-positive patients without ocular symptoms also found no detectable RNA in tears (PMID 32291098). These studies suggest no critical need for re-evaluating current applanation tonometer disinfection processes, at least in eyes without ocular findings.

> If remote perimetry/tonometry are ever going to become viable alternatives to in-clinic testing, now would be the time

Regarding perimetry, some manufacturers have issued new guidelines for disinfecting perimeter bowls with spray misting between patients (https://www.zeiss.com/content/dam/med/ref_international/corona/pdfs/hfa_covid_guidance_en_31_025_0408i_hfa.12415_final.pdf). However, multiple questions remain. Do aerosolized particles remain the bowl space after testing? For how long? Until better data are obtained on these issues, our service has limited visual field testing, encouraged the use of shorter (faster) testing algorithms, and rotated which machine is used to maximize time between tests. If remote perimetry/tonometry are ever going to become viable alternatives to in-clinic testing, now would be the time, and our group is exploring the potential of both.

We urge our readers to read this excellent piece to help formulate their thoughts on how best to keep their patients safe in this new era.

Comment by Michele C. Lim, Sacramento, CA, USA

Shabto and colleagues write an excellent summary of recommendations for hygiene and disinfection for outpatient glaucoma care in the COVID-19 era. So much has changed in our approach to the delivery of health care since the emergence of SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) and this is a timely compilation of practical recommendations for any eye care practice. Many of the cleaning recommendations are easy to follow and most practices are well-versed in the disinfection of tonometer tips and of contact laser lenses but there are two items that are particularly challenging. One, how to clean the bowl of a visual field device and two, the practical implications of cleaning handheld lenses.

The recommendations for cleaning the bowl of the Octopus 900 perimeter and Humphrey visual field analyzers are different. Haag-Streit Diagnostics warns that the bowl of the Octopus is lined with a special paint that could be damaged with detergents but recommends wiping any residue with a soft cloth and soap-suds but they do not offer any evidence that this will eliminate SARS-CoV-2.[1] Carl Zeiss Meditech, Inc. provides updated information in which the bowl should be sprayed lightly with 70% Isopropyl solution should it become contaminated with respiratory droplets.[2] In our practice, to further protect against contamination, we have created an acrylic shield that creates a wall between the patient and perimeter bowl (Fig. 1).

Fig. 1. Acrylic breath shield designed for an automated visual field machine.

Now that patients wear masks to their visit, I notice that the condensation from their breath shoots upwards and may collect on my handheld lens and hand and Shabto and colleagues offer excellent recommendations for lens cleaning. But to do so, we must have duplicates in order to rotate lenses between patients and for large institutions this comes with a large cost. If I soak them in Cidex or hydrogen peroxide, is there a safe location near the exam rooms where patients or children can't access the cleaning solutions? Is it practical to use disposable lenses? Volk sells a disposable 28D handheld lens but at a cost of $14.50 per lens! Would UV light cleaning devices work well to disinfect handheld lenses? In our clinic, we use a UV light disinfection unit (which was intended for CPAP gear) (Fig. 2) to clean handheld lenses and it requires a short 5-minute cleaning cycle. Some studies suggest that one can eliminate SARS-CoV-2 with this methodology.[3,4]

Fig. 2. Ultraviolet light sterilizer.

Since the initial writing of this article, the United States is now in a period of health care restoration and this means the volume of patients will rise in the coming months making it even more essential to understand how to protect both patients and staff from SARS-CoV-2 exposure. The CDC issued recommendations to aid health care organizations in restoring routine patient care and they provide a "Framework for Healthcare Systems Providing Non-COVID-19 Clinical Care During the COVID-19 Pandemic.[5]

Restoring health care in our busy ophthalmology practices will require unique solutions to maintain physical distance between patients once the volume of visits begins to 'ramp up'. At the UC Davis Eye Center, we began reinstating routine patient visits on 5/4/2020 and are currently scheduling at 50% volume to ensure that we can maintain proper patient physical distancing. We allow one person to accompany a patient if needed and we have employed restaurant-style 'pagers/buzzers' to allow patients to wait in their car

or elsewhere so as not to overload waiting rooms. We have created a Saturday imaging (OCT, fundus photos, slit lamp photos) and procedures (visual fields) clinic to decompress the Monday to Friday work week. This Saturday clinic also helps sustain video visits. Video visits have been a challenge to ophthalmology because of its inability to capture the details of an eye exam. We are embarking on a workflow in which patients who come for Saturday imaging or procedures may also have their vision and intraocular pressure measured by technical staff. This can then be followed by a video visit with the physician to discuss diagnoses and treatment plans. Separating the physician-patient visit from imaging/procedures can help decrease the amount of time patients spend in the office. We have also piloted drive-up visits (Fig. 3) in which vision and pressure are checked while the patient remains in their car and this is followed by a video visit with the physician. As we look to the future, most of us realize that life will never be the same again, at least until a SARS-CoV-2 vaccine is created, and we must continue to employ out-of-the-box ideas to sustain our practices.

Fig. 3. Drive-up glaucoma visit with intraocular pressure measurement.

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Comment by Andrew Camp, San Diego, CA, USA

On March 11, 2020 the World Health Organization declared the novel coronavirus disease 2019 (COVID-19) outbreak a pandemic. On March 18, 2020 the American Academy of Ophthalmology recommended that ophthalmologists limit patient visits to urgent and emergent cases in order to decrease virus transmission and conserve medical supplies. Proper hygiene and disinfection protocols became a focal point of interest for safely seeing high risk patients during the early outbreak and for safely increasing patient volume as restrictions began to relax. The authors of this review focus on hygiene and disinfection recommendations for outpatient glaucoma care, although many of the basic principles may be applied broadly across general ophthalmic care as well as for other specialties that require close patient interaction.

A general goal in all care is to decrease or prevent person-to-person viral transmission. Ophthalmologists represent a particularly high at risk physician group for contracting COVID-19.[1] Recommendations include screening patients for COVID-19 symptoms, social distancing when possible by limiting patient numbers in waiting areas, minimizing speaking while in close proximity, and barrier methods such as breath shields. The AAO has updated recommendations since this review was published to include suggesting face coverings for patients and providers as well as eye protection for providers. The use of face masks may decrease transmission of COVID-19 in public settings, but their utility in closer encounters is not yet known.[2] The use of face masks and large breath shields in conjunction appears to be particularly effective at reducing particle transmission.[3]

Exam rooms, waiting areas, and any other place patients congregate should be disinfected between patients. The Environmental Protection Agency maintains a frequently updated list of products that can be used to disinfect surfaces.[4] Offices should have multiple disinfection products available as there is high risk of intermittent shortages of individual products.[5] Any device used during a patient exam should be thoroughly disinfected after use. Slit lamps, lenses, and ocular coherence tomography machines are relatively easy to clean because potentially contaminated surfaces are easily accessible.

Visual field analyzers present a challenge because respiratory droplets may accumulate within the perimetry bowl, but the bowl may be degraded by frequent application of disinfection products. Both Zeiss and Haag-Streit have suggested their respective perimetry bowls may be disinfected with atomized isopropanol or ethanol, but the long-term impact of these products is unknown. Contact tonometer tips should be disinfected with particular caution due to the risk of virus transmission between patients. Non-contact tonometry should not be performed due to the risk of tear aerosolization. However, it should be noted that the rate of viral shedding in tears remains controversial and may be lower than initially thought.[6]

Recommendations regarding the COVID-19 response are frequently changing as more is learned about transmission and infection by the virus. Many of the principles learned during the current pandemic will play a role in the response to future pandemics. There are many opportunities to update and improve glaucoma care as a response to this crisis. **Tele-ophthalmology will likely be increasingly explored as a way to minimize patient exposure and transmission risks.7** Many products such as home tonometry and home perimetry will likely take an increasingly central role in the future of glaucoma care as we adapt to this shifting clinical environment.

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Your Special Attention For

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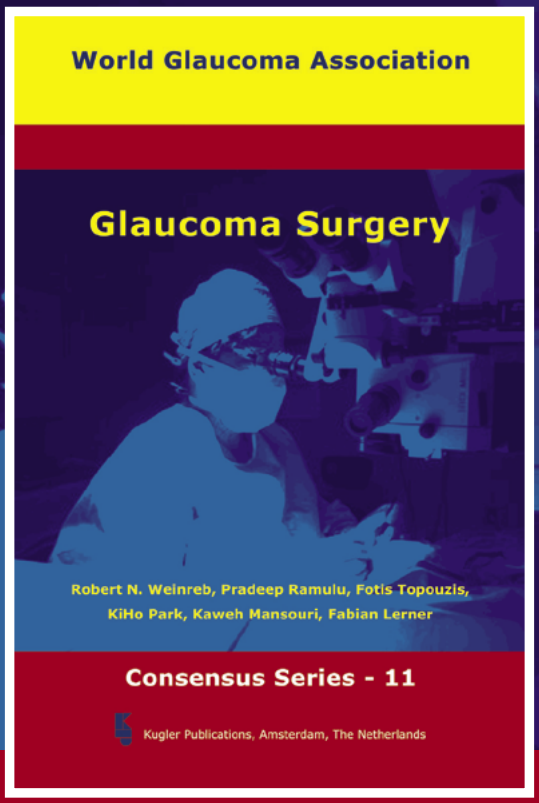

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Editor's Selection

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

Factors of Pseudoexfoliation in a Russian Population

Comment by Miriam Kolko and Anne Horwitz, Copenhagen, Denmark

82600 Prevalence and Associated Factors of Pseudoexfoliation in a Russian Population: The Ural Eye and Medical Study; Bikbov MM, Zainullin RM, Gilmanshin TR, Kazakbaeva GM, Yakupova DF, Nuriev IF, Zaynetdinov AF, Khalimov TA, Panda-Jonas S, Uzianbaeva YV, Rakhimova EM, Rusakova IA, Salavatova VF, Arslangareeva II, Bikbova GM, Nikitin NA, Jonas JB; American Journal of Ophthalmology 2020; 210: 158-166

In the present study, the authors assessed the prevalence of pseudoexfoliation (PEX) and its associations in a Russian population. Despite previous indications of a high prevalence of PEX in the Russian population, only limited evidence exists. The study provides novel information on PEX among Russians by investigating the urban and rural region in the Russian republic of Bashkortostan at the southwestern end of the Ural Mountains. **The authors report an overall prevalence of 3.6% in the population over 40 years.** In accordance with other population studies, prevalence is associated with higher age, increased intraocular pressure and open-angle glaucoma. Previous studies have reported a higher incidence of PEX among women, but the present study did not find such a gender association. PEX material has been described in many parts of the body and thus studies have

previously related PEX to systemic conditions. The present study did not confirm increased risk of systemic conditions, such as diabetes, arterial hypertension or dementia in patients with PEX. While the study is conducted thoroughly and provide important information on PEX in the Russian population, there are some conflicting information and study limitations. The authors conclude that ethnic Russians have higher prevalence of PEX, but also show that **the odds ratio of non-Russians to Russians is 1.5.** As the authors report, the prevalence of PEX in the Russian population may have been underestimated, as subjects who have had previous cataract surgery have been excluded. In summary, the present study is well designed and the size of the study population is relatively large. In addition, substantial ocular and systemic parameters are examined. The study thus provides novel and useful information on the prevalence of PEX in the Russian population.

Pathogenesis

Vitamin D levels and severity of glaucoma

Comment by Shan Lin, San Francisco, CA, USA

82421 Association of severity of primary open-angle glaucoma with serum vitamin D levels in patients of African descent; Ayyagari R, Chen YI, Zangwill LM, Holman M, Dirkes K, Hai Y, Arzumanyan Z, Slight R, Hammel N, Girkin CA, Liebmann JM, Feldman R, Dubiner H, Taylor KD, Rotter JI, Guo X, Weinreb RN; Molecular Vision 2019; 25: 438-445

Ayyagari *et al.*[1] evaluated the potential association of serum vitamin-D levels and severity of primary open-angle glaucoma in subjects of African descent. They used a subset of the enrollees of the African descent and glaucoma evaluation study III (ADAGES III), comprising a total 357 patients. There were 178 normal controls, 178 early POAG subjects (visual field MD better than -4 dB), and 179 advanced POAG subjects (visual field MD worse than -10 dB). The ADAGES III is a large study of the contributions of genotype to the glaucoma phenotype in those of African descent. The present study found that **the mean vitamin-D levels of control subjects (8.02 ± 6.19 pg/ml) and early POAG subjects (7.56 ± 5.74 pg/ml) were significantly more than those with the advanced POAG phenotype (6.35 ± 4.76 pg/ml; p=0.0117 and 0.0543, respectively).** However, there was no difference when comparing the control versus the early POAG groups (p = 0.8508).

Previous association studies have also found a correlation of low vitamin-D levels and presence of glaucoma or severe glaucoma, notably in a South Korean population study and a French case-control study. The current report is the first to identify this type of link in a population of African descent, a group that has the highest risk for glaucoma. Furthermore, those of African descent are at greater likelihood for deficiencies in vitamin D,[2-3] perhaps further exacerbating the risk for glaucoma.

In the larger scheme, vitamin-D deficiency is prevalent in the general population and has been linked to other important disease states such as osteoporosis, cardiovascular disease, diabetes, cancer, autoimmune diseases, depression, and dementia. The latter association is particularly relevant since both dementia and glaucoma are ultimately diseases of neuronal degeneration. More recently, lower levels of vitamin D have also been correlated with possibly greater prevalence and mortality related to the recent COVID-19 pandemic.

Although only an association can be shown in this type of study, **the information can be very helpful to direct future studies regarding the genetics and mechanism of action by which vitamin D may affect glaucoma progression**, as well as serve as a starting point for a potential clinical trial to study whether vitamin D supplementation can be helpful for patients of African descent in preventing glaucoma development and/or progression.

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Quality of Life

Impact of Glaucoma-related Visual Impairment in Childhood Glaucoma

Comment by Andrew Camp, San Diego, CA, USA

82428 Beyond Intraocular Pressure: Visual Functioning and Quality of Life in Primary Congenital Glaucoma and Secondary Childhood Glaucoma; Gothwal VK, Sharma S, Mandal AK; American Journal of Ophthalmology 2020; 209: 62-70

This cross-sectional study explored the effects of childhood glaucoma on visual function (VF) and vision-related quality of life (VRQoL). VF and VRQoL are important outcome measures for glaucoma management as they reflect a patient's experience of their disease by encompassing broad functional and quality of life (QoL) measures that are affected by vision. The conventional objective measures (*e.g.,* intraocular pressure, visual acuity [VA], visual field loss) captured as endopints in many studies may not accurately reflect a patient's subjective experience. Gothwal *et al.* attempt to address this shortcoming by administering subjective **VF and VRQoL tests (the LV Prasad Functional Vision Questionnaire and the Impact of Vision Impairment-Children questionnaire, respectively) to 309 patients with childhood glaucoma**. The subjective questionnaire results were compared to an objective measure of habitual VA of the better eye, and patients were further classified by diagnosis of primary congenital glaucoma (PCG) versus secondary childhood glaucoma (SCG).

The high prevalence of childhood glaucoma in India allowed the authors to survey a large number of patients over the course of the study. **As seen in adults, impaired VA in the better eye correlated to worse VF and VRQoL scores**. Bilateral glaucoma and a greater number of surgeries also correlated with worse VF. **Interestingly, VF and VRQoL were significantly better in PCG compared to SCG patients, despite similar objective measures (age, VA).** The authors theorize that earlier diagnosis and intervention in PCG may lead to better adaptation to the disease. Patients with PCG were diagnosed at an earlier age than SCG (2.3 years versus 4.9 years, respectively), lending credence to this theory, but future work will hopefully address this finding in greater detail. A great deal remains to be learned regarding QoL outcomes in pediatric patients, and this study demonstrates the feasibility of subjective testing in a young population.

Anatomical Structures

See the trabeculum!


Comment by Alex Huang, Los Angeles. CA, USA and Jong Yeon Lee Seongnam, Incheon, South Korea

82570 High-Resolution, Adaptive Optics Imaging of the Human Trabecular Meshwork In Vivo; King BJ, Burns SA, Sapoznik KA, Luo T, Gast TJ; Translational Vision Science & Technology 2019; 8(5): 5

In this study, the authors describe proof-of-concept *in-vivo* human trabecular meshwork (TM) imaging using high-resolution adaptive optics gonioscopy (AOG). AOG can visualize TM beams and presumed TM endothelial cells. They compared the TM appearance between control and pigment dispersion syndrome patients. **Diminished spacing between the beams and enlarged endothelial cells with hyper-reflective foci were observed in pigment dispersion syndrome TM**.

In-vivo TM micrometer-level imaging using AOG has several advantages. For example, subtle differences in TM morphology were seen comparing AOG, scanning electron microscopy (SEM),[1] and *in situ* human two-photon imaging.[2] AOG likely gives a more representative description because it avoids tissue-preparation and fixation-associated artifacts. Also, as AOG is non-invasive, AOG allows for longitudinal patient assessment. Investigators can now study TM age-related changes and the impact of TM-based glaucoma treatments (medications, lasers, or TM-targeted minimally invasive glaucoma surgeries).

> Performing *in vivo* TM imaging with segmental information (such as from aqueous angiography) could yield additional insight into TM biology and potentially lead to novel outflow-based glaucoma therapies

However, several limitations exist. First, AOG cannot query deeper TM structures such as the juxtacanalicular meshwork or Schlemm's canal, which are important parts of aqueous humor outflow resistance. This challenge may be overcome by using longer wavelength lasers.

Additionally, the new concept of segmental aqueous humor outflow is important here. Aqueous angiography has shown the segmental outflow in living non-human primates and humans.[3,4] Different AOG results could have been obtained depending on the location

of the test (high-flow vs. low-flow TM). Therefore, performing *in vivo* TM imaging with segmental information (such as from aqueous angiography) could yield additional insight into TM biology and potentially lead to novel outflow-based glaucoma therapies.

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Do laminar biomechanics depend on Ethnicity?

Comment by Michael Girard, Singapore

80516 Racioethnic differences in the biomechanical response of the lamina cribrosa; Behkam R, Kollech HG, Jana A, Hill A, Danford F, Howerton S, Ram S, Rodríguez JJ, Utzinger U, Girkin CA, Vande Geest JP; Acta biomaterialia 2019; 88: 131-140

Individuals of African descent (AD) have been shown to be three to four times more susceptible to develop primary open-angle glaucoma (POAG) than individuals of European descent (ED). A high POAG prevalence has also been observed in individuals of Hispanic ethnicity (HE). While several explanations have been provided, including differences in blood pressure, in optic nerve blood flow, and in optic nerve head (ONH) anatomy, we have yet to fully grasp the underlying mechanisms in the ethnic groups that are at higher risk of developing glaucoma. Recently, several research groups have hypothesized that it is not only differences in ONH anatomy, but also differences in ONH biomechanical behavior that may provide increased susceptibility to glaucoma.

To this end, the proposed study aimed to assess the biomechanics of ONH tissues in human donor eyes from three ethnic groups (AD, ED, and HE). The authors developed a custom device to pressurize the posterior pole, centered on the ONH, in an ex-vivo setting. The lamina cribrosa (LC) – a critical biomechanical structure of the ONH – was then imaged using second harmonic generation microscopy and local LC strains (deformations) were mapped in 3D for various levels of IOP (from five to 45 mmHg). The authors were able to

map IOP-induced LC strains in 24 healthy eyes, including nine AD, six ED, and nine HE eyes, and found significant differences in the biomechanical behavior of the LC across ethnic groups. Notably, **ED eyes exhibited significantly higher LC strains in the superior quadrant, and interestingly LC strains in ED eyes were considerably less heterogeneous than those observed in AD and HE eyes**, suggesting different underlying connective tissue microarchitecture across these groups. This work provides an important preliminary step to understand how ethnic variations may influence ONH biomechanics and may predispose certain eyes to develop glaucoma.

> The work is not yet able to conclude whether a specific strain pattern for any given ethnicity would be responsible for the development and progression and glaucoma

However, the work is not yet able to conclude whether a specific strain pattern for any given ethnicity would be responsible for the development and progression and glaucoma. Further *ex-vivo* and *in-vivo* studies are warranted. Specifically, the authors would benefit from adding more samples to their study (including glaucoma eyes), as less than ten eyes per group remains on the low side. In addition, since age varied between 53 and 95 years, and is an important factor affecting tissue biomechanics, age-matched groups should also be considered.

Finally, it is also worth noting that the results may not be directly comparable with *in-vivo* data that were, for example, obtained in Fazio *et al.*[1] Performing *ex-vivo* experiments offers a nicely controlled environment where a single load (here IOP) can be studied and varied (here between five and 45 mmHg) independently of all other loads. This has value to better understand the physics of the eye across ethnicities, but this cannot be taken as fully representative of an *in-vivo* setting. Indeed, *in vivo*, multiple loads act simultaneously on the ONH including, but not limited to: IOP, the cerebrospinal fluid pressure, the orbital fat pressure, choroidal swelling during the cardiac cycle, optic nerve traction during eye movements, and the ciliary muscle pulling force transmitted to the ONH via the choroid and Bruch's membrane during accommodation. *In-vivo* ONH strains are thus more representative of what ONH cells directly experience. However, it is important to keep in mind that knowledge from both *in-vivo* and *ex-vivo* strain mapping studies will ultimately be needed to create the best clinical tool to predict visual field progression.

> *In-vivo* ONH strains are thus more representative of what ONH cells directly experience

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Laminar and RNFL defects

Comment by Eun Ji Lee, Seongnam, Gyeonggi-do, Korea

80461 Association Between Lamina Cribrosa Defects and Progressive Retinal Nerve Fiber Layer Loss in Glaucoma; Moghimi S, Zangwill LM, Manalastas PIC, Suh MH, Penteado RC, Hou H, Hasenstab K, Ghahari E, Bowd C, Weinreb RN; JAMA ophthalmology 2019; 137: 425-433

A focal lamina cribrosa (LC) defect is defined as a laminar surface irregularity that interrupts the smooth curvilinear contour of the anterior LC surface, which is usually observed on cross-sectional optic nerve imaging by optical coherence tomography.[1,2] Since focal LC defects were first described in 2012 in glaucomatous eyes,[1] studies have characterized the structure[2-4] and associated clinical features[2,5,6] of these defects in glaucoma, and suggested its pathogenic and clinical significance as a marker of progressive glaucomatous damage.[6-8]

In this longitudinal cohort study, Moghimi *et al.* showed that the mean rate of retinal nerve fiber layer (RNFL) thinning was two-fold faster in eyes with than without LC defects, with the most noticeable RNFL thinning observed at the location of the LC defect. These findings were comparable to those of a previous study, which showed a significant topographic relationship between the optic disc pit and the location of future RNFL thinning.[6] **The authors concluded that the LC defects could be an independent factor for rapid RNFL thinning, and that glaucoma progression might correspond to the location of the LC defect.**

The mechanism underlying the LC defect and its association with glaucoma are poorly understood. The LC defect may indicate a localized susceptibility of the LC to the damaging effects of elevated intraocular pressure (IOP).[3,6] It is also possible that structural alterations in the LC affects the axonal flow of the nearby axons.[5] Alternatively, vascular insufficiency in eyes with LC defects may increase their susceptibility to glaucoma progression.[9]

The authors hypothesized that the importance of each risk factor might differ between eyes with and without LC defects. They therefore assessed the role of each factor in eyes with LC defects. Interestingly, **IOP, which was significantly associated with faster RNFL thinning in eyes without LC defects, was NOT significantly associated with faster RNFL thinning in eyes with LC defects.** Such finding may indicate that factors other than mechanical stress are more important in eyes LC defects. It remains unclear, however, whether the pathogenesis of glaucoma differs in eyes with and without LC defects.

A more pronounced IOP reduction may be required in eyes with LC defects, because these eyes may be more susceptible to glaucoma progression

Without providing a conclusive answer to this question, Moghimi *et al.* cited another study showing regional microvasculature dropout at the locations of LC defects,[9] suggesting that these microvascular alterations may increase the rate of glaucoma progression in these regions.

However, the authors also emphasized that further reduction in IOP may slow glaucoma progression in eyes with LC defects. Thinner cornea, rather than increased IOP, was significantly associated with faster RNFL loss in eyes with LC defects in their study. Corneal thickness may reflect the biomechanical properties of the optic nerve head that is susceptible to glaucoma. In this regard, a more pronounced IOP reduction may be required in eyes with LC defects, because these eyes may be more susceptible to glaucoma progression.

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Basic Science

Myocilin and NTG


Comment by Tin Aung and Eranga Vithana, Singapore

80536 Myocilin Mutations in Patients With Normal-Tension Glaucoma; Alward WLM, van der Heide C, Khanna CL, Roos BR, Sivaprasad S, Kam J, Ritch R, Lotery A, Igo RP, Cooke Bailey JN, Stone EM, Scheetz TE, Kwon YH, Pasquale LR, Wiggs JL, Fingert JH; JAMA ophthalmology 2019; 137: 559-563

Can molecular analysis bring more clarity to the clinical divide of normal-tension glaucoma (NTG) and high-pressure primary open-angle glaucoma (POAG)? This is the question that springs to mind when reading the recent paper by Alward *et al.* Stark lines of clinical classifications have been redrawn for other disease after extensive and systematic molecular characterizations; corneal dystrophies are one such example. This paper is one for blurring the lines however, and demonstrates the molecular complexity of glaucoma and questions this division in glaucoma based on arbitrary measurements of intraocular pressure (IOP).

> This paper demonstrates the molecular complexity of glaucoma and questions this division in glaucoma based on arbitrary measurements of intraocular pressure (IOP)

In this paper, **the authors evaluated the role of the p.Gln368Ter *MYOC* mutation in patients with NTG and found that this mutation was found in patients with IOPs that were 21 mmHg or lower (deemed NTG), although at a frequency that is lower than previously detected in patients with higher IOP**. This suggests that the p.Gln368Ter mutation may be associated with glaucoma in patients with normal IOPs as well as in patients with IOPs that are greater. Moreover, the data suggest that the MYOC gene is associated with glaucoma across a broader range of IOP than was previously recognized.

The authors found eleven p.Gln368Ter mutation carriers with a clinical diagnosis of NTG. Prior to this study only a single NTG patient with this mutation has been described.[1] One would feel more confident if the NTG patients with the p. Gln368Ter mutation had better characterization of pre-treatment IOP profiles. The authors mention that some patients who received a diagnosis of NTG might have had higher unrecognized IOP because of diurnal variation or infrequent testing. Amongst the 11 patients, there are cases one would describe as classic NTG and the association of p.Gln368Ter *MYOC* mutation in this clinical entity is therefore not in question, but the frequency may be lower than that described in

this study and highlights the importance of molecular investigations in well-characterized clinical samples. Nevertheless, one can now safely say *MYOC* is no longer only a gene associated with only high IOP.

> One can now safely say *MYOC* is no longer only a gene associated with only high IOP

Shared genetic risk factors in *clinically different* entities indicate that a lot more is involved in the pathogenesis of a disease. Other genetic variants in the wider genome and non-genetic risk factors may be involved to bring about this clinical heterogeneity for POAG.

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Cellular changes in trabecular cells


Comment by Nils Loewen and Alicja Strzalkowska, Würzburg, Germany

82397 Prion protein modulates endothelial to mesenchyme-like transition in trabecular meshwork cells: Implications for primary open angle glaucoma; Ashok A, Kang MH, Wise AS, Pattabiraman P, Johnson WM, Lonigro M, Ravikumar R, Rhee DJ, Singh N; Scientific reports 2019; 9: 13090

Over-activation of the ROCK pathway causes cytoskeletal changes in trabecular meshwork cells (stress fibers, increased stiffness) and leads to IOP elevation, a mechanism that is now exploited by new therapeutics.[1–3] Ashok *et al.* have a long history of investigating the role and dysfunction of the prion protein (PrP^c). Their more recent interest includes PrP^c's participation in iron metabolism of the posterior[4] and anterior segment of the eye.[5] In this study, the authors describe how PrP^C induces an endothelium-to-mesenchyme-like transition and argue that this is similar to the epithelium-to-mesenchyme transition that PrP^C can induce in neuronal cells through β1-integrin and Rho-ROCK activation.[6–9] The authors do not explain why they think endo- and epithelial function and origins are interchangeable, however. The key pathogenic event in all prion disorders is a change in the conformation of PrP^C to a β-sheet rich PrP-scrapie (PrP^{Sc}) isoform and could also be at fault here.

The authors performed an impressive array of experiments in three different species (bovine, human, murine) including PrP-knockout mice. **Downregulation of PrP^c activated the Rho/ROCK pathway and led to aggregation of β1-integrin, upregulation of fibronectin, collagen 1A, α-SMA and myocilin causing IOP to increase.**

It is tempting to follow the line of thought by the authors that puts prions and PrP^c not only central to neurodegeneration in glaucoma, but also to outflow failure. Both was already suggested by the discoverer of prions, Stanley Prusiner, in 2008 (personal communication). The authors propose a mechanism that incorrectly generalizes that POAG patients have an elevated level of matrix metalloproteinases (MMPs), which cleave PrP^c and thereby further worsen the TM outflow failure. Although there are clinicians on the team, the authors fail to realize that the same MMPs (MMP 2 and 9) they believe to be important in their model of IOP elevation, are actually therapeutically upregulated by laser trabeculoplasty to lower IOP.[10] Patients with prion diseases are also not known to have elevated eye pressures (but do more frequently get tonography[11]), even though prions are typically present in ocular tissue.[12] Conversely, glaucoma patients do not have more PrPc.[13]

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Models of Glaucoma

A model of chronic open-angle, not of acute glaucoma

Comment by Bang Bui, Melbourne, Australia

81229 Intracameral injection of a chemically cross-linked hydrogel to study chronic neurodegeneration in glaucoma; Chan KC, Yu Y, Ng SH, Mak HK, Yip YWY, van der Merwe Y, Ren T, Yung JSY, Biswas S, Cao X, Chau Y, Leung CKS; Acta biomaterialia 2019; 94: 219-231

Progress in understanding glaucoma pathogenesis has been greatly facilitated by establishing robust, simple and repeatable models that recapitulate physiology relevant disease features. More recently, research groups have sought to develop inducible models on a murine platform to capitalize on the many advantages that this widely used laboratory species offers. Further, to exploit rapid developments in imaging and reporter mouse strains, one would want a glaucoma model that retains optical clarity.

To this end, Chan *et al.* developed hyaluronic acid-based polymers that are fluid at room temperature but cross link when gradually warmed by the higher temperatures inside the anterior chamber. **Following careful characterization, a single 1.5 uL injection into the anterior chamber produced significant IOP elevation of 9 mmHg above the fellow control excellent was sustained throughout the four weeks of monitoring.** Importantly the success rate was excellent with ~90% of eye exhibiting significant IOP elevation and any attrition was negligible as no adverse effects were noted.

> The optical clarity presents an advantage over a number of murine mode, making this work a significant contribution to pre-clinical glaucoma modelling

Using mice in which yellow fluorescent protein is expressed under a thy1 neuronal promoter (Thy1-YFP-G), **the authors nicely show a progressive decline in Thy1-YFP cells over the four weeks and thereby longitudinal *in-vivo* imaging is unimpeded in this model**. They also found that IOP elevation led to optic nerve and optic tract damage as evidenced by reduced diffusion anisotropy using diffusion tensor magnetic resonance

imaging. Consistent with what would be expected from chronic IOP related injury, the team demonstrate progressive decline (-1%/day) in visual acuity as measured using the optomotor reflex. Functional deficits specific for retinal ganglion cells could were also observable using the electroretinogram.

This novel simple approach produces robust and sustained IOP elevation, and recapitulates progressive neurodegeneration seen in in human glaucoma. Critically, the optical clarity presents an advantage over a number of murine mode, making this work a significant contribution to pre-clinical glaucoma modelling.

Clinical Examination Methods

Telemetric IOP monitoring

Comment by Tony Realini, Morgantown, WV, USA

82466 Telemetric Measurement of Intraocular Pressure via an Implantable Pressure Sensor-12-Month Results from the ARGOS-02 Trial; Choritz L, Mansouri K, van den Bosch J, Weigel M, Dick HB, Wagner M, Thieme H,; American Journal of Ophthalmology 2020; 209: 187-196

Choritz and colleagues have reported the 12-month outcomes of the ARGOS study, evaluating the safety and preliminary performance of an implantable continuous IOP monitor into the ciliary sulcus at the time of cataract extraction and IOL implantation. The system is in two parts: an implantable microelectromechanical sensor that detects and converts IOP to electrical signals, and an external detector that, when held in close proximity to the eye, activates and downloads IOP data. In this study, 22 eyes with POAG received the device. Surgical complications associated with the device included 5 cases each of iris prolapse (likely related to the requirement to enlarge the phacoemulsification incision to 6mm to accommodate device insertion) and pigment dispersion (also likely related to insertion). Four serious postoperative adverse events were reported, including two cases of severe fibrin reaction in the anterior chamber (both of which resolved with anti-inflammatory therapy), one case of corneal decompensation, and one case of intractable IOP elevation requiring filtering surgery. Mean endothelial cell loss was 9.4% at 12 months (largely related to the single case of corneal decompensation). Performance-wise, **mean IOP measured with the device averaged 3.2 mmHg higher than Goldmann tonometry, while the agreement was high (intraclass correlation coefficient 0.783).** Importantly, the device can be recalibrated post-implantation, minimizing consequences of long-term drift. This device and study represent an important step toward the holy grail of accurate and continuous IOP monitoring in eyes with glaucoma.

This device and study represent an important step toward the holy grail of accurate and continuous IOP monitoring in eyes with glaucoma

While the relationship between IOP and glaucoma has been known for more than a century, we still know remarkably little about the nature of the relationship. That is to say, we do not fully understand which aspects of IOP behavior (mean, peak, variability, extent of time above a certain level, etc.) that increases the risk of progression over time. This gap in our knowledge is attributable in large part to a very low sampling rate – absent reliable and safe self-tonometry or continuous tonometry, we simply cannot collect enough IOP data at three to four office visits per year to characterize IOP behavior robustly enough to elucidate the IOP-progression relationship. This device – or one like it – may help to narrow or close that gap. In the short term, such a device would likely provide an adequate quantity of IOP data to better assess the adequacy of IOP control in a given eye and to assess the efficacy of newly initiated treatments. **In the long term, with a better understanding of the IOP-progression relationship, we may be able to risk-stratify patients at diagnosis based on IOP behavior, which may guide our therapeutic choices.**

Visual Field Progression

Comment by Nathan Radcliffe and Nicholas Tan, New York, NY, USA

82211 Corneal deflection amplitude and visual field progression in primary open-angle glaucoma; Jung Y, Chun H, Moon JI; PLoS ONE 2019; 14: e0220655

Corneal hysteresis is a biomechanical behavior measured with infrared light during variable air-jet applanation and has been convincingly associated with glaucoma development and progression in prospective studies.[1,2] Deformation amplitude is a newer corneal biomechanical parameter derived from the Corneal Visualization Scheimpflug Technology (Corvis ST, Oculus; Wetzlar, Germany) and describes the amount of combined corneal and eye indentation from an impulse of air. Deformation amplitude differs between glaucoma patients and normal patients and is significantly correlated with IOP in both groups.[3]

Corneal deflection amplitude (CDA) describes how much the cornea alone indents after an air puff, separate from the rest of the eye's deformation. Put simply: CDA = deformation amplitude minus eye movement. Given that CDA is calculated using deformation amplitude, there is reason to suspect that IOP correlates with CDA as well.

Jung and colleagues present a retrospective study examining the relationship between CDA and visual field progression**. The authors found that over the course of five reliable visual fields (or three reliable fields over more than three years), a higher CDA was associated with a linear rate of mean deviation worsening** in both univariate and multivariate models. Higher IOP was also associated with progression in the uni- and multivariable models. The authors did not report how *deformation* amplitude was associated with progression. However, there is literature on this topic and analysis would have been easy to perform.[3] While the authors did not find a statistical interaction between CDA and IOP in their multivariable model, they did not report the presence or absence of a correlation between the two.

Like most retrospective studies, in this study CDA was obtained during follow-up or towards the end of the follow-up interval. This is important because CDA is likely a dynamic corneal behavior that changes over time, should be correlated with IOP and medication use, and may be affected by glaucoma progression.

Corneal deflection amplitude is an interesting corneal behavior that may be related to glaucoma progression

In summary, corneal deflection amplitude is an interesting corneal behavior that may be related to glaucoma progression. Jung and colleagues have revealed useful initial findings. **A prospective study accounting for the relationship between CDA and IOP would provide further insight on this potential new risk factor.**

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Exploring ONH deformation with OCT

Comment by Michael Girard, Singapore

81967 In vivo characterization of the deformation of the human optic nerve head using optical coherence tomography and digital volume correlation; Midgett DE, Quigley HA, Nguyen TD; Acta biomaterialia 2019; 96: 385-399

Glaucoma has been referred by many as a biomechanical disorder. After all, the optic nerve head (ONH) is exposed to high levels of biomechanical stress arising from various pressures (including IOP) and from optic nerve traction during eye movements. Such stress levels, when they exceed their homeostatic range may be responsible (in part) for the development and progression of glaucoma. Unfortunately, no biomechanical tests for the ONH currently exist clinically, but research is underway.

In this study, Midgett *et al.* developed OCT-based image processing techniques (digital volume correlation) to map the 3D strains (*i.e.,* deformations) of the ONH following changes in IOP. To achieve this, two OCT scans of the ONH were captured in each subject: before and after a change in IOP. While such techniques have been proposed in the past by other groups, the authors were able to apply them to 3D radial scans of the ONH (instead of raster scans) and used an innovative method to increase IOP by asking three glaucoma-suspect subjects to wear tight-fitting swimming goggles for 15 minutes. In another group of five glaucoma subjects, strains were mapped following IOP lowering surgery. Overall, the authors concluded they could map deformations with a high resolution even with small IOP variations (4 mmHg or less). **They also observed a reduction in tissue compression within the lamina cribrosa (LC) following IOP lowering surgery**. Finally, **the authors were able to establish relationships between LC depth (a parameter that can indicate the movement of the LC with a change in IOP) and LC strains.** Such relationships have value because it is currently much simpler to assess LC depth *in vivo*, and we may be able to use it to predict the underlying tissue compression changes. It is worth mentioning that the authors would benefit from reproducing their results in much larger cohorts, and whether they could confirm that the biomechanical response of the ONH to IOP is indeed associated with visual field loss, as was observed by Tun *et al.*[1]

Moving forward, it is becoming clearer that glaucoma subjects would benefit from a clinical test to assess the robustness of their ONHs

Moving forward, it is becoming clearer that glaucoma subjects would benefit from a clinical test to assess the robustness of their ONHs. Such a test would work by creating a mechanical perturbation (*e.g.*, IOP increase) while observing a response (*e.g.*, tissue displacements with OCT imaging). The method proposed in this publication to raise IOP (tight-fitting swimming goggles) has clear scientific value from a research perspective, but it may not be easily translated clinically owing to patients' discomfort. An alternative could be to map ONH deformations with an existing natural load (*e.g.*, the ocular pulse amplitude), and several research groups are thinking along those lines. In addition, clear biomechanical markers would need to be defined. Strain and stress are extremely useful engineering metrics to understand a biomechanical system, but each is represented by a set of six numbers defined at each single pixel of a ONH, thus causing the problem of 'too much information'. Artificial intelligence may have an opportunity to reduce such complexities into clinically-manageable biomechanical parameters. Mapped strain and stress can also be used to derive ONH biomechanical properties (*i.e.*, stiffness) and this can be done using the virtual fields method or VFM[2] (not to be confused with visual field). Finally, to realistically compare biomechanical results across patients, one would need to subject them to the exact same loads (*i.e.*, identical IOP increase from an identical baseline IOP), but this remains a clinical challenge.

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Structure and Function I

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

82393 Topographic correlation and asymmetry analysis of ganglion cell layer thinning and the retinal nerve fiber layer with localized visual field defects; Casado A, Cerveró A, López-de-Eguileta A, Fernández R, Fonseca S, González JC, Pacheco G, Gándara E, Gordo-Vega MÁ; PLoS ONE 2019; 14: e0222347

Casado *et al.* explored the utility of the central macular full retinal (RTA) and GCL thickness measurements and their vertical asymmetry along the fovea-disc axis to peripapillary retinal nerve fiber layer (pRNFL) thickness measurements for discriminating glaucoma eyes with visual field loss from control eyes with no visual field defects. Three hundred and eighteen eyes of 161 subjects were included. The control group consisted of eyes that

did not have visual field loss and therefore, could have been normal or have had early glaucoma. The investigators limited their analyses to the central 16 macular superpixels (called clusters).

They found similar performance for either GCL clusters (or superpixels) or GCL asymmetry measures comparable to pRNFL especially in eyes with superior VF loss while the pRNFL still performed better in eyes with inferior visual field loss. GCL and RTA asymmetry were measured subjectively. While subjective asymmetry in GCL and pRNFL were correlated with visual field loss, retinal thickness asymmetry did not show a significant difference between control and glaucoma eyes. GCL and pRNFL thickness measurements showed significant correlations with visual field severity stage (-0.334 for the best GCL superpixel and -0.303 for the average pRNFL).

Vertical asymmetry measures are useful for detection of early glaucoma

It is not clear how the proportion of eyes detected with macular measures overlaps with the eyes detected with pRNFL measures. This would have provided a better understanding of how complementary the two type of structural outcomes (macula-based vs. RNFL-based) would be. **Myopic eyes were excluded limiting the generalizability of results to this important subset of patients**. It is conceivable that macular thickness and asymmetry measures would have performed even better if the control group was composed of entirely normal eyes.

This paper adds to the already substantial amount of information in the literature suggesting that vertical asymmetry measures are useful for detection of early glaucoma. It is high time that a user-friendly marker based on vertical macular asymmetry is incorporated into commercial SD-OCT devices so as to facilitate clinical evaluation of eyes suspected of early glaucoma.

Structure and Function II

Comment by Ki Ho Park, Seoul, South Korea

80750 Association Between Parapapillary Choroidal Vessel Density Measured With Optical Coherence Tomography Angiography and Future Visual Field Progression in Patients With Glaucoma; Park HY, Shin DY, Jeon SJ, Park CK; JAMA ophthalmology 2019; 137: 681-688

The nerve fiber bundle of the optic nerve is separated from the choroid by the border tissue of Jacoby. Regarding the role of the choroid in the blood supply to the optic nerve head, controversy persists as to whether the prelaminar region's arterial supply is derived primarily from the peripapillary choroid or the branches of the circle of Zinn-Haller, which is itself supplied by the short posterior ciliary arteries. Previously, Na *et al.* has shown using optical coherence tomography angiography (OCT-A) that the prelaminar region of the optic nerve head might be supplied by the peripapillary choroid in addition to the known major blood supply from the short posterior ciliary arteries.[1] Further, OCT-A has revealed growing evidence that glaucoma is associated with decreased parapapillary choroidal microvasculature.[2,3]

Lower parapapillary choroidal vessel density (VD) with B-zone parapapillary atrophy (PPA) at baseline is associated with future visual field progression

This study by Park and colleagues is the first to demonstrate that lower parapapillary choroidal vessel density (VD) with B-zone parapapillary atrophy (PPA) at baseline is associated with future visual field progression in glaucoma. The clinical relevance of the study is that it is the first prospective one showing that **patients with lower parapapillary choroidal VD at baseline need careful monitoring for future glaucoma progression**.

There are some limitations to this study: (1) As only PPA(+) eyes were included, it is not clear whether the same results may be obtained for PPA(-) eyes or whether PPA itself may be a surrogate factor. Also, the boundary of PPA was delineated on the en face choroidal map of OCT-A, not on disc photography, which might have affected the determined size of PPA;[4] (2) As seen in the figures, retinal blood vessels were included in the analysis of the choroidal VD; (3) Baseline IOP data were not provided or analyzed.

However, the current paper raised the promising possibility that **OCT-A can be a useful tool to complement current structural and functional assessment in glaucoma**. A future longitudinal follow-up study using OCT-A may further clarify the causal relationship between VD and optic nerve damage in glaucoma.

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Artificial Intelligence applications I

Comment by Gustavo de Moraes Moraes and Bruna Melchior Silva, New York, NY, USA

82092 Accurate prediction of glaucoma from colour fundus images with a convolutional neural network that relies on active and transfer learning; Hemelings R, Elen B, Barbosa-Breda J, Lemmens S, Meire M, Pourjavan S, Vandewalle E, Van de Veire S, Blaschko MB, De Boever P, Stalmans I; Acta Ophthalmologica 2020; 98: e94-e100

The lack of symptoms in early glaucoma can lead to late diagnosis; therefore the development of a cost-effective screening method may have an important role in preventing vision loss due to glaucoma.

The objectives of this study were (1) to develop and validate a deep learning glaucoma classifier based on color fundus images of glaucoma patients compared to the clinical diagnosis based on full ophthalmologic examination, tonometry, visual fields, and OCT or HRT; (2) to explore the added value of active learning on top of deep learning for automated glaucoma detection; and (3) to inspect the trained model's decision process using interpretable heatmaps.

A total of 7,038 fundus images passed through quality assessment and were allocated to training (70%), validation (10%), and testing sets (20%). Data augmentation was randomly generated to increase the number of images used to train the convolutional neural network (CNN). Area under the receiver operating characteristic curve (AUC) was selected as main

performance metric, with specificity and sensitivity also reported. The CNN was backed up by the analysis of false positives and false negatives by two ophthalmologists in a blind fashion.

Two trained glaucoma specialists analyzed more than 500 heatmaps and indicated a recurrent pattern in the inferotemporal and superotemporal zones neighboring the optic nerve head (ONH), providing novel insights into the decision-making process of the trained deep learning glaucoma classifier through these maps, suggesting that regions outside the ONH could be valuable in this analysis.

This study yielded a deep learning-based glaucoma classifier that achieved an AUC of 0.995 for patient referral with a 60% decrease in labelling cost through the combination of transfer learning, careful data augmentation, and uncertainty sampling. One major strength was the topographical analysis of individual heatmaps to better understand the reasons for errors.

In combination, these findings could help advance the field of artificial intelligence applied to ophthalmology, especially when insufficient data are available.

Artificial Intelligence applications II

Comment by Minguang He, Guangzhou, P.R. China

82400 Development and Validation of a Deep Learning System to Detect Glaucomatous Optic Neuropathy Using Fundus Photographs; Liu H, Li L, Wormstone IM, Qiao C, Zhang C, Liu P, Li S, Wang H, Mou D, Pang R, Yang D, Jiang L, Chen Y, Hu M, Xu Y, Kang H, Ji X, Chang R, Tham C, Cheung C, Ting DSW, Wong TY, Wang Z, Weinreb RN, Xu M, Wang N; JAMA ophthalmology 2019; 137(12): 1353-1360

Artificial intelligence has been evolving from an innovation from computer science to clinical adoption in many image-driven clinical disciplines, including ophthalmology. This study is perhaps the best example to demonstrate how to develop and validate a deep learning based artificial intelligence classification on fundus photograph. This research team collected and included 241K images from 68K patients for training and then the validation was performed internally among 28K images from the same source and then validated externally among the images collected in three hospitals in China, one population-based sample (Handan Eye Study) and a multiethnic clinic (Hamilton Glaucoma Center) in US. What impress me the most is that the study involved 22 board-certified ophthalmologists to grade nearly 240K images. This is a tremendous amount of efforts. On the other hand, the investigator chose to use Resnet, a neuron network developed in 2015 that allows deeper and more layers to achieve more accurate classification while at the same time avoid the problems of information loss and optimization error when the layers

are too deep although the problem is on its demand on computational power and memory that would compromise its feasibility in real world adoption. Another innovation is their human-computer interaction loop where the manually confirmed false positive images are used for further fine-tuning of the network. One of the interesting findings is that **the accuracy of the CNN trained primarily in Chinese eyes, during external validation, was reduced from hospital-based images collected in Chinese, to population-based Chinese sample and further deteriorate among the images collected at the US-based UC San Diego Hamilton Glaucoma Center** (less than 90% sensitivity and specificity). This highlights the challenges on the generalizability of CNN classification among the images or features that have not been used to train before.

Artificial Intelligence applications III

Comment by Andrew Tatham, Edinburgh, UK

82788 Deep Learning Approaches Predict Glaucomatous Visual Field Damage from OCT Optic Nerve Head En Face Images and Retinal Nerve Fiber Layer Thickness Maps; Christopher M, Bowd C, Belghith A, Goldbaum MH, Weinreb RN, Fazio MA, Girkin CA, Liebmann JM, Zangwill LM; Ophthalmology 2020; 127: 346-356

Deep learning (DL) is a machine learning technique that uses artificial neural networks inspired by the human brain, to learn from large amounts of data.[1] DL algorithms can automatically recognize intricate patterns in high-dimensional data and so are well suited for medical image analysis, including analysis of fundus photographs and optical coherence tomography (OCT).

In this innovative study, Christopher and colleagues developed DL models for detecting eyes with glaucomatous visual field (VF) loss and for predicting the severity of VF damage. Over 1,000 participants were included, with DL models trained to use RNFL thickness maps, RNFL *en-face* images or confocal scanning laser ophthalmoscopy (CSLO) images to predict the presence of VF loss and estimate VF indices including mean deviation (MD) and sectoral pattern deviation (PD).

The best performing DL model, which was based on the RNFL *en-face* image, achieved an area under the receiver operating characteristic curve (AUC) of 0.88 for detecting glaucomatous VF damage. This was significantly better than the performance of raw circumpapillary or global RNFL thickness values (AUC = 0.80 and 0.82 respectively). The RNFL *en-face* DL model also performed well in identifying eyes with early glaucomatous VF damage, defined as a MD > -6dB (AUC = 0.82 for the DL model versus 0.70 for circumpapillary RNFL thickness). In addition, the DL models were better at predicting MD, with the RNFL *en-face* model achieving a R^2 of 0.70 (mean absolute error of 2.5 dB) compared to a R^2 of only

0.45 for circumpapillary RNFL thickness (mean absolute error of 3.7 dB). **The strongest sectoral associations for predicting VF PD from OCT were in the superior nasal and inferior nasal sectors of the VF.**

> This study shows that DL can also be used to directly model structure-function relationships and identify eyes with likely functional loss from OCT imaging

DL algorithms have recently been developed that have similar or better ability to detect glaucoma from color fundus images compared to ophthalmologists[2] and that can improve segmentation and identify neural and connective tissues of the optic nerve head.[3] This study shows that DL can also be used to directly model structure-function relationships and identify eyes with likely functional loss from OCT imaging. The ability to better predict VF loss from OCT may help clinicians more effectively individualize the frequency of VF testing. For example, if the DL algorithm predicts VF loss similar to a patient's previous VF test, the clinician may decide to postpone repeat VF testing, whereas if the algorithm predicts worsening VF, a sooner repeat test may be indicated.

A further potential benefit is that when using OCT in clinical practice, clinicians often may place too much emphasis on the results of automated classifications or on global thickness measures. **A major strength of the DL models is that they used information from the entire scan.** In addition, DL models learnt about the structure-function relationship through training and did not make assumptions about linearity, a potential flaw of previous structure-function models.

> Examining features of imaging, other than thickness, *e.g.*, texture or voxel intensity, may provide additional value for glaucoma detection and monitoring

The observation that DL models based on the RNFL *en-face* images outperformed models based on RNFL thickness maps and CSLO images is interesting. A possible explanation is that RNFL *en-face* images are computed from voxel intensity values within the RNFL, information not available from thickness values alone. This finding provides evidence that examining features of imaging, other than thickness, *e.g.*, texture or voxel intensity, may provide additional value for glaucoma detection and monitoring.

Importantly, the authors also presented an intuitive method for clinicians to visualize the results of the DL model using heat maps to highlight regions of images of most importance in contributing to the classification process. Such a visualization technique could also prove useful in revealing fine-scale information about structure-function relationships.

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Forms of Glaucoma

POAG Genetics and Age of Onset

Comment by Tin Aung and Monisha Nongpiur, Singapore

82271 Association of a Primary Open-Angle Glaucoma Genetic Risk Score With Earlier Age at Diagnosis; Fan BJ, Bailey JC, Igo RP, Kang JH, Boumenna T, Brilliant MH, Budenz DL, Fingert JH, Gaasterland T, Gaasterland D, Hauser MA, Kraft P, Lee RK, Lichter PR, Liu Y, Moroi SE, Myers JS, Pericak-Vance MA, Realini A, Rhee DJ, Richards JE, Ritch R, Schuman JS, S; JAMA ophthalmology 2019; 0:

Disease risk assessments based on genetic variants are rapidly gaining interest in the clinical community as they have the potential to improve health outcomes for a variety of complex diseases. Polygenic risk score (PRS) or genetic risk score (GRS) is a statistical tool that measures an individual's genetic predisposition to specific diseases. With recent advances in our understanding of the genetic basis of primary open angle glaucoma (POAG), there is thus a growing possibility of developing and adapting GRS for clinical use in glaucoma.

> GRS-based genetic risk estimates may aid in early disease detection, thereby allowing for timely initiation of preventive treatment and management strategies

In this paper, Fan and colleagues investigated the association of a GRS that comprised of 12 known POAG genetic risk variants with the age at diagnosis of glaucoma. The single nucleotide polymorphisms (SNPs) that were selected for construction of the GRS were the lead SNPs from the genetic loci with statistical evidence for association with POAG in European white populations. Their study comprised of a total of 3108 individuals with POAG and 3430 controls from the Glaucoma Genes and Environment (GLAUGEN) study and the National Eye Institute Glaucoma Human Genetics Collaboration (NEIGHBOR) study. They found that an increased load of genetic risk variants was associated with an earlier onset of disease. **Affected individuals in the top 5% of the GRS had 5.2 years earlier age at diagnosis of disease compared to those in the bottom 5% GRS**. The findings suggest that GRS-based genetic risk estimates may aid in early disease detection, thereby allowing for timely initiation of preventive treatment and management strategies.

The accuracy and generalizability of a GRS risk estimate is enhanced when the individual variants integrated into the GRS are from within the same population studied. Therefore, despite the presence of a larger number of genomic regions associated with POAG at a

genome-wide level of significance, only the 12 European specific SNPs were selected. The clinical utility of GRS in terms of disease screening and therapeutic intervention are beginning to show promise. We look forward to future advances in improved comprehensiveness and generalizability of GRS for clinical use.

Prevention of PACG

Comment by Benjamin Xu, Los Angeles, CA, USA

80641 Laser peripheral iridotomy for the prevention of angle closure: a single-centre, randomised controlled trial; He M, Jiang Y, Huang S, Chang DS, Munoz B, Aung T, Foster PJ, Friedman DS; Lancet 2019; 393: 1609-1618

Primary angle-closure glaucoma (PACG), the most severe stage of primary angle-closure disease (PACD), is a common cause of permanent vision loss worldwide.[1] Primary angle-closure suspect (PACS), the earliest stage of PACD, is defined as angle closure detected on gonioscopy in two or more quadrants of the anterior chamber angle.[2] Progression from PACS to primary angle closure (PAC) occurs when patients develop peripheral anterior synechiae (PAS) or elevated intraocular pressure (IOP) greater than 21 mmHg. Patients with PAC and PACG benefit from treatment with laser peripheral iridotomy (LPI), which can alleviate angle closure and lower IOP.[3] However, prior to the landmark Zhongshan Angle Closure Prevention (ZAP) trial by He and colleagues, the benefit of treating PACS eyes with LPI was unclear.[4]

> Prior to the landmark Zhongshan Angle Closure Prevention (ZAP) trial, the benefit of treating PACS eyes with LPI was unclear

The ZAP trial was a randomized clinical trial that recruited 889 subjects with bilateral PACS through community-based screening in Guangzhou, China. One eye per subject was randomized to treatment with LPI and the other to observation. This elegant design allowed each subject to act as his/her own control. Subjects were followed for six years, with the primary outcome being progression from PACS to PAC. **While the treatment group had a significantly lower rate of progression compared to the observation group (hazard ratio = 0.53, p = 0.004), the risk of progression was low in both groups**: 0.80% per year in the treatment group and 0.42% per year in the observation group. Based on their cost effectiveness analysis, the authors estimated that 44 and 126 LPI would need to be performed to prevent one case of PAC and PACG, respectively.

Authors estimated that 44 and 126 LPI would need to be performed to prevent one case of PAC and PACG, respectively

While the ZAP trial provides valuable insight into the limited benefit of treating eyes with PACS based on its current definition, **it is important not to over-generalize its results**. The ZAP trial **only studied Chinese subjects between the ages of 50 to 70**. Therefore, it is unclear if an older or multi-ethnic cohort would display similar rates of progression. The ZAP trial also highlights the need for new clinical methods to help clinicians identify PACS patients with higher risk of progressing to PAC and PACG who would benefit from LPI treatment.

IOP and Visual Fields in PACG

Comment by Kaweh Mansouri, Lausanne, Switzerland

82190 Intraocular pressure control and visual field changes in primary angle closure disease: the CUHK PACG Longitudinal (CUPAL) study; Cheung CY, Li SL, Chan PP, Chan NCY, Tan S, Man X, Tham CC; British Journal of Ophthalmology 2020; 104(5): 629-635

An independent role of IOP fluctuations on glaucoma progression in patients with open-angle glaucoma has been widely investigated but still remains controversial. Very little is known on the correlaton between IOP variations and angle-closure glaucoma.

In this well-conducted study by Cheung and colleagues, 240 Chinese PACG patients from a longitudial, observational study from a tertiary center in Hong Kong were included. Over a two-year follow-up, they had four annual IOP measurements and an average five visual field tests.

The investigators found a strong correlation between IOP fluctuation (defined as SD devided by mean IOP) and progression of visual field (both MD and VFI). Interestingly, these observation was found independent of mean IOP, although eyes with 'high-threshold' mean IOP and IOP fluctuation had more rapid VF progression.

One strength of this study includes the inclusion of wide glaucoma severities, whereas previous studies included either mostly advanced cases (AGIS) or early and untreated cases (EMGT).

A surprising finding which needs further research was the strong correlation between male sex and VF progression, independent of other parameters, in contrast to previous studies showing a higher risk for PACG in females.

The main limitation of this study, however, is the lack of continual IOP measurements. Recent reports using continual IOP monitoring have demonstrated the important daily and long-term variations of IOP in open-angle patients. As these technologies become more available in the near future, it is hoped that the role of IOP dynamics ono glaucoma development and progression will be better understood.

Prognostic Factors in Malignant Glaucoma

Comment by Franz Grehn, Wurzburg, Germany

82147 Factors Impacting Outcomes and the Time to Recovery From Malignant Glaucoma; Thompson AC, Vu DM, Postel EA, Challa P; American Journal of Ophthalmology 2020; 209: 141-150

Malignant glaucoma (MG) is a rare but serious event in angle closure glaucoma, typically after trabeculectomy or other filtering procedures. It is characterized by a shallow or flat anterior chamber and moderately or considerably elevated IOP and can lead to a disastrous outcome. It must be differentiated from overfiltration where the IOP is very low.

The paper by Thompson *et al.* retrospectively analyzed 64 eyes of 55 subjects that developed MG after surgical interventions within a 10 years period. The analysis of these cases considered multiple aspects with new information, but **the main hitherto existing recommendations (cycloplegia, carbonic anhydrase inhibitors, hyperosmotics, Nd:YAG hyaloidotomy, anterior chamber reformation, and in particular vitrectomy) were confirmed**. The removal of the lens as one of the mainstays of treatment was also discussed in this series, but 73% of the eyes were already pseudophakic and most of the surgically treated cases underwent simultaneous lens removal at surgery in anyway. Therefore the value of lens removal as part of the intervention in phakic eyes could not be separately analyzed, but can be considered as an essential part of surgical treatment strategy.

In their final statement the authors summarize that they "found that the time to maximal improvement in IOP and BVA was significantly longer than the time to anatomic improvement following treatment of MG. Eyes that underwent trabeculectomy prior to the onset of MG were at a significantly increased risk of prolonged time to recovery in anatomy, BVA, and IOP. Medical management that incorporated clinic-based interventions such as Nd:YAG laser hyaloidotomy, AC reformation, and addition of oral CAIs to maximal topical glaucoma therapy and cycloplegia may help to hasten recovery from MG. Timing of vitrectomy within 30 days may lead to faster improvement in anatomy, BVA, and IOP, but did not ultimately impact whether or not there was complete resolution. We recommend that vitrectomy be combined with lensectomy in phakic eyes to improve the likelihood of

complete resolution of MG. Patients with known risk factors for MG should be considered for prophylactic pars plana vitrectomy at the time of cataract or glaucoma surgery, especially if they are undergoing trabeculectomy surgery."

Medical Treatment

Assessing PG effects on IOP

Comment by Cynthia Roberts, Columbus, OH, USA

81242 Latanoprost treatment differentially affects intraocular pressure readings obtained with three different tonometers; Sánchez-Barahona C, Bolívar G, Katsanos A, Teus MA; Acta Ophthalmologica 2019; 97(8): e1112-e1115

This is a well-designed study of an important question. How much of the intraocular pressure (IOP)-reducing effect of Latanoprost is true pressure reduction, and how much is artifact from alterations in corneal biomechanical properties from the MMP activity in the corneal stroma? **The authors concluded that the apparent treatment induced IOP reduction in previously naïve patients differed by which tonometer was used.** This is incredibly important for glaucoma specialists, since the true IOP reduction is needed to effectively manage patients. However, the conclusions of the current study provide only a part of the answer, while also raising additional questions. Only the original biomechanical parameters from the Corvis ST are used in the current analysis, and not the newest values introduced several years ago and available with all software updates. Several of these new parameters have been shown to be relatively independent from IOP.[1] This is critical when evaluating the effect of an IOP-lowering medication. Due to the nonlinear biomechanical properties of the cornea, as IOP is lowered, the mechanical stress is also lowered, and the stiffness response will be reduced. In other words, any eye with a reduction in IOP, independent of the treatment to induce it, will have a reduction in stiffness response. It requires careful analysis to separate the IOP-reducing effects from the fundamental reduction in corneal stiffness that has been shown to occur with prostaglandin use.[2] The Corvis ST biomechanical parameters chosen in the current study are heavily dependent on IOP, including first applanation time (AT1), second applanation time (AT2), and deformation amplitude (DA).[1] AT1 occurs when the increasing magnitude of the applied air puff reaches a point where it overcomes the resistance of the cornea to deform. The lower the IOP, the sooner this occurs. DA is also primarily a function of IOP, with greater deformation associated with lower IOP. **Therefore, the only biomechanical conclusion that can be drawn from the current study is that IOP was reduced.**

The newer biomechanical parameters from the Corvis ST are a function of the *shape* of the deformation, rather than the magnitude. Integrated Inverse Radius (mislabeled Integrated Radius on the device) has been shown to be very sensitive to small differences in stiffness.[3]

Inverse radius is the definition of curvature, and integrated inverse radius is the area under the concave curvature profile between first and second applanation events. This parameter is robust and avoids potential artifacts from single point terms like maximum inverse radius. DA Ratio is the ratio between central deformation amplitude and peripheral deformation amplitude, and therefore conveys shape. Both Integrated Inverse Radius and DA Ratio are related to corneal stiffness with a smaller value, or smaller change in shape, indicating greater resistance to deformation and a stiffer response. Both are also relatively independent of IOP.[1] There are also three additional metrics of stiffness, which are Stress-Strain Index (SSI)[4] and Stiffness Parameter at first applanation (SP-A1),[5] both related to corneal stiffness, and Stiffness Parameter at highest concavity (SP-HC)[5] which has been shown to be related to scleral stiffness.[6,7,8] With these three metrics, a higher value indicates a stiffer response. In total, these five values would provide valuable information on changes in corneal and scleral stiffness with prostaglandin usage. The authors are encouraged to investigate these values using the data already acquired in the current population.

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A clinical trial in neuroprotection


Comment by Gustavo de Moraes and Bruna Melchior Silva, New York, NY, USA

80737 Investigating the neuroprotective effect of Copolymer-1 in acute primary angle closure - Interim report of a randomized placebo-controlled double-masked clinical trial; Fan KR, Baskaran M, Nongpiur ME, Htoon HM, de Leon JMS, Perera SA, Belkin M, Aung T; Acta Ophthalmologica 2019; 97: e827-e832

Primary angle-closure glaucoma (PACG) is an important cause of bilateral blindness, in particular when resulting from acute primary angle closure (APAC). Thus, it would be important to develop novel therapies to protect retinal ganglion cells (RGCs) after APAC.

Copolymer-1 (Cop-1) is a synthetic antigenic co-polymer that acts by augmenting the body's physiological immune response and repair mechanism, and is used clinically to reduce new brain lesions in patients with multiple sclerosis.[1,2] In previous murine studies, prophylaxis with Cop-1 protected the optic nerve from injury and prevented RGC death.[3]

In this randomized, placebo-controlled, double-masked trial, patients with APAC were randomized to receive either Cop-1 or placebo, in addition to standard medical therapy. Placebo or Cop-1 was administered through subcutaneous injections, one 24h and another one week after APAC presentation. The primary outcome measure was the number of locations progressing on visual fields (SITA Standard algorithm with a 24-2 test pattern) based on pointwise linear regression analysis; as a secondary outcome measure, they investigated the change in RNFL thickness (Cirrus SD-OCT) from baseline to week 16.

A total of 38 patients completed the study, 50% in each randomization group. **The authors found a mean of 0.32 progressing visual field locations in the Cop-1 compared to 2.74 in the placebo group (p = 0.09). In addition, the change in MD between week 16 and baseline was significantly more positive in the Cop-1 group (p = 0.01). Nonetheless, they found no significant difference in mean RNFL change between groups.** No significant adverse events were noted, except for injection site pain in Cop-1 (47.4%) and placebo (26.3%) groups.

This is a first randomized clinical trial reporting a potential new neuroprotective drug to prevent irreversible vision loss following APAC. The results showed less visual field progression after APAC among those receiving the new drug. However, the lack of evidence of concurrent RNFL change warrants further investigation and could potentially argue in favor the using visual fields as primary endpoints in neuroprotection clinical trials. Further research with larger sample size, longer, follow-up time and investigation of different drug doses may help confirm these initial findings.

The lack of evidence of concurrent RNFL change warrants further investigation and could potentially argue in favor the using visual fields as primary endpoints in neuroprotection clinical trials

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Surgical Treatment

SLT or eyedrops first?

Comment by Richard Lee and Eileen Bowden, Miami, FL, USA

80617 Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial; Gazzard G, Konstantakopoulou E, Garway-Heath D, Garg A, Vickerstaff V, Hunter R, Ambler G, Bunce C, Wormald R, Nathwani N, Barton K, Rubin G, Buszewicz M,; Lancet 2019; 393: 1505-1516

Gazzard *et al.* are to be congratulated on their well-designed landmark randomized-controlled study. The LiGHT trial provides insight into the safety, efficacy, cost-effectiveness, and impact on quality of life for initial selective laser trabeculoplasty (SLT) compared to initial medical therapy in treatment naïve open-angle glaucoma and ocular hypertension patients.

The results show that 78% of eyes treated with initial SLT were controlled at 36 months. Patients in the SLT arm were at target intraocular pressure (IOP) for 93% of visits over three years compared with 91% of patients in the medication arm. Eleven eyes in the medication arm went on to require incisional glaucoma surgery while none of the patients in the SLT arm required surgery. No sight-threatening complications were reported in the SLT arm. The initial SLT approach resulted in significant cost savings per patient for the National Health Service (NHS). The primary outcome of the study was health-related quality of life, assessed using questionnaires. No significant differences in responses between the two arms were identified at 36 months.

These results corroborate what has been shown regarding safety and efficacy in previous, smaller studies comparing initial SLT to initial medical therapy.[1,2] **The LiGHT trial has the potential to shift early glaucoma management decision making toward SLT because of compliance, safety, and patient cost savings.** However, caveats need to be considered for broader adoption of SLT.

While the cost-savings in initial treatment with SLT are an important benefit to consider, we should keep in mind that the results of a clinical trial run within the NHS in a hospital-based practice may not be generalizable to other health care systems or to individual private practice ophthalmologists who might not perform large volume glaucoma laser surgery.

Although SLT provides cost savings to the patient, it requires specialized equipment which comes at both large initial and maintenance costs to a clinical practice. Unlike YAG or diode lasers, SLT lasers cannot be used to perform other ocular procedures. Finally, the LiGHT

trial's companion study showed that 25.9% of patients in the SLT arm underwent repeat SLT during the 36-month duration of the trial.[3] Repeat treatment may have additional patient costs which were not captured in the initial study.

SLT is unlikely to have adequate treatment effect in patients requiring very low intraocular pressures

SLT requires specialized skill in examining the angle anatomy and knowing where to treat to achieve effect. Additionally, even in the best hands, **SLT is unlikely to have adequate treatment effect in patients requiring very low intraocular pressures or those with normal-tension glaucoma because of intrinsic trabecular outflow resistance at mid-teens IOP.**

Ultimately, most glaucoma specialists counsel their early glaucoma patients by offering both SLT and medical therapy and allowing the patient to choose their treatment. Patient perceptions of the invasiveness of laser therapy may affect broad adoption of SLT as a primary line treatment for glaucoma.

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Efficacy of first-line SLT

Comment by Florent Aptel, Lyon, France

82879 Efficacy of Repeat Selective Laser Trabeculoplasty in Medication-Naive Open-Angle Glaucoma and Ocular Hypertension during the LiGHT Trial; Garg A, Vickerstaff V, Nathwani N, Garway-Heath D, Konstantakopoulou E, Ambler G, Bunce C, Wormald R, Barton K, Gazzard G,; Ophthalmology 2019; 0:

This study is a post-hoc analysis of the Laser in Glaucoma and Ocular Hypertension (LiGHT) trial aiming to investigate the efficacy and duration of effect of repeat SLT in medication naive POAG and OHT eyes. **One hundred and fifteen eyes of 90 subjects had undergone two SLTs during the initial 18 months of the LiGHT trial**. After the first SLT, **34 were considered as early failure (second SLT two months after the first one) and 81 as later failure (second SLT more than two months after).** Mean IOP was 24.5 ± 6.6 mmHg before the first SLT and 19.1 ± 3.9 mmHg two months after (-5.3 mmHg; - 21.6%). Mean IOP was 21.0 ± 4.2 mmHg before the second SLT and 16.3 ± 3.3 mmHg two months after (-4.6 mmHg; -21.9%), without significant difference between the early and later groups.

To compare the duration of effect after the first and second SLT, a clinical definition of success was used rather than a numerical definition: IOP below target IOP (defined by the clinician) without medications, further laser procedure or glaucoma surgery. The authors demonstrated an equivalent or longer duration of effect after the second SLT compared to the first SLT. Only 38/115 eyes (33%) that underwent a second SLT needed a medical treatment in the 18 months after the second SLT. No adverse events were reported.

The findings of this study are interesting for clinical practice. SLT is frequently used as a first-line treatment in OHT and OAG subjects. When the efficacy is not enough or when the IOP subsequently goes up, the choice between performing a second laser procedure or starting a medical treatment is debated. To date, few studies have been performed and most of them have been retrospective with a small number of patients, and therefore did not fully answer the question. However, the LiGHT trial supports the use of a second SLT when an initial SLT is not enough to reach the target IOP or when the IOP further goes up. One limitation of this study is that the authors did not use a numerical criterion to define the success, and thus it could be difficult to precisely quantify and compare the mid- and long-terms effect after the first and second SLT.

> The LiGHT trial supports the use of a second SLT when an initial SLT is not enough to reach the target IOP or when the IOP further goes up

Trabeculectomy and IOP reduction

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

80683 Changes in choroidal area following trabeculectomy: Long-term effect of intraocular pressure reduction; Kojima H, Hirooka K, Sonoda S, Sakamoto T, Kiuchi Y; PLoS ONE 2019; 14: e0209145

Relevance of choroidal change in glaucoma has long been a focus of interest in glaucoma research. The interest has been boosted recently since the description of parapapillary choroidal microvascular dropout (MvD) using OCT Angiography (OCTA) in glaucomatous eyes. It is acknowledged that choroidal thickness varies according to IOP change. Particularly, several studies demonstrated choroidal thickening weeks or months after trabeculectomy. However, there has been paucity in the literature about longer term effect of IOP lowering on the choroidal thickness. **Kojima *et al*. reported thickening of the macular and peripapillary choroidal thickness after one year after trabeculectomy. Interestingly, the thickening was mostly due to the increases in the interstitial areas, while the luminal area was comparable to the preoperative state.**

An interesting issue regarding the role of choroid in glaucoma is that how the optic nerve head perfusion is related with choroid. While the choroid is responsible for supporting the outer retina, which is considered not to be closely associated with glaucoma, peripapillary choroid is closely related with ONH perfusion. At least, peripapillary choroid and the deep ONH are both supplied from the branches of short posterior ciliary artery. Further, Hayreh has claimed that prelaminar tissue is supplied by the centripetal arterioles entering from the peripapillary choroid based on angiographic studies. According to his concept, the ONH perfusion would be strongly dependent on the choroid. If the choroid is atrophic with obstruction or obliteration of the choroidal vessel, the prelaminar tissue perfusion would be significantly hampered. On the other hand, corrosion casting technique has shown that the prelaminar perfusion is mostly dependent on the branches from the short posterior ciliary artery which directly (*i.e.*, not passing through the choroid) pierces through the sclera. Yet several small centripetal arterioles were found between the peripapillary choroid and the optic nerve head suggesting that prelaminar tissue perfusion is at least partly dependent on the peripapillary choroid.

Slowing of glaucoma progression after IOP lowering treatment may be, at least partly, attributed, to the improved perfusion to the optic nerve

The interstitial tissue contains pigment cells, smooth muscles, neurons, vascular walls, inflammatory cells, and connective tissue. It is unknown whether increases of interstitial tissue alone (*i.e.*, no change in the ruminal area) can increase the blood flow. Therefore, further study is needed to elucidate whether increase of interstitial tissue area without increase of luminal area may increase perfusion. Meanwhile, it is worthy of note that increase of ONH microvasculature has been observed after trabeculectomy in other study. It remains to be determined whether the increase of ONH vasculature is related with increase of choroidal thickness or attributed to reduction of compression of ONH connective tissue, but the finding suggests that slowing of glaucoma progression after IOP lowering treatment may be, at least partly, attributed, to the improved perfusion to the optic nerve head.

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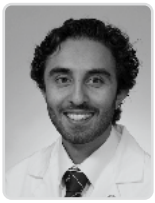
Filtering Surgery with Drainage Devices



Comment by Arshram Sheybani, St. Louis, MO, USA

82692 Novel approaches to model effects of subconjunctival blebs on flow pressure to improve clinical grading systems after glaucoma drainage surgery; Bouremel Y, Lee RMH, Eames I, Brocchini S, Khaw PT; PLoS ONE 2019; 14: e0221715

Bouremel and colleagues address an important issue in their study. Bleb grading systems are fraught with error by nature of their subjectivity. The presence or absence of a bleb leak or microcysts may be concrete depending on examination technique but bleb height, vascularity, and encapsulation grading are completely subjective. The authors present a system that factors bleb pressure into bleb characterization.

> Bleb grading systems are fraught with error by nature of their subjectivity

The purpose of having a reproducible bleb grading system is to identify blebs that may carry risk of complications and also to identify blebs that function optimally. While there is some correlation to bleb shape and functionality, this paper studies an *ex-vivo* and *in-vitro* system to model blebs. Unfortunately, so much of bleb porosity, shape, and functionality is dependent on the wound healing response. In live rabbits, a single passage of balanced salt solution through a bleb (without aqueous flowing through it) resulted in a 75-80% reduction in bleb porosity over 72 hours.[1] **Coupled with the fact that infusion pressures in these experimental blebs was at 5 ul/min, it is difficult to translate the results of Bouremel's paper to clinical practice.**

This paper should encourage additional studies looking to identify objective variables in grading filtering blebs. OCT imaging or metrics to measure bleb porosity may be possible targets of future study. Despite recent studies, there is still a need for a clinically applicable and objective grading system for blebs.

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Phaco with or without Synechialysis in PACG

Comment by Catherine Jui-Ling Liu and Yu-Chieh Ko, Taipei, Taiwan

81991 Efficacy of Phacoemulsification Alone vs Phacoemulsification With Goniosynechialysis in Patients With Primary Angle-Closure Disease: A Randomized Clinical Trial; Husain R, Do T, Lai J, Kitnarong N, Nongpiur ME, Perera SA, Ho CL, Lim SK, Aung T; JAMA Ophthalmology 2019; 137(10): 1107-1113

The additive intraocular pressure (IOP)-lowering effect of goniosynechialysis (GSL) on top of phacoemulsification (PEI) in primary angle-closure (PAC)/PAC glaucoma is controversial.[1-3] Dr. Husain and colleagues are commended for conducting a multicenter randomized clinical trial to compare the efficacy of PEI-GSL versus PEI in 78 eyes with PAC/PACG.[3] All eyes had 90° or more of peripheral anterior synechia (PAS). At 12 months follow-up, **there were no significant differences between the two groups in mean IOP, change in IOP and number of medication from baseline, and success rate** (defined as IOP ≤ 21 mmHg and a decrease in IOP of ≥ 20%).

It is notable that conflicting findings were found in participants from Singapore (N = 30) and Vietnam (N = 30), which the authors attributed to differences in the baseline characteristics between the two study populations. PEI was better than PEI-GSL in the Vietnam

group who had a higher baseline IOP, higher proportion of PACG, and shallower anterior chamber depth (ACD) (1.85 ± 0.13 mm versus 2.42 ± 0.30 mm). We have demonstrated that shallower ACD is associated with better IOP control after PEI in PAC/PACG eyes,[4] indicating that a large lens with pupillary block mechanism plays a more significant role in eyes with shallower ACD. Regretfully the authors did not consider baseline ACD in their Cox proportional hazards regression model.

Phacoemulsification alone is able to decrease the IOP, reduce the extent of PAS and increase aqueous outflow facility

PEI-GSL may result in a greater reduction in iridotrabecular contact and increase in aqueous outflow facility than PEI,[3,5,6] but not necessarily has better IOP-lowering efficacy. These findings could be explained by the fact that PEI alone is able to decrease the IOP, reduce the extent of PAS and increase aqueous outflow facility.[7] The restoration of aqueous outflow facility in re-exposed trabecular meshwork following GSL is uncertain. Current evidence suggests that PEI has comparable IOP-lowering effects as PEI-GSL while having the advantages of lower surgical risk and higher cost-effectiveness.

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Drainage device positioning and Corneal Surgery


Comment by Natali Afshari and Rebecca Lian, San Diego, CA, USA

82062 Outcomes of Descemet Stripping Endothelial Keratoplasty in Eyes With Pars Plana Versus Anterior Chamber Glaucoma Drainage Devices; Kang JJ, Rittterband DC, Lai K, Eisenberg RE, Liebmann JM, Seedor JA; Cornea 2019; 38: 1364-1369

Patients with glaucoma drainage devices (GDDs) have a high rate of graft failure after endothelial keratoplasty (DSEK).[1-2] The mechanism of this increased risk is unknown, but one common hypothesis states that mechanical trauma to the corneal graft by a GDD in the anterior chamber may increase the rate of failure. In this retrospective chart review of 85 eyes, the authors investigate the hypothesis that anterior chamber (AC) GDD may be associated with higher rates of DSEK graft failure than that of pars plana (PP) GDD due to mechanical trauma to the graft. The study found that **patients with past or concurrent AC shunt experienced graft dislocation at a rate of 37.7%, which was not significantly higher than the rate graft dislocation in the PP shunt group (29.2%) (P = 0.56)**. When taking into account the longer follow-up time for the PP shunt group, **there was no significant difference between the rates of secondary graft failure (SGF) for eyes with AC shunts 18.9% and eyes with PP shunts 41.7% (log-rank test P = 0.51)**.

This study by Kang *et al.*, which is the first to compare DSEK outcomes in patients with previous or concurrent AC or PP GDD, demonstrates no association between the rate of DSEK graft failure and GDD placement. However, it is important to note that this study has a small sample size is retrospective and thus not randomized. There are also some significant differences between the comparison groups. The follow-up time was significantly different between these groups with a median follow-up of 41.9 months in the PP shunt group compared to 16.4 months in the AC shunt group (P = 0.001). Furthermore, a much higher proportion of the PP shunt group were concurrent revisions (43.8% versus 18.9%) and concurrent vitrectomy (47.9% versus 5.4%) compared to the AC shunt group, with many of the eyes in the PP shunt group having had a previous AC shunt. Further research, including prospective studies and larger retrospective studies, is required to elucidate the mechanism of DSEK graft failure in eyes with GDDs.

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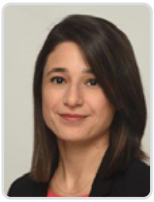
Drainage device positioning and Corneal Surgery




Comment by Huda Sheheitli and Steven Gedde, Miami, FL, USA

82062 Outcomes of Descemet Stripping Endothelial Keratoplasty in Eyes With Pars Plana Versus Anterior Chamber Glaucoma Drainage Devices; Kang JJ, Rittterband DC, Lai K, Eisenberg RE, Liebmann JM, Seedor JA; Cornea 2019; 38: 1364-1369

It is well known that eyes with a history of glaucoma drainage device (GDD) implantation have an increased risk of corneal edema secondary to endothelial cell loss. Potential causes of corneal decompensation include mechanical trauma involving the tube touching the endothelium, foreign body reaction to the tube, disruption of the blood-aqueous barrier, and changes in aqueous circulation and composition with increased inflammatory mediators. Descemet stripping endothelial keratoplasty (DSEK) has become the standard surgical approach for treating endothelial failure. Performing a DSEK in an eye with a GDD can be challenging. The tube can interfere with surgical placement of the graft and may allow intracameral air to escape, especially when the tube is in the anterior chamber (AC). Placement of the tube in the pars plana (PP) may ameliorate these intraoperative challenges, and positions the tube further away from the corneal graft.

Kang and associates retrospectively compared the outcomes of DSEK in eyes with GDD placement in the AC and PP. The study evaluated 85 eyes that underwent DSEK and had previous or concurrent GDD implantation, including 37 eyes with AC tubes and 48 eyes with PP tubes. **Graft dislocation occurred in 35.1% and 29.2% in the AC and PP groups, respectively (p = 0.56). Secondary graft failure developed in 18.9% in the AC group and 41.7% in the PP group (p = 0.51).** The higher rate of graft failure in the PP group was most likely attributable to the longer follow-up (median 41.9 months) relative to the AC group (median 16.4 months), and significant differences between groups were not apparent in Kaplan-Meier survival analysis. Tube location, age, sex, concurrent tube revision, and new tube insertion were not significantly associated with secondary graft failure in multivariable analysis.

> Differing patient characteristics may have directed the surgeon toward insertion of the tube into the AC or PP, and this is a potential source of selection bias

This is the first study to evaluate the outcomes of DSEK in eyes with AC versus PP GDD tube placement. The presumed benefit of improving DSEK outcomes with PP positioning of the tube was not supported by data from this study. However, results should be interpreted in the context of study limitations. Differing patient characteristics may have directed the

surgeon toward insertion of the tube into the AC or PP, and this is a potential source of selection bias. Postoperative endothelial cell counts, corneal thickness measurements, and type of GDD implanted would have been valuable additional data. Some of the patients in the AC group had repositioning of the tube into the ciliary sulcus, which is distinctly different from AC tube placement. The relatively small number of patients in the study reduced its power to detect significant differences, especially in identifying predictors of graft failure. Despite these limitations, the authors are to be congratulated for contributing important new information on the outcomes of DSEK in patients with a GDD.

Bleb-related Infections

Comment by Sasan Moghimi, Tehran, Iran

82693 Trabeculectomy followed by phacoemulsification versus trabeculectomy alone: The Collaborative Bleb-Related Infection Incidence and Treatment Study; Arimura S, Iwasaki K, Gozawa M, Takamura Y, Inatani M; PLoS ONE 2019; 14: e0223439

Trabeculectomy is one of the most effective surgeries for the management of glaucoma.[1] Although Medicare claims data reported a 43% decrease in the number of trabeculectomies in the US.[2] it is still the most common glaucoma procedure in the world. However, cataract progression is one of the common consequence of the procedure.[3] In Advanced Glaucoma Intervention study (AGIS), approximately half of the study patients developed cataract in the first five years of follow-up. Serious postoperative complications are not uncommon after this procedure and are associated with increased risk of cataract formation.[3]

Another common scenario for the glaucoma specialists is patients with coexisting cataract and glaucoma. The options are: to perform cataract extraction followed by trabeculectomy, perform trabeculectomy first followed by cataract extraction, or perform a combined procedure. To decide on the best course of action, it is important to have good quality data. Few studies have assessed the risk associated with phacoemulsification following trabeculectomy over a long-term follow-up period.[4,5]

Arimura and colleagues have published the five-year IOP outcomes of trabeculectomy followed by phacoemulsification in Japanese patients which compared to the outcomes of trabeculectomy alone.[6] A total of 1,098 eyes of patients with glaucoma in Collaborative Bleb-Related Infection Incidence and Treatment Study (CBIITS) who underwent trabeculectomy with 0.04% mitomycin C at 34 clinical centers were evaluated. Patients were enrolled for two years and followed up every six months for up to five years. Surgical failure was defined on the basis of mean IOP as follows; < 20% reduction in preoperative IOP or

postoperative IOP of ≤ 21 mmHg (criterion A), ≤ 18 mmHg (criterion B), or ≤ 15 mmHg (criterion C), respectively. Additionally, surgical failure was defined the case required reoperation for glaucoma or developed loss of light perception or low IOP (≤ 5 mmHg).

In this cohort, 40 eyes that were treated with trabeculectomy followed by phacoemulsification and 208 eyes who had undergone trabeculectomy alone were analyzed. Meaningful differences were found in the five-year cumulative probabilities of success A, and success B (≤ 18 mmHg) between the trabeculectomy followed by phacoemulsification (40%, and 35%) and trabeculectomy alone (59.1%, and 52%.9) groups (P = 0.01 for both).

Optimal time for phacoemulsification to reduce the risk of trabeculectomy failure has been controversial

Optimal time for phacoemulsification to reduce the risk of trabeculectomy failure has been controversial. Bleb remodeling lasts for at least six months after surgery; thus, premature timing of phacoemulsification before the completion of bleb remodeling might accelerate bleb fibrosis and does not recommended.[7] Most of the patients in the present study (36 eyes) underwent phacoemulsification after one year of trabeculectomy. Nonetheless, the authors demonstrated that **shorter time gap between trabeculectomy and phacoemulsification was significantly associated with surgical failure (HR = 1.02**) even with longer gap. **Five eyes were subjected to phacoemulsification within one year after trabeculectomy, and surgical failure on the basis of all criteria was observed in four of the five eyes.** This results are in line with to an earlier study which showed that the hazard ratios are 3.0, 1.7, and 1.3 for six months, one year, and two years after trabeculectomy, respectively.

However, their reported hazard ratios of the time interval between trabeculectomy and phacoemulsification were small and this analysis assumed a linear association between the timing and the outcome. As supported by their data and the previous studies, IOP outcomes were affected more profoundly when the cataract surgery was performed within one year of the trabeculectomy. One should know that the study was not randomized and the patients' characteristics and surgical techniques for trabeculectomy used by the study centers or surgeons were not identical and may subject to biases. For example, one-third of the trabeculectomies has been done using fornix-based approach. Additionally, the trabeculectomy-alone patients were eight years younger, which may affect the surgical success of the filtration surgery.

Cataract surgery within one year after trabeculectomy dramatically affect the success rate and should be avoided unless it is necessary

The current report agrees with other studies that phacoemulsification following trabeculectomy adversely affects surgical outcomes and a shorter time gap between trabeculectomy and phacoemulsification reduces the probability of success. Cataract surgery within one year after trabeculectomy dramatically affect the success rate and should be avoided unless it is necessary.

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Miscellaneous

Sleep apnea and POAG

Comment by Jost Jonas, Heidelberg, Germany

81817 Obstructive Sleep Apnea in Patients With Primary-open Angle Glaucoma: No Role for a Screening Program; Wozniak D, Bourne R, Peretz G, Kean J, Willshire C, Harun S, Villar S, Chiu YD, Smith I; Journal of Glaucoma 2019; 28: 668-675

Obstructive sleep apnea (OSA) has long been debated to be primarily or secondarily be associated with the pathogenesis of glaucomatous optic neuropathy, in particular in patients with so-called normal-(IOP)pressure glaucoma. Wozniak and colleagues re-addressed that question and examined a relatively large group of unselected patients with primary open-angle glaucoma (POAG) (n = 235) and a control group of unselected non-glaucomatous individuals (n = 160). All study participants underwent a nocturnal multichannel cardio-respiratory monitoring. Wozniak and associates found that the prevalence of OSA did not differ significantly between the glaucoma group (58%; 95% confidence interval [CI], 52-65%) and the control group (54%; 95% CI, 47-62%). In a similar manner, the prevalence of moderate and severe OSA did not vary significantly between the glaucoma group and the control group (22% (95% CI, 16-27%) versus 16% (95% CI, 11-22%). By the same token, the apnea-hypopnea index was not significantly associated with the degree of glaucomatous optic nerve damage in a multivariable analysis. The study showed that **OSA, despite being common among patients with POAG, was not associated with POAG** and may thus have no value for a screening examination and may not give clues for the elucidation of the pathogenesis of glaucomatous optic neuropathy.

> The severity of glaucomatous optic nerve damage was not related with the degree of OSA

The study by Wozniak is important since it addressed a clinically and scientifically important topic with a sound study design and since it included a larger study population than most previous investigations addressing the same topic did. The finding that the severity of glaucomatous optic nerve damage was not related with the degree of OSA supports the conclusions and contradicts a potential bias by the selection of study participants. In conclusion, OSA may not play a major role for the pathogenesis and diagnosis of POAG.

Exercise and IOP


Comment by Pradeep Ramulu and Elyse McGlumphy, Baltimore, MD, USA

82262 Long-term regular exercise and intraocular pressure: the Hisayama Study; Fujiwara K, Yasuda M, Hata J, Yoshida D, Kishimoto H, Hashimoto S, Yoshitomi T, Ninomiya T, Sonoda KH; Graefe's Archive for Clinical and Experimental Ophthalmology 2019; 257: 2461-2469

Examining influences of lifestyle or behavior on intraocular pressure may provide an avenue for empowering patients in the treatment of their glaucoma. As a part of the Hisayama Study, a long-term cohort study on cardiovascular disease, Fujiwara and colleagues examined the role of regular exercise and intraocular pressure over a five-year period. Here, a subset of the cohort, including 1871 individuals, not using IOP-lowering medications and with no previous ophthalmic surgery were included in their analyses. To reduce confounding factors, all IOP measurements were obtained within standardized time intervals along with concomitant measurement of blood pressure. Exercise practices, including type of activity, frequency, and duration, were collected using a patient survey. The authors adjusted for multiple other confounding factors such as age, sex, baseline IOP, systolic blood pressure, diabetes, total cholesterol, HDL cholesterol, BMI, waist circumference, smoking, alcohol intake, and work intensity of daily life.

A possible beneficial effect on IOP in older adults which could protect against glaucoma

In multivariable regression analyses, higher exercise frequency and duration were associated with trend towards lower IOP over time as compared to persons who exercised infrequently/for less time. **In subgroup analyses, greater downward IOP trends were seen only in those who exercised frequently (three to six times per week) or for considerable amounts of time (> 210 minutes weekly).** Even then, differences in the IOP trajectory across exercise status were modest (5 year ΔIOP = -0.75 mm Hg in non-exercisers vs. -1.12 mmHg in those exercising 3-6 times weekly), which would have limited protective effects against glaucoma. **Additionally, individuals with incident medical IOP-lowering or surgery were excluded, and we do not know if these outcomes differed by exercise status.** Thus, the article suggests a possible beneficial effect on IOP in older adults which could protect against glaucoma, though further studies including functional outcomes (visual field preservation) and accounting for treatment are required to more strongly establish the possible benefits of exercise.

Extreme exercise and IOP


Comment by Nathan Radcliffe, New York, NY, USA and Daniela Alvarez-Ascencio, Mexico City, Mexico

82547 Impact of resistance training sets performed until muscular failure with different loads on intraocular pressure and ocular perfusion pressure; Vera J, Jiménez R, Redondo B, Torrejón A, de Moraes CG, García-Ramos A; European Journal of Ophthalmology 2019; 0: 1120672119879838

The effects of physical activity on intraocular pressure (IOP) and ocular perfusion pressure (OPP) have been documented in several studies.[1,2] Findings have shown that isometric training can induce transient IOP elevation and OPP decrease, which are associated with glaucoma development and progression. No study has proven a direct association between isometric training and glaucoma progression, but a number of case reports[3-6] have shown worsening of preexisting glaucoma after exercise-related short-term IOP elevation.

Vera *et al.* describe the short-term effects of bench press to muscular failure against different relative loads (65%, 75%, 85%, and 95% 1RM) on the IOP and OPP of 17 healthy active young men. IOP and blood pressure were measured before and after each set. They found significant IOP increase with the three higher loads, proving a positive association between load and effect. OPP showed a clinically irrelevant reduction independent of the load. Based on this, the authors advise against performing bench press to muscular failure with heavy loads in patients with glaucoma or risk factors.

> Advise against performing bench press to muscular failure with heavy loads in patients with glaucoma or risk factors

IOP and OPP are heavily influenced by ocular disease, race, age, sex, exercise type, and position, so resulting effects of this study cannot be extrapolated to other populations or exercises, which is an important limitation pointed out by the authors. Regarding methods, measuring IOP *during* the exercise would give an additional measurement that could be significant. Also, even though there is no gold-standard for measuring ocular blood flow (OBF), Doppler or optical coherence tomography angiography could provide more detailed and adequate information than OPP in eyes with compromised autoregulation mechanisms. Evaluating the duration of IOP and OPP/OBF changes would also provide valuable information.

Isometric training with heavy loads (triggering Valsalva) is associated with IOP increase

Overall, these findings reinforce evidence that isometric training with heavy loads (triggering Valsalva) is associated with IOP increase. Understanding the possible undesirable effects of exercise is important, however research that can be extrapolated to the population of interest, that can provide more information regarding progression is warranted.

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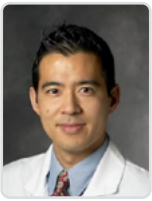
The growing role of smartphones I



Comment by Robert Chang, Palo Alto, CA, USA

82452 Smartphone use in ophthalmology: What is their place in clinical practice?; Hogarty DT, Hogarty JP, Hewitt AW; Survey of Ophthalmology 2020; 65: 250-262

This review article focuses on Apple iOS and Android smartphone ophthalmology-based applications (271 and 170 'apps', respectively) as of June 2019. Since 2007, smartphones have played an increasing role in global ophthalmology and telemedicine ranging from portable vision screening, picture and video sharing, online education, diagnostic decision support tools, and remote eye exams. The authors found three studies comparing distance visual acuity (VA) with Snellen and ETDRS. PEEK Acuity[1] and the Snellen App[2] both had a mean difference of less than one line compared with the corresponding physical chart. However, the third Eye Phone study by Perera C *et al.*[3] found a lot of optotype sizing errors in multiple VA apps, and when the vision was worse than 6/12, the VA results were less reliable. In a 2017 trial by Rono *et al.*[4] of PEEK Acuity App used as a vision screening tool in Kenya compared to standard tumbling E, PEEK had lower specificity and positive predictive value resulting in more unnecessary referrals. This may be due to variable test setup conditions. Given the lack of optotype accuracy standards and test re-test reliability cutoffs, no smartphone visual acuity app can be recommended currently. In terms of glaucoma, smartphone app developers have focused on fundus imaging, *i.e.*, turning a smartphone into an ophthalmoscope, but also have begun to tackle virtual reality (VR) visual fields (VF). In optic nerve imaging, several papers[4,5] have looked at grading cup-to-disc (C/D) ratio from smartphone photos using an attachment such as D-Eye, demonstrating better C/D estimation from the smartphone videos. In a prototype smartphone VR, a study by Tsapakis *et al.* tested a custom-made VF suprathreshold algorithm compared with the Humphrey Field Analyzer. Sensitivities at various dB cutoffs for AUROC ranged from 0.762 for high threshold to 0.837 for low threshold (both $P < 0.001$).[6] In summary, smartphone-based glaucoma apps, including VA testing, smartphone imaging, and VR VF combined with self-tonometry provide an opportunity for ubiquitous smartphone technology to be integrated into remote ophthalmic care 'from anywhere' once further validation is completed and consistent standards are set.

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The growing role of smartphones II

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

82437 Low-cost, smartphone-based frequency doubling technology visual field testing using a head-mounted display; Alawa KA, Nolan RP, Han E, Arboleda A, Durkee H, Sayed MS, Aguilar MC, Lee RK; British Journal of Ophthalmology 2019; Sept. 17 [e-pub ahead of print]

Alawa *et al.* constructed a smartphone-based visual field screening device with the goal of performing frequency doubling testing in a mobile device. They compared results from their instrument to results from the FDT, a commercial frequency doubling instrument, in 19 eyes of ten glaucoma patients, and found no statistically significant differences. **The authors conclude that they have constructed a low-cost, portable visual field screening device that produces comparable results to the Humphrey Zeiss FDT** and may be used as an easily accessible screening tool for glaucoma.

The authors seem to be focused on producing a device that can be used in community-based and internationally based glaucoma screening in settings where electrical power might not be available. Frequency doubling perimetry has been used in population screening for potentially blinding eye disease not restricted to glaucoma[1] and may serve the authors well if employed and interpreted in ways that have worked in the past, for instance focusing on high risk populations, and requiring confirmation tests when encountering apparently abnormal results. It may also be worth noting that population screenings for glaucoma may lead to detection of significant amounts of non-glaucomatous visual field loss as well.[2,3]

This study has significant limitations. The authors have provided no estimates of the size of differences between the two compared devices that might have been detected, given the number of eyes tested. However, they must be aware that their sample size probably was not large enough to support useful quantitative conclusions regarding inter-device comparability. The study was also limited by lack of a control group. The authors point out that their device differs from the commercially available FDT in multiple ways, differences that, until proven otherwise must be viewed as necessitating collection of normative data specific to their device. Unfortunately, the authors seem to have based their screening strategy on an age-adjusted normative study previously performed using the Humphrey Zeiss FDT,[4] and, until proven otherwise, they should assume that their screening device will have a different level of specificity than that of the commercial FDT instrument. It also is not clear that their device's limited, eight bit contrast resolution is adequate, if their goal is to produce comparable results to the Humphrey Zeiss FDT.

In conclusion, **the primary value of this paper may be that it suggests that FDT testing might be possible using a head-mounted smartphone**. Further work will be necessary before we actually know if such an application is now possible or must await further developments in smartphone display technology.

Disclosure

Vincent Michael Patella is at present a paid consultant to the manufacturer of the FDT, Carl Zeiss Meditec Inc, Dublin, CA, USA.

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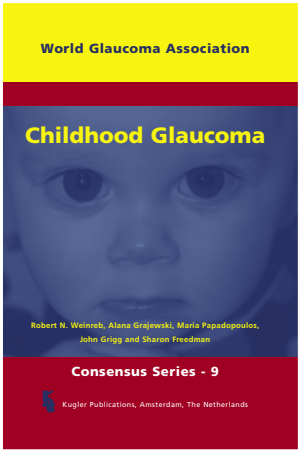
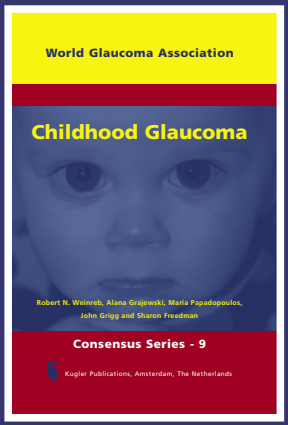
Consensus 9 - Childhood Glaucoma

Edited by: R.N. Weinreb, A.L. Grajewski, M. Papadopoulos, J. Grigg and S. Freedman
2013



The goal of this consensus was to provide a foundation for diagnosing and treating childhood glaucoma and how it can be best done in clinical practice. Identification of those areas for which we have little evidence and, therefore, the need for additional research also was a high priority. We hope that this consensus report will serve as a benchmark of our understanding. However, this consensus report, as with each of the others, is intended to be just a beginning. It is expected that it will be revised and improved with the emergence of new evidence.



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Robert N. Weinreb
Consensus Initiative Chair
World Glaucoma Association

Consensus 9 - Table of contents

SUMMARY CONSENSUS POINTS

Section 1 – Definition, classification, differential diagnosis

1. Childhood glaucoma is intraocular pressure (IOP) related damage to the eye.
   Comment: In addition to the IOP, optic disc appearance and visual fields, the definition of glaucoma also reflects the effect of IOP on other ocular structures in infancy.
2. The interpretation of IOP measurement in infants and young children, especially during examination under anesthesia, can potentially be affected by many factors.
   Comment: Other signs of glaucoma in infants and young children, such as ocular enlargement, Haab striae and increased cup-to-disc ratio, may be more important than the IOP value in the assessment.
3. Childhood glaucoma is classified as primary or secondary. Secondary childhood glaucoma is further classified according to whether the condition is acquired after birth or is present at birth (non-acquired). Non-acquired childhood glaucoma is categorized according to whether the signs are mainly ocular or systemic.
   Comment: Terms such as 'developmental', 'congenital' or 'infantile' glaucoma lack clear definition and their use is to be discouraged.
4. A child should not be labeled as having glaucoma or subjected to surgical treatment unless one is reasonably sure of the diagnosis and has excluded other conditions that may mimic glaucoma.

Section 2 – Establishing the diagnosis and determining glaucoma progression

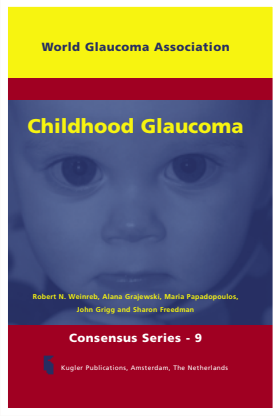
1. Prompt diagnosis of childhood glaucoma and appropriate prompt treatment can minimize the degree of visual impairment.
   Comment: Examination under anesthesia or sedation may be appropriate to make the diagnosis, perform surgery or plan further treatment.
2. A child should not be labeled as having glaucoma or subjected to surgical treatment unless one is reasonably sure of the diagnosis and has excluded other conditions that may mimic glaucoma.
   Comment: If doubt exists about the diagnosis or evidence of progression cannot be determined, then appropriately timed follow-up or examination under anesthesia or sedation is advisable.
   Comment: Children should be encouraged onto the slit lamp for more accurate evaluation [intraocular pressure (IOP) measurement and optic disc assessment] when it appears this may be possible.
3. Glaucoma in children is characterized by the presence of elevated IOP and characteristic optic disc cupping. In addition to these features, glaucoma in infancy is associated with ocular enlargement, buphthalmos.
   Comment: IOP measurement and optic disc appearance are fundamental features of the examination throughout the life of a child with glaucoma. In an infant whose eye is still vulnerable to other effects of elevated IOP, proxies of persistent elevated IOP (enlarging corneal diameter, increasing axial length and progressive myopia) also need to be taken into consideration and regularly assessed.
   Comment: In children, the conclusion with regard to the diagnosis or progression of glaucoma must be based on the overall clinical findings and investigation results.
4. IOP measurement in infancy and early childhood can be influenced by many factors so is often unreliable when used in diagnosis and management.

5. IOP response to anesthetic agents is unpredictable. All inhaled agents lower IOP, sometimes rapidly and profoundly.
   Comment: Chloral hydrate, ketamine and midazolam appear not to lower IOP.
   Comment: Use the same anesthetic for serial examinations.
6. Increasing corneal diameter is the hallmark of all forms of glaucoma in infancy and early childhood.
   Comment: Corneal enlargement due to elevated IOP usually occurs before three years of age. Serial corneal diameter measurements are useful in establishing the diagnosis and in the monitoring of progression of glaucoma up to the age of three years.
   Comment: Central corneal thickness (CCT) should not be used to adjust IOP measurements as its role in childhood tonometry remains to be determined.
7. Gonioscopy is crucial in making the correct diagnosis and for planning surgical treatment. It should be performed at least once when possible.
8. Optic disc appearance is an important and sensitive parameter for both diagnosis and determination of progression in childhood glaucoma.
   Comment: Optic nerve size, the cup-disc ratio, focal areas of rim loss, and nerve fiber layer defects should be documented, preferably through a large pupil.
   Comment: A magnified binocular view is preferable, so attempt to examine a child on the slit lamp as soon as they are cooperative.
   Comment: Documenting the appearance of the disc at baseline and follow-up is desirable in determining both diagnosis and response to treatment.
   Comment: Cupping reversal is common in successfully-treated childhood glaucoma.
   Comment: Automated optic nerve imaging (e.g., OCT) is limited by the lack of normative data and portability of the devices.
9. Rapid changes in refractive status and axial length (AL) determination are helpful in both diagnosing the disease and determining response to treatment while the sclera remains vulnerable to the effects of elevated IOP.
   Comment: AL outside normal limits is strongly suggestive of glaucoma.
   Comment: Continued enlargement of AL beyond the normal range suggests inadequately-treated glaucoma.
   Comment: Progressive myopia is additional evidence of glaucoma progression.
10. Assessment of the visual field in children can be useful but is challenging.
    Comment: It may be helpful to use the shortest possible test (e.g., program 24-2 Sita Fast).
    Comment: Repeat visual fields to confirm deficits. If repeated testing shows consistent findings, the measurements are probably valid.
    Comment: Although there is no normative database for children, age correction of the mean deviation for standard automated perimetry is small (0.7 db/decade). Moreover, useful metrics, such as pattern standard deviation, glaucoma hemifield test and glaucoma change probability, are largely unaffected by age.

Section 3 – Genetics

1. Genetic evaluation of childhood glaucoma is especially important in those types of glaucoma when genotype phenotype correlations are known to exist.
   Comment: The results of these tests may be important in counseling, prognosis and management.

2. There is a known correlation between primary congenital glaucoma (PCG) and mutations in the CYP1B1 gene.
   Comment: Performing carrier testing for at risk relatives is possible if both disease causing alleles of an affected family member have been identified.
3. Families affected by autosomal dominant juvenile open angle glaucoma (JOAG) have been found to have mutations in the MYOC gene.
   Comment: Genetic screening and genetic counseling could be considered in these patients to help diagnose pre-symptomatic cases among first and second degree relatives of these patients.
4. Axenfeld-Rieger anomaly and syndrome have been associated with PITX2 and FOXC1 mutations.
   Comment: PITX2 mutations are more likely to be associated with systemic findings, while the risk of glaucoma is increased with FOXC1 duplications and PITX2 mutations.
   Comment: Prospective parents may consider genetic counseling for risk calculation.
5. Aniridia is usually inherited in an autosomal-dominant fashion with high penetrance and variable expressivity, and it is almost exclusively caused by PAX6 mutations.
   Comment: A child with sporadic aniridia should have ultrasound surveillance for Wilms tumor unless genetic testing rules out a microdeletion involving the Wilms tumor gene.
6. The LTBP2 mutations seem to be involved in complex ocular phenotypes including ectopia lentis, megalocornea (unrelated to elevated intraocular pressure), microspherophakia and associated secondary glaucoma.
7. To optimize genetic counseling for families, accurate clinical ophthalmic diagnosis is critical.
   Comment: Marked variation in penetrance and expression in primary and secondary childhood glaucomas exist, so parents and siblings of an affected child should be examined to provide maximally accurate phenotypic diagnoses for the clinical geneticist.



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8. General pediatric assessment forms an important part of the management for children with glaucoma and can greatly assist in identifying systemic associations and initiating early management.
9. Genetics review plays a number of important roles including confirming or identifying syndromic diagnoses, recurrence risk assessment, genetic diagnosis, interpretation of molecular data, and reproductive counseling where this may be requested by the family after appropriate genetic counseling.

Section 4 – Medications

1. Medications alone rarely show sustained efficacy as primary treatment for glaucoma in infants and young children, especially in primary congenital glaucoma (PCG).
   Comment: Medical therapy is frequently needed as temporizing intraocular pressure (IOP) lowering treatment before surgery or as adjuvant therapy after partially successful surgical procedures in childhood glaucoma.
   Comment: IOP-reducing medication may help reduce corneal edema prior to surgery for childhood glaucoma.
   Comment: Medical therapy should be considered first-line for some cases of childhood glaucoma (e.g., uveitis-related, glaucoma after cataract removal).
2. Childhood glaucomas are heterogeneous in their causation as well as in their responses to different glaucoma medications.
3. Systemic pharmocokinetics for glaucoma medications are different in children than in adults.
   Comment: Systemic absorption can be significant and may be reduced by advising parents to close the lids (if possible), remove excess periocular liquid and perform naso-lacrimal occlusion.
   Comment: Use minimum frequency and concentration to achieve target IOP.
4. Potentially serious or fatal systemic adverse reactions which are rarely seen in adults may occur in young children after exposure to glaucoma medications.
   Comment: Adverse side effects may manifest atypically in children (e.g., nocturnal cough with beta blockers rather than wheeze with reactive airways).
   Comment: Brimonidine should be avoided in young children.
   Comment: Children are more vulnerable to adverse effects of medications as they may be unable to verbalize symptoms and parents may not readily recognize them.
   Comment: Parents must be informed of the potential side effects.
5. Compliance and adherence issues are greater and more complex in children due to their dependence on caregivers or parents, possible lack of cooperation in the administration of treatment, as well as concurrent medical conditions that may complicate medical therapy.
6. Target pressure must be chosen and reassessed with all available information concerning whether glaucoma is adequately controlled.
   Comment: Limitations on ability to perform structural and functional testing of optic nerve make verification of glaucoma control more difficult in children.
7. Consider surgery when medical treatment fails to control glaucoma.
   Comment: Glaucoma therapy in children has to be individualized, especially in situations where the risk of surgery outweighs the benefits of continuing medical therapy.

Section 5 – Glaucoma surgery in children

1. Surgery is a critical component of the management of childhood glaucoma.
   Comment: It is important to prepare patients and parents or caregivers for lifelong follow-up and possible future surgeries.
2. Glaucoma surgery should preferably be performed by a trained surgeon in centers where there is sufficient volume to ensure surgical experience and skill, and safe anesthesia.
   Comment: A long-term surgical strategy including choice of procedures should be based on training, experience, logistics, and surgeon's preference.
   Comment: The first chance for surgery is often the best chance, and it is important to choose the most appropriate operation.
3. Glaucoma surgery in children is more challenging than in adults with a higher failure and complication rate than in adults.
4. Angle surgery (goniotomy and trabeculotomy – conventional or circumferential) is the procedure of choice for primary congenital glaucoma with the exact choice dictated by corneal clarity and the surgeon's experience and preference.
   Comment: Angle surgery success rates for secondary childhood glaucomas are generally not as good as for primary congenital glaucoma (PCG) with certain exceptions [e.g., glaucoma with acquired condition (uveitis) in juvenile idiopathic arthritis (JIA)].
5. Trabeculectomy, when performed by experienced childhood glaucoma surgeons, can be associated with good outcomes in appropriate cases.
   Comment: Anti-scarring agents and other adjunctive techniques may be beneficial.
6. Glaucoma drainage devices (GDD) may offer the most effective long-term intraocular pressure (IOP) control in many childhood glaucomas especially those that are refractory to other surgical treatment.
   Comment: There is no prospective evidence that anti-scarring agents influence drainage device outcomes.
7. Cyclophotocoagulation with the diode laser has limited long-term success and often requires re-treatment and the continuation of medications.
8. Other glaucoma procedures advocated in children for the treatment of glaucoma have not been widely adopted either because of the technical challenges in buphthalmic eyes or because they are yet to be proven efficacious or safe in children.
9. Concurrent with glaucoma therapy, visual development needs to be evaluated and optimized with ametropic correction and amblyopia therapy.
10. With childhood glaucoma surgery, one needs carefully to consider the risks and benefits of each intervention, especially in refractory cases when the fellow eye is healthier, and in only eyes.
    Comment: Whenever possible, the assent of the child should be sought when making these difficult decisions.

Section 6 – Primary congenital glaucoma and juvenile open-angle glaucoma

1. Primary congenital glaucoma (PCG) is the most common non-sydromic glaucoma in infancy and is classified according to onset of signs. Its worldwide incidence is variable and influenced by consanguinity.
2. PCG is usually inherited in an autosomal recessive manner, with a family history reported in 10-40% of cases and is more common in consanguineous populations.

Comment: Mutations in the CYP1B1 gene have been identified and show variable expressivity and phenotypes.

Comment: Clinical screening of current and future siblings is essential if there is parental consanguinity.

3. The pathogenesis of PCG remains uncertain but the immature angle appearance seen clinically is thought to result from the arrested maturation of tissues derived from cranial neural crest cells.
4. PCG is a surgical condition and the surgical procedure of choice is usually angle surgery (goniotomy or trabeculotomy) with high rates of success reported for both in favorable cases and after multiple procedures.

   Comment: Combined trabeculotomy with trabeculectomy as an initial procedure is suggested by some to be more successful than either procedure performed alone in certain populations. There are no supporting prospective comparisons in the literature.
5. Once angle surgery fails, the next procedure of choice is either trabeculectomy or a glaucoma drainage device.
6. Juvenile open-angle glaucoma (JOAG) is a relatively rare form of childhood glaucoma usually presenting after the age of four years, with a normal angle appearance and no signs of other ocular anomalies or systemic disease.
7. Depending on age, medical therapy is the first-line treatment for JOAG, although surgery is often required.
8. Evidence remains weak for the optimum first-line surgical intervention for JOAG.

Section 7 – Glaucoma associated with non-acquired ocular anomalies

1. Children who have non-acquired ocular anomalies often have systemic conditions that require pediatric evaluation and/or treatment.
2. Many non-acquired ocular anomalies are genetic in nature.

   Comment: Screening of family members in such cases and genetic counseling is indicated.
3. Glaucoma related to non-acquired ocular anomalies may be present at birth or may develop over time, so regular lifelong monitoring is necessary.
4. Before glaucoma develops, one should consider treating elevated intraocular pressure (IOP) associated with non-acquired ocular anomalies (secondary ocular hypertension).
5. Infantile onset of glaucoma related to non-acquired ocular anomalies is associated with buphthalmos and the risk of Descemet membrane breaks.
6. Medical treatment is usually first-line, but surgery is often required early for congenital/infantile presentations and should not be delayed.

   Comment: Angle surgery in infants may be effective although the results are usually not as good as for primary congenital glaucoma (PCG).

   Comment: Often trabeculectomy with anti-scarring agents or primary tube surgery is necessary for IOP control.

   Comment: Cyclodestruction may be considered after failed trabeculectomy or tube surgery.
7. There is considerable phenotypic variability associated with genetic mutations recognized in children with non-acquired ocular anomalies.

8. Axenfeld-Rieger (AR) anomaly is recognized now to represent a spectrum of disease previously referred to as Axenfeld anomaly and Rieger anomaly. Axenfeld-Rieger syndrome includes the ocular findings of Axenfeld-Rieger anomaly with the addition of systemic abnormalities.
   Comment: Examination of family members including gonioscopy is important to determine whether the patient is part of a larger pedigree or a new case.
9. Peters anomaly is usually seen as an isolated ocular disorder but can be associated with systemic abnormalities of neural crest origin and is referred to as Peters plus syndrome.
   Comment: It is important to exclude the presence of systemic involvement and when it is present, to co-manage it with a pediatrician.
   Comment: Assessing for glaucoma can be challenging as typical IOP measurement over the central cornea may be inaccurate and the optic discs may not be visible. Measure the IOP in a clear area of cornea if possible.
10. Aniridia is commonly associated with glaucoma and is due to both open- and closed-angle mechanisms.
    Comment: Children with sporadic aniridia should be screened for Wilms tumor.
11. Management of persistent fetal vasculature can be challenging because of the heterogeneity of clinical presentation.
    Comment: Surgical treatment is aimed towards obtaining useful vision and preventing or treating secondary complications such as glaucoma.

Section 8 – Glaucoma associated with non-acquired systemic disease or syndrome

1. Syndromes with system anomalies or systemic diseases that are present at birth can be associated with ocular signs that include glaucoma.
   Comment: Patients should be regularly monitored for glaucoma throughout life and elevated intraocular pressure (IOP) treated, should it occur.
   Comment: Patients also should be assessed for systemic manifestations of their disease.
2. Sturge-Weber syndrome (SWS) is commonly associated with glaucoma.
   Comment: Periocular port-wine marks are associated with ipsilateral glaucoma. Lid involvement and/or episcleral capillary vascular malformation appear to further increase the risk of glaucoma.
   Comment: Choroidal hemangioma increases the risk of serous choroidal effusion and suprachoroidal hemorrhage with surgery, especially if the IOP drops precipitously or hypotony develops. Modifications to the surgical technique must be employed to minimize risk of hypotony.
   Comment: Patients should be assessed, perhaps including neuroimaging, for other manifestations of SWS.
3. Neurofibromatosis (NF1) is uncommonly associated with glaucoma.
   Comment: Optic pathway gliomas affect 12-15% of patients with neurofibromatosis and can present with decreased vision distinct from glaucoma.
4. Ectopia Lentis (EL) can present as an isolated ocular anomaly or be associated with other ocular or systemic findings.
   Comment: Patients with EL are at risk of acute pupillary block.

Comment: All patients without a proven or obvious cause of EL should be tested for homocystinura by urine analysis and investigated for blood homocyteine levels prior to any anesthesia or sedation because of life-threatening vascular risks.
Comment: Patients with Marfan syndrome should have echocardiography and cardiology consultation prior to surgery.

5. Maintain close follow-up for infants with known or suspected congenital rubella, since glaucoma signs might be less evident at birth in some cases.
Comment: Rubella keratitis should be differentiated from corneal findings associated with IOP related corneal edema.

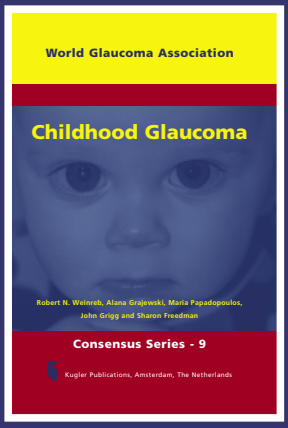
Section 9 – Glaucoma associated with acquired conditions

1. Managing uveitic glaucoma in children is challenging. The control of intraocular inflammation with adequate immunosuppression, topical and/or systemic agents, is a crucial part of management.
Comment: Hypotony is a particular concern with surgery and modifications to the surgical technique must be employed to minimize its risk.
2. Traumatic glaucoma pathogenesis is multifactorial.
Comment: Patients with sickle cell disease (not trait) are at higher risk for rebleed and are likely to develop glaucomatous optic nerve damage, even with only moderately raised intraocular pressure (IOP).
Comment: Management is aimed at controlling IOP and minimizing damage to the cornea and optic nerve. Consider surgical intervention with sustained elevated IOP > 30 mmHg unresponsive to maximum medical therapy or if corneal staining is present.
3. Steroid-induced elevated IOP is not uncommon and may be severe in children treated with ocular and systemic corticosteroids .
Comment: Consider discontinuing the corticosteroid if possible or switching to a steroid sparing agent to ensure underlying disease control, which takes priority.
Comment: IOP elevation may persist for months, years or even become permanent, requiring medical or surgical intervention.
4. Glaucoma secondary to intraocular tumors in children is a relatively rare event.
Comment: Patients can be symptomatic with acute glaucoma due to the fast growth of the tumor, or symptom free in the case of a progressive, slow growing tumor.
Comment: In cases of unexplained glaucoma, the possibility of an intraocular tumor should be considered, especially when a child presents with a severe chronic uveitis associated with high IOP.
Comment: Incisional surgical intervention to lower IOP is contra-indicated for glaucoma secondary to malignant ocular lesions.
5. The causes of retinopathy of prematurity (ROP) induced glaucoma are multifactorial in nature but largely due to secondary angle closure.
Comment: Glaucoma may develop years or decades later in patients with treated or untreated Stage-4 or -5 ROP, so long-term surveillance is warranted.
Comment: IOP elevation may follow laser therapy for threshold ROP.

Section 10 – Glaucoma following cataract surgery

1. Glaucoma following cataract surgery is that which occurs after pediatric cataract removal of either congenital idiopathic cataract, cataract associated with ocular or systemic syndromes and acquired cataract.

2. Glaucoma can occur in aphakic and pseudophakic eyes.
3. Young age at the time of cataract surgery and microcornea increase the risk of glaucoma.
4. Glaucoma usually occurs in eyes with open angles but angle closure can occur, and it is important to elucidate the underlying mechanism when possible (e.g., by gonioscopy).
5. The risk of glaucoma following cataract surgery in children is lifelong, so regular monitoring is necessary.
6. Medical intraocular pressure (IOP) lowering therapy is usually first line treatment for glaucoma following cataract surgery. When medical therapy fails, surgical therapy is indicated but there is no consensus on the preferred approach.



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Consensus Initiative Chair
World Glaucoma Association

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News Flashes

- ★ The pandemic has created the opportunity for our specialty to advance new and innovative methods of health care delivery and accelerate research into making glaucoma care safer, more convenient, and more accessible to our patients than ever before
- ★ If remote perimetry/tonometry are ever going to become viable alternatives to in-clinic testing, now would be the time
- ★ Performing *in vivo* TM imaging with segmental information (such as from aqueous angiography) could yield additional insight into TM biology and potentially lead to novel outflow-based glaucoma therapies
- ★ The severity of glaucomatous optic nerve damage was not related with the degree of OSA
- ★ Slowing of glaucoma progression after IOP lowering treatment may be, at least partly, attributed, to the improved perfusion to the optic nerve
- ★ A more pronounced IOP reduction may be required in eyes with LC defects, because these eyes may be more susceptible to glaucoma progression
- ★ SLT is unlikely to have adequate treatment effect in patients requiring very low intraocular pressures
- ★ Phacoemulsification alone is able to decrease the IOP, reduce the extent of PAS and increase aqueous outflow facility
- ★ Optimal time for phacoemulsification to reduce the risk of trabeculectomy failure has been controversial
- ★ Cataract surgery within one year after trabeculectomy dramatically affect the success rate and should be avoided unless it is necessary
- ★ With the outcomes from LiGHT continuing to demonstrate the favorability of SLT, we are due an evidence-based paradigm shift
- ★ Lower parapapillary choroidal vessel density (VD) with B-zone parapapillary atrophy (PPA) at baseline is associated with future visual field progression
- ★ Advise against performing bench press to muscular failure with heavy loads in patients with glaucoma or risk factors
- ★ Isometric training with heavy loads (triggering Valsalva) is associated with IOP increase
- ★ Corneal deflection amplitude is an interesting corneal behavior that may be related to glaucoma progression
- ★ A possible beneficial effect on IOP in older adults which could protect against glaucoma
- ★ This device and study represent an important step toward the holy grail of accurate and continuous IOP monitoring in eyes with glaucoma
- ★ Bleb grading systems are fraught with error by nature of their subjectivity

- ★ This study shows that DL can also be used to directly model structure-function relationships and identify eyes with likely functional loss from OCT imaging
- ★ Examining features of imaging, other than thickness, e.g., texture or voxel intensity, may provide additional value for glaucoma detection and monitoring
- ★ Prior to the landmark Zhongshan Angle Closure Prevention (ZAP) trial, the benefit of treating PACS eyes with LPI was unclear
- ★ Authors estimated that 44 and 126 LPI would need to be performed to prevent one case of PAC and PACG, respectively
- ★ The LiGHT trial supports the use of a second SLT when an initial SLT is not enough to reach the target IOP or when the IOP further goes up
- ★ GRS-based genetic risk estimates may aid in early disease detection, thereby allowing for timely initiation of preventive treatment and management strategies
- ★ This paper demonstrates the molecular complexity of glaucoma and questions this division in glaucoma based on arbitrary measurements of intraocular pressure (IOP)
- ★ One can now safely say MYOC is no longer only a gene associated with only high IOP
- ★ The optical clarity presents an advantage over a number of murine mode, making this work a significant contribution to pre-clinical glaucoma modelling
- ★ Differing patient characteristics may have directed the surgeon toward insertion of the tube into the AC or PP, and this is a potential source of selection bias
- ★ The work is not yet able to conclude whether a specific strain pattern for any given ethnicity would be responsible for the development and progression and glaucoma
- ★ In-vivo ONH strains are thus more representative of what ONH cells directly experience
- ★ Moving forward, it is becoming clearer that glaucoma subjects would benefit from a clinical test to assess the robustness of their ONHs

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