

What's New and Important in Pediatric Ophthalmology and Strabismus in 2022-23  
Complete Unabridged Handout  
Review of literature Feb 2022- Feb 2023 inclusive

AAPOS Meeting, NY, NY

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## 1. AMBLYOPIA

Binocular amblyopia treatment improves manual dexterity

Birch EE, Morale SE, Jost RM, Cheng-Patel CS, Kelly KR

A prospective study evaluated whether binocular amblyopia treatment remediated fine motor skills impairments in children age <7 years and to compare these results with those in children 7-10 years of Age. Manual dexterity (Movement Assessment Battery for Children–2), visual acuity, fusion, suppression, and stereoacuity were measured at baseline and after 4-8 weeks of binocular amblyopia in 134 children with amblyopia. Baseline manual dexterity standard scores of amblyopic children were significantly below those of controls in both the younger and older groups. After 4-8 weeks of binocular amblyopia treatment, the younger group standard score improved to 9.85 and the older group improved to 8.08, but both groups remained significantly lower than controls. Improvement in manual dexterity standard score was not associated with any baseline factors but was weakly correlated with the amount of visual acuity improvement. This study found that binocular amblyopia treatment improved visual acuity and manual dexterity.

Association of Neighborhood Child Opportunity Index with presenting visual acuity in amblyopic children

Adomfeh J, Chinn RN, Michalak SM, Shoshany TN, Bishop K, Hunger DG, Jastrzembki BG, Oke I

J AAPOS 2023;27:20.e1-5

This study evaluates the use of a novel measure of neighborhood quality, the Child Opportunity Index (COI), for investigating health disparities in pediatric ophthalmology. This study included 1,050 amblyopic children. Children residing in the lowest opportunity neighborhoods correctly identified approximately two fewer letters at presentation with their better seeing eye compared with children from the highest opportunity neighborhoods after adjusting for individual-level factors. No difference was appreciated in the worse-seeing eye. Although statistically significant in the better-seeing eye, the two-letter difference attributable to neighborhood environment may not be clinically significant.

The impact of occlusion therapy and predictors on amblyopia dose–response relationship

Emily White & Leah Walsh. Department of Ophthalmology, Boston Children’s Hospital, Boston, MA, USA;

Faculty of Health, Clinical Vision Science Program, Dalhousie University, Halifax, Nova Scotia, Canada.

Strabismus 30: 2. 78-89

This study aimed to calculate the dose–response relationship and predictors of visual acuity (VA) improvement following occlusion therapy at the IWK Health Center Eye Clinic and to add to amblyopia therapy dose–response relationship literature. A retrospective chart review was performed, considering patients who reached an occlusion therapy outcome at the IWK Eye Clinic between 2012 and 2019. The treatment outcome was defined as equal VA or stable VA for three consecutive clinical visits despite reported compliance. Subjective patching hours from parental reports, not prescribed hours, were used for statistical analyses. One hundred and thirty-four patients (66 females and 68 males) ages 2–11 years were included. Results showed a dose–response relationship of 224 hours/0.1logMAR increase in VA and total dose of 1344 hours for full-time occlusion and 504 hours for part-time occlusion was required to reach outcome VA. The fastest VA improvement occurred with younger age at treatment initiation, during the first 4 weeks of treatment, and in patients with strabismic and/or severe amblyopia. Classification of amblyopia, age, VA chart, initial distance VA (amblyopic eye), and treatment dose predicted the hour dose– response relationship. Dose–response relationship was faster in younger participants, in participants with strabismic and severe amblyopia, and during the first month of occlusion. Additionally, by creating a GLM model of dose–response relationship, relationship calculations can be performed. Therefore, an estimated timeline can be developed to allow allocation of clinical resources and to prepare patients for the treatment duration required and possibly increase treatment compliance. A limitation is that no objective method was used to measure treatment compliance. This limitation is cited as a key obstacle to the current research paradigm within amblyopia treatment literature.<sup>38</sup> Despite not using objective compliance strategies, such as ODM technologies, the results of this study were comparable to previous investigations where compliance had been assessed objectively. Compliance issues were addressed in this study using subjective methods of reported patching hours.

Optical Coherence Tomography Angiography in Patients with Amblyopia Ramin Nourinia, Zhale Rajavi, Hamideh Sabbaghi, Kiana Hassanpour, Hamid Ahmadi, Bahareh Kheiri & Mojtaba Rajabpour. Ophthalmic Research Center, Research Institute for Ophthalmology and Vision Science, Shahid Beheshti University of Medical Sciences, Tehran, Iran  
*Strabismus*, 30:3. 132-138

The goal of this paper was to determine the optical coherence tomography angiography (OCTA) parameters including foveal avascular zone (FAZ) and vessel density (VD) in the amblyopic eyes compared with the fellow sound eyes and the eyes of the non-amblyopic subjects. In this case-control study, a total of 23 eyes from unilateral amblyopic children were included as cases. The sound eye of the amblyopic children was considered as the internal control and the right eyes of the non-amblyopic children were considered as the external control. All participants underwent image recording with OCTA. In the present study, an equal number of 23 unilateral amblyopic eyes and 23 right eyes of non-amblyopic age and sex-matched children were included as the cases and controls, respectively. The average age of participants in the case and controls were  $9.86 \pm 3.12$  and  $8.5 \pm 2.35$  years, respectively. Twelve patients (52.2%) in the case group and 14 subjects (60.9%) in the control group were female. Whole vascular density of the macula in superficial capillary plexuses (SCP) was significantly lower in the external controls compared with the other studied groups ( $P = .026$ ). However, the VD of the deep capillary plexuses (DCP) was significantly greater in the external controls than cases and internal controls ( $P = .029$ ). The average FAZ area was  $0.26 \pm 0.06$  mm<sup>2</sup> in amblyopic eyes that was significantly higher compared with fellow eyes ( $0.21 \pm 0.07$  mm<sup>2</sup>;  $P = .022$ ), but it was not different with non-amblyopic eyes ( $0.22 \pm 0.118$  mm<sup>2</sup>). Based on our findings, there were no significant difference in the cases of foveal, parafoveal, and perifoveal in both superficial and deep vascular densities among amblyopic and non-amblyopic eyes, whereas deep whole density of the amblyopic eyes showed lower percent compared to non-amblyopic ones that indicates decrease blood supply of the amblyopic eyes in this region. Additionally, FAZ was larger in amblyopic eyes than internal controls. The strengths of the present study consist of inclusion of mild-to-moderate amblyopia, and comparison with the fellow eyes of patients with amblyopia as the internal control. Our study findings were not adjusted by the AL measurement. However, the same method of OCT angiography was applied in both patients and healthy controls.

#### Partial Recovery of Amblyopia After Fellow Eye Ischemic Optic Neuropathy

Resnick H, Bear M, Gaier E

[published online ahead of print January 27, 2023]. *J Neuroophthalmol*.

Amblyopia is often thought of as a problem that must be treated and corrected during early childhood if any improvement is to be obtained. However, improvement in visual acuity in an amblyopic eye (AE) has been reported in adulthood in the setting of fellow eye (FE) pathology. Here, the authors perform a retrospective chart review of patients with unilateral amblyopia who suffered from ischemic optic neuropathy (ION) in the FE with the primary goal of quantifying AE VA improvement in this setting. Ultimately, 12 patients over a 14-year period met the strict inclusion/exclusion criteria. The mean age was 67.0 years old at time of FE ION. From baseline measurements through the follow up period, there was a mean improvement in AE VA of 1.5 lines in these patients, with 9/12 experiencing at least 1 line of VA improvement in the AE and 2/12 exhibiting at least 3 lines of improvement in the AE. Additionally, in the 6/12 patient who had reliable HVF testing, mean sensitivity improved by an average of 1.9 dB in the AE over the follow up period.

Overall, the authors conclude that partial, yet clinically significant, improvement in VA in the AE following FE ION is relatively common. They review other reports of VA recovery in the AE following FE pathology in adulthood, positing that the wide variance in rates of improvement suggests that different FE pathologies are stronger drivers of recovery than others.

The authors acknowledge the limitations of their study, as the small sample size and inconsistencies of documentation inherent in retrospective chart review introduce noise into the data. Indeed, because of inconsistent reporting and chart documentation, they were unable to ascertain what effect childhood treatment of amblyopia (which 6/12 patients received) has on potential for AE VA recovery later in life. Additionally, multiple patients had changes in AE refraction during the study period, which may have contributed to their improvement in AE VA in some manner.

Nevertheless, this remains one of the largest studies examining this phenomenon. It provides interesting fodder for future studies regarding neuroplasticity, age, and amblyopia therapy.

### Changes in Choroidal Thickness and Structure Induced by 1% Atropine Instillation in Children With Hyperopic Anisometropic Amblyopia.

Araki S, Miki A, Goto K, et al.

J Pediatr Ophthalmol Strabismus. 2023;60(1):39-45. doi:10.3928/01913913-20220216-03

This small prospective cohort study sought to investigate the effects of Atropine 1% on choroidal thickness and structure of amblyopic and fellow eyes in children with hyperopic anisometropic amblyopia. All 16 children received 1% atropine eye drops in both eyes twice a day for 7 days. In the subfoveal choroidal region, choroidal thickness, total choroidal area, luminal area, and stromal area were measured quantitatively using swept-source optical coherence tomography. The choroidal parameters of the amblyopic and fellow eyes were compared between the baseline and atropine conditions. The authors found that 1% atropine induced an increase in choroidal thickness accompanied by a significant increase in the luminal and stromal areas of the choroid in the fellow eye of patients with hyperopic anisometropic amblyopia, but these changes were smaller in the amblyopic eye. The authors felt that these results implied a role for control of choroidal thickness in amblyopia management. They admit the primary shortcomings of the study: very small sample size and lack of controls.

### Features of the Choroidal Structure in Children With Anisometropic Amblyopia.

Guler Alis M, Alis A.

J Pediatr Ophthalmol Strabismus. 2022;59(5):320-325. doi:10.3928/01913913-20220103-01

This retrospective study sought to examine choroidal structure in 30 children with unilateral anisometropic amblyopia vs 30 healthy age- and sex-matched controls. Choroidal thickness was measured with OCT and examined with the binarization method using ImageJ software (National Institutes of Health). The total choroidal area, stromal area, luminal area, luminal area to stromal area ratio, and choroidal vascular index were calculated. The values were compared by correlating the spherical equivalent (SE) (determined by an autorefractometer) with anterior chamber depth, axial length, central corneal thickness (measured by optical biometry), and choroidal thickness values. The authors found the choroid of the amblyopic eyes to be thicker than that of both the fellow eyes and the control eyes, while no correlation was found between choroidal vascular index and choroidal thickness, anterior chamber depth, axial length, and central corneal thickness. They concluded that in children with anisometropic amblyopia, the total choroidal area was relatively larger in both the amblyopic and the fellow eyes compared to the control eyes, and as a result, both the amblyopic and the fellow eyes also had lower choroidal vascular index values than control eyes. The authors made an interesting point about the adequacy of blood supply to the outer layers of the retina and choroid in amblyopic eyes. Still, the study was limited by its retrospective design.

### Dichoptic and Monocular Visual Acuity in Amblyopia.

Birch EE, Jost RM, Hudgins LA, Morale SE, Donohoe M, Kelly KR.

American Journal of Ophthalmology. 2022 Oct 1;242:209-14.

Outcomes for amblyopia are typically defined based on best corrected visual acuity (BCVA) in the amblyopic eye when the non-amblyopic eye is occluded. The concern is that occlusion of the good eye diminishes the physiologic phenomenon of suppression. The goal of this cross-sectional study was to determine whether dichoptic or monocular viewing was associated with any changes in eye-hand coordination or reading speed. This study included 96 children (42 with amblyopia, 24 with recovered amblyopia, and 30 controls) aged 6-12 years. Participants underwent visual acuity testing using an Optec vision tester (which presents optotypes to the right eye, left eye or both) and visuomotor skill testing including an objective measurement of reading speed and a standardized manual dexterity assessment. The authors found that 81% of amblyopic children and 71% of recovered amblyopic children had better dichoptic than monocular BCVA in the amblyopic eye (though the difference was small at 0.2 logMAR). With regards to dexterity testing, the authors found a weak correlation between the difference between dichoptic and monocular acuity and dexterity and reading speed. Despite these weak correlations, the authors suggest that some children with amblyopia may benefit from additional time for school tasks requiring reading or eye-hand coordination.

Photoscreening for amblyopia risk factors assessment in young children: A systematic review with meta-analysis.

Ferreira A, Vieira R, Maia S, Miranda V, Parreira R, Menéres P.

Eur J Ophthalmol. 2023 Jan;33(1):92-103.

Instrument-based screening for pre-verbal children to detect early risk factors for amblyopia is increasingly adopted in clinical practice, but there is not yet a consensus on the optimal age to begin vision screening. The authors conducted a three-database search (Pubmed, ISI Web of Science, and Scopus) from inception to March 2021. The authors included full-text original articles in which the outcomes of the use of photoscreening in the community for children at or under the age of three were presented. Studies enrolling children under and above the age of three were included if the outcomes for the group of interest had been specified. Thirteen studies were selected among 705 original abstracts. A meta-analysis was used to summarize the referral rate, untestable rate and positive predictive value (PPV). The quantitative analysis included twelve studies enrolling 64,041 children. Of these, 13% (95%CI: 7-19%) were referred for further confirmation of the screening result. Astigmatism was the most common diagnosis both after screening and after ophthalmologic assessment of referred children. The pooled untestable rate and PPV were 8% (95%CI: 3-15%) and 56% (95%CI: 40-71%), respectively. Since there is no global consensus on the optimal age to begin vision screening, magnitude of refractive error must be considered an amblyopia risk factor. Optimization of referral criteria is therefore warranted.

Factors Influencing the Success of Atropine Penalization Treatment in Amblyopia Patients Non-Responsive to Occlusion Treatment.

Sultan P, Demir U, Sonmezay SE, Gungel H. J Binocul Vis Ocul Motil. 2022 Oct-Dec;72(4):212-218.

Epub 2022 Sep 6. PMID: 36067468.

This retrospective study involved 26 participants 10.62 ± 3.42 (5-17) years of age with amblyopia. Those who did not respond to standard occlusion therapy were administered 1% atropine ophthalmic drops in sound eye for at least one year. 61.5% (16/26) responded to atropine. The findings of this study included that in the group who responded to treatment, BCVA pretreatment, after optical correction and after occlusion were significantly higher. There was no significant difference between groups after atropine treatment. The study concluded that BCVA in children with amblyopia who did not respond to occlusion can be improved with atropine but likely more so in patients with poor BCVA at start of atropine. Limitations of this study include the retrospective approach and a small N. The risk of reverse amblyopia, though rare, must also be accounted for when considering atropine as a secondary treatment modality.

The Effect of Refractive Amblyopia on the Frisby Stereotest.

Nanda KD, Nischal KK. J Binocul Vis Ocul Motil. 2023 Jan-Mar;73(1):7-10. Epub 2022 Aug 19. PMID: 35984966.

In this prospective study, 22 patients with unilateral amblyopia aged 4-12 years old were tested for their BCVA in new spectacles released based on cycloplegic refraction. They underwent a full sensorimotor exam which included Frisby Stereotest. Both visual acuity difference between eyes ( $r = 0.64$ ,  $R^2 = 0.41$ ) and amblyopic visual acuity ( $r = 0.73$ ,  $R^2 = 0.53$ )

had a strong correlation with Frisby score. This study concluded that Frisby Stereotest could be a potential surrogate for detecting refractive amblyopia. In patients where visual acuity of each eye tested individually may not be possible or may simply be unreliable, results of stereotest could be helpful in deciding whether to commit to an early intervention (ie. spectacles). Limitation of this study is the small N.

Children With Amblyopia Make More Saccadic Fixations When Doing the Visual Search Task. Nagarajan K, Luo G, Narasimhan M, Satgunam P.

Invest Ophthalmol Vis Sci. 2022 Dec 1;63(13):27. doi: 10.1167/iovs.63.13.27. PMID: 36583877; PMCID: PMC9807179.

The purpose of this study was to compare eye movements in children with and without amblyopia to examine how a visual scene is explored during visual search. Real-world images were displayed to children in control group (n=14 of 6-16 years of age) and cases group with anisometric amblyopia (n=23). Eye movements were then tracked under various viewing conditions randomized to dominant/fellow eye, nondominant/amblyopic eye, and binocular viewing. Search time and accuracy were measured. Each viewing condition had 30 trials (hence 90 for each participants). The study

showed reduced visual search performance in children with anisometropic amblyopia when compared to their normally sighted peers. Children with amblyopia made more saccades and fixations. This study highlights that children with amblyopia can still have function vision difficulties even under binocular conditions and that more emphasis on binocular therapy is needed in managing amblyopia.

#### Multivariable Analyses of Amblyopia Treatment Outcomes from a Clinical Data Registry.

Repka MX, Li C, Lum F.

Ophthalmology. 2023 Feb;130(2):164-166. doi: 10.1016/j.ophtha.2022.09.005. Epub 2022 Sep 11. PMID: 36100075.

This is a retrospective database study presenting a multivariable analysis of factors associated with amblyopia treatment success. Subjects included patients between 3-12 years of age enrolled in the AAO's IRIS registry from 2013-2019. Success was assessed using IRIS-50. The IRIS-50 is an outcome measure for amblyopia treatment developed by the AAO for use with data in the IRIS registry for children specifically for children 3-7 years old, but a secondary analysis was performed for children 8-12 years old. Treatment success was determined by passing at least 1 of the following criteria: Corrected interocular (or if not reported, uncorrected) visual acuity difference of less than 0.23 logMAR 3 to 12 months after first diagnosis of amblyopia, or improvement in the corrected visual acuity of the amblyopic eye of 3 or more Snellen lines (0.30 logMAR) 3 to 12 months after first diagnosis of amblyopia, or final visual acuity in the amblyopic eye of 20/30 or better (0.18 logMAR) 3 to 12 months after first diagnosis of amblyopia. Note that the method of treatment is not available in the IRIS registry. The reported success rates for children 3-7 years old was 77% and for children 8-12 was 55%. For the 3-7 yo group the odds ratio for success in treatment in black children vs. white children (0.71) and for Medicaid vs private insurance (0.65) were statistically significant. For the 8-12yo group, the odds ratios for treatment success in black children vs. white children (0.81), hispanic/latino vs white children (1.16), and Medicaid vs private insurance (0.84) were statistically significant. This study highlights the healthcare outcome disparities associated with race and with insurance coverage, which affects a broad proportion of children in the US (nearly 50% of children have Medicaid). Limitations of this study include lack of data on treatment modality and compliance, loss of follow up, and inadequate documentation.

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#### Visual Acuity Outcomes and Loss to Follow-up in the Treatment of Amblyopia in Children From Lower Socioeconomic Backgrounds.

Hawn S, Yuan SM, Lee AR, Culican SM.

J Pediatr Ophthalmol Strabismus. 2022;59(2):110-117. doi:10.3928/01913913-20210714-01

This single-center retrospective review sought to compare visual acuity outcomes and loss to follow-up after initiation of treatment for unilateral amblyopia in children from different socioeconomic backgrounds. The authors reported outcomes on 73 patients: 28 had Medicaid and 45 had private insurance. Visual acuity improved by 2.86 lines in the Medicaid group and 2.98 lines in the private insurance group ( $P = .84$ ). Number of missed appointments and distance traveled did not correlate with visual acuity improvement. In the loss to follow-up subanalysis, 40 of 141 (28.4%) patients with Medicaid and 11 of 107 (10.3%) patients with private insurance failed to attend a single follow-up visit ( $P = .001$ ). No association was found between loss to follow-up and race, sex, or distance traveled. The authors concluded that visual acuity outcomes of treatment for amblyopia did not differ between patients with Medicaid and patients with private insurance who followed up, and also that patients with Medicaid were much more likely to be immediately lost to follow-up. The authors cite the small sample size, low racial diversity, and lack of a reliable compliance metric (sometimes provider judgment) as limitations, noting specifically that the disproportionately low number of Black patients compared to White patients (outpacing local demographic data) may have been a result of factors eg screening, diagnosis, and referral patterns.

The impact of occlusion therapy and predictors on amblyopia dose–response relationship. WK Eye Clinic, White, Leah; Walsh, Leah. IWK Health Centre, Halifax, Nova Scotia, Canada; Department of Ophthalmology, Boston Children's Hospital, Boston, MA, USA  
*Strabismus*, 30: 2; 78-89

This study aimed to calculate the dose–response relationship and predictors of visual acuity (VA) improvement following occlusion therapy at the IWK Health Center Eye Clinic and to add to amblyopia therapy dose–response relationship literature. A retrospective chart review was performed, considering patients who reached an occlusion therapy outcome at the IWK Eye Clinic between 2012 and 2019. The treatment outcome was defined as equal VA or stable VA for three consecutive clinical visits despite reported compliance. Subjective patching hours from parental reports, not prescribed hours, were used for statistical analyses. One hundred and thirty-four patients (66 females and 68 males) ages 2–11 years were included. Results showed a dose–response relationship of 224 hours/0.1logMAR increase in VA and total dose of 1344 hours for full-time occlusion and 504 hours for part-time occlusion was required to reach outcome VA. The fastest VA improvement occurred with younger age at treatment initiation, during the first 4 weeks of treatment, and in patients with strabismic and/or severe amblyopia. Classification of amblyopia, age, VA chart, initial distance VA (amblyopic eye), and treatment dose predicted the hour dose–response relationship. Dose–response relationship was faster in younger participants, in participants with strabismic and severe amblyopia, and during the first month of occlusion. Additionally, by creating a GLM model of dose–response relationship, relationship calculations can be performed. Therefore, an estimated timeline can be developed to allow allocation of clinical resources and to prepare patients for the treatment duration required and possibly increase treatment compliance.

Using a Smartphone 3-Dimensional Surface Imaging Technique to Manufacture Custom 3-Dimensional-Printed Eyeglasses

Alejandra G. De Alba Campomanes MD MPH, Elana Meer BA MBA, Matthew Clarke MS  
*JAMA Ophthalmol*. Published online September 1, 2022

Children with congenital and acquired craniofacial abnormalities are at high risk for vision loss due to refractive amblyopia as they often have poor adherence to daily glasses wear. The goal of this study was to study commercially available smartphone 3D surface imaging (3DSI) to capture facial anatomy compared to CT or MRI as the basis for custom glasses fit. The key anatomic parameters for glasses fit (face width, distance from ear bridge to nasal bridge, etc) were obtained and compared between imaging modalities. The 3D scan was considered successful if the key fit parameters could be obtained and the difference was less than 5% between MRI and the 3DSI. They found that in the 20 patients aged 1-17 with craniofacial abnormalities, all achieved a successful fit and reported daily glasses adherence without irritation. This study demonstrates that 3DSI and 3D printing technology can produce custom frames for patients with craniofacial anomalies and may help improve glasses compliance among these patients at high risk for vision loss due to refractive amblyopia.

Pujari A, Saluja G, Chawla R, Samdani A, Phuljhele S, Saxena R. Optical coherence tomography angiography in amblyopia: A critical update on current understandings and future perspectives. *Eur J Ophthalmol*. 2022 May;32(3):1324-1332.

To date, the literature on optical coherence tomography angiography (OCTA) findings in amblyopia have been heterogeneous regarding the retino-choroidal vasculature changes found in amblyopic eyes. This study was a retrospective literature review that was conducted using the key words: optical coherence tomography angiography, amblyopia, and OCTA and amblyopia. Of more than 2000 articles initially identified on PubMed Medline, Scopus, and Web of Science databases, the authors excluded letters, correspondences, and isolated OCT studies to focus on 18 original works. Several works have commented on the changes found at the level of the superficial capillary plexus (SCP), deep capillary plexus (DCP), foveal avascular zone (FAZ), peripapillary plexus, and the choriocapillaris in amblyopic eyes, but there is no uniform consensus on the findings of retino-choroidal vasculature distinguishing amblyopic eyes from their fellow control eyes. Gunzenhauser et al found a significant increase in DCP densities after patching therapy for amblyopia, possibly due to vascular re-distribution secondary to increased visual stimuli in the amblyopic eye with treatment. Findings such as these should be explored further and corroborated by other studies to quantify anatomic/vascular changes associated with



amblyopia therapy. Other authors have highlighted the need for improvement in technology with timely updated software to make the assessment of these parameters in amblyopia more homogenous and comprehensive.

Etezzad-Razavi M, Tafaghodi-Yousefi B, Eslampour A, Kiarudi MY, Najjaran M, Momeni-Moghaddam H, Alio JL. Visual outcomes of photorefractive keratectomy in non-children with anisometropic amblyopia: One-year Follow-up Outcomes. *Eur J Ophthalmol.* 2022 Sep;32(5):2615-2621.

This study was an interventional, consecutive, non-comparative prospective evaluation of the safety, efficiency, short term stability, and sensory results of photorefractive keratectomy (PRK) in children with anisometropic amblyopia who were non-compliant with glasses or contact lens correction treatment. Twelve eyes of 12 children between age 6–17 years and anisometropic amblyopia who underwent PRK under general anesthesia to correct the dioptric difference between the eyes were included in this study. A complete ophthalmic assessment including refractive status, uncorrected and corrected distance visual acuity (UDVA & CDVA), and binocular vision status using the Worth 4-dot test and stereopsis were performed before treatment and also at 1, 3, 6, and 12 months after PRK. The mean preoperative CDVA was  $0.34 \pm 0.24$  logMAR which showed a statistically significant improvement at 12 months ( $0.20 \pm 0.19$ ,  $p = 0.024$ ) after surgery compared to the preoperative assessment ( $p = 0.003$ ). The mean preoperative stereoacuity was  $341.9 \pm 245.7$  s of arc, which significantly improved to  $166.6 \pm 87.5$  s of arc 12 months after PRK ( $p = 0.012$ ). The findings in this study suggest PRK is a reasonable alternative to more conventional methods of refractive correction including spectacle or contact lens wear for the treatment of anisometropic refractive amblyopia.

Guagliano R, Barillà D, Bertone C, Montescani S, Verticchio Vercellin AC, Arpa C, Tinelli C, De Angelis G, Quaranta L. Evaluation of macular and optic nerve head parameters in amblyopic eyes: An optical coherence tomography study. *Eur J Ophthalmol.* 2022 Jul;32(4):1991-1996.

The authors focused on evaluating morphological differences in retinal nerve fibers layer (RNFL), optic nerve head (ONH), ganglion cell complex (GCC), and macular thickness between amblyopic and normal eyes from spectral domain optical coherence tomography (SD-OCT). Of 234 eyes in 117 children, four groups emerged: group A (162 eyes of 81 non-amblyopic subjects); group B (32 fellow eyes of 32 subjects with unilateral amblyopia); group C (32 amblyopic eyes of 32 subjects affected by unilateral amblyopia); group D (8 amblyopic eyes of 4 subjects with bilateral amblyopia). Patients underwent SD-OCT for ONH parameters, RNFL, GCC and macular thickness, retina map, and ONH scan quality index (SQI). Two-sided  $p$  values  $< 0.05$  were taken as statistically significant. Based on the results of the study, the authors concluded that amblyopia may affect optic nerve head morphology and central macular thickness but does not seem to affect RNFL and GCC thicknesses when comparing unilateral amblyopic eyes with their fellow control eyes.

Repeatability of the Accommodative Response Measured by the Grand Seiko Autorefractor in Children With and Without Amblyopia and Adults.

Chinn RN, Raghuram A, Curtiss MK, Gehring AM, De Paula AJ, Roberts TL. *American Journal of Ophthalmology.* 2022 Apr 1;236:221-31.

Accommodation is known to affect autorefractor measurements, though the repeatability and reliability of specific autorefractors is unknown in children with and without amblyopia. The goal of this study was to assess the repeatability of measuring the accommodative response using the Grand Seiko autorefractor in children with and without amblyopia. This was a prospective reliability assessment of 24 children with amblyopia, 36 children without amblyopia, and 24 adults. Overall, the authors found that the reliability of the autorefractor was significantly better in non-amblyopic eyes compared to amblyopic eyes: 95% LOA greatest in amblyopic eyes at  $-1.25$  D compared to  $-0.68$  D in non-amblyopic eyes and  $-0.49$  D in adult eyes. The authors conclude that overall, the Grand Seiko autorefractor had high repeatability and reliability in those without amblyopia. They advocate for repeat measurements in children with amblyopia given the lower test-retest reliability.

Patching for Amblyopia: A Novel Occlusion Dose Monitor for Glasses Wearers to Track Adherence.

Ahmad TR, Martinez MC, Tahir S, Nyong'o OL. *J Binocul Vis Ocul Motil.* 2022 Apr-Jun;72(2):69-76.

This pilot study evaluated five children to evaluate a novel occlusion dose monitor (ODM) for glasses wearers. Age of participants was 2-8 years old. A cosmesis test of a sham logger was completed for a 1-week period. Patients were then recruited to test a functional ODM for a 2-week period and their parents were asked to document patch wear in a diary. Feedback was solicited using a modified Pediatric Eye Disease Investigator Group (PEDIG) Amblyopia Treatment Index (ATI). The modified patch did not reduce patients' willingness to wear the patch as compared to a standard patch. ODM-recorded wear correlated with diary-recorded wear. The specific timestamps for wear were identical for patients with good ODM-diary concordance. This ODM device may be useful in future studies as a way of measuring compliance of occlusion in glasses wearer. The limitation of this study was the small population, but this was only a pilot study.

The Impact of Occlusion Therapy on Amblyopia Success Outcomes.

White E, Walsh L.

J Binocul Vis Ocul Motil. 2022 Jul-Sep;72(3):183-190.

This retrospective chart review from 2012-2019 of patients who underwent occlusion therapy for amblyopia investigated the rates of occlusion therapy success. Results showed 90.3% of subjects obtained outcome distance VA of 0.3logMAR, 76%  $\geq 0.3\log\text{MAR}$ , 35%  $\geq 0.2\log\text{MAR}$ , and 6%  $\geq 0.1\log\text{MAR}$  in the amblyopic eye following treatment. Sixty-nine percent of the study population obtained equal vision following occlusion therapy. Only initial VA (amblyopic eye) and initial interocular visual optotype difference at distance predicted post-treatment success. This study emphasizes the importance of compliance and close follow up with occlusion therapy.

Murray J, Gupta P, Dulaney C, Garg K, Shaikh AG, Ghasia FF. Effect of Viewing Conditions on Fixation Eye Movements and Eye Alignment in Amblyopia. Invest Ophthalmol Vis Sci. 2022;63(2):33.

Patients with amblyopia are known to have fixation instability, which arises from alteration of physiologic fixation eye movements (FEMs) and nystagmus. The authors assessed the effects of monocular, binocular, and dichoptic viewing on FEMs and eye alignment in patients with and without fusion maldevelopment nystagmus (FMN). Thirty-four patients with amblyopia and seven healthy controls were recruited. Eye movements were recorded using infrared video-oculography during (1) fellow eye viewing (FEV), (2) amblyopic eye viewing (AEV), (3) both eye viewing (BEV), and (4) dichoptic viewing (DcV) at varying fellow eye (FE) contrasts. The patients were classified per the clinical type of amblyopia and FEM waveforms into those without nystagmus, those with nystagmus with and without FMN. Fixational saccades and intersaccadic drifts, quick and slow phases of nystagmus, and bivariate contour ellipse area were analyzed in the FE and amblyopic eye (AE). The study found that FEMs are differentially affected with increased amplitude of quick phases of FMN observed during AEV than BEV and during DcV at lower FE contrasts. Increased fixation instability was seen in anisometropic patients at lower FE contrasts. Incomitance of eye misalignment was seen with the greatest increase during FEV. Strabismic/mixed amblyopia patients without FMN were more likely to demonstrate a fixation switch where the AE attends to the target during DcV than patients with FMN. The study findings suggest that FEM abnormalities modulate with different viewing conditions as used in various amblyopia therapies. This is important because increased FEM abnormalities could affect the visual function deficits and may have treatment implications.

Hussain Z and McGraw PV. Disruption of Positional Encoding at Small Separations in the Amblyopic Periphery. Invest Ophthalmol Vis Sci. 2022;63(4):15.

Positional judgments in amblyopia are impaired more at the center of the visual field than in the periphery, but the effects of visual field position frequently are confounded with stimulus separation. The purpose of this experiment was to parse the effects of stimulus separation and eccentricity on the positional deficit in amblyopia. Participating subjects adjusted the positions of stimuli of varying separations on isoeccentric arcs. The task was simultaneous bisection and alignment of broadband, high-contrast, uncrowded targets with reference to central fixation. Ten strabismic amblyopes and five normally sighted controls performed the task dichoptically; a subset of amblyopes performed the task monocularly with the amblyopic eye. Spread (inverse of precision) and bias were measured at multiple visual field locations comprising two to three separation X four eccentricity conditions in each visual field quadrant. The study found that, in

normal controls, both spread and bias increased with eccentricity, and spread (but not bias) increased linearly with separation until 7° eccentricity. Strabismic amblyopes showed a different profile: spread and bias were higher at small separations at all eccentricities, such that performance showed a quadratic trend against separation. Thus, at each eccentricity, the difference in performance between groups was largest at the smallest separation. The authors conclude that these results are consistent with disruptions in Weber mechanisms of positional encoding in strabismic amblyopia, and indicate that binocular stimulation by proximal targets produces a loss of spatial precision well beyond the fovea.

Gong L, Wei L, Yu X, Reynaud A, Hess RF, Zhou J. The Orientation Selectivity of Dichoptic Masking Suppression is Contrast Dependent in Amblyopia. *Invest Ophthalmol Vis Sci* 2022;63(6):9. The authors aimed to study the effect of stimulus contrast on the orientation selectivity of interocular interaction in amblyopia using a dichoptic masking paradigm. Eight adults with anisometric or mixed amblyopia and 10 control adults participated in our study. The contrast threshold in discriminating a target Gabor in the tested eye was measured with mean luminance in the untested eye, as well as with a bandpass oriented filtered noise in the other eye at low spatial frequency (0.25 c/d). Threshold elevation, which represents interocular suppression, was assessed using a the dichoptic masking paradigm (i.e. the contrast threshold difference between the target only and masked conditions), for each eye. Orientation selectivity of the interocular suppression as reflected by dichoptic masking was quantified by the difference between the parallel and orthogonal masking configurations. Two levels of mask's contrast (3 times or 10 times that of an individual's contrast threshold) were tested in this study. Results showed that the strength of dichoptic masking suppression was stronger at high, rather than low mask contrast in both amblyopic and control subjects. Normal controls showed orientation-dependent dichoptic masking suppression both under high and low contrast levels. However, amblyopes showed orientation-tuned dichoptic masking suppression only under the high contrast level, but untuned under the low contrast level. The authors demonstrated that interocular suppression assessed by dichoptic masking is contrast-dependent in amblyopia, being orientation-tuned only at high suprathreshold contrast levels of the mask.

Wang X, Song Y, Kiao M, Hess RF, Liu L, Reynaud A. Interocular Transfer: The Dichoptic Flash-Lag Effect in Controls and Amblyopes. *Invest Ophthalmol Vis Sci* 2022;63(2). The mammalian brain can take into account the neural delays in visual information transmission from the retina to the cortex when accurately localizing the instantaneous position of moving objects by motion extrapolation. The authors investigate in this study whether such extrapolation mechanism operates in a comparable fashion between the eyes in normally sighted and amblyopic observers. To measure interocular extrapolation, we adapted a dichoptic version of the flash-lag effect (FLE) paradigm, in which a flashed bar is perceived to lag behind a moving bar when their two positions are physically aligned. Twelve adult subjects with amblyopia and 12 healthy controls participated in the experiment. We measured the FLE magnitude of the subjects under binocular, monocular, and dichoptic conditions. The investigators found that, in controls, the FLE magnitude of binocular condition was significantly smaller than that of monocular conditions, but there was no difference between monocular and dichoptic conditions. Subjects with amblyopia exhibited a smaller FLE magnitude in the dichoptic condition when the moving bar was presented to the amblyopic eye and the flash to the fellow eye (DA condition) compared to the opposite way around (DF condition), consistent with a delay in the processing of the amblyopic eye. The authors state that their observations confirm that trajectory extrapolation mechanisms transfer between the eyes of normal observers whereas such transfer may be impaired in amblyopia. The smaller FLE magnitude in DA compared to DF in patients with amblyopia could be due to an interocular delay in the amblyopic visual system. The observation that normal controls present a smaller FLE in binocular conditions raises the question whether a larger FLE is or is not an indicator of better motion processing and extrapolation.

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## 2. VISION SCREENING

Use of the World Health Organization primary eye care protocol to investigate the ocular health status of school children in Rwanda

Mathenge WC, Bello NR, Hess OM, Dangou JM, Nkurikiye J, Levin AV  
J AAPOS 2023;27:16.e1-6)

This was a cross-sectional population-based study across 19 schools in Rwanda evaluating the World Health Organization (WHO) vision and eye care screening protocol. Visual acuity was measured using a tumbling E Snellen chart (6/60 and 6/12). Abnormal ocular features were identified using a flashlight and history against a checklist. A total of 24,892 children underwent ocular health screening. Of those, 1,865 (7.5%) failed the primary screening; 658 (2.6%) were false positives (35.3% of those who failed screening), and 1,207 (4.8%) true positives. The most frequently observed ocular diagnoses were allergic conjunctivitis (3.11%) and strabismus (0.26%). Refractive error was very rare (0.18%). In this cohort, the results indicate that majority of ocular problems could be identified on visual inspection.

Positive predictive value of dual-modality vision screening in school children 4-7 years of age—a retrospective review in Queensland, Australia

Li Y, Duffy S, Wilks S, Keel R, Beswick R, Dai S  
J AAPOS 2023;27: 22.e1-5

A retrospective review of schoolchildren who underwent vision screening between January 2017 and December 2020 was conducted to evaluate the outcomes and positive predictive value (PPV) of vision screening in school children age 4 to 7 using a dual examination method. A Parr 4m letter-matching vision test with crowding bars and the Spot photoscreener were used. 176,164 children consented to vision screening, 164,890 (93.6%) consented children underwent vision screening, and of those 12,148 (7.4%) were referred for an eye assessment. Of the 8,659 children with a known outcome (71.3% of referred), 6,011 (69.4% of known outcomes) had a confirmed visual abnormality and 2,648 (30.6%) children did not. The PPV was 0.73 when a referral was indicated by the photoscreener result, 0.76 when indicated by visual acuity testing, and 0.91 when indicated by both the photoscreener and visual acuity testing. The dual screening method was effective in identifying visual abnormalities, with higher PPV when both methods indicated a need for referral.

Effectiveness of the Spot Vision Screener using updated 2021 AAPOS guidelines

Peterseim MMW, Trivedi RH, Monahan SR, Smith SS, Bowsher JD, Alex A, Wilson ME, Wolf BJ  
J AAPOS 2023; 27:24.e1-7

Spot Vision screener was evaluated for vision screen validation using the updated 2021 AAPOS vision screening Committee guidelines. Spot screening was successful in 1,036 of 1,090 children (95%). Forty-eight percent of participants were referred for further screening using the Spot manufacturer guidelines, and 40% of all children were found to have a 2021 amblyopia risk factor or visually significant refractive error by gold standard examination. The Spot recommendation compared reasonably well to the 2021 criteria, with an overall sensitivity of 0.88 and a specificity of 0.78. Applying updated guidelines to the Spot for hyperopia, anisometropia, and astigmatism yielded moderate-to-poor sensitivity (0.27-0.77) but excellent specificity (.0.9). The area under the curve of the receiver operating characteristic analysis demonstrates overall good prediction performance for the Spot for each diagnosis—myopia, hyperopia, astigmatism, anisometropia (range, 0.87-0.97). Results of our study suggest increasing the instrument referral criterion for astigmatism from 1.5 D (manufacturer thresholds of the screener used in this study) to 2 D in older children. Decreasing the anisometropia cutoff from 1 D to 0.75 D would improve sensitivity from 0.59 to .0.8. The overall predictive ability of the Spot is good, with a sensitivity of 0.88 and a specificity of 0.78. This study recommends applying specific device refractive referral criteria to maximize screening effectiveness using the updated AAPOS guidelines.

Cycloplegic Autorefraction as a Substitute for Cycloplegic Retinoscopy in the Pediatric Population.

Schott B, Seery C, Wagner RS, Guo S.

J Pediatr Ophthalmol Strabismus. 2022;59(6):422-427. doi:10.3928/01913913-20220321-01

This retrospective chart review sought to evaluate whether cycloplegic autorefraction - obtained in the same eye 30min after administration of a mix of tropicamide, cyclopentolate, and phenylephrine - can provide similar results as cycloplegic retinoscopy. A total of 34 eyes (18 right, 16 left) from 18 patients aged 3-10 years were included in the analysis. The authors found that cycloplegic autorefraction (via Zeiss VISUREF 100) and cycloplegic retinoscopy produced similar results in the absence of ocular abnormality or uncomplicated refractive error in this small population sample, and they concluded that the two techniques were comparable. This small study could have broader application, as it indicates that comprehensive ophthalmologists could obtain reliable refractions on kids - an important consideration in the face of a dwindling pediatric ophthalmology workforce. Still, this is a relatively small study and close attention should be paid to astigmatism correction values, as there were wider confidence intervals there.

Access to Pediatric Eye Care Following Vision Screening.

Chung M, Robinson B, Fukuda M, Dunbar JA, Ulangca RA, Khazaeni LM.

J Pediatr Ophthalmol Strabismus. 2022;59(6):369-374. doi:10.3928/01913913-20220210-04

This observational study sought to quantify the accessibility of eye care providers from photoscreening centers within the vision screening region in relation to population density and median household income using a combination of software to map driving times and registries of optometrists and ophthalmologists. The authors analyzed 290 driving times for 145 photo-screening centers, 147 optometrists, and 7 pediatric ophthalmologists and found that the median driving times from a photoscreening center to the nearest optometrist and ophthalmologist were 4.74 and 25.10 minutes, respectively, with 90% of the screening centers residing within 12.46 and 67.19 minutes of the nearest optometrist and ophthalmologist, respectively. They concluded that most photoscreening centers resided within 5 and 70 minutes of the nearest optometrist and pediatric ophthalmologist, respectively, which reflected the region's greater accessibility to optometrists than to pediatric ophthalmologists. This was an interesting study highlighting the relative paucity of pediatric ophthalmologists in the study area, but its results may already be outdated (from 2015-2016) and it warrants repeating in the post-COVID landscape of even fewer pediatric ophthalmology practices.

Reaching Target Communities in a Community Preschool Vision Screening Program.

Ulangca RA, Oh CJ, Atiga CR, Dunbar JA, Khazaeni LM.

J Pediatr Ophthalmol Strabismus. 2022;59(6):375-379. doi:10.3928/01913913-20220210-01

This observational study sought to create a methodology to identify locations for vision screenings that serve the greatest number of children in the lowest-income communities in southern California. The authors utilized geoinformatics mapping software to visually display the areas of greatest need using the following input: vision screening data from a community vision screening program, child care facility data from California Department of Social Services, and income data from the U.S. Census Bureau. The child care facility data was stratified (ranked 1 to 5) such that it prioritized larger facilities in lower income communities. The authors found a positive correlation between the capacity of the child care facility and the median household income ( $P = .005$ ), and they theorized this was a reflection on the lack of child care facilities for children in zip codes with low median household incomes. They concluded that the use of a scoring system and mapping software can direct vision screening programs to reach a greater number of children with the most efficient use of resources. There were a few inherent limitations here - eg counting only licensed day care facilities, assigning value to capacity - but this study demonstrated a real-world application of bioinformatics which could be leveraged to improve access to pediatric ophthalmology care.

Real-World Application of Home Visual Acuity Testing for Pediatric Teleophthalmology During the COVID-19 Pandemic.

Redmayne JK, Russell HC.

J Pediatr Ophthalmol Strabismus. 2022;59(5):296-302. doi:10.3928/01913913-20220131-01

This small, retrospective study sought to review the real-world accuracy of home visual acuity testing during pediatric teleophthalmology consultations at a single private practice. Home visual acuity findings were compared with the subsequent in-person assessment. The authors included 86 eyes of 43 patients aged 29-173 months, and found that the correlation across all participants was 0.56 ( $P < .001$ ) with limits of agreement between -0.33 logMAR to 0.38 logMAR. This correlation was lower in patients younger than 5 and higher in patients 8 and older. The authors concluded that home visual acuity assessment is more

valuable in older pediatric patients. This was a small, but relevant study, though the likelihood of sustained dependence on teleophthalmology is diminishing.

Teacher and school staff perspectives on their role in school-based vision programs.

Vongsachang H, Callan J, Kretz AM, et al.

Can J Ophthalmol. Dec 2022;57(6):381-387.

This is a qualitative study using focus groups to understand teacher and school staff perspectives about their involvement in school-based vision programs (SBVP). Baltimore and Chicago's public schools were invited to participate between September 2016 and May 2018. Twenty-one focus groups were included. One hundred seventeen participants, 58 from Baltimore and 59 from Chicago. 61.5% were teachers, 12.8% were school staff, and 10.3% did not provide information on their role. The discussion included perceptions and personal experiences with vision and eye care, participation, program strengths and challenges, and suggestions for improvement. In addition, teachers discussed program outreach and promotion of vision health and eyeglasses wear. The study found that teachers and schools are a valuable part of the success of SBVPs. For example, teachers used multiple avenues to communicate with parents, especially explaining program details and facilitating consent returns. Teachers incorporated multiple activities to support the success of the programs. The authors recommend future work to assess the effectiveness of the teachers' strategies, such as incentives for glasses wear and consent form return. Some teachers mentioned concerns with capacity, demands, and stressors, especially in those with low-income, under-resourced schools.

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Web-based visual acuity testing for children.

Eileen E. Birch, PhD, Lindsey A. Hudgins, BA, Reed M. Jost, MS, Christina S. Cheng-Patel, CCRP, CCRC, Sarah E. Morale, BS, and Krista R. Kelly, PhD.

J AAPOS 2022;26:61.e1-5.

Despite the covid-19 pandemic leading to a growing acceptance/need for telemedicine, at-home visual acuity testing remains challenging. This is an issue as inaccurate visual acuities can lead to alterations in clinical decision making. This study evaluated two new at-home visual acuity tests (ATS-HOTV for 3–6-year-olds and E-ETDRS for 7–12-year-olds) to see if visual acuity measured at home yielded results similar to those collected during an office visit using the same test. A total of 65 children were enrolled (34 preschoolers and 31 school aged children). Each child had their visual acuity tested in the office and again at home. Parents were given detailed instructions on how to accurately measure vision. On the ATS-HOTV test, 14 of 68 eyes (21%) had abnormal vision on the in-office test and 12 of 68 eyes (18%) had abnormal vision on the at-home test. The concordance was 97%. On the E-ETDRS test, 22 of 62 eyes (35%) had abnormal vision on the in-office test and 21 of 62 eyes (34%) had abnormal vision on the at-home test. The concordance was 98%. This study is important as it highlights a type of home visual acuity testing that is overall quite accurate. Advantages of these tests are compliance with AAO recommendations, simple calibration, efficient testing, good reliability, ability to test from 20/800 to 20/12, and immediate availability of results. Disadvantages are need for a computer, internet access, and a 3-meter testing distance. Having a more accurate way to test visual acuity at home will allow for great utilization of telemedicine in ophthalmology. It also may allow for greater enrollment into studies for families that would otherwise be unable to travel to the study site for multiple exams.

Prediction and cost-effectiveness comparison of amblyopia screening methods at ages 3-4 years.

Guimaraes SV, Veiga PA, Costa PS, Silva ED.

Eur J Ophthalmol. 2022 Jul;32(4):2034-2040.

This study evaluated different vision screening methods in 3295 children, and using exploratory factor analyses (EFA) of different screening tests, the authors created models of screening strategies using: uncorrected visual acuity (UCVA), Plusoptix measurements (PO), Randot Stereo-test (SR), and Cover-Test (CT). Receiver Operating Characteristic (ROC) curves and confusion matrices were used to compare the performance of different model algorithms to detect efficacy of detecting new amblyopia. Regression analyses revealed that, although all models predicted amblyopia ( $p < 0.001$ ), only models including PO or UCVA had higher prediction capacity ( $R^2 > 0.4$ ) and better discriminating ROC curves ( $AUC > 0.95$ ;  $p < 0.001$ ). For 96% sensitivity, UCVA + PO was the most cost-effective model, since the

estimated average screening costs per treated child almost doubled and tripled if using PO or UCVA alone, versus using both exams. When UCVA + PO is not possible to implement, adding SR to either UCVA or PO resulted in cost-savings of 28% and 18%, respectively. Based on the results, the authors suggest that in a previously unscreened population of children aged 3-4 years old, screening programs should test for UCVA and PO simultaneously, since, for a high level of sensitivity, the combined method is more cost-effective in detecting amblyopia. Minimal benefit for testing SR and CT were found.

Noncycloplegic Compared with Cycloplegic Refraction in a Chicago School-Aged Population.  
Guo X, Shakarchi AF, Block SS, Friedman DS, Repka MX, Collins ME. *Ophthalmology*. 2022 Jul;129(7):813-820. doi: 10.1016/j.ophtha.2022.02.027. Epub 2022 Mar 1. PMID: 35245603.

The study is a retrospective review of > 11,000 school age children comparing noncycloplegic and cycloplegic refraction using an automated auto refractor to compare outcomes. The purpose of the study was to determine if noncycloplegic results could be reliably used in school screening programs to be able to consider prescribing glasses. The results showed that one in 4 school-aged individuals in the study showed at least 1 D more myopic SE refractive error using noncycloplegic autorefraction than cycloplegic autorefraction. These differences were more likely in eyes of individuals with hyperopia, who were younger than 10 years and who were of Hispanic ethnicity. The younger cohort may be more hyperopic and this may account for the greater difference, as well as the decrease in accommodation in older patients. Collectively, these findings support that cycloplegia is more accurate at assessing the total magnitude of refractive error in the school-aged population. Three quarters of school aged children had <1D of myopic SE between cyclo and non-cyclo refractions. The results were closer in older children and in higher myopia. This study is significant because of the prevalence of school screening programs and the challenges of performing cyclo refraction on all individuals screened and may provide some guidance with regard to how to use results of these screenings and whether one could consider prescribing off of these results.

AAPOS uniform guidelines for instrument-based pediatric vision screen validation 2021

Arnold, Robert W. et al.

*Journal of American Association for Pediatric Ophthalmology and Strabismus {JAAPOS}*, Volume 26, Issue 1, 1.e1 - 1.e6

The AAPOS Vision Screening and Research Committees revised guidelines based on expert consensus to help reduce over-referring patients. For automated vision screening devices, AAPOS 2021 recommends the confirmatory examination (age-based cycloplegic comprehensive cycloplegic examination) failure levels to include anisometropia >1.25 D, hyperopia >4.0 D, astigmatism >3.0 D in any meridian and myopia <-3.0D in children <48 months, astigmatism >1.75 D and myopia <2.0 D in children after 48 months, and any medial opacity >1mm and manifest strabismus >8Δ. This update may reduce false-positive referrals in preschoolers and enable research, development and comparable validation of current and emerging instrument based screening technology.

The Effect of Test Method on Visual Acuity in School Children Aged 4-5.

Lewis R, Codina C, Griffiths H.

*Br J Orthopt J*. 2022 Apr 5;18(1):11-17.

The aim of this study involving 4–5-year-old children in the UK was to determine the most clinically and cost-effective method for vision screening. It compared a conventional vision test method to a reversed presentation order of logMAR where letters were presented in ascending size order up to vision threshold. Thirty-four participants completed the study. Test duration was measured in seconds a concentration score was given by the examiner. There was no significant difference in the VA outcomes between each test method ( $p = 0.46$ ). The reversed method was significantly quicker to complete, with a median reduction in test duration of 28 seconds ( $p = 0.002$ ). There was no difference in concentration levels between the test methods. This study highlights that this method which some clinicians may be utilizing in their clinics with optotypes ascending in size may be more efficient.

A Comprehensive Overview of Vision Screening Programmes across 46 Countries.



Carlton J, Griffiths HJ, Mazzone P, Horwood AM, Sloot F; EUSCREEN Study Consortium. Br Ir Orthopt J. 2022 Jun 10;18(1):27-47.

In this study, representatives from 46 countries (42 European, China, India, Malai, and Rwanda) completed a survey on vision screening programmes including epidemiology, administration & general background, existing screening, coverage & attendance, tests, follow-up & diagnosis, treatment, cost & benefit and adverse effects. Infant screening is offered in all countries, whereas childhood vision screening is offered at least once in all countries, but not all regions of each country. All 46 countries provide vision screening between the ages of 3-7 years. Data on screening outcomes for quality assurance was not available from most countries; complete evaluation data was available in 2% of countries, partial data from 43%. This study is reassuring in that though vision screening is variable, some form of vision testing is performed during childhood in these countries.

Using a Computerised Staircase and Incremental Optotype Sizes to Improve Visual Acuity Assessment Accuracy.

O'Connor A, King C, Milling A, Tidbury L.

Br Ir Orthopt J. 2022 Jul 20;18(1):93-100.

In this study, three methods of visual acuity assessment were undertaken: ETDRS, Kay Pictures and computerised Kay Pictures to establish if near continuous incremental optotype display and scoring improves test-retest variability compared to current testing methods. One hundred nineteen adults were tested. Test-retest variability for computerised Kay pictures was 0.01 logMAR ( $\pm 0.04$ ,  $p = 0.001$ ). Good levels of agreement were observed for computerised Kay pictures in terms of test-retest variability, where the test had the smallest mean bias (0.01 logMAR compared to 0.03 and 0.08 logMAR for Kay Pictures and ETDRS respectively) and narrowest limits of agreement. Participants performed better in computerised Kay pictures than Kay Pictures by 0.03 logMAR, and better in ETDRS than computerised Kay pictures by 0.1 logMAR. The most significant limitation of this study was that population was limited to adults. The value of this study was that it revealed another potential method of assessing vision in the clinic and research setting.

Clinical Utility of 'Peekaboo Vision' Application for Measuring Grating Acuity in Children with Down Syndrome.

Sumalini R, Satgunam P, Subramanian A, Conway M.

Br Ir Orthopt J. 2022 May 4;18(1):18-26.

This study compared Teller acuity cards to the Peekaboo Vision iPad grating acuity app in children with Down syndrome and age-matched controls. Thirty-seven children with Down syndrome (males = 23; mean age =  $8.1 \pm 4.2$  years) and 28 controls (males = 15; mean age =  $8.71 \pm 3.84$  years) participated. Time taken to complete the tests was comparable ( $p = 0.83$ ) in children with Down syndrome. Controls were significantly faster with Peekaboo Vision ( $p = 0.01$ ). Mean logMAR acuities obtained with Peekaboo Vision ( $0.16 \pm 0.34$ ) and Teller acuity cards II ( $0.63 \pm 0.34$ ) were significantly different ( $p < 0.001$ ) in children with Down syndrome (mean difference in acuities:  $-0.44 \pm 0.38$  logMAR (95% LoA:  $-1.18$  to  $0.3$ )). For controls, the mean logMAR acuity with Peekaboo Vision ( $-0.13 \pm 0.12$ ) and Teller acuity cards II ( $0.12 \pm 0.09$ ) was also found to be significantly different ( $p < 0.001$ ) (mean difference in acuities:  $-0.24 \pm 0.14$  logMAR (95% LoA:  $-0.51$  to  $0.03$ )). Results of this study show that though these tests cannot be used interchangeably, there is potential to measure visual acuities by other modalities

Zhou R, Pfister T, Liu Y, Chen Q, Donahue SP. Age Does Not Influence the Positive Predictive Value of Vision Screening to Detect Amblyopia Risk Factors. Ophthalmology. 2022 Feb;129(2):230-231. doi: 10.1016/j.ophtha.2021.08.026. Epub 2021 Sep 7. PMID: 34506847.

This is a retrospective chart review evaluating the positive predictive value of vision screening in detecting amblyopia risk factors in children younger than 3yo compared to children between 3-5y at the Vanderbilt Eye Institute. Children between 0-5yo who sought their first comprehensive eye exam after a failed vision screen were included, with  $n=3114$ . The positive predictive value for amblyopia risk factors was 60.5% for  $<3yo$  and 59.5% for 3-5yo. The prevalence of myopia/hyperopia was significantly higher in younger children than in older children, while the prevalence of amblyopia/strabismus was significantly higher in older children. The prevalence of anisometropia was not significantly different. A limitation of this study is

that they could not account for children who did not seek out a comprehensive eye exam at all after a failed vision screen or who were seen elsewhere. This may have skewed the positive predictive value to be higher. There was also no data on the type of vision screening used. Since there was no difference in the positive predictive value between ages, this study demonstrates the effectiveness of vision screening in pre-school aged children.

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### 3. REFRACTIVE ERROR & MYOPIA CONTROL

Role of tutorial classes and full day schooling on self-reported age of myopia onset: findings in a sample of Argentinian adults

Lanca, Carla; Szeps, Abel; Iribarren, Rafael  
JAAPOS. 2022, Vol.26 (6), p.314.e1-314.e6

Etiology of school-age myopia is multifactorial including genetic and environmental factors. Increased near work with educational pressures, reduced outdoor time and participation in after-school tutorial classes have been identified as risk factors for the development of myopia. Younger age of onset of myopia has been shown to be a predictor of high myopia. The authors sought to look at the effect of after school tutorial classes and school schedule in children on age of myopia onset. Adults with myopia were given a questionnaire regarding demographics, school schedule, time spent on near work, time outdoors, and age of onset of myopia. In Argentina, public school institutions have 4 hour per day schedule either in the morning or afternoon while most private school consist of an 8-hour day. The study cohort of adults who had attended after-school tutorial classes or full-day school or who spent more time on near work in childhood had younger self-reported age of myopia onset. The authors found a younger age of myopia onset in adults who reported attending full-day school in childhood compared to adults attending only half days. The authors also found that in their cohort the only risk factor associated with final spherical equivalent in adulthood was age of myopia onset. The authors did not find significant differences based on time of day spent studying or outdoors. The authors postulate that strategies to reduce early myopia onset may prevent development of high myopia. Outdoor school programs may be one way to prevent myopia in young children. A major limitation of this study is recall bias since adults were being asked to self-report all data from childhood.

Refractive error in unilateral Duane syndrome.

Marielle P. Young, MD, Warassabhorn Ployprasith, MD, Ben J. Brintz, PhD, and Tina Rutar, MD.  
JAAPOS 2022;26:247.e1-5.

Tension exerted on the globe by extraocular muscle can influence refractive error, and co-contraction of the lateral and medial rectus muscles in Duane's syndrome exerts tension that manifests as globe retraction and eyelid fissure narrowing. This study compared refractive error between Duane and fellow eyes in unilateral Duane syndrome. A total of 84 patients were included in the study. The study found that Duane eyes had more astigmatism than fellow eyes and that the astigmatism was more likely to be oblique. The fact that the astigmatism was oblique instead of against the rule meant that chronic co-contraction of the horizontal rectus muscles was not the underlying cause. The authors hypothesized several other possible mechanisms including fibrotic lateral rectus muscles exerting more deformational force, upshoots/downshoots of the eye, variable co-contraction of the vertical rectus muscles, or differences in first trimester signaling pathways. No matter what the underlying pathology is, this paper points out the important fact that astigmatism is more common in the Duane eye compared to the fellow eye. As this can lead to anisometropic amblyopia, it highlights the importance of careful monitoring of refractive error in these patients.

Refractive outcomes following unilateral laser treatment for type 1 retinopathy of prematurity.

Sadik Etkay Bayramoglu, MD, Nihat Sayin, MD, and Dilbade Yildiz Ekinci, MD.  
JAAPOS 2022;26:245.e1-6.

Laser photocoagulation is a common treatment for ROP, and a long-term concern after laser treatment is the potential development of myopia. Different studies have shown variable results regarding the refractive outcomes in eyes treated with laser. This study compares refractive and angiographic outcomes in the eyes of infants in whom one eye was treated with laser to type 1 ROP and ROP regressed spontaneously in the other eye. The study included 17 babies (34 eyes – 17 treated, 17 not treated) and showed that laser treatment did not cause a significant myopic change compared with the fellow eye. The authors did not aim to compare laser treatment and intravitreal bevacizumab as the patient characteristics were too different between the groups. The authors only use laser to treat milder, peripheral ROP, so this

may have put their patients at less risk for laser-related myopia given the decreased number of laser shots needed to adequately treat their patients. An advantage to this study is the use of a control eye in the same patient, which eliminates other genetic and environmental factors that could contribute to the development of myopia. While it is reassuring to see that this patient population did not have an increased myopia risk, the generalizability of the results needs to be taken with caution given the relatively mild disease in the eyes that were treated.

#### Effect of the COVID-19 Lockdown on Myopia Progression of School-aged Children: A Retrospective Chart Review.

Hadi DE, Moukhadder HM, Mansour H, Wehbi Z, Ghannam AB, Al-Haddad C.  
J Pediatr Ophthalmol Strabismus. 2022;1-6. doi:10.3928/01913913-20221010-03

This retrospective review of 443 myopic school children (divided into three age groups) sought to study the effect of COVID19-related lockdowns on myopia progression. Annual myopia progression rate (back to January 2016) was computed by dividing the absolute value of the spherical equivalent (SE) difference of two consecutive visits by the duration (in years). Demographic data were retrieved. The authors found that the mean myopic SE increased over time: SE in 2021 was significantly higher than the mean SE in 2016, 2017, 2018, and 2019. Mean SE in 2020 was significantly higher than that in 2016 and 2017. There was no statistically significant difference in the mean annual progression (in diopters/year). For the 3 to 10 years group, the annual SE progression tended to be highest for 2020-2021 and 2019-2020 compared to previous years. The authors concluded that children had more myopia in 2021 and 2020 (during lockdown) compared to previous years. The myopia annual progression tended to be highest in 2020-2021, especially for the younger age group, but the difference was not statistically significant. This was a commendable review of the effect of COVID19-related lockdowns, strengthened by the longitudinal context dating back to 2016.

#### Rise of the Machines? Comparison of Cycloplegic Refraction Using Retinoscopy and the Retinomax K-Plus 5 in Children.

Arnon R, Rozen-Knisbacher I, Yahalomi T, et al.  
J Pediatr Ophthalmol Strabismus. 2022;59(6):380-387. doi:10.3928/01913913-20220211-01

This prospective study sought to compare automated refraction (via Retinomax K-plus 5) versus retinoscopic cycloplegic refraction in 213 children of mean 6.2 years randomized to two pediatric optometrists for the assessments. The authors found strong associations in sphere and spherical equivalent (SE) measurements between the two methods across all ages, and especially in children older than 5 years. In children younger than 5 years, only the axis showed association. The automated screener recorded significantly more hyperopia and more astigmatism in all children, and especially in children younger than 5 years. The authors concluded that the Retinomax K-plus could be used for screening in children older than 5 years, but that it lacked accuracy for treatment and decision-making. This study provides good insight into the utility and limitations of state-of-the-art automated vision screening in children.

#### Development and validation of a novel nomogram for predicting the occurrence of myopia in schoolchildren: A prospective cohort study.

Guo C, Ye Y, Yuan Y, Wong YL, Li X, Huang Y, Bao J, Mao G, Chen H.  
American Journal of Ophthalmology. 2022 Oct 1;242:96-106.

Myopia is increasing in frequency and the most common cause for distance vision impairment. There has been an increase in the incidence of myopia with a prevalence of close to 50% estimated by 2050. Given this, there is increasing interest in determining demographic or anatomic risk factors that may help predict who will develop myopia or myopic progression. To address this, the authors performed a school-based prospective cohort study where they enrolled over 1000 school-aged children in China over a 4 year period. Their goal was to develop a nomogram to predict myopia. The cohort was divided into training and validation arms. Using complex statistics (absolute shrinkage and selection operator regression and multivariable Cox proportional hazard model), the authors identified predictors of myopia. Of the baseline variables they measured, 18 remained candidate indicators of myopia including gender, school area, baseline grade, number of myopic parents, parental high-myopia, paternal educational attainment, maternal educational attainment, average time spent on outdoors, uncorrected visual acuity, spherical

equivalent, axial length, corneal refractive power, near-lateral heterophoria, AC/A ratio, near relative accommodation, positive relative accommodation, and base in and base out break points. The nomogram performed well with area under the ROC curves between 0.74 and 0.86. The authors also created an online myopia risk calculator to assist with clinical decision making. Overall, this is an interesting study that used a large (but homogenous) group of school children to create a nomogram to help predict myopia. This information may be useful in determining which patients would benefit from myopia control interventions.

Effect of COVID-19 lockdown on refractive errors in Italian children aged 5-12 years: A multi-center retrospective study.

Trovato Battagliola E, Mangiantini P, D'Andrea M, Malvasi M, Loffredo L, Scalinci SZ, Comberiat AM, Migliorini R, Pacella E.

Eur J Ophthalmol. 2023 Jan;33(1):112-122.

The authors designed a retrospective multicenter study conducted in Italy of children aged 5-12 years. A total of 803 children were randomly selected for the study if they had undergone an eye exam between 2016 to 2021. Exclusion criteria included presence of ocular comorbidities other than refractive error, such as blepharoptosis, media opacities, corneal or retinal dystrophies, strabismus, amblyopia, or concurrent therapy with atropine 0.01%. In the years prior to COVID-19, the mean spherical equivalent (SE)  $\pm$  SD of healthy age-school children was: 0.54  $\pm$  1.49 D in 2016; 0.43  $\pm$  1.84 D in 2017; 0.34  $\pm$  1.41 D in 2018; 0.35  $\pm$  1.75 D in 2019 (ANOVA,  $p = .659$ ). In 2021, the mean SE changed to -0.08  $\pm$  1.44 D (ANOVA,  $p = .005$ ). The mean age was comparable in all groups (ANOVA,  $p = .307$ ). The prevalence of myopes (SE  $\leq$ -0.5D) and hyperopes (SE  $\geq$  2D) was respectively 24.10% and 9.64% among children aged 60-96 months, and 63.86% and 6.02% among children aged 97-144 months. These values represent a statistically-significant increase in the number of myopes (Chi-square,  $p = .016$ ) and decrease in the number of hyperopes (Chi-square,  $p = .001$ ) in the year following the COVID-19 lockdown, which may be attributable to the lifestyle changes caused by the pandemic that increased time children spent on near-work activities and digital devices and decreased the time they spent outdoors.

Measuring Retinal Thickness and Visual Acuity in Eyes with Different Types of Astigmatism in a Cohort of Hong Kong Chinese Adults.

Liang D, Leung TW, Kee CS.

Invest Ophthalmol Vis Sci. 2023 Jan 3;64(1):2. doi: 10.1167/iovs.64.1.2. PMID: 36595274; PMCID: PMC9819738.

This case-control study involved 3611 records that were reviewed for inclusion criteria (astigmatic group: 18-45 years old, spherical equivalent refraction  $\geq$ -10D and cylinder  $\leq$ -0.75D versus control group: 18-45 years old, spherical equivalent refraction  $\geq$ -10D and cylinder  $\geq$ -0.25D). The aim of this study was to assess for potential differences in retinal thickness in astigmatic eyes. 101 patients were stratified to with-the-rule, against-the-rule and controls. There was a significant difference in best corrected distance VA (BCDVA) among the three groups and macular retinal thickness. There was a positive association detected between BCDVA and macular RT ( $r=0.206$ ,  $P=0.041$ ) after adjusting for age, gender, and axial length. Great retinal thickness and poorer best-corrected visual acuity were found in eyes with with-the-rule astigmatism compared to those in against-the-rule and control. The limitation of this study is that the entire population was Chinese adults. Also, this study was cross-sectional so all findings are simply associations and causal relationship cannot be inferred.

Changes in Shape Discrimination Sensitivity Under Glare Conditions After Orthokeratology in Myopic Children: A Prospective Study.

Su B, Bao Z, Guo Y, Zheng H, Zhou J, Lu F, Jiang J.

Invest Ophthalmol Vis Sci. 2023 Jan 3;64(1):6. doi: 10.1167/iovs.64.1.6. PMID: 36626175; PMCID: PMC9838587.

The purpose of this prospective study was to evaluate and compare the mesopic shape discrimination threshold (SDT), with and without glare, in children before and at 1 week and 1 month after orthokeratology. 90 myopic children between and 8 and 16 years old, SE of -1.00 and -5.00D, astigmatism of less than or equal to -1.5D, and a best-corrected visual acuity of 0 logMAR of better. Right eye of each participant was included. Results showed that orthokeratology treatment for up to 1

month improve the mesopic shape discrimination sensitivity with glare. It did not affect the sensitivity without glare. Change in SDT with glare was negatively associated with baseline spherical equivalent refraction. Children with less myopia at baseline have a great decrease in SDT with glare after orthokeratology than those with more myopia. The study concluded that compared to spectacle lens wear, orthokeratology does not adversely affect visual performance under mesopic conditions.

Exosomal MicroRNA Profiling in Vitreous Humor Derived From Pathological Myopia Patients.

You J, Wu Q, Xu G, Gu C, Allen E, Zhu T, Chen L.

Invest Ophthalmol Vis Sci. 2023 Jan 3;64(1):9. doi: 10.1167/iovs.64.1.9. PMID: 36648415; PMCID: PMC9851280.

This study hypothesized that vitreous and exosomal microRNAs in patients with pathological myopia (PM) may be involved in development of myopia maculopathy by regulating targeted genes as well as the function and metabolism of adjacent or distant tissues. Vitreous samples were collected from patients who underwent surgery for rhegmatogenous retinal detachment, idiopathic ERM, myopic retinoschisis, and macular hole in the Hospital of Fudan University between July 2020 and March 2021. 27 samples were included in this study (12 from control and 15 from patients with PM). The top five downregulate differentially expressed microRNAs that of PM-H (more severe maculopathy) versus PM-L (lower severity of maculopathy) can reflect tendency of deterioration of PM-H myopic maculopathy. MiR-143-3p and miR-145-5p, which were found in WGCNA, may participate in the development of myopic maculopathy. These microRNAs all relate to the insulin resistance pathway. This study is the first to identify a exosomal microRNAs as a molecular risk factor for myopic maculopathy deterioration.

Choroidal Thickness in Early Postnatal Guinea Pigs Predicts Subsequent Naturally Occurring and Form-Deprivation Amblyopia.

Liqin Jiang; Xinyu Liu; Lei Zhou; et al.

Investigative Ophthalmology & Visual Science October 2022, Vol. 62, 10.

The purpose of this study was to identify choroidal characteristics (using guinea pigs (GP) as a proxy for human eyes) associated with susceptibility to the development of myopia. Previously, it has been shown that the human choroid responds to astigmatic defocus. This study compared choroidal properties between pigmented and albino GPs (171 total), measuring biometry, cycloplegic refraction, and ChT. 43 of the GPs underwent 2 week monocular deprivation myopia, after which en face images of the choroid and SS OCT were obtained. They found that for every 10 microns greater the ChT, the refractive error was half a diopter more positive. This is consistent with other studies suggesting that greater ChT could protect from or delay the onset of myopia, and that lower ChT is associated with higher susceptibility to myopia. The authors suggest that the underlying mechanism could be related to dysfunction of the choroidal vascular system.

Children With Amblyopia Make More Saccadic Fixations When Doing the Visual Search Task.

Nagarajan K, Luo G, Narasimhan M, Satgunam P.

Invest Ophthalmol Vis Sci. 2022 Dec 1;63(13):27. PMID: 36583877; PMCID: PMC9807179.

Amblyopia in patients can have functional vision deficits such as reduced reading speed regardless of how good the vision is in the non-amblyopic eye. This was also shown in the adult population. The purpose of this study was to compare saccadic fixations in patients with and without amblyopia in a prospective cross-sectional study. Children ages 6-16 years (n=37) were organized into a control group and a group with anisometropic amblyopia. The amblyopic eye vision cut off was 20/100 or better and non-amblyopic eye was 20/25 or better. Amblyopia was defined as a difference of two lines or greater. They were asked to look for targets in a real world display and the authors used an Eyelink 1000 plus to track eye movements. The viewing conditions were randomized to dominant/fellow eye, nondominant/amblyopic eye, and binocular viewing. Visual search performance was measured combining search time and accuracy. The interocular logMAR visual acuity difference in the control group was 0 and in the amblyopia group was 0.36 +/- 0.14. The study found that amblyopic eyes had the poorest visual search performance. Reaction time was longer in binocular conditions an fellow eye than controls in patients with amblyopia. Children with amblyopia had more saccades, needed to fixate longer, and had more fixations in the target area when compared with controlled. These patterns were also

observed in the fellow eye and in binocular viewing conditions. The authors concluded that patients with amblyopia possibly have functional vision difficulties even when performing a task binocularly. This is important in counselling families with patients with amblyopia in regards to functional vision. More studies need to be conducted to see if there is a difference with patching therapy.

#### miR-328-3p Affects Axial Length Via Multiple Routes and Anti-miR-328-3p Possesses a Potential to Control Myopia Progression

Chung-Ling Liang; Ku-Chung Chen; Edwards Hsi; et al

Investigative Ophthalmology & Visual Science November 2022, Vol.63, 11.

Myopia, and myopia progression, primarily take place in childhood. Reducing the rate of progression by 50% could reduce the prevalence of high myopia by up to 90% according to the WHO. This has prompted research to find more solutions for myopia control outside of atropine and MiSight contact lenses. It has been reported that microRNA-328-3p (m328) could be a risk factor for myopia via suppressing PAX 6 expression, COL1A1, and fibromodulin (FMOD). This study aimed to further investigate the effect of m328 on myopia related genes and then test to see if anti-m328 could be used for myopia control. They found that miR-328 exerts its influence on myopia development via multiple routes, and the role of miR-328 in myopia was further supported by the therapeutic outcome of anti-miR-328 in reducing axial elongation in both mice and rabbits. In their rodent model, the anti-miR-328 eye drop was shown to be noninferior to 1% atropine in suppressing FDM-induced eyeball elongation, suggesting it may be more effective than the low dose atropine we currently use. In the toxicity study, anti-miR-328-3p did not cause any adverse effects in the eyes or elsewhere, suggesting that this possesses potential as a novel therapeutic for myopia control.

#### Myopia Control Effect of Repeated Low-Level Red-Light Therapy in Chinese Children: A Randomized, Double-Blind, Controlled Clinical Trial.

Dong J, Zhu Z, Xu H, He M.

Ophthalmology. 2023 Feb;130(2):198-204. doi: 10.1016/j.ophtha.2022.08.024. Epub 2022 Aug 29. PMID: 36049646.

This is a randomized, double-blind, controlled clinical trial assessing the efficacy and safety of repeated low-level red-light therapy and single vision spectacles vs. sham and single vision spectacles in controlling myopia progression. The study included 112 Chinese children aged 7 to 12 years with myopia of at least  $\geq 0.50$  diopter (D), astigmatism of 1.50 D or less, and anisometropia of 1.50 D or less. The RLRL group was exposed to desktop red-light therapy device twice daily for 3 minutes, with at least 4 hours between sessions for 6 months. The sham device control group received the same intervention with 10% of the original device's power. At the end of 6-months, the spherical equivalent refraction change was 0.06 for treatment group vs -0.11 for sham group, which was statistically significant. Mean axial length change at 6 months was greater for the sham groups vs treatment group (0.13mm vs 0.02mm) and was statistically significant. Changes in AL progressed more slowly for treatment vs sham. Distance visual loss was significantly greater in the sham group compared to treatment group (0.076 logMAR vs. -0.002 logMAR). There were no adverse events reported that were deemed related to the light therapy by the data safety monitoring committee. These results provide new evidence that RLRL treatment may be an effective and safe intervention against myopia progression. Additional investigation on RLRL vs sham vs no treatment would be ideal to better determine if the 10% level light had any treatment effect. A longer duration, past 6-months of follow-up would also shed light on myopia control past this period.

#### Time Outdoors in Reducing Myopia: A School-Based Cluster Randomized Trial with Objective Monitoring of Outdoor Time and Light Intensity.

He X, Sankaridurg P, Wang J, Chen J, Naduvilath T, He M, Zhu Z, Li W, Morgan IG, Xiong S, Zhu J, Zou H, Rose KA, Zhang B, Weng R, Resnikoff S, Xu X.

Ophthalmology. 2022 Nov;129(11):1245-1254. doi: 10.1016/j.ophtha.2022.06.024. Epub 2022 Jun 30. PMID: 35779695

This was a prospective, cluster randomized examiner masked, 3 arm school based trial aiming to evaluate the dose-response efficacy of increasing outdoor time on myopia onset and shift over 2 years. There was a control group, Group I had an additional 40 minutes per day of outdoor time and Group II

had 80 minutes per day of outdoor time. Light exposure was measured by a wearable wrist watch light sensor. At the end of the first year all included children received this device. The primary outcome measured was 2 year cumulative myopia incidence with secondary outcomes the change in SE and AL. The 2 year unadjusted cumulative myopia incidence was 24.9% for control, 20.6% for test I, and 23.8% test II. After adjusting for variables the incidence decreased by 16% in test I and 11% in test II. The risk of myopia incidence was similar between I and II. Cumulative changes in SE and AL in the three groups was not significantly different and mean outdoor time between group I and II were not different, however light intensity was greater in group I and II compared to the control group. Incident myopia risk was decreased by 18 % for every 60 minutes of outdoor time and there was a reduced shift in SE and AL with increasing outdoor time and the protective effect of outdoor time was only seen in those who were nonmyopes. The authors concluded that increasing outdoor time reduced the risk of myopia onset and myopic shift however with a lower than expected effect. There was similar efficacy between the two test groups which was likely related to similar outdoor exposure. Lastly, the protective effect of outdoor time was related to the duration of exposure as well as light intensity. This study is significant in that it attempts a controlled look at the effects on outdoor time and myopia onset as well as progression.

Postoperative Efficacy, Predictability, Safety, and Visual Quality of Laser Corneal Refractive Surgery: A Network Meta-analysis.

Wen D, McAlinden C, Flitcroft I, Tu R, Wang Q, Alió J, Marshall J, Huang Y, Song B, Hu L, Zhao Y, Zhu S, Gao R, Bao F, Yu A, Yu Y, Lian H, Huang J.

Am J Ophthalmol. 2017 Jun;178:65-78. doi: 10.1016/j.ajo.2017.03.013. Epub 2017 Mar 20.

PMID: 28336402

The focus of the assessment was to address the question of the safety and effectiveness of laser refractive surgery to treat amblyogenic anisometropic refractive errors in children 18 and younger. This was a literature search and review using keyword search terms. The inclusion criteria was that the research had to be original, the primary objective was to evaluate the safety and vision outcomes in eyes that had refractive surgery for anisometropic amblyopia, study reported specific outcomes with at least 3 months of follow up, had at least 10 eyes included, children 18 years or younger, and had a statistical analysis. 11 total articles were included with five focusing on myopic refractive errors, 4 on mixed anisometropic refractive error and myopia, 2 on hyperopic anisometropia, 4 on mixed anisometropic refractive error and hyperopia. The authors concluded that the level III evidence review demonstrates that the ability to achieve target refraction within 1D in children was variable but the magnitude of anisometropia decreased. Correction of the anisometropia did not necessarily correlate with visual improvement and that regression of refractive error is a major concern. Because of varying methodologies in studies direct comparison of results was precluded. The paper highlights the need to develop high quality, prospective, randomized control trials with longer follow up with well defined refractive targets and comparison of various techniques as a component.

Myopia incidence and lifestyle changes among school children during the COVID-19 pandemic: a population-based prospective study.

Zhang X, Cheung SSL, Chan HN, et al.

Br J Ophthalmol. 2022 Dec;106(12):1772-1778. doi: 10.1136/bjophthalmol-2021-319307. Because both increased near work time and decreased outdoor time have been implicated in the development of myopia, the authors sought to evaluate the myopia incidence and progression along with lifestyle changes induced by the pandemic. The authors used two separate prospective longitudinal cohorts derived from the Hong Kong Children Eye Study (HKCES, a population-based study of school children age 6-8 years) to create two study groups: 1) COVID-19 cohort of 709 patients recruited between December 2019 and January 2020 with mean age 7 years vs 2) pre COVID cohort of 1084 patients mean age 7 years previously recruited who had 3 year data completed by January 2020 prior to the outbreak. All children underwent a series of eye exams over time and completed questionnaires on screen time, outdoor time, and other lifestyle questions. Notably, the COVID group had a mean followup of 7.9 months compared to mean followup 37 months in the pre-COVID group. In the COVID group, the myopia incidence was 19%, compared to 36% in the pre-COVID group. SER progression in the COVID group was -0.50 over 8 months compared to -1.27 in the pre COVID group over 3 years. Mean axial length elongation was 0.29mm in the COVID group vs 0.88mm in the COVID group. They used a relative risk regression model to account for age and difference in cohort followup time to estimate a ~26% one year



myopia incidence in the COVID group vs ~16% for the pre-COVID group which is significantly different. Total time outdoors decreased from 1.27 hours/day to 0.41 hours/day between the cohorts, and screen time increased to 6.89 hours/day.

While it's difficult to draw too many conclusions based on the differences in followup times, these data do suggest a trend in myopia, axial length, and SER that should be taken seriously. In addition, the drastic change in outdoor time and screen time can have systemic effects beyond ophthalmology and should be addressed.

Association of time outdoors and patterns of light exposure with myopia in children.

Li M, Lanca C, Tan CS, Foo LL, Sun CH, Yap F, Najjar RP, Sabanayagam C, Saw SM.

Br J Ophthalmol. 2023 Jan;107(1):133-139. doi: 10.1136/bjophthalmol-2021-318918. The authors used the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) cohort to study reported time outdoors and light exposure patterns in a cohort of 9 year olds. Parents quantified the average duration their child spent on time outdoors per day (hours/day), in the past month, using a similar questionnaire to the Sydney Myopia Study. The FitSight wrist-worn watch recorded light levels at 1 min intervals, over 14 days during daylight hours to evaluate light exposure. Reported time outdoors was 100 min/day, and average light levels were 458 lux. Greater reported time outdoors was associated with lower odds of myopia. Light levels, timing and frequency of light exposures were not associated with myopia, spherical equivalent or axial length. Encourage patients to get outside!

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Refractive Error Profile of Preterm Infants at 1-Year Follow-up in a Tertiary Care Hospital.

Arora P, Arora K, Utaal SKD, Bansal N.

J Pediatr Ophthalmol Strabismus. 2022;59(3):151-155. doi:10.3928/01913913-20210707-01

This single-center prospective study of 300 consecutive premature infants  $\leq 34$  weeks weighing  $\leq 2,000$ g sought to report refractive outcomes in preterm infants with and without retinopathy of prematurity (ROP) which regressed spontaneously or after laser treatment. Refractive data was available on 277 neonates (554 eyes). On cycloplegic retinoscopy at 1 year of follow-up, the incidence of myopia was 12.29%, 29.55%, and 48.83% in the no ROP, spontaneously-regressed ROP, and laser-treated ROP, respectively ( $P < .05$ ). Moreover, high myopia was most prevalent in the laser-treated group (23.25%). A correlation between birth weight and gestational age with spherical equivalent showed that a low birth weight and a low gestational age are more commonly found in infants with a more negative spherical equivalent. The authors concluded that infants with laser-treated ROP have a higher incidence of myopia than those with spontaneously regressed ROP or no ROP. The authors concede the possibility of sampling bias d/t their status as a tertiary care center and in the acquisition of follow-up data for the more highly myopic subjects (more likely to follow-up).

Rapid progression of myopia at onset during home confinement.

Carolina Picotti, MD, Victoria Sanchez, MD, Leonardo Fernandez Irigaray, MD, Alejandra Iurescia, MD, and Rafael Iribarren, MD.

J AAPOS 2022;26:65.e1-4.

Myopia progression is associated with low outdoor exposure and intensive near work habits. These were common during the initial phases of the covid-19 pandemic when schools were closed, and children were obliged to stay at home. This study aimed to investigate whether pandemic school closures were associated with an increased rate of myopia progression in newly developed myopes. Patients were included in the study who presented with myopia for the first time in a visit between September 2020 to May 2021 and who had two cycloplegic refractions in the years prior to their myopia onset. The study found that the mean rate of myopic shift was  $-0.34$  diopters from 2018-2019 and  $-1.10$  from 2019-2020. This amount of myopic shift is much higher than that reported in other studies that have looked at the rate of myopic shifts at myopia onset ( $-0.72$  D to  $-0.82$  D). This study provides further evidence that the time spent indoors and the near work associated with remote schooling likely increased the rate of myopia progression in children. Studies like this should play a significant role in the future when making decisions regarding school closures and stay-at-home orders.

Anisometropia and refractive status in children with congenital nasolacrimal duct obstruction—a prospective observational study.

Hridya Hareendran, DNB, Fathima Allapitchai, MS, Meenakshi Ravindran, DO, DNB, Kshitij Shukul, DO, DNB, and Ramakrishnan Rengappa, DO, MS.

J AAPOS 2022;26:76.e1-4.

Congenital nasolacrimal duct obstruction (CNLDO) affects 20% of infants worldwide and becomes symptomatic in 5-6% of children. Persistent epiphora in CNLDO may cause defocusing on the retina that could adversely affect emmetropization. Additionally, anatomic abnormalities of the orbit may cause both failure of canalization and ocular biometric changes. The purpose of this study was to prospectively assess refractive status and prevalence of anisometropia in children with unilateral and bilateral CNLDO. A total of 308 patients were included (205 with unilateral CNLDO, 103 with bilateral CNLDO). In unilateral cases, hypermetropia was the most common refractive error in the affected eye; whereas, emmetropia was the most common refractive error in the unaffected eye. In bilateral CNLDO, the prevalence of hyperopia and emmetropia were close to equal. There was a statistically significant difference between the two eyes in unilateral cases but not in bilateral cases with the rate of anisometropia being 11.2% in unilateral cases and only 1.9% in bilateral cases. The mean interocular difference of spherical equivalent and prevalence of anisometropia was higher in children >48 months old. Anisometropia was also greater in patients who required surgery than in those whose obstruction resolved spontaneously. Based on these findings, there is concern that CNLDO may adversely affect visual development in children. Because of this, the authors of this study recommend Crigler massage being initiated immediately upon diagnosis of CNLDO and surgery as soon as children are >1 year old. Although not mentioned by the authors, this may also lend support to the group of pediatric ophthalmologists who prefer to do early probing in the clinic. Overall, this is a well-designed, prospective study with a large study population. Its limitations include its lack of age-matched controls and lack of follow-up after treatment to see if anisometropia resolves. This is an important study that can help guide pediatric ophthalmologists as they educate families of children with CNLDO. It also highlights the importance of doing a cycloplegic refraction on all children who present with CNLDO.

Axial Elongation During Short-Term Accommodation in Myopic and Nonmyopic Children. Invest Ophthalmol Vis Sci. 2022 Mar 2;63(3):12. doi: 10.1167/iovs.63.3.12. PMID: 35275173; PMCID: PMC8934556.

Hughes RPJ, Read SA, Collins MJ, Vincent SJ.

For the same accommodation stimulus, myopic adults and children often exhibit a greater lag of accommodation compared to age-matched emmetropes, which may be due to structural or functional differences in the ciliary muscle and body. For this study, eighteen myopic children (11 males and seven females), with a mean age ( $\pm$  SD) of  $10.1 \pm 1.4$  years (range, 7.3–12.7 years) and noncycloplegic spherical equivalent refraction (SER) of  $-2.08 \pm 0.92$  D (range,  $-0.75$  to  $-3.50$  D), all corrected with single-vision distance spectacles and eighteen nonmyopic children (11 males and seven females) age- and sex-matched to the myopic children, were recruited. A range of ocular biometric measurements were captured during brief accommodation tasks (0, 3, 6, and 9 D) using a Badal optometer. The average central corneal thickness, anterior chamber depth, crystalline lens thickness, anterior segment length, vitreous chamber depth, and axial length were determined for each accommodation stimulus. All biometric parameters, except central corneal thickness, changed significantly during accommodation (all  $P < 0.001$ ). Myopic children exhibited significantly greater accommodation-induced axial elongation than nonmyopic children ( $P = 0.002$ ) at the 3, 6, and 9 D accommodation stimuli, with a mean difference of 7, 10, and 16  $\mu$ m, respectively (all pairwise comparisons,  $P \leq 0.03$ ). The changes in all other biometric parameters were not different between the refractive error groups ( $P \geq 0.23$ ). These findings are supportive of the influence of accommodation and near work in myopia progression.

Exposure to the Life of a School Child Rather Than Age Determines Myopic Shifts in Refraction in School Children. Invest Ophthalmol Vis Sci. 2022 Mar 2;63(3):15. doi: 10.1167/iovs.63.3.15. PMID: 35289844; PMCID: PMC8934557.

Ding X, Morgan IG, Hu Y, Yuan Z, He M.

With the increase in the prevalence of myopia with age in modern societies, it is often assumed that children naturally become myopic as they age. In previous studies, the effect of schooling has almost always been confounded by the synchronous aging of the school children. To resolve the issue, the

authors of this study have used a sample of children who have limited age variation and are educated in the same grade and compared them to children of a similar age who have received more or less education. Participants in this study were drawn from the control group of the Guangzhou Outdoor Activity Longitudinal (GOAL) Trial. Eye examinations and cycloplegic refractions were performed annually in September and October (the beginning months of each school year) from 2009 to 2012. Within the same grade, the mean age increased by about 0.66 years, but the spherical equivalent did not change significantly. However, comparing between grades, even with a lesser age increase of 0.35 years, children who had received one year more of education demonstrated a significantly more myopic spherical equivalent than those who had received less education ( $t$ -test, all  $P < 0.01$ ). Children in the higher grade had a more negative spherical equivalent ( $t$ -test, all  $P < 0.01$ ) and higher myopia incidence ( $\chi^2$  test, all  $P < 0.001$ ), than those in the lower grade at the same age. Increases in age associated with the same average educational experience have little impact on spherical equivalent, but increases in average educational experience associated with smaller changes in age markedly change the spherical equivalent. These results do not establish a causal relationship between the academic education and spherical equivalent. Still, the most likely explanation of these findings is that exposure to a schoolchild's life, rather than age, is the major determinant of myopic shifts in refraction, at least in the early primary school years.

#### Incidence and Progression of Myopia in Early Adulthood

Lee SS, Lingham G, Sanfilippo PG, et al.

JAMA Ophthalmol. Feb 2022; 140(2): 162-169

The goal of this study was to determine how common myopia progression and onset is in early adulthood. While myopia incidence and progression has been described extensively in children, little data exists regarding myopia onset and progression in the early adult cohort. This was a cohort study of 691 young adults from a general population looking at 8 year incidence of myopia and change in ocular biometry and their association with known risk factors for childhood myopia. Participants were examined at age 20 (baseline) and 28 years with biometry, conjunctival ultraviolet autofluorescence photography, and cycloplegic autorefraction. Patients were excluded if they had a history of keratoconus, myopia at baseline, previous corneal surgery, or recent orthokeratology wear. The 8 year incidence of myopia or high myopia were 14.0% and 0.7% respectively, and a 0.50 D myopic shift was observed in 37.8% of participants. Rates of myopia progression and axial length elongation were faster in female participants and those with parental myopia, and the study findings suggest that the protective effects of time outdoors against myopia may continue into young adulthood. This study highlights that eyes may continue to elongate axially during young adulthood which can contribute to increased risk of myopia related complications in young adults, some of who may benefit from myopia control methods.

#### Spectacle Lenses with Aspherical Lenslets for Myopia Control vs Single Vision Spectacle Lenses: A Randomized Clinical Trial

Jinhua Bao PhD, Yingying Huang MD, Xue Li PhD

JAMA Ophthalmol. April 2022; 140(5):472-478

The goal of this study was to evaluate the efficacy of spectacle lenses with highly aspherical lenslets and slightly aspherical lenslets compared with conventional single-vision spectacle lenses in controlling myopia progression throughout 2 years. This was a double-masked randomized control study of 157 children who were randomly assigned in a 1:1:1 ratio to receive spectacle lenses with highly aspherical lenslets (HAL), spectacle lenses with slightly aspherical lenslets (SAL), or single-vision spectacle lenses (SVL). The main outcomes were the two year changes in cycloplegic spherical equivalent refraction (SER), axial length, and their differences between the three groups. They found that at two years children who wore SAL and HAL had reduced rates of myopic progression and axial elongation compared with children in SVL at two years. There was also a dose-dependent effect demonstrated, with children who wore HAL full time demonstrating increased myopic control efficacy. Differences in myopia control efficacy could be linked to differences in lens designs, namely, the concentric ring configuration with aspherical lenslets (this study) and to lens design features such as the amount and area of lens addition or peripheral defocus.

Jeon GS, Hong IH, Lee JH, Song TG, Lee TY, Han JR. Analysis of treatment response about low-dose (0.01%) atropine eye-drops in myopic children. *Eur J Ophthalmol.* 2022 Jul;32(4):2011-2017.

This is a retrospective study evaluating 68 eyes in myopic children between 5 and 15 years of age with myopia progression > 0.50 D/year. Patients treated with low-dose atropine (0.01%) for 12 months were screened and a comparative analysis was conducted between those with a good response to treatment versus those not responding well. Patients were classified as good responders if spherical equivalent refractive error (SE) progression was  $\leq$  0.50 D after 12 months of treatment and poor responders if SE progression was > 0.50 D. The prognostic factors before and after treatment were analyzed in two groups. In the group with a good response (n=37), the mean rate of myopia progression after 12 months of treatment ( $0.36 \pm 0.17$  D) was significantly slower compared with baseline progression ( $p < 0.001$ ). Good responders also have smaller changes in axial length (AL) elongation and SE than poor responders ( $p < 0.001$ ). The study also found that children with a family history of myopia starting at a young age were more likely to be poor responders to the 0.01% dose of atropine and should be considered for treatment using higher doses. AL was also shown to be an important parameter in monitoring treatment response.

Myopia control effect of defocus incorporated multiple segments (DIMS) spectacle lens in Chinese children: results of a 3-year follow-up study.

Lam CS, Tang WC, Lee PH, Zhang HY, Qi H, Hasegawa K, To CH. *Br J Ophthalmol.* 2022 Aug;106(8):1110-1114.

A 2-year double-masked RCT published in 2020 showed that DIMS lens wear slowed childhood adjusted myopia progression significantly by 52% and axial elongation by 62% compared with regular single vision (SV) spectacle lenses wear over 2 years. This follow-up study aimed to see if the slowing of myopia persisted in year 3 in children continuing to wear DIMS lenses, and whether the effect on myopia progression is seen in the 1<sup>st</sup> year of DIMS use by switching the SVL children to DIMS lenses. Both groups were compared to a new historical control group for analysis. 160 Chinese children completed the 2-year RCT and 128 of these agreed to participate in the third-year study with a mean age of 10 years. The primary and secondary outcomes were the changes in spherical equivalent refraction (SER) and axial length (AL) measured in 6 month intervals. The mean annual changes in SER and AL in the DIMS group were  $-0.18 \pm 0.25$ D and  $0.10 \pm 0.09$  mm over 3 years and did not change significantly over time. Myopia progression and axial elongation in the third year were significantly decreased compared with the first two years in the SVL-to-DIMS group. Only 5% and 2% in the DIMS and SVL-to-DIMS groups, respectively, had myopia progression more than 1D in the 3<sup>rd</sup> year. The change in myopia and axial length in both study groups was significantly less than that seen in the historical control group. This study suggests that DIMS lenses slowed myopia progression and axial elongation in children, but recognizes that the optimal age and duration of treatment remains unknown. The authors plan a follow-up study to evaluate the children who stopped the DIMS lenses to look for rebound myopia which will be very interesting.

Two-year add-on effect of using low concentration atropine in poor responders of orthokeratology in myopic children.

Chen Z, Zhou J, Xue F, Qu X, Zhou X. *Br J Ophthalmol.* 2022 Aug;106(8):1069-1072.

A previous preliminary study suggested low concentration atropine used in addition to ortho-k lenses enhanced the myopia control effect in fast myopia progressors. In the current study, the authors sought to investigate the sustainability of this effect by following these children through 2 years of using low concentration atropine in poor responders of ortho-k in myopic children. Axial length measurement was performed in both eyes at baseline and every 6 months after commencing ortho-k lens wear. Subjects who showed axial elongation of 0.30 mm or greater in the first year of ortho-k treatment were given the option to apply one drop of 0.01% atropine nightly before ortho-k lens wear, creating 2 groups: ortho-k + atropine (n=37) vs ortho-k alone (n=36) and these patients were followed for an additional 2 years. AL significantly changed over time showing increase in both study groups, however, AL change was not statistically significantly different between the two study groups. One big limitation of the study was that patients self-selected to the ortho-k + atropine group rather than being randomized. It also leaves of question of whether higher concentrations of atropine may provide more effect.

One-year myopia control efficacy of spectacle lenses with aspherical lenslets.

Bao J, Yang A, Huang Y, Li X, Pan Y, Ding C, Lim EW, Zheng J, Spiegel DP, Drobe B, Lu F, Chen H. *Br J Ophthalmol*. 2022 Aug;106(8):1171-1176.

This study enrolled 173 patients age 8–13 years with myopia of  $-0.75$  D to  $-4.75$  D and tested two different spectacle lens designs for myopia control that induce two different volumes of myopic defocus (VoMD) via aspherical lenslets over a 1 year period. This 2-year clinical trial was designed to be a randomized, controlled, double-masked study with follow-up visits every 6 months and a planned interim analysis after 12 months which is reported here. Both the highly aspheric lens (HAL) and slightly aspheric lens (SAL) groups exhibited less spherical equivalent refraction (SER) than the SVL lens group, and the HAL group displayed less SER progression than the SAL group. Similar findings were demonstrated for axial length elongation, with less elongation in the HAL group compared to SAL and SVL groups. BCVA, adaptation and compliance were not affected by the lens design. Interestingly, 15% of participants wearing HAL and 2% of participants wearing SAL showed a hyperopic shift and a reduction in AL. This phenomenon of a hyperopic shift due to lens compensation has been shown in several animal models but rarely reported in human intervention studies and warrants further investigation as the underlying cause is unknown. We should await the results of the full 2-year trial to better understand the potential benefits of these lenses.

Refractive change and incidence of myopia among rural Chinese children: the Handan Offspring Myopia Study.

Lin Z, Vasudevan B, Gao T, Zhou H, Ciuffreda KJ, Liang Y. *Br J Ophthalmol*. 2022 May;106(5):628-632.

The purpose of this study was to determine the refractive change and incidence of myopia, as well as their risk factors, among rural Chinese children from the Handan Offspring Myopia Study (HOMS), in Handan city, northern China. A total of 878 children, along with at least one of their parents, were recruited for the HOMS in 2010, and then from October 2013 to January 2014, 630 (71.8%, 630/878) of the enrolled children were re-examined, with a mean follow-up time of  $42.4 \pm 1.47$  months the results of which are described in this paper. The cumulative refractive change and axial length change were approximately  $-0.15$  diopter/year and  $0.11$  mm/year, respectively, which is relatively low. The cumulative myopia incidence in the cohort was 22.4%, with an annual myopia incidence of 6.3%. After adjustment, younger age, more myopic baseline refraction, larger difference between cycloplegic and non-cycloplegic refraction, and more myopic paternal refraction were found to be associated with more rapid myopic refractive change.

Progression of myopia in children and teenagers: a nationwide longitudinal study.

Tricard D, Marillet S, Ingrand P, Bullimore MA, Bourne RRA, Leveziel N. *Br J Ophthalmol*. 2022 Aug;106(8):1104-1109.

The aim of this study was to prospectively study myopia progression among children and adolescents in France, as epidemiologic data on myopic European children is currently scarce. The original dataset consisted of anonymized electronic data files collected from 696 French opticians' stores located in all French metropolitan departments between 2013 and 2019. Individuals aged 4-17 years with at least two prescriptions for myopia correction separated by at least 6 months were eligible, and those with high myopia defined as  $SE \leq -6$  D were excluded. Progressors were defined as individuals with a mean rate of progression of myopia exceeding  $-0.50$  D/year. A higher proportion of progressors was noted among children aged 7–9 years (33.1 %) and 10–12 years (29.4%) compared with other groups, among those with  $SE \leq -4.00$  D, and among girls. Age was the most important factor determining the mean progression rate and the proportion of fast progressors, but age is not a monotonic factor, with 7–9 year old myopes progressing faster and both younger and older children progressing more slowly. The reasoning behind this finding is not clear from the study.

Development of the retina and its relation with myopic shift varies from childhood to adolescence.

Jin P, Deng J, Lv M, Sun S, Zhu J, Xu X, He X, Zou H. *Br J Ophthalmol*. 2022 Jun;106(6):825-830.

This study aimed to elucidate the influence of myopia on retinal development in children and adolescents. The longitudinal changes in whole retina, ganglion cell complex (GCC), and outer retinal layer (ORL)

thickness over 1 year were investigated in 769 participants from 6 to 17 years old, and the thickness change of each retinal layer and its relation with myopic shift were analyzed in different age groups. A total of 769 participants with a mean age of  $10.90 \pm 3.10$  years old were enrolled in this study. Girls tended to be more myopic but their AL was shorter than that of boys, and boys had significantly thicker central fovea RT, GCC and ORL than girls at baseline. 44.73% of participants developed a myopic shift during the study period, with an average myopic shift of  $-0.43 \pm 0.47$  D, an increased AL of  $0.24 \pm 0.28$  mm, mean increase in central foveal RT of  $2 \pm 13$   $\mu$ m and mean ORL  $3 \pm 6$   $\mu$ m while GCC thickness was unchanged. The thickness of the central foveal retinal layers was increased in children  $<10$  years but unchanged or decreased in adolescents  $>13$  years. The thickness changes in the retina, GCC and ORL decreased with age. Changes in central foveal retinal thickness (RT) and GCC thickness were independently associated with age and baseline spherical equivalent, while the changes in ORL thickness were associated with age and SE changes. In children 8–9 years, a greater increase was observed in central foveal ORL thickness in those with no myopic shift. The authors concluded that the development of the retina and its relationship with myopia varies from childhood to adolescence, and that children  $< 9$  years old could be susceptible to myopia-related retinal thinning.

#### Efficacy and Safety of 8 Atropine Concentrations for Myopia Control in Children: A Network Meta-Analysis.

Ha A, Kim SJ, Shim SR, Kim YK, Jung JH. *Ophthalmology*. 2022 Mar;129(3):322-333. doi: 10.1016/j.ophtha.2021.10.016. Epub 2021 Oct 22. PMID: 34688698.

This is a network meta-analysis of various atropine dose concentrations for treatment of myopia and was conducted to help draw more decisive conclusions regarding rankings of atropine concentrations for treatment efficacy and safety. The analysis used only RCTs and articles were independently assessed by two investigators. Primary outcomes were the annual change in refraction (diopters/year) and mean annual change in AXL (mm/year). There were multiple secondary outcomes evaluated as well. 16 studies met criteria and concentrations evaluated were 1%, 0.5%, 0.25%, 0.1%, 0.05%, 0.025%, 0.02%, 0.01%. In head-to-head comparison, none of the atropine concentrations were found to be statistically different with the exception of 1% vs 0.1% in mean refraction change. Higher-dose atropine was better at slowing down refractive changes and axial elongation. However, 0.05% showed comparable efficacy to high doses, being third in retarding refractive changes, and second in slowing down axial elongation. In addition, it was the most beneficial with regard to RR of overall myopia progression and it had a better safety profile relative to high-dose atropine. The study had several limitations including: study heterogeneity, based on Asian population, no analysis of myopic rebound, no consideration of other factors in myopia progression and a lack of sufficient data on some concentrations. This study highlights the overall efficacy of atropine vs control group for myopia control, and points to 0.05% as possibly the dose with the greatest efficacy and lowest overall side effect profile.

#### Three-Year Clinical Trial of Low-Concentration Atropine for Myopia Progression (LAMP) Study: Continued Versus Washout: Phase 3 Report.

Yam JC, Zhang XJ, Zhang Y, Wang YM, Tang SM, Li FF, Kam KW, Ko ST, Yip BHK, Young AL, Tham CC, Chen LJ, Pang CP. *Ophthalmology*. 2022 Mar;129(3):308-321. doi: 10.1016/j.ophtha.2021.10.002. Epub 2021 Oct 7. PMID: 34627809.

This was a RCT in the third phase of the LAMP study looking at efficacy of continued treatment during the third year, the long-term efficacy of low dose atropine over 3 years, and the rebound effect with treatment cessation. The primary outcomes were the difference in myopia progression (change in SE and AL), the cumulative myopia progression over 3 years in the continued treatment and the washout subgroup, and the rebound effect and associated factors. The results showed that the differences between the continued treatment and washout subgroups were dependent on atropine concentration and age, i.e the lower the concentration and the older the subject's age the smaller the difference in myopia progression in both groups. In older groups the rebound was smaller in both SE and AL, while in the 6–8-year group the higher atropine dose resulted in greater SE rebound. The conclusions of the study were that: 1) continued atropine treatment in year 3 was better than stopping, 2) effect of 0.05% was double that of 0.01%, 3) greater rebound effect was associated with higher atropine concentration and younger age of cessation 4) all concentrations showed good tolerance. The authors suggest that atropine should be continued for a third year and that weaning from higher to lower concentrations and older age for stopping

treatment provides the lowest rebound effect. Also, they recommend withholding treatment after 3 years and monitoring at 6 months and restarting only when progression noted again. In addition, 0.05% was found to be more efficacious. Some limitations include: Asian population only, the placebo group was switched randomly into different subgroups, thus the third-year results did not have a placebo control group. The take home was that 0.05% is the optimal concentration among all groups even with rebound phenomenon, the third year continues to show efficacy. This is supported by the network meta-analysis found in same issue of journal.

#### Effect of Repeated Low-Level Red-Light Therapy for Myopia Control in Children: A Multicenter Randomized Controlled Trial.

Jiang Y, Zhu Z, Tan X, Kong X, Zhong H, Zhang J, Xiong R, Yuan Y, Zeng J, Morgan IG, He M. *Ophthalmology*. 2022 May;129(5):509-519. doi: 10.1016/j.ophtha.2021.11.023. Epub 2021 Dec 1. PMID: 34863776.

This is a prospective multicenter randomized clinical trial to assess the efficacy and safety of repeated low-level red-light (RLRL) therapy in myopia control. The authors conducted the study over the course of 12 months. Patients were randomized to either single vision spectacles (SVS) or RLRL. The RLRL group was given a device used for amblyopia therapy to take home and completed treatment twice daily with an interval of at least 4 hours for 3 minutes 5 days a week over 12 months. Compliance was monitored through an internet connection that logged usage of the device. The primary outcome was measurement of AL changes at follow up visits compared to baseline. Secondary outcomes included change in cyclorefraction SER and measurement of ACD, corneal curvature, and white to white as well as visual acuity. At the conclusion of the study, AL elongation was 0.13mm in treatment group compared to 0.38mm in the SVS group. This was a 69.4% reduction in progression. As secondary outcomes, SER progression between the two groups was a mean of 0.59 D (76.6% reduction). The other secondary outcomes between the two groups were essentially similar with the exception of uncorrected visual acuity. The proportion of children whose UCVA improved by at least 2 lines was significantly greater in the RLRL group. Treatment compliance revealed that as compliance improved from <50% to >75% efficacy increased from 44.6% to 76.8% in reducing AL elongation and 41.7% to 87.7% in controlling SER progression. This suggests that improved treatment compliance enhanced the effect of RLRL therapy. In sum, the RLRL treatment group slowed axial elongation by 0.26mm and SER progression by 0.59 D compared with SVS. When alternative therapies for myopia control are compared, the efficacy result of this study seems to be competitive. The authors suggest that some areas for future study may include increasing treatment duration and longer treatment time which may improve efficacy. Some limitations include the lack of information about rebound effect when stopping therapy. The authors present a possible new modality in the armamentarium of myopia control that seems to have similar efficacy to current options with low side effect profile though long-term results and rebound possibilities have yet to be studied.

#### The Association of Choroidal Thickening by Atropine With Treatment Effects for Myopia: Two-Year Clinical Trial of the Low-concentration Atropine for Myopia Progression (LAMP) Study.

Yam JC, Jiang Y, Lee J, Li S, Zhang Y, Sun W, Yuan N, Wang YM, Yip BH, Kam KW, Chan HN. *American Journal of Ophthalmology*. 2022 May 1;237:130-8.

Increasing levels of myopia have fueled growing interest in myopia control technologies with a specific interest in their mechanism of action. One of the most common treatments to slow myopia progression is low-concentration atropine, the results of which have been described in several studies including the Low-concentration Atropine for Myopia Progression (LAMP) Study. The goal of this study is to look at the 2 year associations between choroidal thickening and atropine treatment in the LAMP study (a double-blinded randomized controlled trial). Given the proposed role of the choroid in eye growth and refractive error, assessment of choroidal thickness could shed insight into the mechanism of action behind atropine. In the LAMP Study, children were randomized to atropine 0.05%, 0.025%, or 0.01%. In the choroidal thickness study, the authors found that an increase in choroidal thickness was associated with slower myopic progression and decreased axial length elongation. Overall, A concentration dependent trend was observed, where choroidal thickness was greater at higher concentrations of atropine. This study is not able to show causation, but the correlation between spherical equivalent, axial length,

choroidal thickness, and atropine concentration suggest that further studies into the role of the choroid in myopia development are needed.

#### Anisometropia Profile in Elderly Population: Tehran Geriatric Eye Study.

Hashemi H, Jamali A, Nabovati P, Yekta AA, Khabazkhoob M.

J Binocul Vis Ocul Motil. 2022 Jul-Sep;72(3):161-168.

The geriatric population over age 60 years in Tehran, Iran was studied to investigate the distribution and prevalence of anisometropia according to age, gender and ocular biometry. Using the IOL Master and autorefractor, the study revealed that the mean anisometropia in the whole sample was 0.82 D (95% CI: 0.76 - 0.88 D), which increased from 0.62 D (in those aged 60-64 years old) to 1.36 D (in those above 80 years). The prevalence of anisometropia >1 D in total population, males, and females were 23.81%, 24.9%, and 22.76%, respectively. The odds ratio of anisometropia was higher in cases with cataracts, myopia compared to emmetropia, keratometry asymmetry, axial length asymmetry ( $P = .001$ ), and corneal diameter asymmetry (all others,  $P < .001$ ). The results of this study imply more anisometropia in the geriatric population likely affected by the shift in refractive error that occurs with development and progression of cataracts.

#### Effects of General Anesthesia on Ocular Refraction.

Kawai M, Ishikawa H, Tatsui S, Kanayama S, Nakazawa A, Matsuda H, Okamoto H, Shoji N.

J Binocul Vis Ocul Motil. 2022 Jul-Sep;72(3):176-182.

This study evaluated refractive errors of 57 patients under 15 years of age when they were under general anesthesia for strabismus surgery. Objective refraction values, corneal refraction values, and pupil diameter were measured using a HandyRef-K, a hand-held refractive keratometer, in the operating room before and during general anesthesia before strabismus surgery. The spherical power of the myopic eye increased from -0.75 D to -2.29 D (diopter); the cylindrical power increased from -0.90 D to -1.39 D ( $p < .01$  for all). The corneal refractive power decreased by an average of 0.25 D ( $p < .01$ ). The spherical refractive power was negatively correlated with the age and the amount of change between cycloplegia before general anesthesia and during general anesthesia ( $r = -0.32$ ,  $p < .05$ ). The results of this study highlight the limitations of refractions under anesthesia, and that cycloplegic agents should be used to most accurately obtain a refraction under anesthesia especially in children who are challenging to examine in clinic (ie. spectacles being prescribed based off refraction performed as part of exam under anesthesia).

#### Changes to Visual Parameters Following Virtual Reality Gameplay.

Banstola S, Hanna K, O'Connor A.

Br Ir Orthopt J. 2022 Jun 27;18(1):57-64.

This study included 78 participants tested at the University of Liverpool after playing 15 minutes of VR game Beat Saber which incorporated convergence and divergence movements. Of note, all participants had normal binocular vision and visual acuity. Clinical assessments including near point of convergence (NPC) and near point of accommodation (NPA) using the RAF rule; accommodative convergence to accommodation (AC/A) ratio; motor fusion using the prism fusion range (at 33cm), accommodation facility using +2.00/-2.00DS flipper lenses, and stereoacuity using the Frisby stereo test were assessed before and after playing. The binocular accommodative facility improved by 2 cycles per minute (cpm);  $p = 0.004$ . The mean, near horizontal prism fusion range (PFR) base break and recovery points both worsened by of 5.0 dioptres ( $p = 0.003$ ), whereas the mean near horizontal PFR base in recovery point improved by of 4.0 dioptres ( $p = 0.003$ ). The limitations of this study that the population only included patients with normal binocularity/vision and that the findings were limited to only short term effects.

#### Characterizing Refractive Errors, Near Accommodative and Vergence Anomalies and Symptoms in an Optometry Clinic.

Wajuihian SO.

Br Ir Orthopt J. 2022 Jul 14;18(1):76-92.

The purpose of this prospective, cross-sectional study was to determine the frequencies of refractive error, accommodative and vergence anomalies, and their associations with symptoms in sample of Black South Africans. The study was comprised of consecutive participants aged 10-40 years who attended the author's optometry practice in a Black population in South Africa. Visual acuity, refraction, accommodative



and vergence tests were performed. Anomalies were classified as either single measure or syndromes based on the number of failed clinical signs. Accommodative anomalies (63.2%) were more frequent than refractive error (47.6%) and vergence anomalies (51.2%). Headache was the most frequent symptom. This study highlights need for optometric correction of not just refractive errors but also need to address potential accommodative or vergence issues at the time of evaluation.

Prevalence Trend of Myopia after Promoting Eye Care in Preschoolers: A Serial Survey in Taiwan before and during the Coronavirus Disease 2019 Pandemic.

Yang YC, Hsu NW, Wang CY, Shyong MP, Tsai DC.

Ophthalmology. 2022 Feb;129(2):181-190. doi: 10.1016/j.ophtha.2021.08.013. Epub 2021 Aug 21. PMID: 34425129.

This is a retrospective review reporting the prevalence/trends of myopia over 7 years after implementing a policy intervention program promoting outdoor activity in a cohort of 21,761 preschoolers in Yilan, Taiwan. The Yilan Myopia Prevention and Vision Improvement Program (YMPVIP), which began in 2014, implemented countywide eye examinations, including cycloplegic autorefractometry, annually for preschoolers 5 to 6 years of age in Yilan County, Taiwan. Care-giver surveys were also conducted to evaluate risk factors for myopia. The program promoted educational campaigns on preventative strategies of myopia, including classroom lighting and table height, avoiding prolonged near-work, and encouraging 120 minutes of outdoor activity. Of note, there was no suspension of on-site classes in Taiwan during the COVID-19 pandemic, so the program was carried out without significant disruption in 2020. Myopia was defined as  $-0.50$  spherical equivalent, measured by an autorefractor. The results show a significant downward trend in prevalence of myopia from 2014-2016, from 15.5% in 2014 to 8.5% in 2016. After 2016, the prevalence of myopia remained stable after 2016. Overall, the prevalence of myopia decreased by 5.2% from 2014-2020. There was a significant protective effect against myopia in children with a longer duration of exposure to the program. Myopia prevalence did not change significantly during the COVID pandemic. This study shows that school-based prevention program focusing on outdoor activities was effective at reducing the prevalence of myopia in younger children, and that continued exposure to these interventions may be protective against myopia.

Emmetropization during Early Childhood.

Schein Y, Yu Y, Ying GS, Binenbaum G.

Ophthalmology. 2022 Apr;129(4):461-463. doi: 10.1016/j.ophtha.2021.11.021. Epub 2021 Nov 29. PMID: 34856232.

This is a retrospective cohort study performed between 2009-2020 at Children's Hospital of Philadelphia, investigating the rate of emmetropization in early childhood. Subjects included patients who underwent a cycloplegic refraction between 6-8 months of age and again at 12-24 months of age. Subjects must have had refractive error in 1 or both eyes of greater than  $+3.50$  diopters of hyperopia,  $-2.00$  diopters of myopia, or  $+1.50$  diopters of astigmatism. 362 eyes were included. The study found that children with hyperopia or astigmatism emmetropize to a greater degree than children with myopia. The authors note that this is unique compared to previous studies that have shown no significant change in refractive error in hyperopic eyes of older children and suggests a different pattern for younger children. The authors suggest that prescribing glasses early on for children with myopia may be appropriate, as they are less likely to undergo emmetropization before 2. For hyperopia and astigmatism, the decision is less clear, as the children in this study were more likely to undergo emmetropization by age 2 to a refractive error that was not high enough to meet AAO guidelines for prescribing glasses. It may be appropriate to delay glasses and recheck refraction later in infants with hyperopia/astigmatism. We must also take into consideration, however, that there may be a benefit in prescribing glasses during the period that the child has the higher refractive error – this potential benefit was not assessed. Also, the authors did not assess if prescribing glasses after the initial visit had any effect on the rate of emmetropization.

Premyopia at Preschool Age: Population-based Evidence of Prevalence and Risk Factors from a Serial Survey in Taiwan.

Wang CY, Hsu NW, Yang YC, Chen YL, Shyong MP, Tsai DC.

Ophthalmology. 2022 Aug;129(8):880-889. doi: 10.1016/j.ophtha.2022.03.017. Epub 2022 Mar 22. PMID: 35331752.

This is an epidemiologic study reporting the prevalence of pre-myopia and risk factors for pre-myopia in a cohort of 21,761 preschoolers between 5-6 years old in Yilan, Taiwan. The subjects included children enrolled in the Yilan Myopia Prevention and Vision Improvement Program (YMPVIP) between 2014 and 2020, which implemented countywide eye examinations annually and myopia preventative strategies for preschoolers 5 to 6 years of age in Yilan County, Taiwan. Care-giver surveys were also conducted to evaluate risk factors for pre-myopia/myopia. Of note, there was no suspension of on-site classes in Taiwan during the COVID-19 pandemic, so the program was carried out without significant disruption in 2020. Pre-myopia was defined as a refractive state between -0.50 and +0.75. Cycloplegic refractions were performed by a table mounted Topcon autorefractor and was assessed with 3 consecutive readings from the autorefractor. The authors found that 52% of children in the cohort were classified as being premyopic. Significant risk factors for premyopia included male gender, caregiver myopia, and spending >1 hour per weekday on a screen. Protective factors included longer duration longer duration of time enrolled in the program for preventative strategies for myopia and college/higher education level of the caregiver. This study is limited by its lack of ethnic diversity and risk/prevalence of premyopia by be different in other ethnic groups. Given, the high rate of premyopia in their population, the authors suggest that targeted efforts to identify premyopic preschoolers and encouraging early myopia prevention strategies may be beneficial in regions with myopia epidemics.

Sports and Myopia: An Investigation on the Prevalence and Risk Factors of Myopia in Young Sports-Related Groups in Tianjin, China.

Zhang M, Sun Z, Zhu X, Zhang H, Zhu Y, Yan H.  
Invest Ophthalmol Vis Sci 2022;63(6):27.

In this cross-sectional study conducted in Tianjin, China, a cluster sampling method was used to explore the relationship between sports and the prevalence of myopia in young sports-related groups. All participants completed epidemiological questionnaires and ophthalmic examinations. Multivariable logistic regression models were used to explore the potential risk factors of myopia. The study recruited 1401 participants. The prevalence of myopia was 50.18%. The prevalence of low, moderate, and high myopia were 52.63%, 37.41%, and 9.96%, respectively. The odds of having myopia was 1.788 times higher in the indoor sports group than the outdoor sports group (the adjusted odds ratio [OR], 95% confidence interval [CI], 1.391–2.297). Training time of more than 4 h/d (4–6 h/d: OR, 0.539; 95% CI, 0.310–0.938; >6 h/d: OR, 0.466; 95% CI, 0.257–0.844) resulted in a lower risk of myopia. Participants who often used an electronic screen (OR, 1.406; 95% CI, 1.028–1.923) and/or had a family history of myopia (OR, 2.022; 95% CI, 1.480–2.763) were more likely to suffer from myopia. The authors conclude that while outdoor sports do not guarantee protection against myopia, youngsters engaged in outdoor sports had a lower prevalence of myopia than those participating in indoor sports. Electronic screen use, training time, and family history of myopia were also associated with the prevalence of myopia in young sports-related groups.

Association Between Color Vision Deficiency and Myopia in Chinese Children Over a Five-Year Period.

Gan J, Li S, Atchison DA, Kang M, Wei S, He X, et al  
Invest Ophthalmol Vis Sci. 2022;63(2):2.

This five year cohort study in China explored the relationship of color vision deficiency with myopia progression and axial elongation in Chinese primary school children. 2849 grade 1 students (aged 7.1 +/- 0.4 years) from 11 primary schools were enrolled and followed for five years. Cycloplegic autorefraction and axial length were measured annually. Color vision testing was performed using Ishihara's test and the City University color vision test. The study found that the prevalence of color vision deficiency was 1.68% (2.81% in boys and 0.16% in girls). Color-deficient cases consisted of 91.6% deutan and 8.3% protan. The cumulative incidence of myopia was 35.4% (17/48) over the five year study period in the color-vision deficiency group, which was lower than the 56.7% (1017/1794) in the color normal group (P = 0.004). The change in spherical equivalent refraction in the color vision-deficiency group (-1.81 D) was also significantly lower than that in the color normal group (-2.41 D) (P = 0.002). The authors conclude that the lower incidence and slower progression of myopia in children with color-vision deficiency over the five-year follow-up period suggest that color-deficient individuals are less susceptible to myopia onset and development.

#### 4. VISUAL IMPAIRMENT

Interference With the Work of Dog Guides in Public: A Survey

Melissa R. Allman, Kathleen Freeberg, Katy M. Evans

Journal of Visual Impairment & Blindness v116(5) pp.607-616

Dog guide handlers face the challenge of interference with their dogs' work from both people and other dogs. The Seeing Eye (a dog guide school founded in 1929) surveyed its active dog guide handlers to better understand the type and severity of interference they were experiencing and to develop strategies to better equip handlers to deal with the interference. An online survey designed to obtain information the types, frequency, and severity of interference handlers experience from people and other dogs, as well as the setting in which the interference took place, was made available to the active Seeing Eye handlers. The survey was open for one month and was sent to 1761 active Seeing Eye graduates, with a response rate of 29.5%. Eighty-nine percent of handlers had experienced people interfering with the work of their dogs at least occasionally, and 78% experienced interference from other dogs (36% of these were described as aggressive physical contact with their dogs). Interference of all types occurred mostly in public places. This survey identifies the need for a robust public awareness campaign to address the persistent problem of interference with dog guide teams. It also provides a more realistic picture of the challenges handlers may face in public, and provide guidance to better support dog guide handlers to proactively engage the public and manage interference when it occurs.

An Observational Study of Lunchroom Interactions Among Secondary Students With Visual Impairments and Their Peers

Hilary E. Travers and Erik W. Carter

Journal of Visual Impairment & Blindness v116(5) pp.699-710

For students with visual impairments, developing strong social relationships can sometimes be a challenge. Prior and recent research finds these students may find mainstream school settings socially challenging. No studies have examined the naturally occurring social interactions of adolescents with visual impairments during the unstructured context of lunch periods at school. In this study, nine middle and high school students with visual impairments were observed during multiple lunch periods (44 total observations). Three primary variables were measured: social interactions, social engagement, and proximity to others. Notes were also taken on the quality of the interaction (i.e., degree of reciprocity, appropriateness of context, affect of students and their peers, response relevance). Overall, these students sat near peers without disabilities for more than half of the lunch period. However, students interacted with another person during only one-third of lunch periods, more commonly with peers than adults. Students without an additional cognitive impairment had higher quality and more frequent interactions with peers than adults, with the opposite being true for students who had cognitive plus visual impairments. This study demonstrates that some students with visual impairments are socially engaged during the unstructured context of lunch periods, while others (those with additional cognitive impairments) have fewer or low-quality interactions with peers during lunch. This study highlights the cafeteria as a context for educators to support peer interaction and social skill development.

Creation of a National Agenda for STEM Education for Students with Visual Impairments

Tiffany Wild, Xinyue Lu, Stacy M. Kelly, Derrick W. Smith, Danene Fast

Journal of Visual Impairment & Blindness v116(5) pp.749-751

The field of visual impairment has not has the opportunity to engage its community in a common discourse around STEM (science, technology, engineering, mathematics) education or students with visual impairments. There is no focused research agenda, sources for best practices or clear directives for the immediate needs of student with visual impairments regarding STEM education. In this published Comment, the authors, along with its partners, identified existing needs by reviewing available literature and identifying gaps. Based on the reviewed literature, themes within the literature, and its findings, a National Research Agenda was created. The participants identified 12 goals for the National Research Agenda, including: Collaboration, Access to Curriculum, Skills to Succeed in STEM Education, Assessment for STEM Education, Instruction, Early learners, School-Age learners, Identity, Transition and Mentorship, Technology Exploration, Personnel Preparation, and Advocacy. A website containing this information was also developed by the project partners, <https://u.osu.edu/nationalresearchstemvisualimpairment>.

Ophthalmological Findings in Youths with a Newly Diagnosed Brain Tumor  
Myrthe A. Nuijts, MD; Inge Stegemean, PhD; Tom va Seeters, MD, PhD; et al  
JAMA Ophthalmology, October 2022; 140(10):982-993.

This is a cohort study of 170 Dutch patients aged 0 to 18 years with a newly diagnosed brain tumor, enrolled from 4 hospitals in the Netherlands. Children underwent a comprehensive ophthalmology exam within 4 weeks of brain tumor diagnosis, including an orthoptic evaluation. Visual fields were performed on all patients, which were interpreted by two ophthalmologists who were blinded to patient details. Ophthalmologic examination revealed abnormal findings in 134 of 170 patients (78.7%). At the time of diagnosis, 69 patients did not report visual symptoms. Of the patients without symptoms, 45 (65.2%) had abnormal ophthalmologic findings. The most prevalent ophthalmological abnormalities in youths at brain tumor diagnosis were papilledema (52.4%), gaze deficits (33.5%), visual field defects (28.1%), nystagmus (24.8%), strabismus (19.9%), and decreased VA (8.6%). These findings emphasize the importance of standardized ophthalmological evaluation at brain tumor diagnosis regardless of tumor location because timely detection of vision loss and subsequent early referral for visual rehabilitation therapy may be associated with improvement in regaining mobility, activities of daily living, and quality of life among youths with visual impairment.

Impact of Vision Impairment and Ocular Morbidity and Their Treatment on Depression and Anxiety in Children: A Systematic Review.

Li D, Chan VF, Virgili G, Piyasena P, Negash H, Whitestone N, O'Connor S, Xiao B, Clarke M, Cherwek DH, Singh MK, She X, Wang H, Boswell M, Prakalapakorn SG, Patnaik JL, Congdon N.  
Ophthalmology. 2022 Oct;129(10):1152-1170. doi: 10.1016/j.ophtha.2022.05.020. Epub 2022 May 31. PMID: 35660416.

This is a systemic review and meta-analysis summarizing existing evidence to establish whether vision impairment, ocular morbidity, and their treatment are associated with anxiety and depression in children. The analysis included 36 studies, 58% of which were observational studies concerning vision impairment, 22% were observational studies concerning strabismus, and 19% were interventional studies. The studies that reported scores for depression, anxiety and those that included strabismus surgery were included in a meta-analysis. The meta-analysis showed that children with vision impairment have higher depression and anxiety scores than normally sighted children. Studies in which myopia was the cause of vision impairment showed significantly higher depression scores than children with normal vision. There was no difference in anxiety scores between children with myopia and those with other causes of vision impairment. The meta-analysis also showed that strabismus surgery significantly improved symptoms of depression and anxiety. The authors note that the main limitation was the heterogeneity of the studies included. The quality of most included studies was low to moderate, as most studies did not clearly describe sampling methods, did not report the definition of vision impairment, and used various tools to measure depression and anxiety. Despite these limitations, this study does help to emphasize the mental health impact of visual impairment and importance of treatment in strabismus patients.

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Sleep Challenges and Interventions in Children With Visual Impairment.

Ingram DG, Cruz JM, Stahl ED, Carr NM, Lind LJ, Keirns CC.

*J Pediatr Ophthalmol Strabismus*. 2022;59(2):77-86. doi:10.3928/01913913-20210623-01

This cross-sectional survey of parents of children with visual impairment was offered via the National Federation of the Blind and the National Organization for Albinism and Hypopigmentation. Parents of 72 participants (1 to 16 years old) completed the survey: 52 (72%) parents reported that their children had cycles of good sleep and bad sleep, and 50 (69%) parents reported that their child's sleep patterns caused significant stress for them or their family. Scores on the Childhood Sleep Habits Questionnaire (CSHQ) increased (> 41) in 64 (89%) children, indicating a likely clinically significant sleep problem. When compared to normative data from children aged 4 to 10 years, children in the current sample scored higher (more sleep problems) on all eight subscales on the CSHQ. Comorbid developmental delay was most strongly associated with sleep problems. Supplemental melatonin and improving daytime and nighttime schedules or routines were reported as most helpful for sleep. Many families reported a need for further information regarding melatonin use as a supplement. The authors concluded that children with

visual impairment experience clinically meaningful sleep problems, regardless of degree of light perception or visual acuity, and that there was a strong need for increased awareness of and screening for sleep problems in this population.

Visual impairment in rural and migrant Chinese school-going children: prevalence, severity, correction and associations.

Ma Y, Zhang X, He F, Ma X, Yi H, Rose N, Medina A, Rozelle S, Congdon N.

Br J Ophthalmol. 2022 Feb;106(2):275-280.

This was a meta-analysis of 12 cross-sectional school-based studies of a total of 83,273 rural and urban migrant students in China aged 6–17 years. The goal was to investigate the age- and gender-stratified prevalence of visual impairment, estimate the age- and gender-specific rate of glasses ownership among children who need refractive correction, describe the unmet need for glasses among all school children, and examine the extent to which county-level income and population density can explain provincial-level variation in visual impairment and/or glasses ownership rates. Prevalence of visual impairment (uncorrected visual acuity  $\leq 6/12$  in either eye) rose from 19.0% at age 6 to 66.9% at 17, with the overall age-adjusted prevalence higher for girls (35.8%) than for boys (30.1%,  $p < 0.001$ ). The rate of glasses ownership among students who needed them increased from 13.0% at age 6 to 63.9% ( $p < 0.001$ ) at 17 and was significantly higher for girls (37.0%) than boys (34.7%,  $p < 0.001$ ). A 1% increase in per capita gross domestic product was associated with a 4.45% rise in uncorrected visual acuity ( $R^2 = 0.057$ ,  $p = 0.020$ ), indicating that wealth does not appear to be significantly related to glasses ownership rates. A 1% population density increase was associated with an increase in the glasses ownership rate of 6.83%. The unmet need for glasses as a proportion of the student population peaked in junior high school (31.8%), which the authors point out as a critical time to address visual impairment related to refractive error as this is when many rural children leave school and have less access to resources. This study highlights an important public health issue as preventable visual impairment from uncorrected refractive error can have large implications on school success for children and adolescents both in primary school and the possibility of attending university.

Visual impairment and perceptual visual disorders in children with cerebral palsy in Nigeria.

Duke RE, Nwachukwu J, Torty C, Okorie U, Kim MJ, Burton K, Gilbert C, Bowman R.

Br J Ophthalmol. 2022 Mar;106(3):427-434.

The aim of this study is to describe the full spectrum of ocular morbidity and visual impairment including perceptual visual dysfunction (PVD), which the authors define as the 'higher' visual perceptual problems or cognitive visual problems often included as part of the CVI spectrum, and their relation to other disability/comorbidity in a population based sample of children with CP in Cross River State, Nigeria. A total of 388 children with neurologist-confirmed CP and mean age of 9 years were enrolled. Visual problems were reported by caregivers in only 55 (14%) of patients, however, a wide spectrum of ocular morbidity and visual impairment was identified during formal assessment, including: binocular visual acuity impairment, abnormal visual fields, strabismus, abnormal contrast sensitivity, abnormal saccades, refractive errors, accommodative dysfunction, and optic atrophy. Perceptual visual disorders were present in 177 (46%), and the estimated frequency of cerebral visual impairment (CVI) ranged from 16% to 49% if children with optic atrophy were included. These findings confirm that children with CP have a wide spectrum of ocular morbidity and visual impairment, frequently underestimated by caregivers, and that CVI is common in this population.

Distribution and associations of vision-related quality of life and functional vision of children with visual impairment.

Robertson AO, Horvat-Gitsels LA, Cortina-Borja M, Rahi JS.

Br J Ophthalmol. 2022 Sep;106(9):1325-1330.

This study was designed to investigate the distributions and predictors of scores on the VQoL\_CYP (measuring vision-related quality of life) and FVQ\_CYP (measuring functional vision) among children age 8-18 years with visual impairment. Notably, because these instruments are intended for self-completion, not for proxy (parent or clinician) assessment, children with significant additional impairments that impacted on the ability to self-report were not eligible for inclusion in the study. 93 patients participated in the study, which comprised 48% of the total number of those invited to participate. VQoL\_CYP scores ranged from 36.6 to 78.2 (higher score = better VQoL). FVQ\_CYP scores ranged from 23.5 to 70.3

(higher score = worse VQoL). Only 0.4% of the variation in VQoL\_CYP scores was explained, with no associations with the variables of interest. By contrast, 21.6% of the variation in FVQ\_CYP scores was explained, with a gradient of worse acuity and female gender associated with worse self-rated functional vision. We know that vision-related quality of life and functional vision are not readily predicted from sociodemographic or clinical characteristics that ophthalmologists measure, so having tools such as these can offer important insights to our patients.

#### Prevalence and Factors Related to Visual Impairments in Children With Bilateral Cataract Following Surgery and the Potential Need for Education and Rehabilitation Services

Claudia Yahalom, Moria Medezinsky Kochavi, Hadas Mechoulam, Evelyne Cohen, Irene Anteby  
*Journal of Visual Impairment & Blindness* v116(1) pp61-69 2022

Pediatric cataract is a major cause for childhood visual impairment. The authors analyzed the prevalence of children with impaired vision (6/15 or worse) after surgery for bilateral cataract to evaluate factors associated with it and to emphasize the importance for visual rehabilitation including the use of visual aids, education, and social services. This retrospective study reviewed medical records from 55 children who underwent cataract surgery up to age 6 with follow-up of at least 4 years (median 6.8 years). Clinical characteristics studied included visual acuity, presence of nystagmus and/or strabismus, age at surgery, IOL implantation and others. Visual impairment was found in 62.5% of children operated on before 6 months of age and 22.5% in those operated after 6 months of age. Thirty-eight of 55 children had a primary IOL implantation. Nystagmus and microphthalmos were associated with higher rates of visual impairment. The authors conclude that despite early and modern surgery, long term visual outcomes remain poor in children undergoing bilateral cataract surgery at a young age. Discussions with parents regarding visual prognosis should recognize factors associated with visual impairment, such as need for surgery before six months, nystagmus and microphthalmos, and the importance for early visual rehabilitation services. Early referral for visual rehabilitation will optimize quality of life and may allow for a wider range of opportunities as adults.

#### Cultural Diversity in Children's Braille Books

Monique A. Coleman, Judith Harrison

*Journal of Visual Impairment & Blindness* v116(2) pp127-140 2022

Children's books help young readers develop social understanding through recognition of themselves and their worlds and exposure to different cultures and places. Prior analyses have revealed underrepresentation of culturally diverse characters in print children's books. The extent to which braille children's books reflect racial and ethnic diversity has not been investigated. This study analyzed 328 braille books from the online catalogs of Seedlings Braille Books for Children (Seedlings) and National Library Service for the Blind and Print Disabled (NLS), two major braille book publishers and asked the following research questions: 1) What percentage of published children's braille books feature nonwhite primary or secondary characters?; 2) How are culturally diverse characters and cultures represented in published children's braille books?. The study found characters of color were featured in 12 and 14% of children's braille books in the Seedlings and NLS catalogs. Culturally conscious content was found in 68% and 86% of the books with characters of color in the Seedlings and NLS catalogs respectively. The authors note that racially and ethnically diverse children who are blind or have low vision have far fewer opportunities than their white counterparts to experience braille books that represent themselves and their worlds or expose them to different worlds. The study encourages teachers of children with visual impairments to be aware of the literary and social benefits of culturally diverse books and to incorporate more of these books into literary instruction.

#### Graphics Out Loud: Perceptions and Strategic Actions of Students With Visual Impairments When Engaging With Graphics

Kim T. Zebehazy, Adam P. Wilton, Bhagyalaxmi Velugu

*Journal of Visual Impairment & Blindness* v116(2) pp183-193 2022

Facility on graphics use is critical to accessing data visualizations in science, technology, engineering, the arts, and mathematics (STEAM). Efforts to understand the cognitive processes underlying strategic action by students with visual impairments should consider both metacognition ("one's own knowledge concerning one's own cognitive processes and products or anything related to them") and self-regulated learning (student's ability "to inspect, and as they are able, strive to improve how they go about learning").

The authors utilized transcripts of a think-aloud protocol (“voluntary activity in which learners, having been asked to tackle a relevant task, talk their thoughts out loud while they are engaging in that task”) and analyzed them using a priori level one coding based on the Model of Graphic Interpretation (MoGI) followed by second level coding to analyze nuanced commonalities and differences based on performance, medium, and level. The study demonstrated differences in each component of the MoGI for print graphic and tactile graphic users. Higher performers were better able to articulate strategy use and reasons for selecting strategies. The study advocates for use of think-aloud to support assessment and instruction of students with visual impairments to build strategic action and metacognition when engaging with graphics.

#### Clinical Spectrum of Ocular and Visual Dysfunction in Children with Periventricular Leukomalacia: A Need for an Interdisciplinary Approach

Zeynep Kayaarasi Ozturker, Sezin Akca Bayar, Sibel Oto, Sibel Aksoy, Imren Akkoyun, Taner Sezer  
*Journal of Pediatric Neurology* 2022; 20:97-102

This retrospective study evaluated the ocular motility and visual and optic disc abnormalities on children diagnosed with periventricular leukomalacia (PVL). Analysis of 51 consecutive children under 12 years old between 2008 and 2020 who had ophthalmic symptoms and were diagnosed with PVL by MRI was performed. The children were assessed for visual function, strabismus, cycloplegic refraction, fundus exam, and if appropriate, spectral domain OCT and visual field testing. Primary outcome measures were the prevalence and visual and ocular motility dysfunctions. Mean age was 5.72 years, median birth weight was 2740 grams, and median gestational age was 34 weeks. Twenty-one patients (39.6%) had neurological deficit, 11 (21.5%) had intellectual disability, and 19 (37.2%) had no neurological symptoms. Manifest strabismus was present in 35 patients (68.6%; 12 had esotropia, 16 had exotropia, 6 had vertical deviation). Manifest or latent nystagmus was detected in 14 patients (27.4%). Twenty-eight patients had optic nerve abnormality (54.9%; 2 had hypoplastic disc, 14 had optic disc pallor, 7 had large cupping, 5 had total optic atrophy. Ten patients had  $\geq 3.0D$  myopia, 15 had  $\geq 3.0D$  hyperopia, and 8 had  $\geq 2.5D$  astigmatism. Thirteen (25.4%) children had best-corrected vision (Snellen card) between 20/40 and 20/20, 9 (17.6%) had strabismic amblyopia and 6 (11.7%) had anisometropic amblyopia. Subjects able to perform visual field testing (6/51) all had abnormal visual fields with inferior fields being most affected. The authors conclude that 1) children born with PVL are at high risk for developing CVI; 2) strabismus, nystagmus, optic nerve abnormalities, and visual disturbances are the common clinical features of PVL and may sometimes be the only presenting sign; 3) routine ophthalmological screening should be beneficial for children with PVL.

#### The visual consequences of virtual school: acute eye symptoms in healthy children

Hamburger, Jordan L. et al.

*Journal of American Association for Pediatric Ophthalmology and Strabismus {JAAPOS}*, Volume 26, Issue 1, 2.e1 - 2.e5

110 healthy children aged 10 to 17 years enrolled in full-time or hybrid virtual school were assessed with a convergence insufficiency symptom survey (CISS) and asthenopia survey before and after a virtual school session. The average sum of the CISS scores increased from 5.17 before school to 9.82 after ( $P < 0.001$ ), with 61% of children recording an increase in convergence insufficiency symptoms and 17% experiencing severe convergence insufficiency symptoms after school. Average asthenopia symptom scores increased from 1.58 to 2.74 ( $P < 0.001$ ), with 53% of children recording an increase in asthenopia symptoms. Significant increases were seen in 12 of 15 CISS questions and in 4 of 5 asthenopia questions. The study suggests online schooling may contribute to acute ocular symptoms in children.

#### The Impact of Visual Impairment on Completion of Cognitive Screening Assessments: A Post-Hoc Analysis from the IVIS Study.

Bould J, Hepworth L, Howard C, Currie J, Rowe F.

*Br J Orthopt J.* 2022 Jun 30;18(1):65-75.

In this study, 1500 stroke admissions were evaluated for visual impairment to explore whether the presence of visual impairment impacts on completion of cognitive screening. Data from visual function assessments (inclusive of visual acuity, visual fields, eye movements and visual perception evaluation)

were analysed to determine whether presence and/or type of visual impairment impacted on cognitive screening scores achieved. Those who reported visual symptoms performed worse statistically on all cognitive tasks except the recall recognition ( $p = 0.232$ ) and executive tasks ( $p = 0.967$ ). Visual symptoms did not prevent participants from completing every section of the OCS ( $p = 0.095$ ). In certain tasks, those not wearing their required glasses performed worse, including the executive function ( $p = 0.012$ ), broken hearts and sentence reading tasks. The results of this study raises awareness that visual needs to be adequately met (ie. Glasses, larger font, etc) when having patients complete cognitive screening assessments following a stroke.



## 5. NEURO-OPHTHALMOLOGY

The visual morbidity of optic nerve head drusen: a longitudinal review

Gise R, Heidary G

J AAPOS 2023;27:30.e1-5

A retrospective review of medical records of pediatric patients diagnosed with optic nerve head drusen (ONHD) at a single, tertiary care ophthalmology department from January 1, 2010 to July, 1 2018 was conducted for causes of visual morbidity. A total of 213 patients met inclusion criteria. Mean age at diagnosis was 10.13 years, and mean follow-up was 2.76 years. Formal visual fields were available for 208 eyes. Repeatable visual field defects were noted in 24 eyes (11.5%). The most common defect was a nasal step, which occurred in 11 eyes (45.8%). Fifteen eyes had visual field defects at presentation, and 9 eyes developed field loss within 1.39 years of diagnosis. There was no correlation found between intraocular pressure and degree of visual field loss. Choroidal neovascular membranes (CNVM) were clinically apparent in 5 eyes and treatment was required in 3 eyes. Nonarteritic ischemic optic neuropathy developed in 2 eyes. The limitation of the study is that each patient was not followed in the same manner. It is important to note patients with ONHD may be associated with visual morbidity and follow up is warranted to counsel patients and to monitor for treatable disease such as CNVM.

Peripapillary hyperreflective ovoid masslike structures in a pediatric population referred for suspected papilledema.

Elizabeth L. Eshun, BS, J. Cole Gwin, BS, and Lauren C. Ditta, MD.

JAAPOS 2022;26:242.e1-6.

Peripapillary hyperreflective ovoid masslike structures (PHOMS) are an OCT-specific imaging finding (distinct from drusen) that have gained attention as our imaging technology has improved. They have now been shown to be present in several ophthalmic conditions, and their presence causes both elevation and blurring of the disk margin. As this can lead to the appearance of optic nerve swelling, PHOMS may complicate the distinction between papilledema and pseudopapilledema. This study aimed to generate a descriptive analysis of pediatric patients with PHOMS. Forty-seven patients with PHOMS were included in the study, the majority of whom were referred for suspected papilledema. PHOMS were noted to be bilateral and circumferential in nature giving the optic nerve an anomalous appearance. Patients with PHOMS and papilledema had thicker average RNFL compared to patients with drusen or PHOMS alone. In patients with papilledema, there was a statistically significant reduction in the size of PHOMS at follow-up compared to patients who did not have papilledema. This is an important study that adds to recent literature on PHOMS. It provides useful information to help with the differentiation between papilledema and pseudopapilledema. The main limitation of the study is its retrospective/observational nature, so not all patients at the same work-up or length of follow-up.

Bilateral Posterior Cerebral Artery Stroke from COVID-related Multisystem Inflammatory Syndrome in a Child

Wilkinson S, Etheridge T, Swiston C, Vegunta S, Wiggins R, Warner J

J Neuroophthalmol. 2022;42(3):e548-e550.

Multisystem Inflammatory Syndrome in Children (MIS-C) can be caused by COVID-19 and has been associated with numerous thrombotic events. Here, the authors present the first reported case of bilateral posterior cerebral artery (PCA) strokes in a child not on ECMO. Their patient, a 12-year-old girl, presented with fever and abdominal pain prior to acutely decompensating, requiring intubation, sedation, and pressor support. Following an ICU stay and medical management, the patient was discharged on hospital day eight.

In the days following discharge, the patient's parents noted that she was having some difficulty with peripheral vision, so they returned to the hospital. There, visual acuity was noted to be 20/20 OU. The anterior and posterior exams were normal; however, an automated visual field test showed dense, bilateral superior field defects. Subsequent MRA revealed evidence of bilateral PCA strokes. This serves as a reminder that COVID-19 MIS-C is a pro-thrombotic condition that can result in strokes affecting the visual system.

Rare Cause and Manifestation of Horner Syndrome in an Infant

Yin G, Gurney S, Reginald A, Putra J, Wan M

[published online ahead of print January 27, 2023]. *J Neuroophthalmol*.

A 6-day old infant was transferred to a children's hospital for gradually worsening stridor after a relatively uneventful birth. Evaluation by ENT at the children's hospital revealed severe laryngomalacia, and surgical correction was scheduled. Prior to this, the infant was noted to have right-sided ptosis, as well a right-sided miosis (right pupil was smaller in diameter than the left pupil). A cocaine test led to an increase in anisocoria, indicating a potential Horner syndrome. MRI of the head, neck, and chest was then performed, revealing a mass encasing the right carotid artery and exerting a mass effect on the trachea. A biopsy led to a diagnosis of infantile myofibroma, and subsequent treatment resulted in diminished mass size and improved symptoms.

This case serves as a reminder that infantile Horner syndrome necessitates imaging of the head, neck, and chest, as it can be caused by masses along the sympathetic chain, including – in rare instances – myofibromas. Imaging is especially prudent when other worrisome symptoms, such as respiratory distress, are present.

Additionally, the authors report an interesting finding: the ptosis in this patient would transiently resolve, and the anisocoria would temporarily reverse, for a short time each time the patient vomited. Though it is unclear exactly why, the authors present a reasonable hypothesis revolving around the denervation supersensitivity of the Horner pupil and lid. Regardless of the underlying physiology, unusual cases of ptosis and pupillary abnormalities in an infant likely warrants further investigation.

#### Sharp Edge Eye Syndrome: A Case Report and Survey of Self-Identified Individuals

Reynolds M, Katz B, Digre K, Brintz B, Olson L, Warner J

*J Neuroophthalmol*. 2022;42(4):524-529.

Sharp edge eye syndrome (SEES) is a rarely reported condition – indeed, the authors claim to find no other academic reports it – in which “the sufferer experiences ocular pain or discomfort when viewing or mentally imagining a sharp object or edge.” Interestingly, the authors start with a case report wherein the patient is actually the first author of this study. The author/patient describes both physical discomfort (a “sinus ache”) and psychological discomfort upon the viewing or imagining of sharp objects (cutlery, branches, table corners, etc.) that has been present since childhood. Once initiated, the discomfort/pain can last for seconds to hours.

Inspired by this description, the authors then created a survey that was made available on social media pages dedicated to SEES and invited participants in these forums to complete said survey. A total of 77 people completed the survey over a 2-week collection span.

The mean age of respondents was 29 years old, though – importantly for this audience – 92% reported the onset of symptoms in childhood, with a mean age of onset of 10 years old. All reported discomfort from viewing sharp edges or objects, with furniture corners (78%), pencils/pens (68%), and knives (62%) being the most commonly reported triggers. Additional information regarding accompanying symptoms, duration of discomfort, and exacerbating/alleviating factors is provided. Interestingly, 58% of those surveyed reported having generalized anxiety, 57% reported depression, 26% reported migraines, 28% reported Alice in Wonderland Syndrome, and 27% reported visual snow.

The authors conclude by proposing diagnostic criteria for this syndrome and call for further studies into pathophysiology and management. At present, it seems as if the most applicable result of this study would be to screen patients describing SEES for co-morbid psychiatric and neurologic conditions (e.g. anxiety, depression, migraine) and to reassure them that there is no underlying ocular issue.

#### Posterior Reversible Encephalopathy Syndrome With Visual Disturbance In An Adolescent After Overdose With Adderall-XR: A Case Report

Linton E, Pak T, Halhouli O, Field M, Gunderson C, Chung S

[published online ahead of print, 2022 Oct 3]. *J Neuroophthalmol*.

An increasingly common medication in the pediatric population, Adderall (dextroamphetamine/amphetamine) can result in a sympathomimetic toxidrome when taken in excess. Here, the authors report the case of a 14-year-old girl who presented with tachycardia and hypertension following purposeful overdose with Adderall. Six hours after ingestion, the patient reported complete vision loss. An ophthalmologic examination showed NLP vision in both eyes, bilateral mydriasis, and a structurally normal eye exam. There was no visible response to bright light or the OKN drum.

MRI of the head showed multifocal FLAIR hyperintensities throughout the occipital, parietal, and frontal cortices, typical of PRES. The patient recovered her normal 20/20 visual acuity within 48 hours. PRES is a syndrome characterized by development of acute neurologic abnormalities secondary to cerebral endothelial injury and disruption of cerebral autoregulation. When it affects the occipital lobe, it can cause severe bilateral vision impairment. In patients with vision changes, headaches, and/or focal neurologic deficits with the right clinical history, PRES should be considered in the differential of acute vision loss.

#### Intracranial Hypertension Following COVID Vaccination in a Teenager: Case Report and Review of Literature

Jiang Y, Huang J, Shah P, Francis I

[published online ahead of print, 2022 Oct 18]. *J Neuroophthalmol*.

Numerous neurologic and ophthalmologic consequences of both COVID-19 and the COVID-19 vaccination have been reported. Here, the authors describe the case of a 15-year-old girl who developed severe headaches and photophobia two weeks after receiving a dose of the Pfizer COVID-19 vaccination. Her headaches resolved without reported intervention; however, 2 weeks after the headache, she was seen for blurred vision and found to have severe optic disc edema in both eyes, as well as bilateral abduction deficits. MRI was unremarkable, and the opening pressure on her LP was 31. She patient was started on oral acetazolamide and rapidly improved.

Given the onset of headaches with papilledema 2-4 weeks after vaccination, the authors posit that this may be a case of pseudotumor cerebri (PTC) secondary to COVID-19 vaccination. Of note, however, the patient also had a history of iron-deficient anemia (treated with iron supplementation), was using a Vitamin-A derived cream for acne treatment, and had a BMI of 26. Though the temporal relationship is suggestive, it is possible that this young woman, with other known risk factors for PTC, simply developed elevated intracranial pressure for reasons unrelated to vaccination. Nonetheless, it is interesting to contemplate the potential of vaccine- or immune-mediated etiology.

#### Leber Hereditary Optic Neuropathy With Childhood Onset Producing Severe Unilateral Optic Neuropathy With No Relative Afferent Pupillary Defect

Kisilevsky E, Donaldson L, Margolin E

[published online ahead of print, 2022 Jul 8]. *J Neuroophthalmol*.

Leber Hereditary Optic Neuropathy (LHON) is heritable optic neuropathy that typically presents in young men. The authors here describe the case of a 54-year-old man who presented with a long-standing history of unexplained, unilateral vision loss in the right eye as a young child. Exam revealed a pale optic nerve in the affected eye, significant RNFL and GCL thinning, and – interestingly – no relative afferent pupillary defect. The left eye was normal. Extensive work-up was performed and was positive for m.11778G>A mutation, indicative of LHON.

This case is of interest for a couple reasons. First, it represents a childhood onset of LHON that left the fellow eye unaffected for decades. Second, despite significant optic neuropathy, no RAPD was present. The authors suggest that lack of an RAPD despite severe optic neuropathy may be unique to LHON. Additionally, the discussion provides useful information concerning childhood-onset LHON; namely, it is more likely to have an insidious, slow onset (as compared to the classically described acute vision loss) and is more likely to show spontaneous improvement or recovery. These are useful characteristics to keep in mind when confronted with unusual cases of vision loss in children, especially ones in which an anticipated RAPD is not present.

#### McCune-Albright Syndrome: Vision Loss and Strabismus as Initial Symptoms in a Child

Korkmaz I, Demirkilinc Biler E, Simsek D, Palamar M

[published online ahead of print January 27, 2023]. *J Neuroophthalmol*.

McCune-Albright syndrome (MAS) is a rare disorder characterized by fibrous dysplasia (the invasion of normal bone by abnormal fibrous tissue), skin pigmentation, and endocrine abnormalities. These patients can, rarely, present with ophthalmologic abnormalities. In this paper, the case of a 9-year-old boy who presented with decreased vision in the left eye, as well as a left sensory exotropia, is discussed. Exam revealed a central scotoma with significant optic nerve pallor in the left eye. Subsequent MRI showed an expansive bony lesion of the left orbital bones that had resulted in narrowing of the left optic canal and

axial displacement of the left globe. The patient was then referred to endocrinology clinic, where a diagnosis of MAS was made, and therapy was started.

The authors point out that about 30% of patients with fibrous dysplasia have ocular symptoms, albeit typically not as the presenting symptoms. As the pediatric ophthalmologist, it is good to have an awareness of this syndrome in case such a rare case ever presents in clinic.

#### Binocular Horizontal Diplopia Following mRNA-1273 Vaccine

Mahgerefteh J, Oppenheimer A, Kay M

[published online ahead of print, 2022 Apr 27]. *J Neuroophthalmol*.

Abducens nerve palsies have been reported following COVID-19 infections but have not been as frequently reported following vaccinations for COVID-19. Here, the authors describe a 45-year-old woman who developed horizontal diplopia 4 days after receiving her first dose of the mRNA-1273 vaccine (Moderna). Her exam showed bilateral abduction deficits with an 18 prism diopter esotropia in primary gaze. Subsequent MRI revealed bilateral enhancement of the proximal cisternal segment of the sixth cranial nerve. The patient had improved substantially, without intervention, at the 2 month follow up appointment.

Given lack of other comorbidities, the temporal relationship to vaccination, and enhancement seen on MRI, the authors logically conclude that vaccine-induced, immune-mediated inflammation of the cranial nerves is the most likely culprit. Although difficult to prove with certainty, it is useful to know that such side effects are possible with vaccination and, perhaps more importantly, that they seem to resolve without intervention.

#### Ocular Motor Nerve Palsy After Traumatic Brain Injury: A Claims Database Study

Hwan H, Lambert S

[published online ahead of print, 2022 Jun 14]. *J Neuroophthalmol*.

Trauma – specifically, traumatic brain injury (TBI) – is one of the more common causes of acquired cranial nerve palsies. In this study, the authors aim investigate the incidence and characteristics of ocular motor nerve palsies following TBI.

To do this, the authors performed a population-based retrospective cohort study using claims data from the IBM MarketScan Research Databases (2007–2016), a database that includes health insurance claims of more than 240 million patients insured by 350 unique health carriers. Patients with new ocular motor palsy (determined by ICD codes) within 3 months after the diagnosis of TBI were included. Demographic, diagnostic, and surgical data was collected. A total of 8,713,134,185 claims for 123,637,719 patients were analyzed. Of the 1.35 million children (<18 years old) with TBI, 454 (0.026%) had ocular motor nerve palsy. Of the 1.26 million adults who had TBI, 1,397 (0.111%) had ocular motor nerve palsy. Among children, CN6 palsy was the most common (44.7%), followed by CN4 (32.8%) and CN3 palsy (20.0%). Meanwhile, CN4 palsy was the most common among adults (39.2%), followed by CN6 (33.9%) and CN3 palsy (25.2%). More children (16.5%) underwent strabismus surgeries than adults (11.6%). The median time-to-surgery following TBI (if surgery was performed) was 5 months in children and 7 months in adults. Of those with mild TBI, 7.2% underwent strabismus surgery, while 13.6% of those with moderate-to-severe TBI had surgery.

CN4 palsy (52.3%) was more frequent while CN3 palsy (15.5%) was less frequent in patients with mild TBI compared to patients with moderate-to-severe TBI. The authors acknowledge that claims data is far from comprehensive and lacks a significant amount of clinical data. Additionally, unilateral and bilateral cases could not be distinguished (laterality is not included in the ICD9 codes), and only patients under 65 years old are included in the MarketScan database.

Nonetheless, this study is valuable in that it provides us a high-level picture of strabismus following TBI in the US, which in turns provides us with information we can use to inform our patients and our practices.

#### Clinical and Genetic Profile of Leber's Hereditary Optic Neuropathy in a Cohort of Patients From a Tertiary Eye Care Center.

Bhate M, Kulkarni S, Nalawade R, Pujar A.

*J Pediatr Ophthalmol Strabismus*. 2022;59(5):344-349. doi:10.3928/01913913-20220124-02

This single-center retrospective chart review sought to describe the clinical profile at presentation of 55 Indian male patients aged  $23.80 \pm 9.90$  years with LHON of primary and secondary mutations, and describe their treatment outcomes. More than half of the patients ( $n = 32$ ; 58.2%) presented with severe to profound vision impairment in the better eye and 72.7% ( $n = 40$ ) in the worse eye. Bilateral temporal disc pallor was more frequent in 38.2% ( $n = 21$ ) and 36.4% ( $n = 20$ ) had bilateral optic atrophy. Primary single mutations were detected in 61.81% ( $n = 34$ ) and secondary mutations were detected in 38.2% ( $n = 21$ ). The most common mutation was G11778A. One novel secondary mutation (A13615C) was identified in the cohort. Idebenone was used for treatment in 15 patients, and half of them ( $n = 8$ ) showed an improvement in vision at 2 to 7 months of follow-up. This was a notable contribution to the literature of LHON, though generalizability is limited.

#### Characteristics and Outcomes of Idiopathic and Non-idiopathic Ocular Motor Apraxia in Children.

Chang MY, Grosrenaud P, Borchert MS.

J Pediatr Ophthalmol Strabismus. 2022;59(5):326-331. doi:10.3928/01913913-20220106-01

This retrospective chart review sought to compare the presentation of idiopathic vs non-idiopathic ocular motor apraxia in 37 children seen at a single institution over a 10-year period. Among patients with non-idiopathic OMA, Joubert syndrome was the most frequent underlying diagnosis (30%). Strabismus (45% vs 12%,  $P = .04$ ), nystagmus (30% vs 0%,  $P = .02$ ), and vertical saccade involvement (25% vs 0%,  $P = .049$ ) were significantly more common in non-idiopathic than idiopathic OMA, respectively. Neuroimaging abnormalities (90% vs 18%,  $P < .0001$ ) and developmental delays (100% vs 59%,  $P = .002$ ) were also more frequent in non-idiopathic than idiopathic OMA, respectively. Endocrine disorders (most commonly growth hormone deficiency) were diagnosed in 12% and 20% of children with idiopathic and non-idiopathic OMA, respectively ( $P = .67$ ). On survival curve analysis, improvement in OMA occurred faster and more frequently in children with idiopathic than non-idiopathic OMA (median time to improvement 56 vs 139 months, respectively,  $P = .034$ ). The authors concluded that non-idiopathic OMA is associated with a higher rate of vertical saccade involvement, nystagmus, and developmental delays. Interestingly, they advocate for prompt neuroimaging in children with OMA, but only 47% of patients in their study with idiopathic OMA underwent neuroimaging. The main limitation was that this was a retrospective study.

#### Visual outcomes in idiopathic intracranial hypertension in children.

Chiu HH, Reginald YA, Moharir M, Wan MJ.

Can J Ophthalmol. Dec 2022;57(6):376-380. doi:10.1016/j.jcjo.2021.06.009

This is a retrospective cohort study of consecutive children who met the diagnostic criteria for IIH between 2009 and 2020. The goal is to report the visual outcomes. One hundred ten patients were included. Patients were divided into three groups by age. *Prolonged papilledema* was defined as papilledema greater than 12 months while on treatment. Recurrence was defined as signs or symptoms of elevated ICP that required re-initiation of treatment. The primary outcome measure was long-term visual outcomes – mild was defined as 20/40-20/80, and severe as 20/100 or worse. Mild visual field loss as -3 to -7 dB on 24-2 and severe  $\leq 7$  dB. Only children with a detailed visual exam after completion of treatment with resolution of papilledema. Younger patients were less likely to present with headaches and more likely to present with no symptoms of high ICP (both significant). The BMI was normal in children, high-normal in early adolescents, and in the obesity range in later adolescents. Visual outcomes were available for 90 patients. 91% retained normal vision, while the rest had mild visual impairment. OCT data were available for 62 patients; however, the difference between OCT at presentation and after the resolution of papilledema was not statistically significant. The only risk factor for long-term visual impairment was greater severity of papilledema at presentation.

#### Oral fluorescein angiography for the diagnosis of papilledema versus pseudopapilledema in children.

Elhousseiny AM, Fong JW, Hsu C, Grigorian F, Grigorian AP, Soliman MK, Sallam AB, Uwaydat SH, Phillips PH.

American Journal of Ophthalmology. 2023 Jan 1;245:8-13.

Pediatric ophthalmologists are often faced with the conundrum of distinguishing true papilledema from pseudopapilledema. Many examination and diagnostic techniques have been described to attempt to differentiate these conditions. The goal of this retrospective study was to determine the utility of oral fluorescein angiography (FA) in differentiating between these two conditions. The authors included 90 eyes of 45 patients (11 patients with papilledema and 34 with pseudopapilledema) and had two masked

specialists interpret oral FA images as either leakage, no leakage, or borderline leakage. They used this data to determine the sensitivity, specificity, and accuracy of oral FA for distinguishing true papilledema. Overall, they found that there was a high level of inter-grader agreement, but that each grader had an accuracy of only 62% or 69%. Sensitivity was 82% and specificity was 56-65%. While oral FA is appealing due to its relative safety as well as the ability to perform without intravenous access, this study ultimately demonstrates the limitations of diagnosing papilledema based on optic nerve leakage on oral FA. The authors suggest that this diagnostic may be a helpful tool, but ultimately should not be relied upon to definitely differentiate between papilledema and pseudopapilledema.

Low probability of myasthenia Gravis in patients presenting to neuro-ophthalmology clinic for evaluation of isolated ptosis.

Donaldson L, Issa M, Dezard V, Margolin E.  
Eur J Ophthalmol. 2023 Jan;33(1):524-529.

Potential causes of acquired ptosis include third nerve palsy, Horner syndrome, and myasthenia gravis. The authors conducted a retrospective chart review of sixty patients referred to a tertiary neuro-ophthalmology practice with ptosis. Twenty eight (47%) patients had ptosis along with various abnormalities of ocular motility and/or alignment, and 32 (53%) had isolated unilateral ptosis defined as ptosis with absence of diplopia or symptoms of generalized MG (GMG). The causes for ptosis included aponeurotic ptosis due to levator palpebrae dehiscence in the majority (73%) of patients, while 10 (17%) were diagnosed with MG (6 with Ocular MG, 4 with GMG). Diplopia was present in 9/10 patients with MG and 8/10 had abnormal ocular findings on clinical examination such as orbicularis oculi weakness, Cogan's lid twitch or fatigability of ptosis on sustained upgaze. Only one patient referred for isolated unilateral ptosis was diagnosed with OMG and this patient had orbicularis oculi weakness. None of the patients with isolated unilateral ptosis and otherwise normal examination had MG. All patients eventually diagnosed with MG had diplopia or orbicularis weakness on examination. Thus, the yield of investigating patients with isolated ptosis for MG is exceedingly low.

Measurement of Saccade Parameters in Relation to Adaptation to Homonymous Hemianopia.

Howard C, Knox P, Griffiths H, Rowe F.

Br J Orthopt J. 2022 Sep 28;18(1):130-143. doi: 10.22599/bioj.272. PMID: 36247823; PMCID: PMC9524296.

This was a prospective observational case cohort study on adult stroke survivors with new onset homonymous hemianopia. The primary aim of the overall research study was to investigate the factors important for adaptation to post-stroke homonymous hemianopia. 14 of 144 qualified for the study given their ability to visualize targets on the hemianopic side. A saccadometer which uses infrared oculography measured binocular eye movements in the horizontal plane. In 9 of the 14 participants, at four weeks post-stroke, mean ( $\pm$ SD) saccade latency was significantly longer to the hemianopic ( $328.4 \pm 105.9$  ms) compared to the non-hemianopic side ( $234.7 \pm 53.6$  ms;  $t = 4.2$ ,  $df = 8$ ,  $p = 0.003$ ). The number of correct saccadic responses out of 50 was significantly lower to the hemianopic side ( $36.6 \pm 14.1$ ) in comparison to the non-hemianopic side ( $44.4 \pm 7.5$ ;  $t = -3.1$ ,  $df = 8$ ,  $p = 0.014$ ). In two participants studied over an eight-week time period, saccadic differences to the hemianopic side persisted despite apparent recovery of visual field. Study concluded that in those participants that were measurable, there were statistically significant differences in saccade parameters between hemianopic and non-hemianopic sides that persisted post-visual recovery. Limitation of this study was that the majority of patients did not qualify as they could not visualize the target.

A Comparison of the Incidence and Type of Ocular Motility Defects in Patients Presenting to Birmingham Midland Eye Centre Emergency Department during 2019 and 2020 to Assess the Impact of the Covid-19 Pandemic.

Edwards J, Russo E, Auld R.

Br J Orthopt J. 2022 Sep 20;18(1):121-129. doi: 10.22599/bioj.258. PMID: 36212513; PMCID: PMC9503892.

During 2019 and 2020, medical records reviewed for all patients presenting to the Birmingham Midland Eye Center. 221 in 2019 and 260 in 2020 were identified as having an ocular motility defect. In 2019 and 2020, most were of neurogenic etiology, 185 and 222, respectively. The least common etiology was myogenic. A large proportion of the patients who presented to BMEC ED with neurogenic ocular motility

defects had pre-existing conditions; 68.6% in 2019, and 69.8% in 2020. The most common pre-existing condition in all patients was hypertension. No clear association was detected with COVID-19 and slight increase in incidence of ocular motility defects.

Comparative analysis of immunosuppressive therapies for myelin oligodendrocyte glycoprotein antibody-associated optic neuritis: a cohort study.

Xie L, Zhou H, Song H, Sun M, Yang M, Lai YM, Xu Q, Wei S.

Br J Ophthalmol. 2022 Nov;106(11):1587-1595. doi: 10.1136/bjophthalmol-2020-318769.

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a newly recognized auto-antibody-mediated CNS inflammatory disorder, distinct from multiple sclerosis and aquaporin-4 antibody NMO spectrum disorder. There are no standardized attack-prevention regimens, so the authors sought to evaluate the therapeutic action of different immunosuppressants in a bidirectional cohort of 121 patients with MOG optic neuritis. Immunosuppressive therapy (IST) was defined as taking at least one of the following: low-dosage prednisone, azathioprine (AZA), mycophenolate mofetil (MMF), rituximab (RTX) infusion or regular intravenous immunoglobulins (IVIG). About half the cohort were women, and mean age was 17.5 years with median disease duration 34.8 months. Among the 61 children < age 18, 39% received IST at some point. The median age in the adult group was 31 years, and while there was no significant difference in number of relapses between the 2 groups, more adults were prescribed IST (38 vs 24). Pediatric patients were more commonly treated with rituximab, while adult patients were more likely to be treated with mycophenolate mofetil. Patients with IST for at least 6 months were associated with a lower risk of relapse both in the pediatric and adult group. Notably, however, only 46.0% of patients in the no-IST group suffered a relapse attack at a median follow-up of 33.5 months, so the authors suggest that observation after a single attack remains a rational option.

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Visual Outcomes of Optic Pathway Glioma Treated With Chemotherapy in Neurofibromatosis Type 1.

José P, Couceiro R, Passos J, Jorge Teixeira F.

J Pediatr Ophthalmol Strabismus. 2022;59(2):128-135. doi:10.3928/01913913-20210720-02

This two-center retrospective cohort study of 58 children with NF1-associated OPG sought to analyze visual outcomes following chemotherapy w/ vincristine and carboplatin (2003-2016) and/or vinblastine (2017 onwards). Of the 58 children, 24 (41%) received chemotherapy. The median age at diagnosis was 3 years, and 61% of the children were female. From the first visit to the last follow-up visit, there was a statistically significant difference in mean BCVA in eyes in the no treatment group ( $P = .034$ ) but not in eyes in the chemotherapy group ( $P = .824$ ). A moderate and weak positive correlation was found ( $r = 0.58$  and  $r = 0.29$ , respectively). At the last follow-up visit, BCVA remained stable in 73% and improved in 27% of eyes in the no treatment group, and BCVA worsened in 25%, remained stable in 62%, and improved in 13% of eyes in the chemotherapy group. At the last follow-up visit, BCVA and Dodge stage had a weak negative correlation ( $r = -0.06$  and  $r = -0.17$ , respectively). A negative moderate correlation was identified between RNFL thickness and BCVA at the last follow-up visit ( $r = -0.48$  in the no treatment group and  $r = -0.46$  in the chemotherapy group). The authors concluded that children treated with chemotherapy had worse BCVA, although the treatment arrested the decline or improved BCVA in 75% of patients with no major side effects. The authors concede a number of limitations, including: retrospective design, lack of baseline ophthalmic data on some patients, and non-randomized intervention. For these reasons, the results lack generalizability and would benefit from further validation.

Electroencephalography Study of Frontal Lobe Evoked by Dynamic Random-Dot Stereogram. Invest Ophthalmol Vis Sci. 2022 May 2;63(5):7. doi: 10.1167/iovs.63.5.7. PMID: 35522304; PMCID: PMC9078048.

Li Y, Shen L, Sun M.

Stereopsis is an advanced binocular vision function based on binocular simultaneous perception and fusion. The primary visual cortex (V1) neurons participate in the early processing of binocular disparity and then send axons to extrastriate areas (V2 and V3). Then, the visual pathway separates the ventral and the dorsal streams. The classic theory indicates that the dorsal visual pathway runs from the occipital lobe to the parietal lobe and processes motor and spatial information and rough depth perception. Frontal lobes are reciprocally connected with temporal, parietal, and occipital lobes. This study investigated the frontal lobe's cortical electrical activity and electroencephalography (EEG) features evoked by dynamic

random dot stereogram (DRDS) and the functional connectivity between the frontal lobe and occipital lobe when processing 3D perception based on the binocular disparity. 14 healthy young adults (7 male and 7 female participants, aged 20–25 years) took part in the study. The activities of theta-waves and alpha-waves in the frontal lobe were significantly increased when the subjects obtained stereopsis evoked by the binocular disparity above the threshold. Although there were differences in the changes of the maximum powers among the interesting channels, there was no difference between mostly frontal and occipital electrodes analyzed by the multiple comparisons test. The increasing activity of the theta-waves in the frontal lobe was correlated with the occipital lobe activity. These findings indicate that the frontal lobe participates in the process of recognition of 3D shapes. The authors concluded that Theta-waves in the frontal lobe might be crucial in stereo vision.

Use of sweep visual evoked potential in preverbal children with optic nerve hypoplasia.

Bradfield YS, Ver Hoeve JN, Aul B, Struck MC.

J AAPOS. 2022 Jun;26(3):131.e1-131.e6.

Optic nerve hypoplasia (ONH) is one of the leading causes of childhood blindness in developed countries. Final recognition acuities vary widely. The authors sought to evaluate sweep VEP (sVEP) in preverbal children with ONH to assess correlation between sVEP, optic nerve appearance, neurologic status and future recognition acuity with retrospective review of 57 patients. The authors state that the ability to predict final vision in children with ONH may help facilitate early intervention and low vision services. The authors found that children with milder degrees of ONH without neurologic abnormalities had better final vision and patients with severe ONH and neurologic diagnoses had worse vision outcomes. Limitations of this study include retrospective nature and sample size. There are some inherent associations with ONH that complicate the predication of visual acuity prognosis which the authors review. Some experts propose that optic nerve myelination may continue for several years after birth. An early sVEP may underestimate visual prognosis. Hypothyroidism may negatively influence visual improvement and patients in this study did not all have thyroid testing. Children with ONH may have associated foveal hypoplasia. Patients in this study did not have macular OCT imaging. Autism, neurologic abnormalities, and brain based visual impairment may have negatively affected obtaining accurate recognition acuities which may subsequently negatively affect the findings. This study is important to pediatric ophthalmologists in supporting that we may be getting closer to having evidence to help provide prognosis of final visual acuity in patients with ONH but that it is still more complicated that we would like it to be.

Clinical predictive factors for diagnosis of MOG-IgG and AQP4-IgG related pediatric optic neuritis: a Chinese cohort study.

Yang M, Wu Y, Lai M, Song H, Li H, Sun M, Xie L, Zhou H, Xu Q, Wei S, Wu W.

Br J Ophthalmol. 2022 Feb;106(2):262-266.

This was a single-center retrospective cohort study of all patients age <18 years with their first acute optic neuritis (ON) attack. Because pediatric optic neuritis often presents differently from the adult form, the aim of our study was to identify some clinical factors through a systematic testing of MOG-IgG and AQP4-IgG in the cohort to predict the subtype of ON for use in making accurate diagnoses irrespective of glial autoantibody detection. 69 patients were included in the analysis, with 48% categorized as MOG-ON, 25% AQP4-ON, and the remaining 27% seronegative. For predicting pediatric MOG-ON, the most sensitive predictors were 'male or optic disc swelling or bilateral' (sensitivity 0.97 (95% CI 0.82 to 1.00)) and 'follow-up visual acuity (VA) ≤ 0.1 logMAR or optic disc swelling' (sensitivity 0.97 (95% CI 0.82 to 1.00)), and the most specific factor was 'Age ≤ 11 years and simultaneous CNS involvement' (specificity 0.97 (95% CI 0.84 to 1.00)). For predicting pediatric AQP4-ON, the most sensitive predictor was 'Female or without optic nerve swelling' (sensitivity 1.00 (95% CI 0.77 to 1.00)), and the most specific factors were Neurological history (sensitivity 0.94 (95% CI 0.83 to 0.98)) and follow-up VA > 1.0 logMAR (sensitivity 0.96 (95% CI 0.86 to 0.99)). Limitations include small sample size and a Chinese cohort that may not be generalizable to other populations. The authors suggest that using clinical parameters such as these can be useful in diagnosing MOG-IgG and AQP4-IgG related pediatric optic neuritis when there are delays in lab results or glial autoantibody status is not available.



Recovery of Vision after Optic Nerve Sheath Fenestration in Children and Adolescents with Elevated Intracranial Pressure.

Prat DL, Liu GT, Avery RA, Ying GS, Chen Y, Tomlinson LA, Revere KE, Katowitz JA, Katowitz WR. *American Journal of Ophthalmology*. 2022 May 1;237:173-82.

Increased intracranial pressure (ICP) can lead to vision loss through optic nerve swelling and damage and the most common cause of increased ICP is idiopathic intracranial hypertension (IIH). Some have advocated for optic nerve sheath fenestration in fulminant IIH with visual symptoms. The data regarding this approach in children has been limited. The aim of this single center retrospective case series of 14 pediatric patients was to describe the time course to visual recovery and visual outcomes in the nonoperative eye. The cohort had a mean age of 14 years and 5 of the 14 patients underwent bilateral surgery. The majority of the patients had IIH (10 out of 14) and mean follow up time was 16 months. The authors report visual improvement in both the operative eye (from 20/138 to 20/68) and the non-operative eye (20/78 to 20/32). Similarly, mean deviation on visual field improved in both eyes as well. No post-operative complications were observed. The vision improved at all study time points except post-operative day 1. This study is limited by its small numbers and relatively short follow up period, but it is the largest study to date to describe outcomes for children with increased ICP undergoing optic nerve sheath fenestration.

Pineles SL, Henderson RJ, Repka MX, Heidary G, Liu GT, Waldman AT, Borchert MS, Khanna S, Graves JS, Collinge JE, Conley JA, Davis PL, Kraker RT, Cotter SA, Holmes JM; Pediatric Eye Disease Investigator Group. The Pediatric Optic Neuritis Prospective Outcomes Study: Two-Year Results. *Ophthalmology*. 2022 Aug;129(8):856-864. doi: 10.1016/j.ophtha.2022.03.021. Epub 2022 Mar 29. PMID: 35364222.

These are the 2-year results of the Pediatric Optic Neuritis (PON) Prospective Outcomes Study, a nonrandomized observational study at 23 pediatric ophthalmology and neuro-ophthalmology clinics in the US and Canada. Patients included children presenting with their first episode of optic neuritis between 3-16yo enrolled in the PON study who completed the 2-year follow up (28 of 44 children, 64%). The authors report 2-year visual acuity outcomes, recurrence of optic neuritis, and prevalence of neurologic autoimmune disease. Treatment was independently determined by each patient's provider, but all patients received oral corticosteroids at some time during the study period within the first month after onset. The adjusted mean distance high contrast visual acuity at presentation was 0.81 logMAR (~20/125) which improved to 0.11 logMAR (~20/25) at 2 years. The adjusted mean distance low contrast visual acuity improved from 1.45 logMAR (~20/640) to 0.68 logMAR (~20/100). This shows that despite poor VA at onset, most children showed marked improvement in VA at 2 years, with visual acuity improvement seen and sustained after the 6-month follow-up. Associated autoimmune neurologic disease was common. The final diagnoses at 2 years included isolated optic neuritis (39%), MOG-associated demyelination (29%), MS (14%), ADEM (7%), and NMOSD (11%). Two of 12 participants with 2-year follow-up initially diagnosed with isolated optic neuritis developed an associated condition with one recurrence. Two participants with MS had a recurrence in the same eye, while 2 others had a new episode in the unaffected eye. This indicates that patients with an initial diagnosis of isolated optic neuritis may have a lower risk of recurrence and of developing an autoimmune condition later. Nine (32%) of participants at 2 years had poor VA outcome (HCVA <20/50 or LCVA <20/250); all but 2 of these participants had an associated neurologic autoimmune condition.

This study is limited by the large number of participants that did not complete a 2-year follow-up visit. These participants had a higher proportion of isolated ON and worse estimated VA at presentation. The study's results may be biased towards patients presenting with better visual acuity. Regardless, this study provides important information regarding the long-term prognosis for children with optic neuritis, showing that the majority have marked visual improvement by 6 months and insight on recurrence & development of associated neurologic disease.

Bilateral Optic Disc Edema in Multisystem Inflammatory Syndrome in Children Associated With COVID-19  
Dinkin M, Segal D, Zyskind I, Oliveira C, Liu G

*J Neuroophthalmol.* 2022;42(1):e318-e322.

A systemic multisystem inflammatory syndrome (MIS-C) has been described in children with COVID-19. Here, the authors present a case of a 14-year-old male who presented with fever, nausea, malaise and was diagnosed with MIS-C. After improvement of systemic symptoms and vitals, patient was discharged; however, he then developed blurred vision, diplopia, and headache and presented to ophthalmology. Exam revealed a mild right abducens nerve palsy with bilateral papilledema, right greater than left. Patient's symptoms were improving at that time and MRI/MRV were normal except for nonspecific signs of elevated ICP, so LP were deferred in favor of close follow-up. Two weeks later, papilledema, abducens nerve palsy, and symptoms had all resolved.

The authors hypothesize that, in the setting of MIS-C, intracranial hypertension can result from an inflammatory/infectious meningitis or an alteration of CSF fluid dynamics. They review a number of other cases of papilledema in COVID-19/MIS-C in the literature, some of which improved without intervention. It is recommended that pediatric ophthalmologists be aware of the potential association between COVID-19/MIS-C and intracranial hypertension, and children with complaints of headache of visual changes should be examined promptly in this setting.

#### Head Thrusts in Two Children with Unusual Neuroimaging Findings

Salman MS, Bunge M

*J Neuroophthalmol.* 2022;42(1):e427-e429.

The authors present two cases of head thrusts in children.

First, there is a 5-month-old female with right gaze preference, right head turn, and impaired leftward saccades. MRI showed hypoplasia of the right superior colliculus. By age 2 years, gaze preference had resolved, but she still required head thrusts when needing to look quickly to the left. Development was otherwise normal.

Second, there is a 10-month-old male with head thrusts who had difficulty making large, horizontal saccades. MRI at 15 months showed hypoplasia of the superior cerebellar vermis. He was followed until age 7 years, at which point he continued to have impaired horizontal saccades, needing to initiate with a blink. He had normal vertical saccades and no other ophthalmologic abnormalities were present.

Head thrusts in children are an adaptive mechanism typically indicative of impaired saccades, present in syndromes such as Joubert syndrome or ataxia-telangiectasia syndrome. However, the authors also comment on the existence of *infantile-onset saccade initiation delay* (ISID), a condition previously known by the misleading name of "congenital oculomotor apraxia" (the condition is not present at birth and is not a true apraxia, as both voluntary and reflexive saccades are impaired).

In ISID, infants display head thrusts as they develop head control, have hypometric saccades with increased latency, and often must initiate saccades with a blink as they get older. Although the pathogenesis remains uncertain, the authors here implicate the subtle neuroimaging findings (cerebellar and/or midbrain hypoplasia) as potential culprits, as they make structural sense. Further study is warranted, but the pediatric ophthalmologist should be aware of ISID, be prepared to evaluate both voluntary and reflexive saccades in infants, and understand the value of neuroimaging in these cases.

#### Involvement of Ocular Muscles in Patients with Myasthenia Gravis with Nonocular Onset

Lei L, Fan Z, Su S, et al.

*J Neuroophthalmol.* 2022;42(1):e260-e266.

Strabismus surgeons are frequently the first physicians to see patients with new-onset myasthenia gravis (MG) as 50-85% of all MG patients reports ptosis, diplopia, or both as initial symptoms. But, of the patients that are initially diagnosed with MG *without* ocular symptoms, how many go on to develop diplopia or ptosis? The authors seek to answer this question by performing a retrospective review of all patients with MG of nonocular onset at a single institution over a 3-year span that had at least 2 years of follow up.

Of the 54 patient meeting inclusion criteria, 47 (87.0%) developed ocular involvement in the follow-up period – 37 (78.8%) in the first year after diagnosis, then 4 (8.5%) in both the second and third years. Those presenting with bulbar weakness had a significantly higher chance of developing ocular weakness,

while those receiving pyridostigmine and/or immunomodulating therapy had a lower risk of developing ocular weakness.

This study is important to the strabismus surgeon because it emphasizes that patients diagnosed with nonocular MG are quite likely to develop ocular signs/symptoms at some point in their disease course, often within the first year of their diagnosis. These patients should be screened by their neurologist or primary care physician at each visit for ptosis and diplopia and be promptly referred to a strabismus specialist when warranted.

#### Ophthalmological Evaluation in Children Presenting with a Primary Brain Tumor

Nuijts MA, Stegeman I, Porro GL, et al.

*J Neuroophthalmol.* 2022;42(1):e99-e108

Children with a CNS tumor are at high risk for developing visual impairment (VI), with previous studies placing the prevalence of VI in these children at 45-67%. In this study, the authors performed a retrospective review of all pediatric patients newly diagnosed with a primary brain tumor who received treatment at a single oncology referral center over a one-year period, with the goal of assessing the prevalence and type of ophthalmologic abnormalities present in such patients.

Overall, 90 patients were included in the study. The most common tumor was a low-grade glioma (38.9%), followed by medulloblastoma (16.7%), high-grade glioma (10.0%), and germ cell tumor (7.8%). Visual symptoms were present at diagnosis in 43.3% of patients, with the most common being diplopia (22.2%) and decreased vision (21.1%).

Of the 90 patients, 60 (66.7%) had an ophthalmic exam within 6 weeks of diagnosis. At least one ophthalmologic abnormality was found in 47/60 patients (78%). Papilledema was diagnosed in 26/47 patients (55.3%), strabismus in 21/47 (44.7%), gaze deficits in 20/47 (42.6%), nystagmus in 17/47 (36.2%), and optic disc pallor in 7/47 (14.9%). Of the 31 that underwent formal VF testing, 18 (58.1%) had a VF defect.

Of the 60 children who underwent an ophthalmic exam, 23 (38.3%) did not have visual symptoms; however, 13 of these 23 ended up with an abnormal finding on their eye exam (56.5%).

Given the high prevalence of ophthalmologic abnormalities (78%) in pediatric patients with primary CNS brain tumors, even among those without visual symptoms (13/23, 56.5%), the authors conclude that all such patients should be referred for a complete eye exam in a timely fashion. It is also suggested that future work might address the creation of a standardized protocol for ophthalmic evaluation in patients with brain tumors. Prompt recognition, diagnosis, and treatment of VI and ophthalmic abnormalities may help improve visual outcomes.

#### A Pediatric Case of Anti-N-methyl-D-aspartate Receptor Encephalitis Associated with Optic Neuritis

You JY, Lacroix C, Toffoli D

*J Neuroophthalmol.* 2022;42(1):e289-e292.

The authors present a case of a 6-year-old-female with months of headaches, fatigue, and fever who presented following 2 paroxysmal seizures. She was discharged on clobazam. Five months later, she again presented with acute bilateral vision loss in the setting of confusion, irritability, and reclusiveness. Visual acuity was CF OD and 20/800 OS. Exam showed bilateral disc edema with tortuous vessels. MRI showed patchy FLAIR signal, but no clear enhancement of optic nerves. During an extensive work-up, blood and CSF came back positive for anti-NMDAR antibodies and a diagnoses of NMDAR encephalitis. She was treated with steroids and IVIg. Three months later, VA had improved to 20/20 OU with residual optic nerve pallor bilaterally. Behavior and other neurologic symptoms also improved.

Pediatric optic neuritis (ON) is uncommon in NMDAR encephalitis, but has been reported to occur before, concurrent with, or after encephalitis onset. Although not the case here, the authors importantly note that pediatric NMDAR encephalitis has been known to co-occur with demyelinating disorders, such and NMO and MOGAD. Such a co-occurrence has implications for treatment. Therefore, the authors conclude by suggesting that, in rare cases of NMDAR encephalitis and ON, it is important to also test for anti-AQP4

and anti-MOG antibodies to rule out a co-occurrence, especially if imaging is suggestive of a demyelinating disease.

#### Correlation Between Ophthalmologic and Neuroradiologic Findings in Type 1 Neurofibromatosis

Godinho G, Esteves-Leandro J, Alves G, et al.

*J Neuroophthalmol.* 2022;42(1):101-107.

NF1 is a genetic condition that is characterized by both ocular (e.g., Lisch nodules) and neurologic (e.g., optic pathway gliomas, OPG) findings. Recently, OCT and infrared (IR) imaging has demonstrated the frequent presence of choroidal nodules in patients with NF1, though studies describing them are still lacking. These authors set out to better characterize ophthalmic findings in NF1 with multimodal imaging, seeking to determine if there is any relationship between ophthalmic signs and CNS lesions.

All patients at a single tertiary care center with a diagnosis of NF1, a full ophthalmic exam (including OCT), and an MRI within 2 years of said exam were included and retrospectively reviewed. Ultimately, 44 eyes of 22 patients (mean age 16.4 years) were included. Of the 44 eyes, 13 (29.5%) were recorded to have Lisch nodules, while hyperreflective choroidal lesions (HL) were identified on review of OCT/IR imaging in 28 (63.4%) eyes. MRI showed CNS hamartomas in 19/22 (86.4%) of patients and OPGs in 15/44 (35.1%) of eyes.

Interestingly, eyes with OPG had higher number of HLs, and greater HL area, than eyes without OPG. If using a cut-off of 3.5 lesions per eye, the sensitivity and specificity for having an OPG on the MRI were 75% and 80%, respectively (ROC = 0.78). No correlation was detected between the number or area of HL and CNS lesions.

Given these findings, the authors suggest that choroidal findings – namely, hyperreflective lesions thought to represent choroidal nodules – could be used as biomarkers for CNS abnormalities (specifically, OPGs) and may be a useful addition to the diagnostic criteria for NF1, especially as multimodal imaging becomes more common in the pediatric population. Simultaneously, they recognize the weaknesses of their study – it is an observation, retrospective study with a small sample size, and the potential 2-year span between brain MRI and OCT/IR may confound the relationship between MRI and OCT/IR findings. Nevertheless, these proposals are important and merit further study.

#### Etiology and Outcomes of Acquired Pediatric Sixth Nerve Palsies

Chang MY, Borchert MS

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In this study, the authors undertake a retrospective review of all children diagnosed with a sixth nerve palsy at a single institution over a 10-year period, with particular attention paid to whether the palsy was isolated. They also examined the factors associated with spontaneous recovery and the development of amblyopia.

In all, 172 children with a median age of 8.8 years old had an acquired unilateral or bilateral sixth nerve palsy. The etiologies (in descending frequency) were neoplasm (37%), elevated intracranial pressure (19%), trauma (13%), inflammation (9%), infection (8%), presumed post-viral or post-vaccination (6%), idiopathic (4%), and other (4%). But, when the authors analyzed just the 20 children (out of the 172) who had an isolated palsy, the etiologies looked different: presumed post-viral or post-vaccination (50%), idiopathic (30%), neoplasm (10%), trauma (5%), and other (5%).

The authors then move on to their outcome analysis. In total, 59% of children experienced spontaneous recovery at a median time of 12 weeks. On multivariate regression, older age and nontumor etiology were the two significant predictors of spontaneous resolution, while younger age was the sole significant predictor of amblyopia development.

In summary, pediatric sixth nerve palsies often have a serious neurologic etiology, with tumor and elevated ICP being the most common. However, when looking solely at isolated cases of sixth nerve palsy, a full 80% of cases are secondary to post-viral/post-vaccination/idiopathic causes, while only 10% were due to tumors. As such, the authors recommend that, while neuroimaging should be promptly performed in all nonisolated cases of pediatric sixth nerve palsy, it may be reasonable to defer imaging in isolated cases, with the caveat that imaging is needed if 1. New neurologic/ophthalmologic symptoms arise or 2. Spontaneous resolution does not occur within 3 months. This is the major clinical take-home point of the study.

The main weakness of the study, acknowledge by the authors, is that only 55% of the cases met criteria for outcome analysis due to insufficient follow up. Additionally, the study was performed at a large tertiary care center, which may misrepresent the underlying etiologies in the population as a whole.

#### Increase in Pediatric Pseudotumor Cerebri Syndrome Emergency Department Visits, Inpatient Admissions, and Surgeries During the COVID-19 Pandemic

Chang MY, Yim CK, Borchert MS

*J Neuroophthalmol.* 2022;42(1):e87-e92

The COVID-19 pandemic disrupted normal patterns of healthcare use and physical activity and led to an increase in childhood obesity rates over the past few years. Given the known association between pseudotumor cerebri syndrome (PTCS) and obesity, the authors attempt to determine if these changes in obesity rates affected rates and characteristics of pediatric PTCS.

The authors examined all pediatric emergency department (ED) and inpatient encounters with a diagnosis of definite PTCS (either new or exacerbated) between March 19<sup>th</sup>, 2015, and February 20<sup>th</sup>, 2021 at a single tertiary care center. Encounters prior to March 20<sup>th</sup>, 2020 (the start of the local “stay at home” order) were consider pre-pandemic, while all later encounters were considered to occur during the pandemic.

A total of 62 encounters met inclusion criteria, with 36 encounters happening in the 5-year pre-pandemic period and 26 occurring during the 1-year pandemic period (March 20<sup>th</sup>, 2020 to February 20<sup>th</sup>, 2021). Clearly, the average monthly number of ED/inpatient encounters for PTCS was significantly higher during the pandemic than during the prior 5-year period. Children presenting with PTCS during the pandemic were more likely to be post-pubertal, were older, and were more likely to be obese. Additionally, compared to the pre-pandemic group, patients seen during the pandemic were more likely to have a fulminant presentation, worse presenting visual acuity, and higher likelihood of needing surgical intervention.

The authors conclude that the frequency of ED/inpatient encounters for pediatric PTCS increased during the pandemic. Moreover, the severity of these presentations (as measured by presenting VA and need for surgical intervention) worsened. They attribute this primarily to increases in obesity seen during the pandemic, but also acknowledge that delay of care secondary to pandemic-related obstacles may play a role as well. Overall, this demonstrates that it is important for pediatric ophthalmologists to continue to advocate for improved access to care among our patients and to be aware that the COVID-19 pandemic may increase the frequency and severity of presenting PTCS in our patient populations.

#### Induced Pluripotent Stem Cells for Inherited Optic Neuropathies-Disease Modeling and Therapeutic Development

Harvey JP, Sladen PE, Yu-Wai-Man P, Cheetham ME

*J Neuroophthalmol.* 2022;42(1):35-44

The inherited optic neuropathies (IONs) cause severe visual impairment in both children and adults and, at present, are not readily treatable. The discovery of a technique for reprogramming somatic nondividing cells into induced pluripotent stem cells (iPSCs) has, however, opened up possibilities in the field of ION research and treatment, which the authors review here.

To start, the paper emphasizes the utility of iPSCs in disease modeling. Using various techniques, the field has established 2-dimensional protocols to generate retinal ganglion cell (RGC) models of Leber Hereditary Optic Neuropathy and Dominant Optic Atrophy (among others), providing insights into the disease mechanisms driving RGC loss in these genetic conditions.

On the treatment side, the authors state that IONs are ideal targets for iPSC-based therapy. Researchers aim to use iPSCs as an autologous source of specific cell types, which could then be used to replace damaged tissues in certain disease processes. There are many challenges, however, to doing this with RGCs, as the delicate and specific nature of organization and connections of the RGCs make them difficult to integrate into a larger structure. Techniques will need certainly further refinement before this could be available for humans. Additionally, the authors discuss the use of gene editing technology (i.e.,

CRISPR/Cas9) to correct the causative genetic variants in iPSC-derived cells, which is a potentially exciting avenue of future treatment.

Although the application of iPSCs in ION is still in its nascent stages, it holds significant promise. It is important for ophthalmologists to be aware of these new treatment modalities that may become available for our patients within their lifetimes.

#### Long-Term Development and Progression of Peripapillary Hyper-reflective Ovoid Mass-like Structures: Two Case Reports

Kim MS, Hwang JM, Woo SJ

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Peripapillary hyper-reflective ovoid mass-like structures (PHOMS), an OCT finding thought to represent axoplasmic flow stasis, can be seen in cases of papilledema, optic disc drusen, and tilted discs. The authors here report two cases of (PHOMS) in the pediatric population, with special attention paid to how these structures progress with age.

In the first case, a healthy 6-year-old female was found to have mild myopia and slight tilting of the disc (with visible nasal crescent) in both eyes. Over the course of 6 years (until age 12), serial photos revealed increasingly tilted disc and worsening peripapillary atrophy that accompanied an increase in myopia. Additionally, OCT by age 12 showed distinct nasal PHOMS in both eyes.

In the second case, a 5-year-old female with history of infantile esotropia had routine fundus photos that showed normal optic nerves. By ages 9, 12 and 13, the right optic nerve head had become progressively more tilted with blurring and elevation of the nasal margins accompanied by “pinkish deposits” confluent with the nasal disc. OCT of the right eye revealed a corresponding PHOMS in the right eye but not in the left eye, which had a normal-appearing optic disc. Both eyes had a significant myopic shift during this time.

From these cases, the authors surmise that disc tilting secondary to a myopic shift can induce mechanical stress on the optic nerve head, which may be associated with the development and progression of PHOMS. Pediatric ophthalmologists should be aware of this potential association when evaluation abnormal appearing nerves in children, particularly those with increasing myopia.

#### Multidomain Cognitive Impairment in Children with Pseudotumor Cerebri Syndrome

Mahajnah M, Suchi AT, Zahakah H, et al.

*J Neuroophthalmol.* 2022;42(1):e93-e98

A few small studies have shown that adults with pseudotumor cerebri syndrome (PTCS) may end up with chronic neurocognitive deficits, even in the setting of prompt and appropriate treatment. The authors here attempt to determine if similar neurocognitive issues arise in children with PTCS.

Patients less than 18 years old who were diagnosed with PTCS over a 5-year span at 2 medical centers were included in the study; 26 children met criteria. Of these, 12 were actively being treated with acetazolamide, while 14 had been treated with acetazolamide but were off the drug at time of testing. Additionally, 56 healthy children were recruited to serve as a control group. Demographics were the same between the two groups.

All participants underwent a neurocognitive evaluation using the NeuroTrax computerized battery. Children with PTCS were tested 3 months after initial diagnosis. Overall, children with PTCS scored significantly lower than their healthy peers in global cognitive score, verbal memory, nonverbal memory, executive function, attention, and information processing speed. Within the PTCS group, there was no statistical difference between those under treatment and those who had completed treatment.

The authors hypothesize that the possible neurocognitive impairment may be secondary to headaches, underlying emotional state, drug side effects, or the disease itself.

One must note that, although 3 months may be long enough to move past the “acute” phase of PTCS, testing children with PTCS only 3 months after their diagnosis (with approximately 50% still on actively being treated) may not be the best representation of long-term neurocognitive outcomes. Nevertheless, this study is valuable in that it provides some evidence of neurocognitive issues in children with PTCS.

Pediatric ophthalmologists should be on the lookout for such issues in these patients, asking parents about schoolwork and school performance so interventions can be provided when needed. Longer term studies are needed to truly determine if there are any lasting neurocognitive effects from PTCS.

#### Optic Nerve Aplasia

Saffren BD, Yassin SH, Geddie BE, et al.

*J Neuroophthalmol.* 2022;42(1):e140-e146

Optic nerve aplasia (ONA) is a rare ocular anomaly characterized by the absence of optic nerve, retinal vasculature, and retinal ganglion cells. By reaching out via the International Pediatric Ophthalmology Listserv, the authors were able to identify and collect clinical information on 9 cases of true ONA, ages 10 days to 2 years.

Of these patients, 6/9 were male, and 7/9 had bilateral ONA. The most common reasons for presentation were abnormal eye movements (3/9) or microphthalmia (3/9). All had anterior segment abnormalities, including microcornea (8/9) and aniridia (3/9, 2 of whom had glaucoma). On fundus examination, all patients had absence of the optic nerve and retinal vessels in the affected eye(s); 7/9 had no identifiable macular structures, 3/9 had retinal dysplasia, and 2/9 had retinal absence or atrophy.

Five of the patients had systemic issues, including skeletal abnormalities, short stature, and developmental delay. All patients had neuroimaging; other than absent optic nerves/chiasm/tracts, no other abnormalities were appreciated. The authors note it is particularly interesting that the neurohypophyseal structures were normal in all patients, given that neurohypophyseal abnormalities are seen in up to 64% of patients with optic nerve hypoplasia.

The authors acknowledge the limitations of their small sample size, and the potential referral bias inherent in asking a listserv to voluntarily provide cases. Nonetheless, when dealing with rare diseases, even small groups of patients are interesting. When caring for patients with ONA, neuroimaging is recommended, as is a careful anterior exam given the anterior segment issues – and cases of glaucoma – seen in this cohort.

#### Reversible Nutritional Deficiency-Related Conjunctival Xerosis and Optic Neuropathy Secondary to an Exclusively Potato-Based Diet

Bailey MD, Mortensen PW, Raviskanthan S, Lee AG

*J Neuroophthalmol.* 2022;42(1):e323-e325

The authors present a case of a previously healthy 13-year-old male who presented with painless, progressive vision loss in both eyes. Exam showed a visual acuity of NLP OD and 20/125 OS, bilateral conjunctival xerosis, and bilateral optic nerve pallor. History was significant for a restricted diet, with the patient eating only “potato products” for many years.

Extensive work-up for optic neuropathy, including neuroimaging, was unremarkable with the exception of critically low levels of vitamin A and low levels of vitamins B2, B12, and E. He was started on vitamin supplementation and a new nutrition regimen. Two months later, his VA had improved to LP OD and 20/20 OS with resolution of conjunctival xerosis.

Restrictive diets are relatively common in children, especially those with neurologic or developmental disabilities. In cases of progressive and painless vision loss, it is important to always remember to inquire into the child’s dietary preferences.

#### Sixth Nerve Palsy in Pediatric Inflammatory Multisystem Syndrome Temporally Associated with Severe Acute Respiratory Syndrome Coronavirus 2 Infection

Hernandez-Garcia E, Arriola-Villalobos P, Burgos-Blasco B, Morales-Fernandez L, Gomez-de-Liaño R

*J Neuroophthalmol.* 2022;42(1):e406-e407

A systemic multisystem inflammatory syndrome has been described in children with COVID-19. Here, the authors present a case of a 3-year-old male who presented with fever and headache with elevated inflammatory markers and met criteria for COVID-19-related inflammatory syndrome. He was treated with antibiotics, steroids, aspirin, and immunoglobulin and discharged after 7 days. Five days after discharge,

he developed an acute horizontal diplopia, worse in the right gaze. Exam revealed an esotropia of 15 PD in primary position with abduction limitation of -3 in the right eye. Neurologic exam was unremarkable, as was the MRI. No further treatment was initiated, and the sixth nerve palsy resolved completely within 4 weeks.

The authors suggest that sixth nerve palsy must be considered a potential inflammatory complication of COVID-19. It is recommended that pediatric ophthalmologists be aware of the potential association between COVID-19 and inflammatory cranial nerve palsies.

#### Unilateral Abducens Nerve Palsy with Bilateral Retinitis: A Rare Presentation of Cat Scratch Disease Levy-Neuman S, Paz T, Leiba H, et al.

*J Neuroophthalmol.* 2022;42(1):e371-e373

The authors report the case of a 47-year-old female who presented with acute onset horizontal diplopia. Exam revealed a left-sided abducens nerve palsy. Extensive work-up was performed and returned positive for *B. henselae* IgM and IgG. Patient endorsed recent contact with cats. A few days after presentation, she noted visual disturbances, and scattered white lesions were seen on fundus exam throughout the retina of both eyes. Patient was started on oral prednisone and doxycycline. All symptoms and ophthalmic findings returned to normal within one month.

This case report is of interest in that it describes an unusual etiology of a sixth nerve palsy – namely, cat-scratch disease (CSD). In the presence of visual disturbances or typical fundus findings, CSD may be included on the differential of a sixth nerve palsy.

#### Optic Nerve Abnormalities in Morning Glory Disc Anomaly: An MRI Study Nguyen DT, Boddaert N, Bremond-Gignac D, Robert MP

*J Neuroophthalmol.* 2022;42(2):199-202

Morning Glory Disc Anomaly (MGDA) is often first identified in children and is known to be associated with certain neurologic abnormalities, most notably cerebral vascular anomalies. Here, the authors identified all patients with MGDA on fundus photography seen at a single institution over a 10-year span with appropriate neuroimaging in order to ascertain if there is any connection between MGDA and optic nerve enlargement or optic pathway glioma, which has been reported.

In all, 9 patients with a median age of 14 months (at time of diagnosis) met inclusion criteria. All cases of MGDA were unilateral. The most common presenting sign was strabismus, though cataracts and retinal detachments were also common in the group. On MRI, cases were mostly characterized by an irregular thickness of the optic nerve on the side of the MGDA – for example, the affected optic nerve might be thin intraorbitally and thickened intracranially. No case had enhancement with contrast. In the 4 cases with serial imaging, no growth or change of the optic nerve was noted.

The authors conclude that irregular optic nerve thickness from the orbit to the chiasm seems to be the rule in MGDA and likely points to a developmental anomaly and not to an optic pathway glioma, as some have previously suggested. The risk of “progression” of any optic nerve abnormalities in these patients is low.

#### Interobserver and Intra-Observer Reliability of Eyelid Tests for Ocular Myasthenia Gravis

Jienmaneechotchai T, Apinyawasisuk S, Jariyakosol S, Hirunwiwatkul P

*J Neuroophthalmol.* 2022;42(2):230-233

Lid fatigability test (LFT), Cogan lid twitch (CLT), and forced eyelids closure test (FECT) are common screening tests for ocular myasthenia gravis (OMG); however, as subjective tests, different providers may have different opinions and grading criteria for each test.

In this study, the primary author recorded a video each of the three above tests (LFT, CLT, FECT) on adult patients presenting with ptosis of any origin in a 1-year span. These videos were then presented, in random order, to three neuro-ophthalmologists (NO) and three general ophthalmologists (GO), who graded each test as positive or negative. Three months later, the same videos in a different order were again presented to and graded by the same six ophthalmologists.

Among both NOs and GOs, interobserver reliability (using Fleiss' kappa) was highest for CLT (0.77 and 0.66 – 3 months later – for NOs compared to 0.58 and 0.54 for GOs), followed by FECT (0.62 and 0.66 compared to 0.47 and 0.31) and LFT (0.50 and 0.54 compared to 0.39 and 0.31). In each case, reliability



was greater for NOs than GOs. Similarly, intraobserver reliability was highest for CLT, followed by FECT and LFT among NOs; intraobserver reliability varied greatly within the CO group. This study has a few limitations – most significantly, the tests were graded on video and not live (i.e., with the patient in clinic). Nonetheless is important because it brings awareness to the somewhat limited interobserver and intraobserver reliability of OMG clinical tests while highlighting that CLT is the most consistent test, for both experienced NOs and GOs. For those of us who diagnose and treat OMG, it is a study worth knowing.

#### Ocular Motor Nerve Palsy After Traumatic Brain Injury: A Claims Database Study

Hwan H, Lambert S

*J Neuroophthalmol.* 2022; epub ahead of print.

Trauma – specifically, traumatic brain injury (TBI) – is one of the more common causes of acquired cranial nerve palsies. In this study, the authors aim investigate the incidence and characteristics of ocular motor nerve palsies following TBI.

To do this, the authors performed a population-based retrospective cohort study using claims data from the IBM MarketScan Research Databases (2007–2016), a database that includes health insurance claims of more than 240 million patients insured by 350 unique health carriers. Patients with new ocular motor palsy (determined by ICD codes) within 3 months after the diagnosis of TBI were included. Demographic, diagnostic, and surgical data was collected.

A total of 8,713,134,185 claims for 123,637,719 patients were analyzed. Of the 1.35 million children (<18 years old) with TBI, 454 (0.026%) had ocular motor nerve palsy. Of the 1.26 million adults who had TBI, 1,397 (0.111%) had ocular motor nerve palsy. Among children, CN6 palsy was the most common (44.7%), followed by CN4 (32.8%) and CN3 palsy (20.0%). Meanwhile, CN4 palsy was the most common among adults (39.2%), followed by CN6 (33.9%) and CN3 palsy (25.2%).

More children (16.5%) underwent strabismus surgeries than adults (11.6%). The median time-to-surgery following TBI (if surgery was performed) was 5 months in children and 7 months in adults. Of those with mild TBI, 7.2% underwent strabismus surgery, while 13.6% of those with moderate-to-severe TBI had surgery.

CN4 palsy (52.3%) was more frequent while CN3 palsy (15.5%) was less frequent in patients with mild TBI compared to patients with moderate-to-severe TBI.

The authors acknowledge that claims data is far from comprehensive and lacks a significant amount of clinical data. Additionally, unilateral and bilateral cases could not be distinguished (laterality is not included in the ICD9 codes), and only patients under 65 years old are included in the MarketScan database.

Nonetheless, this study is valuable in that it provides us a high-level picture of strabismus following TBI in the US, which in turns provides us with information we can use to inform our patients and our practices.

#### A Case of Isolated Bilateral Trochlear Nerve Schwannomas

Froines CP, Van Brummen AJ, Francis CE

*J Neuroophthalmol.* 2022;42(1):e394-e395

The authors present a case of a 34-year-old male who presented with slowly worsening vertical diplopia and headaches over 7 years. Motility exam showed significant underaction of the right superior oblique. Alternate cover test revealed alternating hypertropias in side gaze with a right hypertropia in primary and a small V-pattern esotropia. Overall, the clinical picture fit with bilateral fourth cranial nerve palsies, right worse than left.

An MRI was obtained and showed 2 isointense lesions along the proximal trochlear nerves that enhanced with contrast, most consistent with bilateral trochlear schwannomas. NF2 genetic testing was negative. Serial MRIs showed continue growth of the lesions. Patient eventually underwent stereotactic radiosurgery and a left inferior rectus recession with resolution of diplopia.

Trochlear schwannomas are rare, especially when bilateral. Treatment modalities may include stereotactic radiosurgery and strabismus surgery, as demonstrated in this patient, with good results.



## 6. NYSTAGMUS

### Demographic and Clinical Characteristics of 600 Children With Nystagmus

Hertle RW, Evliyaoglu F, McRitchie B.

J Pediatr Ophthalmol Strabismus. 2022;1-5. doi:10.3928/01913913-20221026-02

This single-center, prospectively developed database sought to characterize nystagmus in a large, international cohort of 600 patients from 38 states and 30 countries aged from birth to 18 years. The authors found that: 58% were female, 55% were race other than White, 75% had infantile nystagmus syndrome, 17% had neurologically significant nystagmus, 7% had fusion maldevelopment nystagmus syndrome, 64% had strabismus, 56% had an anomalous head posture, 94% had a significant refractive error, 64% had an associated ophthalmic abnormality (excluding ametropia), and 45% had an associated systemic condition. Special testing showed abnormalities in 67% and 95% had treatment directed at their nystagmus. The authors concluded that infantile nystagmus syndrome was most common, and that eye movement recordings should be used to aid in accurate diagnosis and classification. provide a path toward accurate diagnosis and classification. One limitation was the absence of genetic testing.

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### Nystagmus in Down Syndrome - a Retrospective Notes Review.

Oladiwura D, Shweikh Y, Roberts C, Theodorou M.

Br Ir Orthopt J. 2022 Jun 21;18(1):48-56.

This retrospective study of 51 subjects with Down Syndrome and nystagmus was conducted at Moorfields Eye Hospital. The mean age at presentation was 5.1 years (range 0–26 years). The mean binocular LogMAR visual acuity was 0.55(95%CI 0.53–0.57), mean refractive error was –1.8 Dioptre Sphere, DS (95% CI – 5.251.63) with –1.2 Dioptre Cylinder, DC (95% CI – 1.6–0.7). Ocular misalignment was found in 50% of patients. A diagnosis of Fusion Maldevelopment Nystagmus Syndrome (FMNS) was made in 6.3%, Infantile Nystagmus Syndrome (INS) in 8.4% and ABducting nystagmus/Inter-Nuclear Ophthalmoplegia (INO) in 2.1%. The descriptive term ‘Manifest Horizontal Nystagmus’(MNH) was used in the majority, highlighting the difficulties in clinically differentiating the subtypes of nystagmus in DS. Eleven patients had associated cataract. Additional diagnoses unrelated to DS were made in 10.4%. This study highlights that though INS is most common in DS, other possible etiologies for nystagmus need to be considered (ie. visually significant cataracts).

### Zahidi AAA, McIlreavy L, Erichsen JT, Woodhouse JM.

Visual and Refractive Status of Children with Down’s Syndrome and Nystagmus. Invest Ophthalmol Vis Sci. 2022;63(2):28.

Children with Down’s syndrome (DS) are known to have poorer visual acuity than neurotypical children. One report has shown that children with DS and nystagmus also have poor acuity when compared to typical children with nystagmus. What has not been established is the extent of any acuity deficit due to nystagmus and whether nystagmus affects refractive error within a population with DS. Clinical records from the Cardiff University Down’s Syndrome Vision Research Unit were retrospectively reviewed. Binocular visual acuity and refraction data were recorded for 50 children who had DS and nystagmus and 176 children who had DS but no nystagmus. Data were compared between the two groups and with published data for neurotypical children with nystagmus. The study confirms the deficit in acuity in DS, compared to neurotypical children, of approximately 0.2 logMAR and shows a deficit attributable to nystagmus of a further 0.2 logMAR beyond the first year of life. Children with both DS and nystagmus clearly have a significant additional impairment. Children with DS have a wide range of refractive errors, but nystagmus increases the likelihood of myopia. Prevalence and axis direction of astigmatism, on the other hand, appear unaffected by nystagmus. The authors conclude that nystagmus confers an additional visual impairment on children with DS and must be recognized as such by families and educators so that these children can receive targeted support.

## 7. PREMATURITY

None in last 6 months

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Association between Retinal Microanatomy in Preterm Infants and 9-Month Visual Acuity

Kai Seely MHSc, Shwetha Mangalesh MD, Liangbo Shen MD

JAMA Ophthalmol. June 2022; 140(7):688-706

Infants born prematurely are at risk for several ophthalmologic complications that can result in poor visual acuity (VA), including retinopathy of prematurity (ROP), optic atrophy, cataracts, strabismus, and cortical visual impairment. Preterm infants without retinal abnormalities on ophthalmoscopic examination can have poor vision outcomes, as reported in a 6-year follow-up of infants treated for severe ROP that found more than 50% of eyes with essentially normal retinal appearance had VA worse than 20/40 and more than 10% had VA worse than 20/200. Most of these infants had no apparent risk factors for cortical visual impairment. This study sought to use bedside handheld OCT to evaluate if there is an association between retinal microanatomy in preterm infants at 40 weeks PMA and their grating visual acuity at 9 months corrected age. 118 infants were enrolled, and monocular grating acuity was obtained in both eyes in 67. Those patients were imaged with bedside OCT and included in the primary analysis. 16 eyes (13%) underwent treatment for ROP (either intravitreal bevacizumab injection or laser photocoagulation) prior to 40 weeks PMA, and 4 eyes underwent treatment after 40 weeks PMA. Overall, 76 eyes (62%) had macular edema. The distribution of edema was similar between eyes with subnormal vs normal VA at 9 months 'corrected age. The ellipsoid zone was absent at the foveal center in 111 eyes (91%). RNFL thinning across the papillomacular bundle (PMB) was associated with poorer 9 month VA, independent of birth weight, gestational age, need for ROP treatment, and macular microanatomy. The authors hypothesize that RNFL thinning across the PMB may be an early biomarker of global disruptions in neurodevelopment that put infants at risk for poor visual outcomes. Evaluation of RNFL thickness across the PMB near term may assist in early identification of preterm infants at risk of developing poorer vision and in need of extended follow-up or vision rehabilitation, even in the absence of severe ROP on clinical examination.

Vitreous opacities in infants born full-term and preterm by handheld swept-source optical coherence tomography

Scoville, N. Maxwell et al.

Journal of American Association for Pediatric Ophthalmology and Strabismus {JAAPOS}, Volume 26, Issue 1, 20.e1 - 20.e7

A investigational hand-held swept-source optical coherence tomography (SS-OCT) imaging was performed on term and premature infants at 12 and 48 hours after birth. 3-masked graders analyzed the images. Punctate vitreous opacities were present in 25 of 28 term infants (89%) and 41 of 50 premature infants (82%). Dice coefficient and F1 scores for intergrader agreement were 0.99 0.03 and 0.77 0.31, respectively. Vitreous opacity density was 0.118 0.187 in prematurely born infants and 0.031 0.118 in infants born at term (P 5 0.009). In the former, vitreous opacity density was associated with ROP zone (P 5 0.044) and stage (P 5 0.031), intraventricular hemorrhage (P 5 0.028), subchorionic hemorrhage (P 5 0.026), and African American race (P 5 0.023). In the latter, vitreous opacity density was associated with maternal diabetes (P 5 0.049). This study finds frequent vitreous opacities in both term and premature infants, with a higher density in those premature and with severe ROP.

Optic Nerve Head Morphology in Adults Born Extreme, Very, and Moderate Preterm With and Without Retinopathy of Prematurity: Results From the Gutenberg Prematurity Eye Study. Fieß A, Gißler S, Mildenerger E, Urschitz MS, Zepp F, Hoffmann EM, Brockmann MA, Stoffelns B, Pfeiffer N, Schuster AK. American Journal of Ophthalmology. 2022 Jul 1;239:212-22.

Preterm birth effects optic nerve head morphology, which may be related to an interruption of normal neurologic tissue development and decreased cortical volume. Adults with a history of preterm birth may mistakenly be diagnosed with glaucoma or other optic neuropathies given abnormal optic nerve head morphology related to prematurity. The goal of this study was to quantify optic nerve head morphology in

adults with a history of extreme, very, and moderate preterm birth. This study is part of the Gutenberg Prematurity Eye Study, which is a retrospective cohort study with a prospective arm evaluating adults ages 18-52 years. This study evaluated 743 eyes of 393 adults and assessed vertical cup-to-disc ratio, optic disc area and morphology based on nonmydriatic photos. The authors found that adults with a history of preterm birth had significantly higher vertical cup-to-disc ratios compared to the full term control group. Interestingly, those with ROP requiring treatment had smaller vertical cup-to-disc ratios. This study was performed at a single center in Germany, which may limit the generalizability of these findings to other populations. Ophthalmologists should be aware of the prevalence of increased vertical cup-to-disc ratio in adults with a history of prematurity and should consider this in their differential diagnosis of optic nerve pathology in this population.

Prevalence of the Infantile Strabismus Complex in Premature Children With and Without Periventricular Leukomalacia.

Khanna S, Sharma A, Ghasia F, Tychsen L.

American Journal of Ophthalmology. 2022 Apr 4.

Premature children are frequently diagnosed with periventricular leukomalacia (PVL), the most common type of brain damage seen in children with a history of prematurity. Given the neural mechanisms underlying binocularity and eye alignment, some hypothesize that higher rates of strabismus will be seen in children with a history of PVL. This retrospective case-controlled study of 98 children (67 with PVL and 31 without PVL). The goal was to determine whether rates of strabismus differed based on the presence and severity of PVL. Overall, strabismus was documented in 61% of children with mild PVL, 74% with moderate PVL, and 88% with severe PVL. Esotropia predominated with a 3.5:1 ratio compared to exotropia. The authors conclude that infantile strabismus is very common in children with PVL and generally correlates with PVL severity. The authors posit that perinatal brain damage is the likely reason for such a high prevalence of strabismus in this population.

## 8. RETINOPATHY OF PREMATURITY

Ocular and developmental outcomes of a dosing study of bevacizumab for retinopathy of prematurity  
Wallace DK, Hercinovic A, Freedman SF, Crouch ER, Bhatt AR, Hartnett E, Yang MB, Rogers DL,  
Hutchinson AK, Good WV, Repka MX, Li Z, Beck RW, Kraker RT, Cotter SA, Holmes JM,  
on behalf of the Pediatric Eye Disease Investigator Group  
J AAPOS 2023;27:10.e1-8

This is a report of 2-year ocular and developmental outcomes for infants receiving low doses of intravitreal bevacizumab for type 1 retinopathy of prematurity (ROP). A total of 120 premature infants (mean birthweight, 687 g; mean gestational age, 24.8 weeks) with type 1 ROP were enrolled in a multicenter, phase 1 dose de-escalation study. One eye per infant received 0.25 mg, 0.125 mg, 0.063 mg, 0.031 mg, 0.016 mg, 0.008 mg, 0.004 mg, or 0.002 mg of intravitreal bevacizumab; fellow eyes when treated received one dosage level higher. At 2 years, 70 of 120 children (58%) underwent ocular examinations; 51 (43%) were assessed using the Bayley Scale of Infant and Toddler Development. Correlation coefficients for the association of total dosage of bevacizumab with Bayley subscales were - 0.20 for cognitive, - 0.15 for motor, - 0.41, and - 0.19 for language. Fourteen children (21%) had myopia greater than 5.00 D in one or both eyes, 7 (10%) had optic nerve atrophy and/ or cupping, 20 (29%) had strabismus, 8 (11%) had manifest nystagmus, and 9 (13%) had amblyopia. In this study cohort, there was no statistically significant correlation between dosage of bevacizumab and Bayley scores at 2 years. However, the sample size was small and the retention rate relatively low, limiting our conclusions. Rates of high myopia and ocular abnormalities do not differ from those reported after larger bevacizumab doses.

Smartphone application links severity of retinopathy of prematurity to early motor behavior in a cohort of high-risk preterm infants

Rodriguez SH, Blair MP, Timtim E, Millman R, Si Z, Wroblewski K, Andrews B, Msall ME, Peyton C  
J AAPOS 2023;27:12.e1-7

General Movement Assessment (GMA) was evaluated with the Motor Optimality Score Revised (MOS-R) as a neurodevelopmental marker in infants with retinopathy of prematurity (ROP). Infants were screened prospectively for ROP at 3 months' post-term age using a smartphone application to complete the GMA and MOS-R. Of 105 enrolled infants, 83 completed the study. Of these, 54 (65%) had any ROP, 32 (39%) had severe ROP, and 13 (16%) had type 1 ROP. The proportion with aberrant GMA was significantly higher in infants with severe ROP compared with infants who had milder ROP. Although the presence of any ROP, stage of ROP, and severe ROP each predicted lower MOS-R scores on univariate analyses, only severe bronchopulmonary dysplasia and markers of brain injury remained significant in the multivariate analysis. The GMA was a convenient, short-term method of data collection with low attrition. Although severe ROP initially appeared linked to poor early motor scores, this association is likely confounded by neurological and respiratory complications, which frequently accompany severe ROP.

Quantitative analysis of tear angiogenic factors in retinopathy of prematurity: a pilot biomarker study  
Magnani JE, Moinuddin O, Pawar M, Sathrasala S, McCaffery H, Vartanian RJ, Besirli CG  
J AAPOS 2023;27:14.e1-6

In this nonrandomized controlled investigation, tear and saliva samples collected from 20 premature infants during serial ophthalmic examination were analyzed using enzymelinked immunoassay with results analyzed as a function of disease stage and need for treatment to aid in diagnosis of retinopathy of prematurity (ROP). Tear volume was directly correlated with corrected gestational age. Tear VEGF levels from samples corresponding to stage 3 ROP were 47.9% lower than in samples corresponding to stage 0-1 and 49.1% lower than in samples corresponding to stage 2 ROP. There were no between-group differences after normalizing tear VEGF by saliva VEGF levels. Tear/saliva ratio for Angiopoietin-1 (Ang-1) was 200% greater and tear/ saliva ratio for Angiopoietin-2 (Ang-2) was 165% greater in samples corresponding to stage 2 versus stage 0-1 ROP disease. Ang-1/Ang-2 ratio was lower in samples from infants who developed stage 2 or worse ROP than in samples from infants who never developed worse than stage 1 ROP. In this study cohort, cytokines involved in the pathophysiology of ROP could be reliably identified in and analyzed from infant tears, and showed variation with ROP severity.

Structural and refractive outcomes of intravitreal ranibizumab followed by laser photocoagulation for type 1 retinopathy of prematurity.

Hoppe C, Holt DG, Arnold BF, Thinda S, Padmanabhan SP, Oatts JT.

J AAPOS. 2022 Dec;26(6):305.e1-305.e6.

Treatment for retinopathy of prematurity (ROP) has a long history of evolution which continues today. Cryotherapy, laser photocoagulation and now anti-vascular endothelial growth factor (anti-VEGF) have all been identified by studies as effective treatments. Current therapy includes early laser photocoagulation and/or anti-VEGF injections. Some studies show a higher prevalence and severity of myopia in infants treated with laser compared to anti-VEGF. This fact, as well as the thought that laser may be more stressful to the infant leads some to advocate for anti-VEGF injection over laser photocoagulation especially for posterior disease. There is still controversy concerning details surrounding ideal anti-VEGF treatment use (dosing, timing, systemic consequences, and risk of recurrence and reactivation, etc). The authors use retrospective review to evaluate refractive and structural outcomes for patients with Type 1 ROP treated with anti-VEGF and delayed laser defined as any laser treatment administered at least 2 weeks and less than 1 year after the initial anti-VEGF treatment of ranibizumab. All patients were initially treated with intravitreal ranibizumab for Type 1 ROP. The timing of delayed laser treatment was scheduled after any reactivation was identified. The authors demonstrate that combined anti-VEGF ranibizumab and delayed laser therapy resulted in satisfactory refractive and structural outcomes for their cohort at 2 years of age. Authors postulate that initial anti-VEGF treatment allows for additional retinal vascularization while subsequent delayed laser photocoagulation provides for definitive treatment truncating the period of observation monitoring for late reactivation. Refractive outcomes in this cohort gave a mean spherical equivalent (SE) of -1.09 D. Prevalence of strabismus in this cohort was 32% consistent with previously reported outcomes. Prevalence of amblyopia in previous studies after ROP laser is reported as 5-10%. The authors note a 19% frequency for amblyopia in their cohort and postulate it is related to extremely low birth weight compared with other studies. Limitations of the study include small sample size and 2-year follow-up. Larger randomized trials are still necessary to evaluate monotherapy vs combination therapy.

Premature infants with gestational age less than 25 weeks require increased ophthalmology resources for retinopathy of prematurity

Vivian S Hawn, Rakin Muhtadi, Pamela Suman, Mariam S Latuga, Graham Quinn, Umar Mian.

J AAPOS. 2022 Dec;26(6):307.e1-307.e5.

Low birth weight (BW) and low gestational age (GA) are associated strongly with developing any-stage retinopathy of prematurity (ROP) as well as severe active ROP. Survival of extremely premature infants continues to increase in developed countries. The authors used a retrospective study to compare the examination and treatment rates for retinopathy of prematurity (ROP) of infants born at GA less than 25 weeks and those born at GA of at least 25 weeks. Secondary outcome was to examine risk factors for developing Type 1 ROP. Since current screening guidelines have high sensitivity but low specificity, there is a significant increasing burden on a small group of pediatric ophthalmologists who screen for ROP. In this cohort, complete screening required an average of 3.1 inpatient visits and 1.6 outpatient examinations per infant for the 395 subjects. The under 25 weeks GA group had almost 3 times the number of inpatient examinations compared to the GA greater than or equal to 25 weeks. In this cohort, GA < 25 infants had increased rate of Type 1 ROP (21%) compared with GA greater than or equal to 25 weeks (2.1%). Literature shows mixed results as to effects of comorbidities in Type 1 ROP. The authors found only GA to be statistically significantly associated with type 1 ROP on multivariable analysis. Limitations of the study include retrospective nature, single institution, small number of patients, and variability in observers. The authors clearly demonstrate that decreasing mortality for infants born less than 25 weeks gestation in NICU's require increased resources including the workload for pediatric ophthalmologists who screen, treat and care for this group of patients.

G-ROP criteria for predicting retinopathy of prematurity among neonates with different birth weight percentiles

ROP

Asli Okbay Gunes, Sevilay Topcuoglu, Gokhan Celik, Osman Kizilay, Muhammed Ali Recai, Akyurekli, Nilgun Karadag, Elif Ozalkaya, Guner Karatekin  
J AAPOS.2022 Dec;26(6):309.e1-309.e5.

The Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study showed that adding postnatal weight gain to birth weight and gestational age detected 100% of cases with type 1 retinopathy of prematurity (ROP) while reducing the ROP examinations by 30%. Current ROP screening guidelines have high sensitivity for detection of ROP but poor specificity for treatment-requiring ROP (TR-ROP). In order to reduce the number of exams for infants and make better use of resources, the addition of suboptimal weight gain has been suggested to be added to predictive models. Small for gestational age infants are at greater risk for suboptimal postnatal growth factor. The authors sought to determine if SGA status affected the sensitivity and specificity of the G-ROP model. The authors found sensitivity of G-ROP for predicting any stage of ROP was lower for their cohort but the sensitivity for predicting TR-ROP was excellent (100%). Authors postulate this may be explained by epidemiologic factors. The number of exams was reduced by 25%. Several perinatal morbidities are significantly associated with TR-ROP. When these were added to the model, sensitivity increased as well as the number of infants to be examined. Care must be taken to not generalize these results to low-income countries where TR-ROP incidence is higher and ROP occurs in more preterm infants until more research is conducted to test the G-ROP model in these countries.

ROP screening with the Pictor Plus camera: a telemedicine solution for developing countries.

Viviane Lanzelotte, MD, Alan Araujo Vieira, MD, PhD, Ana Beatriz Monteiro Fonseca, DSc, Jose Eduardo da Silva, MD, Barbara Gonet, MD, and Arnaldo Costa Bueno, MD, PhD.  
JAAPOS 2022;26:244.e1-6.

Screening for ROP (especially in developing countries) continues to be an area that poses challenges for ophthalmologists and neonatologists. This study assesses the feasibility of using the Volk Pictor Plus portable noncontact ophthalmic camera in detecting ROP by identifying the presence of vascular changes in the posterior pole. The study was designed to make the examination procedure feasible for telemedicine application. The study included 712 images that were evaluated by 3 observers. Observer 1 performed a BIO examination that was used as the gold standard for interobserver agreement analyses. Observers 2 and 3 examined the photos. The study showed a sensitivity of 63.2-65.8% and a specificity of 98.4-100%. Interobserver agreement results were strong. The sensitivity obtained in this study was lower than previous studies likely due to the real-life scenario set up in this study where patient's images were evaluated without any selection for images with vascular changes. This study gives additional data to show the potential usefulness of a portable noncontact camera for ROP screening. While it is not a perfect instrument, it is likely to be useful in the quest to screen more babies for ROP. Since one of the main obstacles to ROP screening by telemedicine is high equipment cost, this camera has the advantage of being 10% of the cost of a wide-field camera. In addition, it is easier to use by trained nonmedical staff given its noncontact nature.

Characteristics of Spontaneously Regressed Retinopathy of Prematurity at Termination of Acute Retinal Screening Examinations Using a Novel Grading System

Ness PJ, Andaluz-Scher L, Leverant RM, Chebolu A, Barry GP.

J Pediatr Ophthalmol Strabismus. 2022;1-6. doi:10.3928/01913913-20221010-01

This single-center retrospective chart review of 521 infants sought to characterize the residual retinal changes of spontaneously regressing retinopathy (at least Stage 1 ROP). The authors developed a novel grading system to characterize the presence of residual fibrotic retinal tissue at termination of acute ROP screening examinations as well as type of residual fibrotic retinal tissue, persistent avascular retina, vitreous hemorrhage, and retinal detachment. A total of 255 eyes met inclusion criteria. A total of 206 of 255 eyes (81%) showed persistent avascular retina, whereas 57 of 255 eyes (22%) showed residual fibrotic retinal tissue at termination of acute screening. The authors concluded that residual fibrotic retinal tissue and persistent avascular retina are common after spontaneous regression of ROP, though the clinical implications of this warranted further study.



Ketamine Analgesia as an Alternative to General Anesthesia During Laser Treatment for Retinopathy of Prematurity.

Sanatkar M, Dastjani Farahani A, Bazvand F.

J Pediatr Ophthalmol Strabismus. 2022;59(6):416-421. doi:10.3928/01913913-20220225-01

This small study sought to determine the safety and efficacy of ketamine analgesia as an alternative to general anesthesia during laser treatment for retinopathy of prematurity (ROP). 18 premature neonates undergoing laser treatment were administered 1 mg/kg of ketamine. If the neonate exhibited movement or distress during the procedure, incremental doses of ketamine were administered. Perioperative ventilation status, severity of pain during the procedure, surgeon satisfaction, and perioperative events were recorded. 16/18 patients tolerated sedation without events. The Premature Infant Pain Profile (PIPP) scores during the procedure were 5 or less in 12 neonates (44.4%), 5 to 10 in 4 neonates (22.2%), and greater than 10 in 2 (11.1%) neonates. Three neonates had perioperative events, which resolved completely with minimal intervention. None of the neonates needed intubation perioperatively, and hemodynamic instability, hypotension, and bradycardia were not recorded in any of the neonates during or after the procedure. The authors concluded that ROP laser treatment could be performed under ketamine sedation with few perioperative complications, and perhaps even in the NICU. Albeit small, this was an interesting study raising the possibility of shorter procedure times in more convenient clinical environments.

Characterization of Errors in Retinopathy of Prematurity Diagnosis by Ophthalmologists-in-Training in the United States and Canada

Al-Khaled T, Patel SN, Valikodath NG, et al.

J Pediatr Ophthalmol Strabismus. 2022;1-7. doi:10.3928/01913913-20220609-01

This prospective cohort study of 32 ophthalmologists-in-training at 6 training centers in the US and Canada sought to identify factors that lead to misdiagnosis of ROP. They were presented 20 web-based cases of ROP using wide-field retinal images, and they were asked to diagnose plus disease, zone, stage, and category for each eye. Responses were compared to a consensus reference standard diagnosis for accuracy. The authors found that the category of ROP was misdiagnosed at a rate of 48%, and that classification of plus disease was most commonly associated with misdiagnosis of treatment-requiring and type 2 or pre-plus disease. The diagnostic error rate of postgraduate year (PGY)-2 trainees was significantly higher than PGY-3 trainees. The authors concluded that integration of structured learning for ROP in residency education may improve diagnostic competency - a point which reinforces the need for fellowship training in diagnosis and management of ROP.

Characterization of Errors in Retinopathy of Prematurity Diagnosis by Ophthalmologists-in-Training in Middle-Income Countries

Patel SN, Al-Khaled T, Kang KB, et al.

J Pediatr Ophthalmol Strabismus. 2022;1-9. doi:10.3928/01913913-20220609-02

This prospective cohort study of 200 ophthalmologists-in-training at programs in Brazil, Mexico, and the Philippines sought to identify factors that lead to misdiagnosis of ROP. They were presented 20 web-based cases of ROP using wide-field retinal images, and they were asked to diagnose plus disease, zone, stage, and category for each eye. Responses were compared to a consensus reference standard diagnosis for accuracy. The authors found that the category of ROP was misdiagnosed at a rate of 48% - 59% for all countries. The error rate in identifying type 2 or pre-plus disease was 77%, with a tendency for overdiagnosis. Misdiagnosis of treatment-requiring ROP as type 2 ROP was most commonly associated with incorrectly identifying plus disease. The authors concluded that identification of plus disease was the salient factor leading to incorrect diagnosis. Just like the US/Canada based study, this study reinforces the need for fellowship training in diagnosis and management of ROP.

Yum HR, Park SH. Clinical features of premature twin babies with intersibling asymmetry of retinopathy of prematurity severity.

Can J Ophthalmol. Oct 2022;57(5):337-343.

This is a retrospective chart review of 105 premature twin pairs born between March 2009 and September 2018. This study aimed to assess the clinical features of premature twin babies showing intersibling asymmetry in the severity of ROP and risk factors associated with developing higher-stage ROP. The selection was based on a) two or more stages of difference between siblings, b) one sibling

requiring treatment and the other having no ROP or spontaneous regressing ROP, c) one sibling having APROP, and the other having staged ROP or no ROP. Seventy-three twin pairs showed symmetry in disease severity. Thirty-two pairs (30.5%) showed intersibling asymmetry of ROP severity. 43.8% met criteria A, 28.1% met criteria B, and 28.1% met criteria C. Twenty-one infants required treatment. The mean GA was  $28.7 \pm 3.3$  weeks, and the mean BW was  $1270 \pm 340$ g. The duration of oxygen supplementation was significantly longer in those with more severe ROP. The need for transfusions was also significantly higher for siblings with more severe ROP. Oxygen supplementation duration was the only statistically significant independent risk factor associated with severe ROP. Other systemic risk factors did not reach statistical significance likely. The authors mentioned the small sample size as a possible culprit for their results. This study highlights the importance of oxygen supplementation in twins as the cause of intersibling ROP asymmetry.

#### Association Between Retinopathy of Prematurity in Very-Low-Birth-Weight Infants and Neurodevelopmental Impairment.

Han G, Lim DH, Kang D, Cho J, Guallar E, Chang YS, Chung TY, Kim SJ, Park WS.  
American journal of ophthalmology. 2022 Dec 1;244:205-15.

Distinguishing neurodevelopmental outcomes as they relate to retinopathy of prematurity (ROP) is challenging due to significant co-variables such as gestational age and birth weight which independently affect neurodevelopment. The goal of this prospective cohort study was to evaluate the impact of ROP severity on neurodevelopmental outcomes in a cohort of 1039 infants who were very-low-birthweight (VLBW) and developed ROP. Participants underwent testing with the Bayley Scales of Infant and Toddler Development (2<sup>nd</sup> edition). This study was performed with data obtained from the Korean Neonatal Network and compared these participants to VLBW babies without ROP. Of their cohort, 449 of the 1093 infants required ROP treatment. Compared to the no ROP group, the odds ratio for any neurodevelopmental impairment in those with ROP not requiring treatment was 1.13 and increased to 1.72 in those with ROP requiring treatment. 37.6% of the cohort had neurodevelopmental impairment and their analysis showed that ROP itself was an independent risk factor for neurodevelopmental impairment in this cohort. There was no association between type of ROP treatment (laser versus anti-VEGF) and neurodevelopmental outcomes. While this study may be limited in its generalizability due to the study population, it does provide insight into the relationship between ROP and neurodevelopment with implications into future studies looking at adolescence and adulthood.

#### Accidentally diagnosed ocular abnormalities identified during close screening for retinopathy of prematurity. Ozturk T, Durmaz Engin C, Karatas Yigitaslan E, Yaman A, Berk T. Eur J Ophthalmol. 2022 Nov;32(6):3267-3273.

The authors retrospectively reviewed the charts of 1568 preterm infants who had been screened for retinopathy of prematurity (ROP). Abnormal ocular findings other than ROP were diagnosed in 296 infants (19.2%). Tunica vasculosa lentis was the most common finding (25%), followed by vitreous or retinal hemorrhages (17.2%) and retinal white lesions (16.6%). The retina was the most frequently involved anatomic site when pathologic conditions were identified. Other frequent ocular findings included optic disc cupping, congenital cataract, optic nerve hypoplasia, choroidal nevus, persistent fetal vasculature, lid hemangioma, and tilted disc. However, life-threatening pathologies such as lipemia retinalis and even retinoblastoma were also diagnosed. The authors conclude that ophthalmologists must be aware of concurrent ocular pathologies in premature children undergoing screening for ROP that may be vision or life-threatening.

#### Comparison of Fluorescein Angiography Findings in Stage 3 Retinopathy of Prematurity in Zone II Treated With or Without Anti-VEGF.

Vural A, Demirayak B, Ozbas M, Onur IU, Celik G.  
Eur J Ophthalmol. 2022 Nov;32(6):3281-3288.

The authors defined late-stage fluorescein angiography (FA) findings in patients who received anti-vascular endothelial growth factor (VEGF) agents (intravitreal bevacizumab or aflibercept) as a treatment for stage 3 retinopathy of prematurity (ROP) in zone II. Vascular abnormalities, such as vascular leakage, shunts at the vascular-avascular junction, periarteriolar areas with hypoperfusion, fine branching and blunt termination of the vessels and, were recorded. FA findings revealed leakage in the eyes of 27.69%

of the infants in the anti-VEGF-treated group and in 21.7% of the untreated group ( $p = 0.638$ ). Among the abnormal vascular findings in the peripheral retina, the ratios of fine branching and blunt termination, numbers of shunts along the vascular-avascular junction, and sizes of periarteriolar areas of hypoperfusion were significantly larger in the untreated group than in the treated group ( $p < 0.05$ ;  $p < 0.01$ ). The gestational ages and birth weights were significantly lower ( $p \leq 0.05$ ) in infants with vascular findings in both groups. The authors conclude that vascular abnormalities in the peripheral retina are likely due to the ROP itself. Although these abnormalities were detected by FA imaging in both treated and untreated infants with ROP, they were significantly less frequent in patients treated with anti-VEGF, indicating that anti-VEGF treatments have a partially positive effect on the retinal vascularization process.

Effect of laser photocoagulation, antiangiogenic therapy or a combined treatment on refractive outcomes of newborns with ROP.

Del Portillo MC, Navarro PI, Duran D, Serrano JC  
Eur J Ophthalmol. 2022 Nov;32(6):3295-3302.

This retrospective, cross-sectional study evaluated the refractive outcome after treatment with laser photocoagulation, intravitreal injection, or both, for the treatment of type 1 ROP and/or aggressive posterior ROP. Seventy-seven eyes (56 patients) with ROP treated with laser, intravitreal injection, or a combination of both were included. Median gestational age was 29 weeks (IQR = 3), median birth weight was 1100 (IQR = 335) and mean corrected age at the time of treatment was 37.3 weeks (SD 2.2). Refractive outcomes were reported at two different time points (1-3 years after treatment and 3-5 years after treatment) in both spherical equivalent (SE) terms and also in defocus equivalent (DE) terms. The defocus equivalent was first described by Holladay et al in 1991 to measure refractive error after refractive surgery and may be a more accurate measurement of visual acuity and optical clarity. For this cohort of patients, the refractive status in spherical equivalent terms for the first refraction had a median of -0.50 diopters and in defocus terms, 4.00 diopters (D). For the second refraction, refractive outcomes were found to be -3.00 diopters and 4.00 diopters (D), respectively. The Pearson correlation test result for the first measurement was 93% ( $p = 0.000$ ) and for the second evaluation was 99% ( $p = 0.000$ ). Low birth weight had a statistically significant association to the increase of the refractive outcome. The high correlation between SE and DE for refractive errors allows us to confirm that DE is an appropriate metric to report refractive outcomes in this group of patients due to the presence of combined refractive refractive errors.

Pulmonary Hypertension in Preterm Infants Treated With Laser vs Anti-Vascular Endothelial Growth Factor Therapy for Retinopathy of Prematurity

Christopher R. Nitkin, MD1; Nicolas A. Bamat, MD, MSCE2; Joanne Lagatta, MD, MS3; et al  
JAMA Ophthalmol. 2022;140(11):1085-1094.

This is a retrospective cohort study of 1477 infants at 48 tertiary children's hospitals investigating if intraocular anti-vascular endothelial growth factor (VEGF) agents used to treat retinopathy of prematurity (ROP) are associated with an increased risk of pulmonary hypertension (PH) requiring medical therapy. Anti-vascular endothelial growth factor (VEGF) therapy for ROP has potential ocular and systemic advantages compared with laser, but the systemic risks of anti-VEGF therapy in preterm infants are poorly quantified. The main measure of this study was whether the patient newly required pulmonary vasodilators at least 7 days after ROP therapy was compared between exposure groups, matched using propensity scores generated from preexposure variables, and adjusted for birth year and hospital. The odds of receiving an echocardiogram after 30 days of age was also included to adjust for secular trends and interhospital variation in PH screening. More infants who received anti-VEGF therapy were treated for PH, but when adjusted for hospital and year, this was not statistically significant. These findings suggest exposure to anti-VEGF may be associated with PH, although they could not exclude the possibility of residual confounding based on systemic comorbidities or hospital variation in practice.

The Male to Female Ratio in Treatment-Warranted Retinopathy of Prematurity: A Systematic Meta-Analysis

Sandra Hoyek, MD1; Bryan L. Peacker, BA1; Luis A. Acaba-Berrocal, MD2; et al  
JAMA Ophthalmol. 2022;140(11):1110-1120

This is a systematic review and meta-analysis that included 316 studies with a total of 31,026 treated patients, investigating the association of sex with treatment-warranted ROP. They found that a higher percentage of males were treated for ROP (55%), a higher percentage of males met the screening criteria for ROP compared with female infants, and the odds of receiving treatment for ROP was similar between screened male and female infants. To further investigate the reason for this imbalance, two more meta-analyses were conducted. The first one included 50 studies reporting data on birth weight, gestational age, and postconceptual age at first treatment. The goal was to assess whether known risk factors for ROP were sex variable. However, treated male and female infants were comparable across these variables. Second, they evaluated the effects on income level and geography on outcomes. The hypothesis was that countries with lower income levels may have less advanced neonatal care, which could highlight an underlying fragility of male neonates with a greater imbalance in the treatment ratio. While there was a trend toward a greater ratio of male infants being treated in countries with lower income levels, the difference was not statistically significant. Through this meta-analysis, they concluded that more male infants were treated for ROP than female infants, and they believe that clinical studies on ROP screening and treatment will need to account for sex as variable that may impact outcomes. Additionally, from a clinical standpoint, understanding that male infants are more likely to require treatment and the underlying causes are not necessarily clear, it might be prudent to monitor these patients more frequently.

#### Association of Optical Coherence Tomography-Measured Fibrovascular Ridge Thickness and Clinical Disease Stage in Retinopathy of Prematurity.

Thanh-Tin P. Nguyen, MD; Shuibin Ni, MS; Susan Ostmo, BS; et al.  
JAMA Ophthalmol. 2022; 140(11):1121-1127.

This is a cross-sectional longitudinal study which compared OCT-based ridge thickness calculated from OCT B-scans by a masked examiner to the clinical diagnosis of 2 masked examiners using traditional ROP stage classifications. The goal was to evaluate whether optical coherence tomography (OCT)-derived retinal thickness measurements at the vascular-avascular junction are associated with clinical diagnosis of ROP stage. A total of 128 separate OCT examinations from 50 eyes of 25 patients were analyzed. Higher disease classification was associated with higher axial ridge thickness on OCT, with mean (SD) thickness measurements of 264.2 (11.2)  $\mu\text{m}$  ( $P < .001$ ), 334.2 (11.4)  $\mu\text{m}$  ( $P < .001$ ), and 495.0 (32.2)  $\mu\text{m}$  ( $P < .001$ ) for stages 1, 2, and 3, respectively. They also found a decrease in ridge thickness following treatment with bevacizumab. These results suggest that OCT-based quantification of peripheral stage in ROP may be an objective and quantitative biomarker that may be useful for clinical diagnosis and longitudinal monitoring and may have implications for disease classification in the future. Despite the presence of standard photographs for instruction and comparison, there is inter observer variability for all components of the ICROP classifications due to a variety of factors (difficulty of examination, training differences). While not yet widely available, these results suggest that OCT may one day be used for ultra-widefield anatomic staging of ROP, more precisely characterizing the degree and extent of peripheral pathology. OCT is also superior to the ophthalmoscopic examination for identifying early vitreoretinal traction, which means surgical intervention could be timed early to prevent retinal detachments.

#### Decreased Levels of Erythrocyte Membrane Arachidonic and Docosahexaenoic Acids Are Associated with Retinopathy of Prematurity

Tessa Gillespie; Esther Kim; Tristan Grogan; et al.

Investigative Ophthalmology & Visual Science November 2022, Vol. 63, 23.

This is a prospective observational study of babies with ROP to investigate the role of red blood cell membrane (RBCM) arachidonic acid (ARA) and docosahexaenoic acid (DHA) in the regulation of ROP. ARA and DHA regulate retinal inflammation and angiogenesis, and have been implicated as therefore playing a role in ROP development and progression. During the third trimester of pregnancy, the placenta transfers ARA and DHA from the pregnant mom to the fetus, and many VLBW infants are born prior to the full transfer. Postnatally, VLBW infants depend on parenteral nutrition and intravenous lipid emulsions (ILEs) that fail to match in utero accretion rates for ARA and DHA. As a result, VLBW infants quickly develop a persistent ARA and DHA deficiency. In a randomized controlled trial in Sweden, enteral ARA and DHA supplementation was associated with a 50% decrease in severe ROP. They found that in the first 4 weeks after birth, infants with any ROP and infants with more severe ROP, including those

requiring treatment, had lower RBCM ARA and DHA status over the first month of life compared to infants who did not develop ROP or treatment-requiring ROP. Overall, this study indicates that ARA and DHA deficiency may be a modifiable risk factor for ROP.

Pediatric Eye Disease Investigator Group. Low- and Very Low-Dose Bevacizumab for Retinopathy of Prematurity: Reactivations, Additional Treatments, and 12-Month Outcomes.

Freedman SF, Hercinovic A, Wallace DK, Kraker RT, Li Z, Bhatt AR, Boente CS, Crouch ER, Hubbard GB, Rogers DL, VanderVeen D, Yang MB, Cheung NL, Cotter SA, Holmes JM; Ophthalmology. 2022 Oct;129(10):1120-1128. doi: 10.1016/j.ophtha.2022.05.019. Epub 2022 Jun 1. PMID: 35660415; PMCID: PMC9509410.

This study reports the 12-month outcomes of a masked, multicenter, dose de-escalation study on 120 infants with type 1 ROP treated with low-dose or very low-dose intravitreal bevacizumab. Among 120 infants initially enrolled, 98 completed the 12-month examination. The doses used for study eyes included 0.25mg, 0.125mg, 0.63mg, or 0.31mg in the low-dose group and 0.016mg, 0.008mg, 0.004mg, or 0.002mg in the very low-dose group. The relative risks for additional treatment at each initial dose and for each category of type 1 ROP did not show any clear trend. A trend toward the very low doses having earlier reactivation was seen, 76.4 days compared to 85.7 days in the low-dose group. No relationship was seen between total bevacizumab dose in the eye and cycloplegic refractive error or anisometropia at 12-months. In eyes receiving laser for reactivation, no relationship was found between post-menstrual age (PMA) at time of laser and refractive error at 12-months or between PMA at time of laser and high myopia at 12 months. No relation was seen between anterior segment abnormalities, strabismus, nystagmus, or amblyopia and total bevacizumab dose at 12-months. Limitations of this study include variations in management strategies for reactivation and peripheral avascular retina, limited number of subjects in each cohort, and no photographic documentation of initial type 1 ROP or extent of final vascularization.

Retinopathy of Prematurity Treatment Trends from 2003 to 2020 in the United States.

Khan SI, Ryu WY, Wood EH, Moshfeghi DM, Shah JK, Lambert SR.

Ophthalmology. 2022 Oct;129(10):1216-1218. doi: 10.1016/j.ophtha.2022.06.008. Epub 2022 Jun 15. PMID: 35714734; PMCID: PMC9509438.

This study evaluated the use of laser and anti-VEGF and associated adverse outcomes for ROP between 2003 and 2020, using data from the Optum's Clinformatics Data Mart Database. All infants born since Jan 1, 2003 with ICD9/10 code related to prematurity and studied all infants with a birth weight of <1500g or gestational age <30 weeks. ROP status was determined using ICD codes. Interventions were assessed using CPT codes of anti-VEGF therapy, laser, and incisional retinal detachment repair. Of the high-risk infants with a diagnosis of ROP, 5.8% required treatment with laser, anti-VEGF, or both. Laser was the most common treatment (80.7%). Anti-VEGF monotherapy increased between 2009-2011 and 2015-2017. The majority of combination patients received injection before laser. Extremely low birth weight (<1000g) was not associated with anti-VEGF vs laser. The year of management closer to 2017 independently was associated with increased anti-VEGF use. Female infants were less likely to receive anti-VEGF. There was no difference in the occurrence of stage 4 or 5 ROP in infants receiving laser or anti-VEGF. This study is limited by its lack of data because of ICD coding and generalizability beyond privately insured children in the Clinformatics database.

Retinopathy of Prematurity Injection Consortium. Practice Patterns and Outcomes of Intravitreal Anti-VEGF Injection for Retinopathy of Prematurity: An International Multicenter Study.

Patel NA, Acaba-Berrocal LA, Hoyek S, Fan KC, Martinez-Castellanos MA, Baumal CR, Harper CA 3rd, Berrocal AM;

Ophthalmology. 2022 Dec;129(12):1380-1388. doi: 10.1016/j.ophtha.2022.07.009. Epub 2022 Jul 19. PMID: 35863512.

This is an international, multicenter, retrospective series to report practice patterns of intravitreal injections of anti-VEGF for ROP and outcomes data between 2007-2021. Twenty-three sites (16 US, 7 non-US) participated. The study included 1677 eyes receiving intravitreal anti-VEGF. Mean gestational age at the time of treatment was 25.7 weeks and mean birth weight was 787 grams. A 30 gauge needle was most used (51%) and performed in the infero-temporal quadrant (51.3%). The distance from the limbus ranged

from 0.75mm to 2mm, with 1mm being the most common (65%). Bevacizumab was used in 71.4% of eyes, ranibizumab in 24.4%, and aflibercept in 3%. The most common dose of anti-VEGF used was 0.625 mg for bevacizumab (64%), 0.15 mg for ranibizumab (50%), and 1 mg (86%) for aflibercept, which are all half of the adult dose. Most patients (90.7%) had bilateral injections. Thirty-six percent of eyes required retreatment with laser or anti-VEGF – 80% were retreated with laser alone, 10% with anti-VEGF alone, and 10% with both. Regarding the percentage of patients requiring retreatment based on medication choice, it was 28.7% with bevacizumab, 61% with ranibizumab, and 14% with aflibercept. The complication rate was low at 0.9% (self-resolving vitreous hemorrhage, cataract due to lens injury, subconjunctival hemorrhage, corneal abrasion). Notably, there were no reported cases of endophthalmitis or retinal detachments. Infants in the US have lower average birth weight and gestational age compared to the non-US group. Bevacizumab was the preferred medication for both regions. Retreatments with re-injection or laser were significantly higher in the US group compared to the non-US group. There was no difference in the incidence of complications. The US sites versus non-US sites had higher rates of primarily prophylactic post-injection laser (average, 59.32% vs. 26.67%). The US- versus non-US sites had a lower tolerance for remaining avascularity at 60 weeks, with 36% versus 0% stating that no avascularity is allowable and 14% versus 50% accepting avascularity in all of zone III or greater at this time-point. A limitation of this study is that long-term outcomes, including the rate of retinal detachment, could not be determined in this cohort. The number of sites that participated was also limited, so they could not determine if there was significant variability depending on international socioeconomic status, geography, or population. Overall, this study does provide valuable information regarding practice patterns and outcomes in infants with ROP who receive anti-VEGF injection.

A Network Meta-Analysis of Retreatments Rates following Bevacizumab, Ranibizumab, Aflibercept, and Laser for Retinopathy of Prematurity.

Chang E, Josan AS, Purohit R, Patel CK, Xue K.

Ophthalmology. 2022 Dec;129(12):1389-1401. doi: 10.1016/j.ophtha.2022.06.042. Epub 2022 Jul 14.

PMID: 35842190.

This study is a network meta-analysis comparing bevacizumab, ranibizumab, aflibercept, and laser treatment as primary therapies for ROP in terms of retreatment rate. Thirty studies were included in the meta-analysis. For type 1 ROP, all treatment modalities demonstrated high efficacy. The single treatment success rate for bevacizumab was 87%, ranibizumab 74%, aflibercept 80.7%, and laser 89.3%. Twenty of the studies included in the meta-analysis reported time to retreatment. Laser was associated with a 62% reduction in risk of needing retreatment compared to ranibizumab in type 1 ROP, but this was not seen for aflibercept or bevacizumab. The combined mean time to secondary treatment following primary treatment with anti-VEGF were 9.29 weeks for ranibizumab, 11.36 weeks for bevacizumab, and 12.96 weeks for aflibercept. There was a statistically significant difference in time to retreatment between both bevacizumab and aflibercept compared to ranibizumab. There was no association found between retreatment rates and gestational age, birth weight, or post-menstrual age at treatment. The authors also performed a separate analysis on just zone 1 ROP, which included 10 studies. The analysis showed that all modalities had high efficacy rates and that bevacizumab was associated with a 67% risk reduction in retreatment compared to laser. There was no data available for aflibercept in this analysis. The general observation was that ranibizumab may have a higher rate of retreatment, however this was not statistically significant. The authors hypothesize that this may be due to the shorter half-life of ranibizumab in the non-vitreotomized eye. Limitations of this meta-analysis include the inherent heterogeneity among the studies included and the paucity of data on aflibercept--final data for the FIREFLY RTC (aflibercept vs. laser) has not been released at the time of this publication).

Structural outcome after surgery for stage 5 retinopathy of prematurity based on the new international classification ICROP3

Mano F, Iwahashi C, Kuniyoshi K, Kusaka S. *Retina*. 42(10):1950-1957, October 2022.

With the new ICROP3 nomenclature dividing Stage 5 ROP into 5a, 5b, and 5c, there is need for further study of the clinical implications of each of those stages. The authors retrospectively reviewed the records of 54 eyes of 34 patients who underwent vitrectomy for Stage 5 ROP by a single surgeon over a 17-year period in Japan. The authors used the new ICROP3 classification to identify 18 eyes with 5A, 33 eyes

with 5B, and 3 eyes with 5C. Complete retinal reattachment was achieved in 16 eyes (88.9%) with 5A and 13 eyes (39.4%) with 5B. The 3 eyes with 5C were considered inoperable. Iatrogenic retinal tears occurred during surgery in 13 eyes (4 with 5A and 9 with 5B). At the end of vitrectomy, seven eyes with high vascular activity received intravitreal bevacizumab. None of those 7 patients developed post-operative vitreous hemorrhage or glaucoma, while 13 eyes (27.2%) of those who did not receive bevacizumab developed one of these complications. The authors concluded that the new ICROP3 sub-categories for Stage 5 ROP are useful for predicting final anatomic success, and they suggest that intraoperative intravitreal bevacizumab may reduce postoperative complication rates.

Long-term effects of anti-VEGF monotherapy for retinopathy of prematurity on the retinal and refractive development of eye

Sukgen EA, Atalay HT, Özdek Ş.

*Retina* 42(11):p 2194-2202, November 2022. | DOI: 10.1097/IAE.0000000000003590

Though anti-VEGF injections have become a key tool in the management of ROP, it is still not well understood how they might affect the foveal development, maturation of the retina, axial growth, and emmetropization mechanisms of the eye. The authors retrospectively reviewed the records of all babies treated with anti-VEGF monotherapy at their institution in Turkey over a period of 4.5 years, including only babies who had an eye exam after 24 months of corrected age. A total of 36 eyes of 18 children met inclusion criteria. Treatment was with bevacizumab in 10 eyes, with ranibizumab in 14 eyes, and with aflibercept in 12 eyes. The mean spherical equivalent was  $-0.25 \pm 1.82$ ; axial length was  $20.81 \pm 0.62$  mm. Twenty-one of 36 eyes (58%) were found to have persistent avascular retina, 6 of them in Zone II. Spectral domain OCT was available for 18 eyes. The ellipsoid zone developed normally in all 18, but eight eyes had shallow or absent foveal pit. This study was limited by its small sample size, variety of anti-VEGF medications used, and its retrospective nature, but it invites further study into the long-term development of eyes treated with anti-VEGF medications for ROP.

Rate of and time to complete retinal vascularization in premature infants and associated factors

Lai TT, Yang CM, Hsieh YT, Yeh PT, Huang CW, Tsai CY.

*Retina* 43(1):p 102-110, January 2023.

There is ongoing debate regarding management of babies with persistent avascular retina (PAR) after retinopathy of prematurity, and the authors argue that more longitudinal data is needed on vascular growth and time to complete vascularization in order to further clarify growth patterns and define PAR. They retrospectively reviewed the eye exams of all babies screened for ROP at the National Taiwan University Hospital over a 3-year period and documented time of complete vascularization. A total of 490 babies had complete records of retinal vascularization outcomes, of whom 439 (89.6%) achieved complete vascularization at an average age of 45.39 weeks gestational age. In babies who fully vascularized, 95% had vascularized by 64 weeks gestational age. ROP developed in 118 infants (22.6%), 33 of whom (6.10%) received anti-VEGF injections. Of the 51 babies who did not fully vascularize, 25 had received anti-VEGF injections (representing 83% of their anti-VEGF treated eyes), 25 had developed ROP that did not require treatment, and 1 had no history of ROP. No infant with incomplete vascularization required surgical intervention during the study period. Lower birthweight and history of anti-VEGF injection were the only two predictors of incomplete vascularization.

Prenatal maternal characteristics associated with retinopathy of prematurity

Strawbridge JC, Chu A, Dammann O, Hanson J, Janzen C, Tsui I.

*Retina*. 43(2):230-237, February 2023.

As advances in neonatal care have improved the number of infants surviving to be at risk of ROP, there has been increased attention on the identification of risk factors associated with greater ROP incidence and severity. The role of prenatal factors has not been adequately studied. The authors retrospectively reviewed the records of all babies referred for ROP screening at UCLA over a 10 year period, excluding babies born at or later than 30 weeks gestational age. They also excluded infants whose mothers had unavailable medical records. Maternal data gathered included age at delivery, race, ethnicity, insurance type (private vs Medicaid), smoking status during pregnancy, and maternal morbidities (pregestational

hypertension, diabetes, chorioamnionitis, etc). Babies were classified as having Type 1 ROP, low-grade ROP, or no ROP. A total of 236 babies met the study criteria. The only maternal characteristics found to be associated with a significantly high of any-stage ROP were Medicaid insurance and chorioamnionitis. Medicaid insurance was not associated with increased risk of Type 1 ROP, though infants born to Hispanic, Black, and Asian mothers did have higher risk of Type 1 ROP compared to infants born to white mothers. The authors argue that physicians should consider these prenatal factors alongside infant comorbidities and post-natal course when characterizing infants as high-risk for ROP.

Development and validation of a new clinical decision support tool to optimize screening for retinopathy of prematurity.

Pivodic A, Johansson H, Smith LEH, et al.

Br J Ophthalmol. 2022 Nov;106(11):1573-1580. doi: 10.1136/bjophthalmol-2020-318719.

This research group previously published WINROP, and more recently published prediction model for ROP requiring treatment, DIGIROP-Birth, for infants born at GA 24–30 weeks, estimating individual risks at an early stage based on birth characteristics alone (GA, birth weight and sex). In the current study, they extended DIGIROP-Birth into DIGIROP-Screen to also include ROP progression data with the intention of creating a clinical decision support tool to reduce the burden of ROP screening sessions using known risk factors at birth and postnatal parameters as well as statistical approaches which enable risks to vary over time. The aim was to develop and validate models with 100% sensitivity to capture all infants requiring treatment and the highest specificity to reduce examinations in infants not developing severe ROP in the cohort using parameters that were easily available to ophthalmologists. They used data from the Swedish National Registry for ROP (~97% coverage rate) and included 6991 infants born between 2007 and 2017 in the model development group. External validation groups were taken from registries in Germany, Boston, and Utah. The US cohorts included infant weight data which were used to compare this model to 4 other ROP models (WINROP, CO-ROP, CHOP-ROP, OMA-ROP). For infants at PNA 6–14 weeks, sensitivity was 100% (equal or higher sensitivity and specificity compared with other models). The model isn't perfect: it did misclassify one infant with VACTERL as not needing screening, and it doesn't include micropreemies <24 weeks GA, but does show promise in reducing the screening burden for ROP. The authors state that the algorithm must be validated in any new cohort before being adopted to show that the same 100% sensitivity and high specificity apply, and if not, modifications can be made for that specific cohort.

Macular sensitivity assessment and fixation analysis using microperimetry in children with retinopathy of prematurity.

Ozen Tunay Z, Idil A.

Br J Ophthalmol. 2022 Dec;106(12):1767-1771. doi: 10.1136/bjophthalmol-2021-319352.

This was a retrospective cohort study of 51 formerly preterm children with mean age of 10 years at the time of study investigating retinal sensitivity and fixation stability using microperimetry. There were 3 groups: children with spontaneously resolved ROP vs children with ROP treated with laser vs controls without ROP. Mean average threshold (AT) for macular sensitivity were not significantly different among the groups, but it was abnormal in 29% of the entire study population. It was better in older children >11 years old. Fixation stability was also similar among the groups but was noted to be unstable in 27% of of the study population. Of note, gestational age and birthweight were significantly different among the 3 groups with the laser treatment group having lower GA and BW. ROP itself or laser treatment did not have a significant affect on macular light sensitivity or fixation stability in this cohort.

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Incidence and Risk Factors for Retinopathy of Prematurity in a Portuguese Cohort.

Almeida AC, Brízido M, Teixeira S, Coelho C, Borrego LM, Correia M.

J Pediatr Ophthalmol Strabismus. 2022;59(4):254-260. doi:10.3928/01913913-20220104-01

This retrospective case series sought to evaluate the incidence and risk factors for retinopathy of prematurity (ROP) in two Portuguese neonatal units with a sub-analysis of infants with a gestational age (GA) of 28 weeks or older. A total of 475 infants were included with a median GA of 30 weeks (range: 23 to 36 weeks) and a median birth weight of 1,229 grams (range: 408 to 2,620 grams). ROP was diagnosed in 113 infants (23.8%) and 29 (6.1%) were treated. In the multivariate analysis, GA and hyperglycemia were significantly associated with severe ROP ( $P < .001$ ). In the subgroup analysis of infants with a GA of



28 weeks or older, bronchopulmonary dysplasia, late-onset sepsis, and hyperglycemia were linked to severe ROP. The authors concluded that the incidence of ROP in the cohort fell within the range of other high-income countries, and that hyperglycemia overpowered all of the other risk factors. Although rare, more mature infants were also at risk for severe ROP. Infants with older GA shared the same group of risk factors, but bronchopulmonary dysplasia seemed to play a greater role. The study was limited by its small sample size.

Application of the Postnatal Growth and Retinopathy of Prematurity (G-ROP) criteria at a tertiary referral hospital.

Ijeoma Chinwuba, MD, G. Baker Hubbard, MD, Prethy Rao, MD, MPH, Natalie Weil, MD, and Amy K. Hutchinson, MD.

J AAPOS 2022;26:66.e1-4.

Retinopathy of prematurity is a potentially blinding disorder that is increasing in prevalence as medical advances allow for lower mortality among premature infants. Screening for this condition is important as timely treatment can prevent devastating sequelae. Although the current screening process is highly sensitive, it is nonspecific, and only 5-10% of patients undergoing screening require treatment for ROP. As these exams can strain resources and place unnecessary stress on neonates, efforts are underway to improve the specificity of screening recommendations. Along these lines, a new screening criterion that takes into account postnatal growth was developed (G-ROP). This allowed for the gestational age criterion to be reduced to <28 weeks and the birth weight criterion to be reduced to <1051 grams. This study set out to evaluate the G-ROP screening criteria when applied to a population of premature infants at a tertiary referral children's hospital. A total of 896 children were included in the analysis. Treatment for ROP was required in 121 infants. The sensitivity of the G-ROP BW and GA criteria alone to identify treatment-requiring patients was 99.2% with all but one of the treated patients being successfully identified. This one child had a very unusual and aggressive case that is not commonly seen in a 29-week-old infant. The child eventually progressed to bilateral tractional retinal detachments despite appropriately timed laser treatment, which brought into question whether there was other underlying pathology. This study was unable to comment on exactly how many children would have needed to be screened with all the G-ROP criteria as they did not have accurate growth and hydrocephalus data for many of the children who were transferred in from outside hospitals. This study supports the potential utility of the G-ROP model and highlights the importance of appropriate records being available upon transfer of premature infants to accurately apply these screening criteria. External validation of these criteria that could reduce the burden of ROP screening while still maintaining high sensitivity is incredibly important to reduce the burdens of screening on pediatric ophthalmologists, the NICU staff, and premature infants.

A retrospective analysis of ultra-widefield photograph (Optos) documentation of retinopathy of prematurity at a tertiary eye care outpatient setup: the Indian Twin Cities ROP Study, report number 11.

Sushma Jayanna, DNB, Komal Agarwal, FRCS, Virangi Doshi, MBBS, Rakshi Ugandhar Reddy, B Optom, Hasnat Ali, MBA, Avantika Dogra, MS, Brijesh Takkar, MS, Hitesh Agarwal, FRCS, Tapas Ranjan Padhi, MS, Srilakshmi Chittabathini, Msc, and Subhadra Jalali, MS.

J AAPOS 2022;26:68.e1-6.

Ultrawide-field imaging to assess ROP offers advantages over current imaging modalities because it is noncontact and has a large field of view with a single capture. It also has the fastest image acquisition time and can be done in an outpatient setting. The purpose of this study was to demonstrate the usefulness of UWF photography for documentation of ROP in the outpatient clinic of a south Indian tertiary eye care center. Imaging was performed in the following manner: after feeding and burping, the baby was wrapped in a warm, clean cloth; proparacaine drops were placed in the eyes followed by a pediatric lid speculum; a modified flying baby position was maintained with one arm supporting the chest/chin and one supporting the head; the pupil was aligned by moving the head. Total time for preparation and image acquisition was 5-7 minutes. A total of 247 infants underwent imaging, of which 187 captured good-quality images. Of those 187 infants, 22 (11.7%) had findings that were discordant with binocular indirect ophthalmoscopy. No posterior disease was missed, but 4 infants who received treatment would NOT have been treated based solely on UWF photography. Of the 60 babies who did not

have high quality images, 41 required interventions. This study demonstrates the utility of UWF fundus photography in documentation of ROP in a high-volume outpatient clinic setting. This technique results in images out to the periphery and obviates the need for separate equipment to photograph adults and babies. While a great adjunct to BIO, UWF photographs do not appear to be a replacement for physical examination given the limitations in image quality and discordance between BIO and UWF photographs.

Cost comparison of using reusable versus disposable equipment for retinopathy of prematurity screening rounds.

Jennifer M. Chang-Wolf, BSE, Evan R. Myers, MD, MPH, Sharon F. Freedman, MD, and S. Grace Pralapakorn, MD, MPH.  
J AAPOS 2022;26:82-84.

Maintaining sterile equipment during ROP screening examinations is important to avoid spreading infections between screened infants. Two methods of maintaining sterility have been proposed: purchasing enough sets of reusable equipment to cover the maximum number of examinations expected per day or using disposable equipment. The purpose of this study was to determine which of these methods is most cost effective. Monte Carlo simulations were performed to compare costs of using reusable versus disposable equipment for each level NICU. Simulations incorporated costs associated with purchasing and autoclaving equipment, estimated numbers of ROP screening exams per infant, annual discount rate, and the assumption that enough reusable equipment must be purchased to cover the maximum number of examinations performed per day on ROP screening rounds. Using these simulations, the authors estimate that using reusable equipment is less expensive than using disposable equipment. Although there were costs associated with purchasing and autoclaving reusable equipment, using reusable equipment becomes less expensive than disposable equipment within 5 years, assuming instrument longevity. A limitation of the study is longevity; however, there is a supplemental calculator that allows readers to vary inputs to fit their specific situation. This increases generalizability and provides a great resource to people doing ROP screenings to help them implement the most cost-effective strategy for maintaining sterile equipment.

Beccasio A, Mignini C, Caricato A, Iaccheri B, Di Cara G, Verrotti A, Cagini C. New trends in intravitreal anti-VEGF therapy for ROP. *Eur J Ophthalmol.* 2022 May;32(3):1340-1351.

Studies on the new anti-VEGF agents to treat ROP introduced from 2011 to 2021 were collected and analyzed using the PubMed platform. The search was performed with the use of the following terms: "Retinopathy of prematurity", "anti-VEGF agents", "Ranibizumab", "Pegaptanib", "Bevacizumab", "Aflibercept" and "Conbercept". Only full-length publications in English language were evaluated, including case reports, case series, retrospective studies and prospective trials. Pegaptanib is an RNA aptamer which acts as a selective inhibitor of VEGF 165 and its treatment effect was monitored by Autrada et al on 76 newborns with ROP zone I/II stage 3+. There was a stable regression of ROP in 89.7% of eyes treated with double strategies and 60.8% of eyes after only laser photocoagulation. ROP recurrence rates were higher in those eyes treated with laser only versus those with laser-supplemented by pegaptanib. Ranibizumab is a recombinant humanized monoclonal antibody fragment designed to bind and inhibit all biologically active isoforms of human VEGF with a higher affinity than Bevacizumab. One of the largest randomized, open-label clinical trials evaluating ranibizumab was performed by Stahl et al. In this study, 214 patients were included and divided into three groups, comparing two different doses of Ranibizumab (0.25 mg vs 0.1 mg) with laser therapy. They obtained a good response with regression of ROP in all 3 groups. The highest rate of effectiveness was obtained in Ranibizumab 0.25 mg group which, in conclusion, is considered a superior treatment compared to conventional laser therapy. Aflibercept is a chimeric protein, defined as a "trap molecule" with 3 binding sequences from VEGFR1 (VEGF receptor 1) fused to the constant (Fc) region of human IgG. These characteristics confer much higher VEGF binding affinity than that obtainable with antibodies. A retrospective study by Sukgen et al compared the results of ranibizumab and aflibercept treatment in 63 newborns with posterior ROP, deducing a higher frequency and earliness of recurrences in Ranibizumab group. The rate of recurrence was 48,1% for Ranibizumab at a time of  $8.2 \pm 0.92$  weeks from injection and it was 13,9% for Aflibercept at  $14.2 \pm 1.03$  weeks after treatment. Conbercept is a recombinant fusion protein composed of the second Ig domain of VEGFR1 and the third and fourth Ig domain of VEGFR2 to the constant region (Fc) of

human IgG1.<sup>56</sup> It binds all VEGF isoforms and PGF with high affinity. A recent prospective multicenter trial found no statistically significant difference in the recurrence rate of ROP in eyes treated with Conbercept (16.67%) and those treated with Ranibizumab (23.34%). Ranibizumab appears to have the highest recurrence rate when compared with Bevacizumab, Aflibercept and Conbercept, probably due to its lower absorption and shorter half-life. Overall effectiveness of these anti-VEGF agents is related to severity and location of ROP. The authors assert the need for multicentric trials to confirm effectiveness, tolerability, and safety profiles of new anti-VEGF agents.

Retinopathy of prematurity classification updates: possible implications for treatment.

Fielder AR, Quinn GE, Paul Chan RV, Holmström GE, Chiang MF; ICROP 3 Classification Committee. J AAPOS. 2022 Jun;26(3):109-112.

This opinion piece seeks to raise a discussion on how ROP classification may affect indications for treatment and whether potential changes should be codified by collaborative research and/or expert consensus opinion. The article reviews several refinements included in ICROP3.

It first addresses Zone discussing location of notch and subdivision of Zone II. ICROP3 subdivides Zone II into posterior and anterior to highlight the probability that posterior disease will more likely require treatment. Location of the notch previously was not considered in ETROP. ICROP3 asks the question of whether the more posterior location of the notch defines the overall zone which affects decision for treatment. The second issue raised highlights that aggressive posterior ROP (AP-ROP) may be located more anteriorly and can occur along with traditional stage 3 ROP. The article also discusses the important fact that the definition and awareness of pre-plus and plus disease is fluid over time and that does not always proceed in a stepwise fashion further bringing into question when treatment is appropriate. The authors wish to construct a more “fine-tuned” algorithm based on a fuller description of ROP components. This article is important to pediatric ophthalmologists who screen and treat ROP because the ICROP3 Classification Committee acknowledges the difficult and complex decisions that those who screen deal with on a weekly basis suggesting that research and consensus opinion may both be necessary in answering these complicated questions.

The time and financial ramifications of providing services for retinopathy of prematurity at a single inner-city institution in the United States: a pilot study.

Hawn VS, Muhtadi R, Oliviera J, Suman P, Quinn G, Mian U. J AAPOS. 2022 Jun;26(3):135.e1-135.e4.

As the survival of premature infants increases, the demand for ROP screening and treatment will increase accordingly. ROP may result in blindness and requires a regimented schedule and timing to prevent vision loss. Inpatient reimbursement rates, time away from outpatient clinic and surgery, travel time, inadequate assistance by NICU staff, unpredictability of time in NICU and travel, as well as liability and malpractice are all “costs” to those limited and decreasing numbers of pediatric ophthalmologists that screen for ROP. The authors of this study sought to evaluate the time required for ROP services and to approximate compensation to better understand the implications of providing the necessary ROP screening and treatment. The data presented by the authors shows a substantially negative profit margin for both screening and treatments using average annual costs and margins for inpatient ROP activity despite ROP screening being a highly cost-effective way to significantly decrease ocular morbidity and blindness for this population. With the ever-increasing population of premature infants who will need to be screened, it is imperative to structure reimbursement in a more transparent and equitable method to incentivize providers to perform this necessary work. The importance of this article goes beyond pediatric ophthalmology and should be shared with our neonatology colleagues as well as hospital administrators to help them understand the true “work” associated with providing ROP services.

Systemic conbercept pharmacokinetics and VEGF pharmacodynamics following intravitreal injections of conbercept in patients with retinopathy of prematurity.

Cheng Y, Sun S, Deng X, Zhu X, Linghu D, Sun X, Liang J. Br J Ophthalmol. 2022 Sep;106(9):1295-1300.

Conbercept is a novel recombinant fusion protein composed of human VEGF receptor 1 (domain 2), VEGF receptor 2 (domains 3 and 4) and the Fc fragment of human IgG1. This was a multicenter,

prospective, nonrandomized study to evaluate serum VEGF and drug levels in patients with ROP following intravitreal conbercept. Forty infants (20 males and 20 females) with APROP or type 1 ROP treated at two centers in China January – September 2020 were enrolled and all received intravitreal conbercept 0.25 mg/0.025 mL as the primary treatment. Blood samples were collected before and 1 week and 4 weeks after injection. The serum VEGF level at 1 week was significantly lower ( $p < 0.05$ ) than that at baseline, and at 4 weeks, it was significantly higher ( $p < 0.05$ ) than that at 1 week. There was no significant difference ( $p > 0.05$ ) between baseline and 4 weeks after injection. It was below the limit of quantitation (BLOQ) at 4 weeks after injection. Limitations include small sample size and short follow-up period. In addition, the authors note 24 eyes suffered recurrence after vascular regression (30%), and 14 of these eyes (17.5%) received a second injection. The timing of this injection is not clear from the text but worth noting it may influence serum VEGF levels if it occurred within the 4 week study period. While no systemic complications or ocular side effects were reported in this study, the long-term potential effects resulting from anti-VEGF therapy and specifically conbercept remain unknown.

Comparison of clinical outcomes of conbercept versus ranibizumab treatment for retinopathy of prematurity: a multicenter prospective randomized controlled trial.

Wu Z, Zhao J, Lam W, Yang M, Chen L, Huang X, Wei M, Yang H, Lv F, Zhang F, Zeng J, Zhang GM. *Br J Ophthalmol*. 2022 Jul;106(7):975-979.

Conbercept is a recombinant fusion protein said to have multiple targets, stronger affinity and the ability to inhibit neovascularization. It was first approved by China Food and Drug Administration for intravitreal injection in treating age-related macular degeneration in 2013. This RCT was designed to directly compare the recurrence rates and related outcomes between intravitreal injection of conbercept (IVC, 0.25mg/0.025mL) and intravitreal injection of ranibizumab (IVR, 0.25mg/0.025mL) in ROP treatment. Sixty infants from multiple centers in China were enrolled between May 2017 and February 2019. All eligible infants were examined by 2 experienced retina experts to confirm eligibility and randomized via 1:1 proportion using a computer-generated randomization schedule. Followup exams occurred at 1, 2, 4, 6, 8, 10, 12, 18 and 24 weeks after the treatment. After the primary injection, a total of 10 eyes of 5 infants (16.7%) developed ROP recurrence in the IVC group, and 14 eyes of 7 infants (23.34%) developed ROP recurrence in the IVR group. There was no significant difference between the two groups. Two of the recurrent eyes in the IVR group were treated with a second IVR while the rest of the recurrences were treated with laser. There was no difference in time interval between treatments or PMA at time of primary treatment or secondary treatment between the eyes with recurrent disease in the two groups. Two eyes in the IVC group and one eye in the IVR group developed a cataract post treatment; no other injection-related complications were reported. The authors concluded there was no significant statistical difference in the recurrence rate between IVC and IVR for treating ROP within 6 months and therefore conbercept is a reasonable choice for anti-VEGF therapy in ROP. Limitations included small sample size and relatively short followup period. They were able to obtain fluorescein angiography on a small subset of infants with disease recurrence (5 patients, 10 eyes) which may provide additional information regarding the vascular structure if more studies could be obtained.

Low fraction of fetal hemoglobin is associated with retinopathy of prematurity in the very preterm infant.

Hellström W, Martinsson T, Morsing E, Gränse L, Ley D, Hellström A. *Br J Ophthalmol*. 2022 Jul;106(7):970-974.

Recent preliminary evidence suggests that a low fraction of HbF is an independent predictor for ROP in preterm neonates, suggesting that perhaps HbF might protect from oxidative stress. The current source of RBCs for transfusions to preterm infants is blood derived from adult donors, which does not contain HbF. This retrospective cohort study included 452 infants with GA <30 weeks and was designed to investigate whether the degree of loss of HbF was associated with later ROP. The fraction of HbF (%) was inversely associated with severe ROP. The cohort was divided into quartiles based on HbF% and the infants with an HbF (%) in the lowest quartile had an OR of 22.0 for developing any ROP, compared with infants an HbF in the highest quartile. The relationship between low HbF and later ROP was independent of GA at birth, SGA and sex. Limitations include the high frequencies of co-morbidities in this population, clinical interventions, and the integration of new clinical routines throughout the study period, however, it brings up an interesting component of neonatal care and ROP worth further investigation. The authors note there is an ongoing multicenter randomized trial investigating the potential beneficial role of minimizing the loss of endogenous blood components in a clinical setting.

Artificial Intelligence for Retinopathy of Prematurity: Validation of a Vascular Severity Scale against International Expert Diagnosis.

Campbell JP, Chiang MF, Chen JS Collaborative Community in Ophthalmic Imaging Executive Committee and the Collaborative Community in Ophthalmic Imaging Retinopathy of Prematurity Workgroup. *Ophthalmology*. 2022 Jul;129(7):e69-e76. doi: 10.1016/j.ophtha.2022.02.008. Epub 2022 Feb 12. PMID: 35157950; PMCID: PMC9232863.

The purpose of this study was to compare the validity of the vascular severity score as an output of the ROP AI software as a medical device (SaMD) compared to an expert group of clinicians. The goal was to determine whether the current algorithm which was based on a reference standard diagnosis of a small group of experts reflects the broader community of ROP assessment of plus disease and overall severity. The study compared clinical diagnostic labels for stage 1 to 3 and plus disease assigned by the ICROP3 committee with the output of the i-ROP to investigate the clinical validity, of the vascular severity score. Images were classified by the ICROP3 clinicians for a score of 1-9 for plus datasets and similar classification for stage classification. The images were also labeled with deep learning-derived scores from the i-ROP DL algorithm and automated vascular severity scores from 1-9 were assigned. In the ICROP group there was variability on agreement of plus except at the extremes of the spectrum and for the stage dataset there was more variability in stage 1 and 2 ROP. Key findings were that the deep-learning derived quantitative vascular severity score correlated well with the expert labels of plus disease and diagnosis of peripheral stage. In addition, although ROP stages and plus were represented ordinally, it was found that most experts diagnosed on a continuum which may suggest that a quantitative vascular severity score (VSS) may be appropriate output for ROP SaMD. The ICROP data acknowledges that preplus and plus disease run a spectrum and clinical judgment needs to be applied to treatment decisions. It is important that minimal acceptable criteria have not yet been established such as improved clinical diagnostic performance with an assistive device compared with the reference standard. These criteria need to be higher in autonomous devices given the potential morbidity of missed diagnosis. The authors conclude that the study demonstrates that both plus and stage are a continuum and can be quantified using deep learning. This is one potential application to move from qualitative vs quantitative diagnosis. The use of ROP SaMD for treatment decisions will need validation in a clinical trial setting. If this can be accomplished it could have a significant impact on blindness secondary to ROP in the future especially in developing countries.

Changes in institutional oxygen saturation targets are associated with an increased rate of severe retinopathy of prematurity

Liu, Tianyu et al.

*Journal of American Association for Pediatric Ophthalmology and Strabismus {JAAPOS}*, Volume 26, Issue 1, 18.e1 - 18.e6

This is a secondary analysis of data to evaluate the effect of changes in institutional peripheral oxygen saturation (SpO<sub>2</sub>) targets, made in response to recent randomized trials, on risk of developing severe retinopathy of prematurity (ROP). A total of 8,142 infants underwent ROP examinations at 21 hospitals during the two study periods: 5,716 in 2006-2012; 2,426 in 2015-2017. Fourteen hospitals increased SpO<sub>2</sub> targets, and 7 hospitals did not. Hospitals that increased targets had a 3% increase in severe ROP; hospitals without SpO<sub>2</sub> changes had a 2% decrease. The difference in change of severe ROP between groups of hospitals was significant. This study finding should be considered when managing oxygen levels in the context of mortality and other outcomes.

Implementation of telemedicine screening for retinopathy of prematurity in 6 neonatal units rural areas in Guatemala

Asturias, Ana L. et al. *Journal of American Association for Pediatric Ophthalmology and Strabismus {JAAPOS}*, Volume 26, Issue 1, 22.e1 - 22.e5

The findings of telemedicine retinopathy of prematurity (ROP) screening program in rural areas of Guatemala operated by trained technicians were reported. The National ROP Program Guidelines screening criteria was used, retinal images were obtained by a technician and graded by

ophthalmologists experienced in ROP. Infants with pre-plus or plus disease were referred for clinical examination. Screening was discontinued when the retinal vessels were normal in zone II for 2 consecutive visits, or the infant reached 45 weeks postmenstrual age. A total of 418 of 1,890 eligible infants (22.1%) were screened. Mean GA was 33.9 2.2 weeks (range, 27-36), and mean BW 1728.3 379.3 g (range, 840–2830 g). Thirtythree infants (8.6%) developed plus or pre-plus disease, and 19 (58%) underwent ophthalmologic examination. Fifteen infants were confirmed with type 1 ROP, and 14 were treated. Mean GA of treated infants treated was 33.6 3.0 weeks (range, 32-34.9), and mean BW was 1,646 245.8 g (range, 1100–1774.1 g).<sup>78</sup> The infants who were enrolled in ROP screening was low and may be attributed to high mortality rates, babies discharged before their first screening and parents failing to return. Attendance for the ophthalmologist exam was also poor. The ease of implementing telemedicine and training technicians and improving access to an ophthalmologist for exam and treatment may improve ROP care in rural areas.

Real-world visual outcomes of laser and anti-VEGF treatments for retinopathy of prematurity. Gundlach BS, Kokhanov A, Altendahl M, Suh SY, Fung S, Demer J, Pineles S, Khitri M, Chu A, Tsui I. *American Journal of Ophthalmology*. 2022 Jun 1;238:86-96.

Several landmark studies have evaluated the treatment outcomes for laser and anti-VEGF for the treatment of retinopathy of prematurity (ROP). While landmark papers such as the Early Treatment for Retinopathy of Prematurity (ETROP) trial are useful to provide evidence-based guidance for ROP treatment and outcomes, the controlled setting of a large, multi-center clinical trial may not be representative of real world outcomes. Additionally, there is still emerging data regarding the long-term outcomes of laser compared to anti-VEGF. The goal of this paper was to characterize visual outcomes for children screened for ROP. This was a single center retrospective study of 350 eyes of 175 children screened over a 9 year period (the remainder of the 539 infants did not have outpatient clinical data available). In this cohort, 15 eyes received primary anti-VEGF treatment and 59 received primary laser therapy. The authors found that infants receiving laser therapy were more likely to have severe myopia, though the odds ratio was low (1.02-1.3). There was a higher risk of optic atrophy in the laser group as well with a similar odds ratio. There were no differences in the rates of strabismus or myopia. Infants treated with anti-VEGF typically had more posterior disease. This study is limited by its retrospective nature, missing data, and single clinical site, but does provide useful information supporting the advantages of anti-VEGF for posterior ROP.

Validation of the Postnatal Growth and Retinopathy of Prematurity Screening Criteria in a Taiwanese Cohort. Huang CW, Yeh PT, Tsao PN, Chou HC, Chen CY, Yen TA, Huang HC, Lai TT. *American Journal of Ophthalmology*. 2022 May 1;237:22-31.

Developing more precise screening criteria for retinopathy of prematurity (ROP) could eliminate unnecessary examinations and decrease the workload for pediatric ophthalmologists who screen and treat premature infants. Several criteria have been proposed including that proposed in the Postnatal Growth and Retinopathy of Prematurity (G-ROP) Study. That tool predicted 100% of infants with type 1 ROP and led to a 30% reduction in examinations. The goal of this study was to validate the G-ROP screening criteria in a new population – Taiwanese infants. This was a retrospective cohort study of 303 preterm infants at a single center in Taiwan. with the goal of determining the performance of G-ROP in a new population. Overall, the G-ROP screening criteria performed well in this cohort with a 96.6% sensitivity and 42.3% specificity (ideal for a screening test for a condition with high risk of morbidity). Employing this screening criteria would've reduced the number of examinations by around 33%. A simplified model (uniformly considering 180 g of weight gain as the threshold of slow weight gain for each 10-day-interval) improved performance even more. Overall, the authors report good validation of the G-ROP screening criteria in a new population and caution that retrospective validation is important prior to applying the criteria to new populations.

Longitudinal Change of Refractive Error in Retinopathy of Prematurity Treated With Intravitreal Bevacizumab or Laser Photocoagulation.

Wiecek E, Akula JD, Vanderveen DK, Mantagos IS, Wu C, Curran AL, De Bruyn H, Peterson B, Fulton AB.

American Journal of Ophthalmology. 2022 Aug 1;240:252-9.

Refractive outcomes following treatment for retinopathy of prematurity (ROP) are often included in treatment decision making, with some evidence suggesting lower rates of high myopia following treatment with anti-VEGF compared to laser treatment. This retrospective cohort study included 88 infants, of which 22 underwent anti-VEGF treatment, 48 underwent laser, and the remaining 18 received both. Baseline characteristics were relatively similar between groups with the exception of higher birthweight in the laser group and more posterior disease in the anti-VEGF group. Ultimately, the authors found that laser was a risk factor for more rapidly progressive myopia, even when correcting for stage and zone of ROP. The paper contains a nice graph which shows the results of a linear mixed-effects model in which predictions of spherical equivalent refractive error are shown based on group. Ultimately, the authors find that the number of spots is correlated with the degree of myopia. The authors posit that even if laser is eventually performed following anti-VEGF, the decrease in number of laser spots may ultimately benefit the patient with regards to lower levels of myopia.

Comparison between oral and intravenous ultrawide-field fluorescein angiography in the clinical follow-up of children with a history of retinopathy of prematurity or prematurity

Ling XC, Chou HD, Liu L, Wang NK, Lai CC, Chen KJ, Hwang YS, Wu WC.

*Retina*. 2022 Jul 1;42(7):1330-1337. doi: 10.1097/IAE.0000000000003451. PMID: 35723921.

Fluorescein angiography (FA) is a useful tool for observation of vascular pathology during both the acute phase of retinopathy of prematurity (ROP), as well as in long-term follow-up. However, intravenous (IV) administration of fluorescein can be challenging in the pediatric population. The authors sought to compare the quality of images obtained using oral or IV ultrawide-field FA in children with a history of ROP or prematurity. A total of 107 children participated, with 71 children receiving IV fluorescein (average age  $7.39 \pm 1.95$  years) and 36 children receiving oral fluorescein (average age  $6.83 \pm 2.12$  years). Image quality analysis revealed that 91.5% of IV FA images had excellent image quality compared with only 55.6% of oral FA images. However, 83.3% of oral-contrast images were still rated as having either good or excellent image quality. The average time required for first dye appearance and peak fluorescence were significantly shorter in the IV FA group than in the oral FA group, while peak intensity was higher in the IV group. The authors conclude that while IV FA was more likely to produce higher-quality images, oral FA is still an effective and useful alternative to the IV route in the long-term evaluation of ROP pediatric patients.

## 9. Strabismus

Nasal insertion of the superior oblique tendon presenting as Brown syndrome Ahmed Awadein, Ahmed Adel Youssef & Jylan Gouda, Ophthalmology Department, Cairo University Faculty of Medicine.

Strabismus, 30: 3. 146-149

Anomalous ocular muscle insertions are a rare cause of ocular motility disturbances. In this paper, they report the clinical presentation and the intraoperative findings of two cases with an abnormally nasally inserted superior oblique tendons presenting with a Brown syndrome-like clinical picture. Case no 1 was a 5-year-old girl presenting with a chin up position. There was bilateral limitation of elevation in adduction,  $-4$  on the right side and  $-3$  on the left side with  $+1$  downshoot on adduction on either side Patient was orthotropic in down-gaze with small V-pattern exotropia. Case no 2 was a 4-year-old boy presenting with an esotropia of  $35\Delta$  that was partially corrected with his spectacles to  $20\Delta$ . Ductions showed  $-4$  defective elevation in adduction of the right eye. Surgical exploration in both cases revealed abnormal nasal insertion of the superior oblique tendons. The line of insertion had a convexity facing supero-nasally. The posterior fibers were inserted 7–8 mm posterior and just nasal to the nasal border of the superior rectus insertion, while the anterior fibers were shorter and inserted 5 mm nasal and 4 mm posterior to the nasal edge of superior rectus insertion. In both cases, there was an improvement in the elevation on adduction after superior oblique lengthening. The conclusion was that abnormal nasal insertion of the superior oblique muscle enhances the depressor effect of the muscle and can create a Brown-like picture. Limitations of this paper was that there were only 2 cases that were studied.

Objective excyclotorsion increases with aging in adults.

Akihiko Oohira. Department of ophthalmology, Wakaba Eye Hospital, Tokyo.

Strabismus, 30:4. 183-189

It has been reported that the disc-fovea angle (DFA), a measure of objective cyclotorsion, increases with age. DFA was measured in three age groups of adults and the effects of age, sex, and laterality on DFA is reported. A retrospective study was performed on patients who had a glaucoma checkup or who visited for suspected cataract, who underwent fundus photography between 2013 and 2021. Patients with visual acuity 27 mm, strabismus or ocular diseases affecting fusion were excluded. DFA was measured from digital fundus photographs obtained from 249 participants comprising three age groups (group I,  $44.4 \pm 0.5$  years,  $n = 58$ ; group II,  $63.7 \pm 3.6$  years,  $n = 129$ ; group III,  $81.0 \pm 3.8$  years,  $n = 62$ ). The sum of right- and left-eye DFAs is named as total DFA. Dunnett's post-hoc test after ANOVA showed that the left-eye DFA and total DFA of group III were significantly larger than those of group I ( $p = .01$  and  $p < .01$ , respectively). Total DFA of female participant ( $15.6 \pm 4.7^\circ$ ,  $n = 168$ ) was significantly larger than that of male participant ( $13.9 \pm 4.3^\circ$ ,  $n = 81$ ) ( $p < .01$ ). The DFA of the left eye ( $8.2 \pm 3.5^\circ$ ,  $n = 249$ ) was significantly larger than that of the right eye ( $6.8 \pm 3.3^\circ$ ,  $n = 249$ ) ( $p < .001$ ). Group III was subdivided based on eye dominance (right eye dominance,  $n = 36$ ; left eye dominance,  $n = 13$ ; NA,  $n = 13$ ). The DFA in the nondominant eye ( $9.7 \pm 4.6^\circ$ ) was significantly larger than that in the dominant eye ( $7.4 \pm 3.7^\circ$ ) ( $p < .01$ ). This study found a slight increase of DFA with age. Furthermore, DFA in female or DFA in the left-eye was larger than DFA in male or in the right-eye. This study had some limitations. First, measuring objective cyclotorsion using fundus photographs allows systematic errors. The participant's head is not fixed firmly by an apparatus, such as a bite bar, which may permit small head (and eye) position changes while taking photographs. Second, the number of participants may not be large enough to determine the small but significant difference in DFA among the subgroups of healthy people. Difference among the size of the subgroups might have affected the results. Third, only Japanese patients were analyzed. Further studies including other races may uncover possible ethnic differences.

Aetiologies of acquired pediatric sixth nerve palsies in a U.K. based population

Megan J. Evans, Helen L. Ellis & Jay E. Self. Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton.

Strabismus, 30: 4. 196-199

Due to the low incidence of sixth cranial nerve palsies in children, there has been limited evidence published on this subject, especially from a population based within the UK. The incidence of etiologies has been found to vary significantly within the literature, especially with regard to neoplasms. The main aim of this study is to present the etiologies of newly diagnosed pediatric sixth nerve palsies in a UK-based population. We also take into consideration if the palsies were isolated or associated with other



neurological signs or symptoms. Retrospective data collection was carried out on the medical records of 50 pediatric patients with a new-onset sixth nerve palsy. They all presented to a large tertiary referral hospital in the South of the UK between 1 January 2007 and 31 December 2017. Data collected for each patient included age, gender, ethnicity, unilateral versus bilateral, other signs and symptoms, etiology, where the patient first presented, and whether the palsy was the first presenting feature. Thirty-three (66%) patients had a new-onset sixth nerve palsy in conjunction with other neurological signs or symptoms and were considered non-isolated. Seventeen cases (34%) were found to be isolated. Etiologies included high intracranial pressure (18%), neoplasm (14%), surgery for neoplasm (14%), viral (14%), infection (12%), trauma (8%), idiopathic (6%), benign space-occupying lesion (4%), congenital (2%), inflammation (2%), Alexander's disease (2%), Kawasaki syndrome (2%), and diabetes (2%). Our study found nonisolated sixth nerve palsies to be the most common presentation. These patients had a high number of potentially sinister etiologies, the most common being high intracranial pressure followed by post-surgery for neoplasm and neoplasm. Isolated sixth nerve palsies were more commonly due to viral or idiopathic etiology; however, two cases of benign space-occupying lesion and one of neoplasm were identified. This study, like those of previous authors, is limited by relatively small case numbers due to the low incidence of sixth nerve palsies in children. As a large tertiary referral hospital, bias may also be present due to the larger numbers of acutely unwell children seen within our hospital. A significant number of our patients were second opinions from other hospitals or departments such as the pediatric ward and oncology and as anticipated tended to be the more unwell patients. Patients presenting to eye casualty or GP were more likely to be those with an isolated sixth and of a viral or idiopathic nature.

Association between near viewing and acute acquired esotropia in children during tablet and smartphone use

Esther Van Hoolst, Liesbet Beelen, Ivo De Clerck, Louise Petit, Irina Balikova, Ingele Casteels, Maria Dieltiens & Catherine Cassiman. Department of Ophthalmology, University Hospitals Leuven, Leuven. *Strabismus* 30:2. 59-64

In this study, they investigated a possible association between the acute onset of esotropia and tablet or smartphone use in children. They characterized the clinical aspects of esotropia associated with tablet or smartphone use. The medical records of 10 children aged between 5 and 15 years old with presumably tablet or smartphone associated esotropia were reviewed regarding orthoptic examination and cycloplegic refraction. Legal guardians of the children were asked to fill in a questionnaire regarding tablet and smartphone use of their child. This questionnaire was also conducted in a control group of age-matched children. The results of this questionnaire were compared to search for possible determinants of tablet or smartphone associated esotropia. All 10 patients presented with a comitant esotropia ranging from 8 to 45 prism diopters with no significant difference between near and far. The mean age of onset was 9.8 years. Cycloplegic refraction showed a mild hyperopia in eight patients, a mild myopia in one patient and emmetropia in the other patient. All patients had near full refractive correction at the onset of esotropia. Diplopia was reduced after visual hygiene recommendations, however in six patients, strabismus surgery was needed. The working distance was significantly shorter in the 10 cases compared to the controls. In children with acute acquired esotropia, they found a statistically significant association with a smaller working distance during tablet or smartphone use compared to age-matched controls. They hypothesize that intensive near viewing can be a precipitating factor in this type of esotropia.

Limitations of our study are the small heterogeneous case group of ten AACE patients with a known excessive smartphone or tablet history, and the fact that the questionnaire for the control group was conducted with children visiting the ophthalmology department at University Hospital Leuven. These results thus do not entirely represent tablet and smartphone use in the normal population, although it can be assumed that this is only a limited bias. Further, the working distance was not measured by the investigators and depended on the assumption of the parents. It is important to note that the statistical analysis demonstrates an association between working distance and esotropia, however this does not prove a causal relationship. The control group is larger than needed given that no power calculation was performed before onset of the study. However, in studies where cases are limited, a larger control-to case ratio might increase statistical power and does not affect further statistical analysis.

Acute Comitant Esotropia in a Child: A Rare Complication of COVID-19

Kaplan T, Kramer A, Brodsky M

[published online ahead of print, 2022 Jul 18]. *J Neuroophthalmol*.

COVID-19 has been reported to be associated with a variety of ophthalmic conditions. Here, the authors describe a case of a previously healthy 5-year-old girl who presented with sudden-onset esotropia (which occurred the morning of her initial presentation) in the setting of lethargy, decreased appetite, altered mentation, and gait instability. On exam, she had 20/20 visual acuity in both eyes, full ocular motility without abduction deficit in either eye, and a comitant, constant esotropia of 25 prism diopters. There was no significant hyperopia, and the remainder of the ocular exam was normal. Medical work-up was positive for an active COVID-19 infection.

A sedated MRI of the brain and orbits was unremarkable; interestingly, however, her esotropia had resolved upon awakening from the general anesthesia. Her lethargy and gait abnormalities resolved over the course of a few weeks. On follow up exam 6 weeks after presentation, the patient remained orthotropic.

In the absence of other predisposing factors, her acute, acquired, comitant esotropia and other symptoms were attributed to COVID-19 viral encephalopathy. It is unclear why the esotropia resolved so quickly after general anesthesia, but it seems possible that viral encephalopathy may be associated with acute, acquired, comitant esotropia in children.

#### Vestibular Schwannoma Presenting As An Acute Cranial Nerve Six Palsy

Karimaghahi S, Mortensen P, Raviskanthan S, Lee A

[published online ahead of print, 2022 Apr 19]. *J Neuroophthalmol*.

Vestibular nerve schwannomas are a relatively common intracranial tumor originating from Schwann cells of the vestibular nerve. Though such tumors typically present with hearing loss, the authors describe a case of a 38-year-old man who first presented with acute onset of horizontal diplopia in the setting of a year of headaches, asymmetric (but previously undiagnosed) hearing loss, and vertigo. Ophthalmologic exam revealed unilateral abducens nerve palsy and bilateral optic disc edema. MRI showed a large cerebello-pontine angle (CPA) mass with cystic degeneration exerting a mass effect on the pons, medulla, and left cerebellar hemisphere.

In this case, the unusual presence of an abducens nerve palsy in setting of a vestibular schwannoma may have been secondary to cystoid degeneration and mass effect on the sixth cranial nerve or from the obstructive hydrocephalus and subsequent elevated intracranial pressure that resulted. In patient with new-onset abducens nerve palsy with hearing loss or cerebellar signs, a vestibular schwannoma should remain on the differential.

#### Pseudoabducens Palsy of Lutz

Sharma A, Kim D, Fraser A

*J Neuroophthalmol*. 2022;42(4):e598-e599.

In this case report, the authors present an interesting clinical diagnosis in a 40-year-old woman who presented with two years of diplopia in left gaze as well as left-sided facial numbness. The patient was orthotropic in primary and right gaze but had a 10 prism diopter esotropia in left gaze. Smooth pursuit to left showed a very mild abduction deficit. However, voluntary leftward saccades showed a marked abduction lag in the left eye, though the final amplitude of the saccade was close to normal. Leftward saccade also revealed an adducting nystagmus in the right eye. An MRI of the brain was normal, as was acetylcholine receptor antibody testing.

This clinical picture is consistent with the diagnosis of pseudoabducens palsy of Lutz, an entity characterized by orthophoria in primary gaze, worsening of abduction with saccades vs. smooth pursuit, and preservation of reflexive saccades. The ipsilateral abduction slowing and contralateral adducting nystagmus, interestingly, are the converse of the better-known findings in INO. Although the cause remains unknown, it is hypothesized to localize to the midbrain or rostral pons, likely secondary to a lesion below the resolution of current MRIs. Obviously rare, it is prudent for the strabismologist to simply be aware of such a condition, as it could first present with a complaint of diplopia.

#### Is There Gender Bias in Perceptions of Strabismus Among Adults?

Thuma TBT, Gunton M, Zhang QE, Sharpe J, Gunton KB.

*J Pediatr Ophthalmol Strabismus*. 2022;1-6. doi:10.3928/01913913-20221025-01

This study sought to investigate the effect of gender, type, and size of horizontal deviation on the perceived severity or need for intervention for strabismus among adults in the general population. The authors digitally manipulated eight photographs of individuals aged 25 to 35 years to create 30 prism diopters (PD) of exotropia, 30 PD of esotropia, 50 PD of exotropia, and 50 PD of esotropia in both men and women. They then surveyed 203 adults and asked if these subjects needed strabismus surgery. Participants ranked men with both large esotropia and large exotropia as needing correction more urgently than similar women. Photographs with exotropia were perceived as more severe than photographs with esotropia. Respondents' gender, age, or history of strabismus did not significantly impact their rankings. The authors concluded that male photographs were perceived as having a greater need for strabismus intervention than female photographs despite similar type and size of deviations and that exotropia was perceived as more severe than esotropia for smaller deviations only. This was an interesting survey of unconscious biases in the perception of strabismus which helps place into context our adult patients' motivations for seeking strabismus care.

Association of Pediatric Strabismus and Functional Impairment: A Cross-sectional Nationwide Analysis [published online ahead of print, 2022 Sep 14].

Cheng BT, Kim AB, Nadimpalli S, Pineles SL, Kurup SP.

J Pediatr Ophthalmol Strabismus. 2022;1-9. doi:10.3928/01913913-20220728-01

This study sought to examine the association of childhood strabismus with functional limitation to identify particular domains of impairment. The authors analyzed 201 children ages 5 to 17 years with strabismus enrolled in the 1996-2015 Medical Expenditure Panel Surveys. Functional impairment was assessed using the Columbia Impairment Scale (CIS), whereby a CIS score of 16 or greater defined clinically significant functional impairment. Multivariate regression models adjusted for age, sex, race, ethnicity, household income, geographic location, and insurance type were constructed to examine the association of strabismus diagnosis with overall impairment and individual domains of function. The authors found that children with strabismus had higher rates of clinically significant functional impairment compared to those without strabismus (15.1% vs 9.1%, adjusted odds ratio [95% CI]: 1.82 [1.11 to 2.97],  $P = .02$ ). Moreover, strabismus diagnosis was associated with higher rates of problems with getting along with their mother (1.70 [1.21 to 2.40],  $P = .003$ ) and father (1.66 [1.16 to 2.38],  $P = .006$ ), getting along with other children (1.67 [1.16 to 2.40],  $P = .006$ ), behavior at home (1.94 [1.37 to 2.74],  $P = .0002$ ), staying out of trouble (1.52 [1.04 to 2.23],  $P = .03$ ), nervousness (1.49 [1.05 to 2.11],  $P = .02$ ), and getting involved with sports and hobbies (1.55 [1.03 to 2.34],  $P = .04$ ). The authors concluded that childhood strabismus was associated with 1.8-fold greater odds of clinically significant functional impairment, with greater dysfunction in specific relationship and behavioral domains. The authors recognize the major limitation in this study: self-reported diagnoses which included strabismus. This likely led to under-representation of strabismus in the study sample and an over-representation of perceived problems therefore associated with strabismus (recall bias). Still, an interesting use of survey data.

Application of Soft Directional Prismatic Contact Lenses to Correct Diplopia [published online ahead of print, 2022 Sep 14].

Parolini B, Penzani R, Pascotto P.

J Pediatr Ophthalmol Strabismus. 2022;1-5. doi:10.3928/01913913-20220727-01

This small prospective study sought to verify whether diplopia d/t strabismus <8PD could be corrected with soft contact lenses containing directional prismatic correction. The authors enrolled patients with vertical and/or horizontal diplopia. The patients underwent a complete examination and then had custom contacts made of Benz G5X material - developed for this study. All patients were first corrected with prismatic glasses, and then they were asked to wear custom-made directional prismatic contact lenses. Only 8 patients, but the soft directional prismatic contact lenses resolved diplopia in 100% of patients and all patients reported greater comfort and quality of vision with directional prismatic contact lenses. The authors concluded that strabismus within 8 PD could be corrected through the use of soft directional prismatic contact lenses, obtaining greater quality of vision free of aberrations, though the maximum deviation corrected was 6 PD in total, and up to 3.5 PD in one eye. If repeatable in a larger cohort, this is an exciting development in the management of microstrabismus amounts patients who cannot or will not wear glasses.

Masquerading Superior Oblique Palsy.

Demer JL, Clark RA.

American Journal of Ophthalmology. 2022 May 23.

When evaluating a patient with vertical strabismus, the Parks–Bielschowsky three-step test is often used to distinguish whether the deviation is the result of a superior oblique palsy. A positive three-step test is typically defined as an ipsilateral hypertropia which increases in contralateral gaze and ipsilateral head tilt, based on the idea of unopposed activity of the inferior oblique muscle. This prospective cross-sectional study aimed to identify other pathology which mapped to a superior oblique palsy based on the three-step test. The authors performed surface coil magnetic resonance imaging in 83 patients with clinically diagnosed superior oblique palsy. Overall, they found that only 57 patients (69%) had superior oblique atrophy on imaging. There were no distinguishable differences in superior oblique palsy and masquerades based on results of three-step testing, degree of hypertropia, or degree of incomitance in ipsilateral versus contralateral head tilt. The authors suggest that MRI may be a useful adjuvant in determining whether a patient that passes the three-step test truly has a superior oblique palsy.

Sensory eye dominance following surgically correction for acute acquired concomitant esotropia of adulthood.

Shi C, Chen B, Yu X, Yao Z.

Eur J Ophthalmol. 2023 Jan;33(1):83-91.

The authors used a binocular phase combination paradigm to assess the ocular dominance of 22 patients who underwent surgery for acute acquired comitant esotropia (AACE) in childhood and regained normal stereopsis after the surgery but later developed recurrent AACE requiring additional surgery. The data from these patients were compared with 14 adult controls who had no history of strabismus or strabismus surgery. The sensory eye dominance was quantified as the interocular contrast ratio, termed balance point, at which each eye contributed equally to the perception of cyclopean grating. The authors found that normal controls had a mean balance point value close to unity ( $0.96 \pm 0.01$ ), whereas adult AACE patients exhibited apparent interocular imbalance ( $0.76 \pm 0.04$ ), which was significantly different from the control group (Mann-Whitney  $U = 135$ ,  $P < 0.001$ , two tailed). In addition, the balance point of adults with AACE did not correlate with the interval between onset of esotropia and the surgery ( $r = -0.262$ ,  $p = 0.239$ ), or the length of postoperative follow-up period ( $r = 0.127$ ,  $p = 0.575$ ). For patients with AACE of adulthood whose eyes had previously been straightened surgically in childhood, there was found to be a residual sensory imbalance which may be a potential risk factor for developing recurrent AACE later in life.

Clinical Characteristics of Acquired Diplopia in Adults.

Christoff A..

J Binocul Vis Ocul Motil. 2022 Oct-Dec;72(4):243-247. PMID: 36279482.

This was a retrospective cross-sectional study of adult patients (>18 years of age) who presented to one orthoptist with chief complaint of diplopia. Of the 224 evaluated, 23 patients reported past ocular history of early-childhood strabismus. Only 5 had amblyopia. Cranial nerve paresis (ie CNIV) was followed by age-related divergence insufficiency esotropia as the most common cause of strabismus. Treatment wise, 53% had been treated with prisms and 20% with Bangert foil occlusion. Surgery was recommended in 5% (11 patients). None were treated with opaque occlusion (“pirate style”). The limitation of this study is that the participants reflect one provider’s population of patients which may vary greatly from another provider or even another practice in another location (ie. demographic of patient population).

Using the White Disk Test to Predict Fusional Potential.

Tibi C, McKeown CA, Capó H. J Binocul Vis Ocul Motil. 2022 Oct-Dec;72(4):219-222. Epub 2022 Aug 22. PMID: 35994693.

This study included 12 patients who underwent the white disk test as part of their evaluation for binocular torsional diplopia. Eleven participants had both vertical and horizontal strabismus and one patient had vertical only. Eleven participants were able to experience single binocular vision with white disk test. In 10 of the 11 participants, postoperative fusion was predicted with the white disk test, and 8 experienced

improved postoperative stereopsis. The limitation of this study is that the white disk test is not a widely used test and staff would have to be trained (video of how to perform test is included in publication). Synoptophore evaluation is often not readily available in most strabismus clinics lacking equipment, and the white disk test may be an alternative.

Utilising Virtual Clinics and Orthoptists to Aid COVID-19 Service Recovery in Adult Strabismus.

Francis JE, Rhodes M, Simmons J, Choi J.

Br Ir Orthopt J. 2022 Nov 7;18(1):144-151.

This prospective data analysis utilized data from virtual strabismus clinics from January 2015 to November 2021 to assess how effective strabismus services involving orthoptists as the first consultant was during the pandemic. The care pathway involving all new referrals to adult strabismus being seen first by orthoptist and then being triaged to either an orthoptic clinic for non-surgical management, doctor for test results and surgical management, or discharge. During the pandemic, this pathway was adapted to involve telephone consultation with the orthoptist prior to in person evaluation with orthoptist. The following orthoptist visits or doctor's clinic visit were either in person or telephone consultation. With this adapted workflow, mean wait times during pandemic was 10.9 weeks compared to 21 weeks when service re-opened in July 2020. In person consultation for non-surgical cases dropped from 47.7% to 16.3%. With this modified pathway, 24.6% of patients were signed up for procedures after only the first visit. This study highlights how modifications made during COVID in many clinical pathways has improved efficiency and accessibility to care in the NHS. The limitation of this study is that it may not be applicable in the United States or other countries depending on the infrastructure of healthcare and payor systems.

Visual Crowding Reveals Field- and Axis-Specific Cortical Miswiring After Long-Term Axial Misalignment in Strabismic Patients Without Amblyopia.

Huang Y, Liu Z, Chen Z, Zhan Z, Gao L, Hu J, Wu Y, Yan FF, Deng D, Huang CB, Yu M. Invest

Ophthalmol Vis Sci. 2023 Jan 3;64(1):10.

This study conducted at Zhongshan Ophthalmic Center involved 19 patients with exotropia, 21 with esotropia and 14 age-matched normal controls. Patients with vertical, paralytic or restrictive strabismus, accommodative esotropia, acute concomitant esotropia, nystagmus or history of ocular surgery or prism correction were excluded. Real-time eye tracking was used to ensure gaze-contingent display and examine visual crowding in these patients and the controls. This study found that patients with strabismus without amblyopia showed significantly larger critical spacing with nasotemporal asymmetry in only the radial axis that related to the strabismus pattern, with exotropia exhibiting stronger temporal hemifield crowding and esotropia exhibiting stronger nasal hemifield crowding, in both the deviated and fixating eyes. Moreover, the magnitude of crowding change was related to the duration and degree of strabismic deviation. Limitation of this study is the small N and the focus only on horizontal visual fields. Study highlights the complex relationship between strabismus and peripheral vision.

Eye Movements But Not Vision Drive the Development of Palisade Endings.

Genova Carrero-Rojas; Paula M Calvo; Thomas Lischka; et al.

Investigative Ophthalmology & Visual Science October 2022, Vol. 63, 15.

The goal of this study was to test whether vision or eye movements drive postnatal development of palisade endings in extraocular muscles (EOMs). Proprioception of the EOMs is still not understood, but palisade endings (specialized peripheral axons at muscle-tendon junctions) are one of the candidates for understanding how the eye transmits signals about the tension of EOMs to the brain. This group studied cats, as they are also a frontal-eyed species. One group underwent visual deprivation, and one underwent eye immobilization by patching and botulinum neurotoxin (BoNT-A) injection, respectively. The eyes were later harvested, and EOMs were tested to see how the development of palisade endings was affected by each environment. In the group that had undergone unilateral visual deprivation, there was no affect on palisade development between the two eyes (using the fellow eye as a control). Similarly, palisade endings were present in both eyes in subjects who underwent bilateral visual deprivation. In contrast, subjects who had unilateral BoNT-A injections displayed palisade endings that were decreased in size with less axonal branching and less synaptophysin. This demonstrated that, when vision is prevented, palisade endings develop normally, but when eye movements are prevented palisade ending

development is altered and the number of palisade endings is reduced. These findings suggest that eye movements, but not vision, play an essential role for the postnatal maturation of palisade endings.

#### Temporal Eye-Hand Coordination During Visually Guided Reading in 7- to 12- Year- Old Children With Strabismus.

Krista Kelly; Dorsa Norouzi; Mina Nouradanesh; et al.

Investigative Ophthalmology & Visual Science November 2022, Vol.63, 10.

Childhood strabismus, even with proper treatment, can lead to binocular dysfunction, motor deficits, and amblyopia persisting into adulthood. Ocular motor deficits typical of strabismus include fixation instability, decreased vergence, and abnormal saccade initiation and execution. Most ocular motor studies have focused on adults with strabismus and little is known about ocular motor development in children with treated strabismus. This study enrolled 30 children aged 7-12 diagnosed with esotropia and 32 age similar control children without strabismus. They found that children treated for strabismus have prolonged saccade onset latency during visually guided reaching while viewing binocularly, consistent with previous studies in strabismic adults. Longer latencies may point to an immaturity of controlling visual fixation that occurs before saccade onset, meaning there may be a delay in processing the visual information about the location and distance of the target, converting that information into a planned motor command (i.e., the saccade), and then executing that motor command. Understanding this switch and the processes underlying impairments in eye-hand coordination may lead to interventions targeted at preventing or lessening this latency in strabismic children.

#### Microstimulation of Interstitial Nucleus of Cajal Evokes Directionally Disconjugate Eye Movements in Monkeys with Pattern Strabismus.

Adam Pallus; Mark Walton

Investigative Ophthalmology & Visual Science November 2022, Vol. 63 6.

Pattern strabismus is characterized by a horizontal misalignment of the eyes that varies with vertical eye position. This disorder has traditionally been described, and treated, as overaction or underaction of the oblique muscles. In recent years, evidence has accumulated that indicate that the disorder is associated with abnormal cross-talk between brainstem pathways that contribute to the horizontal and vertical components of eye movements. The present study was designed to investigate the hypothesis that the key abnormalities are at the level of, or downstream from, the interstitial nucleus of Cajal (INC). This study used two macaque monkeys. One of the monkeys (ET1) had an induced constant esotropia in one of the subjects using botox in the lateral rectus. The other monkey (XT1) had an A-pattern exotropia induced by bilateral medial rectus tenotomy during the first week of life. Microstimulation was then applied to the INC in these monkeys once they reached maturity. They found that most of the evoked movements in these monkeys with A pattern strabismus were disconjugate, implying an underlying neural abnormality is involved with pattern strabismus as opposed to a purely peripheral mechanism.

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#### Comparison of Long-term Stereoacuity Improvement Between Patients With Initial Subnormal Stereopsis and Nil Stereopsis in Refractive Accommodative Esotropia.

Mohan K, Sharma SK.

J Pediatr Ophthalmol Strabismus. 2022;59(4):248-253. doi:10.3928/01913913-20211115-02

This retrospective chart review sought to compare improvement in long-term stereoacuity between patients with refractive accommodative esotropia (RAET) with initial subnormal stereopsis (between 120 and 1,980 arcsec of stereoacuity) and nil stereopsis, who had a minimum of 5 years of follow-up. A total of 79 patients (mean age:  $6.3 \pm 1.9$  years) were included: 31 patients with initial subnormal stereopsis and 48 patients with nil stereopsis. The mean follow-up time was  $11.7 \pm 1.8$  years (range: 5 to 21 years). At the last follow-up visit, a greater number of patients with initial subnormal stereopsis demonstrated improvement in stereoacuity and also achieved 60 arcsec of stereoacuity compared with those with nil stereopsis. Age at onset, duration of esodeviation, mean hyperopia, amblyopia, anisometropia, and follow-up duration were not significantly different between the initial subnormal stereopsis and the nil stereopsis groups. The initial mean near and distance deviations with hyperopic correction were significantly smaller in patients with initial subnormal stereopsis. A significantly greater number of patients with initial sub-normal stereopsis had fusion at distance. The authors concluded that patients with RAET with initial subnormal stereopsis have greater chances of stereoacuity improvement and recovery of 60

arcsec of stereoacuity than those with nil stereopsis, though the latter group may still develop normal stereoacuity. Smaller initial deviations with hyperopic correction and fusion at distance indicate a favorable prognosis for stereoacuity improvement. This study has many strengths - chiefly the duration of follow-up - but a major limitation is the unreliability of the duration and nature of esodeviation at the time of presentation, which has major implications about potential for restoration of binocular sensory fusion.

Isolated Abducens Palsy due to COVID19. Bingöl Kızıltunç, Pınar, Seven, Mehmet Yunus, Atilla, Huban. School of Medicine, Department of Ophthalmology, Ankara University, Ankara. *Strabismus*, 30: 1, 35-37

Although coronavirus disease-2019 (COVID-19) is mainly a respiratory system disease, neurological complications due to peripheral and central nervous system involvement may be seen in these patients. In this case report, we described a patient with isolated abducens nerve palsy after COVID-19. The patient was a healthy 28-year-old man who developed isolated abducens nerve palsy 10 days after COVID-19. He had no systemic risk factors. He had 20 PD left esotropia (ET) at distance and 16 PD left ET at near in primary position and ET increasing to 25 PD in left gaze. He had left abduction deficiency. His cranio-orbital magnetic resonance imaging findings were normal. He was diagnosed as left isolated abducens nerve palsy and his findings were recovered after 2 months. COVID-19 may cause ocular motor nerve palsies. Although the pathological mechanism remains unclear, direct viral invasion, inflammatory and immune mechanisms may play role. Further case reports and studies are needed to support these findings.

Association between near viewing and acute acquired esotropia in children during tablet and smartphone use. Van Hoolst, Esther, Beelen, Liesbet De Clerck, Ivo. Department of Ophthalmology, University Hospitals Leuven, Leuven; Faculty of Medicine, KU Leuven, Leuven. *Strabismus*, 30: 2, 59-64

This article investigated a possible association between the acute onset of esotropia and tablet or smartphone use in children. We characterized the clinical aspects of esotropia associated with tablet or smartphone use. The medical records of 10 children aged between 5 and 15 years old with presumably tablet or smartphone associated esotropia were reviewed regarding orthoptic examination and cycloplegic refraction. Legal guardians of the children were asked to fill in a questionnaire regarding tablet and smartphone use of their child. This questionnaire was also conducted in a control group of age-matched children. The results of this questionnaire were compared to search for possible determinants of tablet or smartphone associated esotropia. All 10 patients presented with a comitant esotropia ranging from 8 to 45 prism diopters with no significant difference between near and far. The mean age of onset was 9.8 years. Cycloplegic refraction showed a mild hyperopia in eight patients, a mild myopia in one patient and emmetropia in the other patient. All patients had near full refractive correction at the onset of esotropia. Diplopia was reduced after visual hygiene recommendations, however in six patients, strabismus surgery was needed. The working distance was significantly shorter in the 10 cases compared to the controls. In children with acute acquired esotropia, we found a statistically significant association with a smaller working distance during tablet or smartphone use compared to age-matched controls. We hypothesize that intensive near viewing can be a precipitating factor in this type of esotropia. Limiting factors included the small size of the study population

Association of Strabismus with Mood Disorders, Schizophrenia, and Anxiety Disorders Among Children Yoon Lee MD, Michael Repka MD MBA, Marcy Borlik MD MPH *JAMA Ophthalmol.* April 2022; 140(4):373-381

This study sought to evaluate the association between strabismus and mental illness in the pediatric population. This is a cross-sectional study using commercial insurance claims from 2007-2017 to identify patients under the age of 19 with a diagnosis of strabismus and an age matched cohort of children without a diagnosis of eye disease other than refractive error. These charts were then reviewed for the presence of a concomitant mental illness claim. Patients with adjusted odds ratios for the association of mental illness with strabismus were 2.01 (95% CI, 1.99-2.04) for anxiety disorder, 1.83 (95% CI, 1.76-1.90) for schizophrenia, 1.64 (95% CI, 1.59-1.70) for bipolar disorder, 1.61 (95% CI, 1.59-1.63) for depressive disorder, and 0.99 (95% CI, 0.97-1.02) for substance use disorder. There was a moderate association between each strabismus type (esotropia, exotropia, and hypertropia) and anxiety disorder,

schizophrenia, bipolar disorder, and depressive disorder; odds ratios ranged from 1.23 (95% CI, 1.17-1.29) for the association between esotropia and bipolar disorder to 2.70 (95% CI, 2.66-2.74) for the association between exotropia and anxiety disorder. This study highlights the association of mental illness with strabismus, and should alert providers to counsel children and their caregivers on the risk for mental illness.

#### Nationwide Incidence of Thyroid Eye Disease and Cumulative Incidence of Strabismus and Surgical Intervention in Denmark

Lena Boulakh MD, Birte Nygaard MD PhD, Toke Bek MD

JAMA Ophthalmol. June 2022; 140(7):667-673.

This study sought to determine the Danish nationwide incidence of thyroid eye disease (TED), and the cumulative incidence of strabismus and surgical interventions in TED. This cohort study included 4106 patients diagnosed with TED aged 18-100. The mean numerical national incidence was 5.0 per 100000 person-years overall, with a 4:1 ratio of women to men with TED. Mean age of onset was 51.3 years, with most patients being hyperthyroid at the time of diagnosis. The 4 year cumulative incidence of strabismus was 10%, strabismus surgery 8%, and orbital decompression 5%. Their data helps to provide more clinical data on TED in this population and can be used to help inform patients and implement health care strategies.

#### Factors associated with the effectiveness of part-time patching for intermittent exotropia in children.

Choi H, Kim SJ, Jung J, Lee JE, Kim SY, Lee SU.

Eur J Ophthalmol. 2022 Jul;32(4):2026-2033.

This is a prospective observational study, in which 186 patients diagnosed with IXT were enrolled. Outcome measures included office-based control scales, magnitude of exo-deviation, and stereoacuity at near and distance after daily patching for 2 hours. We analyzed the clinical data and demographic factors association with improvement of IXT. The study was completed by 152 subjects of total enrolled patients who were followed for 1 year. Decrease in the magnitude of exo-deviation, improvement of control, and/or gain of stereoacuity were observed in 31.6% patients of the recruited subjects after part-time patching. Multivariate analyses showed that prognostic factors determining improvement to part-time patching included convergence insufficiency (CI) type IXT ( $p = 0.016$ ), poor distance stereopsis ( $p = 0.044$ ), and large exotropic deviation at distance ( $p = 0.025$ ). The authors conclude that CI-type exotropia, large distance magnitude of exo-deviation, and poor distance stereopsis may be associated with a better response to part-time patching, which can be a useful non-surgical treatment alternative to delay surgery in these cases.

#### Microstructural properties of major white matter tracts in constant exotropia before and after strabismus surgery.

Wang Y, Wang X, Shi H, Xia L, Dong J, Nguchu BA, Uwisengeyimana JD, Liu Y, Zhang D, Feng L, Qiu B. Br J Ophthalmol. 2022 Jun;106(6):870-877.

In this study, the authors sought to investigate the differences in tract-microstructures between patients with XT and healthy controls, assess the changes in tract properties pre- and post-surgery, and evaluate the relationship between altered features and ocular dominance which is common in strabismus patients. 19 patients with mean age 23 years with constant exotropia and no stereopsis were enrolled in the study. Presurgery and postsurgery MRI images were collected on 15/19 subjects with a time interval of about 6 months, and 11 of these patients performed ocular dominance testing. While all postoperative XT patients restored normal stereopsis, ocular dominance was still noted to be abnormal after successful XT surgery in 9/11 patients tested. Analysis of MRI imaging showed that the mean diffusivity of postoperative patients decreased significantly along left anterior thalamic radiation (ATR), left arcuate fasciculus (AF), left corticospinal tract (CST), left cingulum cingulate (CGC) and left inferior fronto-occipital fasciculus. Because these changes were associated with indicators of balanced input, the authors infer that microstructural changes of the visual spatially related fiber bundles might contribute to the restoration of stereopsis, and the balanced binocular input may be more conducive to the improvements and restoration of binocular visual function. More research needs to be done in this interesting area.



Applying Normal PedEyeQ Thresholds to Assess Eye-related Quality of Life among Children with Strabismus.

Hatt SR, Leske DA, Wernimont SM, Bothun ED, Birch EE, Holmes JM.

*J Binocul Vis Ocul Motil.* 2022 Apr-Jun;72(2):92-96.

This study evaluated 98 children with strabismus with the PedEyeQ (Functional Vision, Bothered by Eyes/Vision, Social, and Frustration/worry domains) to determine the proportion of children with below normal scores. Previously published normal (5th percentile) thresholds were applied to calculate proportions with below-normal scores for each domain. For the Child PedEyeQ more than 20% of 5- to 11-year-olds scored below normal, on all but the Social domain, whereas more than 50% of 12- to 17-year-olds scored below normal on all domains. On the Proxy PedEyeQ, more than 50% scored below normal on all domains when parents reported on 5- to 11-year-olds and 12- to 17-year-olds. For the Parent PedEyeQ, more than 50% of the parents of both 5- to 11-year-olds and 12- to 17-year-olds scored below normal on all domains. This study emphasizes the impact on the daily lives of children with strabismus.

Evaluation of Diplopia by Emergency Medicine Physicians and Consulting Neurologists.

Feng Y, Commiskey PW, Deveney TK, De Lott LB, Trobe JD

*J Neuroophthalmol.* 2022;42(1):e230-e239

New-onset diplopia can stem from non-urgent/benign causes or from serious neurologic pathology. Differentiating the two is essential, yet the responsibility of making that distinction often falls on non-ophthalmologists, such as emergency medicine physicians (EMPs) and/or consulting neurologists (CNs). This study aims to determine the diagnostic accuracy of these non-ophthalmology physicians in cases of previously undiagnosed diplopia.

The authors performed a retrospective chart review to identify 100 consecutive emergency room patient encounters in which diplopia was a primary complaint. In all these cases, the patient was originally evaluated by an EMP and – ultimately – by an attending neuro-ophthalmologist, whose diagnosis was considered the “gold standard.” Additionally, a CN was called to evaluate 42 of the 100 patients.

The authors developed a “best ED practice” guidelines for 19 common diagnoses in patients with diplopia (e.g., third nerve palsy, sixth nerve palsy, myasthenia, monocular diplopia, etc.). They also developed three grading scales (derived from previous neuro-ophthalmic literature and consultation with neuro-ophthalmologists) to judge exam proficiency, diagnostic proficiency, and proficiency in ordering appropriate diagnostic tests, using the “best ED practice” guidelines as the gold standard comparison.

Of the 100 patients, 55 had a single cranial nerve palsy, 14 had a decompensated phoria, 10 had monocular diplopia, and 8 had a skew deviation, with less frequent causes making up the remainder. EMPs made no diagnosis or an incorrect diagnosis in 88 (88%) of the 100 encounters while ordering 14 unindicated and 12 incorrect studies (mostly noncontrast CT scans). CNs made an incorrect diagnosis in 13 (31%) of the 42 encounters while ordering 6 unindicated and 2 incorrect studies. The authors acknowledge that the somewhat subjective nature of their “gold standard” criteria may affect these numbers, but the overall story remains the same – the diagnosis of diplopia in the ED setting is often inaccurate/incomplete.

This study is important in that it reminds us of the specialized nature of our training and the value that ophthalmologic consultation can provide in the ED setting. Additionally, it provides an excellent list of 9 areas of “targeted teaching” that ophthalmologists can provide to our ED and neurology colleagues.

Gradenigo Syndrome in a 14-Year-old Girl as a Consequence of Otitis Media with Effusion

Bonavia L, Jackson J

*J Neuroophthalmol.* 2022;42(1):e408-e409

Gradenigo Syndrome (GS) is characterized by the triad of unilateral/bilateral acute otitis media, facial pain, and cranial nerve (CN) 6 palsy. Here, the authors report the case of a 14-year-old female who presented with diplopia and left-sided, intractable headache. Exam revealed a left sixth nerve palsy with bilateral tympanic membrane perforation. MRI showed T2 hyperintensities at the left petrous apex with

diffusion restriction, ring enhancement, and loss of bony trabecular pattern. This led to a diagnosis of GS. IV antibiotics were initiated and the sixth nerve palsy resolved within 5 days.

Although overall uncommon, GS has a predilection for the pediatric population and can be deadly if untreated. As such, it is an important diagnosis to consider in any child with a sixth nerve palsy, especially in the setting of ear infection, upper respiratory symptoms, or facial pain.

#### Development and Preliminary Validation of a Virtual Reality Approach for Measurement of Torsional Strabismus

Bindiganavale M, Buickians D, Lambert SR, Bodnar ZM, Moss HE

*J Neuroophthalmol.* 2022;42(1):e248-e253

Measurement of torsional deviation in strabismus is an important part of the ophthalmic exam and may inform treatment choices. However, at present, the most common way of clinically measuring torsion is with the double Maddox rod (DMR) test, which is subjective and can be prone to imprecise measurements and administrator error. The authors seek to develop and evaluate a new way to quantify cyclodeviations.

The study used an iPhone (6 or above) and a commercial virtual reality (VR) viewer (Merge AR/VR headset) to create a “virtual” DMR test. Similar to the traditional DMR (T-DMR), the iPhone/VR viewer set-up (VR-DMR) presents a separate line to the right and left eye. The patient is tasked with rotating the axis of one line (via input buttons on the VR viewer) until the two lines are perceived to be parallel. The software then calculates the relative cyclodeviation present.

The authors recruited 20 strabismus subjects and 11 control subjects, each of whom completed 3 trials of T-DMR and 3 trials of VR-DMR testing. Both T-DMR and VR-DMR trials showed similar test-retest reliability. Variation was larger for VR-DMR than T-DMR, and VR-DMR measurements were biased to be smaller than T-DMR measurements. Measurements for T-DMR and VR-DMR were highly correlated ( $r^2=0.94$ ).

Of the 31 subjects, 17 (including the only 2 pediatric patients) found VR-DMR easier, 9 had no preference, and 5 found T-DMR easier.

This study is limited by its low sample size, especially regarding patients with vertical strabismus (only 1/20 strabismus patients had a vertical deviation). Additionally, the VR headset did not allow for glasses wear, which may have influenced results. Nevertheless, the authors do demonstrate that quantifying torsional cyclodeviation using VR-based tools is feasible and shows promise in the burgeoning field of at-home diagnostics. Such tools merit further study and development.

#### Extraocular Muscle Volumetry for Assessment of Thyroid Eye Disease

Bontzos G, Papadaki E, Mazonakis M, et al.

*J Neuroophthalmol.* 2022;42(1):e274-e280

Thyroid eye disease is an autoimmune condition that is, at least in part, characterized by enlarged extraocular muscles (EOM) with relative sparing of the tendinous insertion. The most common approach to diagnosing and quantifying EOM enlargement is by measuring the diameter or cross-sectional area of the EOMs in a CT scan. In this study, the authors sought to determine the optimal EOM measurement – EOM diameter, cross-sectional area, or volume – for use in TED diagnosis, hypothesizing that measuring EOM volume may be superior to the more standard measurements.

In this prospective, cross-sectional study, 47 eyes of 47 patients with clinically diagnosed, untreated TED were compared to 47 eyes of 47 patients with no known orbital pathology. All patient received an orbital CT scan. Total EOM volume (sum of the medial, lateral, inferior, and superior rectus), MR volume, IR maximal horizontal diameter, and MR maximal horizontal diameter were determined. Mean total EOM volume was  $7.31\text{cm}^3$ , mean MR volume was  $2.38\text{cm}^3$ , mean IR maximal diameter was  $7.15\text{mm}$ , and mean MR maximal diameter was  $6.67\text{mm}$  in the TED group. All values were significantly larger than the control group ( $4.87\text{cm}^3$ ,  $1.49\text{cm}^3$ ,  $5.04\text{mm}$ , and  $4.91\text{mm}$ , respectively) with  $p<0.001$ .

The authors conclude that there was no significant difference between individual muscle diameter measurements as compared to total EOM or individual EOM volume measurements when it comes to utility in TED identification and diagnosis. Thus, a simple 2D measurement (i.e., maximal horizontal diameter) is likely sufficient if a quantification of EOM enlargement in potential TED is needed. The utility and importance of this paper lies in the specific mean diameter numbers of EOMs. As strabismus surgeons who can be involved in the diagnosis and evaluation of TED, having a set of mean EOM diameters in both TED and controls allows for a quick, quantifiable manner in which to evaluate a CT scan for the presence of TED. Although far from a definitive diagnostic criterion, it may be a useful addition to the evaluation.

#### Isolated Fourth Nerve Palsy as the Presenting Sign of Clival Chordoma

Hall MN, Raviskanthan S, Mortensen PW, Lee AG

*J Neuroophthalmol.* 2022;42(1):e391-e393

Isolated fourth nerve palsies are a relatively common cause of strabismus in both children and adults. They are most frequently congenital/decompensated, traumatic, or ischemic in etiology; rarely, they can be caused by a tumor, as in this case of a 67-year-old female with hypertension who presented with one year of progressively worsening oblique diplopia. Exam revealed an incomitant left hypertropia with a pattern consistent with a left fourth nerve palsy. There were no other neurologic abnormalities. An MRI was performed, which showed a large left-sided clival mass. Staged surgical debulking was performed, and pathology revealed the mass to be a clival chordoma.

This report shows that, although compressive lesions are an uncommon cause of an isolated fourth nerve palsy, it is worth considering in progressively worsening cases. Additionally, the ophthalmologist should consider neuroimaging in patients with chronic, progressive fourth nerve palsies.

#### The "Eyelet Sign" as an MRI Clue for Inflammatory Brown Syndrome

Fires FC, Landau K, Kottke R, et al.

*J Neuroophthalmol.* 2022;42(1):115-120

Brown syndrome (BS) is a motility disorder characterized by restriction of elevation in adduction that can be both congenital and acquired. Acquired BS has several underlying etiologies, one of which is inflammation of the superior oblique tendon-trochlea complex. The authors here present a case series of 6 patients (2 adult, 4 pediatric) with acquired inflammatory BS and suggest a characteristic MRI finding that points to an inflammatory condition.

In each of these 6 patients, an inflammatory/idiopathic etiology was suspected based on clinical presentation. Subsequent MRIs in all 6 revealed "circumferential contrast enhancement of the trochlea with central sparing where the tendon passes, reminiscent of an eyelet." Thus, the authors coin the term "eyelet sign" to denote this MRI finding, suggesting the presence of this sign can help confirm the diagnosis of an inflammatory BS. This is a useful finding to keep in mind when ordering an MRI for suspected BS. However, it must be noted that such a sign only suggests the presence of inflammation at the tendon-trochlea complex and not a specific cause of said inflammation, be it idiopathic or associated with a systemic inflammatory disease.

#### Vertical Comitance of Hypertropia in Congenital and Acquired Superior Oblique Palsy

Demer JL

*J Neuroophthalmol.* 2022;42(1):e240-e247

Differentiating congenital from acquired superior oblique (SO) palsy is an important clinical distinction that is not always obvious. Recently, some have posited that *hypertropia (HT) greater in upgaze (compared to downgaze)* is characteristic of decompensated, congenital SO palsy and is never present in acquired (e.g., ischemic, traumatic, or tumorous) SO palsy. This study seeks to test the validity of this assertion.

The author begins by rigorously defining a "SO palsy," a label he suggests has been used too broadly to describe all manner of vertical deviations. To accomplish this, the study defines a SO palsy as a "disorder of the trochlear nerve causing contractile deficiency of the SO muscle," as demonstrated by subnormal

ipsilesional SO size on MRI. In this manner, the paper attempts to avoid the confounding data that would come with the inclusion of vertical deviations that mimic – but are not truly – SO palsies.

Using this criterion, the author identifies cases of cyclovertical strabismus in which of unilateral atrophy of the SO belly was confirmed on MRI. After exclusion criteria are applied, we are left with 9 patients with unequivocal history of congenital onset SO palsy (“congenital”), 7 with unequivocal acquired onset (“definite acquired”), and 14 with new SO palsy but no obvious etiology or inciting event (“progressive acquired”).

On average, HT was 8.4D less in upgaze than downgaze in congenital and 3.7D less in the pooled group of acquired SO palsy. Only 3 of 9 (33%) cases of congenital SO palsy met the proposed criterion of *HT greater in upgaze than downgaze*; however, 9 of 22 cases (41%) of acquired SO palsy met this criterion, including 2 of 7 definite acquired cases.

Thus, in this group of patients with SO palsy confirmed by atrophy of the ipsilesional SO belly on MRI, HT was not characteristically greater in upgaze than downgaze in congenital SO palsy. This *refutes* the previously proposed statement that HT greater in upgaze than downgaze is characteristic of congenital SO palsy. It is suggested that ophthalmologists not rely solely on this exam finding to differentiate congenital and acquired SO palsy.

#### Bilateral Abducens Nerve Palsies After Middle Meningeal Artery Embolization for Chronic Subdural Hematoma

Raviskanthan S, Mortensen PW, Zhang YJ, Lee AG

*J Neuroophthalmol.* 2022;42(2):e505-e507

Middle meningeal artery embolization (MMAE) has been recently described as a treatment for subdural hematomas (SDH). Potential complications are still being discovered. Here, the authors present a case of a 37-year-old male with bilateral SDHs who underwent MMAE and developed new horizontal diplopia immediately following the operation. Ophthalmic exam revealed an esotropia with bilateral abduction deficits, consistent with bilateral sixth nerve palsies. Repeat neuroimaging showed no change in SDH or other obvious etiology.

Given the temporal relationship to the MMAE, the authors posit that the procedure may have caused the bilateral abducens nerve palsies, although they cannot definitively rule out traumatic, ischemic, or non-localizing increased or decreased intracranial pressure. It is worth being aware of this (potential) cause of a sixth nerve palsy.

#### Clinical Characteristics for Predicting Recovery of Acquired Fourth Cranial Nerve Palsy

Kim JH, Choi HY, Jeon H

*J Neuroophthalmol.* 2022;42(2):234-238

This study retrospectively reviewed all consecutive cases of acquired, unilateral fourth nerve palsy at a single institution over a 10-year span that had greater than 6 months of follow-up. In all, 35 patients with an average age of 55.94 years old met criteria. The most common cause of fourth nerve palsy in this cohort was traumatic (40.0%), followed by ischemic (37.1%), intracranial mass (11.4%), other (8.6%), and idiopathic (2.9%).

Of these 35 patients, 23 (65.7%) achieved complete recovery (defined as the absence of hypertropia and subjective diplopia) in an average time span of  $3.91 \pm 4.03$  months. Compared to those that did *not* achieve complete recovery, those that did completely recover were older, had less severe superior oblique underaction, and had less severe fundus torsion. Indeed, 10/11 patients (90.9%) without subjective cyclotorsion fully recovered, while only 13/24 patients (54.1%) with subjective cyclotorsion achieved complete recovery.

In a binary logistic regression analysis, worse superior oblique underaction and increased fundal torsion remained significant risk factors for incomplete recovery, as did an underlying etiology of intracranial tumor (compared to an ischemic cause). Interestingly, the degree of ocular misalignment did not appear to be associated with odds of recovery.

The study concludes that severe superior oblique underaction, large fundus torsion, and intracranial mass (rather than ischemic cause) may be associated with poorer outcomes in acquired fourth nerve palsy. Over 50% of patients, in line with past literature, achieve complete recovery, with ischemic fourth nerve palsies having a better prognosis. This information helps us to better inform adult patients about expected outcomes and prognosis of their acquired fourth nerve palsy.

Neuro-Behçet Disease Causing Nuclear/Fascicular Fourth Nerve Palsy  
Kisilevsky E, Margolin EA

*J Neuroophthalmol.* 2022;42(2):e517-e519

Behçet disease (BD) is a multisystemic inflammatory disease characterized by oral ulcers, genital ulcers, and uveitis. Neuro-BD (NBD) is rare manifestation of BD and typically affects the brainstem, causing ophthalmoplegia, cerebellar ataxia, hearing loss, and/or facial palsy. Here, the authors present a case of a 25-year-old male with acute onset of vertical diplopia in the setting of known BD on azathioprine. Exam revealed a right hypertropia with a pattern fitting a right fourth cranial nerve palsy. There was no preceding trauma. Brain MRI was performed and revealed an enhancing lesion in the left midbrain and left cerebellar peduncle, suggesting involvement of the left nucleus and/or fascicle of the fourth nerve (which decussates and would therefore cause a right fourth nerve palsy, as seen here).

In summary, the authors affirm that BD can present with cranial nerve palsies due to the disease's predilection for the brainstem. Although a rare cause of a cranial nerve palsy and acute diplopia, it is important to recognize when NBD may be present.

Gradenigo Syndrome: Mimicker of Slipped Muscle and Shunt Failure  
Seeds A, Coleman SL, Strul S

*J Neuroophthalmol.* 2022;42(1):e410-e411

Gradenigo Syndrome (GS) is characterized by the triad of unilateral/bilateral acute otitis media, facial pain, and cranial nerve (CN) 6 palsy. Typically secondary to untreated otitis media, GS is uncommon today given our readily available antibiotics. However, here the authors describe a case of GS following strabismus surgery.

A 2-year-old male with a history of traumatic brain injury and LP shunt, intermittent exotropia, and bilateral DVD underwent a bilateral lateral rectus recession (BLR) of 6mm, left inferior oblique anteriorization, and right inferior oblique recession. On POD2, patient had bilateral abduction deficits with an esotropia of 25 in primary position. After a period of close monitoring without improvement, exploratory surgery to retrieve a suspected slipped lateral rectus was performed; however, both LR were in the correct position (recessed 6mm from original insertion). Patient underwent MRI to evaluate for a potential shunt malfunction, which revealed bilateral otitis media. Patient was started on amoxicillin and had complete resolution of both abducens nerve palsies within a month.

Although quite rare, GS should remain in mind in cases of pediatric sixth nerve palsies in children unable to accurately verbalize facial or ear pain, especially in the setting of upper respiratory symptoms.

From monocular photograph to angle lambda: A new clinical approach for quantitative assessment.  
Rateaux M, Bremond-Gignac D, Robert MP.

*J Binocul Vis Ocul Motil.* 2022 Jul-Sep;72(3):169-175.

In this study, monocular photographs were used to assess angle lambda in 20 healthy eyes. Pentacam was used as a comparison. The mean value of angle lambda was  $+2.61^\circ \pm 2.92^\circ$  and  $2.63^\circ \pm 2.85^\circ$  in both picture series, respectively, and Lin's repeatability coefficient was 0.99 - with a systematic deviation of  $-0.071^\circ$  compared to Pentacam assessment. Angle lambda distribution was in range with values from the literature. The results of this study show that a less costly approach to measuring angle lambda is possible using simple photography.

Comparison Between the Deviations After 1 and 24 Hours of Diagnostic Occlusion for Basic and Divergence Excess Types of Intermittent Exotropia.

Mohan K, Sharma SK.

J Pediatr Ophthalmol Strabismus. 2022;59(1):41-45.

Published January 1, 2022

This prospective study sought to compare changes in deviation 1 and 24hrs after diagnostic monocular occlusion for basic and divergence excess types of intermittent exotropia. Patients with basic intermittent exotropia had statistically significant differences in the mean near and distance deviations before and after 1-hour occlusion and before and after 24-hour occlusion, but there was no statistically significant difference between the deviations after 1- and 24-hour occlusion. Patients with divergence excess intermittent exotropia had statistically significant differences between the mean near deviation before and after 1-hour occlusion and before and after 24-hour occlusion, but there was no statistically significant difference between the deviation after 1- and 24-hour occlusion. There were no statistically significant differences between the mean distance deviations before and after 1-hour occlusion, before and after 24-hour occlusion, and after 1- and 24-hour occlusion. There was no statistically significant difference in the number of patients who had a clinically significant (5 PD or greater) increase in the near and distance deviations after 1 hour versus 24 hours of occlusion in patients with basic type intermittent exotropia ( $P = .74$  and  $P = 1.00$ , respectively) and also in those with divergence excess type exotropia ( $P = .43$  and  $P = 1.00$ , respectively). The authors concluded that diagnostic monocular occlusion for 1 hour is sufficient in patients with basic and divergence excess types of intermittent exotropia. This was a simple, but effective study at clarifying the proposed distinction between 1 and 24hr diagnostic occlusion.

Comparison of Long-term Stereoacuity Improvement Between Patients With Initial Subnormal Stereopsis and Nil Stereopsis in Refractive Accommodative Esotropia

Mohan K, Sharma SK.

Pediatr Ophthalmol Strabismus. 2022;1-6.

Pre-publication. Posted online January 26, 2022.

The purpose of this retrospective review was to compare the improvement in long-term stereoacuity between 79 children (mean age  $6.3 \pm 1.9$  years) with refractive accommodative esotropia (RAET) and subnormal stereopsis (31 children) and no stereopsis (48 children) who were followed for mean  $11.7 \pm 1.8$  years (range: 5 to 21 years). In the current study, 97% of patients in the initial subnormal stereopsis group had an improvement in stereoacuity compared to 40% of patients in the nil stereopsis group at a mean follow-up of 12 years. 68% of patients in the initial subnormal stereopsis group demonstrated 60 arcsec of stereoacuity compared to 19% of patients in the nil stereopsis group. The authors conclude that chances of improvement in stereoacuity and recovery of a normal stereoacuity (60 arcsec) are significantly greater in patients with initial subnormal stereopsis than in patients with nil stereopsis, and also that the absence of stereopsis at initial assessment does not preclude recovery of normal stereopsis on long-term follow-up. This study was commendable in its duration of follow-up spanning greater than a decade. Its conclusions will be useful for counseling families.

Relationship Between the Clinical Factors and Deviation Control in Intermittent Exotropia.

Gökgöz Özişik G, Gokgoz G, Caglar C, Cakmak HB.

J Pediatr Ophthalmol Strabismus. 2022;59(1):53-59.

Published January 1, 2022.

The purpose of this study was to establish whether clinical factors were correlated with deviation control in intermittent exotropia. The authors retrospectively studied 54 patients with intermittent diplopia. They found a mild correlation between age with total exotropia control score and age with the control of near exotropia control score ( $r = 0.320$ ,  $P = .018$  and  $r = 0.339$ ,  $P = .012$ , respectively). The angle of deviation at near showed a significant moderate correlation between total exotropia control score and near exotropia control score ( $r = 0.523$ ,  $P < .001$  and  $r = 0.780$ ,  $P < .001$ , respectively). The deviation angle at distance showed a mild correlation with distance exotropia control score and total exotropia control score ( $r = 0.423$ ,  $P = .001$  and  $r = 0.288$ ,  $P = .034$ , respectively). The angle of deviation at distance showed a mild correlation with the angle of deviation at near ( $r = 0.359$ ,  $P = .008$ ). The deviation angle at distance was established as an independent factor for predicting total exotropia score ( $P = .037$ ,  $P = .015$ , respectively). The authors concluded that a high deviation angle correlates positively with poor deviation control and that the distance deviation angle is an independent predictor of total deviation control for the first time in the literature. This was an interesting study despite its small size and it warrants recognition as such.

Series of cases of acute acquired comitant esotropia in children associated with excessive online classes on smartphone during COVID-19 pandemic; digital eye strain among kids (DESK) study-3. Amit Mohan, Pradhnya Sen, Deepti Mujumdar, Chintan Shah & Elesh Jain. Children Eye Care Center, Department of Pediatric Ophthalmology and Strabismus, Sadguru Netra Chikitsalya and Postgraduate Institute of Ophthalmology, Chitrakoot, MP, India  
Strabismus 2021, VOL. 29, NO. 3, 163–167

Extra time of sitting in front of a digital device is required for e-learning by children during Corona virus (COVID-19) pandemic can lead to many ocular problems including digital eye strain (DES). In view of increased incidence of DES in children, multiple studies had been conducted in central India to assess the eye strain in children due to excessive online classes as a research project named “Digital eye strain among kids (DESK) study.” This study DESK-3 aimed to report series of cases of acute acquired comitant esotropia (AACE) in children attending online classes during COVID-19 pandemic. Children aged 6–18 years with recent onset of esotropia of < 1-month duration without any similar history in past presented in month of July-August 2020 at a tertiary children eye care hospital were evaluated. Data collection included age and gender of child, presence or absence of diplopia, visual acuity, duration of smartphone use, duration of online classes, angle of deviation for near and distance and cycloplegic refraction. Total eight children of AACE were included in the study. The mean age of children was  $12.5 \pm 4.2$  years. All eight were males. The mean duration of smartphone use was  $4.6 \pm 0.7$  hours per day. All children were attending online classes > 4 hours per day on smartphone of average size 5.5 inches. Five children were emmetropic, one myopic, one pseudo myopic and one hyperopic. The angle of deviation for near and distance were  $48.1 \pm 16.4$  PD and  $49.3 \pm 15.9$  PD respectively with normal ocular motility. Seven children complained of horizontal diplopia in all gazes. Neurological examination and CT scan of brain and orbit was normal in all patients. Two months before the lockdown only one case was identified as compared to eight during the lockdown. Their conclusion is that prolonged near work during smart phone use for e-learning might lead to the development of AACE in children. The main drawback in this study is the small number of patients and the follow-up duration. They also don't establish what the patterns of patients with ET has been in the past in the same tertiary center.

## 10. STRABISMUS SURGERY

No-split, no-tenotomy transposition of only the superior rectus muscle combined with medial rectus recession in patients with complete abducens nerve palsy

Akbari MR, Reza T, Sadeghi M, Masoomian B, Mirmohammadsadeghi A  
J AAPOS 2023;27:26.e1-4

The outcomes of no-split, no-tenotomy transposition of only the superior rectus muscle combined with medial rectus recession in patients with complete abducens nerve palsy was evaluated. A total of 8 patients with abducens nerve palsy underwent a procedure, whereas the temporal margin of the superior rectus muscle, 10 mm posterior to the insertion, was secured with a nonabsorbable suture and sutured to the sclera at a distance of 12 mm from the limbus in the superotemporal quadrant, halfway between the superior rectus and lateral rectus. In this small cohort, the procedure improved esotropia and abduction limitation without inducing significant vertical deviations or torsional diplopia. The limitation of the study is the small sample size, the variable medial rectus recession, the use of two stacked prisms over the affected eye for measurement of large deviations, lack of head turn measurement, lack of fundus torsion measurement, and lack of stereopsis measurement.

Conventional surgery versus botulinum toxin injection for the management of esotropia in children with Down syndrome.

Taghreed Alnajjar, MD, Goraka Sesma, MD, and Shatha Alfreihi, MD.  
JAAPOS 2022;26:251.e1-4.

This study compares the success rates of strabismus surgery and botulinum toxin injection (BTX) in treating esotropia in patients with Down Syndrome (DS). They found a significant difference in median angle of deviation between the surgery (0 PD) and BTX groups (22.5 PD). The cumulative success rate was also higher in the surgery group (65%) compared to the botox group (30%). The success rate in the BTX group was lower than that found in several other studies. The authors hypothesized that this may be due to the high level of amblyopia in the BTX group, the large angle of pre-op deviations in the patients included in this study, generalized hypotonia in the DS population, and/or a possible differential response to botulinum toxin in patients with DS. This is an important study to help define the role of botulinum toxin injections for treatment of strabismus in patients with Down Syndrome. While the surgery group had clearly superior results, there are still some scenarios where botulinum toxin may have a benefit such as in sick kids who can only tolerate a short anesthetic or in difficult to measure patients where botox injections could result in some improvement allowing incisional surgery to be delayed to a time when more accurate measurements can be obtained.

Postoperative diplopia test—repeatability and prediction of surgical outcomes.

Laura Catherine Jane Jarwick, BMedSci, MMedSci, Kate Taylor, BSc, Alan John Connor, FRCOphth, and Caroline Sarah Fieldsend, BMedSci.  
JAAPOS 2022;26:252.e1-5.

The postoperative diplopia test (PODT) is a preoperative test used to investigate the risk of diplopia developing after surgery. It is used in patients without the potential for binocular single vision considering nonfunctional strabismus surgery. The first purpose of this study was to evaluate the test-retest and interobserver reliability of the PODT method. The second purpose was to investigate the predictive value of the test for assessing risk for postoperative diplopia. More than half of the patients showed consistent results with repeated PODT testing; however, some patients showed substantial variability between tests, including some who reported diplopia on one instance of PODT but had no diplopia on the other PODT. As for post-operative diplopia, among patients who reported no diplopia over the range tested on PODT, none had persistent diplopia after surgery. Among 14 patients who experienced diplopia during PODT, 2 had persistent diplopia at 3 months post-op. Four patients with diplopia on PODT were within their suppression zone postoperatively, and 3 of these (75%) experienced no persistent diplopia, as predicted; 5 were predicted to be outside of their suppression zone postoperatively, yet 4 of these (80%) experienced no persistent diplopia. Thus, the additional predictive value of suppression zones in the presence of any diplopia on PODT appears questionable. The study suggests that further testing with PAT or botulinum toxin injection could be used to better stratify risk in patients who do have diplopia on



PODT. I think the most important thing this study points out is that the risk of intractable diplopia after nonfunctional strabismus surgery is rare but possible. It is very important to adequately counsel patients about the risk, especially if they have any diplopia on PODT.

Treatment of convergence insufficiency type intermittent exotropia with bupivacaine injection to the medial rectus combined with lateral rectus recession.

Adem Tellioglu, MD, Osman Bulut Ocak, MD, Asli Inal, MD, Ceren Gurez, MD, Selcen Celik, MD, Derya Ozkan Tellioglu, MD, and Birsen Gokyigit, MD.

JAAPOS 2022;26:249.e1-5.

Intermittent exotropia is the most common form of exotropia with convergence insufficiency type being a subset where the deviation is greater at near than in the distance. Bupivacaine injection has been proposed as a possible treatment option for CI-IXT. It works by increasing the contraction power of the injected muscle by causing changes in the muscle structure and length. This study assessed the outcomes of BPX injection in the medial rectus muscle combined with lateral rectus recession in patients with CI-IXT. Thirty eyes were included in the study – 10 received BPX injection in one MR combined with LR recession in the same eye, 20 received unilateral LR recession alone. In the BPX group, 70% of patients had a successful outcome compared with 60% in the control group. Reoperation was required in 20% of the BPX patients and 25% of the control patients. Most interestingly, the dose response per mm of LR recession alone was greater at distance than at near; whereas, the dose response of LR recession combined with BPX was greater at near than in the distance. This makes this an especially appealing operative choice in patients with convergence insufficiency. While this approach is theoretically interesting, there are significant limitations to this study. The study is limited by its retrospective design, short follow-up period, and small number of cases; however, the most concerning limitation is the control group is not an exact comparison as those patients did not have convergence insufficiency. It also does not compare BTX treatment to MR resection. Considering that all of the patients in the study were already undergoing an incisional procedure on their LR, there was not anesthetic benefit to using BTX instead of MR resection; however, this is an interesting thing to consider in a patient where anterior segment ischemia is of higher concern.

Applications of bupivacaine in the non-surgical treatments of strabismus: a review Mohammad Yaser Kiarudi, Seyed Hossein Ghavami Shahri, Acieh Es'haghi, Bahare Gharib & Mohammad-Reza Ansari-Astaneh. Eye Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

Strabismus 30:4. 204-208

Bupivacaine (BUP) is an anesthetic from the family of aminoacyl anesthetics and has the highest myotoxicity among other groups of anesthetics. Intramuscular injection of BUP first causes acute fibriform lysis and subsequently with the regeneration process, stronger myofibrils are formed within 3–4 weeks. Satellite cells, which are actually myogenic stem cells, are preserved in the early stage and during the destruction of muscle fibers. In fact, these cells are responsible for the subsequent regeneration of fibers. BUP is one of the few medicines that is able to increase muscle strength. In animal studies on rabbits, a decrease has been observed in the diameter of the global layer in the first week and an increase in type-I myosin occurs after 60 days, especially in the global muscle layer. There are numerous studies according to BUP injection for the non-surgical management of horizontal strabismus. To intensify the effects of the injection, botulinum toxin injection can also be used simultaneously in the antagonist muscles. In general, although the rate of improvement in strabismus varied among different studies, BUP injection alone corrects about 5– 8 prism diopters. Together with botulinum toxin, BUP corrects about 15 prism diopters. The stability of this improvement is up to 10 years after injection. No significant difference has been observed in response rate between patients with esotropia and exotropia. Unlike the large molecule of botulinum toxin, which spreads slowly to its site of action, the BUP molecule is small and must be in direct contact with myofibrils before absorption into the bloodstream to exert its effect. Therefore, the injection volume should be about 3 cc with a concentration of 0.75 g per deciliter. Although BUP is promising non-surgical strabismus management, especially in small angle and residual horizontal strabismus, however, it has its own limitations. The need for direct infusion of a relatively large volume of BUP may be one of its major drawbacks that limits its usage in an office method.

Correction of horizontal and torsional compensatory head posture in infantile nystagmus syndrome using horizontal rectus muscle recession and resection with vertical transposition Vibha Baldev, Shailja Tibrewal, Soveeta Rath & Suma Ganesh. Department of Pediatric Ophthalmology, Strabismus and Neuro-ophthalmology, Dr. Shroff's Charity Eye Hospital, New Delhi  
Strabismus 30: 3. 139-143

Infantile nystagmus syndrome (INS) is often characterized by an identifiable null zone. When the null zone is not in the straight-ahead gaze, a compensatory head posture (CHP) is adopted by the patient to achieve best possible vision. Various surgical procedures have been recommended to correct a CHP which is clinically predominant in one dimension of yaw (lateral rotation), pitch (anterior or posterior flexion/extension) or roll (lateral flexion). However, the presence of a complex CHP which is clinically evident in more than one dimension, warrants either a combination of multiple techniques or a stepwise approach. We report the case of a 26-year-old male with INS with an eccentric null and a multi-dimensional complex CHP of 30° left face turn, 20° right head tilt and 10° chin depression. The patient was managed by all four horizontal rectus muscle recession and resection with full tendon vertical transposition to address the face turn and head tilt. He underwent lateral rectus muscle (LR) recession with upward transposition and medial rectus muscle (MR) resection with downward transposition in the right eye. MR recession with upward transposition and LR resection with downward transposition were performed in the left eye. Postoperatively, the head posture improved significantly for both distance and near viewing. The chin depression also reduced after the procedure. He developed transient diplopia due to a small vertical deviation after the surgery, which was managed by prisms and fusional exercises. Thus, horizontal rectus muscle recession and resection combined with vertical transposition may be helpful to simultaneously improve the head tilt associated with the face turn, obviating the need for vertical rectus muscle or oblique muscle surgery

Small vertical deviations and motility disturbance in extreme gaze may be expected after this procedure, as seen in this case. The vertical transposition of a rectus muscle which is recessed by a large amount may be unpredictable and might have been the reason for the induced incomitant strabismus. One should explain the possibility of diplopia and the need for prism therapy in the postoperative period to the patient before performing this procedure. Further studies with bigger sample size are warranted to assess the outcome of this procedure

#### Temporal Slant Recession of the Inferior Rectus Muscle: A Simple Surgical Treatment for Diplopia Caused by Small Vertical Deviations

Brodsky M

[published online ahead of print, 2022 Aug 2]. *J Neuroophthalmol*.

Small, symptomatic vertical deviations – which can be neurologic, orbital, or idiopathic in origin – are a common cause of symptomatic, bothersome diplopia in the elderly. Prism, botulinum toxin, and traditional strabismus surgery (i.e. standard recessions) all have their downsides when it comes to correcting such small deviations. Various surgical techniques have been described to help improve these small vertical deviations, including partial tendon recession procedures. The author here describes his outcomes using temporal slant procedures of the inferior rectus muscle (TSRIRM), a type of partial tendon recession, in adults with small (<7 PD), isolated hyperdeviations.

The procedure begins with exposure of the temporal edge of the IR muscle. A 6-0 Vicryl suture is placed through the temporal pole of the IR, followed by an 80-90% temporal tenotomy of the muscle at the insertion. The temporal edge is then sutured to the globe posterior to its original insertion, recessing 1mm for every 1.5 PD of vertical deviation (e.g. would recess 2mm for a 3 PD deviation).

Of the 11 patients undergoing this procedure, 9 were deemed to be operative successes, as defined by resolution of diplopia post-operatively at 2 and 6 months. Both failures had intermittent diplopia secondary to residual or recurrent intermittent hypertropia.

It must be noted that all patients included had objective or subjective excyclotorsion prior to the procedure. This was part of the reason for choosing a temporal slant, as such a procedure (akin to a nasal transposition of the IR) will theoretically cause a small degree of desired incyclotorsion. Additionally, all patients included here had minimal lateral incomitance.

In all, the TSRIRM seems to be a useful procedure in small, symptomatic vertical deviations. Importantly, as noted by the author, care should be taken to measure torsion and account for any incomitance in the pre-operative measurements, as that could affect the choice of procedure.

Split Tendon Medial Transposition of Lateral Rectus for Pediatric Complete Oculomotor Palsy  
Zhang K, Varma H, Cao Y, Shah V

[published online ahead of print, 2022 Nov 7]. *J Neuroophthalmol*.

Complete oculomotor nerve palsies are a surgical challenge, particularly in children. The authors review the use of a split tendon medial transposition of the lateral rectus (STMTLR) in 5 consecutive children with complete oculomotor nerve palsies at a tertiary care center.

To start, the authors helpfully review the STMTLR procedure and provide photos of each step. In their cohort of 5 patients, all 5 tolerated the procedure without complications. Four of the patients regained some amount of adduction, with an average improvement in exodeviation of ~40 PD. Two of the five achieved orthotropia.

In all, the paper concludes that the STMTLR is a viable surgical option in children with complete oculomotor palsy for the experienced strabismus surgery, although the study is weakened slightly by poor follow up (secondary to COVID 19) and a small cohort.

Analgesia in Postoperative Adult Strabismus Patients. *J Pediatr Ophthalmol Strabismus*.

Rho J, Gannon E, Smith C, Hoehn ME.

2023;60(1):e5-e7. doi:10.3928/01913913-20221118-01

This survey of pediatric ophthalmic surgeons on analgesia for postoperative adult strabismus patients indicates that 65% prescribed acetaminophen and/or nonsteroidal anti-inflammatory drugs (NSAIDs), and 12% to 16% prescribed opioids. Most surgeons reported reasonable control of pain regardless of analgesia. Acetaminophen and/or NSAIDs may adequately control pain, although certain circumstances may warrant opioid prescriptions. This is a useful benchmark to guide prescription patterns in the management of postoperative pain in adult strabismus patients.

Duane Retraction Syndrome: The Role of Botulinum Toxin A Injection in Adults and Its Impact on Quality of Life in an Indian Population.

Anand K, Hariani A, Kumar P, Rastogi A, Dutta P, Krishnan A.

*J Pediatr Ophthalmol Strabismus*. 2023;60(1):46-51. doi:10.3928/01913913-20220324-01

This small interventional case series reported the outcome of Botox for management of Duane syndrome. The authors injected the horizontal recti of 25 adults then followed them at 1 day, 10 days, and 3 months after injection. The outcome was categorized on the basis of deviation/abnormal head posture/overshoots as: (1) significant improvement (< 8 prism diopters [PD]/< 5 degrees/≤ grade 1); (2) partial improvement (8 to 20 PD/5 to 15 degrees/≤ grade 2); and (3) no improvement (> 20 PD/> 15 degrees/≥ grade 3). Patients with partial/significant improvement were considered to have a favorable outcome. The impact on quality of life was assessed using the Adult Strabismus-20 Questionnaire scores 10 days after injection. The authors found overall, a significant reduction in ocular deviation in esotropic and exotropic Duane retraction syndrome at 10 days (P = .001) and 3 months (P = .04) after botulinum toxin injection. The abnormal head posture improved from 11.58 ± 7.43 to 7.86 ± 6.25 degrees at 10 days. Botulinum toxin had a positive impact on the Adult Strabismus-20 Questionnaire scores, which significantly improved (P < .05) at 10 days. A favorable outcome was noted in 21 patients at 10 days but only 4 patients at 3 months. Three patients developed ptosis and 1 patient with orthotropic Duane retraction syndrome developed transient exotropia. The authors concluded that Botox in adults w/ DRS can have a useful diagnostic role by providing insight (into who might benefit from further treatment) and setting realistic expectations. Meanwhile, it also provided a positive impact on quality of life.

Diclofenac Versus Corticosteroids Following Strabismus Surgery: Systematic Review and Meta-analysis.  
Karam M, Alsaif A, Al-Naseem A, et al.

*J Pediatr Ophthalmol Strabismus*. 2022;1-11. doi:10.3928/01913913-20221011-01

This meta-analysis reported outcomes of diclofenac vs corticosteroids following strabismus surgery, specifically: discomfort, chemosis, inflammation, conjunctival gap, intraocular pressure, and conjunctival injection and, secondarily, conjunctival congestion, discharge, and drop intolerance. They found 8 studies with a total sample of 469 eyes. At weeks 1 and 4 postoperatively, there were no statistically significant differences between the diclofenac and corticosteroid groups, except for conjunctival injection at week 1 favoring diclofenac. At week 2, all primary outcomes favored diclofenac. Conjunctival congestion was

significantly improved for dexamethasone, whereas discharge and drop intolerance was not statistically different. The authors concluded that diclofenac is comparable to various corticosteroids when used following strabismus surgery and that it yielded significant improvements in discomfort, conjunctival chemosis, inflammation, conjunctival gap, intraocular pressure, and conjunctival injection, mainly at 2 weeks postoperatively. Although this meta-analysis, its results are worth studying in a prospective, controlled manner given potential implications for practice change across the field.

#### Botulinum Toxin Injection in Horizontal Rectus Muscles Without Electromyography Using an Open Sky Versus a Closed Sky Technique.

Kassem RR, Badr RAA, Al Zarea BKA, et al.

J Pediatr Ophthalmol Strabismus. 2022;59(6):388-395. doi:10.3928/01913913-20220210-03

This retrospective study of 135 patients with horizontal strabismus who received Botox injections were reviewed to determine whether EMG was necessary and to compare “open” vs “closed” techniques of injection. Anesthesia was achieved with sevoflurane or propofol in children, and with topical benoxinate hydrochloride in adults. Patients received a bilateral injection of 2.5 to 15 IU of botulinum toxin, without electromyographic control, into the medial or lateral rectus muscles to correct esotropia or exotropia, respectively. An open sky technique was used in 31 patients, and a closed sky technique was used in 104 patients. Postoperative alignment within 10 prism diopters (PD) of orthotropia was considered a successful outcome. The authors found that a successful outcome at 6 months of follow-up was achieved in 47% of all patients: 59% of patients in the open sky group and 44% of patients in the closed sky group ( $P = .151$ ). Botulinum toxin injection corrected a mean of  $14 \pm 9.705$  PD in patients in the open sky group and  $31 \pm 20.589$  PD in patients in the closed sky group to obtain mean residual angles of  $21 \pm 16.692$  and  $13 \pm 11.901$  PD, respectively. They concluded that EMG assistance was not remarkably different from injections without EMG, and that closed technique is favored to shorten operative times and postoperative convalescence, and to reduce the risk of postoperative adhesions and scarring, which made re-operations difficult. This is an important and informative study of sufficient power to guide clinical decision-making, but it is worth noting a prospective, randomized trial would be more internally valid.

#### Outcomes of a Simple Lateral Rectus Belly Transposition Procedure Combined With Ipsilateral Antagonist Recession for Vertical Rectus Palsy.

Xia W, Ling L, Wen W, et al.

J Pediatr Ophthalmol Strabismus. 2022;59(6):396-404. doi:10.3928/01913913-20220211-02

This small retrospective study of 10 pts with IR palsy and 3 pts with SR palsy reported the outcomes of lateral rectus belly transposition (LRBT; w/o splitting or disinsertion) combined with ipsilateral antagonist recession. The mean postoperative follow-up time was  $20.4 \pm 8.0$  months. Eleven patients (84.6%) underwent simultaneous recession of the ipsilateral antagonist muscle of the palsied vertical rectus. After surgery, the mean vertical deviation improved from  $31.4 \pm 16.4$  to  $1.9 \pm 3.6$  prism diopters (PD) ( $P < .001$ ). The mean vertical duction limitation of the palsied muscle improved from  $-2.7 \pm 0.6$  to  $-0.6 \pm 0.5$  ( $P = .001$ ). In one patient, the scleral fixation suture was removed due to continuous reverse vertical diplopia. The total success rate was 76.9%. No induced horizontal deviation was noted. Anterior segment ischemia or other severe surgical complications did not occur. The authors concluded that the LRBT procedure can be effective, safe, and reversible in patients with vertical rectus palsy. It allows for the option of simultaneous ipsilateral antagonist recession, and it is especially valuable in patients whose vertical duction deficiency is worse in abduction but mild in adduction. Of course, this was limited by sample size.

#### Comparative Study of Bilateral Versus Unilateral Strabismus Surgery in the Management of Lateral Incomitance in Intermittent Exotropia

Anand K, Krishnan A, Kumar P, et al.

J Pediatr Ophthalmol Strabismus. 2022;1-5. doi:10.3928/01913913-20220810-01

This prospective, randomized, interventional comparative study compared outcomes of 40 patients who underwent bilateral asymmetric lateral rectus recession vs 40 patients who underwent unilateral lateral rectus recession and medial rectus resection. Surgical outcome was considered successful if the primary deviation was within  $\pm 8$  prism diopters (PD) and lateral incomitance was less than 5 PD. The authors found no statistically significant difference in the postoperative lateral incomitance between the two groups ( $P = .25$ ), but a statistically significant difference was observed between preoperative and

postoperative lateral incomitance in each group ( $P < .0001$ ). They concluded that both procedures are equally efficacious in achieving acceptable ocular alignment and improving significant lateral incomitance in patients with intermittent exotropia with deviations between 15 and 35 PD without causing significant motility limitation. This was a well-designed prospective study with clinically relevant results.

#### Comparison of Unilateral Versus Bilateral Lateral Rectus Recession for Small Angle Intermittent Exotropia: Outcomes and Surgical Dose-Responses.

Lee MH, Smith DR, Kraft SP, Wan MJ.

*J Pediatr Ophthalmol Strabismus*. 2022;59(5):350-355. doi:10.3928/01913913-20220131-03

This single-center retrospective cohort study compared the outcomes of unilateral lateral rectus recession vs bilateral lateral rectus recession for treatment of small-angle (16-20PD) intermittent exotropia. The primary outcome was success (exotropia  $< 10$  PD of esotropia  $< 5$  PD, no decrease in stereopsis  $> 0.6$  log arcsec, and no reoperation) at 12 months postoperatively. Secondary outcomes included survival analysis of time to surgical failure, surgical dose-response, and improvement in central fusion or stereopsis. The authors found that 13 of 27 patients (46%) in the bilateral lateral rectus recession group and 19 of 28 patients (70%) in the unilateral lateral rectus recession group met criteria for success, but this was not a statistically significant difference ( $P = .10$ ). Survival analysis showed a trend toward a higher rate of failure in the bilateral lateral rectus recession group compared to the unilateral lateral rectus recession group ( $P = .04$ ). The mean surgical dose-response was 1.7 PD/mm at 1 week and 1.0 PD/mm at 12 months for the bilateral lateral rectus recession group, and 2.0 PD/mm at 1 week postoperatively and 1.4 PD/mm at 12 months postoperatively for the unilateral lateral rectus recession group. There were no cases of long-term postoperative lateral incomitance in either group. They concluded that unilateral lateral rectus recession and bilateral lateral rectus recession had similar success rates for small angle intermittent exotropia after at least 12 months of follow-up. Albeit a small study, this was an interesting comparative analysis because it raises the option of “muscle-sparing” approach to intermittent XT.

#### Nasal transposition of the split lateral rectus muscle for strabismus associated with bilateral 3rd-nerve palsy.

Oke I, Lorenz B, Basiakos S, Gokyigit B, Dodd MM, Laurent E, Hunter DG, Goberville M, Elkamshoushy A, Tsai CB, Orge F, Velez F, Jeddawi L, Gravier N, Li N, Shah A, Dagi L.

*American Journal of Ophthalmology*. 2022 Oct 1;242:165-72.

Bilateral third nerve palsies are notoriously challenging to manage and multiple surgical approaches have been described. The goal of this international, multicenter, retrospective case series was to determine the success rate and complications associated with nasal transposition of the split lateral rectus muscle (NTSLR). The study included 34 patients with a median age of 46 years. The median pre-operative deviation was 90 prism diopters of exotropia. In the cohort, 35% underwent bilateral NTSLR and 65% underwent unilateral NTSLR with an alternative surgery on the contralateral eye. For their primary outcome of success, defined as horizontal alignment  $\leq 15$  prism diopters in primary gaze, there was a 50% success rate which did not vary based on whether surgery was performed bilaterally or unilaterally. Intraoperative challenges occurred in 18% of cases and potentially vision-threatening complications occurred in 21% of cases, with the most common being choroidal effusion followed by IOP elevation. The authors also found a surgical dose relationship between pre-operative deviation and post-operative alignment.

#### Different Surgical Approaches for treatment of isolated dissociated vertical deviation without inferior oblique overaction.

Fu L, Zhu B, Yang D, Yan J.

*Eur J Ophthalmol*. 2022 Nov;32(6):3237-3243.

This study evaluated the surgical results of superior rectus recession (SRR) and inferior oblique anterior transposition (IOAT) for cases with isolated bilateral dissociated vertical deviation (DVD) without inferior oblique overaction (IOOA). A retrospective review was conducted for cases with isolated bilateral DVD without IOOA who were surgically treated using either bilateral SRR (SRR group) or IOAT (IOAT group). Pre- and post-operative ocular motility, ocular alignment, amount of DVD and complications were compared between the two groups. Records from 37 cases were reviewed. Preoperative levels of DVD ( $M \pm SD$ ) in the SRR group ( $N = 18$ ) of  $19.88 \pm 6.72$  prism diopter (PD) in the right eye and  $19.54 \pm 5.64$

PD in the left eye, were reduced to  $4.94 \pm 7.26$  PD and  $4.11 \pm 3.91$  PD respectively after surgery ( $P < 0.0001$  for both). Preoperative levels of DVD ( $M \pm SD$ ) in IOAT group ( $N = 19$ ) of  $15.89 \pm 6.35$  PD in the right eye and  $18.58 \pm 9.27$  PD in the left eye, were reduced to  $3.42 \pm 4.49$  PD and  $3.42 \pm 4.88$  PD respectively after surgery ( $P < 0.0001$  for both). Inferior oblique (IO) muscle function remained normal after surgery. Overall, outcomes within the SRR group revealed that 10 patients showed a complete resolution of their condition, 6 had improved alignment, and 2 experienced no improvement. In the IOAT group, 13 patients showed a complete resolution of their condition, 5 had improved alignment, and 1 did not improve. There were no statistically significant differences between the two groups ( $Z = 0.48$ ). The results of this study suggest that SRR and IOAT were both effective in treating isolated DVD without IOOA.

Surgical outcomes of medial Rectus advancement for consecutive exotropia.

Spieler R, Achiron A, Qassoom A, Bachar Zipori A, Spieler O.

Eur J Ophthalmol. 2022 Nov;32(6):3244-3249.

A retrospective chart review of patients undergoing medial rectus advancement surgery for consecutive exotropia after esotropia surgery were evaluated from 2000 to 2020. A successful surgical outcome was defined as alignment within 10 PD of orthophoria at last follow-up. Twenty patients (11 males and 9 females) with mean postoperative follow-up from the re-operation surgery of  $34.7 \pm 29.2$  months were included. Of the 20 reoperated patients, 9 (45.0%) patients underwent MR advancement alone and 11 (55.0%) underwent MR advancement with LR recession. At the latest follow-up examination, 9 (45.0%) patients had a successful result. Nine patients had undercorrection and 2 had overcorrection. The two groups were similar in the preoperative amount of mean exotropia,  $23.3 \pm 9.9$  PD in the success group and  $29.8 \pm 14.0$  PD in the failure group. On the last follow-up examination, the amount of mean deviation was  $2.7 \pm 2.6$  PD exotropia in the success group and  $13.4 \pm 23.6$  PD exotropia in the failure group. Medial rectus advancement for the correction of consecutive exotropia was successful in almost half of the cases. Failure was usually due to undercorrection. This study is limited by the small number of cases reviewed. The results may also be skewed by the fact that the results were not stratified based on the type of surgery performed (MR advancement alone versus MR advancement with LR recession). Details regarding the initial esotropia patients should also be included so that surgical results can be more appropriately compared between cohorts.

Large bilateral medial rectus recession versus three-to-four horizontal muscle surgery for large-angle esodeviations.

Torre Franca AB Jr, Santiago APD.

Eur J Ophthalmol. 2022 Nov;32(6):3250-3257.

In order to address the ongoing debate regarding the best surgical approach to address large-angle esodeviations greater than 50 prism diopters, the authors looked at a total of 74 medical records retrospectively, comparing the surgical outcomes of bilateral medial rectus (BMR) recession versus BMR recession in addition to 1 or 2 lateral rectus resections (3 or 4 muscle surgery). The mean age at onset of esodeviation was  $2 \pm 2.9$  years old, and the mean age at surgery was  $14 \pm 12.5$  years, with a mean of  $12 \pm 12.1$  years from onset to surgery. The mean follow-up period was 9.9 months (range 6-24). The mean preoperative deviation at near was  $59.3 \pm 13.6$  PD (range: 35-95) while at distance was  $58.5 \pm 13.6$  PD (range 10-95). The most common type of esotropia (ET) was infantile ET (45%), followed by basic ET. There were three outcomes studied: (1) Success, (2) Recurrence and (3) Overcorrection or consecutive exotropia. A successful outcome was defined as distance alignment in primary position, within 10 prism diopters of orthotropia or  $0 \pm 10$  prism diopters exotropia to 10 prism diopters esotropia, with appropriate refractive correction. Recurrence was defined as a final alignment of more than 10 prism diopters of ET. Overcorrection or consecutive exotropia was defined as more than 10 prism diopters of exotropia. Patients who underwent reoperation, by definition, were counted as recurrence before the time of the reoperation. Of those who underwent BMR recessions, a total 25 patients had successful alignment (48.1%), 22 had recurrence (42.3%) while 5 patients had overcorrection (9.6%). Twelve patients (54.5%) underwent three-to-four horizontal extraocular rectus muscles surgery: 12 patients (54.5%) had successful alignment, 7 patients (31.8%) had recurrence and 3 patients had overcorrection (13.6%). Based on the Fisher exact test, however, there was no sufficient evidence to indicate that the surgical outcome is related to the type of surgery performed ( $p$ -value = 0.7100)

The results of this study suggest that neither BMR recession nor 3 or 4 muscle surgery for large-angle esotropias greater than 50 prism diopters show superiority over the other technique. In BMR recession, there was a drastic decline in the successful outcomes after 1 year, and outcomes for 3–4 muscle surgery reached a plateau after 1 year. The presenting angle of deviation was noted to be linked to more likelihood of recurrence or overcorrection. Some of the limitations of this study include its small sample size and retrospective nature.

Outcomes and risk factors of surgical management of thyroid eye disease-related diplopia.

Laezza MP, Concilio M, Giordano M, Lanni V, Iuliano A, Strianese D.

Eur J Ophthalmol. 2022 Nov;32(6):3679-3684.

The authors evaluated surgical outcomes in patients with thyroid eye disease and assessed whether any temporizing treatment measures prior to surgery improved the surgical success rate. The study was designed as a retrospective review and looked at several variables including clinical patient features, smoking status, preceding steroid therapy, orbital radiation therapy and orbital decompression. Seventy-nine patients were included in the study. Ninety-five surgical procedures were performed on 92 eyes. A significant overall improvement of ocular motility was reported ( $p < 0.001$ , paired t-test) after surgery. The success rate was determined by grading the subjective resolution of the diplopia, using a qualitative scale: excellent in the absence of diplopia in all gazes, good in the absence of diplopia in primary position downgaze, and poor when additional surgery and/or prismatic correction were needed. Forty-five (57%) patients had excellent outcomes, twenty-three (29%) had good outcomes and eleven (14%) had poor outcomes. The average number of muscles operated was significantly greater in patients who underwent orbital decompression ( $1.58 \pm 0.63$ ;  $p = 0.0082$ ; 95% CI 1.413-10.214). Quantitative and qualitative outcomes were not associated with the preceding therapy: steroid ( $p = 0.75$ ), radiotherapy ( $p = 0.95$ ) or orbital decompression ( $p = 0.25$ ). The success rate was no different between adjustable and fixed sutures ( $p = 0.8$ ). Strabismus surgery in TED patients resulted in a high success rate in reducing diplopia and improving ocular motility. The success rate was not negatively associated with previous therapies.

Timely Surgery in Intermittent Exotropia.

Jiménez-Romo CA, Rangel-Padilla A, Páez-Garza JH.

J Binocul Vis Ocul Motil. 2023 Jan-Mar;73(1):21-27. Epub 2023 Jan 9. PMID: 36622863.

This retrospective study involved 97 patients divided into two groups treated surgically for intermittent exotropia, those who had surgery less than or equal to 4 years or those who had surgery at greater than 4 years. They were evaluated on postoperative day 1, month 1, and year 1. At year follow up, there was no significant difference between two groups in ocular alignment or sensory outcomes.

Comparison of Unilateral and Bilateral Surgical Approaches for the Treatment of Age-Related Divergence Insufficiency Esotropia.

Bunyavee C, Archer SM, Wu CY, Del Monte MA.

J Binocul Vis Ocul Motil. 2022 Oct-Dec;72(4):205-211. Epub 2022 Aug 29. PMID: 36037434.

This retrospective study was conducted at the Kellogg Eye Center at the University of Michigan and involved 62 cases of involutional divergence insufficiency esotropia to compare unilateral medial rectus recessions ( $n=24$ ), unilateral recession-resection with adjustable suture ( $n=18$ ) and bilateral medial rectus recession with fixed sutures ( $n=20$ ). Between the first and the last group, postoperative distance deviations were not statistically different for those with distance esodeviation  $< 15$ PD. If deviation was greater, 15-20PD, postoperative distance deviations in all groups were statistically different. The second group of patients had the highest overall success rate. The study group concluded that unilateral medial rectus recession with or without lateral rectus resection and bilateral medial rectus recessions produced similar results. The limitation of this study was that it was retrospective, and multiple surgeons were involved. Decision to pursue one surgical approach to another could have affected outcome.

Conservative and Surgical Management of Unilateral and Bilateral Internuclear Ophthalmoplegia (INO)-A Retrospective Analysis.

Simmons J, Rhodes M.

Br J Orthopt J. 2022 Nov 7;18(1):152-158.

This was a retrospective study involving 33 patients diagnosed with INO (unilateral or bilateral) seen between April 2008 and August 2016. 20 cases were unilateral and 13 were bilateral INOs. The most common etiologies were stroke/infarction and MS overall, but for unilateral INOs, most were secondary to stroke. Most cases of bilateral were due to MS. Occlusion as the most common method of addressing INO per orthoptic management. Most patient manifest an exotropia at distance and near. However some showed no deviation in primary position (7 had exophoria). The manuscript reviews two surgical cases both of which had residual deviation successfully managed with prisms. Limitations of this study include the retrospective approach, and it remains unclear how monocular occlusion was decided over surgery in the majority of the cases (ie. were patients too ill to be symptomatic?).

Adjustable Suture Technique Is Associated with Fewer Strabismus Reoperations in the Intelligent Research in Sight Registry.

Oke I, Hall N, Elze T, Miller JW, Lorch AC, Hunter DG; IRIS Data Analytics Committees.

Ophthalmology. 2022 Sep;129(9):1028-1033. doi: 10.1016/j.ophtha.2022.04.021. Epub 2022 Apr 30. PMID: 35500607

This was a retrospective cohort study looking at the reoperation rate within 1 year of initial strabismus surgery. The authors found that in 18% of cases adjustable sutures were used. Overall, 7% of patients required reoperation with older age and prior surgery(40% higher) being significant. They were slightly less likely to have been treated with adjustable sutures. The study showed that there was a lower risk of reoperation within 1 year in those patients who had adjustable suture compared with non-adjustable. The authors suggest that the net benefit of reducing costs associated with reoperation may outweigh the additional time and effort required to perform the adjustable suture technique. The study is important because of its data regarding the techniques, but more significantly highlights the use of the IRIS registry to assess data in large cohorts that would otherwise be difficult to collect and analyze.

Superior oblique split lengthening procedure for brown syndrome, outcomes and complications.

Alhamzah A, Alshareef MF, Shabar R, Alfreihi SH.

Br J Ophthalmol. 2022 Oct;106(10):1469-1472. doi: 10.1136/bjophthalmol-2020-317831.

This is a retrospective chart review of 18 patients with Brown Syndrome who underwent superior oblique split lengthening procedure from 2013-2019 by 4 different surgeons at a single tertiary care institution. Details of the procedure are described in the article. Pros include teachable surgical approach and no synthetic material. Mean followup was 27 months and mean degree of limitation of elevation on adduction was significantly improved postoperatively. The numbers were too small to do any meaningful analysis, but the article does nicely describe another technique for treatment for Brown Syndrome. A prospective study would be helpful to better understand long term success and complications.

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Clinical Profiles and Surgical Outcomes of Strabismus Following Orbital Wall Fractures: A Large Cohort From a Tertiary Eye Care Center.

Bhate M, Deshmukh A, Bothra N, Kekunnaya R, Badakere A, Sharma A.

J Pediatr Ophthalmol Strabismus. 2022;59(3):172-179. doi:10.3928/01913913-20210916-01

This single-center retrospective review sought to report the strabismus surgery outcomes of 347 consecutive patients who presented after orbital wall fractures. Fracture of the orbital floor in isolation or in combination with other walls was more frequently noted in 72.3% of patients (n = 251). The resultant strabismus included paralytic, restrictive, or both etiologies. Exotropia was noted most frequently in 25.65% of patients (n = 89), followed by exotropia with hypotropia in 20.75% of patients (n = 72). Just 10% of patients with strabismus (n = 34) underwent surgical correction for strabismus after at least 6 months of observation after injury. Preoperative diplopia was observed in 79.41% of patients (n = 27) and persisted after strabismus surgery in 15% of patients (n = 6). A successful outcome regarding the postoperative angle of deviation of 10 prism diopters or less horizontal and/or 5 prism diopters or less of vertical deviation with elimination of diplopia was observed in 41.17% of patients. The size of the cohort reported here is a strength of the study, though, as the authors note, the retrospective design and loss to follow-up are limitations.



Scleral Perforation as a Complication of Strabismus Surgery: A Literature Review.  
Hashim I, Al-Haddad C.

J Pediatr Ophthalmol Strabismus. 2022;59(4):214-223. doi:10.3928/01913913-20211019-02

The aim of this review was to report the existing literature on the incidence, risk factors, treatment, and outcomes of scleral perforation as a vision-threatening complication of strabismus surgery. The authors found the incidence range of scleral perforation/penetration between 0.3% and 7.8%. Rectus muscle recession was the most commonly mentioned risk factor among the studies. Other risk factors were myopia, previous extraocular muscle surgery, surgeon experience, S-24 needle use, muscle reattachment posterior to the original insertion site, operating on a horizontal rectus muscle, and young age. Different views existed in the literature regarding scleral perforation management. Some ophthalmologists advocated management by cryopexy or indirect ophthalmoscopic laser uniformly, whereas others reserved it for more complicated cases. Antibiotic therapy for endophthalmitis prophylaxis was recommended by one study and shown to be practiced by some ophthalmologists. This was an important summary and review of literature on an important complication of strabismus surgery.

Psychosocial Improvements in Children and Their Parents Following Strabismus Surgery.

Temeltürk RD, Koçer AM, Yaşar HH.

J Pediatr Ophthalmol Strabismus. 2022;59(4):261-268. doi:10.3928/01913913-20211130-02

This single-center cross-sectional study sought to evaluate the psychosocial effects of strabismus surgery on the psychiatric symptoms and quality of life of children with strabismus and their parents before and after intervention. Children with strabismus between 6 and 18 years old ( $n = 39$ ) and their parents ( $n = 39$ ) completed Child Behavior Checklist and Pediatric Quality of Life Inventory as well as The State-Trait Anxiety Inventory for Children and Beck Anxiety Inventory. All assessments were conducted before and 3 months after strabismus surgery. The authors found that children with strabismus had significantly fewer psychiatric problems and a better quality of life after the surgery ( $P < .001$ ). Following surgery, decreased symptom levels of anxiety scores were also obtained from children and their parents ( $P < .001$ ). The amount of ocular realignment was directly correlated with improvement in social and attention problems among children ( $r = 0.354$  and  $r = 0.324$ , respectively;  $P < .05$ ). The authors concluded that successful strabismus surgery had positive effects on psychosocial functioning and quality of life in children and their families. The use of multiple, validated survey tools is a strength of this study. Some limitations, however, are the small sample sizes, use of the same questionnaire before and after, and lack of a control group (e.g. accommodative ETs who got specs and did not undergo surgical management).

Medial Rectus Muscle Resection Versus Plication: A Comparison of Conjunctival-Scleral Thickness Measured by AS-OCT.

Suzuki H, Hikoya A, Inagaki R, et al.

J Pediatr Ophthalmol Strabismus. 2022;59(4):274-278. doi:10.3928/01913913-20220131-02

This prospective observational study sought to compare conjunctival-scleral thickness on AS-OCT at 1.5mm, 4mm, and 5.5mm posterior to the scleral spur before and after (at 3 and 6 months) medial rectus muscle resection and plication for XT among children 5 years and older. The authors reported outcomes of 11 subjects who underwent resection and 9 who underwent plication. The respective conjunctival-scleral thicknesses before and 3 and 6 months after surgery in the resection group were as follows: 0.76, 0.90, and 0.86 mm at the limbus; 0.86, 1.18, and 1.12 mm at the insertion; and 1.04, 1.41, and 1.33 mm at the tendon. Corresponding values in the plication group were as follows: 0.74, 0.87, and 0.81 mm at the limbus; 0.84, 1.16, and 1.08 mm at the insertion; and 1.00, 1.39, and 1.27 mm at the tendon. No between-group differences were observed at any location or time. They concluded that no differences in conjunctival-scleral thickness were observed between the resection and plication groups before surgery or at 3 months and 6 months postoperatively. The study was limited by small sample sizes in both groups; there was insufficient data to elucidate a dose-dependent difference in conjunctival-scleral thickness.

Evaluation of macular vessel density changes after strabismus surgery using optical coherence tomography.

Aldo Vagge, MD, PhD, Paolo Nucci, MD, Lorenzo Ferro Desideri, MD, Valeria Testa, MD, Matteo Scaramuzzi, MD, Gabriele Siccardi, MD, Francesco Bonsignore, Massimiliano Serafino, MD, and Carlo E. Traverso, MD.

J AAPOS 2022;26:71.e1-4.

The anterior ciliary arteries, which supply ~70% of the anterior segment vascular supply, travel through the rectus muscles and can be injured during strabismus surgery. Because of this, there is growing interest in changes to ocular blood flow following eye muscle surgery. This study aimed to compare retinal vessel density in patients before and after strabismus surgery using swept-source optical coherence tomography angiography (SS-OCTA). A total of 92 eyes were included in the study, and images were obtained pre-operatively (T0), on post-operative day #1 (POD1), and on post-operative day #30 (POD30). Vascular density of the deep capillary plexus (DCP) was 50.20 +/- 5.57 at T0, 52.74 +/- 4.77 on POD1, and 50.92 +/- 4.58 on POD30. The differences were statistically significant for T0 versus POD1 (P<0.05) but not for T0 versus POD 30 (P=0.33). Vascular density of the choriocapillaris layer (CCL) was 50.72 +/- 4.80 at T0, 53.59 +/- 3.65 on POD1, and 51.39 +/- 4.64 on POD30. The differences were statistically significant for T0 versus POD1 (P<0.05) but not for T0 versus POD 30 (P=0.49). There were no differences seen in the vascular density of the superficial retinal capillary plexus (SCP). This study showed a transient increase in CCP and DCP that normalized by one month following strabismus surgery. Increased in retinal vascular density may be due to compensatory mechanisms protecting the anterior segment from ischemia caused by anterior ciliary artery damage. The transient changes observed in this study compared to the more sustained changes observed in other studies may be due to the authors' use of a fornix approach. This study is limited by its small sample size and varied surgeries; however, its results give reassurance that at least some vascular changes induced by damage to the ciliary arteries during eye muscle surgery are transient. With further support, this may give additional reason to consider fornix incisions when performing eye muscle surgery, especially in cases with high risk of anterior segment ischemia.

Response to botulinum neurotoxin injections in large-angle infantile esotropia: a post hoc analysis.

Ismail Mayet, FRCO, Naseer Ally, MMED, Hassan Dawood Alli, MMED, Susan Williams, PhD, and Mohammed Tikly, PhD.

J AAPOS 2022;26:79.e1-5.

In sub-Saharan Africa, infantile esotropia accounts for up to three-quarters of childhood strabismus. Botulinum toxin (BNT) has gained popularity as an alternative to surgery given the challenges to timely surgical intervention in resource-constrained settings. Previous studies have shown satisfactory outcomes in 37% of children with infantile esotropia treated with BNT, and an average change in angle of 37 prism diopters from a mean baseline of 38 prism diopters. It remains unclear whether the change in the degree of esotropia depends on the size of the baseline deviation, and there are few reports on the outcomes of subsequent surgery following BNT. This study aimed to address these questions. The study included 117 children who were split into two groups based on size of their deviation (group 1 less than or equal to 60 prism diopters and group 2 greater than 60 prism diopters). Mean reduction in baseline angle was 34.5 PD for the overall cohort (31.5 PD in group 1, 37.3 PD in group 2) with only 5 patients reverting to their baseline angle. Successful outcome was achieved in 30 patients (20 in group 1 – 36.4% and 10 in group 2 – 16.2%). The mean number of BNT injections was 2.2 +/- 0.7. Younger age and larger baseline angle were both associated with larger absolute change in angle from baseline. Of the children who underwent surgery following unsuccessful BNT injection, 22 had sufficient follow-up, of whom 20 were aligned within 10 PD of orthotropia following one operation. This study helps to clarify previously unanswered questions regarding BNT treated of infantile esotropia. It showed that age and angle of deviation were significant predictors of the magnitude of response and that surgery following unsuccessful BNT injection was 90% successful when operated for the revised angle. Prior treatment with BNT allowed for smaller recessions with subsequent surgery than would have otherwise been required. This paper provides good support for initial treatment of infantile esotropia with BNT, especially for young patients with smaller angles of deviation. As there does is a good degree of surgical success following BNT injection, there appears to be little downside to first intervening with BNT, especially in areas with limited medical resources.

Surgical outcome of graded Harada-Ito procedure in the treatment of torsional diplopia – a retrospective case study with long-term results. Flodin, Sara; Karlsson, Per, Rydberg, Agneta, Andersson Grönlund, Marita, Pansell, Tony., Department of Clinical Neuroscience, Division of Eye and Vision, Karolinska Institutet, Stockholm

Strabismus 30:1, 8-17

The goal of the surgery to review and evaluate the surgical outcomes of the Fells-modified Harada-Ito procedure using a dosage scale approach with long-term follow up in patients with torsional diplopia. The records of patients who underwent the modified Harada-Ito procedure by the same surgeon during 2012–2019 were retrospectively reviewed regarding pre- and post-operative data and individual dose-scale used for the surgery. The modified Harada-Ito procedure involved advancing the anterior half of the superior oblique tendon toward the inferior edge of the lateral rectus muscle by a distance determined using a five-graded scale. A total of 27 patients (mean age 57.6 years, range, 22–81 years; 10 female) were included. Evaluating surgical outcome showed a significant difference in pre- to post-operative cyclodeviation ( $p = <0.001$ ). Pre-operative mean extorsion was  $-10.4^\circ$  and mean torsional correction achieved was  $7.7^\circ$ . The dose-effect relationship showed a wide spread effect, yet yielded a high success rate. All but two patients were symptom free from their torsional diplopia at the last post-operative evaluation, on average 24 months after surgery. Post-operative results and the dose-effect of the modified Harada-Ito corresponded with the aimed-for correction of torsional diplopia. Fusion evaluation and individually based pre-operative assessments proved essential in determining individual doses for successful surgical outcomes

The Efficacy of Bupivacaine for the treatment of strabismus.

Farrelly-Waters, Martha; Smith, Joe; Parmar, Krishan.

Strabismus, 30:1, 42-47

Bupivacaine (BPX) is a widely used local anesthetic. Ophthalmologists have found a unique use of BPX to alter the elasticity and contractile properties of extraocular muscles to straighten strabismus. The utilization of BPX to treat strabismus has been well documented. The purpose of this review is to examine the overall efficacy of BPX when used in isolation for the treatment of strabismus, based on the published literature. Methodology: A literature search was carried out to identify papers published between the years 1980 and 2021, which examined the impact of BPX as a stand-alone treatment for strabismus. Results: Eight articles were identified as matching the inclusion criteria. The authors reported that volumes of  $\leq 1.00$  mL are unlikely to be significant enough to improve ocular alignment and increasing volume strength is associated with greater changes in ocular alignment. The overall change in ocular alignment varied from 0–16PD between the different studies included, with similar effects being noted for deviations between 10 and 20PD and deviations as large as 55PD. It has been documented that there is no significant difference in the outcomes of BPX treatment for esotropia and exotropias, but some clinical differences have been noted with esotropia (or the lateral rectus) responding better to BPX. Bupivacaine has been demonstrated to be less effective in patients with chronic nerve palsies. All but one author documented increases in the injected muscle's volume and maximum cross-sectional area from month one to three followed thereafter by a gradual decrease in both measurements. It was noted that despite the reduction in both measurements, the change in ocular alignment continued to show improvements. No sight-threatening or persistent complications were reported within any of the studies or case reports included within this review. In the interest of patient experience, the majority of patients reported that BPX improved their eye alignment, while a third reported feelings of discomfort during the procedure. Conclusion: Bupivacaine is a viable option for the treatment of small angle deviations and is not recommended for use in long-standing cranial nerve palsies or those associated with atrophy. Care is needed in determining the required dose to avoid the need for re-injection and impacting patient experience.

Long-term astigmatism changes following horizontal muscle recession: a prospective cohort study.

Paraskevopoulos, Konstantinos; Karakosta, Christina; Kokolaki, Anna; Droutsas, Konstantinos; Georgalas, Ilias; Papakonstantinou, Dimitrios. Department of Ophthalmology, Penteli General Hospital for Children, Athens, Greece

Strabismus, 30: 2, 90-98

The aim of this study is to evaluate those changes in astigmatism two and 12 months following unilateral recession of horizontal rectus muscles in children. The authors prospectively evaluated 66 children with esotropia or exotropia, that would undergo a unilateral recession strabismus surgery. Comparisons were made between the 66 eyes that would undergo strabismus surgery and the fellow unoperated 66 eyes of the same children. The 66 eyes that would undergo strabismus surgery were divided into medial (38 eyes) and lateral (28 eyes) rectus muscle subgroups, and further, into subgroups based on the astigmatism axis preoperatively (with-the-rule astigmatism: 35 eyes, no astigmatism: 20 eyes, oblique astigmatism: 10 eyes, against-the-rule astigmatism: 1 eye). All patients were examined one day preoperatively, and then, two and 12 months postoperatively. Paired tests were conducted, and the significant level was set to 0.05 or was adjusted for subgroups. Mean age of children included was 6.73 years (SD = 3.19). Mean astigmatism values preoperatively, 2 and 12 months postoperatively were 0.92D (SD = 0.95), 1.45D (SD = 1.04) and 1.50D (SD = 1.10), respectively, for the eyes that underwent strabismus surgery. A statistically significant mean increase of 0.58D in astigmatism values in the eyes that underwent strabismus surgery was observed 12 months postoperatively ( $p < .005$ ). Astigmatism values in the eyes that did not undergo strabismus surgery did not statistically significantly change during the observation period. The increase of the absolute values of astigmatism in medial and lateral rectus muscle subgroups was similar, 0.59D (SD = 0.10) and 0.57D (SD = 0.11), respectively. For the eyes that had with-the-rule astigmatism and no astigmatism preoperatively, a statistically significant increase was shown 12 months postoperatively (0.64D and 0.66D respectively) ( $p < .005$ ). Changes in astigmatism were observed in the eyes which underwent recession of horizontal rectus muscles compared to the fellow eyes, which did not undergo any intervention. An increase in cylindrical power was noted in the eyes that had with-the-rule and no astigmatism prior to surgery. This increase may be interpreted by the decreased tension of the recessed rectus muscle following strabismus surgery. Decreased forces, caused by the recessed horizontal rectus muscle, acting on the sclera on 180-degree meridian may lead to corneal flattening on this particular meridian and consequently, a corneal steepening on the 90-degree meridian. These changes seem to be stable during the first 12 postoperative months. The limitations include retrospective nature of the study as well as the small sample size.

#### Effect of Modified Vertical Rectus Belly Transposition vs Augmented Superior Rectus Transposition Plus Medial Rectus Recession for Chronic Sixth Nerve Palsy: A Randomized Clinical Trial

Jing Yao MD, Chao Jiang MD, Xiyang Wang MD

JAMA Ophthalmol. Published online August 4, 2022

The goal of this was to examine if modified vertical rectus belly transposition plus medial rectus recession (mVRBT-MRc) is more effective than augmented superior rectus transposition plus medial rectus recession (aSRT-MRc) for Chinese patients with chronic sixth nerve palsy. The main outcome was the change of horizontal deviation in primary position from baseline to 6 months. 25 patients were enrolled in this parallel design, double-masked, single-center randomized control study from January 2018 to May 2021 and randomly assigned to the VRBT group or the SRT group. The baseline main horizontal deviation was 65.7 PD in the VRBT group and 60.5 PD in the SRT group. Similar amounts of MRc were performed in each group. At 6 months, more esotropia was corrected in the VRBT group than in the SRT group, favoring the VRBT procedure. Four times as many participants in the VRBT group than in the SRT group had more than 60Δ of esotropia corrected. Correspondingly, no VRBT participant was undercorrected, whereas 5 SRT participants (45%) had residual esotropia of more than 10Δ and needed additional treatments. Of these undercorrected participants, 4 had a preoperative esotropia of more than 60Δ. Based on these results, mVRBT-MRc was found to be superior to aSRT-MRc in patients with large esotropia of more than 60Δ.

Surgical treatment of consecutive exotropia: Comparison of different surgical methods applied to one eye in one session.

Sefi-Yurdakul N, Oto S, Pelit A.

Eur J Ophthalmol. 2022 May;32(3):1411-1416.

Forty-nine patients with consecutive XT after esotropia surgery (21 female, 28 male) were studied in this retrospective review to compare the different surgical methods performed on a single eye in a single surgery for this particular diagnosis. The factors that affect the post-operative success for these patients were also evaluated. Records from July 1999 to January 2020 were included. The mean age of overall

patients was 22.97 years at surgery for consecutive XT. Patients with a follow-up of 6 months or more were divided into four groups: those undergoing with medial rectus (MR) advancement (Group 1, n=10), MR advancement with resection (Group 2, n=12), MR advancement and lateral rectus (LR) recession (Group 3, n=13), and MR advancement, MR resection, and LR recession (Group 4, n=14). The groups did not display significant differences in terms of surgery ages, gender, refraction values, visual acuity, amblyopia, inferior oblique overaction, limitation of adduction, surgical success rates, and follow-up time ( $p > 0.05$ ). Patients of Group 4 had larger preoperative and postoperative deviation, while Group 1 had smaller deviations ( $p < 0.05$ ). The surgical success rates of Groups 1, 2, 3, 4 were 90%, 75%, 76.9%, and 50%, respectively ( $p = 0.192$ ). A final deviation of  $<10$  PD was considered as surgical success. The authors did not specify if the measurement cutoff for surgical success differed for over-corrections.

Comparison of horizontal muscle transposition and Inferior oblique weakening combined with horizontal surgery in V-pattern exotropia.

Yalcin E, Sultan P.

Eur J Ophthalmol. 2022 Jul;32(4):1971-1977.

The objective of this retrospective study was to compare the effects of horizontal muscle transposition and inferior oblique weakening combined with horizontal surgery (unilateral or bilateral) performed for V-pattern exotropia (XT). 52 patients who underwent horizontal surgery due to V-pattern XT and were followed for at least 6 months were divided into two groups. Group 1 (n = 26) consisted of patients who underwent vertical transposition of the rectus muscles combined with horizontal surgery, and Group 2 (n = 26) consisted of patients who underwent inferior oblique weakening combined with horizontal surgery. Horizontal surgery included both bilateral and unilateral procedures by one surgeon. The two groups were compared before and after surgery in terms of visual acuity, refractive errors, deviation angles, pattern strabismus, fusion, stereopsis, over/under correction and surgical success. Surgical success was described as  $\leq 10^\Delta$  of residual exotropia (under-correction) and  $\leq 5^\Delta$  of (over-correction). The demographic parameters of the patients, including age, age at surgery, sex distribution, follow-up time, visual acuity, spherical equivalent, presence of stereopsis, fusion, amblyopia and type of horizontal rectus surgery performed did not significantly differ between the groups ( $p > 0.05$ ). Although the number of overcorrections were comparable between groups, the undercorrection rate was significantly higher in Group 1 (42.3% vs 3.8%,  $p = 0.003$ ). The comparisons of postoperative stereopsis, fusion and pattern collapse were significantly not different between groups. The surgical success rate was significantly higher in Group 2 compared to Group 1 (96.2% vs 61.5%,  $p = 0.007$ ). There was no statistically significant difference in pattern collapse between the two groups; however, the post-operative degree of pattern was smaller in Group 2 after surgery ( $p = 0.003$ ) despite the lack of pattern difference between groups prior to surgery. The authors also concluded that oblique weakening was more successful in terms of post-operative alignment and pattern collapse.

Pujari A, Rakheja V, Modaboyina S, Das D, Tripathi M, Phuljhele S, Saxena R, Agarwal T, Sharma N, Titiyal JS. Simulation of complex strabismus surgical procedures on goat eyes.

Eur J Ophthalmol. 2022 Jul;32(4):1978-1990.

Due to the lack of good simulation and animal models to practice strabismus surgery during residency training, the authors assessed whether goat eyes could be a valid alternative. Goat eyes obtained from a local slaughterhouse were evaluated for intactness of the globe, teno-conjunctival layering, and the extraocular muscle features were documented, and the eyes with more than 15-mm muscle length were included. The goat eye often possesses three to five muscles. One among them has an insertion like that of superior oblique muscle, and rest have an insertion like that of horizontal recti muscles. The authors performed complex procedures like transpositions, Knapp procedure, Nishida procedure, Faden operation, Harada Ito, superior oblique tuck, and Y splitting procedures on 50 goat eyes over the course of two years. They concluded that by simulating the recti and the oblique muscles in goat eyes, novel complex strabismus surgical procedures can be practiced in a very predictable way and can be used to enhance teaching and surgical practice in residency training programs.

Medial rectus disinsertion for management of chronic complete sixth nerve palsy.

Bagheri A, Veisi A, Tavakoli M.

Eur J Ophthalmol. 2022 Sep;32(5):2622-2629.

In this study, the authors reported on the outcomes of the medial rectus (MR) disinsertion procedure for the management of refractory esotropia (ET) with or without Abnormal head posture (AHP) in longstanding, complete sixth nerve palsy. This study was designed as a retrospective case series of patients with sixth nerve palsy who suffered from residual ET and diplopia following conventional surgeries to correct their strabismus (i.e. medial rectus recession, lateral rectus resection/plication, and vertical rectus transposition procedures) and underwent a MR disinsertion procedure between April 2017 and February 2020. This procedure was offered to the patients who declined to use prism and did not wish to perform surgery on the fellow eye. The demographic and clinical data, including sex, age, visual acuity, pre and postoperative angle of strabismus, duction limitations, results of forced duction and force generation tests, details of prior strabismus surgeries, orbital CT scan findings, and follow up duration were collected from the medical records. The procedure was conducted under general anesthesia through a limbal conjunctival incision, by disinserting the MR muscle from the sclera, resecting it 8 mm, and allowing it to retract in the orbit. Six patients enrolled in this study, including 4 females and 2 males. The mean age of patients was  $35.0 \pm 14.0$  years (range of 15 to 55 years), and the mean follow-up was  $15.3 \pm 5.9$  months. The underlying etiology of sixth nerve palsy was trauma in 4 patients, nasopharyngeal carcinoma in 1 patient, and congenital in 1 patient. The mean pre-op ET was  $35.0 \pm 18.4$  prism diopters (PD) in primary position before MR disinsertion, which improved to  $14.2 \pm 17.4$  PD after the procedure. Four cases needed additional complementary surgeries to improve residual ET in primary position. No case developed overcorrection. Abduction deficiency was  $-5.0 \pm 1.3$  before MR disinsertion, which improved to  $-2.8 \pm 0.5$  units at last follow-up. The mean of induced adduction deficiency was  $-2.9 \pm 0.4$  units at last follow-up. All patients were diplopia-free in primary position without AHP after the final surgery. The authors conclude that MR disinsertion is a procedure that can be offered to patients with refractory diplopia with or without AHP due to sixth nerve palsy after failure of the standard surgeries and can help to alleviate diplopia in the primary gaze position. However, this study is limited by its small sample size, retrospective design, and lack of detail on the additional complementary surgeries necessary to achieve an optimal surgical outcome in two-thirds of the patient sample.

Treatment of partially accommodative esotropia in children using a medial rectus muscle fenestration technique

Elkhawaga, Mohamed et al.

Journal of American Association for Pediatric Ophthalmology and Strabismus {JAAPOS}, Volume 26, Issue 1, 14.e1 - 14.e5

Children with partially accommodative esotropia without high ratio of accommodative convergence to accommodation were prospectively enrolled and underwent fenestration of bilateral medial rectus muscle. In this fenestration technique, two splitting incisions are made by blunt dissection parallel to the muscle fibers on the superior and inferior borders of the medial rectus muscle, leaving a thin strip of muscle fibers on each edge. The wide, central part of the muscle is excised from its insertion to a point 5–8 mm from the insertion, depending on the angle of the esotropia. Sutures are not used in this procedure. A total of 61 children were included. The procedure was well tolerated by patients and reduced the angle of esotropia for distance from 22.20D 4.22D to 2.72D 4.71D ( $P < 0.001$ ) and caused no incomitance or distance-near disparity. Satisfactory horizontal alignment defined as alignment within 8D of orthotropia at distance was achieved in 88% of the cases at 3-6 months' follow-up. There were no overcorrections.

Conventional surgery versus botulinum toxin injections for partially accommodative esotropia

AlShammari, Sara et al.

Journal of American Association for Pediatric Ophthalmology and Strabismus {JAAPOS}, Volume 26, Issue 1, 16.e1 - 16.e6

To compare the effects of botulinum toxin injection (BTX) to bilateral medial rectus recession (BMR) in partially accommodative esotropia (PAET) medical records of children 1-14 years of age treated for PAET with BMR or BTX between 2010 and 2020 at a single institution were reviewed retrospectively. PAET was defined as residual esotropia of at least 14D after 6 weeks of continuous wear of full cycloplegic refraction ( $>+2.5$  D). Success was defined as esotropia of 0D-10D after a single surgery or  $>1$  BTX injections. In this cohort study, BMR had a higher success rate than BTX. Conventional surgery allowed for shorter follow-up and fewer complications than BTX in the treatment of PAET.

Risk Factors for Reoperation after Strabismus Surgery among Patients with Thyroid Eye Disease.

Hwang B, Heo H, Lambert SR.

American Journal of Ophthalmology. 2022 Jun 1;238:10-5.

Strabismus associated with thyroid eye disease can be challenging to treat with unpredictable outcomes. Several small studies have attempted to quantify the rate of reoperation following strabismus surgery for thyroid eye disease and have reported rates between 13-55%. This study used an insurance claims database to determine patient or operative factors associated with strabismus reoperation. Over a 16 year period, the study identified 448 patients with TED who underwent strabismus surgery with mean follow up of 5 years following surgery, of whom 111 (25%) underwent a reoperation. Among all variables assessed, only the number of muscles operated on at the time of first surgery was a predictor for higher rates of reoperation. This was also associated with shorter time to reoperation. This study is at risk for standard limitations associated with retrospective studies and studies using insurance claims. Additionally, the follow up time of 5 years may limit the long-term generalizability of these results. This study is the largest to date to evaluate strabismus surgery in patients with thyroid eye disease and establishes information that can be used to help counsel patients in this population considering undergoing strabismus surgery.

Strabismus surgery decreases the risk of injuries in pediatric patients in the OptumLabs Data Warehouse.

Pineles SL, Repka MX, Yu F, Velez FG, Perez C, Sim D, Coleman AL.

American journal of ophthalmology. 2022 Apr 1;236:147-53.

There is growing literature to suggest a correlation between injuries and strabismus in adults and children, though a prior study from the same group did not show a benefit to strabismus surgery in preventing injuries in adults. Using a large insurance claims database, the authors sought to quantify the incidence of injuries in children with strabismus analyzed by whether or not they underwent strabismus surgery. The study included over 344,000 patients with strabismus, of which close to 8% underwent strabismus surgery. The most common types of strabismus were esotropia (53%) and exotropia (47%). The incidence of injuries in those with strabismus without surgery was 30% compared to 22% in those with strabismus who had undergone strabismus surgery. The authors conclude that strabismus surgery was associated with a 15% decreased risk of injury over 4 years of follow up. This study, like any insurance claims, is limited by the reliability of coding, which may not be reflective of true or accurate medical diagnoses. Additionally, no data was available on type or severity of strabismus or injury, limiting the results as well. Despite these limitations, the authors advocate that strabismus surgery could potentially improve overall childhood health.

Impact of Adding Augmented Superior Rectus Transpositions to Medial Rectus Muscle Recessions When Treating Esotropic Moebius Syndrome.

Warkad VU, Hunter DG, Dagi AF, Mackinnon S, Kazlas MA, Heidary G, Staffa SJ, Dagi LR.

American Journal of Ophthalmology. 2022 May 1;237:83-90.

Moebius syndrome is a rare disorder in which cranial nerves 6 and 7 do not develop or function normally. Several approaches have been proposed to address the esotropia seen in this condition including bilateral medial rectus muscle recession (BMR) with or without a lateral transposition of the superior rectus muscle (SRT). This retrospective, single center review evaluated 20 children with Moebius syndrome treated over a 16 year period. As expected, all children had abduction deficits. 75% had esotropia in primary gaze. Eight were included in the analysis for final outcome, of which 5 underwent BMR and the remaining underwent BMR+SRT. The pre-operative deviation was significantly higher in the BMR+SRT group (70 PD) compared to the BMR group (40 PD). Overall, the authors found a greater reduction in esotropia in the BMR+SRT group and suggest that BMR alone is sufficient for pre-operative deviations < 50 PD. The difference in baseline characteristics between the two groups and the small number of patients included in analysis (8) limit the power of this study, but it does provide useful information regarding surgical treatment for a rare cause of esotropia in children.

Comparison of the Accuracy of Anterior Segment Optical Coherence Tomography and Ultrasound Biomicroscopy in Localizing Rectus Muscle Insertions.

Mirmohammadsadeghi A, Hamzeh N, Ghassemi F, Akbari MR.

J Binocul Vis Ocul Motil. 2022 Apr-Jun;72(2):86-91.

In this study, anterior segment OCT was compared to UBM to localize rectus muscle insertions in 27 patients (39 rectus muscles). Ninety two percent of UBM measurements (36 muscles) were within 1 mm, one was within 1-1.5 mm, and 2 were within 1.5-2 mm of surgery measurements. Eighty five percent of AS-OCT measurements (33 muscles) were within 1 mm, 5 were within 1-1.5 mm, and one was within 1.5-2 mm of surgery measurements. In all cases, the mean absolute error of the UBM ( $0.54 \pm 0.44$ ) and AS-OCT ( $0.51 \pm 0.36$ ) showed no significant difference ( $p = .76$ ). The results of this study indicate that anterior segment OCT and UBM may be used interchangeably to localize rectus muscle insertions.

Non-absorbable versus Absorbable Sutures for Medial Rectus Advancement in Consecutive Exotropia, a Pilot Randomized Clinical Trial.

Akbari MR, Veisi A, Mirmohammadsadeghi A.

J Binocul Vis Ocul Motil. 2022 Jul-Sep;72(3):139-146.

This was a pilot randomized clinical trial of 40 subjects with consecutive exotropia who underwent unilateral medial rectus advancement with or without resection to compare non-absorbable and absorbable sutures. Thirty-three patients (18 in the non-absorbable and 15 in the absorbable group) had completed the study. The amount of the final correction of the distance and near deviation was not statistically different between the groups ( $P = .80$  and  $P = .99$ , respectively). At the final examination, the exoshifts for distance and near were not statistically different between 2 groups ( $p = .61$  and  $0.54$ , respectively). At the final examination, the success was obtained in 12 patients (66.7%) and 8 patients (53.3%) in the non-absorbable and absorbable group, respectively ( $p = .73$ ). The results of this study confirms the suspicion of many surgeons that absorbable sutures which are less prone to causing inflammation can be used instead of non-absorbable sutures when advancing muscles for consecutive strabismus.

Unilateral Horizontal Rectus Muscle Recessions for Pediatric Comitant Strabismus.

Merrill KS, Areaux RG Jr.

J Binocul Vis Ocul Motil. 2022 Jul-Sep;72(3):147-150.

This retrospective chart review compared bilateral horizontal muscle recessions to unilateral horizontal rectus muscle recession. Primary successes were defined as maximum distance deviation at post-operative month 3: -12 to +5 for ET, -5 to +12 for XT. Rates of postoperative horizontal incomitance >5 PD and success for small medium, and large (in mm, respectively, ET: <5, 5-6 mm, >6; XT: <8, 8-10, >10) recessions were analyzed. Seventeen ETs and 40 XTs were analyzed. Overall primary success was 71.9% ( $p = .02$ ). Significantly, 80% (95% CI: 67.60,92.40) XTs succeeded. ETs were equally likely to succeed (53.9%) or fail (47.1%) ( $p = .22$ ). For patients without significant preoperative incomitance, average incomitance was 3.90 PD (95% CI: 0.20, 7.60) for ETs; 5.48 PD (95% CI: 3.65, 7.32) for XTs. Not surprisingly, this study showed that success was more likely in small to medium deviations with less risk of incomitance, but in larger deviations, success less likely and incomitance more frequent.

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## 11. ANTERIOR SEGMENT

Primary aphakia: clinical recognition is the key to diagnosis

Sushmita Kaushik, Sagarika Snehi, Savleen Kaur, Anupriya Kaur, Sandeep Choudhary, Faisal Thattaruthody, Surinder Singh Pandav.

J AAPOS. 2022 Dec;26(6):298.e1-298.e5.

Congenital primary aphakia (CPA) is a rare anterior segment dysgenesis resulting from aborted lens development early in gestation secondary to a mutation in FOXE3 gene. Abnormal lens development is associated with other anterior segment ocular disorders. CPA is also called sclerocornea. The authors used a retrospective case series to review ultrasound biomicroscopy (UBM) and clinical photos to identify 12 children with congenital primary aphakia and determine treatment outcomes of the cohort. In this cohort, 5 had bilateral glaucoma, 2 had unilateral glaucoma and 5 had bilateral microphthalmos. This cohort and other studies have identified a typical silvery-blue appearance of the cornea in children with CPA. A recent multicenter study also identified optic nerve colobomas using MR imaging. It is important to take this into consideration when assessing optic nerve damage from elevated pressure that could be optic nerve coloboma. Anterior segment dysgenesis including absence of trabecular meshwork and Schlemm's canal contributes to glaucoma when the ciliary body is intact. This article is important to pediatric ophthalmologists because CPA should be recognized in order to avoid incisional surgery which can result in postoperative phthisis bulbi. Conservative management with aphakic glasses, glaucoma medications, and limited cyclophotocoagulation may provide best management for patients with CPA.

Ocular surface characteristics in pediatric vernal keratoconjunctivitis: a clinico-cytological study.

Shilpa Sabu, MD, Noopur Gupta, MS, PhD, Nimmy Raj, MD, Arnav Panigrahi, MBBS, Neiwete Lomi, MD, Murugesan Vanathi, MD, Praveen Vashist, MD, MSc, Seema Sen, MD (Pathology), and Radhika Tandon, MD, FRCOphth.

JAAPOS 2022;26:240.e1-6.

The purpose of this study was to investigate tear film dynamics, meibomian gland morphology, and cytological changes for a holistic and objective assessment of the ocular surface in children with vernal keratoconjunctivitis. Sixty-eight VKC patients were included along with thirty-three age-matched controls. The Ocular Surface Disease Index questionnaire (OSDI) was used to assess severity of dry eye symptoms. The mean OSDI score was 30.7 in the VKC group and 16.1 in the control group. VKC severity was positively correlated with OSDI score. The Ocular Surface Analyzer was used to assess tear meniscus height (TMH), the quantity (LLT) and quality of the lipid layer, meibomian gland morphology, meibomian gland distortion, and meibomian gland loss (MGL). There were no differences in TMH values between the groups (indicating a normal aqueous layer of the tears), but the lipid layer of the tear film was significantly thinner in children with VKC. Impression cytology was used to assess goblet cell density, grade of squamous metaplasia, and presence of inflammatory cells. There was a significant association and positive correlation between the grading of squamous metaplasia and severity of VKC. This is an impressive study that explores the ocular surface characteristics of VKC through both subjective and objective means. The OSA is shown to provide a comprehensive evaluation of all the layers of the tear film, which could allow for more targeted treatment approaches. I think one of the more interesting take-aways is that the average duration of disease was 4.1 +/- 2.8 years in these "newly diagnosed" VKC patients. It would be interesting to find a cohort who were diagnosed/treated earlier in the course of their disease to see when the changes in meibomian gland morphology start to occur. It would also be interesting to see how the parameters change as patients are treated for their VKC.

Almeida GC, Guido RC, Balarin Silva HM, Brandao, CC, de Mattos LC, Lopes BT, Machago AP, Ambrosio R. New artificial intelligence index based on Scheimpflug corneal tomography to distinguish subclinical keratoconus from healthy corneas. J Cataract and Refract Surg 2022;48(10):1168-1174.

The BESTi, an index derived from multiple logistic regression analysis and combining 22 variables from corneal Scheimpflug tomography, was used to identify a cutoff point to measure differences in corneal tomography findings between subclinical keratoconus in 1 eye, corneal ectasia, and healthy corneas. The study was conducted at 2 private eye centers in Brazil. 187 eyes with very asymmetric ectasia and with normal corneal topography and tomography (VAE-NTT), 2296 eyes with healthy corneas (control group), and 410 eyes with ectasia were included. BESTi outperformed both the Belin-Ambrosio Deviation Index

and the Pentacam random forest index, both high sensitivity and high specificity indices already used to differentiate subclinical keratoconus from normal eyes, facilitating early detection of ectasia in subclinical keratoconus. Studies with increased sample size and possible integration with direct and indirect biomechanical parameters may further improve detection. Importance: New use of AI to facilitate diagnosis of subclinical KCN may help identify at-risk patients in a timelier fashion.

Correlation between Placido-disc and rotating Scheimpflug keratometric findings before and after corneal crosslinking in children with keratoconus.

Polido J, Xavier dos Santos Araujo ME, H. Wakamatsu T, T. Lopes B, Alexander JG, Cabral T, Ambrosio Renato Jr, Freitas D.

J Cataract and Refract Surg 2022;48(10):1183-1189.

Two devices commonly used by clinicians to evaluate keratoconus, Placido-disc-based topography and rotating Scheimpflug cameras, often have poor repeatability and agreement when measuring steeper and irregular ectatic corneas. This prospective nonrandomized open study performed in Brazil evaluated the correlation between Placido-disc and rotating Scheimpflug keratometric findings in children with progressive keratoconus before and after corneal crosslinking and investigated whether these limits of agreement varied according to disease severity. 44 eyes of 44 patients 8-16 years were analyzed. In summary, the keratometric measurements obtained using rotating Scheimpflug and Placido-disc technology were found to be closely correlated but not interchangeable before and after CXL in pediatric patients. Agreement between devices was found to be better after CXL and in mild keratoconus compared to advanced keratoconus. Main limitation of study: intraexaminer and interexaminer reliability and reproducibility not analyzed.

High Load of Demodex in Young Children With Chalazia

Xiao Y, Gao L, Shen L, Yang C.

J Pediatr Ophthalmol Strabismus. 2022;1-7. doi:10.3928/01913913-20221025-02

This case-control prospective study reported the correlation between demodicosis and pediatric chalazia among pediatric patients in Shanghai, China. The authors collected 101 patients with chalazia and 42 patients without chalazia, sampled their eyelashes, and examined for demodex using light microscopy. They found that the Demodex count and prevalence of the chalazia group was much higher than that of the control group ( $3.06 \pm 3.48$  vs  $0.64 \pm 1.17$ ;  $P \leq .001$ ; 73.3% vs 35.7%,  $P \leq .001$ ). Furthermore, the Demodex count and prevalence of the multiple chalazia subgroup was much higher than that of the single chalazion subgroup ( $3.49 \pm 3.72$  vs  $2.00 \pm 2.52$ ;  $P = .043$ ; 79.2% vs 58.6%,  $P = .035$ ). The Demodex count and prevalence of the chalazia with skin erosion subgroup was much higher than that of the without skin erosion subgroup ( $3.54 \pm 3.14$  vs  $2.55 \pm 3.76$ ;  $P = .012$ ; 82.7% vs 63.3%,  $P = .027$ ). After adjustment for age and gender, Demodex count (odds ratio: 1.873; 95% confidence interval: 1.155 to 3.040;  $P = .011$ ) but not presence ( $P = .643$ ) was significantly correlated with chalazia. They concluded that Demodex mites were more prevalent and quantitative in children with chalazia, and children with severe chalazia had higher Demodex prevalence and quantity. High Demodex count rather than presence of it was associated with chalazia. Although this was a localized study with limited generalizability, it raised a salient concern about sampling for Demodex amongst all pediatric patients with multiply recurrent chalazia.

Visual and surgical outcomes of limbal dermoid excision at a tertiary care eye hospital.

AlGhadeer H, Kirat O, Vargas J, AlBadr L, Khandekar R.

Eur J Ophthalmol. 2023 Jan;33(1):587-594.

This was a retrospective cohort study evaluating visual and surgical outcomes after surgery to remove limbal dermoid lesions. The medical records of patients with limbal dermoids presenting between January 2012 and December 2020 were evaluated for patient demographics, best-corrected visual acuity (BCVA), symptoms, anterior segment examination, and refraction. The outcomes included cosmesis, complications, graft transparency, and BCVA at the last follow-up. Fifty-one eyes from 50 patients (27 males) were evaluated. The median age at the time of surgery was 11.5 years (interquartile range, IQR: 0.0-45.7). The median follow-up time was 5 years (IQR: 4-6). Goldenhar syndrome was noted in 5 patients (10%). The indications for surgery were cosmetic concerns ( $n = 20$ , 39%), anisometropia ( $n = 3$ , 6%), decreased vision ( $n = 4$ , 8%), and growth or dellen formation ( $n = 2$ , 4%). Forty-eight eyes

underwent surgical excision of the limbal dermoid. Surgical techniques included simple excision (n = 12, 23.5%), amniotic membrane transplantation (n = 16, 31.4%), lamellar keratoplasty (n = 15, 29.4%), and penetrating keratoplasty (n = 5, 9.8%). The most common complications were corneal scarring (n = 19, 37.2%), corneal vascularization (n = 2, 3.9%), and infection (n = 1, 2%). Astigmatism > 1 D was observed in 34 (66.7%) eyes after dermoid surgery (p < 0.001). There were no complications in 14 eyes (27%), BCVA was > 20/60 in 43 eyes (84.3%), and only two eyes had BCVA < 20/400. Surgical management of limbal dermoids offers promising functional and anatomic outcomes. However, postoperative astigmatism may require further follow-up and management.

Topical cenegermin 0.002% for pediatric neurotrophic keratopathy.

Elhusseiny AM, Traish AS, Saeed HN, Mantagos IS.

Eur J Ophthalmol. 2022 Nov;32(6):3420-3424.

A retrospective chart review of children under the age of 18 years diagnosed with neurotrophic keratopathy (NK) at Boston Children's Hospital/Massachusetts Eye and Ear Infirmary and treated with topical cenegermin 0.002% ophthalmic solution between June 2018 and June 2021 was performed. Data collection included etiology of NK, age at time of initiation of topical cenegermin, laterality, ethnicity, gender, history of previous ocular therapy, pre- and post-therapy best corrected visual acuity, pre- and post-therapy cornea examination, any adverse events from topical cenegermin, associated ocular conditions, and history of ocular surgeries. The current study includes four eyes of four pediatric patients with a mean age of  $4.5 \pm 2.0$  years at the time of initiation of topical cenegermin therapy. The mean time from NK diagnosis until start of topical cenegermin drops was  $5.2 \pm 4.3$  months and mean follow-up time was  $15 \pm 9.6$  months. In all four patients, marked improvement in epitheliopathy was demonstrated after completion of therapy. Best corrected visual acuity was measurable in 3 eyes of 3 patients, and it improved from a mean of  $0.07 \pm 0.01$  to a mean of  $0.29 \pm 0.26$  (P = 0.3). No adverse events related to cenegermin therapy were noted. Based on the findings in this study, the authors suggest that topical cenegermin is effective in improving corneal healing for pediatric NK.

Microbiological Characteristics of Ocular Surface Associated With Dry Eye in Children and Adolescents With Diabetes Mellitus.

Chen Z, Jia Y, Xiao Y, Lin Q, Qian Y, Xiang Z, Cui L, Qin X, Chen S, Yang C, Zou H.

Invest Ophthalmol Vis Sci. 2022 Dec 1;63(13):20. doi: 10.1167/iovs.63.13.20. PMID: 36538004; PMCID: PMC9769747.

In this study, samples of 65 children and adolescents with diabetes, (31 and 34 children with dry eyes (DM-DE group)) and non-DE (DM-NDE), and 33 healthy controls of the same age without diabetes (NDM group) were collected. Saline swab used to wipe the participants' eyelid skin twice. Then a tear test paper was used to collect tears from the eyes. Collected samples were placed in a tube containing DNA protecting fluid and then cryopreserved and used for testing and DNA extraction. The phyla and genera (Bacteroidetes, Tenericutes, and Firmicutes and Lactococcus, Bacteroides, Acinetobacter, Clostridium, Lactobacillus, and Streptococcus) were observed to be significantly different between the DM-DE and other two groups. These phyla and genera have been reported to be involved in the pathogenesis of DE in the past. The decrease and change of normal dominant bacteria on the ocular surface in patients with DM-DE may play a role in the occurrence and pathology of DE. There were significant differences in the dominant bacteria of the ocular surface among the three groups (P < 0.05), and the abundance of OSM in children with DM-DE was higher than that in children with NDM. Compared with that in the children with NDM, the microbial diversity was increased in children with DM-DE, and more diverse communities were likely to cause diseases, which may be the reason for the high incidence of DE in children with diabetes. The limitation of this study was the low prevalence of DE in healthy participants. The authors indicate that the process of collecting tears may have affected composition of tears and analysis.

Insufficient Dose of ERCC8 Protein Caused by a Frameshift Mutation Is Associated With Keratoconus With Congenital Cataracts.

Hao XD, Yao YZ, Xu KG, Dong B, Xu WH, Zhang JJ.

Invest Ophthalmol Vis Sci. 2022 Dec 1;63(13):1.

In this study, clinical and genetic analysis was utilized to detect genetic mutations and investigate underlying pathogenic mechanisms in patients with keratoconus and congenital cataracts. A Chinese family with KC with congenital cataracts, 262 additional patients with sporadic KC, 20 patients with

sporadic congenital cataract, and 210 unrelated healthy controls were recruited. A novel frameshift mutation of ERCC8 (NM\_000082.3: c.394-398del, p. L132Nfs\*6) was found to be responsible for familial keratoconus with congenital cataracts.

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#### Detecting Keratoconus: Feasibility and Findings in Three Pediatric Risk Groups.

Neustein RF, Lenhart PD.

J Pediatr Ophthalmol Strabismus. 2022;59(2):94-101. doi:10.3928/01913913-20210802-01

This prospective study sought to examine the utility of three corneal screening devices (Pentacam, Orbscan, ORA) in three groups of patients: Trisomy 21 (group 1), patients with a first-degree relative with keratoconus (group 2), and control patients (group 3). The authors reported data on 54 patients aged from 7 to 17 years (mean: 11.74 years), including 12 (55%) w/ Trisomy 21, 21 (87%) with 1st deg relative w/ KCN, and 21 (88%) controls. The Pentacam values by group were central corneal thickness of 524, 543, and 542  $\mu\text{m}$  ( $P = .36$ ); thinnest point of 498, 536, and 534  $\mu\text{m}$  ( $P = .03$ ); corneal front mean keratometry of 44.9, 43.2, and 43.2 ( $P = .01$ ); and quality score of 1.42, 0.22, and 0.04 ( $P < .0001$ ), respectively. Orbscan values by group were central corneal thickness of 493, 551, and 550  $\mu\text{m}$  ( $P = .01$ ) and thinnest point of 451, 536, and 538  $\mu\text{m}$  ( $P < .0001$ ), respectively. ORA values by group were corneal hysteresis of 10.6, 12.1, and 11.6 ( $P = .124$ ); corneal resistance factor of 9.9, 11.8, and 11.6 ( $P = .03$ ); and waveform score of 5.6, 7.6, and 7.3 ( $P < .0001$ ), respectively. The authors concluded that compared to patients with first-degree relatives w/ keratoconus and control patients, those with Trisomy 21 completed fewer tests reliably, and they had thinner corneas, steeper corneas, and lower corneal resistance factors. The authors concede that a major limitation in the generalizability of the study was low recruitment overall and relatively unequal sample sizes.

#### Results of Follow-up in Pediatric Keratoconus Treated With Intracorneal Ring Segments Implantation Alone or in Combination With Corneal Cross-linking.

Méndez EA, Roys N, Mejía ME, Plata MC, Rosenstiehl SM.

J Pediatr Ophthalmol Strabismus. 2022;59(2):118-127. doi:10.3928/01913913-20210719-02

This single-center descriptive, retrospective observational study sought to report visual and topographic outcomes of pediatric keratoconus with intracorneal ring segments (ICRS) implantation alone or in combination with accelerated corneal cross-linking (A-CXL). The authors reported outcomes on 26 eyes of 19 patients with a mean age of  $16.5 \pm 1.8$  years who were followed for a median time of 39.6 months (IQR = 30). Of these 26 eyes, 16 eyes (61.5%) received ICRS implantation with A-CXL and 10 eyes (38.4%) received ICRS implantation only. Global results (including both groups) were: (1) median UCVA improved from 0.90 LogMAR (IQR = 0.85) to 0.54 logMAR (IQR = 0.70); (2) median BCVA improved from 0.43 logMAR (IQR = 0.39) to 0.30 logMAR (IQR = 0.26); and (3) median spherical equivalent of -5.37 D (IQR = -5.28) improved to -4.12 D (IQR = -3.57). There was a reduction in half of the sphere and cylinder. The median maximum keratometry improved from 54.40 D (IQR = 7.4) to 49.80 D (IQR = 5.3). The median asphericity improved from -1.18 (IQR = 0.70) to -0.75 (IQR = 0.68). No patient presented with complications before or after surgery. The authors concluded that ICRS implantation only or in combination with A-CXL induced visual and topographic improvement in patients with keratoconus, and that it seemed to be a safe procedure to delay or avoid corneal transplantation in the pediatric population. They conceded, however, that their follow-up interval was short, their sample sizes were small, their corneal implantation techniques were non-standardized, and the application of A-CXL was not clearly defined in all patients because of the retrospective design. This was an interesting proof of concept investigation that deserves further prospective study.

Simantov I, Or L, Gazit I, Dubinsky-Pertzov B, Zadok D, Pras E, Hartstein M, Einan Lifshitz A. Seven years follow-up of corneal cross-linking (CXL) in pediatric patients: Evaluation of treated and untreated eye. Eur J Ophthalmol. 2022 May;32(3):1482-1490.

This is a retrospective cohort study evaluating long term keratoconus progression in pediatric patients treated with cross-linking (CXL). Data on 60 eyes of 30 patients, 18 years old or younger, who underwent CXL in at least one eye were collected and analyzed. Follow-up measurements taken from the treated and untreated eye up to 7 years after CXL treatment were compared to baseline measurements. Parameters included uncorrected distance visual acuity (UCDVA), best-corrected spectacle visual acuity

(BCSVA), manifest refraction, pachymetry, corneal tomography, and topography. The mean age of patients included in the study was  $16 \pm 2.1$  years. There was no statistically significant difference in UCDVA and BCSVA in the treated eyes compared to fellow untreated eyes. The mean average keratometry showed a significant flattening (from  $49.95 \pm 4.04$  to  $47.94 \pm 3.3$  diopters (D);  $p < 0.001$ ), However there was no change in the mean maximal keratometry. The mean minimal corneal thickness (MCT) showed a significant mild reduction of  $26 \mu\text{m}$  ( $p = 0.006$ ). Although statistically insignificant, the mean manifest cylinder was also reduced to 2D ( $p = 0.15$ ). During the follow-up period, eight untreated eyes (26.6%) deteriorated and underwent CXL, while only one treated eye (3.33%) required an additional treatment. The authors conclude that CXL is a safe and effective procedure in halting keratoconus progression in the pediatric population. They assert that the fellow, untreated eye requires careful monitoring as 25% of these patients will require CXL in that eye during a period of 7 years.

Elbaz U, Ong Tone S, Fung SSM, Mireskandari K, Ali A. Evaluation of dry eye disease in children with blepharokeratoconjunctivitis.

*Can J Ophthalmol.* Apr 2022;57(2):98-104. doi:10.1016/j.jcjo.2021.02.017

This is a prospective cross-sectional study that aims to evaluate the symptoms and signs of dry eye disease in children with blepharokeratoconjunctivitis(BKC). The authors recruited 25 patients (50 eyes)-- Twenty-two eyes in the BKC group and 28 healthy controlled eyes. BKC eyes were quiescent, as per the authors. The mean age was similar for both groups, 12.4 years and 14.5 years for BKC and controls, respectively. All participants underwent a Dry eye assessment questionnaire, tear film osmolarity, Schirmer's test without anesthesia, tear film break-up time, corneal fluorescein staining (CFS), and lissamine green conjunctival staining (LGCS). The authors analyzed the data based on all eyes, worse eyes, and mean. An unmasked examiner collected the diagnostic tests. Only corneal fluorescein staining reached statistical significance. CDEA scores did not differ between groups. Demographics of the population are not included in the manuscript. The study is limited by the small sample size, unmasked researchers, and cross-sectional nature.

## 12. CATARACT

Central corneal thickness profile in relation to pediatric cataract morphology.

Abdelrahman M. Elhousseiny, MD, Jylan Gouda, MD, Christina Farag, MD, Muhammad Z. Chauhan, MS, MA, Shaimaa A. Arfeen, MD, and Hala M. Elhilali, MD.

JAAPOS 2022;26:260-262.

The purpose of this study was to evaluate the differences in mean pre-operative central corneal thickness (CCT) in eyes with pediatric cataract related to the presence or absence of persistent fetal vasculature (PFV). The study included 569 eyes with cataracts (47 anterior, 99 posterior, 93 nuclear, 272 total, and 58 other), 46 of which had PFV. Average CCT was 569  $\mu$ m. CCT was highest in the anterior cataract group and lowest in the other cataract group; however, there was no statistically significant difference in CCT between the different cataract morphologies. In unilateral cases, CCT was higher in the cataractous eye than in the noncataractous eye. CCT was also thicker in cataractous eyes with PFV compared with non-PFV cataractous eyes. The authors were not sure why the PFV eyes had thicker CCT. They hypothesized that it may be due to disturbed perfusion to the anterior segment or that it could be immunological in nature. Either way, they point out that the thicker corneas in PFV may lead to an overestimation of IOP on applanation. This highlights the importance of checking CCT in cataract patients, especially in those with PFV, and using that knowledge to interpret IOP in the correct context.

Epidemiology of ectopia lentis and outcomes after surgery in a Danish population.

Rasul A, Roos L, Groth K, Riise P, Bach-Holm D, Kessel L

J Cataract and Refract Surg 2022;48(12):1394-1402.

This retrospective cohort study reviewed the records of 72 patients born after 1980 with nontraumatic ectopia lentis who were seen at two clinics in Copenhagen from 1983-2019. About 95% of the patients had bilateral ectopia lentis. About half (52.8%) of these patients had cataract surgery at a median age of 8.4 years (range 0.8-39.0 years). Median follow up was 2.3 years (range 0-25.7 years). Nearly half (47.2%) of these patients had Marfan syndrome while 5.6% had biallelic variants in ADAMTSL4. About a quarter (23.7%) of the operated patients received an intraocular lens implant. After surgery, corrected distance visual acuity improved from 0.7-0.2 logMAR (median) in right eyes and from 0.7-0.3 logMAR in left eyes. While 56.8% of patients did not have any surgery-related complications, 3 eyes had a perioperative tear in the posterior capsule, 3 eyes had transient postoperative ocular hypertension, and 2 eyes developed persistent ocular hypertension. Importance: Interestingly, there were no cases of postoperative retinal detachment.

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Management of cataracts secondary to intravitreal chemotherapy injections for retinoblastoma seeding.

Koç İ, Taylan Şekeroğlu H, Kıratlı H, Lotfisağdıç S.

Eur J Ophthalmol. 2022 May;32(3):1766-1771.

This retrospective study consisted of a cohort of five eyes of five retinoblastoma patients who developed cataracts secondary to intravitreal chemotherapy administration and who subsequently underwent cataract surgery. All patients underwent lensectomy and anterior vitrectomy with/without intraocular lens implantation via clear corneal approach. All patients received intraoperative intravitreal melphalan (35-40 mcg) and topotecan (10-20 mcg) at the end of cataract surgery as a preventative measure against retinoblastoma spread. Injections were repeated as needed in monthly follow-ups. Main outcome measures were enucleation rate and disease-free survival time. The age at surgery ranged between 5 and 10 years. Follow-up time varied from 12 to 16 months. Treatment-free period before surgery ranged between 3 and 20 months. Time from last injection to cataract detection was: 2, 2, 10, 6, and 7 months; and time from last injection to cataract surgery was: 8, 3, 20, 7, and 15 months in cases 1-5, respectively. None of the eyes required enucleation. Tumor control was achieved in all patients at the end of follow-up. As part of the treatment for retinoblastoma, injections of melphalan and topotecan into anterior parts of the vitreous may lead to cataract formation. These cataracts can be safely managed with lensectomy and anterior vitrectomy, along with intravitreal administration of melphalan and topotecan at the conclusion of the surgery as a precautionary measure against the potential risk of extraocular spread.

### Congenital primary aphakia

Ernst, Julia et al.

Journal of American Association for Pediatric Ophthalmology and Strabismus {JAAPOS}, Volume 26, Issue 1, 4.e1 - 4.e5

A multicenter retrospective consecutive case series from five academic centers in England and North America was conducted to describe the natural history, management, and visual outcomes in children with congenital primary aphakia (CPA). 27 eyes of 14 patients were included. 13 had bilateral CPA, 1 had unilateral CPA. Mean age at diagnosis was 18 months (median, 21; range, 0.5-144). Of 11 patients who underwent genetic testing, 9 had FOXE3 pathogenic variants. In all patients, visual acuity at presentation was not better than fixing and following light. Typical findings included silvery appearance of the cornea with vascularization (96%), glaucoma (81%), iridocorneal adhesions (74%), optic nerve coloboma (55%), abnormal vitreous (33%), retinal detachment (30%), and aniridia with hypoplasia of ciliary body (19%). Surgical interventions in select patients included penetrating keratoplasty (PKP), glaucoma drainage device implantation, and cyclophotocoagulation (CPC). Visual outcomes are generally poor with risk of phthisis bulbi and spontaneous corneal perforation.

### Referral patterns for infantile cataracts in two regions of the United States

Huang, Laura C. et al.

Journal of American Association for Pediatric Ophthalmology and Strabismus {JAAPOS}, Volume 26, Issue 1, 6.e1 - 6.e5

This is a retrospective medical records review of children 0 to 1 years of age with congenital or infantile cataracts at Stanford University and Emory University. 111 children were included 74% were initially evaluated by a primary care doctor and 49% referred directly to a pediatric cataract surgeon. 15% were referred to an eye care provider before 6 weeks of age and initial evaluation by a pediatric eye surgeon was delayed until after 6 weeks of age. The patterns were similar between two institutions. Though not all cataracts require surgical intervention, those that do require it have a better visual outcome with early intervention. This study begins to help understand referral patterns and prompt future studies that will investigate barriers to prompt referrals.

### Increased Incidence of Mental Disorders in Children with Cataract: Findings from a Population-based Study.

Al-Bakri M, Skovgaard AM, Bach-Holm D, Larsen DA, Siersma V, Kessel L.

American Journal of Ophthalmology. 2022 Apr 1;236:204-11.

There is a growing body of literature assessing the increased risk of mental health problems seen in children with chronic disease. Given the timing and chronicity of the diagnosis and treatment of childhood cataracts, the authors sought to evaluate the relationship between this diagnosis and mental health disorders. This is a population-based study in Denmark of children born between 2000 and 2017. The authors included children with cataracts as well as controls matched by age, sex, and municipality (1:10 ratio ultimately including 485 children with cataract and 4358 controls). They used ICD-10 diagnostic codes to identify both children with cataracts as well as children diagnosed with neurodevelopmental and other mental disorders including substance misuse, psychosis, mood disorders, anxiety, depression, eating disorders, etc. The authors found an increased odds ratio for mental disorders in children with cataract – nearly double compared to controls. This risk was higher for children diagnosed with cataract in the first 3 years of life. Results are limited by issues inherent to retrospective studies using medical coding. The authors conclude that physicians treating children with cataracts should be aware of this correlation and advocate for screening and connection to psychiatric care.

### Sonic Hedgehog Intron Variant Associated with an Unusual Pediatric Cortical Cataract.

Young T, Whisenhunt KN, LaMartina SM, Hewitt AW, Mackey DA, Tompson SW

Invest Ophthalmol Vis Sci 2022;63(6):25.

This study conducted in the United States and Australia used a series of specific methods to identify the genetic basis of an unusual pediatric cortical cataract demonstrating autosomal dominant inheritance in a large European–Australian pedigree. The authors identified a SHH intron variant that cosegregates with an unusual pediatric cortical cataract phenotype. SHH is important for lens formation, and mutations in its receptor (PTCH1) cause syndromic cataract. The data implicate increased function of an enhancer important for SHH expression primarily within developing eye tissues.

### 13. CATARACT SURGERY

The contribution of intraocular lens calculation accuracy to the refractive error predicted at 10 years in the Infant Aphakia Treatment Study.

Oke I, VanderVeen DK, McClatchey TS, Lambert SR, McClatchey SK; Infant Aphakia Treatment Study Group.

J AAPOS. 2022 Dec;26(6):294.e1-294.e5.

Intraocular lens (IOL) calculation and IOL power selection in pediatric patients can be much more challenging than in adult patients. The difficulty in obtaining measurements and variability in axial growth of the child's eye make the long-term refraction unpredictable. The authors sought to determine the relative contribution of IOL calculation accuracy and ocular growth variability to the long-term refractive error predicted following cataract surgery. The authors used pseudophakic eyes of children in the Infant Aphakia Treatment Study (IATS) calculating the initial absolute prediction error (APE) and 10-year APE using initial biometry, IOL parameters, postoperative refractions, and mean rate of refractive growth. The group was divided into children with low-initial APE and a high initial APE and the 10-year APE was compared between the two groups. There was no significant difference in APE 10 years following surgery between the 2 groups due to the high variability in the rate of refractive growth of the operated eye. Additional research is needed to better identify factors that explain the variability improving long-term refractive outcomes. Limitations include small sample size which may not detect smaller differences in prediction error. Selection bias may have occurred because of exclusion of patients not meeting criteria. The article is important to pediatric ophthalmologists because it highlights the need for continued research into predicting long-term refraction after cataract surgery with IOL which can be a continued source of frustration for surgeons and their patients/families.

Late surgery for unilateral persistent fetal vasculature: long-term visual and anatomic outcomes.

Bata BM, Khalili S, Ali A, Wan MJ, Mireskandari K.

J AAPOS. 2022 Dec;26(6):296.e1-296.e5.

Persistent fetal vasculature (PFV) results from failure of the tunica vasculosa lentis and/or the hyaloid artery regression causing anterior and posterior structural changes with obstruction of the visual axis. Retrospective review was used to report visual and anatomic outcomes in patients who underwent surgery for PFV between 7-48 months of age with a mean follow-up of 73.7 +/-46.7 months. The authors have previously published a similar study of patients with unilateral PFV operated on before age 7 months in which 33 % obtained functional visual acuity better than 1.0 logMAR. The authors used a homogeneous group of patients with PFV with no significant posterior pathology (retinal detachment, retinal folds, FEVR, etc). The authors found in the cohort of patients with surgery after 7 months of age that 40% obtained visual acuity better than 1.0 logMAR. This is comparable to and slightly higher to the 33% achieved in the group operated on prior to 7 months of age. The authors postulate that the older group may have had milder lens opacities and amblyopia allowing for better outcomes. None of the patients developed glaucoma or ocular hypertension. The authors theorize that surgery at an older age was protective since several studies, including IATS, have demonstrated that younger age at time of surgery is a risk factor for development of glaucoma. The rate of other adverse events and need for additional surgery was low in this cohort. Limitations of this study include its retrospective nature and small number of patients. This study is important in demonstrating that delayed surgery may achieve functional visual acuity and is less likely to result in adverse events including glaucoma.

Predictive Accuracy of the Hill-RBF 2.0 Formula in Pediatric Eyes: Comparison of 5 Intraocular Lens Formulas [published online ahead of print, 2022 Sep 14].

Rastogi A, Singiri D, Kumar P, Thakar M, Baidur S, Bhardwaj A.

J Pediatr Ophthalmol Strabismus. 2022;1-6. doi:10.3928/01913913-20220811-01

This single-center observational study of 99 cataractous eyes from 70 children aged 4-18 sought to compare the predictive accuracy of the Hill RBF 2.0 formula vs the Barrett II, Hoffer Q, SRK/T and Holladay 1 formulae. The Lenstar LS-900 was used for optical biometry, and the IOL power was selected using the Hill-RBF formula. The authors found that the Hill-RBF formula had the lowest MAE, which was significantly lower than the Holladay 1 and Hoffer Q formulas. However, the difference in MAE between



the Hill-RBF and the SRK/T and Barrett Universal II formulas was not statistically significant ( $P > .05$ ). The Hill-RBF group had the maximum percentage of eyes with residual error within  $\pm 0.50$  D of the target refraction. They concluded that the Hill-RBF method that uses artificial intelligence and works independent of specific anatomical features is non-inferior to the Barrett Universal II, Hoffer Q, SRK/T, and Holladay 1 formulas in pediatric eyes. This study was interesting, but of limited generalizability because of the sample characteristics.

Pediatric cataract surgery: considerations and updates in diagnosis and management.

Jody N, Santana M, Rudell J.

Curr Opin Ophthalmol. Jan 1 2023;34(1):58-63.

This is a literature review on the recent updates in the diagnosis and management of pediatric cataracts, emphasizing published literature over the past two years. The goals of surgery remain unchanged – to minimize sensory deprivation amblyopia and to optimize visual development. Recent trends include smaller incisions, especially when the surgical plan is to leave the child aphakic. In addition, 25-G paracentesis wounds are created to limit wound leakage and postoperative infections. Studies reported that the suture-related complications are mildly related to using Nylon or Vicryl for wound closure, with no consistent benefit to using either suture other than removing the suture postoperatively. Moreover, studies have suggested that suturing surgical wounds may not be necessary for all children, especially older ones and that sutureless surgery reduces the increased astigmatism and amblyopia risk associated with sutures. For anterior capsule management, femtosecond laser has become more popular. For posterior capsule management, recent studies questioned the need for anterior vitrectomy to prevent PCO formation – studies suggest that posterior optic capture is a viable approach to reduce VAO without the need for an anterior vitrectomy. Additionally, a study suggests that targeting  $\alpha 5 \beta 1$  integrin signaling pathway may lead to PCO prevention. Regarding IOL and calculations, IATS reported that 10.5 years after surgery, there was no difference in visual acuity in those treated with IOL vs. aphakia. Several recent studies show a trend for increased accuracy with the use of the Barrett Universal II formula. The ideal IOL material has not been identified. Intracameral moxifloxacin has an equivalent safety profile to subconjunctival antibiotics. Regarding postoperative complications, IATS found a 22% risk of glaucoma at ten years, with younger age at the time of surgery as the only significant factor. A retrospective cohort using claims data showed that children younger than 13 years have a 0.51% incidence of endophthalmitis within 90 days. In conclusion, there are still significant gaps in knowledge, and the authors recommend further studies to elucidate these gaps.

Nationwide Incidence of Infantile Cataract Surgery and Risk of Secondary Glaucoma in a Population-based Birth Cohort.

Choe S, Ha A, Choi S, Baek SU, Kim JS, Jeoung JW, Park KH, Kim YK.

American Journal of Ophthalmology. 2023 Feb 1;246:130-40.

Estimates of infantile cataract and glaucoma following cataract surgery frequency can be challenging due to the rarity of these conditions as well as heterogeneous populations and reporting. The goal of this population-based retrospective cohort study was to assess the nationwide incidence of these conditions in a Korean population. To do this, the authors use the Korean National Health Claims database to identify patients who underwent cataract surgery over a 10 year period (sample data from 2008-2018, >9.5 million in the database). Based on their search, they identified 692 patients who underwent cataract surgery and estimated an incidence of 5.10-9.29 cases per 100,000. In their cohort, 14% developed glaucoma with a mean time of 4.7 years to develop. The authors present the first population-based study of the incidence of infantile cataract in Korea. This information may help physicians and policy makers as it relates to health system planning.

Pediatric Cataract Surgery: Rate of Secondary Visual Axis Opacification Depending on Intraocular Lens Type.

Küchlin S, Hartmann ES, Reich M, Bleul T, Böhringer D, Reinhard T, Lagrèze WA.

Ophthalmology. 2022 Sep;129(9):997-1003. doi: 10.1016/j.ophtha.2022.05.007. Epub 2022 May 17.

This was a retrospective chart review of the time course of VAO after primary implantation of single piece acrylic (SPA), 3-piece acrylic (3PA) and bag-in-lens (BAL) IOLs over 20 years in one department. VAO

occurred in 13 eyes of 10 patients and was the most common cause of additional surgery. Median time to VAO was 10 months and patients were generally younger and had worse post-operative visual acuity. VAO was higher in SPAs compared to 3PLs. Only age at surgery was statistically significant on univariate analysis. The authors concluded that SPA was strongly associated with VAO development. The suggestion is that they differ in their haptics and configuration of lens posterior surface. The two most important conclusions of the paper is that VAO is age dependent, occurs within 1-2 years of surgery and is influenced by lens type.

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#### Suture Selection for Incision Closure in Pediatric Cataract Surgery: A Dilemma for Pediatric Ophthalmologists.

Agarwal P, Maan V, Sutar S, Chauhan L.

J Pediatr Ophthalmol Strabismus. 2022;59(4):243-247. doi:10.3928/01913913-20211111-02

This single-center, prospective, non-randomized cohort study sought to measure and compare suture-related complications in pediatric cataract surgery (performed by a single surgeon) where closure was performed with 10-0 nylon suture followed by suture removal within 1 to 2 weeks after surgery in the first eye, followed by a 10-0 polyglactin suture left in situ for the second eye. The authors reported outcomes of 82 eyes of 41 children observed for 3 months after surgery. Of the 10-0 nylon sutures, 2 (4.9%) were loose and 2 (4.9%) had underlying corneal edema. The remaining sutures (n = 37, 90.2%) were removed within 1 to 2 weeks after surgery. Of the 10-0 polyglactin sutures, 5 (12.2%) were loose, 2 (4.9%) were vascularized, and 3 (7.3%) had mucus infiltration. These sutures (n = 10, 24.3%) were removed 2 to 5 weeks after the second eye surgery. The remaining polyglactin sutures (n = 31, 75.6%) were left in situ. The authors concluded that a higher frequency of suture-related complications was observed with the 10-0 polyglactin sutures than the 10-0 nylon sutures. The authors recommended using 10-0 nylon sutures with suture removal within 1 to 2 weeks after surgery over using 10-0 polyglactin sutures for incision closure in pediatric cataract surgeries. This study had great internal validity because of same-subject (crossover) design, and so offers valuable insight into head-to-head comparison between the two closure techniques.

#### Visual Acuity and Ophthalmic Outcomes 5 Years After Cataract Surgery Among Children Younger than 13 Years

Michael Repka MD MBA, Trevano Dea MPH, Raymond Kraker MSPH

JAMA Ophthalmol. March 2022; 140(3): 269-276

The goal of this study was to examine outcomes and complications from a large pediatric cataract surgery registry to provide estimates of visual outcomes and 5 year cumulative incidence of adverse events. This prospective cohort study used data from the PEDIG registry, and patients were enrolled from 61 eye care practices in the US, Canada, and the UK. Patients were included if they underwent lensectomy under the age of 13 from June 2012 to July 2015. The medical records were then reviewed annually thereafter for 5 years until September 2020. The 5-year cumulative incidence of glaucoma or glaucoma suspect was highest in patients with bilateral aphakia and lowest in patients with unilateral pseudophakia. Overall, glaucoma related adverse events were reported in 14% of children without a pre operative diagnosis of glaucoma or ocular trauma. For infants with bilateral cataracts, there were no differences in VA at 5 years between those who underwent surgery before 6 weeks of age, from 6 weeks to less than 3 months of age, and from 3 to 6 months of age. However, in infants with unilateral cataracts, better VA was observed when lensectomy was performed at a younger age. Refractive error after primary IOL implantation was tightly clustered around emmetropia. The 5-year cumulative incidence of surgery to clear the visual axis was highest in unilateral pseudophakic eyes (34%), with patients requiring anterior vitrectomy, Nd:YAG capsulotomy, or both. Rates of surgery to clear the visual axis was lower when anterior vitrectomy was performed at the time of lensectomy. Overall, 19 eyes (2%) experienced a retinal detachment. This study highlights the need for ongoing monitoring after pediatric cataract surgery to detect glaucoma, visual axis obscuration causing reduced vision, and refractive error.

#### Outcomes of bilateral cataract surgery in children 2-7 years of age: a comparison to surgery in toddlers and infants.

Adams C, Alex AA, Trivedi RH, Wilson ME.

J AAPOS. 2022 Jun;26(3):133.e1-133.

The authors used retrospective review to evaluate the outcomes of bilateral cataract surgery in children 2-7 years old from their own institution and compare them to bilateral infant and toddler outcomes of the Toddler Aphakia Pseudophakia Study (TAPS) registry. The authors aptly name their study Surgical Treatment Outcomes and Refractive Management (STORM) of Cataracts in Kids (STORM Kids). The Infant Aphakia Treatment Study (IATS) taught us that in children less than 7 months of age primary intraocular lens (IOL) placement is associated with a higher incidence of adverse events (AEs) and surgical reoperation. Current recommendations support use of IOL's in children over 7 months of age and it is widely accepted in children older than 2 years of age. The authors state that STORM Kids is the first targeted report of surgical outcomes in children 2-7 years of age. This study is consistent with previous studies in showing AEs are more common in children under the age of 7 months of age. The authors describe visual axis obstruction (VAO) from posterior capsule opacification (PCO) decreasing significantly in older children especially with primary posterior capsulotomy and anterior vitrectomy. Infants with an intact posterior capsule required surgery for visually significant PCO in 62% of patients. Previous studies note decreasing occurrence of glaucoma as children were older at the time of their first surgical intervention. The authors of this study report no glaucoma related AEs in the older cohort. TAPS study reported poor vision in 6.25% of patients while the STORM group had poor vision in 2% of the patients. Pre- and post-operative recognition is sometimes difficult to obtain because of cooperation. The authors describe several limitations including retrospective analysis, nonrandomization, and a lack of standard data collection. The study is important in that the author's data suggests that lensectomy with primary IOL placement combined with posterior capsulotomy and anterior vitrectomy should be considered as an alternative to aphakia in the older age group of 2-7 years. More study in other centers and evidence will be necessary to support this conclusion.

Immediate versus delayed sequential bilateral cataract surgery in children: a cost-effectiveness analysis  
Cernat A, Jamieson M, Kavelaars R, Khalili S, Bhambhwani V, Mireskandari K, Moretti ME.  
Br J Ophthalmol. 2022 Feb;106(2):211-217.

This is a retrospective cost analysis of children who underwent immediate sequential bilateral cataract surgery (ISBCS) or delayed sequential bilateral cataract surgery (DSBCS) at a tertiary referral paediatric hospital in Ontario, Canada, which has a universal, single-payer system. The cohort included all patients who underwent ISBCS or DSBCS under age 2 years over a 10-year period with or without primary IOL implantation, with the DSBCS group having surgery on the second eye within 8 weeks of the first surgery. Both interventions were modelled over an 8-week time horizon to ensure that all surgery-related costs were captured, but not those related to pre-existing conditions. Surgical effectiveness was measured by clear visual axis bilaterally. Both health system (direct healthcare costs usually incurred by the third-party payer) and societal perspectives (i.e., direct healthcare costs of the surgery, indirect costs like productivity losses for parents due to time off work, etc) were reported. Both ISBCS and DSBCS were found to be equally effective in terms of a clear visual axis bilaterally. Compared with DSBCS, ISBCS resulted in average cost-savings of \$3,775.59 per patient from the societal perspective. From the health system perspective, ISBCS resulted in cost savings of \$2,199.65 compared with DSBCS. The mean overall cost of undergoing ISBCS was \$16,003.66 (95% CI: \$11,096.29 – \$22,720.33) from the societal perspective, while the mean overall cost of undergoing DSBCS was \$19,779.25 (95% CI: \$13,319.61 – \$28,566.18). While multiple factors go into the decision to pursue ISBCS vs DSBCS in children, this study demonstrates the cost-effectiveness and equal efficacy of ISBCS.

Intraocular lens implantation with flattened flanged intrascleral fixation technique in pediatric aphakia  
Ucar, Fikret

Journal of American Association for Pediatric Ophthalmology and Strabismus Volume 26, Issue 1, 8.e1 - 8.e7

Clinical outcomes of use of an intraocular lens (IOL) implant with flattened flange for intrascleral fixation in pediatric aphakia without adequate capsular support was evaluated. A total of 21 eyes of 16 patients were included. Mean patient age at time of surgery was 7.1- 3.8 years (range, 2-15). Mean follow-up time after surgery was 2.0 years. The mean preand postoperative best-corrected visual acuities were 1.03 to 0.49 logMAR and 0.33 to 0.44 logMAR, respectively. The mean preoperative astigmatism was 2.2 to 0.9 D; and the mean postoperative astigmatism, 1.8 to 0.8 D. The mean IOL tilt was 3.2 to 3.1 (range, 0-10). The mean endothelial loss was 4.8%. Postoperatively, one of the haptics was partially visible in the

scleral tunnel in one eye of a patient with Marfan syndrome. This suggests that this flattened haptic IOL may be a good option for scleral fixated IOL implant.

#### In-the-Bag Versus Ciliary Sulcus Secondary Intraocular Lens Implantation for Pediatric Aphakia: A Prospective Comparative Study.

Liu Z, Lin H, Jin G, Tan X, Qu B, Jin L, Chen X, Wang W, Han X, Xu J, Ying G.

American journal of ophthalmology. 2022 Apr 1;236:183-92.

Pediatric ophthalmologists are often faced with a challenging decision when encountering an aphakic child who needs intraocular lens implantation. Two possible techniques include placing a lens in the bag or the ciliary sulcus. The goal of this prospective, comparative study was to evaluate outcomes for each of these approaches. The study included 355 aphakic eyes of 202 children who underwent cataract extraction prior to age 2. 40% of eyes underwent in the bag implantation and the remainder in the sulcus. The decision between the two surgical techniques was based on the amount of residual lens capsule. Sulcus placement was associated with higher risk of adverse events (24% compared to 6%) as well as lens decentration. Final best corrected visual acuity was slightly better in the in the bag group. This study demonstrates interesting clinical differences in surgical technique for secondary IOL implantation in aphakic children. It is possible that individual patient factors such as sulcus and capsule anatomy influenced outcomes regardless of surgical technique. Additionally, as a single center study, the generalizability of these results to other patient populations or surgeons is uncertain.

#### Deviations From Age-Adjusted Normative Biometry Measures in Children Undergoing Cataract Surgery: Implications for Postoperative Target Refraction and IOL Power Selection.

VanderVeen DK, Oke I, Nihalani BR.

American Journal of Ophthalmology. 2022 Jul 1;239:190-201.

Intraocular lens (IOL) power selection in children undergoing cataract surgery is challenging due to variation in biometric variables which vary by person and also change with age. In this American Ophthalmological Society (AOS) thesis, the goal is to evaluate whether children whose eyes deviate from age-normal biometry have differing levels of myopic shift following cataract surgery. This was a retrospective, single center study of 162 eyes with cataracts with median follow up of close to 10 years. The authors provide age-related stratification of myopic shift following cataract surgery. For example, children aged 0-2 years had a 5.0 D myopic shift. Older children (aged 8-10 years) had a less significant myopic shift of 1.0 D. Other associations with more myopic shift included lower keratometry and male gender. The authors conclude that nomograms for IOL power selection based on age are useful and adjustments can be made for children who have lower keratometry than expected (and are expected to have more myopic shift).

#### Posterior continuous curvilinear capsulorhexis with anterior vitrectomy vs. optic capture buttonholing without anterior vitrectomy in pediatric cataract surgery.

Kohnen T, Davidova P, Lambert M, Wenner Y, Zubcov A.

J Cataract Refract Surg 2022;48:831-837.

Different surgical approaches have been described to reduce posterior capsular opacification, the most frequent complication after pediatric cataract surgery. This prospective, randomized clinical trial conducted at Goethe University in Frankfurt, Germany was done to investigate long-term complications after pediatric cataract surgery with implantation of a heparin-coated polymethyl methacrylate intraocular lens (PMMA IOL) and posterior continuous curvilinear capsulorhexis (PCCC) with anterior vitrectomy vs PCCC without anterior vitrectomy with optic capture buttonholing. Eyes with unilateral or bilateral congenital cataract without further pathologies or previous surgeries were randomly assigned in 2 groups: cataract removal, IOL implantation, and PCCC with anterior vitrectomy (group A) or posterior optic buttonholing without anterior vitrectomy (group B). Main outcome measures were posterior capsule opacification (PCO), complication rates, and refractive development. 58 eyes of 41 pediatric cataract surgery patients were included. The mean age at the time of operation was 66.05 months ( $\pm 29.39$ ). In group A (n = 26), 2 eyes required treatment for PCO, whereas the optic axis remained clear in all eyes in group B (n = 30). Group B had a slightly lower complication rate. The mean spherical equivalent after a mean postoperative follow-up of 6.5 years was  $-0.11 \pm 2.51$  diopters (D) (-5.0 to +4.0 D) in group A and  $-0.08 \pm 2.14$  D (-5.0 to +4.0 D) in group B (statistically insignificant). The authors conclude that optic

capture with a heparin-coated PMMA IOL is a safe technique in the prevention of secondary cataract formation without a higher rate of complications and without the need for vitrectomy. A shortcoming of this study was that it did not examine subgroups based on age.

\*with Comment by Sukhija J, Savleen K. and Reply by authors in same issue

Accuracy of intraocular lens power formulas for eyes with scleral-sutured intraocular lenses in congenital ectopia lentis.

Lian Z, Cao Q, Qi H, Young CA, Zhang X, Jin G, Zheng D.

J Cataract Refract Surg 2022;48:469-474.

Ocular biometric parameters in congenital ectopia lentis are characterized by long eyes, flat corneal curvature, and high astigmatism which makes IOL calculations difficult. This retrospective consecutive case series of 158 eyes of 158 patients (ages 12.8 $\pm$ 10.7 years) was conducted at Zhongshan Ophthalmic Center, Guangzhou, China, to compare the accuracy of intraocular lens (IOL) power calculation formulas in eyes with congenital ectopia lentis (CEL) that underwent scleral-fixated IOL implantation. The authors compared the prediction errors (PE) of the spherical equivalent of 8 formulas: Barrett Universal II (BUII), Emmetropia Verifying Optical (EVO), Haigis, Hoffer Q, Holladay 1, Kane, Hill-RBF 3.0, and SRK/T. Results: All formulas before constant optimization produced myopic PEs. After optimization, the SRK/T and EVO formulas had the lowest median absolute error and the highest percentage of PE in the range within  $\pm$ 0.50 D for CEL patients with scleral-sutured IOL implantation. Therefore, these two formulas are recommended for calculation of power of scleral-sutured IOLs in eyes with congenital ectopia lentis.

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## 14. GLAUCOMA

Retinal injury identified by overhead-mounted optical coherence tomography in two young children with infantile-onset glaucoma

Alvarez-Falcón S, Glaser T, Go MS, Chen X, Freedman SF, El-Dairi M  
J AAPOS 2023;27:28.e1-6

Retinal findings identified by imaging overhead-mounted optical coherence tomography (OCT) in 2 children with infantile-onset glaucoma were reported. A total of 41 children (71 eyes with glaucoma) were imaged before age 2 years. Macular imaging identified both inner and outer retinal thinning in 3 eyes of 2 young children (both eyes of a child with newborn primary congenital glaucoma (PCG) and 1 eye of a child with glaucoma following cataract surgery), which remained stable over time. These findings were present in 2 of 41 children (4.9%) and 3 of 71 eyes (4.2%) imaged with Flex-OCT. Neither highest IOP, CD, nor AL at imaging differentiated the 3 eyes with retinal changes from the larger group. Three eyes of 2 young children with refractory glaucoma of different etiologies and highly elevated IOP demonstrated areas of inner and outer retinal thinning, consistent with retinal injury from probable prior macular ischemia. This study highlights a new retinal finding the need for continued investigation of the pathophysiology of the disease.

Topical netarsudil 0.02% as adjunctive therapy in refractory pediatric glaucoma

Abdelrahman M Elhusseiny, Javaneh Abbasian  
J AAPOS. 2022 Dec;26(6):300.e1-300.e5.

The authors used retrospective review to evaluate the efficacy of topical netarsudil 0.02% as adjunctive therapy in children with refractory pediatric glaucoma. Pediatric glaucoma is most often treated surgically. Glaucoma medications are necessary to temporize until surgical intervention can occur or when intraocular pressure (IOP) cannot be controlled. The mechanism of action is inhibition of the Rho kinase signaling pathway improving aqueous outflow through trabecular meshwork. A total of 21 eyes of 16 patients were included in cohort with a history of previous glaucoma surgery and multiple medications prior to starting netarsudil. The IOP was significantly reduced from  $26.3 \pm 6.2$  mm Hg before topical netarsudil to  $19.6 \pm 6.02$  mm Hg at 1 month in 15 eyes ( $P < 0.01$ ),  $18.2 \pm 6.9$  mm Hg at 3-months in 18 eyes ( $P < 0.01$ ),  $18.3 \pm 7.3$  mm Hg at 6 months in 13 eyes ( $P = 0.01$ ),  $17.6 \pm 5.07$  mm Hg at 9 months in 14 eyes ( $P = 0.002$ ), and  $17.4 \pm 3.1$  mm Hg at 12 months in 13 eyes ( $P = 0.002$ ). Additional glaucoma surgery was required in 43% of eyes due to failure of topical netarsudil to reduce IOP despite initial decrease. One eye had persistent elevation despite addition of topical netarsudil. Common adverse ocular events included congested conjunctival vessels and subconjunctival hemorrhage. No serious adverse events were reported in this cohort. The authors conclude that in this cohort of patients with refractory glaucoma, adding topical netarsudil reduced IOP which may delay further surgery. Limitations of this study are: retrospective review, small sample size, short variable follow-up, differences in age, type of pediatric glaucoma, variability between patients in IOP measurement instrument and various treatment regimens. Further research is needed to evaluate the safety and efficacy of netarsudil in children with glaucoma.

Diagnostic yield of next generation sequencing gene panel assays for early-onset glaucoma in an ethnically diverse population

Maria Fernanda Villalba, Alana L Grajewski, Mustafa Tekin, Guney Bademci, Ta C Chang  
J AAPOS. 2022 Dec;26(6):302.e1-302.e6.

Childhood glaucoma is a heterogeneous group of disorders with an extensive classification including primary, secondary and associated with systemic syndromes. Many variants as well as recessive and dominant inheritance patterns have been described that are associated with early onset glaucoma. Next-generation sequencing panels for a specific type of disease has become a valuable tool when investigating eye diseases. Multiple tools have been developed for early onset glaucoma with varying reported results. The authors used retrospective review to evaluate their own early-onset glaucoma panel as well as similar panels from third party labs for diagnostic yield and to identify patient traits associated with increased diagnostic yield. The authors specified estimated age of onset as before or after 3 years of age. The authors included 118 patients which was ethnically diverse: Black 42%, White 25%, Hispanic 29%, and 5% as other or did not disclose. A causative agent in the group with onset prior to age 3 had an

overall diagnostic yield of 32% as contrasted with the onset after age 3 where only 5% had variants identified. Patients who identified as White had a statistically significant higher diagnostic yield than those who identified as non-White. The yield was also statistically higher in patients with ocular anomalies while co-existing systemic disease did not improve the diagnostic yield. With respect to in-house testing, the diagnostic yield was 13% while patients tested with third-party panels had a diagnostic yield of 31%. The authors attribute this difference to a higher number of patients with onset before age 3 and had additional ocular anomalies. For patients with onset prior to age 3 years, the diagnostic yield for in-house and third-party panels was the same. It is important to note that a molecular diagnosis was not obtained in 81% of patients. The importance of improving the diagnostic yield is several fold: improved counseling for patients, possible better prognostic predictions, and possible precision medicine treatments. Limitations of the study include a wide spectrum of glaucoma phenotypes in this study resulting in a smaller sample size for each genetic condition. The high number of identified variants of uncertain diagnostic yield and lack of a specific molecular diagnosis reminds pediatric ophthalmologists to prepare patients for the fact that although genetic panel testing is an important new tool, it may result in ambiguous or no answers. There is more work to be done.

Agreement of iCare IC200 tonometry with Perkins applanation tonometry in healthy children.  
Theo Stoddard-Bennett, BS, Nicholas J. Jackson, MPH, PhD, Laura Robbins, OD, Phillip Villanueva, CO, Soh Youn Suh, MS, MD, Joseph L. Demer, MD, PhD, Stacy L. Pineles, MS, MD, and Simon S. M. Fung, MD, FRCOphth.

JAAPOS 2022;26:235.e1-5.

The purpose of this study was to assess the interdevice agreement between the iCare and Perkins applanation tonometry in pediatric patients. Forty-two children were included in the study. Each participant underwent IOP measurement using both the iCare and Perkins tonometers. The order of tonometers was randomized. After IOP was obtained using both devices, the central corneal thickness was measured. The mean difference between the iCare and Perkins tonometers was +0.72 mmHg. The iCare-Perkins difference was >2 mmHg in 35.7% and <2 mmHg in 9.52%. Absolute agreement between the tonometers was 0.63. The study found no significant correlation between CCT and the mean IOP measured by iCare or Perkins tonometry. CCT was also not associated with differences in IOP between the two tonometers. This study is important given the advantages to using rebound tonometry in a pediatric population. Given that the mean absolute difference between the tonometers was <1 mmHg in healthy children, the authors recommend the use of iCare in nonglaucomatous children. They caution that IOP readings that suggest glaucoma should be rechecked with Perkins tonometry.

Ahmed glaucoma valve implantation with and without Ologen adjuvant in pediatric glaucoma.  
Ahmed S. Elwehidy, MD, PhD, Nader H. L. Bayoumi, MD, FRCS, Sherein M. Hagra, MD, and Shereen Elshaer, MD.

JAAPOS 2022;26:238.e1-6.

The aim of this study was to compare outcomes of Ologen augmentation of Ahmed Glaucoma Valve (AGV) vs AGV implantation alone in children with uncontrolled glaucoma after initial surgery. Ologen is a biodegradable type-I collagen matrix that decreases early post-operative scarring and prevents collapse of the subconjunctival space. The design was a prospective interventional randomized study with all surgeries performed by the same surgeon. Thirty-three eyes of thirty-three children were included in the study. At 24 months follow-up, there was a significant reduction in IOP and in the number of IOP-lowering medications in both groups. Both groups also followed the same pattern with an initial marked reduction in IOP, gradual smooth rise, fall, and final slow shallow rise in IOP. The AGV-Ologen group demonstrated marginally lower IOP values that reached statistical significance at all follow-up points. The difference between the success rates at 24 months was not statistically significant between the groups. No vision threatening complications were noted in either group. This is an important study given the difficulties in treating childhood glaucoma. While the Ologen led to statistically lower IOP values at follow-up, the clinical significance of these differences is questionable. On the other hand, the authors did note more frequent bleb encapsulation and post-op IOP spikes in the absence of Ologen, but these differences were not statistically significant. The main limitation of this study was the small number of eyes and short follow-up period (relative to the length of life of these patients). It would also be interesting to know the cost of the Ologen in order to help determine if the cost is worth the possible small benefit.

Anterior segment optical coherence tomography findings in the Infant Aphakia Treatment Study (IATS): a secondary analysis of a randomized clinical trial.

Allen D. Beck, MD, Sharon F. Freedman, MD, Azhar Nizam, MS, and Scott R. Lambert, MD, for The Infant Aphakia Treatment Study Group.

JAAPOS 2022;26:229.e1-6.

This study used anterior segment optical coherence tomography (AS-OCT) to assess the anterior chamber in the participants of the Infant Aphakia Treatment Study (IATS) at 10 years of age. AS-OCT has an advantage over gonioscopy and ultrasound biomicroscopy in that it is a non-contact study, which makes it much easier to perform in children. There was no significant difference in anterior chamber angle or angle opening distance for nonglaucomatous, glaucomatous, and fellow eyes. There were also no differences between fellow and treated eyes or between intraocular lens and contact lens groups. This study confirms that most cases of glaucoma following congenital cataract surgery are open angle. Unfortunately, it does not help shed any light onto the underlying pathophysiologic mechanism for the development of post-operative glaucoma. Future studies including additional angle findings and comparing eyes pre- and post-operatively may be helpful to further delineate the underlying cause for this common form of childhood glaucoma.

Netarsudil-induced corneal honeycombing in childhood glaucomas.

Shikha Gupta, MD, Karthikeyan Mahalingam, MD, Monika Arora, MS, Abhishek Singh, B. Optom, Somya Kumari, MD, and Viney Gupta, MD.

JAAPOS 2022;26:257-260.

Netarsudil is a hypotensive drug that reduces IOP by increasing trabecular outflow, reducing aqueous humor production, and decreasing episcleral venous pressure. Cases of corneal honeycombing have recently been reported in adults. This study was undertaken to assess risk factors and compare the clinical characteristics of pediatric eyes that developed corneal epithelial honeycombing. Sixteen patients were included in the study, and nine (56%) of them developed corneal honeycombing. This led to decreased visual acuity in the patients able to participate in quantitative measures of acuity. The findings were transient and resolved within 1-3 weeks after stopping the drug. The children who developed honeycombing were younger, more often had a history of prior corneal edema, and had higher baseline IOP compared to those who did not. It was hypothesized that the enhanced permeability of tight junctions along with improved endothelial function resulted in enhanced fluid transport from the endothelium to the stroma and into the epithelium. The fluid then becomes trapped in the epithelial cells leading to honeycombing. This is an important paper pointing out a seemingly common side effect of a newly approved IOP lowering drug. While the study was limited by a small sample size and the concurrent use of other glaucoma medications, it illustrates that corneal appearance needs to be monitored closely in patients on netarsudil.

Outcomes of inferonasal glaucoma drainage device surgery in the management of childhood glaucoma.

Amal Al-Lozi, MD, Allison C. Umfress, MD, Sandra S. Stinnett, PhD, and Sharon F. Freedman, MD.

JAAPOS 2022;26:232.e1-7.

The purpose of this study was to evaluate outcomes of glaucoma drainage devices (GDD) placed in the inferonasal quadrant in children. Sixty-eight eyes from fifty-two patients were included in the study. The most common diagnoses were primary congenital glaucoma and glaucoma following cataract surgery. The most common reasons for inferonasal GDD placement were previous superotemporal quadrant GDD and reservation of ST quadrant for further surgery. For all eyes, the mean IOP was reduced from 29.7 to 21.3 mmHg. There was no significant difference in the number of IOP-lowering medications required before and after surgery. Twenty-eight eyes (41%) met pre-determined success criteria with the rest being deemed surgical failures. Reasons for failure included IOP above target, restrictive strabismus, retinal detachment, and endophthalmitis. Most within the failure group (97%) required additional glaucoma surgery. The success rate of 49% is less than inferonasal GDDs in adults (80-88% at 2 years) and less than superotemporal GDDs in children (64-94% at 2 years). This study was limited by its retrospective nature, small sample size, lack of control group, and limited follow-up. It is still an important



study considering the limited data in the literature about inferonasal placement of GDDs in children. This is a procedure that warrants further study aimed at determining factors that may improve outcomes.

Pediatric glaucoma suspects: characteristics and outcomes.

Stephanie N. Kletke, MD, FRCSC, Monte D. Mills, MD, Lauren A. Tomlinson, BS, Yinxi Yu, MS, Gui-shuang Ying, PhD, and Gil Binenbaum, MD, MSCE.

JAAPOS 2022;26:236.e1-6.

The purpose of this study was to determine the characteristics and outcomes of pediatric glaucoma suspects (GS) and to evaluate the risk factors for progression to glaucoma. While GS status is well studied in the adult literature, there is a dearth of knowledge in the pediatric literature. This study aims to fill that gap. A retrospective sequential cohort study was conducted at the Children's Hospital of Philadelphia. Children were considered glaucoma suspects based on at least one and no more than 3 of the following criteria: optic nerve appearance, ocular hypertension, family history of glaucoma/GS, periocular lesion associated with glaucoma, systemic or genetic association, history of blunt ocular trauma, or other ocular anomalies. A total of 887 children met the criteria and were included in the study. For children who had at least one follow-up exam, 14 (2.9%) converted to a diagnosis of glaucoma, 324 (67%) kept their status as a glaucoma suspect, 148 (30%) were considered to have pseudoglaucomatous or physiologic cupping, and 1 (0.2%) developed treatment-requiring ocular hypertension. Baseline IOP  $\geq$  24 mmHg and presence of a periocular lesion were associated with a higher risk for progression to glaucoma; however, baseline CDR and family history of glaucoma were not. This is an important study as it looks to identify potential risk factors for glaucomatous progression in pediatric GS. As this makes up a big part of a pediatric ophthalmologist's practice, future studies looking to help develop guidelines for management of these patients would be very helpful.

Intraoperative Mounted Optical Coherence Tomography Findings Following Reversal of Optic Nerve Head Cupping in Childhood Glaucoma.

Glaser TS, Go MS, Kelly MP, El-Dairi MA, Freedman SF.

American Journal of Ophthalmology. 2022 Nov 1;243:109-17.

Optic nerve cupping reversal has been described in the setting of treated childhood glaucoma. In adults, studies have shown that this cupping reversal does not correlate with improvement in optic nerve retinal nerve fiber layer (RNFL) thickness when measured with optical coherence tomography (OCT). This retrospective observational case series aimed to describe OCT-identified optic nerve structural changes in children with reversal of optic nerve cupping. The study included 18 eyes of 14 patients with childhood glaucoma who underwent imaging with intraoperative mounted OCT. The mean age of the cohort at time of surgery was 1.14 years and mean IOP reduction was 45%. Global thickness of the RNFL was 93.1 microns before and after IOP reduction and optic nerve cupping. While this study used a non-FDA approved imaging system which is not widely available, it does add to the literature supporting the idea that optic nerve cupping reversal is an anatomic but not physiologic or functional change. Understanding this phenomenon may help clinicians determine baseline optic neuropathy in children with glaucoma (even if their cup:disc ratio has improved in the setting of cupping reversal).

Risk Factors for Glaucoma Drainage Device Exposure in Children: A Case-Control Study.

Jomar DE, Al-Shahwan S, Al-Beishri AS, Freidi A, Malik R.

American Journal of Ophthalmology. 2023 Jan 1;245:174-83.

Glaucoma drainage device (GDD) exposure is a serious concern in children with glaucoma, as it can lead to endophthalmitis and poor visual outcomes. The aim of this retrospective case-control study was to evaluate patient characteristics associated with GDD exposure in children. This single center study included 21 eyes of 21 children with glaucoma and GDD exposure and 115 eyes of 115 children with glaucoma without GDD exposure. The authors estimated an overall incidence of 4.25% of GDD exposure based on their cohort. The risk factors that they found associated with GDD exposure included multiple previous ocular surgeries, longer follow-up duration, combined procedure at the time of primary implantation, and a younger age at the time of primary implantation. The mean time between implantation and exposure was 20 months. Age at implantation was 6 years (exposure group) compared to 12 years (control group). One limitation of this case-control study is that it did not include matching. Despite this,

the study provides useful information with regards to risk factors and may be useful for surgeons in planning the risks and benefits discussion with parents prior to proceeding with GDD implantation.

Glaucoma management in congenital ectropion uveae: Surgical outcomes from a large tertiary referral center in South India.

Mandal AK, Gothwal VK.

Eur J Ophthalmol. 2023 Jan;33(1):324-332.

This study was a retrospective chart review of all patients with congenital ectropion uveae (CEU) treated surgically from 1990 to 2019. Primary combined trabeculotomy-trabeculectomy (CTT), trabeculectomy with and without mitomycin-C (MMC) (0.2 mg/mL for 1 min) and transscleral cyclophotocoagulation (TSCPC) were performed. Intraocular pressure (IOP)  $\geq 6$  and  $\leq 16$  mmHg without medications was considered as complete success and IOP  $\leq 16$  mmHg with the use of up to 2 medications as qualified success. A total of 26 eyes of 21 patients were identified with a median age of 7 years (range, 6 days to 19 years) at the time of glaucoma surgery. Median follow-up was 51.1 months (range, 7-244.6 months). Primary CTT was performed in 17 eyes (65%), trabeculectomy in 5 eyes (19%) with application of MMC in 2 eyes, and 3 eyes (12%) underwent TSCPC. One painful blind eye (4%) underwent enucleation. Mean IOP reduced from  $30.8 \pm 7.6$  mmHg on a mean of  $1.3 \pm 0.8$  glaucoma medications preoperatively to a mean IOP of  $15.2 \pm 5.9$  mmHg ( $P < 0.0001$ ) on a mean of  $0.2 \pm 0.5$  medications postoperatively at final follow-up ( $P = 0.0009$ ). Complete success was achieved in 20 eyes, and qualified success in 2 eyes. CTT is a safe and effective primary procedure for management of early-onset glaucoma in CEU.

Trabeculectomy with or without adjuvant MMC is a viable second line of treatment in late-onset glaucoma with CEU for IOP control.

Neovascular Glaucoma in Children: A case series and a review of the literature.

Nieves-Moreno M, Peralta J, Noval S.

Eur J Ophthalmol. 2022 Nov;32(6):3289-3294.

The authors present three uncommon cases of neovascular glaucoma (NVG) in children. In adults, the most common causes of NVG are central vein retinal occlusion, proliferative diabetic retinopathy, and carotid artery obstructive disease, which are uncommon in children. Two cases were secondary to a retinal vasoproliferative tumor: one in a patient with neurofibromatosis type 1 and the other with exudative retinopathy secondary to mild retinopathy of prematurity. The third case was secondary to a central retinal vein occlusion secondary to an optic nerve glioma. Vision in the affected eye was severely impaired in all the children with NVG. The diagnosis and treatment of neovascular glaucoma in children is challenging and often a complication of a systemic or late-stage ocular condition. An appropriate diagnosis and estimation of the visual potential are essential to determine the correct treatment, especially in young children.

Barriers and adherence to glaucoma medication in a paediatric glaucoma population: A cross-sectional survey in central Saudi Arabia.

Al-Dawood A, Ahmad K, Al-Salman S, Al Hussan F, Al Houssien A, Al-Shahwan S, Khandekar R, Edward DP.

Eur J Ophthalmol. 2022 Nov;32(6):3451-3460.

This cross-sectional study was completed at the King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia during 2016-2017. Parents of children aged 6 months to 15 years with a history of glaucoma were interviewed. Rasch analysis was performed to assess the psychometric properties of the developed 12-item barriers-to-adherence tool (BAT-12) and to identify barriers deemed highly important. The 12-items were adapted from previous studies examining different barriers to adherence in different populations. Medication adherence was assessed by asking parents a series of closed-ended questions about the frequency of missed medications. Determinants of missed medications on at least 1 out of the last 3 days were examined using Poisson regression. One hundred and six parents were interviewed. The 12-item scale had acceptable psychometric properties. Barriers deemed important were forgetfulness (logit -0.59), complex dosing regimen (logit 0.09), and being too busy with other work/activities (logit 0.14). When asked how often, on average, their child missed the prescribed medication, 26 (24.5%) reported daily, 17 (16.0%) reported a few times per week, and 32 (30.2%) reported once per week. A third of parents ( $n = 37$ , 34.9%) reported having missed giving all drops on at least one day in the last 3 days. Poisson regression with robust variance revealed that increase in age of the child (prevalence ratio, 1.08 [95% CI,

1.03-1.14];  $p = 0.003$ ) and increase in parents' barriers score (prevalence ratio, 2.13 [95% CI, 1.49, 3.03];  $p < 0.001$ ) were significantly associated with having missed medications on at least one out of the last three days while adjusting for the effect of father's current employment status and area of residence. This study highlights poor adherence to glaucoma medications among children with glaucoma in this specific population.

Combined nasal goniotomy - temporal trabeculotomy (NGTT) for circumferential angle surgery in primary congenital glaucoma.

Abdelrahman AM, Amin RH.

Eur J Ophthalmol. 2022 Nov;32(6):3470-3475.

Fifteen eyes of eleven children (3-12 months old at presentation) were enrolled in this study after the establishment of PCG diagnosis based on the criteria placed by the World Glaucoma Association. Combined nasal goniotomy and temporal trabeculotomy were performed on each eye in an attempt to achieve almost 360 degrees of circumferential angle surgery without disturbing the superior 180 degrees of conjunctiva to preserve it for future filtering glaucoma surgeries. By the first month after the procedure, the average IOP was  $10.5 \pm 4.3$  mmHg with a 65.3% reduction from average pre-operative IOP. This IOP reduction remained largely stable at the 3rd, 6th and 12th months after surgery with average IOP measurements of  $11.9 \pm 4.65$ ,  $11.8 \pm 2.77$  and  $13 \pm 2.82$  mmHg (60.7%, 61.1% and 57.2% reduction from pre-operative average). All but one patient undergoing this procedure achieved IOP reduction (93.3%), with minor complications in 4 out of 15 eyes (26.6%) that did not affect IOP outcome. Nine out of fifteen eyes completed 18 months post-operative follow-up visits with a successfully maintained target average IOP of  $13.3 \pm 3.0$  mmHg (57.2% reduction). All of the mean IOP readings during post-operative follow-up period were significantly lower when compared to pre-operative IOP ( $p < 0.0001$ ). Only one eye had persistently elevated IOP of 26 mmHg at 1st and 3rd months post-operatively that necessitated a subsequent subscleral trabeculectomy which succeeded in controlling the pressure bringing it down to 15 mmHg on topical medications. Nasal goniotomy - temporal trabeculotomy (NGTT) is the combination of two well established surgeries that exploits the advantages of circumferential angle surgery while sparing the superior conjunctiva completely for future surgeries if needed. This new procedure was safe and effective in lowering IOP by an average of 60% from pre-operative IOP with a sustained effect up to 18 months post-operatively. Based on the findings of this study, the authors suggest that NGTT should be added to the armamentarium of the surgical techniques to treat infantile glaucomas.

Whole-Exome Sequencing Reveals Novel NDP Variants in X-Linked Familial Exudative Vitreoretinopathy.

Peng Y, Zhao R, Dai E, Peng L, He Y, Li S, Yang M.

Eur J Ophthalmol. 2022 Nov;32(6):3220-3226.

The authors were interested in investigating the causative variants in three unrelated Chinese families with familial exudative vitreoretinopathy (FEVR) by performing genetic testing. The three probands and their family members experienced a comprehensive age-appropriate eye examination and genetic analysis. Luciferase assay was performed to evaluate impacts of variants on Norrin/ $\beta$ -catenin signaling activity. Two novel NDP variants were associated with FEVR in three families, including c.17T>C (p.Leu6Pro) in family 1 and c.58G>A (p.Gly20Arg) in families 2 and 3. These two variants were co-segregated with the disease phenotypes within each family. In addition, both variants resulted in compromised Norrin/ $\beta$ -catenin signaling activity. This finding adds to the current spectrum of genetic mutations associated with FEVR.

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Success Rate of Augmented Trabeculectomy in Primary Congenital Glaucoma.

Jabeen S, Noorani S, Memon MN, Zaheer N.

J Pediatr Ophthalmol Strabismus. 2022;59(3):180-186. doi:10.3928/01913913-20211027-01

This single-center prospective study sought to evaluate the outcome of trabeculectomy augmented w/ MMC in primary congenital glaucoma in children younger than 2 years old who were observed for  $\geq 1$  year. Trabeculectomy success was defined as an intraocular pressure (IOP) of 21 mm Hg or less without (absolute success) or with (qualified success) topical antiglaucoma medications. Surgical success was assessed at 1, 6, and 12 months after the procedure. The authors reported outcomes of 74 eyes of 42 children whose mean age was  $11.7 \pm 8.5$  months. The mean IOP after surgery was significantly lower than the preoperative IOP ( $P < .0001$ ). Absolute success was observed in 98.6%, 50%, and 27% of eyes

at 1, 6, and 12 months, respectively. Qualified success was achieved in 1.4%, 36.5%, and 48.6% of eyes at 1, 6, and 12 months, respectively. Overall success of the procedure was 100% at 1 month but reduced to 86.5% at 6 months and 75.7% at 12 months. In 24.3% of eyes, IOP was not controlled even with adjunctive topical glaucoma medications and was considered a failure. Postoperative complications were shallow anterior chamber (10.8%), collapsed anterior chamber (1.3%), and choroidal detachment (12.0%). Complications were managed conservatively, and 6 eyes needed surgical intervention. The authors concluded that augmented trabeculectomy is a useful primary procedure in children with primary congenital glaucoma, but that topical glaucoma medications may be needed to supplement the success of the procedure. The authors note lack of long-term follow-up as a limitation, but it is worth noting that the study population was fairly homogenous and this may limit generalizability of the study outcomes.

The outcomes of trans-scleral cyclophotocoagulation in pediatric glaucoma secondary to Sturge-Weber syndrome.

Adi Mohammed Al Owaifeer, MBBS, Abdulsalam Tayi Almutairi, MD, and Konrad Schargel, MD, PhD. J AAPOS 2022;26:78.e1-5.

Sturge-Weber syndrome (SWS) is a disorder characterized by vascular malformations affecting the eye, skin, and leptomeninges. Glaucoma is commonly seen in this disorder with an incidence reported from 42-71%. While some cases can be managed medically, many require surgical intervention. Surgical intervention in these children is complicated by higher risk of postoperative complications and the young age of patients. Because of this, alternative treatments may be helpful. This study reports on the use of transscleral cyclophotocoagulation (TSCPC) in pediatric patients with glaucoma secondary to SWS. A total of 22 eyes were included. Following treatment with TSCPC, mean IOP (intraocular pressure) dropped from 28 +/- 4.5 mmHg to 20.3 +/- 3.7 mmHg at 36 months (P = 0.02). The number of glaucoma medications decreased from 3.5 +/- 0.7 pre-operatively to 2.6 +/- 1.4 at 1-month post-op (P= 0.01); however, it returned to pre-operative levels during the following intervals. The cumulative probability of success was 72.7% at 12 months, 62.3% at 24 months, and 54.5% at 36 months. The only risk factor for failure was older age (greater than or equal to 2 years old) at the time of treatment. One eye developed hypotony and choroidal effusion; however, there were no vision-threatening complications recorded. While cyclodestruction is not a standard first-line intervention, this study shows that it can be a helpful tool in the treatment of glaucoma in SWS. Given the high risk of developing choroidal detachment following incisional surgery for glaucoma in SWS patients, TSCPC may be a desirable alternative as it is not expected to procedure a sudden drop in IOP intraoperatively. This is an important study that may help with the treatment of glaucoma in this complex patient population.

Psychosocial indicators of primary congenital glaucoma and filtering surgeries impacts on children and family's quality of life.

Silva AOD, Rolim-de-Moura C, Botelho NLP, Gracitelli CP, Ferraz NN. Eur J Ophthalmol. 2022 Jul;32(4):1997-2004.

The authors aimed to evaluate the effects of glaucoma filtering surgeries on the quality of life (QOL) of children with primary congenital glaucoma (PCG) and their families. The participants were parents/caregivers of children with bilateral PCG who underwent filtering surgery on one or both eyes and no previous diagnosis of ocular, systemic, neurological, or psychiatric disease. This prospective cross-sectional study collected data through a psychological inquiry that included questions related to: knowledge about the disease, the feelings at the moment of the diagnosis, expectation and comprehension of the treatment and the surgery, the child's behavior due to the visual impairment, family and social interactions as well as expectations about the child's future. The Children's Visual Function Questionnaire (CVFQ) was also used to collect data about the child's global health, his/her performance in daily activities, social behavior, personal traits, visual impairment, and eye care impacts on the family's dynamics. The associations between the CVFQ scores and visual acuity, intraocular pressure, optic disk cupping, horizontal corneal diameter, axial length, number of surgeries, and hypotensive eye drops were investigated. The mean age of the nine mothers interviewed and their children (six boys and three girls) was 29 ± 5 years and 35 ± 18 months, respectively. The psychosocial indicators determined were emotional impact of the diagnosis, disease knowledge, mother and family's feelings on facing the surgical treatment, surgical result comprehension, treatment adherence, child's emotional and behavioral reactions, social support, and future expectations. In CVFQ analysis, QOL score was strongly associated

with visual acuity ( $r = -0.79$ ;  $p = 0.01$ ). Besides the treatment score was correlated to intraocular pressure ( $r = -0.68$ ;  $p < 0.05$ ), optic disk cupping ( $r = -0.85$ ;  $p = 0.03$ ), and corneal diameter ( $r = -0.69$ ;  $p = 0.02$ ). Correlations were not found for number of surgeries and eye drops. The authors concluded that psychological inquiry and CVFQ were useful to identify the psychosocial indicators of PCG and its treatment repercussions and to comprehend the negative impact of this disease on the children's QOL and on their families' dynamics.

Co-existing lacrimal drainage anomalies in eyes with congenital Glaucoma.

Senthil S, Ali MJ, Chary R, Mandal AK.

Eur J Ophthalmol. 2022 Sep;32(5):2683-2687.

The authors conducted this retrospective analysis of children  $\leq 1$ -year with co-existing congenital glaucoma (CG) and congenital nasolacrimal duct obstruction (CNLDO) between 1998 and 2019 to evaluate the occurrence of co-existing CNLDO and other lacrimal anomalies in eyes with CG. During the study period, 51 children (73 eyes) had co-existing CG and CNLDO. The prevalence of CNLDO in CG was 2.5% (51/1993) and the prevalence of CG among CNLDO was 0.8% (51/6203). Among the children with CNLDO, 68 eyes (93.1%) had simple CNLDO, and 5 eyes (6.9%) had complex CNLDO. Associated lacrimal anomalies were present in 7/73 eyes, including congenital lacrimal fistula in two eyes, upper punctal agenesis and upper mid-canalicular obstruction in two eyes each, and upper single canalicular-wall hypoplasia in one eye. Lacrimal syringing and probing were successful in 69/72 eyes (95.8%) and failed in 3 eyes (4.2%). These 3 eyes had complex CNLDO and underwent Dacryocystorhinostomy (DCR) with Mitomycin-C and intubation. Sixty-two eyes underwent combined trabeculotomy and trabeculectomy, and two eyes underwent trabeculectomy. Among children aged  $\leq 1$ -year presenting with congenital glaucoma, coexisting lacrimal drainage anomalies were noted in 2.5% of patients, and simple CNLDO was the most common of the lacrimal drainage findings.

Long-term outcomes in Primary congenital glaucoma, aniridia and anterior segment dysgenesis.

Magan T, Tanner A, Fajardo-Sanchez J, Lim KS, Goyal S, Rodrigues I, Amaya L, Trikha S, Kulkarni A, Hammond C, Lascaratos G, Yu-Wai-Man C.

Eur J Ophthalmol. 2022 Sep;32(5):2920-2927.

This was a retrospective consecutive series between 1990-2021 evaluating patients with congenital glaucoma, aniridia, and anterior segment dysgenesis to determine long-term outcomes. A total of 41 eyes of 21 patients were included. Primary diagnoses were primary congenital glaucoma in 16 eyes (39.0%), aniridia in 14 eyes (34.2%), and anterior segment dysgenesis in 8 eyes (19.5%). Sixteen eyes (39.0%) had one or more glaucoma surgery or laser procedures for advanced glaucoma, and the long-term follow-up was  $12.8 \pm 3.6$  years. There was a significant decrease in postoperative IOP (mmHg) at 3 months ( $16.5 \pm 1.6$ ;  $p = 0.0067$ ), 6 months ( $18.7 \pm 2.1$ ;  $p = 0.0386$ ), 12 months ( $18.6 \pm 1.7$ ;  $p = 0.0229$ ), 3 years ( $14.7 \pm 1.2$ ;  $p = 0.0126$ ), 5 years ( $15.5 \pm 1.8$ ;  $p = 0.0330$ ) and 10 years ( $15.4 \pm 2.3$ ;  $p = 0.7780$ ), compared to preoperatively ( $24.1 \pm 2.6$ ). Surgical success (complete and qualified) was 62.5%, 50.0%, 43.8%, 46.2%, 45.5% and 28.6% at 3 months, 6 months, 12 months, 3 years, 5 years and 10 years, respectively. There was no significant change in the number of anti-glaucoma drugs postoperatively ( $p > 0.05$ ). Four eyes (25.0%) had postoperative complications (hyphema, hypotony) that resolved after conservative management. Surgical management of these complex eyes with advanced glaucoma is challenging. Overall, the cohort had good surgical outcomes with a significant decrease in IOP by 36.1% after long-term follow-up.

Etiology and outcomes of childhood glaucoma at a tertiary referral center.

Tam EK, Elhusseiny AM, Shah AS, Mantagos IS, VanderVeen DK.

J AAPOS. 2022 Jun;26(3):117.e1-117.e6.

Large studies of pediatric glaucoma populations are limited and studies that exist show variations of prevalence of subtypes and outcomes depending upon the population studied and definitions/classifications used to define the study group. The authors use retrospective record review to describe etiology, clinical features, and outcomes for children with glaucoma at a tertiary referral center from 2014-2019 using Childhood Glaucoma Research Network classification system (CGRN). Secondary glaucomas were most common with glaucoma following cataract surgery (GFCA) and secondary glaucomas associated with syndromes. This is consistent with other US studies and may represent referral bias and a tendency for congenital cataract surgery occurring earlier in developed countries which

may be associated with a higher risk of GFCS. The authors found many patients were glaucoma suspects using CGRN classification and were excluded. It is important in studies conducted prior to CGRN classification, to determine if glaucoma suspects were excluded when reviewing results. Successful control of IOP was achieved in 80.4% of eyes at the time of the study. The mean number of surgeries per patient increased with duration of follow-up. Amblyopia was the most common cause of vision loss in patients with childhood glaucoma in this study. In patients with profound loss vision loss due to optic nerve damage, a period of poor compliance with care was identified. The authors identified limitations with the study: incomplete data, incomplete documentation, and variable methods of measurement of intraocular pressure. This study is important to pediatric ophthalmologists because it demonstrates the need to counsel families that controlling the eye pressure is only the first step and that battling amblyopia will be a long-term challenge to preserve good vision

#### Consanguinity and severity of primary congenital glaucoma.

Gupta V, Bhandari A, Gupta S, Singh A, Gupta A.

J AAPOS. 2022 Jun;26(3):119.e1-119.e5.

The authors performed a case-control retrospective review to evaluate the severity of primary congenital glaucoma (PCG) among children born of consanguineous marriage. It is a rare disease with an autosomal recessive inheritance pattern. The incidence is increased with consanguinity and large family size. There is a lack of evidence as to whether consanguinity is an independent risk factor for severity of PCG. The most common gene mutations associated with PCG are in CYP1B1 and LTBP2. Less commonly MYOC mutations and PLOD2 are associated with PCG. The prevalence of CYP1B1 mutations in PCG varies widely from 20% to 100% and tends to be higher in populations with higher consanguinity. The authors show consanguinity is associated with worse presenting severity and surgical outcomes. A grading system for PCG is proposed. The authors review several limitations including retrospective study, single ethnicity, possibility of multiple generation involvement, and age of presentation being affected by awareness in consanguineous families. Authors propose that consanguinity is a potential confounder to be considered when studying outcomes in children with PCG.

#### Viscocanalostomy combined with trabeculotomy for management of refractory primary congenital glaucoma.

Vahedian Z, Fakhraie G, Ahmed AH.

J AAPOS. 2022 Jun;26(3):121.e1-121.e6.

Angle surgery is accepted first line treatment for primary congenital glaucoma. Most but not all patients respond to angle surgery. Trabeculectomy, a penetrating technique, may be considered as a second procedure but is associated with complications in children. Nonpenetrating procedures, such as deep sclerectomy and viscocanalostomy, have recently been reported to have success (80%) in intraocular pressure (IOP) control in adults. Nonpenetrating techniques reduce IOP by increasing outflow with unroofing Schlemm canal. The authors used a prospective study to assess the outcome of nonpenetrating glaucoma surgeries, specifically viscocanalostomy combined with trabeculotomy (VCO+tbo) in patients who failed initial angle surgery. The authors report IOP was reduced to <21 mm Hg in 59% of patients with a mean IOP reduction of 14 mm Hg. Survival rates were 71.6%, 61.7%, and 57.6%, respectively, at postop years 1,2, and 3. Children with neonatal-onset disease responded less well than those that presented between the first month and first year of age. This may be due to more severe dysgenesis in neonatal onset. Complications were limited with self-resolving postop hyphema and iatrogenic cyclodialysis. Limitations of the study were lack of control group and small sample size. The authors conclude viscocanalostomy combined with trabeculotomy may be a reasonable choice for second surgery in children who fail first angle surgery. This study is important to pediatric ophthalmologists who treat PCG by offering a successful way to augment second surgery.

#### Ologen augmentation of Ahmed valves in pediatric glaucomas

Jacobson A, Bohnsack BL.

J AAPOS. 2022 Jun;26(3):122.e1-122.e6. doi: 10.1016/j.jaapos.2022.02.009.

Glaucoma drainage devices (GDD) are often used in cases not responding to angle surgery. Initial success in controlling IOP (80-90%) which often decreases to 50% by 5 years. Early flow of aqueous in valved Ahmed GDD's may encourage inflammation resulting in plate encapsulation and hypertensive

phase associated with worse long-term outcomes. Ologen, a biodegradable type I collagen matrix, has shown some success in adults decreasing hypertensive phase and increasing Ahmed success. The authors previously demonstrated in a small cohort that Ologen augmentation of Ahmed glaucoma devices (OAGD) increased success and survival rates compared to Ahmed valve alone. The authors in this retrospective interventional case series present outcomes of a larger group of pediatric patients with longer follow-up who underwent OAGD. Complete success (IOP 5-20 mm Hg without glaucoma meds or additional surgery) was obtained in 77% of eyes with 1- and 3- year survival rates of 82% and 60%. Complete or qualified success (IOP control maintained with or without medications) was achieved in 100% of eyes. No visually devastating complications were encountered. These results differ from what is found in adults. The authors theorize that children may have a short early inflammatory cicatricial response when Ologen has its greatest effect. Limitations include retrospective method, small sample size, and limited follow-up. This study is important to pediatric ophthalmologists who treat refractory glaucoma in offering an augmentation to improve outcomes when treating with GDD's.

Incidence and outcomes of microbial keratitis after cyclophotocoagulation to treat childhood refractory glaucoma.

Sesma G, Ahmad K, AlBakri A, Awad A, Malik R.

J AAPOS. 2022 Jun;26(3):124.e1-124.e5

The authors used a one-armed cohort study with retrospective review to determine the incidence and outcomes of microbial keratitis (MK) following cyclophotocoagulation (CPC) for treatment of refractory childhood glaucoma (CG). In the group of 312 children who underwent CPC in the study the incidence of MK was 1.8% compared to 0.11 cases per 10,000 children in the general population. The mean interval of occurrence was delayed at 4 years after treatment. Streptococcus pneumonia and Staphylococcus epidermidis were the most common bacteria identified in patients with MK. The 3 and 9 o'clock positions were intentionally avoided to avoid nerve damage. Neurotrophic keratitis has been described after CPC. Preserved corneal sensation with pain associated with MK was significantly and positively associated with resolution of MK in this study. Limitations of the study included small sample size and no routine assessment of corneal sensation prior to treatment. This study highlights the occurrence of microbial keratitis and the importance of sparing corneal innervation by avoiding the 3 and 9 o'clock positions of the corneoscleral region during CPC. It is important to include this possible complication in risks discussion prior to treatment to ensure early detection and treatment if MK occurs.

The risk of uveitis due to prostaglandin analogs in pediatric glaucoma.

Bello NR, LaMattina KC, Minor JM, Utz VM, Dong K, Levin AV

J AAPOS. 2022 Jun;26(3):126.e1-126.e5.

Current guidelines caution against use of prostaglandin analogs (PGAs) in patients with uveitic glaucoma because of previous studies showing use of PGAs as a cause of uveitis. Several more recent studies challenge this recommendation. The authors undertook a retrospective review to determine the incidence of uveitis in children with and without a history of uveitis on PGAs. Records were specifically reviewed for the initial occurrence or worsened uveitis during the first year of therapy on PGAs. In total, the authors observed 1,352 child-months of PGA therapy without the development of uveitis attributable to PGA use. Of the 147 eyes, 5 experienced 8 episodes of uveitis during the first year of PGA therapy. In these cases, a prescribed or unprescribed decrease in topical or systemic medication that modulated inflammation took place. Once the immune modulating drugs were reinstated, the uveitis resolved suggesting the lapse in immune modulating drug and not PGA use was the cause of the uveitis recurrence. Limitations of this study were dual center study, retrospective review, and PGAs other than latanoprost were poorly represented. Also, the 1-year period chosen for monitoring was derived from the occurrence in the adult population. This time period for recurrence may not have been generalizable to the pediatric population. The authors propose that their study provides evidence that PGAs are not likely to induce uveitis in children for glaucoma and may also be true for children with a history of prior uveitis. They suggest that further research is needed to determine if use of PGAs causes recurrence of uveitis or affects the ability to taper steroids. This article is important to pediatric ophthalmologists who treat children for glaucoma who may have been avoiding the use of prostaglandins for therapy.

Clinical profile and outcome of early surgery in neonatal-onset glaucoma presenting over a 5-year period. Kaushik S, Dhingra D, Arora A, Singh MP, Kaur S, Joshi G, Snehi S, Gupta G, Pandav SS. *Br J Ophthalmol.* 2022 Mar;106(3):368-375.

This prospective cohort study examined the frequency of neonatal-onset glaucoma (NOG) encountered in a tertiary care glaucoma facility in India, their underlying diseases, and outcomes at least 1 year following early surgery. Babies who presented after 3 months of age were excluded, even if the history suggested NOG, to remove the bias of delayed surgery, as well as those who did not complete at least 1 year of follow-up. Out of 457 new patients with childhood glaucoma who presented to the clinic during the 5 year study period, 84 infants had a history of onset at birth (18.4%), and 53 babies met the inclusion criteria (77.3% with bilateral disease). The most common diagnosis was PCG in 35 infants (66%), while 8 had congenital ectropion uveae, 3 babies had congenital rubella, and the rest were a mix of Peter's anomaly and axenfeld reiger. Combined trabeculotomy-trabeculectomy (CTT) with mitomycin-C was the most commonly performed procedure (66 of 94 eyes (70 %)). Goniotomy was done in nine eyes (9.6%). Additional glaucoma surgery for IOP control was required in 43 of the 94 eyes (45.7%). The mean follow-up period was 33±18.4 months (95%CI 29.2 to 36.7 months). The outcome was significantly better in the PCG cohort, and Peters Anomaly eyes fared the worst. Optical penetrating keratoplasty was done in 16 eyes, (all of which failed) and 3 babies required lensectomy for cataracts in addition to glaucoma surgery. The best visual outcome was in the PCG group without keratoplasty (58 eyes), in which 28.3% had good vision (better than LOGMAR 0.5). While the authors conclude that early detection and intervention for NOG is a child's best chance at obtaining useful vision, the study reminds us that NOG is a severe disease requiring multiple surgeries and follow-up visits and continues to have a guarded prognosis.

Minimally invasive glaucoma surgery in childhood glaucoma.

Go MS, Freedman SF.

*Curr Opin Ophthalmol.* Mar 1 2022;33(2):91-96.

This is a comprehensive review of published case series, cohorts, and case reports on the use of minimally invasive glaucoma surgery (MIGS) on childhood glaucoma. The authors review the data on circumferential ab interno trabeculotomy (GATT and Trab360), partial ab interno trabeculotomy [ Kahoooh Dual blade (KDB) and trabectome], Xen Gel Stent, and other MIGS [endocyclophotocoagulation(ECP)]. Most published experience has been with GATT and Trab 360, which suggest similar efficacy and safety as circumferential ab externo trabeculotomy. A retrospective consecutive case series of children with PCG compared GATT using the iTrack vs. ab externo microcatheter assisted trabeculotomy. 89% in GATT and 73% in MAT achieved the definition of complete surgical success at 12 months. A multicenter retrospective case series evaluated the use of Trab360 and reported similar success. There was poor success of Trab360 in cases of nonacquired systemic syndrome and nonacquired ocular anomalies. However, their use may be more challenging in eyes with indistinct landmarks, altered angle anatomy, hazier corneas, and lower scleral rigidity. Postoperative data on KDB and trabectome suggest limited surgical success, and data is limited. Xen Gel Stent implantation appears to be more difficult in children; thus, the ab externo approach may be preferred to ensure subconjunctival placement; long-term complications and outcomes are unknown. Data on other MIGS such as ECP is limited, and surgeons should exercise caution due to reported complications such as retinal detachments, loss of vision, and chronic hypotony. This comprehensive review sheds light on the current published data and helps surgeons understand the role of MIGS in the treatment of childhood glaucoma.

Juvenile open angle glaucoma: current diagnosis and management.

Ciociola EC, Klifto MR.

*Curr Opin Ophthalmol.* Mar 1 2022;33(2):97-102.

This is a review of new research on the epidemiology, genetics, pathophysiology, and surgical and medical treatment of JOAG from the last two years. On average, the diagnosis was 10-12 years, slightly more prevalent in males, and the majority of patients have bilateral involvement. A large study classified JOAG in 4 subgroups: 1) normal appearing irides and angles with low mean IOP, 2) earliest age and featureless angle, 3) high IOP, high iris insertion or prominent iris processes, 4) abnormal iris feature with high IOP. Another study reported that myopes with at least -1.00 were 18 times more likely to glaucoma progression compared with subjects with milder or no myopia. JOAG was found to be strongly associated with lesser vascular density, given the large IOP fluctuations. Genetically, it has been associated with



CPAMD8, MYOC, and CYP1B1. A study suggested that genetic screening for MYOC should be targeted toward cases with familial rather than sporadically. JOAG is often refractory to medical treatment alone, and selective laser trabeculoplasty was found to significantly lower IOP and reduce the need for further medications or surgery in 43% of eyes at 12 months of follow-up. However, eventually, JOAG patients require surgical intervention. A cohort suggests that tube shunt surgeries may be preferable to trabeculectomy in JOAG, given the likelihood of fibrosis in younger patients and the risk of using antimetabolites. MIGS have surged as an alternative, and GATT has been reported successful in JOAG. Success was reported in 81% at 18 months. Another study found that 360-degree catheter trabeculotomy was successful in 100%, 270-360 degrees was 67%, and less than 180 degrees was 50%. This study highlights the importance of earlier diagnosis as many of these patients present with advanced glaucoma, and the majority will require surgical intervention and topical adjuvant therapy.

Use of a Novel Microshunt in Refractory Childhood Glaucoma: Initial Experience in a Compassionate Use/Early Access Cohort.

Brandt JD.

American Journal of Ophthalmology. 2022 Jul 1;239:223-9.

Adult glaucoma specialists have access to an arsenal of so-called minimally invasive glaucoma surgery (MIGS) devices. While data for these devices in adults with glaucoma is growing, evidence for their use in children is extremely limited. The goal of this paper was to evaluate the efficacy of a newer device, a novel polymer-based microshunt (Preserflo) in refractory childhood glaucoma. This was a prospective single center case series of 12 eyes of 12 children with refractory glaucoma who underwent shunt placement under an FDA compassionate use investigational device exemption. The device is implanted following a mitomycin C injection and delivered in an ab externo fashion. The device creates a pathway between the anterior chamber and sub-Tenon's space. The author reports good results with a low complication rate (though taken in the context of a small n). Of the 12 eyes, 3 failed at 1, 3, and 6 months. In the remaining eyes that did not fail, 2 required medications for IOP control and the remainder were managed on no medications. While this is a small case series, it offers the first look into the role of a novel microshunt in the management of refractory childhood glaucoma.

A prospective study of intraocular pressure spike and failure after gonioscopy-assisted transluminal trabeculotomy in juvenile open-angle glaucoma: A prospective study of GATT in JOAG.

Shi Y, Wang H, Oatts JT, Xin C, Yin P, Zhang L, Tian J, Zhang Y, Cao K, Han Y, Wang N.

American Journal of Ophthalmology. 2022 Apr 1;236:79-88.

Gonioscopy-assisted transluminal trabeculotomy (GATT) is being used increasingly to treat juvenile open-angle glaucoma (JOAG). Two important post-operative scenarios include transient intraocular pressure (IOP) elevation and longer-term surgical failure. The mechanism and risk factors behind each of these are not clearly defined. The goal of this prospective, interventional case series was to evaluate risk factors for surgical failure in children with JOAG undergoing GATT. Success was defined as IOP less than 22 mmHg with at least 20% reduction from pre-operative IOP. The study included 70 eyes of 70 children with JOAG. The authors found a very high incidence of post-operative IOP spike (74%) which was likely explained by closure of ciliary body clefts or effusions (as imaged on AS-OCT). At 1 year, success rates were 74% (no medications) and 91% (medications). There was an association between a long post-operative IOP spike and surgical failure as well as older age at time of surgery. While this single center study may not be generalizable to all populations, the authors demonstrate the mechanism behind post-GATT IOP elevation and identify risk factors for failure which may help surgeons in pre-operative discussions with patients with JOAG.

Decision Tree Algorithm– Based Prediction of Vulnerability to Depressive and Anxiety Symptoms in Caregivers of Children With Glaucoma.

Wy S, Choe S, Lee YJ, Bak E, Jang M, Lee SC, Ha A, Jeoung JW, Park KH, Kim YK.

American Journal of Ophthalmology. 2022 Jul 1;239:90-7.

Childhood glaucoma, like many other potentially blinding conditions in childhood, is a chronic condition which can be associated with mental health challenges including depression and anxiety. In addition to the child, the caregivers of the child may also suffer from these consequences. The goal of this cross-sectional study was to determine the incidence of depressive and anxious symptoms in caregivers of

children with glaucoma and use this data to inform a decision tree model. This study included the administration of two survey tools to parents of children with glaucoma: the Patient Health Questionnaire (PHQ-9) and the Generalized Anxiety Disorder (GAD-7) Assessment. Parents were divided into 3 groups based on whether their child had primary childhood glaucoma, secondary childhood glaucoma, or glaucoma suspect. The authors found no difference in survey responses between the 3 groups. The authors propose risk factors which may predict mental illness in caregivers including more than 2 glaucoma surgeries and visual acuity worse than logMAR 0.4 in the better seeing eye. It may be challenging to predict which caregivers are susceptible to mental illness, but this preliminary study sheds insight into patient factors which may contribute to an increased risk.

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## 15. REFRACTIVE SURGERY

None in the last 6 months

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Developmental Improvement in Children With Intellectual Disability After Photorefractive Keratectomy for Severe Isoametropia.

Paysse EA, Kong L, Achim C, Weikert MP, Whitlow BT, Romany G, Coats DK.

American Journal of Ophthalmology. 2022 Mar 1;235:15-23.

Refractive surgery in children is controversial due to unclear data about long-term outcomes and the unpredictability associated with performing refractive surgery on an eye expected to undergo age-related changes in keratometry and refraction. Some have proposed refractive surgery as a good option for children with intellectual disability who also have severe anisometropia, a risk factor for amblyopia and irreversible vision loss. This prospective interventional case series of 16 children aged 2-8 years aimed to describe outcomes of photorefractive keratectomy (PRK) with a specific focus on developmental improvement. The primary outcome of the study was the developmental quotient (DQ), a ratio of the subject's developmental age divided by the subject's chronological age. One year following PRK, the authors report improvement in the DQ in all domains measured including receptive and expressive communication, written communication, interpersonal skills, and coping. This study is a small case series, but provides important information for a rare treatment for a unique patient population. The authors argue that PRK should be considered in intellectually disabled children not only to improve vision, but also to possibly improve development and quality of life for patients and families.

## 16. GENETICS

Longitudinal Changes in Vision and Retinal Morphology in Wolfram Syndrome.

O'bryhim BE, Samara A, Chen L, Hershey T, Tychsen L, Hoekel J. American journal of ophthalmology. 2022 Nov 1;243:10-8.

Wolfram syndrome (WFS, OMIM #222300), or DIDMOAD, is a rare monogenetic syndrome that consists of diabetes insipidus (DI), diabetes mellitus (DM), optic nerve atrophy (OA), and sensorineural deafness (D). The goal of this single-center, cohort study is to report long-term ophthalmic findings in Wolfram syndrome. A total of 38 participants were studied, who underwent a complete ophthalmic examination as well as optical coherence tomography imaging of the macula and nerve on an annual basis. Participants completed a mean of 6.44 years of follow-up (range 2-10 years). Visual acuity declined over time in all participants, with a mean slope of 0.059 logMAR/y (95% CI = 0.07-0.05 logMAR/y), although nearly 25% of participants experienced more rapid visual decline. RNFL thickness decreased in superior, inferior, and nasal quadrants ( $\beta = -0.5 \mu\text{m}/\text{y}$ ,  $-0.98 \mu\text{m}/\text{y}$ ,  $-0.28 \mu\text{m}/\text{y}$ , respectively). OPL lamination was noted in 3 study participants, 2 of whom had autosomal dominant mutations. Our study describes the longest and largest natural history study of visual acuity decline and retinal morphometry in Wolfram syndrome to date. Results suggest that there are slower and faster progressing subgroups and that OPL lamination is present in some individuals with this disease.

Retinal Development in Infants and Young Children With Albinism: Evidence for Plasticity in Early Childhood.

Lee H, Purohit R, Sheth V, Maconachie G, Tu Z, Thomas MG, Pilat A, McLean RJ, Proudlock FA, Gottlob I.

American journal of ophthalmology. 2023 Jan 1;245:202-11.

Albinism is a group of disorders of melanin biosynthesis characterized by cutaneous and/or ocular hypopigmentation, nystagmus, strabismus, refractive errors, foveal hypoplasia, and optic nerve misrouting. The goal of this prospective, comparative cohort optical coherence tomography study is to investigate the time course of foveal development after birth in infants with albinism. Thirty-six children with albinism were recruited. All participants were between 0 and 6 years of age and were seen at Leicester Royal Infirmary. A total of 181 mixed cross-sectional and longitudinal optical coherence tomography examinations were obtained, which were analyzed for differences in retinal development in comparison to 297 cross-sectional control examinations. Normal retinal development involves migration of the inner retinal layers (IRLs) away from the fovea, migration of the cone photoreceptors into the fovea, and elongation of the outer retinal layers (ORLs) over time. In contrast to controls where IRL migration from the fovea was almost completed at birth, a significant degree of IRL migration was taking place after birth in albinism, before arresting prematurely at 40 months postmenstrual age (PMA). This resulted in a significantly thicker central macular thickness in albinism ( $\Delta = 83.8 \pm 6.1$ ,  $P < .0001$  at 69 months PMA). There was evidence of ongoing foveal ORL elongation in albinism, although reduced in amplitude compared with control subjects after 21 months PMA ( $\Delta = -17.3 \pm 4.3$ ,  $P < .0001$ ). We have demonstrated evidence of ongoing retinal development in young children with albinism, albeit at a reduced rate and magnitude compared with control subjects. The presence of a period of retinal plasticity in early childhood raises the possibility that treatment modalities, which aim to improve retinal development, could potentially optimize visual function in albinism.

CRB1-Associated Retinal Dystrophies: Genetics, Clinical Characteristics, and Natural History.

Varela MD, Georgiou M, Alswaiti Y, Kabbani J, Fujinami K, Fujinami-Yokokawa Y, Khoda S, Mahroo OA, Robson AG, Webster AR, AlTalishi A. CRB1-Associated Retinal Dystrophies: Genetics, Clinical Characteristics, and Natural History.

American Journal of Ophthalmology. 2023 Feb 1;246:107-21.

The purpose of this multicenter international retrospective cohort study is to analyze the clinical characteristics, natural history, and genetics of CRB1-associated retinal dystrophies. Review of clinical notes, ophthalmic images, and genetic testing results of 104 patients (91 probands) with disease-causing CRB1 variants. The mean age of the cohort at the first visit was  $19.8 \pm 16.1$  (median 15) years, with a mean follow-up of  $9.6 \pm 10$  years. Based on history, imaging, and clinical examination, 26 individuals were diagnosed with retinitis pigmentosa (RP; 25%), 54 with early-onset severe retinal dystrophy / Leber congenital amaurosis (EOSRD/LCA; 52%), and 24 with macular dystrophy (MD; 23%). Severe visual

impairment was most frequent after 40 years of age for patients with RP and after 20 years of age for EOSRD/LCA. Longitudinal analysis revealed a significant difference between baseline and follow-up best-corrected visual acuity in the 3 subcohorts. Macular thickness decreased in most patients with EOSRD/LCA and MD, whereas the majority of patients with RP had increased perifoveal thickness. A subset of individuals with CRB1 variants present with mild, adult-onset RP. EOSRD/LCA phenotype was significantly associated with null variants, and 167\_169 deletion was exclusively present in the MD cohort. The poor OCT lamination may have a degenerative component, as well as being congenital. Disease symmetry and reasonable window for intervention highlight CRB1 retinal dystrophies as a promising target for trials of novel therapeutics.

Three-year results of phase I retinal gene therapy trial for CNGA3-mutated achromatopsia: results of a non randomised controlled trial.

Reichel FF, Michalakis S, Wilhelm B, Zobor D, Muehlfriedel R, Kohl S, Weisschuh N, Sothilingam V, Kuehlewein L, Kahle N, Seitz I.

British Journal of Ophthalmology. 2022 Nov 1;106(11):1567-72.

Achromatopsia (ACHM) is a well-characterized form of IRD affecting the cone photoreceptors and daylight vision. Mutations in CNGA3 and CNGB3 account for around 80% of all ACHM cases and cause disease following an autosomal recessive inheritance pattern, making it good targets for gene replacement strategies. The aim of this study is to determine long-term safety and efficacy outcomes of a subretinal gene therapy for CNGA3-associated achromatopsia. We present data from an open-label, nonrandomised controlled trial (NCT02610582). Nine patients were treated in three escalating dose groups with subretinal AAV8.CNGA3 gene therapy between November 2015 and October 2016. After the first year, patients were seen on a yearly basis. Safety assessment constituted the primary endpoint. On a secondary level, multiple functional tests were carried out to determine efficacy of the therapy. No adverse or serious adverse events deemed related to the study drug occurred after year 1. Safety of the therapy, as the primary endpoint of this trial, can, therefore, be confirmed. The functional benefits that were noted in the treated eye at year 1 were persistent throughout the following visits at years 2 and 3. While functional improvement in the treated eye reached statistical significance for some secondary endpoints, for most endpoints, this was not the case when the treated eye was compared with the untreated fellow eye. The results demonstrate a very good safety profile of the therapy even at the highest dose administered. The small sample size limits the statistical power of efficacy analyses. However, trial results inform on the most promising design and endpoints for future clinical trials. Such trials have to determine whether treatment of younger patients results in greater functional gains by avoiding amblyopia as a potential limiting factor.

Fibrillin-1 gene mutations in a Chinese cohort with congenital ectopia lentis: spectrum and genotype–phenotype analysis.

Chen Z, Chen T, Zhang M, Chen J, Deng M, Zheng J, Lan LN, Jiang Y.

British Journal of Ophthalmology. 2022 Dec 1;106(12):1655-61.

The fibrillin-1 (FBN1) gene encodes a 350 kDa cysteine-rich glycoprotein that serves as the principal structural component of microfibrils, which contribute to the force-bearing capacity of connective tissue such as blood vessels, ligaments and bones. The goal of this study is to identify the mutation spectrum and genotype–phenotype correlations of fibrillin-1 mutations in a Chinese cohort with congenital ectopia lentis (EL). Patients clinically suspected of congenital zonulopathy were screened using panel-based next-generation sequencing followed by multiplex ligation-dependent probe amplification. All the probands were subjected to thorough ocular examinations. Molecular and clinical data were integrated in pursuit of genotype–phenotype correlation. A total of 131 probands of FBN1 mutations from unrelated families were recruited. Around 65% of the probands were children younger than 9 years old. Overall, 110 distinct FBN1 mutations were identified, including 39 novel ones. The most at-risk regions were exons 13, 2, 6, 15, 24 and 33 in descending order of mutation frequency. The most prevalent mutation was c.184C>T (seven, 5.34%) in the coding sequence and c.5788+5G>A (three, 2.29%) in introns. Missense mutations were the most frequent type (103, 78.63%); half of which were distributed in the N-terminal regions (53, 51.46%). The majority of missense mutations were detected in one of the calcium-binding epidermal growth factor-like domains (62, 60.19%), and 39 (62.90%) of them were substitutions of conserved cysteine residues. Microspherophakia (MSP) was found in 15 patients (11.45%). Mutations in the middle region (exons 22–42), especially exon 26, had higher risks of combined MSP (OR, 5.51 (95%

CI 1.364 to 22.274),  $p=0.017$ ). This study extended the knowledge of the FBN1 mutation spectrum and provided novel insights into its clinical correlation regarding EL and MSP in the Chinese population.

CYP1B1 and MYOC variants in neonatal-onset versus infantile-onset primary congenital glaucoma. Kaushik S, Luthra-Guptasarma M, Prasher D, Dhingra D, Singh N, Kumar A, Sharma SP, Kaur H, Snehi S, Thattaruthody F, Pandav SS.

British Journal of Ophthalmology. 2023 Feb 1;107(2):227-33.

Primary congenital glaucoma (PCG) is a potentially blinding disease, mainly presenting as a developmental abnormality in the trabecular meshwork (TM), resulting in raised intraocular pressure (IOP). The purpose of this manuscript is to compare CYP1B1 and MYOC variants in a cohort of neonatal-onset (NO) and infantile-onset (IO) primary congenital glaucoma (PCG). This prospective observational study included 43 infants with PCG (14 NO and 29 IO) presenting between January 2017 and January 2019 with a minimum 1-year follow-up. CYP1B1 and MYOC genes were screened using Sanger sequencing with in-silico analysis of the variants using Polymorphism Phenotyping v.2 and Protein Variation Effect Analyser platforms. Allelic frequency was estimated using Genome Aggregation Database (gnomAd). Disease presentation and outcome were correlated to the genetic variants in both groups. Babies with CYP1B1 mutations had more severe disease at presentation and worse outcomes. Six of 14 (42.8%) NO glaucoma and 5 of 29 (17.2%) IO harboured CYP1B1 mutations. Five of six babies in the NO group and three of five in the IO group harboured the variant c.1169G>A, [p.R390H]. They required more surgeries and had a poorer outcome. On in-silico analysis c.1169G>A, [p.R390H] scored very likely pathogenic. Two patients in the IO group who had the c.1294C>G, [p.L432V] variant had a good outcome. Five of 14 NO-PCG and 8 of 29 IO-PCG harboured the variant c.227G>A, [p.R76K] in the MYOC gene, which was scored benign by in-silico analysis, and was also found in 2 of 15 normal controls. Patients with CYP1B1 pathogenic variants had a poorer outcome than those without. We found more NO PCG babies with CYP1B1 mutations compared with IO PCG. This may be one of the reasons for NO PCG having a poorer prognosis compared with IO PCG.

Charles Bonnet syndrome in patients with Stargardt disease: prevalence and risk factors.

Dhooge PP, Teunisse RJ, Liefers B, Lambertus S, Bax NM, Hoyng CB, Cruysberg JR, Klevering BJ.

British Journal of Ophthalmology. 2023 Feb 1;107(2):248-53.

Charles Bonnet syndrome (CBS) is characterised by visual hallucinations in patients with vision impairment in the absence of an alternative secondary cause (eg, psychopathology, neurological disease or certain medications). Eighty-three patients with Stargardt disease were screened for CBS. They underwent a full eye examination. All patients completed the social functioning domain of the 36-Item Short Form Health Survey questionnaire. Participants suspected of CBS were interviewed to further evaluate their visual hallucinations. CBS prevalence was 8.4%. Six out of seven patients with CBS were women. CBS was not associated with age ( $p=0.279$ , Mann-Whitney). Patients with CBS had a significant lower social functioning score ( $p<0.05$ , Mann-Whitney). All seven patients with CBS were in the category of vision impairment (visual acuity  $<6/12$ , but  $\geq 3/60$ ). Moreover, first hallucinations manifested after a drop in visual acuity. The retinal atrophic area of the worst eye tended to be lower in the CBS group (range 0.11–9.86 mm<sup>2</sup>) as compared with controls (range 0–180 mm<sup>2</sup>). There was no relation between the position of the scotoma and the location of the visual hallucinations. The relative high CBS prevalence in STGD1 suggests that CBS may be more prevalent in younger ophthalmic patients than currently presumed. In this specific group of patients, we established social isolation and acquired vision impairment as risk factors for CBS. There was a female preponderance among patients with CBS. Age and retinal pigment epithelium atrophy were not identified as significant risk factors. We should actively diagnose CBS in patients of any age who fulfil the criteria for the category vision impairment, especially in cases where social isolation is suspected.

MACULAR MICROVASCULATURE IN X-LINKED RETINOSCHISIS: Optical Coherence Tomography and Optical Coherence Tomography Angiography Study.

Kwon HJ, Kim YN, Min CH, Kim YJ, Lee J, Lee JY, Yoon YH.

Retina. 2022 Oct 1;42(10):1939-49.

X-linked retinoschisis (XLRS) is a hereditary early onset degenerative retinal disease characterized by radial pattern of foveal schisis and deterioration in visual acuity. Abnormal expression of retinoschisin,

which is caused by RS1 gene mutation, is the known causative of the disease. The study aimed to evaluate the macular microvasculature of X-linked retinoschisis (XLRS) and identify correlations between vascular changes, structural changes, and functional outcome. Genetically confirmed XLRS patients and healthy control subjects underwent complete ophthalmic examination, dilated fundoscopic examination, optical coherence tomography, and optical coherence tomography angiography. A total of 17 eyes of 9 XLRS patients and 22 eyes of 11 control subjects were examined from July 2018 to August 2020. Flow density in the deep capillary plexus at foveal and parafoveal area decreased in XLRS patients compared with control subjects ( $P = 0.014$  and  $0.001$ , respectively), whereas foveal avascular zone area and perimeter remarkably increased ( $P = 0.015$  and  $0.001$ , respectively). Although outer and total retinal layers were significantly thicker in XLRS, inner retinal layer was thinner with reduced photoreceptor layer thickness and shortened photoreceptor outer segment length ( $P < 0.001$  and  $P < 0.001$ , respectively). Foveal flow loss in deep capillary plexus, foveal avascular zone enlargement, thinner inner retina and photoreceptor layer thickness, and shortened photoreceptor outer segment length correlated with best-corrected visual acuity. X-linked retinoschisis eyes exhibit decreased flow density in the deep capillary plexus and variable foveal avascular zone with enlarged perimeter. Structural deterioration of the photoreceptor best reflects the degenerative changes, whereas microvascular alteration shows considerable correlation with functional outcome in XLRS.

Lrp5 biallelic mutations cause a higher incidence of severe phenotype compared with Lrp5 monoallelic mutation.

Chen C, Zhang X, Peng X, Hu F, Cheng Y, Zhao P.  
Retina. 2022 Oct 1;42(10):1958-64.

Familial exudative vitreoretinopathy (FEVR) is a hereditary vitreoretinal disorder characterized by the absence of peripheral retinal vessels. The goal of this study is to analyze the clinical features of *LRP5* gene mutation-related familial exudative vitreoretinopathy and explore the potential phenotype-genotype correlation on *LRP5* gene. Eighty-seven familial exudative vitreoretinopathy (FEVR) families with *LRP5* mutations were selected from 722 FEVR patients, which were divided into 2 groups, including 22 autosomal-recessive FEVR (ar-FEVR) families and 65 autosomal-dominant FEVR (ad-FEVR) families. No significant difference between the *LRP5* null mutation subgroup and the *LRP5* missense mutation subgroup was observed in the proportion of FEVR stage and the ratio of ocular involvement. Instead, a significant difference between the *LRP5* ar-FEVR subgroup and the *LRP5* ad-FEVR subgroup was observed in the proportion of FEVR stage and the ratio of binocularly severe phenotype. The probands with *LRP5* gene recessive mutation showed a higher incidence of severe phenotype. Moreover, the ratio of binocularly severe patients in ar-FEVR was nearly 3.5 times higher than that in ad-FEVR. The severity of phenotype was more likely to be related to the synergistic effect of the variants.

Topical Carbonic Anhydrase Inhibitors in the Long-Term Treatment of Juvenile X-Linked Retinoschisis.  
Schmitt MA, Wang K, DeBenedictis MJ, Traboulsi EI.  
Retina. 2022 Nov 1;42(11):2176-83.

Juvenile X-linked retinoschisis (XLRS; OMIM #312700), one of the more common inherited retinal dystrophies in males, has an estimated incidence between 1 in 5,000 and 1 in 25,000 in the male population. The goal of this study is to describe the response to long-term topical dorzolamide treatment in patients with juvenile X-linked retinoschisis and cystic-like foveal lesions. This was a retrospective interventional case series that included 18 eyes of 10 patients with genetically confirmed juvenile X-linked retinoschisis examined at the Cleveland Clinic Cole Eye Institute, a tertiary referral center, between 2005 and 2021. Patients were treated with topical 2% dorzolamide two to three times daily in both eyes. Two eyes were excluded because of retinal detachment. The mean follow-up was 8.38 years (SD, 3.41 years). The mean baseline and final central subfield thickness was  $429.88 \mu\text{m}$  (SD,  $143.36 \mu\text{m}$ ) and  $372.28 \mu\text{m}$ , respectively (SD,  $147.13 \mu\text{m}$ ,  $P = 0.10$ ). The mean baseline and final logarithm of minimum angle of resolution visual acuity was 0.45 (SD, 0.17) and 0.34, respectively (SD, 0.22,  $P < 0.01$ ). None of the patients experienced any side effects from topical dorzolamide. The study data support previous reports of improved visual acuity in X-linked retinoschisis patients on topical dorzolamide treatment. This is the longest follow-up for a series of juvenile X-linked retinoschisis patients treated with a topical carbonic anhydrase inhibitor to date. A large, prospective, randomized clinical trial is needed to provide stronger evidence regarding the efficacy of topical carbonic anhydrase inhibitors in juvenile X-linked retinoschisis.

## TRANSPLANTATION OF SUBRETINAL STEM CELL-DERIVED RETINAL PIGMENT EPITHELIUM FOR STARGARDT'S DISEASE: A PHASE I CLINICAL TRIAL.

Fernandes MR, Lojudice FH, Ribeiro LZ, da Cruz NF, Polizelli MU, Cristovam PC, Innocenti F, Morimoto L, Magalhães Jr O, Sallum JM, Sogayar MC.

RETINA. 2022 Aug 17:10-97.

Stargardt disease, the most prevalent retinal dystrophy in young populations, is an autosomal recessive condition caused by ABCA4 gene mutations, which encodes a transmembrane protein expressed specifically in the retinal photoreceptors. In this prospective, Phase I clinical trial, human embryonic stem cell retinal pigment epithelial cells in suspension were injected into the subretinal space in eyes with the worse best-corrected visual acuity (BCVA). After vitrectomy/posterior hyaloid removal, a partial retinal detachment was created and the human embryonic stem cell retinal pigment epithelial cells were administered. Phacoemulsification with intraocular lens implantation was performed in eyes with lens opacity. All procedures were optical coherence tomography-guided. The 12-month follow-up included retinal imaging, optical coherence tomography, visual field/electrophysiologic testing, and systemic evaluation. The main outcome was the absence of ocular/systemic inflammation or rejection, tumor formation, or toxicity during follow-up. The mean baseline BCVAs in the phacoemulsification and no phacoemulsification groups were similar ( $1.950 \pm 0.446$  and  $1.575 \pm 0.303$ , respectively). One year postoperatively, treated eyes showed a nonsignificant increase in BCVA. No adverse effects occurred during follow-up. Intraoperative optical coherence tomography was important for guiding all procedures. This surgical procedure was feasible and safe without cellular migration, rejection, inflammation, or development of ocular or systemic tumors during follow-up.

## Symptomatic Early-onset X-linked Retinoschisis: Clinical Presentation and Outcomes.

Piquin G, Abdelmassih Y, Martin G, Edelson C, Metge F, Caputo G, Chapron T.

RETINA. 2022 Aug 17:10-97.

X-linked retinoschisis (XLRS) is one of the most common pediatric retinal dystrophies with a worldwide prevalence between 1/5,000 and 1/20,000. In this retrospective consecutive case series, children diagnosed with symptomatic X-linked retinoschisis younger than 2 years were included. Seven patients (14 eyes) with a mean age of  $17.14 \pm 6.28$  months were included. Strabismus was the most common presenting symptom (6 of 7 patients, 86%). Clinical signs at the first diagnosis included peripheral retinoschisis in 13 eyes (13/14, 93%), of which 5 (5/13, 38%) were bullous, vitreous hemorrhage in 3 eyes (3/14, 21%), and retinal detachment in 3 eyes (3/14, 21%). The macula was involved in all eyes: It was detached in 2 eyes (2/14, 14%) and involved in the peripheral schisis in 4 eyes (4/14, 29%). In all remaining eyes, optical coherence tomography revealed foveoschisis. Six eyes (6/14, 42%) received surgery. At the last follow-up, visual acuity, when available, ranged from no light perception to 20/40, and no children had persistent retinal detachment. Children with early-onset X-linked retinoschisis had severe forms. All children had peripheral retinoschisis which was often bullous and extended to the macula. Diagnosis is often clinical but handheld optical coherence tomography can be helpful in atypical forms. Complications requiring surgical management are frequent.

## Mutations in SCN11A cause orofacioidigital syndrome due to minor intron splicing defects affecting primary cilia.

Iturrate A, Rivera-Barahona A, Flores CL, Otaify GA, Elhossini R, Perez-Sanz ML, Nevado J, Tenorio-Castano J, Triviño JC, Garcia-Gonzalo FR, Piceci-Sparascio F.

The American Journal of Human Genetics. 2022 Oct 6;109(10):1828-49.

Orofacioidigital syndrome (OFD) is a genetically heterogeneous ciliopathy characterized by anomalies of the oral cavity, face, and digits. We describe individuals with OFD from three unrelated families having bi-allelic loss-of-function variants in SCN11A as the cause of their condition. SCN11A encodes a protein recently shown to be a component of the human minor spliceosome. However, so far the effect of loss of SCN11A function on human cells had not been assessed. Using a comparative transcriptome analysis between fibroblasts derived from an OFD-affected individual harboring SCN11A mutations and control fibroblasts, we identified a set of genes with defective minor intron (U12) processing in the fibroblasts of the affected subject. These results were reproduced in SCN11A knockout hTERT RPE-1 (RPE-1) cells engineered by CRISPR-Cas9-mediated editing and in SCN11A siRNA-treated RPE-1 cultures. Notably, expression of TMEM107 and FAM92A encoding primary cilia and basal body proteins, respectively, and



that of DERL2, ZC3H8, and C17orf75, were severely reduced in SCN1M1-deficient cells. Primary fibroblasts containing SCN1M1 mutations, as well as SCN1M1 knockout and SCN1M1 knockdown RPE-1 cells, were also found with abnormally elongated cilia. Conversely, cilia length and expression of SCN1M1-regulated genes were restored in SCN1M1-deficient fibroblasts following reintroduction of SCN1M1 via retroviral delivery. Additionally, functional analysis in SCN1M1-retrotransduced fibroblasts showed that SCN1M1 is a positive mediator of Hedgehog (Hh) signaling. Our findings demonstrate that defective U12 intron splicing can lead to a typical ciliopathy such as OFD and reveal that primary cilia length and Hh signaling are regulated by the minor spliceosome through SCN1M1 activity.

Individuals with heterozygous variants in the Wnt-signalling pathway gene FZD5 delineate a phenotype characterized by isolated coloboma and variable expressivity.

Holt R, Goudie D, Verde AD, Gardham A, Ramond F, Putoux A, Sarkar A, Clowes V, Clayton-Smith J, Banka S, Cortazar Galarza L.

Ophthalmic Genetics. 2022 Nov 2;43(6):809-16.

Anophthalmia, microphthalmia and coloboma are a genetically heterogeneous spectrum of developmental eye disorders. Recently, variants in the Wnt-pathway gene Frizzled Class Receptor 5 (FZD5) have been identified in individuals with coloboma and rarely microphthalmia, sometimes with additional phenotypes and variable penetrance. This report presents eight new families with FZD5 variants and ocular coloboma. Three individuals presented with additional syndromic features, two explicable by additional variants in other genes (SLC12A2 and DDX3X). In two families initially showing incomplete penetrance, re-examination of apparently unaffected carrier individuals revealed subtle ocular colobomatous phenotypes. Finally, we report two families with microphthalmia in addition to coloboma, representing the second and third reported cases of this phenotype in conjunction with FZD5 variants. These findings indicate FZD5 variants are typically associated with isolated ocular coloboma, occasionally microphthalmia, and that extraocular phenotypes are likely to be explained by other gene alterations.

Fleck-like lesions in CEP290-associated leber congenital amaurosis: a case series.

Aleman TS, O'Neil EC, Uyhazi KE, Parchinski KM, Santos AJ, Weber ML, Colclough SP, Billek AS, Zhu X, Leroy BP, Bedoukian EC.

Ophthalmic Genetics. 2022 Dec 5:1-0.

Leber Congenital Amaurosis (LCA) describes an infrequent (prevalence 1:30 000–1:80 000) genetically and phenotypically heterogeneous group of conditions characterized by a severe retina-wide, progressive photoreceptor degeneration resulting in profound vision loss during the first year of life, with later childhood presentations overlapping with the term of Early-Onset and Severe Retinal Dystrophies or Degenerations (EOSRD). This is a retrospective review of records of five patients with CEP290-LCA. Patients had comprehensive ophthalmic evaluations. Visual function was assessed with full-field electroretinograms (ffERGs) and full-field sensitivity testing (FST). Multimodal imaging was performed with spectral domain optical coherence tomography (SD-OCT), fundus autofluorescence (FAF) with short- (SW) and near-infrared (NIR) excitation wavelengths. All patients showed relative structural preservation of the foveal and near midperipheral retina separated by a pericentral area of photoreceptor loss. Yellow-white, fleck-like lesions in an annular distribution around the near midperiphery co-localized with hyperreflective lesions on SD-OCT. The lesions located between the inner segment ellipsoid signal and the apical retinal pigment epithelium (RPE). The inner retina was normal. Longitudinal observations in one of the patients indicates the abnormalities may represent an intermediate stage in the degenerative process between the near normal appearing retina previously documented in young CEP290-LCA patients and the pigmentary retinopathy observed along the same region in older individuals. We speculate that fleck-like lesions in CEP290-LCA correspond to malformed, rudimentary or degenerated, including shed, photoreceptor outer segments. The topography and possible origin of the abnormalities may inform the planning of evolving genetic therapies for this disease.

Effects of duration and number of symptoms on vision-related anxiety in patients with Inherited Retinal Diseases.

Popova LT, Abuzaitoun RO, Abalem MF, Andrews CA, Mondul AM, Lacy GD, Musch DC, Jayasundera KT.

Ophthalmic Genetics. 2022 Dec 2:1-8.

Patients with Inherited Retinal Diseases (IRDs) are at increased risk for vision-related anxiety due to progressive and irreversible vision loss. This was a single-center, retrospective cross-sectional study at a large academic center. 128 adults with an IRD and without other significant eye conditions were recruited between December 2016 and March 2020. Participants were asked about the duration and number of symptoms they had in the following vision domains: reading, contrast vision, color vision, glare/light sensitivity, night vision, and peripheral vision. The outcomes of interest were the two domains of the Michigan Vision-Related Anxiety Questionnaire (MVAQ), rod- and cone-function related anxiety. We conducted an adjusted analysis to isolate the independent effect of duration and number of symptoms on vision-related anxiety. Of 126 participants had complete data, 62 (49%) were female and 64 (51%) were male, with an average age of 49 years (range: 18–87). Patients with duration of symptoms for greater than 25 years had an adjusted anxiety theta that was one-half standard deviations lower than patients with symptoms for less time. Patients with higher number of symptoms had higher anxiety theta after adjusting for confounding variables ( $p < 0.0001$ ). The number of symptoms but not the duration of symptoms, is an independent risk factor for vision-related anxiety. Patients with more symptoms are at higher risk for vision-related anxiety. Having symptoms for longer than 25 years may reduce this anxiety.

Ocular findings and a comparative study of hair, skin and iris color in Chinese patients with albinism.  
Arcot Sadagopan K, Teng CH, Hui G, Lin DL.

Ophthalmic Genetics. 2022 Nov 2:1-6.

Oculocutaneous albinism (OCA) could be either non-syndromic or syndromic. There are significant challenges in clinically recognizing and differentiating Hermansky-Pudlak syndrome (HPS) from non-syndromic OCA. A total of 63 patients were evaluated. Forty-five patients had non-syndromic OCA (11 OCA1B, 24 OCA2, 9 OCA4, and 1 OCA6), 5 patients had OA and 13 patients had HPS. All 3 BLOC-related HPS categories were seen (1 with BLOC1, 7 with BLOC-2 and 5 with BLOC-3 related HPS). All patients with OA were hyperopic, had darker fundus pigmentation, but had poor foveal development. All HPS patients had lighter fundus pigmentation. The degree of fundus pigmentation correlated positively with the iris pigmentation and also with the foveal development only in OCA2. Careful observation of the phenotype by comparison of the skin, hair, iris colour, with the degree of fundus pigmentation and foveal development may help clinically differentiate HPS from OCA patients of Chinese ethnicity even in the absence of any bleeding tendency.

KCTD1 and Scalp-Ear-Nipple ('Finlay-Marks') syndrome may be associated with myopia and Thin basement membrane nephropathy through an effect on the collagen IV  $\alpha 3$  and  $\alpha 4$  chains.

Wang D, Trevillian P, May S, Diakumis P, Wang Y, Colville D, Bahlo M, Greferath U, Fletcher E, Young B, Mack HG.

Ophthalmic Genetics. 2023 Jan 2;44(1):19-27.

Scalp-Ear-Nipple syndrome is caused by pathogenic KCTD1 variants and characterised by a scalp defect, prominent ears, and rudimentary breasts. We describe here further clinical associations in the eye and kidney. Fifteen affected members from two unrelated families with p.(Ala30Glu) or p.(Pro31Leu) in KCTD1 were examined for ocular and renal abnormalities. Five males and 10 females with a median age of 40 years (range 1–70) with pathogenic variants p.(Ala30Glu) ( $n = 12$ ) or p.(Pro31Leu) ( $n = 3$ ) in KCTD1 were studied. Of the 6 who underwent detailed ophthalmic examination, 5 (83%) had low myopic astigmatism, the mean spherical equivalent of 10 eyes was 2.38D, and one (17%) had hypermetropic astigmatism. One female had a divergent strabismus. Five individuals had renal cysts (5/15, 33%), with renal biopsy in one demonstrating a thinned glomerular basement membrane identical to that seen in Thin basement membrane nephropathy (AD Alport syndrome). In the eye, KCTD1 and its downstream targets, TFAP2, and the collagen IV  $\alpha 3$  and  $\alpha 4$  chains localised to the cornea and near the retinal amacrine cells. In the kidney, all these proteins except TFAP2 were expressed in the podocytes and distal tubules. TFAP2B and COL4A4 knockout mice also had kidney cysts, and COL4A3 and COL4A4 knockout mice had myopia. Individuals with a pathogenic KCTD1 variant may have low myopic astigmatism and represent a further rare genetic cause for a thinned glomerular basement membrane.

Association of Missense Variants in VXS2 With a Peculiar Form of Congenital Stationary Night Blindness Affecting All Bipolar Cells

Vasily M. Smirnov, MD; Mattieu P. Robert, MD, PhD; Christel Condroyer; et al

JAMA Ophthalmol. 2022;140(12):1162-1173

This is a retrospective case series of 3 patients of 140 genetically unsolved CSNB cases, with the goal of identifying an underlying genetic defect. They were diagnosed based on the presence of infantile nystagmus, low visual acuity, myopia, night blindness from birth, an otherwise normal retinal exam, and classic ERG findings. Blood samples from all cases and all available family members were collected for genetic research and whole genome sequencing. After this, 4 candidate genes were identified (ITIH2, PRDM10, VSX2, and BCR). The cohort of 140 genetically unsolved CSNB was then screen for VSX2 variants, and an additional patient was identified who had previously had a negative result on a genetic panel which included all known-to-date CSNB-associated genes. The VSX2 gene mutation was chosen because this variant was absent in population databases, and found in parents consistent with autosomal-recessive inheritance. The VSX2 gene is also associated with microphthalmia with coloboma, cataract, and iris abnormalities. Although only identified in 3 patients from 2 families, patients harboring missense mutations in VSX2 demonstrate a phenotype consistent with CSNB with dysfunctional bipolar cells.

Risk of secondary tumours in patients with non-metastatic and metastatic human retinoblastoma.

Sadeghi R, Pirankuraim H, Javanshir ST, Arabi M, Bereimipour A, Javanshir HT, Mahmoodzadeh H, Nayernia K.

Eye (Lond). 2022 Dec 17. doi: 10.1038/s41433-022-02345-3. Epub ahead of print. PMID: 36528757.

In many cases, dysfunction of the RB1 gene is the leading cause of secondary tumours due to retinoblastoma. This study aimed to evaluate the incidence of other secondary tumours in children with retinoblastoma. 1170 high-expression genes and 960 low-expression genes between non-invasive and invasive retinoblastoma were isolated. After examining the signal pathways, authors observed bladder cancer and small-cell lung cancer in the overexpressed genes and cancers of endometriosis, prostate, non-small cell lung cancer, glioblastoma and renal cell carcinoma in low-expression genes. Based on the P-value index, non-small cell lung cancer, prostate and bladder cancers had the highest risk, and endometriosis cancer showed a lower probability of developing a secondary tumour in patients with retinoblastoma. In addition, the network between proteins also showed us that TP53, CDK2, SRC, MAPK1 proteins with high expression and JUN, HSP90AA1, and UBC proteins with low-expression play a significant role in candidate cancers. Bioinformatics analysis showed that seven cancers are strongly linked to retinoblastoma cancer. More research is needed to understand the best way to care for children who have been treated for retinoblastoma and the need for surveillance.

Stickler syndrome - lessons from a national cohort.

Snead MP, Richards AJ, McNinch AM, Alexander P, Martin H, Nixon TRW, Bale P, Shenker N, Brown S, Blackwell AM, Poulson AV.

Eye (Lond). 2022 Oct;36(10):1966-1972. doi: 10.1038/s41433-021-01776-8. Epub 2021 Oct 5. PMID: 34611315; PMCID: PMC8491173.

The Stickler syndrome is part of the spectrum of inherited vitreoretinopathies. It is the most common cause of retinal detachment in childhood and the most common cause of familial retinal detachment. The Stickler Highly Specialized Service (HSS) has assessed 1673 patients from 785 families over 10 years. Using a combination of accurate phenotyping and molecular genetic analysis, the underlying genetic mutation was identified in over 95% of cases, including those with deep intronic mutations likely to be missed by conventional exome panel analysis and which require whole gene sequencing and supplementary functional analysis to confirm pathogenicity. This article summarises ten selected briefcase histories from the national dataset with key learning points from each, including risk of retinal detachment and recommendation for prophylactic treatment. In contrast to many other blinding retinal conditions, blindness through giant retinal tear detachment, particularly in children, is largely preventable provided these high-risk groups are identified and appropriate evidence-based prophylaxis is offered.

Gene therapy: perspectives from young adults with Leber's congenital amaurosis.

Napier MP, Selvan K, Hayeems RZ, Shuman C, Chitayat D, Sutherland JE, Day MA, Héon E.

Eye (Lond). 2022 Nov;36(11):2088-2093. doi: 10.1038/s41433-021-01763-z. Epub 2021 Sep 16. Erratum in: Eye (Lond). 2022 Feb 25;: PMID: 34531550; PMCID: PMC9581997.

This paper investigates Leber congenital amaurosis (LCA) patients' expectations, decision-making processes and gene therapy-related concerns. Young adults with a clinical diagnosis of LCA were

recruited through the Ocular Genetics Programme at the Hospital for Sick Children. A single investigator (MPN) conducted 30–70 min semi-structured telephone interviews with ten patients and analyzed following the principles of qualitative description. Study participants were aware of ongoing gene therapy research trials and actively sought information regarding advances in ophthalmology and vision restoration. The majority of participants would enrol or were enrolled in a gene-replacement therapy trial, while a minority were ambivalent or would not enrol if provided an opportunity. Participants attributed different values to clinical trials, which influenced their willingness to participate. In this study, the definition of meaningful improvement in vision varied between participants. Most participants wanted to improve their independence through new abilities, including reading text and driving. Intrinsic factors related to coping, adaptation to vision loss and resilience also influenced decision-making. This study highlights the complex factors involved in gene-therapy-related decision-making. It acts as a proponent for adopting patient-centred care strategies when counselling individuals considering gene therapy or clinical trial participation.

Clinical features and genetic spectrum of NMNAT1-associated retinal degeneration.

Yi Z, Li S, Wang S, Xiao X, Sun W, Zhang Q.

Eye (Lond). 2022 Dec;36(12):2279-2285. doi: 10.1038/s41433-021-01853-y. Epub 2021 Nov 26. PMID: 34837036; PMCID: PMC9674661.

The paper systematically analyze the NMNAT1 variant spectrum and frequency, the associated phenotypic characteristics, and potential genotype-phenotype correlations based on the author's data and literature review. 11 NMNAT1 variants, including two novel variants, detected in 8 families in their cohort and 91 families reported in the literature were analyzed. Among 125 patients, 92.9% showed onset of disease in the first year after birth, and 89.0% of patients showed visual acuity of 0.05 or lower. All of the 39 patients with fundus photos available presented disciform macular atrophy with generalized tapetoretinal dystrophy. Most (54/80, 67.5%) of causative NMNAT1 variants were missense. The most frequent variants in Caucasian and Asian population are p.E257K and p.R237C, respectively. Different variant hot spots of NMNAT1 were observed in different populations.

Biallelic variants in coenzyme Q10 biosynthesis pathway genes cause a retinitis pigmentosa phenotype. Jurkute N, Cancellieri F, Pohl L, Li CHZ, Heaton RA, Reurink J, Bellingham J, Quinodoz M, Yioti G, Stefanidou M, Weener M, Zuleger T, Haack TB, Stingl K; Genomics England Research Consortium; Hoyng CB, Mahroo OA, Hargreaves I, Raymond FL, Michaelides M, Rivolta C, Kohl S, Roosing S, Webster AR, Arno G.

NPJ Genom Med. 2022 Oct 20;7(1):60. doi: 10.1038/s41525-022-00330-z. PMID: 36266294; PMCID: PMC9581764.

The aim of this study was to investigate coenzyme Q10 (CoQ10) biosynthesis pathway defects in inherited retinal dystrophy. Patients included in this study had RP phenotypes and negative genotypes for known genes. The CoQ10 status of the human plasma was determined in some of the study patients. 13 individuals from 12 unrelated families harbored candidate pathogenic genotypes in the genes: PDSS1, COQ2, COQ4, and COQ5. The PDSS1 variant c.589 A > G was identified in three affected individuals from three unrelated families on a possible ancestral haplotype. Three variants (PDSS1 c.468-25 A > G, PDSS1 c.722-2 A > G, COQ5 c.682-7 T > G) were shown to lead to cryptic splicing. 6 affected individuals were diagnosed with non-syndromic retinitis pigmentosa, and 7 had additional clinical findings (hearing loss, cardiac disease, kidney disease). This study provides evidence of CoQ10 biosynthesis pathway gene defects leading to non-syndromic retinitis pigmentosa in some cases and expands genetic testing. Oral supplementation of CoQ10 is not helpful because CoQ10 does not cross the blood-brain barrier and does not penetrate the retina. Idebenone does penetrate and may be an alternative treatment.

RP2-Associated X-linked Retinopathy: Clinical Findings, Molecular Genetics, and Natural History.

Georgiou M, Robson AG, Jovanovic K, Guimarães TAC, Ali N, Pontikos N, Uwaydat SH, Mahroo OA, Cheetham ME, Webster AR, Hardcastle AJ, Michaelides M.

Ophthalmology. 2022 Nov 22:S0161-6420(22)00916-2. doi: 10.1016/j.ophtha.2022.11.015. Epub ahead of print. PMID: 36423731.

In light of newly developed gene therapies currently in clinical trials for RP2 this paper aims to describe in detail the clinical course and functional and anatomic characteristics of RP2-associated retinal degeneration. The authors analyze 54 molecularly confirmed patients from 38 pedigrees. 28 disease-

causing variants were identified (20 not previously described). Identified variants included 8 frameshift alterations (28.6%), 7 missense (25.0%), 6 nonsense (21.4%), and 3 splice site changes (10.7%). One patient had a whole gene deletion, and 3 patients had smaller deletions. No genotype-phenotype correlations were observed. 53 patients (98.1%) presented with retinitis pigmentosa. The mean age of onset (range  $\pm$  standard deviation [SD]) was 9.6 years ( $1-57 \pm 9.2$  years). 44 patients (91.7%) had childhood-onset disease, with mean age of onset of 7.6 years. The most common first symptom was night blindness (68.8%). Mean BCVA (range  $\pm$  SD) was 0.91 logarithm of the minimum angle of resolution (logMAR) ( $0-2.7 \pm 0.80$ ) and 0.94 logMAR ( $0-2.7 \pm 0.78$ ) for right and left eyes, respectively. 18 patients (34%) had low vision. The majority (17/22) showed electroretinogram (ERG) evidence of rod-cone dystrophy. Pattern ERG P50 was undetectable in all but 2 patients. A range of FAF findings was observed, from normal to advanced atrophy. There were no statistically significant differences between right and left eyes for ellipsoid zone width (EZW) and outer nuclear layer (ONL) thickness. The mean annual rate of EZW loss was 219  $\mu\text{m}/\text{year}$ , and the mean annual decrease in ONL thickness was 4.93  $\mu\text{m}/\text{year}$ . No patient with childhood-onset disease had an identifiable ellipsoid zone (EZ) after the age of 26 years at baseline or follow-up. Four patients had adulthood-onset disease and a less severe phenotype.

Optical genome mapping and revisiting short-read genome sequencing data reveal previously overlooked structural variants disrupting retinal disease-associated genes.

de Bruijn SE, Rodenburg K, Corominas J, Ben-Yosef T, Reurink J, Kremer H, Whelan L, Plomp AS, Berger W, Farrar GJ, Ferenc Kovács Á, Fajardy I, Hitti-Malin RJ, Weisschuh N, Weener ME, Sharon D, Pennings RJE, Haer-Wigman L, Hoyng CB, Nelen MR, Vissers LELM, van den Born LI, Gilissen C, Cremers FPM, Hoischen A, Neveling K, Roosing S. *Genet Med.* 2022 Dec 16:100345. doi: 10.1016/j.gim.2022.11.013. Epub ahead of print. PMID: 36524988. Structural variants (SVs) are essential in inherited retinal diseases (IRD). Although the identification of SVs significantly improved upon the availability of genome sequencing, it is expected that the involvement of SVs in IRDs will be higher than anticipated. Authors reanalyzed short-read genome sequencing data (427 IRD cases) and found 30 pathogenic SVs affecting, among other genes, USH2A ( $n = 15$ ), PRPF31 ( $n = 3$ ), and EYS ( $n = 2$ ). Eight of these (>25%) were overlooked during previous analyses. The paper showed that SV prioritization and more rigorous interpretation guidelines will prevent missing pathogenic events in future analyses. Particular attention should be paid to cases with one allele finding matching the phenotype.

Distinct Roles of Histone Lysine Demethylases and Methyltransferases in Developmental Eye Disease. Reis LM, Atilla H, Kannu P, Schneider A, Thompson S, Bardakjian T, Semina EV. *Genes (Basel).* 2023 Jan 14;14(1):216. doi: 10.3390/genes14010216. PMID: 36672956; PMCID: PMC9859058.

Genes encoding for histone lysine methyltransferases (KMTs) and demethylases (KDMs) are involved in complex human syndromes, termed congenital regulopathies. The involvement of these genes in developmental ocular phenotypes suggests that individuals with structural eye defects, especially when accompanied by craniofacial, neurodevelopmental and growth abnormalities, should be examined for possible variants in these genes. The paper describes nine heterozygous damaging genetic variants in KMT2D (5) and four other histone lysine methyltransferases/demethylases (KMT2C, SETD1A/KMT2F, KDM6A and KDM5C) in unrelated families affected with developmental eye diseases, such as Peters anomaly, sclerocornea, Axenfeld-Rieger spectrum, microphthalmia and coloboma. All nine alleles were novel and five of them occurred de novo; five variants resulted in premature truncation, three were missense changes and one was an in-frame deletion/insertion; and seven variants were categorized as pathogenic or likely pathogenic and two were variants of uncertain significance. This study expands the phenotypic spectra associated with KMT and KDM factors and highlights the importance of genetic testing for correct clinical diagnosis.

Whole-Exome Sequencing and Copy Number Analysis in a Patient with Warburg Micro Syndrome. Wang Q, Qin T, Wang X, Li J, Lin X, Wang D, Lin Z, Zhang X, Li X, Lin H, Chen W. *Genes (Basel).* 2022 Dec 14;13(12):2364. doi: 10.3390/genes13122364. PMID: 36553631; PMCID: PMC9777746.

Warburg Micro syndrome (WARBM) is an autosomal recessive neuro-ophthalmologic syndrome characterized by microcephaly, microphthalmia, congenital cataracts, cortical dysplasia, corpus callosum hypoplasia, spasticity, and hypogonadism. WARBM is divided into four subtypes according to the causative genes, of which RAB3GAP1 (OMIM# 602536) accounts for the highest proportion. 2 novel mutations are described in 2 individuals with syndromic congenital cataracts. The present study expands the genotypic and phenotypic spectrum of WARBM. It suggests applying whole exome sequencing (WES) and CNV analysis for the early diagnosis of syndromic diseases in children with congenital cataracts.

Diagnostic Yield of Genetic Testing for Ocular and Oculocutaneous Albinism in a Diverse United States Pediatric Population.

Chan KS, Bohnsack BL, Ing A, Drackley A, Castelluccio V, Zhang KX, Ralay-Ranaivo H, Rossen JL. *Genes (Basel)*. 2023 Jan 3;14(1):135. doi: 10.3390/genes14010135. PMID: 36672876; PMCID: PMC9859104.

The diagnostic yield of genetic testing for ocular/oculocutaneous albinism (OA/OCA) was assessed on 53 patients with a clinical diagnosis of OA/OCA between 2006-2022. Genetic diagnostic yield was defined as the detection of pathogenic/likely pathogenic variant(s) matching the anticipated inheritance for that gene-disease relationship. Variant reclassifications of those with uncertain significance (VUS) variants and without positive diagnostic yield were completed. Overall initial genetic diagnostic yield of OA/OCA was 66%. There was no significant difference ( $p = 0.59$ ) between race and ethnicities (Black (78%), White (59%), Hispanic/Latino (64%)); however, the diagnostic yield of OA (33%) was significantly lower ( $p = 0.007$ ) than OCA (76%). Causative variants in OCA2 (28%) and TYR (20%) were most common. Hermansky-Pudlak syndrome variants were identified in 9% of patients. Reclassification of VUS in non-diagnostic cases resulted in genetic diagnoses for 29% of individuals and increased overall diagnostic yield to 70% of all subjects. The presence or absence of cutaneous involvement of albinism significantly affects genetic diagnostic yield.

Phenotype-Based Genetic Analysis Reveals Missing Heritability of KIF11-Related Retinopathy: Clinical and Genetic Findings.

Chang H, Zhang X, Xu K, Li N, Xie Y, Yan W, Li Y.

*Genes (Basel)*. 2023 Jan 13;14(1):212. doi: 10.3390/genes14010212. PMID: 36672954; PMCID: PMC9858922.

10 individuals from 7 unrelated families harboring a pathogenic monoallelic variant in KIF11 are described in this study. The condition is inherited in an autosomal dominant pattern and is characterized by microcephaly, ocular anomalies (including chorioretinopathy), and congenital lymphedema of the lower limbs. Patients usually present special facial appearances, including upslanting palpebral fissures, a broad nose with a rounded tip, a long philtrum and a thin upper lip, a prominent chin, and prominent ears. Pathogenic variants in KIF11 are associated with familial exudative vitreoretinopathy (FEVR) phenotype. The patients in this study showed high phenotypic variability, and two families exhibited incomplete penetrance. Ocular manifestations and characteristic facial features were observed in all patients, as well as microcephaly in seven patients, intellectual disability in five patients, and lymphedema in one patient. The key retinal features for KIF11-related retinopathy were retinal folds, tractional retinal detachment, and chorioretinal dysplasia. All seven probands had more severe visual defects than other affected family members. The findings widen the genetic spectrum of KIF11 variants.

Retinal detachment in Loeys-Dietz syndrome.

Maghsoudi D, Nixon TRW, Snead MP.

*Am J Med Genet A*. 2022 Dec 18. doi: 10.1002/ajmg.a.63077. Epub ahead of print. PMID: 36529632.

Loeys-Dietz syndrome (LDS) is an autosomal-dominant connective-tissue disorder with vascular and musculoskeletal abnormalities similar to Marfan syndrome. Heterozygous missense variants in TGFBR1, encoding one subunit of the transforming growth factor-beta receptor, are associated with the disease. However, unlike Marfan, retinal detachment (RD) is rarely reported, and screening protocols do not currently feature ophthalmic assessment or RD counseling. Authors report a 5-generation family affected by LDS, where RD occurred in six eyes of four individuals. All affected individuals were diagnosed with type-V LDS (TGF $\beta$ 3 pathogenic variant c.899G>A, p.(Arg300Gln)). Other notable ophthalmic features

include unusual keratometry (cornea plana), abnormal biometry, and severe hayfever requiring long-term sodium cromoglycate treatment. The authors argue for screening for retinal detachment in these patients.

Short stature, hearing loss, retinitis pigmentosa, and distinctive facies syndrome: A case report.

Reeves A, Ojha K, Meddaugh H, Zambrano RM.

Am J Med Genet A. 2022 Dec;188(12):3535-3539. doi: 10.1002/ajmg.a.62964. Epub 2022 Sep 7. PMID: 36069504.

Short stature, hearing loss, retinitis pigmentosa, and distinctive facies (SHRF) Syndrome was 1st described in 2016 in 3 patients with childhood myopia, early onset retinitis pigmentosa, progressive sensorineural hearing loss, hypothyroidism, short stature, brachydactyly, recognizable facial gestalt, premature aging, and mild intellectual disability. Whole exome sequencing revealed homozygous or compound heterozygous missense variants in the EXOSC2 gene. This paper presents a new patient with a pathogenic variant in the same gene in a similar but milder phenotype.

Expanding SPG7 dominant optic atrophy phenotype: Infantile nystagmus and optic atrophy without spastic paraplegia.

Seo Y, Lim HT, Lee BJ, Han J.

Am J Med Genet A. 2023 Feb;191(2):582-585. doi: 10.1002/ajmg.a.63037. Epub 2022 Nov 11. PMID: 36367250.

Spastic paraplegia is a neurodegenerative disorder characterized by progressive leg weakness and spasticity due to the degeneration of corticospinal axons. Pathogenic variants in the SPG7 gene which encodes paraplegin cause hereditary spastic paraplegia as an autosomal recessive trait. Various ophthalmological findings, including optic atrophy, ophthalmoplegia, or nystagmus, have been reported in patients with spastic paraplegia type 7. This paper reports a 15-year-old male patient with a novel heterozygous variant, c.1224T>G:p.(Asp408Glu) in SPG7 (NM\_003119.3), causing early onset isolated optic atrophy and infantile nystagmus diagnosed before the onset of neurological symptoms. Therefore, SPG7 should be considered a cause of infantile nystagmus with optic atrophy.

LRP5 biallelic mutations cause a higher incidence of severe phenotype compared with LRP5 monoallelic mutation

Chen C, Zhang X, Peng X, Hu F, Cheng Y, Zhao P. *Retina*. 42(10):1958-1964, October 2022.

Of six causative genes known to cause familial exudative vitreoretinopathy (FEVR), the most common cause is the gene LRP5. Mutations in this gene can cause either autosomal-dominant FEVR or autosomal-recessive FEVR. There has been evidence that autosomal-recessive FEVR can be more severe, but the authors argue that the detailed association between genotype and phenotype remains unclear. They retrospectively characterized 87 patients from China with FEVR caused by a mutation in LRP5 to better describe the associated phenotypes. An autosomal-recessive mutation was found in 22 patients, while an autosomal dominant mutation was found in 65. The severity of their disease was classified according to a reported classification system, where Stages I, II, and III were classified as "mild phenotype" and Stage IV and V were classified as "severe phenotype." Of the 22 patients with ar-LRP5, 43 eyes were affected. Thirty-three of those 43 eyes (75%) had a severe phenotype. Thirteen of the 22 patients with ar-LRP5 had a severe phenotype in both eyes. Of the 65 patients with ad-LRP5, 119 eyes were affected, among which only 54 eyes (45%) demonstrated a severe phenotype. Only 11 of the 65 patients had a severe phenotype in both eyes. The authors concluded that the severity of the FEVR phenotype correlates with the inheritance pattern of the LRP5 mutation.

De Novo Mutations Contributes Approximately 7% of Pathogenicity in Inherited Eye Diseases.

Li W, He XD, Yang ZT, Han DM, Sun Y, Chen YX, Han XT, Guo SC, Ma YT, Jin X, Yang HM, Gao Y, Wang ZS, Li JK, He W.

Invest Ophthalmol Vis Sci. 2023 Feb 1;64(2):5.

This study aims to address the genetic profile in inherited eye diseases (IEDs). The authors performed a retrospective review of a large cohort of proband-parent trios of Chinese origin. Over 1000 patients were included in this study. The phenotypes were diverse, as these patients were recruited for genetic diagnostic studies without specification of phenotype. The overall diagnostic yield was 48.67%, with 108 IED-causative genes identified. Of these, 6.76% were attributed to de novo mutations, with the highest

incidence in aniridia, Marfan syndrome, and retinoblastoma. The incidence of de novo mutations in offspring showed a trend of correlation with older parental age though not statistically significant. This study demonstrates that de novo mutations represent an important etiology for inherited eye diseases.

Insufficient Dose of ERCC8 Protein Caused by a Frameshift Mutation Is Associated With Keratoconus With Congenital Cataracts.

Hao XD, Yao YZ, Xu KG, Dong B, Xu WH, Zhang JJ.

Invest Ophthalmol Vis Sci. 2022 Dec 1;63(13):1.

This study identified a novel frameshift mutation of ERCC8 (NM\_000082.3: c.394-398del, p. L132Nfs\*6) as a pathogenic variant responsible for the phenotype of familial keratoconus with congenital cataract. In this study, the authors identified a family of two patients (proband and her son) with congenital cataract as well as keratoconus. Whole exome sequencing was performed on the affected family members, which identified ERCC8 as a candidate gene with a frameshift mutation. ERCC8 was previously reported to be associated with congenital cataract phenotype in Cockayne syndrome. This mutation was genotyped in additional 262 keratoconus patients unrelated to this family, as well as 20 congenital cataract patients. This mutation was found to be absent in healthy controls. Immunofluorescent staining study showed ERCC8 protein to be highly expressed in mouse corneal stroma. In vitro cell line experiments demonstrated that the mutant proteins of ERCC8 were degraded, this ERCC8 protein insufficiency reduced DNA damage repair ability of human corneal fibroblast (HTK) and lens epithelial cells (HLEC) treated with hydrogen peroxide, leading to both cells showing higher DNA damage levels. These results suggested that ERCC8 plays an important role in the normal function of corneal stromal and lens epithelial cells. This study shows convincing data of the important role of ERCC8 in corneal formation and a novel frameshift mutation as a causative variant of keratoconus as well as congenital cataract as the clinical phenotype.

miR-328-3p Affects Axial Length Via Multiple Routes and Anti-miR-328-3p Possesses a Potential to Control Myopia Progression.

Liang CL, Chen KC, Hsi E, Lin JY, Chen CY, Tseng JK, Juo SH.

Invest Ophthalmol Vis Sci. 2022 Nov 1;63(12):11.

This study explores the effect of miR-328-3p on other myopia-related genes, as well as the possibility of using this as a drug target for myopia control. miR-328-3p is a previously identified microRNA, a noncoding, short single-stranded RNA molecule, that could be a risk factor for myopia through epigenetic regulation of PAX6 by suppressing its expression. In this study, the authors used in vitro studies to show that miR-328-3p dose-dependently decreased both mRNA and protein expression of fibromodulin (FMOD) and collagen1A1 (COL1A1), which are major components of the sclera, with reduced protein levels having been reported to contribute to myopia development. Chromatin immunoprecipitation (ChIP) study showed that retinoic acid binds to miR-328-3p promoter and up-regulates miR-328-3p expression. In myopic animal studies, anti-miR-328-3p was as effective as 1% atropine and had a dose-dependent effect on suppressing axial elongation. These new findings show that miR-328-3p may play a role in myopia development through multiple routes, and that agents decreasing the expression of this micro RNA is a potential novel therapy method for myopia control.

Congenital ankyloblepharon in a newborn with an IRF6 mutation.

Uddin O, Choi JH, Causey E, Levin MR, Alexander JL.

J AAPOS. 2023 Jan 11:S1091-8531(23)00003-4.

This case reports describes a full-term infant born with multiple congenital abnormalities including bilateral ankyloblepharon, oral adhesions, incomplete cleft palate, webbing of the fourth and fifth toes, and excess tissue folds on the great toes. Genetic testing identified a mutation of the interferon regulatory factor 6 (IRF6) gene (c.250C.T, p.Arg84Cys, heterozygous), resulting in a diagnosis of popliteal pterygium syndrome. The IRF6 gene encodes a transcription factor involved in craniofacial and skin development. Mutations in IRF6 can lead to various disorders, including Van Der Woude and popliteal pterygium syndromes. In infants with congenital ankyloblepharon, it is important to identify the genetic etiology as the associated syndromes can present with other symptoms that can impact development,



including nutritional and respiratory challenges, and mobility issues due to webbing across major joints. It is important to incorporate genetic counseling in the care of the patient.

Ophthalmic manifestations of Lamb-Shaffer syndrome: a case presentation and literature review.

Mahmud H, Gustainis D, Jackson-Cook C, Couser N.

J AAPOS. 2022 Sep 13:S1091-8531(22)00420-7.

This study characterized ophthalmic manifestations of Lamb-Shaffer syndrome, caused by haploinsufficiency of SOX5, which is a family of proteins that play an integral role in the development of chondrocytes, oligodendrocytes, and neurons. Patients with Lamb-Shaffer syndrome exhibit distinctive characteristics including intellectual delay and dysmorphic facial features. This case report describes a child with Lamb-Shaffer syndrome, who has nystagmus, exotropia, and astigmatism. The authors then performed a literature review of 73 reported cases, 40 of which included description of ophthalmic findings. Among these patients, 73% were reported have strabismus, 20% with optic nerve abnormalities, 22.5% with refractive error (mostly myopia and astigmatism), and 15% with epicanthal bands. Other less common features include abnormal palpebral fissures, amblyopia, and blue sclera. 54.8% of all reported cases had some ophthalmic abnormality. This study provides the first comprehensive description of ocular findings in Lamb-Shaffer syndrome, which are common and diverse in phenotype. Further studies of SOX5 in eye development may help with elucidating the mechanism of disease.

Diagnostic yield of next generation sequencing gene panel assays for early-onset glaucoma in an ethnically diverse population.

Villalba MF, Grajewski AL, Tekin M, Bademci G, Chang TC.

J AAPOS. 2022 Dec;26(6):302.e1-302.e6.

Early-onset glaucoma, defined as glaucoma onset before age 40, is a potentially sight-threatening condition with high heritability. Next generation sequencing is a cost-effective alternative to individual gene screening that could expedite its diagnosis. The diagnostic yield of multigene panel assays for early-onset glaucoma varies according to the tested population. In this study, the authors examined diagnostic yield of next generation sequencing panels in their cohort, and aimed to identify population characteristics that increase such yield. A retrospective review of the medical records of consecutive patients evaluated for early-onset glaucoma at a single institution over a 5 year period was performed. All patients had undergone next generation sequencing panels for molecular diagnosis. A total of 118 patients were included, in 22 of whom (19%) a causative variant was identified. Both in-house and third-party early-onset glaucoma gene panels were used. The in-house panel was performed in 82 patients, and a molecular diagnosis was identified in 13%. The remaining 36 patients underwent the third-party panels 31% identified a molecular diagnosis. However, when adjusted for early onset before age 3, both in-house and third-party panels identified molecular diagnosis in 32% of patients. In contrast, for patients with onset age after 3, total diagnostic yield was only 5%. Additionally, diagnostic yield varied significantly with ethnicity. It has been reported that populations identifying as Black are disproportionately affected by glaucoma. In this cohort, 42% of the patients identified as Black, yet most remain without a molecular diagnosis. This suggests either that there remain genes to be discovered for monogenic glaucoma or that the pattern of inheritance is complex and different approaches such as increasing the diversity of genome-wide association studies are needed. This study highlights the importance of gene panels in helping achieve molecular diagnosis, and identifies areas where additional research are much needed for better understanding of disease etiology, particularly in patients with older age of onset, and in patients who identify as non-White.

Smith-Lemli-Optiz syndrome: importance of ophthalmology referral and follow-up.

López-Cañizares A, Al-Kharsan H, Fernandez MP, Lin BR, Goduni L, Berrocal AM.

J AAPOS. 2022 Dec 21:S1091-8531(22)00790-X.

Smith-Lemli-Optiz syndrome (SLOS) is an autosomal recessive disorder caused by mutations in the 7-dehydrocholesterol reductase (DHCR7) gene. This results in reduced cholesterol and increased 7-dehydrocholesterol (7DHC) levels. SLOS is characterized by intellectual disability, behavioral

abnormalities, and atypical craniofacial features, including ptosis, microcephaly, and micrognathia. Self-injurious behavior, such as head banging, has been reported in more than half of SLOS patients. Ophthalmic abnormalities previously reported in association with SLOS include blepharoptosis, cataracts, optic nerve hypoplasia, choroidal hemangiomas, and aniridia. The authors report a case of a teenage patient with SLOS and head banging behavior who presented with vision decrease suspected by parents. His visual acuity was 20/80 in the right eye and no light perception in the left eye. Exam revealed dilated, tortuous vessels, peripheral avascularity, and an attached retina in the right eye. The left eye had vitreous hemorrhage precluding visualization. During surgery, the patient was found to have a vitreous hemorrhage with chronic tractional retinal detachment in the left eye caused by proliferative vitreoretinopathy. Despite anatomic reattachment of retina, vision in the left eye did not improve. This is the first known report of vitreoretinopathy including chronic retinal detachment in SLOS, presumably from repeated trauma of head banging. The authors recommend routine eyes exams in SLOS patients who exhibit self banging behavior

Inflammation after Voretigene Neparovec Administration in Patients with RPE65-Related Retinal Dystrophy.

Kessel L, Christensen UC, Klemp K.

Ophthalmology. 2022 Nov;129(11):1287-1293. doi: 10.1016/j.ophtha.2022.06.018. Epub 2022 Jun 26. PMID: 35760216

This is a retrospective review of patients treated with voretigine neparovec in Denmark designed to examine the incidence of intraocular inflammation following treatment. There were 23 eyes in 12 patients included in the study. All patients had undergone surgery with a standardized prophylactic protocol of oral and topical dexamethasone. Nine patients developed vitritis all of them after cessation of dexamethasone. Inflamed eyes did not differ from uninflamed eyes other than BMI being higher in those with inflammation. The authors propose that this may be due to lack of weight-adjusted dosing of steroids. The authors concluded that patients should be monitored closely after stopping prophylactic immunosuppression and ensure that viral vectors are removed from the vitreous cavity which may reduce the risk of inflammation. It is also noted that the inflammation was not associated with visual decline. This study is important as it highlights the risk of inflammation after treatment with VN and the importance of post-operative monitoring.

*Fibrillin-1* gene mutations in a Chinese cohort with congenital ectopia lentis: spectrum and genotype-phenotype analysis.

Chen Z, Chen T, Zhang M, Chen J, Deng M, Zheng J, Lan LN, Jiang Y.

Br J Ophthalmol. 2022 Dec;106(12):1655-1661. doi: 10.1136/bjophthalmol-2021-319084.

This study contributes helpful information for genetic counselors. It investigated the spectrum of FBN1 mutations with the goal of identifying the at-risk regions and hotspots for FBN1 mutations in a Chinese cohort of congenital zonulopathy (mainly ectopia lentis). They also looked for possible correlations between FBN1 and microspherophakia. 131 patients from unrelated families with FBN1 mutations were recruited and overall there were 110 unique mutations identified (including 39 novel mutations). Most (65%) were <9 years old. The regions harboring the most mutations and, thus, considered most at risk of mutation were exons 13, 2, 6, 15, 24 and 33 in descending order of frequency. Missense mutations were the most frequent type (79%); half of which were distributed in the N-terminal regions. Microspherophakia was found in 11.5% of patients, and mutations in the middle region (22-42, especially exon 26) had 5x higher risk of combined microspherophakia.

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Heterozygous UCHL1 loss-of-function variants cause a neurodegenerative disorder with spasticity, ataxia, neuropathy, and optic atrophy.

Genet Med. 2022 Aug 19:S1098-3600(22)00843-7. doi: 10.1016/j.gim.2022.07.006. PMID: 35986737.

Park J, Tucci A, Cipriani V, Demidov G, Rocca C, Senderek J, Butryn M, Velic A, Lam T, Galanaki E, Cali E, Vestito L, Maroofian R, Deininger N, Rautenberg M, Admard J, Hahn GA, Bartels C, van Os NJH, Horvath R, Chinnery PF, Tiet MY, Hewamadduma C, Hadjivassiliou M, Tofaris GK; Genomics England Research Consortium, Wood NW, Hayer SN, Bender F, Menden B, Cordts I, Klein K, Nguyen HP, Krauss

JK, Blahak C, Strom TM, Sturm M, van de Warrenburg B, Lerche H, Maček B, Synofzik M, Ossowski S, Timmann D, Wolf ME, Smedley D, Riess O, Schöls L, Houlden H, Haack TB, Hengel H. Ubiquitin C-terminal hydrolase L1 (*UCHL1*), has been associated with autosomal recessive spastic paraplegia type 79 (SPG79), characterized by early-onset cerebellar ataxia, spastic paraplegia, and optic atrophy. The authors present a cohort of 34 participants carrying 13 heterozygous predicted loss-of-function (LoF) variants in 15 families and a novel variant (inframe insertion) in 3 families in *UCHL1*, causing an autosomal dominant inherited neurodegenerative disorder with a distinct phenotype. Affected individuals mainly presented with spasticity (24/31), ataxia (28/31), neuropathy (11/21), and optic atrophy (9/17). Disease onset varied from childhood to age 70 (median 49) years with slow progression of the movement disorder according to medical history.

Identification of autosomal recessive novel genes and retinal phenotypes in members of the solute carrier (SLC) superfamily.

Genet Med. 2022 Jul;24(7):1523-1535. doi: 10.1016/j.gim.2022.03.020. PMID: 35486108.

Millo T, Rivera A, Obolensky A, Marks-Ohana D, Xu M, Li Y, Wilhelm E, Gopalakrishnan P, Gross M, Rosin B, Hanany M, Webster A, Tracewska AM, Koenekoop RK, Chen R, Arno G, Schueler-Furman O, Roosing S, Banin E, Sharon D.

In this paper, the clinical and genetic aspects of solute carrier (SLC) genes in inherited retinal diseases (IRDs) were evaluated using Exome sequencing data. Homozygous pathogenic variants were found in 6 SLC genes. 2 candidate novel genes, *SLC66A1*, causing autosomal recessive retinitis pigmentosa (ARRP), and *SLC39A12*, causing autosomal recessive mild widespread retinal degeneration with marked macular involvement. 1 homozygous null variant in *SLC37A3* causing ARRP. A *SLC4A7*-c.2007dup resulting in ARRP and a variant in *SLC24A1* resulting in either ARRP or congenital stationary night blindness.

Autosomal Recessive Stickler Syndrome.

Genes (Basel). 2022 Jun 24;13(7):1135. doi: 10.3390/genes13071135. PMID: 35885918; PMCID: PMC9324312.

Nixon TRW, Richards AJ, Martin H, Alexander P, Snead MP.

Stickler syndrome (SS) is a genetic disorder with manifestations in the eye, ear, joints, face, and palate. Usually inherited dominantly due to heterozygous pathogenic variants in the collagen genes *COL2A1* and *COL11A1*, it can rarely be inherited in a recessive fashion from variants in *COL9A1*, *COL9A2*, and *COL9A3*, *COL11A1*, as well as the non-collagen genes *LRP2*, *LOXL3* and *GZF1*. Recessive SS has been reported less frequently than dominant SS, but has now been described in 40 patients from 23 families, all of which are reviewed in this paper. The most common forms of recessive SS result from variants affecting genes *COL9A1*, *COL9A2*, and *COL9A3*. All patients are myopic, mostly high myopia (>-6D), and most have abnormal vitreous, usually hypoplastic. 18% of patients had a retinal detachment. All patients have sensorineural hearing loss, mainly reported as moderate to severe. Joint pain was a feature in 15% of patients. Cleft palate is associated with type XI collagen variants, as well as the non-collagen genes, but is so far unreported with type IX collagen variants. This cohort of patients is rather young (mean age of 11 years old), which makes evaluating the risk of retinal detachment difficult. The authors concluded that autosomal recessive Stickler syndrome should be in the differential of patients with the clinical appearance of Stickler syndrome but negative family history.

Prevention of Blindness in Stickler Syndrome.

Genes (Basel). 2022 Jun 26;13(7):1150. doi: 10.3390/genes13071150. PMID: 35885933; PMCID: PMC9318672.

Alexander P, Snead MP.

Although retinal detachment surgery in the general population has a high success rate, outcomes from surgical repair in Stickler syndrome patients are notoriously poor, providing a solid argument for prophylactic intervention. This paper reviews the major published clinical studies evaluating different prophylaxis methods and strategies. All of the studies on this topic were retrospective. They demonstrate an overwhelming support for the use of prophylactic retinopexy in the patients with Stickler syndrome using laser. There has been no head-to-head comparative study to evaluate the efficacy of laser

retinopexy versus cryotherapy retinopexy to prevent retinal detachment. The location of retinopexy within the retina is likely to be much more important than the modality of treatment.

*GUCY2D*-Related Retinal Dystrophy with Autosomal Dominant Inheritance-A Multicenter Case Series and Review of Reported Data.

Genes (Basel). 2022 Feb 8;13(2):313. doi: 10.3390/genes13020313. PMID: 35205358; PMCID: PMC8872159.

Neubauer J, Hahn L, Birtel J, Boon CJF, Charbel Issa P, Fischer MD.

This study describes 25 patients (17 female, range 12-68) with *GUCY2D*-related AD-COD/CORD from three major academic centers in Europe and reviews the previously published data of 148 patients. Overall, the onset of first symptoms was reported at a median age of 7 years (interquartile range 5-19 years,  $n = 78$ ). It mainly consisted of reduced VA, photophobia, and color vision abnormality. Fundus autofluorescence imaging ( $n = 20$ ) was abnormal in 19 out of 20 patients with central hyper- and hypo-fluorescence (9/20), central reduced autofluorescence (6/20), increased central autofluorescence (1/20), bull's eye pattern (2/20), and an unspecified pattern was present in one patient. The disease showed a high degree of inter-eye symmetry in terms of VA ( $n = 165$ , Spearman's  $\rho = 0.85$ ,  $p < 0.0001$ ) and foveal thickness (Spearman's  $\rho = 0.96$ ,  $n = 38$ ,  $p < 0.0001$ ). Disease progression was assessed by plotting VA as a function of age ( $n = 170$ ). A linear best-fit analysis suggested a loss of 0.17 logMAR per decade ( $p < 0.0001$ ). It is estimated that severe vision loss (logMAR  $> 1.0$ ) is reached, on average, at the age of 38. The most common mutations were p.(Arg838Cys) and p.(Arg838His). The codon 838 of *GUCY2D* is considered a mutational hotspot due to its nucleotide sequence—CGC—which is prone to spontaneous deamination of methylated cytosine. Gene replacement therapy will likely not be effective for *GUCY2D*-related COD/CORD because it will not address the presumed dominant-negative disease mechanism. However, gene-editing tools, such as CRISPR/Cas9, provide potential opportunities to disrupt the dominant allele. Natural history studies show symmetry of the disease as the basis of a one-sided treatment, with the fellow eye serving as the internal control. As cones are primarily affected in this disease and VA is a cone-driven visual function, this will also reflect disease progression and/or the efficacy of any treatment. The difficulty here lies in the linearity of photoreceptor degeneration. Once foveal cone photoreceptors have died, no significant VA gain is to be expected. There may only be a small window of opportunity to gain VA by treating dysfunctional cone photoreceptors before they die.

The CGG repeat expansion in *RILPL1* is associated with oculopharyngodistal myopathy type 4. Am J Hum Genet. 2022 Mar 3;109(3):533-541. doi: 10.1016/j.ajhg.2022.01.012. Epub 2022 Feb 10. PMID: 35148830; PMCID: PMC8948162.

Yu J, Shan J, Yu M, Di L, Xie Z, Zhang W, Lv H, Meng L, Zheng Y, Zhao Y, Gang Q, Guo X, Wang Y, Xi J, Zhu W, Da Y, Hong D, Yuan Y, Yan C, Wang Z, Deng J.

Oculopharyngodistal myopathy (OPDM) is a rare hereditary neuromuscular disease presenting with progressive ptosis, ophthalmoparesis, facial and masseter weakness, dysphagia, and muscle weakness of distal limbs. The major myopathological features showed chronic myopathic changes with rimmed vacuoles and filamentous intranuclear inclusions. The authors of this study present a novel CGG repeat expansion in the 5' UTR of *RILPL1* is associated with familial and simplex OPDM type 4. Methylation analysis indicates that the methylation levels in *RILPL1* were unaltered in OPDM4 individuals. Analyses of muscle biopsies suggested that the expanded CGG repeat might be translated into a toxic poly-glycine protein that co-localizes with p62 in intranuclear inclusions. Moreover, analyses suggest that the toxic RNA gain-of-function effects also contributed to the pathogenesis of this disease. Intriguingly, all four types of OPDM have been found to be associated with the CGG repeat expansions located in 5' UTRs. This finding suggests that a common pathogenic mechanism, driven by the CGG repeat expansion, might underlie all cases of OPDM.

Personalized genetic counseling for Stargardt disease: Offspring risk estimates based on variant severity. Am J Hum Genet. 2022 Mar 3;109(3):498-507. doi: 10.1016/j.ajhg.2022.01.008. Epub 2022 Feb 3. PMID: 35120629; PMCID: PMC8948157.

Cornelis SS, Runhart EH, Bauwens M, Corradi Z, De Baere E, Roosing S, Haer-Wigman L, Dhaenens CM, Vulto-van Silfhout AT, Cremers FPM.

Stargardt disease is an autosomal recessive disease due to variants in the *ABCA4* gene. An autosomal recessive disease displays a classical Mendelian inheritance pattern when all the pathogenic variants in

one implicated gene consistently affect the clinical phenotype. Several human disorders, however show an atypical autosomal recessive inheritance due to the existence of variants that result in different levels of residual protein function, meaning that different combinations of variants can thus correlate with a spectrum of phenotypes or even the absence of a clinical manifestation. This concern needs careful consideration in Stargardt disease because of the high frequency of pathogenic *ABCA4* variants in the general population. In this cross-sectional study, 1,619 *ABCA4* variants from 5,579 individuals with Stargardt disease were collected and categorized by (1) severity based on statistical comparisons of their frequencies in affected individuals versus the general population, (2) their observed versus expected homozygous occurrence in affected individuals, (3) their occurrence in combination with established mild alleles in affected individuals, and (4) previous functional and clinical studies. The genotypes with two alleles from the same severity category have an occurrence of that category's sum allele frequency squared, while genotypes of two variants of two different categories have an occurrence of two times the multiplication of the categories' sum allele frequency. The authors assume that the frequencies of severe, moderately severe, mild<sup>CP</sup>, mild<sup>IP</sup>, and wild-type alleles add up to a total of 100%, that allele and genotype frequencies remain relatively stable throughout time, that the Stargardt disease prevalence is equal in all analyzed populations, and that genetic variation was spread evenly through the population, even though this is not the reality. The risk of disease for the offspring highly depends on the genotype of the affected individual. The combination of a severe *ABCA4* variant with any other pathogenic *ABCA4* variant will cause disease, The risk for offspring of an affected individual with the "severe/severe" genotype or a "severe/mild with complete penetrance" genotype to develop Stargardt disease at some moment in life was estimated at 2.8%-3.1% (1 in 36-32 individuals) and 1.6%-1.8% (1 in 62-57 individuals), respectively. The risk of developing disease in childhood was estimated to be 2- to 4-fold lower: 0.68%-0.79% (1 in 148-126) and 0.34%-0.39% (1 in 296-252), respectively. The risks for offspring of unaffected *ABCA4* variant carriers vary tremendously, and the severity of the *ABCA4* allele is the most important determinant. When an *ABCA4* variant carrier from a Stargardt disease family (for instance, a child or genetically tested sibling of an individual with the disease) will have a child with an unaffected non-tested individual who does not have relatives with Stargardt disease, the recurrence risk varies between 0.13% (1 in 782, for carriers of a mild<sup>IP</sup> allele) and 1.5% (1 in 65, for carriers of a severe allele). In conclusion, the authors propose an expanded genotype-based personalized counseling to appreciate the variable recurrence risks for Stargardt disease-affected individuals. This represents a conceptual breakthrough for risk calculations for many other inherited diseases.

#### Genotypic and Phenotypic Spectrum of Foveal Hypoplasia: A Multicenter Study.

Ophthalmology. 2022 Jun;129(6):708-718. doi: 10.1016/j.ophtha.2022.02.010 PMID: 35157951; PMCID: PMC9341240.

Kuht HJ, Maconachie GDE, Han J, Kessel L, van Genderen MM, McLean RJ, Hisaund M, Tu Z, Hertle RW, Gronskov K, Bai D, Wei A, Li W, Jiao Y, Smirnov V, Choi JH, Tobin MD, Sheth V, Purohit R, Dawar B, Girach A, Strul S, May L, Chen FK, Heath Jeffery RC, Aamir A, Sano R, Jin J, Brooks BP, Kohl S, Arveiler B, Montoliu L, Engle EC, Proudlock FA, Nishad G, Pani P, Varma G, Gottlob I, Thomas MG. A multicenter, observational study of 907 patients with a confirmed molecular diagnosis of albinism, *PAX6*, *SLC38A8*, *FRMD7*, *AHR*, or achromatopsia from 12 centers in 9 countries (n = 523) or extracted from publicly available datasets from previously reported literature (n = 384) analyzed to characterize the genotypic and phenotypic spectrum of foveal hypoplasia (FH). The Leicester Grading System is divided into 4 grades of typical FH (grades 1–4) and 1 grade of atypical FH, which is associated with photoreceptor degeneration. The mean age of the cohort was 22.7 years (standard deviation, 16.7 years), with a higher proportion of male individuals (53.6%) than female individuals (46.4%). Among individuals with variants in genes linked to typical FH (n = 597), we observed typical FH in 81.6%. In the achromatopsia cohort (n = 310), atypical FH was observed in 67.4% of cases. Atypical FH had a significantly worse visual acuity ( $P < 0.0001$ ) than the typical FH group and the normal foveal morphology group. Further analysis with typical FH split into each grade of FH revealed significant ( $P < 0.05$ ) differences in visual acuity for all pairwise comparisons except between grade 2 and 3 FH. The breakdown of genetic etiologies of typical FH (n = 487) included albinism (67.5%), *PAX6* variants (21.8%), *SLC38A8* variants (6.8%), *FRMD7* variants (3.5%), and *AHR* variants (0.4%). Grade 4 FH was the most frequently reported grade of FH in this study (43.1%), and grade 2 was the least prevalent (14.0%). There was a significant difference in the grade of FH and photoreceptor specialization (PRS+ vs. PRS–)

between the genetic etiologies (chi-square = 60.4,  $P < 0.0001$ ). All *SLC38A8* variants were PRS– cases (adjusted z-score = 4.0,  $P = 0.003$ ). In contrast, all *FRMD7* variants were PRS+ (adjusted z-score = 6.3,  $P < 0.0001$ ). Likewise, subanalysis for albinism showed a significant difference in the grade of FH (PRS+ vs. PRS–) between the albinism subtypes (chi-square = 31.4,  $P < 0.0001$ ). Post hoc analysis showed that HPS (adjusted z-score = 2.7,  $P = 0.0065$ ) and OA (adjusted z-score = 4.5,  $P < 0.0001$ ) were associated with only PRS– cases; however, OCA had a spectrum of both PRS+ and PRS– cases (adjusted z-score = 5.6,  $P < 0.0001$ ). The authors conclude that in typical FH, arrested retinal development occurs earlier in *SLC38A8*, OA, HPS, and AHR variants and later in *FRMD7* variants. The defined time period of foveal developmental arrest for OCA and *PAX6* variants seems to demonstrate more variability. The findings provide mechanistic insight into disorders associated with FH and have significant prognostic and diagnostic value.

Inflammation after voretigene neparvovec administration in patients with RPE65-related retinal dystrophy. *Ophthalmology*. 2022 Jun 24:S0161-6420(22)00477-8. doi: 10.1016/j.ophtha.2022.06.018. Epub ahead of print. PMID: 35760216.

Kessel L, Christensen UC, Klemp K.

The paper reports on the prevalence of intraocular inflammation after Luxturna in a cohort of Twelve patients. They received gene therapy as standard-of-care for bi-allelic RPE65-related retinal disease. Bilateral treatment was performed in 11 patients and unilateral treatment in one patient. Patients had been followed clinically before and after the treatment. Standard anti-inflammatory prophylaxis included oral prednisolone and topical dexamethasone. Oral prednisolone was initiated 3 days before surgery with a dose of 1 mg/kg body weight and a maximum dose of 40 mg/day. Five days after surgery on the last eye (12 days after first eye surgery), the dose was lowered to 0.5 mg/kg body weight (maximum 20 mg/day) which was further reduced to 0.5 mg/kg body weight every second day for another 5 days. Topical dexamethasone was administered 4 times daily for 4 weeks in each treated eye (Spersadex Comp, Thea Nordic, containing 1 mg/ml dexamethasone-sodium-phosphate and 5 mg/ml chloramphenicol). Whilst on oral prednisolone, the patients also received a daily oral dose of 20 mg omeprazole (10 mg/day for children <20 kg) and a supplement of calcium and vitamin D. 9 out of 23 eyes had vitritis. The median time to resolution of vitritis from the time of treatment was 89 days. Four eyes also presented with outer retinal infiltrates at the time of vitritis. Inflammation subsided on immunosuppressant therapy. The presence of inflammation did not adversely affect visual outcome after the therapy. The authors report new atrophic areas after voretigene neparvovec administration in six eyes. In two eyes the atrophic areas were observed at the site of injection. Still, in the remaining 4 eyes, the atrophic areas were associated with prior vitritis and outer retinal infiltrates. In one eye outer retinal infiltrates were demonstrated to precede later development of atrophy. The recommended daily dose and duration of prednisolone treatment may be insufficient in some patients and it might be necessary to increase the dose in those with high body mass index or those whose family members have responded with intraocular inflammation after gene therapy.

Adeno-Associated Virus Serotype 2-hCHM Subretinal Delivery to the Macula in Choroideremia: Two-Year Interim Results of an Ongoing Phase I/II Gene Therapy Trial.

*Ophthalmology*. 2022 Jun 15:S0161-6420(22)00438-9. doi: 10.1016/j.ophtha.2022.06.006. PMID: 35714735.

Aleman TS, Huckfeldt RM, Serrano LW, Pearson DJ, Vergilio GK, McCague S, Marshall KA, Ashtari M, Doan TM, Weigel-DiFranco CA, Biron BS, Wen XH, Chung DC, Liu E, Ferenchak K, Morgan JIW, Pierce EA, Elliott D, Bennett J, Comander J, Maguire AM.

This paper presents the results of the prospective, open-label, nonrandomized, dose-escalation, phase I/II clinical trial of the subretinal delivery of a recombinant adeno-associated virus serotype 2 (AAV2) vector carrying a human choroideremia (CHM)-encoding cDNA in CHM. Patients received unioocular subfoveal injections of low-dose (up to  $5 \times 10^{10}$  vector genome [vg] per eye,  $n = 5$ ) or high-dose (up to  $1 \times 10^{11}$  vg per eye,  $n = 10$ ). Fifteen participants with CHM aged 20 to 57 years confirmed positive for loss-of-function mutations in *CHM* were included in this study. This “Spark Therapeutics” vector, like that generated by Nighstar/Biogen, is an AAV serotype 2 vector containing a constitutive promoter-driving expression of the human CHM cDNA but differs substantially in terms of its composition and methods of purification. Surgical delivery methods also differ. An effort was made to include patients with relatively preserved foveas. During the 2 years of follow-up, most patients did not report a noticeable change in

vision on visual field questionnaires. Baseline VA in the operated eye (the worse VA or nonpreferred eye) ranged from 20/40 to 20/16. Except for a transient loss of VA during the first week after the surgery caused by the intraocular air bubble, all patients, except those with acute postoperative foveal changes (09 and 13), recovered to within baseline values by study day 90. Patient 09 lost acuity from 20/20-1 to 20/200 in the operated eye and showed a slow partial recovery (to 20/50) at study day 180. Four of 15 patients had borderline VA gains (patients 01 and 03, +5 letters; 12, +8; 15, +6) that exceeded the intervisit variability. Patients 05, 07, 08, and 14 showed mildly decreased VA approximately 18 months postinjection, related to worsening of posterior capsular opacification. Baseline foveal sensitivities measured with static perimetry were slightly reduced compared with normative ranges ( $37.6 \pm 3.4$  decibels [dB]) and nearly identical for the intervention ( $33.4 \pm 2.5$  dB) and uninjected ( $33.3 \pm 2.5$  dB) eyes. At 1 month after the interventions, most patients had minor foveal thinning that did not exceed (except patients 09 and 13) the intervisit variability of the measures in the unoperated eye ( $2 \text{ SD} = 0.12$ ). Two patients had adverse events- acute changes in foveal anatomy (09, foveal thinning; 13, macular hole). In conclusion, in this study, visual acuity has not improved significantly from baseline; the rate of disease progression was not significantly different compared with the control eyes. Long-term follow-up will continue for these patients.

The role of maternal age & birth order on the development of unilateral and bilateral retinoblastoma: a multicentre study.

Eye (Lond). 2022 Mar 31. doi: 10.1038/s41433-022-01992

Lloyd P, Westcott M, Kaliki S, Ji X, Zou Y, Rashid R, Sultana S, Sherief ST, Cassoux N, Diaz Coronado RY, Garcia Leon JL, López AMZ, Polyakov VG, Ushakova TL, Roy SR, Ahmad A, Harby LA, Berry JL, Kim J, Polski A, Astbury NJ, Bascaran C, Blum S, Bowman R, Burton MJ, Foster A, Gomel N, Keren-Froim N, Madgar S, Stacey AW, Mohamed A, Zondervan M, Sagoo MS, Fabian ID, Reddy MA. Large retrospective cohort analysis for factors influencing the development of de novo germline pathogenic variants in RB1. 688 patients from 11 centres in 10 countries were analysed using a series of statistical methods. No associations were found between advanced maternal age, birth order or GDP per capita and the ratio of bilateral to unilateral retinoblastoma cases ( $p$  values = 0.534, 0.201, 0.067, respectively), indicating that these factors do not contribute to the development of a de novo pathogenic variant. The cohort lacks a definitive control group and genetic testing.

Decreased Levels of DNA Methylation in the PCDHA Gene Cluster as a Risk Factor for Early-Onset High Myopia in Young Children.

Swierkowska J, Karolak JA, Vishweswaraiyah S, Mrugacz M, Radhakrishna U, Gajicka M. Invest Ophthalmol Vis Sci. 2022 Aug 2;63(9):31.

This is a cohort study looking at DNA methylation pattern based on genome-wide methylation data of 18 Polish children with early onset high myopia (HM), compared to a control group. Genes overlapping CG dinucleotides with decreased methylation level in HM cases were assessed by enrichment analyses. Genes with CG dinucleotides in promoter regions were further evaluated based on exome sequencing data. The authors identified *PCDHA10* that overlaps intronic regions of *PCDHA1–9* of the *PCDHA* gene cluster in myopia 5q31 locus. Also, two single nucleotide variants, rs200661444 and rs246073, previously found as associated with a refractive error in a genome-wide association study, were revealed within this gene cluster. Additionally, genes previously linked to ocular phenotypes, myopia-related traits, or loci, including *ADAM20*, *ZFAND6*, *ETS1*, *ABHD13*, *SBSPON*, *SORBS2*, *LMOD3*, *ATXN1*, and *FARP2*, were found to have decreased methylation. The results suggest that epigenetics may play a role in early onset high myopia, and differential CG dinucleotide methylation has potential to be used as noninvasive biomarkers.

Clinical and Genetic Analysis of RDH12-Associated Retinopathy in 27 Chinese Families: A Hypomorphic Allele Leads to Cone-Rod Dystrophy.

Wang J, Wang Y, Li S, Xiao X, Yi Z, Jiang Y, Li X, Jia X, Wang P, Jin C, Sun W, Zhang Q. Invest Ophthalmol Vis Sci. 2022 Aug 2;63(9):24.

In this cohort study of 29 patients from 27 Chinese families with *RDH12* associated retinal dystrophy, the authors sought to elucidate the genotype-phenotype correlation of biallelic variants. Two distinct phenotypes were observed: early-onset and generalized retinal dystrophy with severe impairment of rods and cones in 24 patients (82.8%), and late-onset cone-rod dystrophy (CORD) with central macular atrophy in 5 patients from 5 unrelated families (17.2%), in which a hypomorphic allele (c.806C>G/p.Ala269Gly) was shared by all 5 patients. Patients with late-onset CORD were relatively stable and had little progression, thought to be due to retinol dehydrogenase activity being partially maintained by the hypomorphic allele. This study demonstrates the importance of genetic testing in prognostication of *RDH12* retinopathy.

Dominant Cone Rod Dystrophy, Previously Assigned to a Missense Variant in *RIMS1*, Is Fully Explained by Co-Inheritance of a Dominant Allele of *PROM1*.

Martin-Gutierrez MP, Schiff ER, Wright G, Waseem N, Mahroo OA, Michaelides M, Moore AT, Webster AR, Arno G; Genomics England Research Consortium.

Invest Ophthalmol Vis Sci. 2022 Aug 2;63(9):14.

Autosomal dominant cone rod dystrophy 7 (CORD7) was initially linked to the gene *RIMS1* as reported in a 4-generation British family in 1998. The authors of this study aimed to investigate the validity of this association, and to further characterize the genetic cause of this condition. The allele frequency of *RIMS1* c.2459G>A, p.Arg820His, was investigated in the Genomes Aggregation Dataset and found to have a maximal carrier frequency of >1:5000 in Europeans, and it is considered too high for a fully penetrant dominant vision loss variant. Further, whole genome sequencing was performed for members of the CORD7, with cytogenetic analysis performed to rule out interchromosomal translocation. A previously well-characterized *PROM1* variant: c.1118C>T, p.Arg373Cys, was detected in 9 affected members of the CORD7 family. One affected family member is now known to have macular dystrophy in the absence of *RIMS1* p.Arg820His, but unavailable for *PROM1* testing. Clinical analysis of affected family members and 27 individuals with retinopathy associated with the same – *PROM1* – variant showed consistent phenotypes. Therefore, the authors conclude that the disease entity CORD7 is unlikely to be related to *RIMS1* mutation, and is instead consistent with *PROM1* retinopathy.

UBE2T/STAT3 Signaling Promotes the Proliferation and Tumorigenesis in Retinoblastoma.

Xu N, Cui Y, Shi H, Guo G, Sun F, Jian T, Rao H.

Invest Ophthalmol Vis Sci. 2022 Aug 2;63(9):20.

The Ubiquitin-conjugating enzyme 2T (UBE2T) belongs to the members of the ubiquitin E2 family and a ubiquitin conjugation (UBC) domain is contained. UBE2T participates in the process of ubiquitin activation, and its function is important for regulation of DNA damage. UBE2T has been shown to play an oncogenic role in various human malignancies, and high expression of this gene was associated with poor survival in these cancers. This study aims to address the role of UBE2T in retinoblastoma. The expression of UBE2T in normal retina and retinoblastoma was analyzed using the Gene Expression Omnibus (GEO) databases, and its expression was immunohistochemically evaluated in 29 retinoblastoma sections and 5 normal retinas. The authors found higher UBE2T expression in retinoblastoma than normal retina in GEO datasets and tissues. Higher immunoreactive score of UBE2T was associated with poorly differentiated retinoblastoma, and high-risk histopathological factors. In vivo studies demonstrated that knockdown of UBE2T inhibited subcutaneous tumor growth in a retinoblastoma cell line. Mechanistic studies showed that UBE2T knockdown induced down-regulation of phosphorylation of STAT3 and its downstream genes in vitro and in vivo. This study shows that UBE2T plays a role in retinoblastoma pathogenesis, and it may be a biomarker for high risk disease, as well as provide a potential target for therapeutics.

Sonic Hedgehog Intron Variant Associated With an Unusual Pediatric Cortical Cataract.

Young TL, Whisenhunt KN, LaMartina SM, Hewitt AW, Mackey DA, Tompson SW.

Invest Ophthalmol Vis Sci. 2022 Jun 1;63(6):25.

The authors of this study previously reported a large Australian family of European descent that variably presented with four ocular phenotypes: (1) pediatric cortical cataracts (PCC), (2) familial exudative



vitreoretinopathy, (3) asymmetric myopia with astigmatism, and (4) primary open-angle glaucoma. The pedigree revealed that the PCC phenotype segregated in an autosomal dominant inheritance pattern, suggesting a single genetic cause. In this study, the authors report the identification of an associated variant. DNA from affected individuals were exome sequenced. Additionally, DNA from affected and unaffected individuals were genotyped, and multipoint linkage and haplotyping were performed. Rare small insertions/deletions and single-nucleotide variants (SNVs) were identified in the disease-linked. Combined Annotation Dependent Depletion analysis predicted variant deleteriousness. The results led to the discovery of a predicted highly deleterious novel substitution within intron-1 of the *sonic hedgehog signaling molecule (SHH)* gene, which is known to be important for lens formation. Cell-based assay data showed this variant causes enhanced gene expression. This study identified a new SHH intron variant associated with pediatric cortical cataract, and suggests that in hereditary pediatric cataract, SHH pathway genes should be evaluated.

Phenotype-Based Genetic Analysis Reveals Missing Heritability of ABCA4-Related Retinopathy: Deep Intronic Variants and Copy Number Variations.

Tian L, Chen C, Song Y, Zhang X, Xu K, Xie Y, Jin ZB, Li Y.  
Invest Ophthalmol Vis Sci. 2022 Jun 1;63(6):5.

*ABCA4* is associated with inherited retinal degeneration and has a high carrier frequency of approximately 1:20. Biallelic *ABCA4* variants cause *ABCA4*-related retinopathies with extensive clinical heterogeneity. More than 1600 disease-causing *ABCA4* variants have been identified. This study of a cohort of 33 unrelated patients with *ABCA4*-related retinopathy carrying a monoallelic variant in *ABCA4* aims to identify pathogenic deep intronic variants (DIV) and copy number variation (CNV). Next generation sequencing of the whole *ABCA4* sequence, including coding and noncoding regions, was performed to detect deep intronic variants (DIVs) and copy number variations (CNVs) in these patients. The authors identified eight missing pathogenic *ABCA4* variants in 60.6% of the patients, including 5 DIVs and 3 CNVs. Minigene assays showed that the novel DIVs activated cryptic splice sites leading to the insertions of pseudoexons. The novel CNVs consisted of one gross deletion of 1273 bp (exon 2) and two gross duplications covering 25.2 kb (exons 28–43) and 9.4 kb (exons 38–44). These findings further explain the genotype-phenotype correlation of this autosomal recessive disease in patients who were previously thought to have a monoallelic variant, demonstrating the importance of identification of pathogenic DIVs and CNVs in genetic diseases.

Different Phenotypes Represent Advancing Stages of ABCA4-Associated Retinopathy: A Longitudinal Study of 212 Chinese Families From a Tertiary Center.

Wang Y, Sun W, Zhou J, Li X, Jiang Y, Li S, Jia X, Xiao X, Ouyang J, Wang Y, Zhou L, Long Y, Liu M, Li Y, Yi Z, Wang P, Zhang Q.  
Invest Ophthalmol Vis Sci. 2022 May 2;63(5):28.

This retrospective study of 228 Chinese patients with *ABCA4* related retinopathy, including 42 with longitudinal follow-up, aims to evaluate the variation in phenotype and natural progression of this disease. Of 185 patients with available fundus images, 107 (57.8%) showed focal lesions restricted to the central macula without flecks. Among these 107 patients, 30 patients (28.0%) initially presented with relatively preserved visual acuity and minimal retinal changes on fundus photograph. A pigmentary change in the posterior pole was observed in 22 of 185 patients (11.9%), and this change mimicked retinitis pigmentosa in 10 cases (45.5%). Follow-up visits and sibling comparisons demonstrated disease progression reflected in the change in clinical appearance. An earlier age of onset was associated with a more rapid decrease in visual acuity ( $P = 0.03$ ). Patients with two truncation variants had an earlier age of onset compared to those with one truncation and one missense mutation. This study demonstrates that that phenotypic variation in *ABCA4* related retinopathy may be in part due to the progressive nature of the disease.

Central Visual Function and Genotype-Phenotype Correlations in PDE6A-Associated Retinitis Pigmentosa.

Kuehlewein L, Straßer T, Blumenstock G, Stingl K, Fischer MD, Wilhelm B, Zrenner E, Wissinger B, Kohl S, Weisschuh N, Zobor D; RD-CURE Consortium. Invest Ophthalmol Vis Sci. 2022 May 2;63(5):9.

Autosomal recessive retinitis pigmentosa (arRP) can be caused by mutations in the phosphodiesterase 6A (*PDE6A*) gene. In this retrospective study, the authors describe the natural course of disease progression with respect to central retinal function (assessed by visual acuity, contrast sensitivity, and color vision) and establish a detailed genotype–phenotype correlation. Forty-four patients (26 females; mean age  $\pm$  SD, 43  $\pm$  13 years) with a confirmed genetic diagnosis of *PDE6A*-associated arRP underwent comprehensive ophthalmological examinations. Different mutation variants were correlated with varying levels of severity of disease as determined by central visual function. Annual decline rate of central visual function was found to be small, though a limitation of this study is that the mean and median follow up time is only a little over 2 years. This study provides further information on the *PDE6A*-associated arRP. The genotype-phenotype information may help with prognosis counseling as well as determining eligibility criteria for future clinical trials.

Retinal Phenotype of Patients with *CLRN1*-Associated Usher 3A Syndrome in French Light4Deaf Cohort. Smirnov VM, Nassisi M, Mohand-Saïd S, Bonnet C, Auboïs A, Devisme C, Dib T, Zeitz C, Loundon N, Marlin S, Petit C, Bodaghi B, Sahel JA, Audo I. Invest Ophthalmol Vis Sci. 2022 Apr 1;63(4):25.

Biallelic variants in *CLRN1* are responsible for Usher syndrome 3A and nonsyndromic rod–cone dystrophy (RCD). This study of 4 unrelated patients from France, 3 of whom had mean follow up of 11 years (one patient only had baseline exam), aimed to characterize phenotype of RCD associated with *CLRN1* variants. Median BCVA at baseline was 0.2 logMAR (range, 0.3–0). ffERG responses were undetectable in all subjects. The III4e isopter of the Goldmann visual field was constricted to 10°. The retinal phenotype was consistent in all patients: small whitish granular atrophic areas were organized in a network pattern around the macula and in the midperiphery. OCT showed intraretinal microcysts in all patients. All patients with follow up data experienced a progressive BCVA loss and further visual field constriction. Four distinct pathogenic variants were identified in our patients: two missense and two frameshift variants. This study characterized *CLRN1* associated to be a severe photoreceptor dystrophy with whitish granular posterior pole appearance and cystic maculopathy. Notably, patients have early onset, all four with symptoms of night blindness by age 10-12. It is also a progressive disease. This is helpful for prognosis counseling and may provide therapeutic target for future studies.

*ABCA4* c.859-25A>G, a Frequent Palestinian Founder Mutation Affecting the Intron 7 Branchpoint, Is Associated With Early-Onset Stargardt Disease

Corradi Z, Salameh M, Khan M, Héon E, Mishra K, Hitti-Malin RJ, AlSwaiti Y, Aslanian A, Banin E, Brooks BP, Zein WM, Hufnagel RB, Roosing S, Dhaenens CM, Sharon D, Cremers FPM, AlTalbish A. Invest Ophthalmol Vis Sci. 2022 Apr 1;63(4):20.

This study characterized an *ABCA4* intron 7 variant, c.859-25A>G, identified in Palestinian probands with Stargardt disease (STGD) or cone-rod dystrophy (CRD). The authors studied the effect of this variant on the *ABCA4* mRNA and retinal phenotype. Genetic sequencing revealed c.859-25A>G in 10 Palestinian probands from Hebron and Jerusalem. In silico analysis was performed using SpliceAI, which predicted a significant effect of exon 8 skipping and two partial inclusions of intron 7, each having a deleterious effect, likely to induce nonsense-mediated RNA decay and result in the absence of *ABCA4* activity. Phenotype characterization revealed that patients who are homozygous for this allele but have no other known pathogenic mutations had mean visual acuity of 1.1 logMAR, indicating legal blindness (at mean age of 12 years), and all had foveal atrophy. This study highlights the relevance of splicing prediction tools to identify elusive splice-altering variants that have the potential to strongly impact genetic diagnosis, and the importance of studying intronic variants in genetic diseases.

New *COL6A6* Variant Causes Autosomal Dominant Retinitis Pigmentosa in a Four-Generation Family. Vaclavik V, Tiab L, Sun YJ, Mahajan VB, Moulin A, Allaman-Pillet N, Munier FL, Schorderet DF.

Invest Ophthalmol Vis Sci. 2022 Mar 2;63(3):23.

The study was conducted in a four-generation Swiss/French family. Eighteen patients were affected with typical retinitis pigmentosa. The transmission pattern of this four-generation family was consistent with autosomal dominant inheritance. Affected members have symptoms of slowly declining visual acuity, constricted visual field, and on exam have macular edema, and atrophy and bone spicules typical for RP. A genome-wide linkage analysis was performed, as well as whole exome sequencing in 3 of the affected individuals. *COL6A6* was identified as a candidate gene. *COL6A6* (collagen type VI alpha 6 chain, *Col6a6*) is a gene that encodes a large lamina basal component protein. Immunohistochemistry studies in healthy human retinas from enucleated eyes showed expression of *col6a6* in the retina with a dot-like signal at the base of the inner segments of photoreceptors and in the outer plexiform layer. More studies are needed to further validate these findings, and *COL6A6* may be a gene to add to the adRP panel.

Association of Novel Loci With Keratoconus Susceptibility in a Multitrait Genome-Wide Association Study of the UK Biobank Database and Canadian Longitudinal Study on Aging.

He W, Han X, Ong JS, Hewitt AW, Mackey DA, Gharahkhani P, MacGregor S; International Glaucoma Genetics Consortium.

JAMA Ophthalmol. 2022 Jun 1;140(6):568-576.

Keratoconus is a corneal ectasia that is potentially debilitating, requiring corneal transplant in advanced cases. Recent estimates of the prevalence of keratoconus based on results of Scheimpflug imaging in young adults are as high as 1.2%. Family-based studies suggest there is a hereditary component to keratoconus, with first-degree relatives of cases having as much as a 67-fold increased risk relative to that of the general population. Obtaining a sufficiently large keratoconus data set for a genome-wide association study (GWAS) is difficult, so most genes for keratoconus remain undetected. As an alternative to performing GWAS of keratoconus directly, recent GWASs of quantitative corneal parameters have proven useful. Central corneal thickness (CCT) is one of the most heritable quantitative traits in humans, with heritability estimates as high as 95%. Keratoconus patients typically have thinner corneas, thus CCT is a directly relevant quantitative phenotype. Corneal resistance factor (CRF), another quantitative corneal parameter, refers to the indication of the overall resistance or elasticity of the cornea. CRF is significantly decreased in eyes with keratoconus. Genetic factors play an important role in CRF variation as well. Previous research has found that the prevalence of keratoconus varies by ancestry, and that CCT and CRF also differ between ancestries. This study aims to identify novel keratoconus loci using CCT and CRF. This multitrait GWAS used European ancestry CRF data from UK Biobank (UKB) ( $n = 105\,427$ ) and the Canadian Longitudinal Study on Aging (CLSA) ( $n = 18\,307$ ) and European ancestry CCT data from the International Glaucoma Genetics Consortium (IGGC) ( $n = 17\,803$ ). The CRF and CCT variants in published keratoconus data sets (4669 cases and 116 547 controls) were compared. The GWAS included 4 cohorts: 105 427 UKB European ancestry, 5029 UKB South Asian ancestry, 902 UKB East Asian ancestry, and 18 307 CLSA European participants. A total of 369 CRF and 233 CCT loci were identified, including 36 novel CRF loci and 114 novel CCT loci. Twenty-nine CRF loci and 24 CCT loci were associated with keratoconus. Polygenic risk scores (PRS) were constructed using CRF- and CCT-associated variants and published keratoconus variants. The PRS result showed that adding a CRF- or CCT-based PRS to the keratoconus PRS from previously published variants improved the prediction area under the receiver operating characteristic curve (from 0.705 to 0.756 for CRF and from 0.715 to 0.755 for CCT). These findings support the use of multitrait modeling of corneal parameters so that larger data sets can be used to identify new keratoconus risk loci and enhance polygenic risk score models.

Pineoblastoma Without Retinal Tumors in a Patient With a Mosaic Retinoblastoma Pathogenic Variant.

Mustafi D, Waligorski N, Paulson V, Cole B, Crotty EE, Stacey AW.

JAMA Ophthalmol. 2022 Apr 1;140(4):437-439.

Retinoblastoma is the most common pediatric ocular malignancy, affecting 1 child in 14000 live births. Between 3% and 5% of patients with germline variants in the retinoblastoma (*RB1*) gene develop a midline intracranial neoplasm, most commonly a pineoblastoma. These intracranial tumors usually arise in the pineal or sellar region and are referred to as trilateral retinoblastoma when associated with preceding or concurrent retinal tumors. However, trilateral retinoblastoma is thought to develop independently of intraocular retinoblastoma. *RB1* pathogenic variants have not traditionally been

considered in patients with isolated pineoblastoma. This is a case report of a patient with de novo, mosaic retinoblastoma with a pineoblastoma as the primary tumor without ocular involvement. This patient's tumor pathology revealed small round blue cells consistent with pineoblastoma. Sequencing of the tumor tissue was negative for *DICER1* gene variants but positive for a pathogenic *RB1* c.1215+1G>A variant with loss of heterozygosity resulting in biallelic inactivation. This *RB1* variant was identified in the peripheral blood at a 4% allele fraction, verifying a low-level mosaic *RB1* variant. Dilated fundus exams at a regular interval showed no intraocular tumors, including at the most recent exam 1.5 years after diagnosis of pineoblastoma. This study highlights the importance of paired testing to increase the detection rate of low level mosaic variants. Further, it raises the importance of evaluating for *RB1* pathogenic variants in young children with pineoblastoma.

Short-term Assessment of Subfoveal Injection of Adeno-Associated Virus-Mediated hCHM Gene Augmentation in Choroideremia Using Adaptive Optics Ophthalmoscopy.  
Morgan JIW, Jiang YY, Vergilio GK, Serrano LW, Pearson DJ, Bennett J, Maguire AM, Aleman TS.  
JAMA Ophthalmol. 2022 Apr 1;140(4):411-420.

In gene therapy for retinal degeneration diseases, subretinal injection forcefully detaches the neural retina from the retinal pigment epithelium, potentially damaging photoreceptors and/or retinal pigment epithelium cells. This study uses adaptive optics scanning light ophthalmoscopy (AOSLO) to assess the short-term integrity of the cone mosaic following subretinal injections of adeno-associated virus vector designed to deliver a functional version of the *CHM* gene (*AAV2-hCHM*) in patients with choroideremia. This is a longitudinal case series study that enrolled 9 adult patients with choroideremia who underwent unioocular subfoveal injections of *AAV2-hCHM*. Imaging pre and post injection (1 month) of bilateral macula was performed using a custom-built multimodal AOSLO. Postinjection cone inner segment mosaics were compared with preinjection mosaics at multiple regions of interest. OCT and dark-adapted cone sensitivity was also acquired. Postinjection AOSLO images showed preservation of the cone mosaic in all 9 *AAV2-hCHM*-injected eyes. Mosaics appeared intact and contiguous 1 month postinjection, with the exception of foveal disruption in 1 patient. Optical coherence tomography showed foveal cone outer segment shortening postinjection. Cone-mediated sensitivities were unchanged in 8 of 9 injected and 9 of 9 uninjected eyes. One participant who underwent uneventful surgery showed acute loss of foveal optical coherence tomography cone outer segment-related signals along with cone sensitivity loss that colocalized with disruption of the mosaic on AOSLO. This study is an important evaluation of the safety of subfoveal injection therapy. The results provide evidence in support of subfoveal injections being generally safe. Minor foveal thinning observed following surgery corresponds with short-term cone outer segment shortening rather than cone cell loss, and the study mentions preliminary data of the foveal thickness slowly recovering over 6 months postinjection. This is an important aspect of safety profile of this drug delivery mechanism.

Expanding the phenotypic spectrum of pathogenic variants in the *PRRT2* gene: bilateral papilledema and abducens nerve palsies secondary to pseudotumor cerebri syndrome.

Ng JKY, Sadia R, Ram D, Jones EA, Biswas S.  
J AAPOS. 2021 Dec;25(6):364-366.

Pathogenic variants in the proline-rich transmembrane protein 2 (*PRRT2*) gene are associated with a wide range of clinical expressions but most commonly paroxysmal kinesigenic dyskinesia, benign familial infantile epilepsy, paroxysmal kinesigenic dyskinesia with infantile convulsions (PKD/IC), and hemiplegic migraine. This case report describes an 8-year-old girl with known heterozygosity for the *PRRT2* c.649dupC;p.Arg217 pathogenic variant, who was diagnosed with acute onset esotropia, papilledema, and bilateral abduction deficit consistent with bilateral abducens nerve palsy. Her work up included a normal MRI, lumbar puncture with increased opening pressure, and she was subsequently diagnosed with pseudotumor cerebri syndrome (PTCS). She was treated with oral acetazolamide, with resolution of symptoms by 2 months follow up. A previous report of another patient with heterozygous pathogenic *PRRT2* variants described an episode of acute onset of unilateral abducens nerve palsy with high lumbar puncture opening pressure, although without papilledema; symptoms also quickly resolved with acetazolamide. These two cases together suggest a possible rare association pseudotumor cerebri syndrome and pathogenic variants in *PRRT2* gene. Further studies are needed to elucidate this possible

connection. However, in patients with known PRRT2 pathogenic variants, new onset headache or esotropia should undergo work up for PTCS.

Microphthalmia and orbital cysts in DiGeorge syndrome.

Chandramohan A, Sears CM, Huang LC, Beres S, Fredrick D, Kossler AL.

J AAPOS. 2021 Dec;25(6):358-360.

This is a case report of a 4-month-old with known DiGeorge syndrome (22q11.2 deletion), confirmed through genetic testing soon after birth, with developmental abnormalities of large ventricular septal defect, interrupted aortic arch, Hirschsprung's disease, and noted scattered intracranial hemorrhages on imaging, who presented for evaluation of a left orbital mass with unidentifiable intraconal optic nerve on initial MRI. The patient was noted to have bilateral microphthalmia. The right eye had microcornea, partial aniridia, a slightly subluxed lens, and a large chorioretinal coloboma involving the optic nerve and macula. The left eye was noted to have restricted extraocular movements and was obscured by an inferior orbital mass protruding into the lower eyelid, causing mechanical ectropion. The left eye was also noted to have microcornea, and complete chorioretinal coloboma, with visible retrolental persistent fetal vasculature (PFV) stalk. MRI also showed a large intraconal cyst extending from the left optic nerve head and causing superior displacement of the left globe. Ocular findings in DiGeorge syndrome, including eyelid abnormalities, posterior embryotoxon, Peters anomaly, and colobomas, are largely due to early developmental dysgenesis. Microphthalmia with orbital cysts, a presentation on the spectrum of colobomatous eye disorders, should be noted as a possible manifestation of DiGeorge syndrome-related ocular dysgenesis. Although DiGeorge syndrome is normally associated with mild ocular complications, this case illustrates that more extreme forms of ocular and orbital malformation are possible.

Aqueous humor as a surrogate biomarker for retinoblastoma tumor tissue.

Raval V, Racher H, Wrenn J, Singh AD.

J AAPOS. 2022 Jun;26(3):137.e1-137.e5.

The authors of this study aims to demonstrate the feasibility of identifying a germline RB1 pathogenic variant in retinoblastoma (RB) from an aqueous humor (AH) sample. Three eyes of 3 RB patients who underwent enucleation were included in this study; peripheral blood, fresh tumor tissue, and aqueous humor (AH) were obtained. After isolation of the cell-free DNA (cfDNA), sequence analysis of RB1 was performed. In all 3 cases, concordant RB1 mutations were identified in the tumor and AH samples. In one of these cases, it was also identified in the peripheral blood sample (absent in the other two patients' blood sample). This study shows that AH can serve as an important surrogate for tumor tissue in the genetic diagnosis of RB. AH can be access much easier during treatment, so this may be a way to access tumor DNA without enucleation. However, a limitation is that the concentration of cfDNA in AH is correlated to tumor burden. The success in these three eyes may be related to the eyes having greater tumor burden necessitating enucleation. Further studies in retinoblastoma eyes with lower tumor burden would be needed to validate this method.

Consanguinity and severity of primary congenital glaucoma.

Gupta V, Bhandari A, Gupta S, Singh A, Gupta A.

J AAPOS. 2022 Jun;26(3):119.e1-119.e5.

Primary congenital glaucoma (PCG) is a rare, vision-threatening disease that presents within the first year of life. PCG occurs in both sporadic and familial patterns. Inheritance is autosomal recessive in most familial cases and there is an increased incidence with consanguinity. This retrospective cohort study evaluates the severity of primary congenital glaucoma (PCG) among children born of consanguineous marriage. Medical records of unrelated consanguineous patients and unrelated nonconsanguineous (control) PCG patients seen at a single tertiary eye care facility were reviewed. Those with a minimum of 5 years' follow-up were included. A total of 130 PCG patients were included: 30 patients born of consanguineous marriage and 100 nonconsanguineous control patients. The median age of presentation for consanguineous cases was 3 months (range, 1-36) compared with 10 months (range, 2-24) for nonconsanguineous cases ( $P < 0.001$ ). Mean corneal diameter for consanguineous cases was 13 mm and for nonconsanguineous cases was 12.41mm ( $P = 0.002$ ). Consanguineous cases also had a significantly

higher prevalence of corneal haze persisting after surgery ( $P < 0.001$ ) and need for repeat IOP-lowering surgery ( $P = 0.039$ ). The consanguineous group had 44 eyes (73%) with severe PCG compared with 69 (34.5%) in the nonconsanguineous group ( $P < 0.001$ ). In this study cohort, children with PCG born of consanguineous parents were more severely affected at presentation and had worse surgical outcomes compared with children born of nonconsanguineous parents. Founder effect with consanguinity cannot be ruled out, since this study lacks genetic diagnosis for each patient. However, consanguinity should be considered as a risk factor for severe disease in the treatment of PCG, and should be considered as a confounder in studies evaluating outcomes.

Ophthalmic abnormalities in Wieacker-Wolff syndrome.

Comlekoglu T, Kumar V, King K, Al Saif H, Li R, Couser N.

J AAPOS. 2022 Apr;26(2):91-93.

Wieacker-Wolff syndrome is an X-linked condition caused by variants of the ZC4H2 gene that results in in utero muscular weakness that manifests clinically as arthrogryposis congenita as well as facial and bulbar weakness. The authors report the case of a young girl with a de novo pathogenic deletion in the ZC4H2 gene and clinical features consistent with Wieacker-Wolff syndrome. This study provided aggregated data from other reports, and found that the most common ophthalmic manifestations being ptosis and strabismus, which may reflect a broader abnormality of muscular control or neuromuscular development within the syndrome. Additionally, female patients more frequently had strabismus (62.5% vs 28.9%) and deep-set eyes (33.3% vs 15.8%), whereas male patients more frequently displayed ptosis (76.3% vs 45.85), upslanting palpebral fissures (23.7% vs 4.2%), oculomotor apraxia (15.8% vs 8.3%), delayed pupillary responses (10.5% vs 4.2%), and nystagmus (10.5% vs 8.3%). Total number cases reported for Wieacker-Wolff syndrome is small, and future genotype–phenotype correlations should be performed to better understand the ophthalmic manifestations. This study shows that ocular symptoms are common and eye exams should be a part of the medical evaluation for this syndrome.

Commonly occurring genetic polymorphisms with a major impact on the risk of nonsyndromic strabismus: replication in a sample from Finland.

Plotnikov D, Pärssinen O, Williams C, Atan D, Guggenheim JA.

J AAPOS. 2022 Feb;26(1):12.e1-12.e6.

Genetics plays an important role in isolated nonsyndromic strabismus. Recent studies of individuals of European ancestry have identified three regions of the human genome containing “copy number variant” polymorphisms associated with isolated esotropia. This study aims to replicate associations between previously discovered polymorphisms in the WRB and TSPAN10 genes and strabismus in an independent Finnish cohort, and to calculate their population attributable risk. The FinnGen project is a large existing database (183,694 participants genotyped for 655,973 markers) that aims to identify genotype-phenotype correlations in the Finnish population. Polymorphisms in WRB (rs2244352) and TSPAN10 (rs6420484) were investigated in individuals from the FinnGen study group who had a diagnosis of strabismus (including three categories: “all subtypes”, “convergent concomitant strabismus”, and “divergent concomitant strabismus”). The authors found WRB polymorphism was associated with “all subtypes” of strabismus (OR=1.08;  $P=0.008$ ) and divergent strabismus (OR = 1.11;  $P = 0.046$ ) but not with convergent strabismus ( $P = 0.41$ ). The WRB polymorphism had a population attributable risk of 3.4% for all strabismus subtypes and 4.7% for divergent strabismus. The TSPAN10 polymorphism was associated with all three strabismus phenotypes: all subtypes (OR = 1.08;  $P = 0.002$ ), convergent strabismus (OR = 1.19;  $P = 0.001$ ) and divergent strabismus (OR= 1.20;  $P = 7.21E-05$ ). The population attributable risk for the TSPAN10 polymorphism was 6.0% for any strabismus, 13.3% for convergent strabismus, and 13.9% for divergent strabismus. The genetic association of WRB and TSPAN10 polymorphisms were replicated in this Finnish cohort, which, independent of other risk factors, are responsible for up to 20% of isolated cases of strabismus in Finland, similar to previous findings in the UK cohort. These findings help elucidate the understanding of the genetic basis of strabismus.

Ocular and adnexal anomalies in Treacher Collins syndrome: a retrospective multicenter study.

Rooijers W, Schreuder MJ, Loudon SE, Wan MJ, Dunaway DJ, Padwa BL, Forrest CR, Koudstaal MJ, Caron CJJM.

J AAPOS. 2022 Feb;26(1):10.e1-10.e6.

Treacher Collins syndrome (TCS) is a rare craniofacial disorder characterized by bilateral hypoplasia of facial structures and periorbital, ocular, and adnexal anomalies. It is an autosomal dominant inherited syndrome with mutations in TCOF1 on chromosome 5q31.3-q33.3, which encodes for the Treacle protein, a protein involved in neural crest cell (NCC) formation. The purpose of this multicenter retrospective review study was to report the prevalence of ocular and adnexal anomalies in TCS and to identify patients at risk for visual impairment. A total of 194 patients were included, of whom 49.5% were examined by an ophthalmologist or optometrist. Primary ocular anomalies were reported in 98.5% of cases, secondary anomalies in 34.5%, strabismus in 27.3%, refractive errors in 49.5%, and visual impairment in 4.6%. The results found no association between ocular anomalies and visual impairment or between the severity of TCS and ocular anomalies or visual impairment, except for an increased prevalence of secondary ocular anomalies in patients with more severe manifestations of TCS. This descriptive study of ocular findings in TCS in a large cohort reiterates the high prevalence of ocular anomalies in TCS, and highlights the importance of eye exams for TCS patients.

Congenital primary aphakia.

Ernst J, Medsing A, Scanga HL, Hiasat J, Moore W, Ali A, Levin AV, Stahl ED, Nischal KK.

J AAPOS. 2022 Feb;26(1):4.e1-4.e5.

Congenital primary aphakia (CPA) is a rare anomaly in which the lens fails to form. A normal lens is essential for the development of a transparent normal cornea. Eyes with CPA show severe panocular dysgenesis, including microphthalmia, retinal dysplasia, and corneal opacity. CPA is associated with pathogenic variants in FOXE3 (forkhead box E3), which encodes a transcription factor specifically expressed during lens development in the lens epithelium. Pathogenic variants of FOXE3 can give rise to a wide range of phenotypes, largely but not exclusively connected to lens development, with different patterns of inheritance. This multicenter retrospective consecutive case series from five academic centers in England and North America aims to describe the natural history, management, and visual outcome in children with CPA. Twenty-seven eyes of 14 patients were included. Thirteen patients had bilateral CPA, and 1 patient had unilateral CPA. Mean age at diagnosis was 18 months. Of 11 patients who underwent genetic testing, 9 had FOXE3 pathogenic variants. One patient displayed characteristic features of Wolf-Hirschhorn syndrome, confirmed by karyotyping. The remaining patient was found to have a novel heterozygous PAX2 missense variant of uncertain significance. Phenotypically, findings included silvery appearance of the cornea with vascularization (96%), glaucoma (81%), iridocorneal adhesions (74%), optic nerve coloboma (55%), abnormal vitreous (33%), retinal detachment (30%), and aniridia with hypoplasia of ciliary body (19%). Surgical interventions in select patients included penetrating keratoplasty, glaucoma drainage device implantation, and cyclophotocoagulation. Of note, nearly all eyes that underwent PKP ended in phthisis due to tractional retinal detachment. This study shows that CPA has poor visual outcome due to multiple associated ocular anatomical anomalies. Surgery should be considered with caution. The goal of care is to maintain control IOP and avoid phthisis.

Autosomal recessive congenital hereditary corneal dystrophy associated with a novel SLC4A11 mutation in two consanguineous Tunisian families.

Chibani Z, Abid IZ, Söderkvist P, Feki J, Aifa MH.

Br J Ophthalmol. 2022 Feb;106(2):281-287.

This study aimed to explore CHED in Tunisia by performing a phenotypic and genetic analysis on 2 large consanguineous Tunisian families affected with CHED. There were 4 total affected members with autosomal recessive CHED. All coding exons of SLC4A11 gene known to be associated with CHED and their exon-intron boundaries regions were amplified with PCR for all affected family members and a selection of non-affected members (6 total). To identify sequence variations, the sequencing results from all subjects (affected and healthy) were compared with wild type SLC4A11 sequence, and the effect of c.1434\_1436del mutation was also assessed. Mutation screening of the SLC4A11 gene by Sanger sequencing revealed a novel deletion mutation: c.1434\_1436del resulting in a non-frameshift deletion of a Leucine, p. Leu479del, localized in exon 11 of the SLC4A11 gene. This mutation was found in a homozygous state in all 4 affected members while the parents were heterozygous for the mutation highlighting an autosomal recessive mode of inheritance. These results expand the mutational spectrum

of CHED and further illustrate the genetic heterogeneity of this disease potentially leading to an accurate clinical and genetic diagnosis. Improved understanding of SLC4A11 dysfunction in CHED may lead to a better comprehension of the pathobiology of this inherited corneal disease.

CRB1-associated retinal dystrophies in a Belgian cohort: genetic characteristics and long-term clinical follow-up.

Talib M, Van Cauwenbergh C, De Zaeytijd J, Van Wynsberghe D, De Baere E, Boon CJF, Leroy BP. *Br J Ophthalmol*. 2022 May;106(5):696-704.

Mutations in the CRB1 gene account for 7%–17% of LCA cases, and 3%–9% of isolated, non-syndromic, autosomal recessive RP patients, making it one of the most common genetic causes of both LCA and RP. CRB1 mutations are also associated with rare cases of cone-rod dystrophy or macular dystrophy. To date, more than 230 pathogenic variants in CRB1 have been reported. Human subretinal gene therapy is being developed for CRB1-associated retinopathies, so the authors sought to publish a thorough investigation into the natural history and longitudinal characteristics in a large cohort of Belgian patients with CRB1-associated inherited retinal dystrophies. 40 patients were included from 35 families, 38% with LCA, 55% with RP and 8% with macular dystrophy. The median age at symptom onset or diagnosis was during the first year of life for patients with LCA, 5 years for patients with RP, and 18 years for patients with (initial) isolated macular dystrophy. The posterior segment findings described were typical for what is known about these IRDs and a descriptive table is included in the paper. The rate of BCVA decline in the better-seeing eye was 15.2%/year in patients with RP and 8.2%/year for LCA, indicating earlier intervention is best to preserve vision in these patients as expected.

Leber congenital amaurosis/early-onset severe retinal dystrophy: current management and clinical trials.

Daich Varela M, Cabral de Guimaraes TA, Georgiou M, Michaelides M.

*Br J Ophthalmol*. 2022 Apr;106(4):445-451.

This review provides an update of the treatments that are currently available and those that are in clinical trial for LCA and early-onset severe retinal dystrophy (EOSRDs). Several LCA/ EOSRD-associated genes have been targeted for gene supplementation therapy, in which a viral vector delivers DNA to the cells' nuclei leading to the transcription of a functional protein. For example, clinical trials targeting replacement of RPE65 have been in development since 2007, with Luxturna as the first and only gene therapy for an IRD approved by the Food and Drug Administration (2017) and is the only treatment trial for RPE65 that reached phase III. Biallelic variants in GUCY2D account for 10%–20% of cases worldwide, mostly associated with LCA but also some forms of cone or cone/rod dystrophy. A subretinal gene therapy aiming to preserve the structure of rods and cones is currently in phase I/II trials. A compassionate use gene therapy study is ongoing in the UK for AIPL1-LCA, responsible for only 1-2% of cases, in infants and young children with remaining outer retinal layers at the central macula. Another method of gene therapy consists of gene editing and post-transcriptional regulation. The first interventional phase I/II clinical trial treating individuals with CEP290-related LCA is underway utilizing an antisense oligonucleotide (AON) developed to block the aberrant splicing event and restore normal splicing. The first CRISPR-mediated retinal gene therapy clinical trial using EDIT-101 is ongoing, testing a subretinal injection of an AAV5 vector containing *Staphylococcus aureus* Cas9 and CEP290-specific guide RNAs. Visual cycle modulators have been under development for the last 10 years, with the aim of either decreasing the accumulation of various retinoid derivatives or to supply deficient compounds. Several studies are looking for ways to provide an exogenous supply of 11-cis-retinal which may prevent (or slow) photoreceptor degeneration. Subretinal transplantation of human embryonic stem cell derived RPE cells has been undertaken in individuals with AMD and Stargardt, and now are being attempted for the first time in patients with RP and LCA. Finally, some promise has been shown in the field of optogenetics for RP patients, which aims to repurpose second-order and third-order neurons of the visual pathway (bipolar and ganglion cells), so the authors believe this may also work for LCA patients. Many exciting trials on the horizon!

Novel disease-causing variant in RDH12 presenting with autosomal dominant retinitis pigmentosa.

Muthiah MN, Kalitzeos A, Oprych K, Singh N, Georgiou M, Wright GA, Robson AG, Arno G, Khan K, Michaelides M.

*Br J Ophthalmol*. 2022 Sep;106(9):1274-1281.



Twelve patients with a diagnosis of rod-cone dystrophy and a single, heterozygous, plausibly pathogenic variant in RDH12 were identified from a single family in the UK. Six patients first noted nyctalopia in their early-to-mid teenage years, and manifested signs of a rod-cone dystrophy in an age range of 12–72 years (at time of this study). Visual acuity ranged from –0.1 to 0.2 logMAR, however, reduced acuity appeared to be associated with macular edema rather than duration of disease. Five additional members of the family were examined. All were asymptomatic, and had a normal eye examination. The rare RDH12 variant was not identified in four of these individuals who underwent genotyping. fundus autofluorescence, OCT, Goldmann kinetic perimetry, ERG, and Confocal images to assess cone density are all described for the various patients. These findings indicate that the new variant in RDH12 is associated with a rod-cone dystrophy with variable expression.

Commonly occurring genetic polymorphisms with a major impact on the risk of nonsyndromic strabismus: replication in a sample from Finland

Plotnikov, Denis et al.

Journal of American Association for Pediatric Ophthalmology and Strabismus {JAAPOS}, Volume 26, Issue 1, 12.e1 - 12.e6

This study evaluated the associations between polymorphisms in *WRB* and *TSPAN10* genes and strabismus in a Finnish cohort. The *WRB* polymorphism was associated with “all subtypes” of strabismus and divergent strabismus but not with convergent strabismus. The *WRB* polymorphism had a population attributable risk of 3.4% for all strabismus subtypes and 4.7% for divergent strabismus. The *TSPAN10* polymorphism was associated with all three strabismus phenotypes: “all subtypes”, convergent strabismus and divergent strabismus. The population attributable risk for the *TSPAN10* polymorphism was 6.0% for any strabismus, 13.3% for convergent strabismus, and 13.9% for divergent strabismus. This study replicated the genetic associations with strabismus in a Finnish cohort and are responsible for 20% of isolated cases of strabismus in Finland, a similar estimate in other European populations.

Neonatal-Onset Congenital Ectropion Uveae May Be Caused by a Distinct CYP1B1 Pathologic Variant.

Kaushik S, Choudhary S, Kaur A, Srivastava P, Pokharel B, Akella M, Pandav SS.

American Journal of Ophthalmology. 2022 Jul 1;239:54-65.

Neonatal-onset congenital ectropion uveae (NO-CEU) is a rare, distinct phenotype of childhood glaucoma in which there is bilateral ectropion uveae, iris hypoplasia, and severe glaucoma. This was a prospective cohort study of 13 infants with NO-CEU with the goal of describing underlying genetic changes associated with the condition. Twelve of the 13 patients were found to have variants in CYP1B1. The authors describe the specific genotypes, with an emphasis on [c.1169G > A(p.Arg390His)]. They also described better visual outcomes in children with [c.1325del(p.Pro442GlnfsTer15)]. While this is a small study, it is the first to report the phenotype-genotype correlation in a very rare type of congenital glaucoma.

Dominant Optic Atrophy: How to Determine the Pathogenicity of Novel Variants?

Zehden JA, Raviskanthan S, Mortensen PW, et al.

*J Neuroophthalmol.* 2022;42(2):149-153

Autosomal dominant optic atrophy (ADOA) is the most common inherited optic neuropathy and is typically secondary to mutations in the *OPA1* gene. Over 450 pathogenic variants in *OPA1* have been documented. However, nonpathogenic variants of the *OPA1* gene are also common, which can make establishing the responsibility of a newly discovered variant for an otherwise-unexplained optic neuropathy a challenge. This paper details the process of establishing pathogenicity of a newly-described variant using the case of a 15-year-old female – otherwise healthy with 20/100 VA OU, normal neuroimaging, and unexplained optic neuropathy – as an illustrative example.

This patient underwent genetic testing for *OPA1*, which revealed a novel heterozygous variant, the duplication of an A nucleotide (c.1974dup) leading to frameshift with premature truncation p.(Gln659Thrfs\*4). There was no family history. Her father was confirmed as a healthy carrier of the same mutation upon further genetic testing.

The authors point out that establishing pathogenicity can be simple in cases in which a. the mutation has been previously reported to cause ADOA or b. there is a clear family history consistent with an autosomal

dominant inheritance pattern. However, in cases like the example presented here, the fact that clinical severity varies between and within families, even with the same mutation, makes establishing pathogenicity difficult. The paper then describes a few tools/tips that can be used in this pursuit:

1. Nomenclature: Genetic diagnosis critically depends on accurate, standardized description. Authors recommend using nomenclature of the Human Genome Variation Society, version 2.0.
2. Databases: Pathogenic variants are generally very rarely represented in the population, while frequently identified variants are rarely pathogenic. Large genetic databases can be helpful for this.
3. Computational (*in silico*) Predictive Programs: The more a sequence is conserved during evolution, the more its change is likely to be deleterious; conversely, a nonconserved sequence more easily tolerates nonpathogenic variations. Thus, using computer programs to examine homologous proteins between species can help predict the pathogenic or nonpathogenic character of a mutation
4. Aggregators: There are now programs that, using artificial intelligence, aggregate information from available databases and *in silico* predictions to interpret the pathogenicity of new variants. *VarSome* is, according to this publication, the most widely used. In this 15-year old's case, *VarSome* "unambiguously" predicted that the variant discovered is pathogenic.

Overall, this paper is important because it highlights resources that all ophthalmologists can use when confronted with novel genetic variants. Additionally, it emphasizes the continually evolving nature of our understanding of genetic disease and how staying up to date on the topic can help improve care for our patients.

RDH12 retinopathy: clinical features, biology, genetics and future directions.

Daich Varela M, Michaelides M.

Ophthalmic Genetics. 2022 May 1:1-6.

Retinol dehydrogenase 12 (RDH12) is a small gene located on chromosome 14, encoding an enzyme capable of metabolizing retinoids. It is primarily located in photoreceptor inner segments and thereby is believed to have an important role in clearing excessive retinal and other toxic aldehydes produced by light exposure. Clinical features: RDH12-associated retinopathy has wide phenotypic variability; including early-onset severe retinal dystrophy/Leber Congenital Amaurosis (EOSRD/LCA; most frequent presentation), retinitis pigmentosa, cone-rod dystrophy, and macular dystrophy. It can be inherited in an autosomal recessive and dominant fashion. RDH12-EOSRD/LCA's key features are early visual impairment, petal-shaped, coloboma-like macular atrophy with variegated watercolour-like pattern, peripapillary sparing, and often dense bone spicule pigmentation. Future directions: There is currently no treatment available for RDH12-retinopathy. However, extensive preclinical investigations and an ongoing prospective natural history study are preparing the necessary foundation to design and establish forthcoming clinical trials. Herein, we will concisely review pathophysiology, molecular genetics, clinical features, and discuss therapeutic approaches.

Severe retinal complications in Knobloch Syndrome-Three siblings without clinically apparent occipital defects and a review of the literature.

Arepalli S, DeBenedictis MM, Yuan A, Traboulsi EI.

Ophthalmic Genetics. 2022 Apr 8:1-9.

Knobloch syndrome (MIM #267750) is an autosomal recessive disease that results from pathogenic variants in the COL18A1 gene. Collagen XVIII and its derivative protein, endostatin, are components of basement membranes and integral to ocular development. Knobloch syndrome is characterized by retinopathy and occipital scalp, brain and skull defects. This reports on three siblings, born to consanguineous parents, two of whom with genetically confirmed Knobloch syndrome due to a homozygous pathogenic variant c.4054\_4055del; p.Leu1352Valfs\*72 in COL18A1. With the lack of classic occipital findings, an initial diagnosis of familial exudative vitreoretinopathy was entertained in these siblings because of the history of retinal detachments, retinal pigmentary changes and abnormal vitreous. The diagnosis of Knobloch syndrome was eventually made through molecular genetic testing using an extensive panel. In one patient presenting with acute retinal detachment and posteriorly dislocated intraocular lens implant, reattachment surgery was successful in stabilizing vision. The clinical

diagnosis of Knobloch syndrome can be difficult to reach in the absence of the typical occipital scalp defects. A careful medical history, detailed clinical examination and molecular genetic testing will reveal the correct diagnosis of Knobloch syndrome in atypical cases.

Novel RCBTB1 variants causing later-onset non-syndromic retinal dystrophy with macular chorioretinal atrophy.

Catomeris AJ, Ballios BG, Sangermano R, Wagner NE, Comander JI, Pierce EA, Place EM, Bujakowska KM, Huckfeldt RM.

Ophthalmic Genetics. 2022 May 4;43(3):332-9.

Inherited retinal dystrophies (IRDs) are a genetically and phenotypically diverse group of diseases that affect more than 2 million individuals worldwide and result in significant visual disability and blindness. Variants in RCBTB1 were recently described to cause a retinal dystrophy with only eight families described to date and a predominant phenotype of macular atrophy and peripheral reticular degeneration. This retrospective analysis of genetic and clinical features was performed three unrelated individuals of French-Canadian descent with rare biallelic RCBTB1 variants were identified. All individuals shared a novel p.(Ser342Leu) missense variant; one patient was homozygous whereas the other two each possessed a second unique novel variant p.(Gln120\*) and p.(Pro224Leu). All three had macula-predominant disease with symptom onset in the fifth decade of life. This report adds to the genetic diversity of RCBTB1-associated disease. These cases confirm the later-onset, relative to many other retinal dystrophies, and macular focus of disease described in most cases to-date. They are thus a reminder of considering hereditary disease in the differential for later-onset macular atrophy.

The prophylaxis of fellow-eye retinal detachment in stickler syndrome: a retrospective series.

Ripandelli G, Rossi T, Pesci FR, Cecere M, Stirpe M.

Retina. 2022 Feb 1;42(2):250-5.

The Stickler syndromes (SS) encompasses a spectrum of at least 6 different inherited connective disorders affecting 1:7,500 live births, transmitted as an autosomal dominant and less commonly, recessive disease. Retrospective review of 52 Stickler syndrome patients who received a 6-mm wide, 360° encircling scleral buckling. Thirty-nine (75%; Cryo + Group) also received cryo treatment, whereas the remainder 13/52 (25% Cryo – Group) did not. Fellow eyes in patients with Stickler syndrome which underwent combined scleral buckle with peripheral cryopexy in this series were less likely to progress to retinal detachment than eyes undergoing scleral buckle alone.

Hyperreflective foci as important prognostic indicators of progression of retinitis pigmentosa.

Huang CH, Yang CH, Lai YJ, Hsiao CK, Hou YC, Yang CM, Chen TC.

Retina. 2022 Feb 1;42(2):388-95.

Seventy seven retinitis pigmentosa cases were retrospectively reviewed. Hyperreflective foci were classified according to the location in optical coherence tomography: outer layers within the macula (HRF-outer-central), macular border beyond the central 3 mm (HRF-outer-perifoveal), and choroid (HRF-choroidal). The mean logMAR best-corrected visual acuity decreased from  $0.59 \pm 0.66$  (20/78 in Snellen) to  $0.74 \pm 0.81$  (20/106 in Snellen) in 1 year. Sixty-six (42.9%), 105 (68.2%), and 98 (63.6%) eyes were classified to HRF-outer-central, HRF-outer-perifoveal, and HRF-choroidal group, respectively.

Hyperreflective foci were positively correlated with poorer vision, central macular thinning, and ellipsoid zone disruption (all  $P < 0.001$ ). Worse vision was associated with older age, macular involvement, and the coexistence of two or three HRF groups ( $P = 0.014, 0.047, 0.019, <0.001$ , respectively).

Hyperreflective foci developed more frequently in patients with thick choroid than in those with thin choroid. The coexistence of three HRF groups was correlated with quicker visual deterioration ( $P = 0.034$ ). Hyperreflective foci are common in retinitis pigmentosa and can be a negative prognostic indicator of macular thickness and visual preservation. Thick choroid was associated with all groups of HRFs, especially HRF-choroidal.

The spectrum of internal limiting membrane disease in Alport syndrome: a multimodal imaging study.

Cicinelli MV, Ritter M, Ghossein C, Aschauer C, Laccione F, Nagel M, Schmidt-Erfurth UM, Jampol LM, Gill MK.

Retina. 2022 Feb 1;42(2):274-82.

Alport syndrome (AS) is a genetic disorder affecting approximately one in 5,000 to 10,000 people, accounting for 3% of children with chronic kidney disease and 0.2% of adults with end-stage renal disease in the United States. It is characterized by microscopic hematuria, progressive kidney failure, hearing loss, and ocular abnormalities. Forty-two eyes of 21 patients (11 men; age  $36.6 \pm 12.9$  years) were included. Macular spectral-domain optical coherence tomography revealed ILM granularity, more frequent in X-linked Alport syndrome and corresponding to dot maculopathy on color fundus. Mid-peripheral spectral-domain optical coherence tomography scans revealed multilamellated ILM in eight eyes (19%), presumably progressive, which corresponded to a cavitory pattern on en-face OCT. En-face OCT revealed multiple areas of retinal nerve fiber layer dehiscence in the macula, overlapping with vascular lacunae on optical coherence tomography angiography, and a coarse arrangement of retinal nerve fiber layer above and below the temporal raphe in 20 eyes (52%). Multimodal imaging allowed for the detection/characterization of retinal findings (ILM granularity, progressive ILM lamellation, retinal nerve fiber layer dehiscence, vascular lacunae, and coarse arrangement of retinal nerve fiber layer toward the disc) as multifaceted manifestations of ILM disease in Alport syndrome.

Retinitis Pigmentosa Sine Pigmento: Clinical Spectrum and Pigment Development.

Lee EK, Lee SY, Ma DJ, Yoon CK, Park UC, Yu HG.

Retina. 2022 Apr 1;42(4):807-15.

Retinitis pigmentosa (RP) is an inherited retinal disorder that is characterized by the primary degeneration of rod and cone photoreceptors, and it causes subsequent irreversible vision loss. More than 1.5 million individuals are affected globally, with a prevalence of approximately 1:4,000. Medical records of 810 consecutive patients with RP and assessed serial ultra-widefield fundus photography, fundus autofluorescence, and optical coherence tomography images were reviewed. Of the 774 patients with RP who met the inclusion criteria, 88 were diagnosed with RP sine pigmento, with a prevalence of 11.4%. The mean age of the patients was 35.57 years compared with 49.83 years for patients with typical RP. Fifty-nine patients (67%) demonstrated minimal color change, whereas 29 (33%) presented with grayish flecks in the retinal pigment epithelium on fundus photography. All patients with RP sine pigmento had abnormalities on fundus autofluorescence, and the commonest fundus autofluorescence findings were punctate or reticular hypoautofluorescence. Of the 62 patients without pigmentation at the first visit and at the follow-up visits, 14 (22.6%) had developed pigmentation at their follow-up visit, with an average time of 3.92 years. Most patients retained a visual acuity of  $\geq 20/50$  within the age of 50 years. Diagnosis based solely on ophthalmoscopic findings is difficult in patients with retinitis pigmentosa sine pigmento. Multimodal imaging can provide insights into the clinical characteristics of retinitis pigmentosa sine pigmento, and fundus autofluorescence is particularly useful for evaluating and diagnosing these patients.

Sibling concordance in symptom onset and atrophy growth rates in Stargardt disease using ultra-widefield fundus autofluorescence.

Jeffery RC, Thompson JA, Lo J, Lamey TM, McLaren TL, De Roach JN, Azamanov DN, McAllister IL, Constable IJ, Chen FK.

Retina (Philadelphia, Pa.). 2022 Aug;42(8):1545.

Stargardt disease (STGD1, OMIM #248200), caused by biallelic variants in the ATP-binding cassette transporter subfamily A4 (ABCA4) gene, is one of the most common inherited retinal diseases (IRDs) and accounts for 12% of IRD-related blindness certification. The study investigated concordance in symptom onset, well-defined dark autofluorescence area (DAF), and growth rate (GR) between Stargardt disease siblings at an age-matched time point. Overall 39 patients from 19 families were recruited. In 16 families, age-matched best-corrected visual acuity and DAF were compared between siblings. In 8 families, DAF GR was compared. The median (range) absolute difference in age at symptom onset between siblings was 3 (0–35) years. Absolute intersibling differences in age-matched best-corrected visual acuity were greater than interocular differences ( $P = 0.01$ ). Similarly, absolute intersibling differences in DAF area and radius were greater than interocular differences ( $P = 0.04$  for area and  $P = 0.001$  for radius). Differences between absolute interocular and intersibling GR were not statistically significant ( $P = 0.44$  for area GR and  $P = 0.61$  for radius GR). There was significant discordance in age-matched best-corrected visual acuity and DAF beyond the expected limits of interocular asymmetry. Lack of significant intersibling differences in GR warrants further investigation.

Autosomal dominant müller cell sheen dystrophy: Clinical, Histopathologic, and Genetic Assessment in an Extended Family With Long Follow-Up.

Dalma-Weiszhausz J, Chacón-Camacho O, Chevez-Barrios P, Zenteno JC, Franco-Cárdenas V, García-Montaño LA, Pérez-Bravo J, García-Montalvo IA, Jiménez-Sierra JM, Dalma A.

Retina. 2022 May 1;42(5):981-91.

Autosomal dominant Müller cell dystrophy is a rare condition we described in 1991. It is characterized by a striking sheen appearance on the retinal surface with progressive retinal changes leading to disorganization and atrophy with a decreased b-wave electroretinograms. Fifteen subjects from three generations of one family were found with the disease, without gender predilection. Findings include a decreased visual acuity, abnormal cellophane-like sheen of the vitreoretinal interface, a “plush” nerve fiber layer, and characteristic macular changes. Electroretinogram showed a selective b-wave diminution. Intravenous fluorescein angiogram presented perifoveal hyperfluorescence and capillary leakage. Spectral-domain optical coherence tomography revealed cavitations involving inner and later outer retinal layers with later disorganization. Histopathologic findings included Müller cell abnormalities with cystic disruption of inner retinal layers, pseudoexfoliation in anterior segment, and amyloidosis of extraocular vessels. Pedigree analysis suggests an autosomal dominant inheritance with late onset. DNA analysis demonstrated a previously undescribed heterozygous missense p.Glu109Val mutation in transthyretin.

Transcorneal Electrical Stimulation Therapy May Have A Stabilization Effect on Multifocal Electroretinography for Patients with Retinitis Pigmentosa.

Dizdar Yigit D, Sevik MO, Şahin Ö.

Retina. 2022 May 1;42(5):923-33.

Retinitis pigmentosa (RP) is characterized by progressive, peripheral vision loss because of impairment of photoreceptor cells and retinal pigment epithelium. There is no established therapy. This study assesses the effects of Transcorneal Electrical Stimulation on several objective and subjective measures of visual function in retinitis pigmentosa. Transcorneal Electrical Stimulation was applied monocularly, 30 minutes/week for 6 months. The progression in multifocal electroretinography might have been stabilized with Transcorneal Electrical Stimulation. Further studies with larger sample sizes are needed.

Effect of oral carbonic anhydrase inhibitor on cystoid macular edema associated with retinitis pigmentosa: An OCT and OCT Angiography Study.

Yeo JH, Min CH, Yoon YH.

Retina (Philadelphia, Pa.). 2022 Sep;42(9):1796.

Retinitis pigmentosa (RP) causes night blindness and progressive peripheral visual field loss, with gradual deterioration of central visual acuity. The development of ocular complications, including cystoid macular edema (CME), can further reduce visual acuity at any stage of the disease. The prevalence of RP-associated CME (RP-CME), as detected by optical coherence tomography (OCT), ranges between 5.5% and 49%. This retrospective cohort study included 59 eyes from 39 patients with RP-CME who underwent at least 3 months of oral CAI treatment. Thirty-three eyes (55.9%) demonstrated a positive response to treatment, and 26 eyes (44.1%) did not. Compared with nonresponding eyes, responding eyes had a significantly higher frequency of multilayer CME than CME limited to the inner nuclear layer ( $P = 0.016$ ). Subgroup analysis within the responding group revealed that improvements in visual acuity were more likely in eyes with fovea-involving CME and a higher baseline external limiting membrane and ellipsoid zone width. Microvascular parameters showed no significant changes after treatment. Eyes with CME extending to the outer nuclear layer or central fovea, and higher initial photoreceptor integrity may be prognostic factors associated with structural and functional improvements after carbonic anhydrase inhibitors treatment. Early treatment of multilayer CME with foveal involvement seems to be crucial in preventing irreversible photoreceptor damage.

Randomised study evaluating the pharmacodynamics of emixustat hydrochloride in subjects with macular atrophy secondary to Stargardt disease.

Kubota R, Birch DG, Gregory JK, Koester JM.

British Journal of Ophthalmology. 2022 Mar 1;106(3):403-8.

Stargardt disease is a rare, inherited, degenerative disease of the retina that is the most common type of hereditary macular dystrophy. Currently, no approved treatments for the disease exist. The purpose of this study was to characterise the pharmacodynamics of emixustat, an orally available small molecule that

targets the retinal pigment epithelium-specific 65 kDa protein (RPE65), in subjects with macular atrophy secondary to Stargardt disease. In this multicentre study conducted at six study sites in the USA, 23 subjects with macular atrophy secondary to Stargardt disease were randomised to one of three doses of daily emixustat (2.5 mg, 5 mg or 10 mg) and treated for 1 month. The primary outcome was the suppression of the rod b-wave recovery rate on electroretinography after photobleaching, which is an indirect measure of RPE65 inhibition. Subjects who received 10 mg emixustat showed near-complete suppression of the rod b-wave amplitude recovery rate postphotobleaching (mean=91.86%, median=96.69%), whereas those who received 5 mg showed moderate suppression (mean=52.2%, median=68.0%). No effect was observed for subjects who received 2.5 mg emixustat (mean=-3.31%, median=-12.23%). The adverse event profile was consistent with prior studies in other patient populations and consisted primarily of ocular adverse events likely related to RPE65 inhibition. This study demonstrated dose-dependent suppression of rod b-wave amplitude recovery postphotobleaching, confirming emixustat's biological activity in patients with Stargardt disease. These findings informed dose selection for a 24-month phase 3 trial (SeaSTAR Study) that is now comparing emixustat to placebo in the treatment of Stargardt disease-associated macular atrophy.

Leber congenital amaurosis/early-onset severe retinal dystrophy: current management and clinical trials. Varela MD, de Guimaraes TA, Georgiou M, Michaelides M.

British Journal of Ophthalmology. 2022 Apr 1;106(4):445-51.

Leber congenital amaurosis (LCA) is a severe congenital/early-onset retinal dystrophy. Given its monogenic nature and the immunological and anatomical privileges of the eye, LCA has been particularly targeted by cutting-edge research. In this review, we describe the current management of LCA, and highlight the clinical trials that are on-going and planned. RPE65-related LCA pivotal trials, which culminated in the first Food and Drug Administration-approved and European Medicines Agency-approved ocular gene therapy, have paved the way for a new era of genetic treatments in ophthalmology. At present, multiple clinical trials are available worldwide applying different techniques, aiming to achieve better outcomes and include more genes and variants. Genetic therapy is not only implementing gene supplementation by the use of adeno-associated viral vectors, but also clustered regularly interspaced short palindromic repeats (CRISPR)-mediated gene editing and post-transcriptional regulation through antisense oligonucleotides. Pharmacological approaches intending to decrease photoreceptor degeneration by supplementing 11-cis-retinal and cell therapy's aim to replace the retinal pigment epithelium, providing a trophic and metabolic retinal structure, are also under investigation. Furthermore, optoelectric devices and optogenetics are also an option for patients with residual visual pathway. After more than 10 years since the first patient with LCA received gene therapy, we also discuss future challenges, such as the overlap between different techniques and the long-term durability of efficacy. The next 5 years are likely to be key to whether genetic therapies will achieve their full promise, and whether stem cell/cellular therapies will break through into clinical trial evaluation.

CRB1-associated retinal dystrophies in a Belgian cohort: genetic characteristics and long-term clinical follow-up.

Talib M, Van Cauwenbergh C, De Zaeytijd J, Van Wynsberghe D, De Baere E, Boon CJ, Leroy BP.

British Journal of Ophthalmology. 2022 May 1;106(5):696-704.

Inherited retinal dystrophies (IRDs) comprise a genetically and clinically heterogeneous group of disorders, characterised by progressive degeneration of photoreceptors. The most severe form of IRD is Leber congenital amaurosis (LCA), with an estimated prevalence of 1:33 000–1:81 000. Mutations in the CRB1 gene account for 7%–17% of LCA cases, and 3%–9% of isolated, non-syndromic, autosomal recessive RP patients, depending on geographic location, making it one of the most common genetic causes of both LCA and RP. Forty patients from 35 families were included (ages: 2.5–80.1 years). In patients with a follow-up of >1 year (63%), the mean follow-up time was 12.0 years (range: 2.3–29.2 years). Based on the patient history, symptoms and/or electroretinography, 22 patients (55%) were diagnosed with retinitis pigmentosa (RP), 15 (38%) with Leber congenital amaurosis (LCA) and 3 (8%) with macular dystrophy (MD), the latter being associated with the p.(Ile167\_Gly169del) mutation (in compound heterozygosity). MD later developed into a rod-cone dystrophy in one patient. Blindness at initial presentation was seen in the first decade of life in LCA, and in the fifth decade of life in RP. Eventually, 28 patients (70%) reached visual acuity-based blindness (<0.05). Visual field-based blindness (<10°) was documented in 17/25 patients (68%). Five patients (13%) developed Coats-like exudative

vasculopathy. Intermediate/posterior uveitis was found in three patients (8%). Cystoid maculopathy was common in RP (9/21; 43%) and MD (3/3; 100%). Macular involvement, varying from retinal pigment epithelium alterations to complete outer retinal atrophy, was observed in all patients. Bi-allelic CRB1 mutations result in a range of progressive retinal disorders, most of which are generalised, with characteristically early macular involvement. Visual function and retinal structure analysis indicates a window for potential intervention with gene therapy before the fourth decade of life in RP and the first decade in LCA.

Novel disease-causing variant in RDH12 presenting with autosomal dominant retinitis pigmentosa. Muthiah MN, Kalitzeos A, Oprych K, Singh N, Georgiou M, Wright GA, Robson AG, Arno G, Khan K, Michaelides M.

British Journal of Ophthalmology. 2022 Sep 1;106(9):1274-81.

Twelve individuals from a four-generation British pedigree underwent ophthalmic examination and genotyping using next generation sequencing. Eight family members were confirmed as affected by genotyping heterozygous for RDH12 c.763delG. Visual acuity ranged from -0.1 to 0.2 logMAR. Affected individuals had constricted visual fields. A parafoveal and peripapillary ring of hyper-autofluorescence was seen initially, and with progression the area of perfoveal hypo-autofluorescence increased to involve the parafoveal area. Mild retinal thinning was identified on OCT imaging with reduction in both foveal total retinal and outer nuclear layer thickness. Cone densities along the temporal meridian were reduced in affected individuals compared with normative values at all temporal eccentricities studied. One individual with incomplete penetrance, was identified as clinically affected primarily on the basis of AO imaging. Full-field electroretinography demonstrated a rod-cone pattern of dysfunction and large-field pattern electroretinography identified peripheral macular dysfunction. This novel heterozygous variant RDH12 c.763delG is associated with a rod-cone dystrophy with variable expression. Determination of the degree of penetrance may depend on the modality employed to phenotypically characterise an individual. This rare and specific heterozygous (dominant) variant is predicted to result in a gain of function, that causes disease in a gene typically associated with biallelic (recessive) variants.

North Carolina macular dystrophy shows a particular drusen phenotype and atrophy progression.

Birtel J, Gliem M, Herrmann P, Neuhaus C, Holz FG, MacLaren RE, Scholl HP, Issa PC.

British Journal of Ophthalmology. 2022 Sep 1;106(9):1269-73.

The goal of this study is to provide a comprehensive multimodal retinal imaging characterisation of patients with North Carolina macular dystrophy (NCMD). Twenty-one subjects were included in this study age at examination between 6 and 81 years; showed phenotypic characteristics of NCMD. Small drusen-like deposits were found in all affected individuals, either tightly grouped in the macula, or surrounding atrophic or fibrotic macular alterations. These small subretinal lesions showed an increased fundus autofluorescence and were associated with only mild irregularities on optical coherence tomography imaging. Similar drusen-like deposits were regularly seen in the peripheral fundus, predominantly temporally and often with a radial distribution. Two patients showed a bilateral chorioretinal atrophy and two had a macular neovascularisation (MNV). Findings from follow-up examinations were available from 11 patients. The retinal phenotype remained overall stable, except for two patients: one patient with atrophy showed a distinct growth of the atrophic lesions on longitudinal AF imaging over a review period of 14 years. One patient with MNV showed a unilateral decline of best-corrected visual acuity. Genetic testing identified the single nucleotide variant chr6:100040987G>C upstream of the PRDM13 gene in all family members with NCMD phenotype. Although the prognosis of this developmental condition is overall better than for other macular diseases with drusen, patients may be at risk of developing MNV or enlargement of pre-existing atrophy.

Personalized genetic counseling for Stargardt disease: Offspring risk estimates based on variant severity. Cornelis SS, Runhart EH, Bauwens M, Corradi Z, De Baere E, Roosing S, Haer-Wigman L, Dhaenens CM, Vulto-van Silfhout AT, Cremers FP.

The American Journal of Human Genetics. 2022 Mar 3;109(3):498-507.

Recurrence risk calculations in autosomal recessive diseases are complicated when the effect of genetic variants and their population frequencies and penetrances are unknown. An example of this is Stargardt disease (STGD1), a frequent recessive retinal disease caused by bi-allelic pathogenic variants in ABCA4. In this cross-sectional study, 1,619 ABCA4 variants from 5,579 individuals with STGD1 were collected

and categorized by (1) severity based on statistical comparisons of their frequencies in STGD1-affected individuals versus the general population, (2) their observed versus expected homozygous occurrence in STGD1-affected individuals, (3) their occurrence in combination with established mild alleles in STGD1-affected individuals, and (4) previous functional and clinical studies. We used the sum allele frequencies of these severity categories to estimate recurrence risks for offspring of STGD1-affected individuals and carriers of pathogenic ABCA4 variants. The risk for offspring of an STGD1-affected individual with the “severe|severe” genotype or a “severe|mild with complete penetrance” genotype to develop STGD1 at some moment in life was estimated at 2.8%–3.1% (1 in 36–32 individuals) and 1.6%–1.8% (1 in 62–57 individuals), respectively. The risk to develop STGD1 in childhood was estimated to be 2- to 4-fold lower: 0.68%–0.79% (1 in 148–126) and 0.34%–0.39% (1 in 296–252), respectively. In conclusion, we established personalized recurrence risk calculations for STGD1-affected individuals with different combinations of variants. We thus propose an expanded genotype-based personalized counseling to appreciate the variable recurrence risks for STGD1-affected individuals. This represents a conceptual breakthrough because risk calculations for STGD1 may be exemplary for many other inherited diseases.

CRB1-Associated retinal dystrophies: a prospective natural history study in anticipation of future clinical trials.

Talib M, van Schooneveld MJ, Wijnholds J, van Genderen MM, Schalijs-Delfos NE, Klaver CC, Talsma HE, Fiocco M, Florijn RJ, Jacoline B, Cremers FP.

American Journal of Ophthalmology. 2022 Feb 1;234:37-48.

The purpose of this single-center, prospective case series is to investigate the natural disease course of retinal dystrophies associated with crumbs cell polarity complex component 1 (CRB1) and identify clinical end points for future clinical trials. An investigator-initiated nationwide collaborative study that included 22 patients with CRB1-associated retinal dystrophies. Based on genetic, clinical, and electrophysiological data, patients were diagnosed with retinitis pigmentosa (19 [86%]), cone-rod dystrophy (2 [9%]), or isolated macular dystrophy (1 [5%]). Analysis of the entire cohort at 2 years showed no significant changes in BCVA ( $P = .069$ ) or V4e isopter seeing retinal areas ( $P = .616$ ), although signs of clinical progression were present in individual patients. Macular sensitivity measured on microperimetry revealed a significant reduction at the 2-year follow-up ( $P < .001$ ). FST responses were measurable in patients with nonrecordable electroretinograms. On average, FST responses remained stable during follow-up. In CRB1-associated retinal dystrophies, visual acuity and visual field measures remain relatively stable over the course of 2 years. Microperimetry showed a significant decrease in retinal sensitivity during follow-up and may be a more sensitive progression marker. Retinal sensitivity on microperimetry may serve as a functional clinical end point in future human treatment trials for CRB1-associated retinal dystrophies.

Foveal hypoplasia grading in 95 cases of congenital aniridia: correlation to phenotype and PAX6 genotype.

Daruich A, Robert MP, Leroy C, de Vergnes N, Beugnet C, Malan V, Valleix S, Bremond-Gignac D. American Journal of Ophthalmology. 2022 May 1;237:122-9.

Congenital aniridia (MIM\_106210) is a rare congenital panocular disorder defined as a complete or partial absence of the iris, which is often combined with developmental abnormalities of the cornea, lens, optic nerve, and fovea causing severe visual impairment. Human PAX6 (MIM#607108) is the major gene responsible for autosomal dominant forms of congenital aniridia. Ninety-five consecutive patients with high-quality spectral-domain optical coherence tomography records and available genotype were included in a single referral center. Iris hypoplasia was classified as complete, presence of iris root or remnants, and mild atypical aniridia. Spectral-domain optical coherence tomography images were assessed to classify foveal hypoplasia as grade 1 to 4 and to determine mean thicknesses for retinal layers. For statistical analysis 1 eye for each patient was used and 1 member of the same family has been included ( $n = 76$  eyes). Most eyes ( $n = 158/169$ , 93.5%) showed variable degree of foveal hypoplasia. PAX6-positive patients presented higher degree of foveal hypoplasia than patients negative for PAX6 ( $P < .0001$ ). PAX6 deletions, PAX6 variants subjected to nonsense-mediated decay and C-terminal extension variants were mostly associated with grade 3 or 4 foveal hypoplasia. Deletions restricted to the 3' flanking regulatory regions of PAX6 were associated with grade 1 or 2 foveal hypoplasia ( $P < .0001$ ). Best-corrected visual acuity was higher and foveal outer retinal layers were thicker in patients with deletions in the 3' regulatory region of PAX6 ( $P = .001$  and  $P < .0001$ ). Patients with missense mutations presented with variable degree of foveal hypoplasia. The degree of foveal



hypoplasia was most frequently correlated with the severity of iris defects, with 95% of eyes with complete aniridia presenting grade 3 or 4 foveal hypoplasia ( $P = .005$ ). However, among eyes with mild iris phenotype, 70% ( $n=9/13$ ) showed severe foveal hypoplasia. All types of PAX6 variants, even those associated with mild iris defects, may be at risk for severe foveal hypoplasia with poor visual prognosis, except for deletions restricted to the 3' regulatory PAX6 regions.

Neonatal-Onset Congenital Ectropion Uveae May Be Caused by a Distinct CYP1B1 Pathogenic Variant. Kaushik S, Choudhary S, Kaur A, Srivastava P, Pokharel B, Akella M, Pandav SS. *American Journal of Ophthalmology*. 2022 Jul 1;239:54-65.

This prospective cohort study reports underlying genetic variants of recently described distinct phenotype of newborn glaucoma: neonatal-onset congenital ectropion uveae (NO-CEU). Thirteen children with clinical diagnosis of NO-CEU who had completed 1-year follow-up after glaucoma surgery and had undergone clinical exome sequencing (CES) by selective capture and sequencing of the protein-coding regions of the genes including 19 candidate genes for NO-CEU were assessed. All 13 patients diagnosed with NO-CEU had onset of glaucoma at birth and severe bilateral disease. Twelve of 13 (92.3%) patients harbored CYP1B1 variants. Nine of these 12 patients (83.3%) were homozygous for [c.1169G>A(p.Arg390His)] in exon-3 of CYP1B1, with 5 common homozygous single-nucleotide polymorphisms flanking the pathogenic variant. They had intractable glaucoma and required multiple surgeries. Six patients had persistent corneal opacities, necessitating optical iridectomies. Three patients were compound heterozygous for CYP1B1 variants, showing [c.1169G>A(p.Arg390His)] along with [c.1103G>A(p.Arg368His)], [c.1103G>A (p.Arg368His)] along with [c.1403\_1429dup(p.Arg468\_Ser476dup)], and [(c.1063C>T(p.Arg355Ter)] along with [c.1325del(p.Pro442GlnfsTer15)]. These patients had better visual outcomes. NO-CEU appears to be a phenotypic marker for specific CYP1B1 genotypes, one of which is [c.1169G>A(p.Arg390His)] in our study population. Phenotype recognition is helpful to characterize the underlying genetic variants.

Three-year safety results of SAR422459 (EIAV-ABCA4) gene therapy in patients with ABCA4-associated Stargardt disease: An open-label dose-escalation phase I/IIa clinical trial, cohorts 1-5.

Parker MA, Erker LR, Audo I, Choi D, Mohand-Said S, Sestakauskas K, Benoit P, Appelqvist T, Krahmer M, Ségaut-Prévost C, Lujan BJ.

*American Journal of Ophthalmology*. 2022 Mar 4.

ABCA4-related retinopathy (OMIM #248200) results from biallelic mutations in ABCA4 and causes a spectrum of retinal phenotypes including fundus flavimaculatus, juvenile onset macular dystrophy, cone-rod dystrophy with or without foveal sparing, and, in the most severe cases, generalized rod-cone dystrophy. This reports on the safety of a nonrandomized multicenter phase I/IIa clinical trial using recombinant equine infectious anemia virus expressing ABCA4 (EIAV-ABCA4) in adults with Stargardt dystrophy due to mutations in ABCA4. Patients received a subretinal injection of EIAVABCA4 in the worse-seeing eye at 3 dose levels and were followed for 3 years after treatment. The subretinal injections were well tolerated by all 22 patients across 3 dose levels. There was 1 case of a treatment-related ophthalmic serious adverse event in the form of chronic ocular hypertension. The most common adverse events were associated with the surgical procedure. In 1 patient treated with the highest dose, there was a significant decline in the number of macular flecks as compared with the untreated eye. However, in 6 patients, hypoautofluorescent changes were worse in the treated eye than in the untreated eye. Of these, 1 patient had retinal pigment epithelium atrophy that was characteristic of tissue damage likely associated with bleb induction. No patients had any clinically significant changes in best-corrected visual acuity, static perimetry, kinetic perimetry, total field hill of vision, full field electroretinogram, or multifocal ERG attributable to the treatment. Subretinal treatment with EIAV-ABCA4 was well tolerated with only 1 case of ocular hypertension. No clinically significant changes in visual function tests were found to be attributable to the treatment. However, 27% of treated eyes showed exacerbation of retinal pigment epithelium atrophy on fundus autofluorescence. There was a significant reduction in macular flecks in 1 treated eye from the highest dose cohort. Additional follow-up and continued investigation in more patients will be required to fully characterize the safety and efficacy of EIAV-ABCA4.

The pattern of retinal ganglion cell loss in Wolfram syndrome is distinct from mitochondrial optic neuropathies.

Barboni P, Amore G, Cascavilla ML, Battista M, Frontino G, Romagnoli M, Caporali L, Baldoli C, Gramegna LL, Sessagesimi E, Bonfanti R.  
American Journal of Ophthalmology. 2022 Apr 20.

This Retrospective, comparative cohort study describes the clinical phenotype of a cohort of patients with Wolfram syndrome (WS), focusing on the pattern of optic atrophy correlated with brain magnetic resonance imaging (MRI) measurements, as compared with patients with OPA1-related dominant optic atrophy (DOA). 25 patients with WS and 33 age-matched patients affected by OPA1-related DOA were included. Optic atrophy was present in 100% of patients with WS. VA, MD, and RNFL thickness loss were worse in patients with WS with a faster decline since early age as compared with patients with DOA, who displayed a more stable visual function over the years. Conversely, GCL sectors were overall thinner in patients with DOA since early age compared to patients with WS, in which GCL thickness started to decline later in life. The neuroradiologic subanalysis on 11 patients with WS exhibited bilateral thinning of the anterior optic pathway, especially the prechiasmatic optic nerves and optic tracts. Optic tract thinning was significantly correlated with GCL thickness but not with RNFL parameters. Results showed a generally more severe and diffuse degeneration of both anterior and posterior visual pathways in patients with WS, with fast deterioration of visual function and structural OCT parameters since early age. The pattern observed with OCT suggests that retinal ganglion cell axonal degeneration (ie, RNFL) precedes cellular body atrophy (ie, GCL) by about a decade. This differs substantially from DOA, in which a more stable visual function is evident with predominant early loss of GCL, indirectly supporting the lack of a primary mitochondrial dysfunction in patients with WS.

Leber Hereditary Optic Neuropathy Gene Therapy: Adverse Events and Visual Acuity Results of all Patient Groups.

Lam BL, Feuer WJ, Davis JL, Porciatti V, Yu H, Levy RB, Vanner E, Guy J.  
American Journal of Ophthalmology. 2022 Mar 7.

Phase 1 clinical trial assessing safety of gene therapy in G11778A Leber hereditary optic neuropathy (LHON). Patients with G11778A LHON and chronic bilateral visual loss >12 months (group 1, n = 11), acute bilateral visual loss <12 months (group 2, n = 9), or unilateral visual loss (group 3, n = 8) were treated with unilateral intravitreal AAV2(Y444,500,730F)-P1ND4v2 injection with low, medium, high, and higher doses to worse eye for groups 1 and 2 and better eye for group 3. Incident uveitis (8 of 28, 29%), the only vector-related adverse event, resulted in no attributable vision sequelae and was related to vector dose: 5 of 7 (71%) higher-dose eyes vs 3 of 21 (14%) low-, medium-, or high-dose eyes ( $P < .001$ ). Incident uveitis requiring treatment was associated with increased serum AAV2 neutralizing antibody titers ( $p=0.007$ ) but not serum AAV2 polymerase chain reaction. Improvements of  $\geq 15$ -letter BCVA occurred in some treated and fellow eyes of groups 1 and 2 and some surrogate study and fellow eyes of natural history subjects. All study eyes (BCVA  $\geq 20/40$ ) in group 3 lost  $\geq 15$  letters within the first year despite treatment. G11778A LHON gene therapy has a favorable safety profile. Our results suggest that if there is an efficacy effect, it is likely small and not dose related. Demonstration of efficacy requires randomization of patients to a group not receiving vector in either eye.

Capturing the pattern of transition from carrier to affected in Leber's hereditary optic neuropathy.

Carbonelli M, La Morgia C, Romagnoli M, Amore G, D'Agati P, Valentino ML, Caporali L, Cascavilla ML, Battista M, Borrelli E, Di Renzo A.  
American Journal of Ophthalmology. 2022 May 2.

The goal of this observational case series was to capture the key features patterning the transition from unaffected mutation carriers to clinically affected Leber hereditary optic neuropathy (LHON), as investigated by optical coherence tomography. Four unaffected eyes of 4 patients with LHON with the first eye affected were followed across conversion to affected, from 60 days before to 170 days after conversion. While the presymptomatic stage was characterized by a dynamic thickening of sector 8, the beginning of the conversion coincided with an increase in the thickness of the sectors bordering the papillo-acular bundle (6 and 7 for the inferior sectors, 10 and 11 for the superior sectors) synchronous with the thinning of sectors 8 and then 9. Conversely, the GCL did not undergo significant changes until the onset of visual loss when a significant reduction of thickness became evident. In this study we demonstrated that the thinning of sector 8 can be considered the structural hallmark of the conversion from the presymptomatic to the affected state in LHON. It is preceded by its own progressive thickening

extending from the optic nerve head toward the macula and occurs regardless of the amount of swelling of the rest of the peripapillary fibers.

WFS1-Associated Optic Neuropathy: Genotype-Phenotype Correlations and Disease Progression.

Majander A, Jurkute N, Burté F, Brock K, João C, Huang H, Neveu MM, Chan CM, Duncan HJ, Kelly S, Burkitt-Wright E.

American Journal of Ophthalmology. 2022 Apr 22.

The goal of this multicenter cohort study was to evaluate the pattern of vision loss and genotype-phenotype correlations in WFS1-associated optic neuropathy (WON). The study involved 37 patients with WON carrying pathogenic or candidate pathogenic WFS1 variants. Genetic and clinical data were retrieved from the medical records. Thirteen patients underwent additional comprehensive ophthalmologic assessment. Deep phenotyping involved visual electrophysiology and advanced psychophysical testing with a complementary metabolomic study. Twenty-two recessive and 5 dominant WFS1 variants were identified. Four variants were novel. All WFS1 variants caused loss of macular retinal ganglion cells (RGCs) as assessed by optical coherence tomography (OCT) and visual electrophysiology. Advanced psychophysical testing indicated involvement of the major RGC subpopulations. Modeling of vision loss showed an accelerated rate of deterioration with increasing age. Dominant WFS1 variants were associated with abnormal reflectivity of the outer plexiform layer (OPL) on OCT imaging. The dominant variants tended to cause less severe vision loss compared with recessive WFS1 variants, which resulted in more variable phenotypes ranging from isolated WON to severe multisystem disease depending on the WFS1 alleles. The metabolomic profile included markers seen in other neurodegenerative diseases and type 1 diabetes mellitus. WFS1 variants result in heterogeneous phenotypes influenced by the mode of inheritance and the disease-causing alleles. Biallelic WFS1 variants cause more variable, but generally more severe, vision and RGC loss compared with heterozygous variants. Abnormal cleftlike lamination of the OPL is a distinctive OCT feature that strongly points toward dominant WON.

## 17. TRAUMA

Pediatric Eyelid and Canalicular Lacerations: Epidemiology and Outcomes.

Huang J, Rossen J, Rahmani B, Mets-Halgrimson R.

J Pediatr Ophthalmol Strabismus. 2023;60(1):33-38. doi:10.3928/01913913-20220321-02

This retrospective review sought to characterize the epidemiology, presenting features, and clinical course of eyelid lacerations at a single center. A total of 165 patients were identified, of whom 136 had at least 1 week of follow-up and were further assessed for postoperative complications. The most common mechanisms of injury were dog bites (62, 38%), falls (33, 20%), and being struck by an object (22, 13%). Eyelid margin involvement was present in 108 patients (65%) and canalicular involvement in 77 patients (47%). Risk factors for canalicular involvement were hook-related injury, eyelid margin involvement, and lower eyelid injury. Thirty-three patients (24%) had postoperative complications, most commonly ptosis (7, 5%), premature stent loss (7, 5%), and eyelid margin notching (6, 4%). There was no association between postoperative complication and antibiotic use, delayed repair, or wound class. The authors concluded that

Conclusions: Hook-related injury, eyelid margin involvement, and lower eyelid injury are risk factors for canalicular involvement. Postoperative complications of eyelid lacerations are generally minor and are not associated with perioperative factors. Close postoperative follow-up is needed to monitor for complication development. The authors concede that the major limitation was its retrospective design, which could predispose to overestimation of complication rate. In addition, the sample population at this single-center Level I pediatric trauma center may not produce generalizable conclusions.

Evidence-Based Screening to Optimize the Yield of Positive Ophthalmologic Examinations in Children Evaluated for Suspected Child Abuse.

Su M, Taylor K, Stoutin J, Shaver C, Recko M.

J Pediatr Ophthalmol Strabismus. 2022;59(5):310-319. doi:10.3928/01913913-20220216-01

This single-center retrospective review sought to determine non-ocular findings associated with significant retinal hemorrhages in cases of suspected child abuse. The authors collected data on 274 children 36mo or younger in whom there was concern for child abuse and who underwent an ophthalmology consultation. They found that the presence of one or more abnormal neuroimaging findings had the strongest association with a univariate OR 170. Multivariate analysis found relationships among: abnormal neuroimaging, Glasgow Coma Scale score less than 15, altered mental status on examination, seizure activity, vomiting, bruising, scalp hematoma/swelling, and skull fractures. The authors propose an evidence-based screening algorithm to increase the yield of positive dilated examinations and decrease the burden of potentially unnecessary child abuse ophthalmologic examinations. This is a valuable contribution to the literature on ophthalmic evaluation in suspected child abuse. Perhaps with more broad adaptation, the proposed algorithm might be implemented broadly.

Sensorimotor Outcomes in Pediatric Patients With Ocular Trauma in Baltimore.

Junn S, Pharr C, Chen V, et al.

J Pediatr Ophthalmol Strabismus. 2022;59(5):303-309. doi:10.3928/01913913-20220126-01

This single-center retrospective review reported the sensorimotor outcomes of 80 pediatric patients aged 0.4-17.7 years with traumatic open globe injuries. They collected data included the mechanism of injury, length of time of visual deprivation, initial and final visual acuity, additional eye pathologies, and demographic factors such as age and sex. They found that among children with more than 6 mo of follow-up, 77.4% developed poor stereopsis and 50% developed strabismus, and this was more likely associated with a lower trauma score (POTS), indicating greater injury. They concluded that strabismus and poor stereopsis are common in pediatric open globe injuries and that these outcomes are associated with poor presenting visual acuity, more severe ocular trauma, and a lower presenting POTS. The authors conclude that results are skewed by retrospective design and availability of complete records on a relatively small subset of pediatric ocular trauma patients.

Change in Incidence and Severity of Abusive Head Trauma in the Paediatric Age Group Pre- and During COVID-19 Lockdown in the North East of England.

Salisbury T, Qurashi N, Mansoor Q.

Br Ir Orthopt J. 2022 Aug 23;18(1):101-110. doi: 10.22599/bioj.265. PMID: 36117555; PMCID: PMC9414736.

Data from a major tertiary referral hospital in the UK was collected to investigate if there was a change in incidence and severity of abusive head trauma in children between initial 3 months of first COVID-19 lockdown to incidence and severity noted in same time period in preceding year. 5/61 in of the referrals in pre-lockdown had confirmed AHT and 4/40 during lockdown group had confirmed AHT. Ophthalmology notes were reviewed if available. A 34% reduction of referrals for AHT were made during the lockdown period compared to prelockdown. Ophthalmic examination had not been performed on any patients during the pre-lockdown periods. 2 children (50%) had an eye exam performed during the lockdown period. Only one of these two children had ophthalmic findings. Study concluded that there was no significant change in incidence or severity of AHT in the pediatric population during the COVID-19 lockdown in North East of England. The limitations of this study include retrospective approach and relative lack of eye exams on most of the AHT patients so the incidence of eye findings in AHT is unknown in this study population.

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Epidemiology of Ocular Injuries Related to Toy Guns in Pediatric Patients From 2000 to 2019.  
Oydanich M, Uppuluri A, Zarbin MA, Bhagat N.

J Pediatr Ophthalmol Strabismus. 2022;59(3):e29-e31. doi:10.3928/01913913-20220314-01

This retrospective cross-sectional epidemiologic study used the National Electronic Injury Surveillance System (NEISS) to evaluate and characterize the ED visits for pediatric ocular injuries related to toy guns between 2000 and 2019. Of the 8,630 injuries caused by projectiles released from toy guns, 5,154 (60%) occurred in preschool and elementary school-aged children, and 3,476 (40%) occurred in middle and high school-aged children. Most injuries occurred in White children (4,871; 56%). Contusions were the most common injury (4,905; 57%), and open globe injuries were uncommon (97; 1.1%). Most injuries occurred at home (4,991; 58%). Most injuries occurred in males (6,768; 78.4%). The authors note that the highest risk of ocular injury occurred in young children, and therefore propose the need for intervention to prevent this.

A National Analysis of Ophthalmic Features and Mortality in Abusive Head Trauma  
Yesha Sha BSA, Mustafa Iftikhar MD, Grant Justin MD

JAMA Ophthalmol. March 2022;140(3):227-234.

The goal of this study was to describe the prevalence and economic burden of abusive head trauma (AHT) and identify factors associated with mortality. This was a retrospective, cross-sectional study using the Nationwide Emergency Department Sample (NEDS) database to identify 12,287 emergency department visits in the US for patients younger than 5 years old with a primary diagnosis of abusive head trauma between January 2006 and December 2018. They found that the incidence of AHT cases decreased by 6.7% each year, and that 5.3% of the patients died during the course of their hospital visit. The majority of the patients were younger than 1 year old (57.3%) and male (59.2%). After controlling for demographics, the factors associated with increased mortality were age greater than 1 year old, first or second income quartile, presenting in the midwestern US or a level 1 trauma center, orbital and skull fractures, cerebral edema, intracranial or retinal hemorrhage, and hypoxic ischemic brain injury. This study highlights that health care disparities may be present in the treatment of AHT. Given the increased risk of mortality in the midwest and low income families, public health efforts to raise awareness and decrease prevalence of AHT may be targeted towards these areas.

Surgical Outcome and Prognostic Factors Following Ophthalmic Surgery in Abusive Head Trauma  
Ho MC, Wu AL, Wang NK, Chen KJ, Hwang YS, Lai CC, Wu WC

Retina. 2022 May 1;42(5):967-972. doi: 10.1097/IAE.0000000000003421. PMID: 35125478.

Vitrectomy is sometimes indicated in the management of abusive head trauma (AHT), but few studies have evaluated efficacy of vitrectomy in children with AHT. The authors retrospectively reviewed the charts of all children younger than 3 years who were diagnosed with AHT at their tertiary referral center over the course of 19 years. Of 75 children diagnosed with AHT, fourteen patients (18 eyes) were found to have eventually undergone vitrectomy. Mean age at diagnosis was 8 months, and surgery occurred

between 2 weeks and 3 months after diagnosis in all but one eye. Indications for surgery included non-resolving vitreous hemorrhage, multilayers hemorrhages involving the macula, macular pucker, macular hole, retinoschisis, and retinal detachment. After a mean follow-up of 77 months, the final BCVA was less than 20/200 in 13 eyes (72%) and better than 20/40 in only 3 eyes (17%). Eight eyes developed cataracts postoperatively which required additional surgery. Retinal attachment at the final follow-up was observed in 17 eyes (94%). Nine eyes had developed optic atrophy, which was found to be associated with a worse final BCVA. The authors conclude that while timely surgery may help to reduce vision loss from deprivation amblyopia, visual outcomes are typically poor in children with AHT severe enough to require vitrectomy. In children with a pre-operative diagnosis of optic atrophy, surgeons should carefully weight the benefits and risks of surgery, as visual outcomes are particularly poor in this group.

## 18. RETINA

Macular thickness variation and interocular symmetry by gestational age in preterm school-age children  
José L Torres-Peña 1, Ana I Ortueta-Olartecoechea 2, Alicia Muñoz-Gallego 2, Cristina López-López 2, Maria J Torres-Valdivieso 3, Javier de-la-Cruz 4, Pilar Tejada-Palacios 2  
J AAPOS. 2022 Dec;26(6):311.e1-311.e8.

Several studies report significantly thicker central macula and absent foveal pit in preterm infants thought to be due to an alteration in migration of inner retinal neurons. Data for macular symmetry has been studied in adults with glaucoma as a method for early diagnosis. Data for healthy children has been published but has not been published for preterm infants. The authors sought to examine changes in the macular thickness profile according to gestational age (GA) as a primary outcome and to assess interocular symmetry in the maculae of children born very premature. The authors included children born less than 32 weeks GA and low birthweight less than 1500 grams. All participants were examined between 5 and 8 years of age. Patients born full-term were recruited who had no history of ophthalmologic disease or significant refractive error. Consistent with previous studies, the authors found that the macula central thickness was significantly thicker in preterm children than in term children. The authors found that preterm children have very high macular symmetry like children born full-term. The authors describe main limitation to study as OCT image quality influencing inclusion or exclusion which could negatively influence representation of children with developmental delay.

Early Presentation of Susac Syndrome in a 7 year old

Egan R, Brown A, Grillo E

[published online ahead of print, 2022 Jul 12]. *J Neuroophthalmol*.

Susac Syndrome is an autoimmune condition characterized by encephalopathy, hearing loss, and vision loss secondary to retinal arterial occlusions. Though it typically occurs in adults, cases have been reported in children. Here, the authors present one such case of a 7-year-old girl who presented with confusion, paranoia, and gait difficulty. Work-up revealed sensorineural hearing loss and multiple lesions of the corpus collusum. Although the eye exam was normal and the retina was without arterial occlusions on funduscopy and fluorescein angiogram, the patient still met the (somewhat controversial) criteria of Susac syndrome and was treated with steroids and IVIg. This led to resolution of symptoms. The authors suggest that pediatric ophthalmologists be aware that Susac syndrome exists in the pre-pubertal population.

Assessment of the Optic Disc and Retinal Microvasculature by Optical Coherence Tomography Angiography in Patient with Pediatric Migraine

Kurtul BE, Sipal C, Akbas Y

[published online ahead of print, 2022 Aug 2]. *J Neuroophthalmol*.

Migraine, a chronic neurovascular disorder with a prevalence of close to 10% in children, is associated with changes in cerebral vascular tone. This leads to transient hypoperfusion, which could – it has been theorized – lead to cerebral, retinal, or choroidal damage over time. The authors use OCT-A technology to assess the ocular microvasculature in pediatric patients with migraines and compare it to age- and sex-matched controls.

This cross-sectional study was performed at a single institution and recruited both the subjects and the controls from a pediatric ophthalmology clinic. None of the migraine patient, it is interesting to note, had visual aura. The OCT-A images were all obtained by a single photographer at the same time of day (10AM-12PM) to rule out any changes due to diurnal variation. In all, 46 eyes from 23 patients were included in both the migraine and control groups, both of which had very similar baseline characteristics. There was no significant difference in RNFL thicknesses, foveal avascular zone, deep vessel densities, or optic disc capillary densities between the groups. However, the children with migraines had increased retinal thickness at the fovea and decreased superficial retinal vessel density compared to control patients. Although small, this study suggests that pediatric patients with migraines may have altered retinal vasculature and thickness compared to other children. Whether these findings are caused by, or simply associated with, migraines, as well as the clinical significance of such findings, has yet to be determined. It is an interesting area for further study.

Retinal Development in Infants and Young Children With Albinism: Evidence for Plasticity in Early Childhood.

Lee H, Purohit R, Sheth V, Maconachie G, Tu Z, Thomas MG, Pilat A, McLean RJ, Proudlock FA, Gottlob I.

American journal of ophthalmology. 2023 Jan 1;245:202-11.

Foveal hypoplasia is a well-described finding in albinism, though the longitudinal characterization of these retinal changes have not been well characterized. It is known that normal retinal development requires migration of the inner retinal layers and that this is likely disrupted in albinism. The goal of this prospective cohort study was to describe the longitudinal changes that occur with retinal development in a cohort of 36 children with albinism. To do this, the authors performed serial optical coherence tomography (OCT) imaging and compared these to controls. Overall, central macular thickness was significantly thicker in those with albinism compared to controls (84 microns thicker). Additionally, the authors identified a reduction in outer retinal layer elongation in albinism compared to controls. One limitation of this study is that there was a broad range of foveal hypoplasia in their cohort, thus trends may have been less apparent. This study provides real-world diagnostic data with the potential to shed insight into the mechanism of abnormal retinal development in children with albinism. The authors also propose that these retinal diagnostics may play a useful role in future clinical trial outcomes.

Symptomatic early-onset X-linked retinoschisis: clinical presentation and outcomes

Piquin G, Abdelmassih Y, Martin G, Edelson C, Metge F, Caputo G, Chapron T.

Retina 43(2):p 348-355, February 2023. | DOI: 10.1097/IAE.0000000000003667

X-linked retinoschisis is typically diagnosed at school age, and there has been limited discussion in the literature of children with early-onset retinoschisis. The authors retrospectively reviewed the records of 7 children diagnosed at their institution prior to the age of 2 and documented their presenting findings, need for surgical intervention, and final visual outcomes. Six children presented due to strabismus, and one child due to poor tracking. Thirteen of 14 eyes had peripheral retinoschisis at time of diagnosis, which compares to less than half of eyes in children with classic retinoschisis. The macula was involved in all eyes. Three eyes had retinal detachments, and another three had vitreous hemorrhage. Six eyes required surgical intervention. Final visual acuity at last follow-up ranged from 20/40 to NLP. The authors concluded that children with early-onset x-linked retinoschisis are more likely to have severe disease, with greater need for surgery and worse visual outcomes.

Combined hamartoma of the retina and retinal pigment epithelium at pediatric age: surgical versus conservative approach

Ozdek S, Ucgul AY, Hartnett ME, et al.

Retina 43(2):p 338-347, February 2023. | DOI: 10.1097/IAE.0000000000003652

Combined hamartoma of the retina and the retinal pigment epithelium (CHRRPE) is characterized by a hamartoma of the neurosensory retina and RPE with overlying glial cell proliferation, often leading to retinal pucker and distortion. Surgical intervention is generally indicated in the presence of an epiretinal membrane causing macular distortion or tractional retinal detachment. No previous study has evaluated the characteristics and outcomes of CHRRPE in the pediatric population specifically. The authors conducted a multicenter retrospective analysis of 62 eyes of 59 children (average age 7.7 years) at diagnosis. Twenty-one eyes of 20 patients underwent pars plana vitrectomy, while the other 41 eyes of 39 patients were managed conservatively. Visual acuity was able to be measured in 47 eyes. Best-corrected visual acuity improved in 11 of 16 eyes that underwent PPV (68.8%), versus only 4 of 31 eyes that were managed conservatively (12.9%). Mean central foveal thickness decreased in the intervention group from 602.0  $\mu\text{m}$  to 451.2  $\mu\text{m}$ , while it increased from 709.5 to 791.0  $\mu\text{m}$  in the conservative group. The authors concluded that vitreoretinal surgery is safe and effective in improving vision and reducing retinal distortion in children with CHRRPE.

27-gauge pars plana/plicata vitrectomy for pediatric vitreoretinal surgery

Ung C, Yonekawa Y, Chung MM, et al.

Retina 43(2):p 238-242, February 2023. | DOI: 10.1097/IAE.0000000000003662



Traditional vitrectomy used 20-gauge instrumentation, but this has largely been replaced by small-gauge vitrectomy using 23-gauge or 25-gauge instrumentation. New technology has allowed for the use of 27-gauge (27-G) vitrectomy, which offers potential advantages of greater ability to create self-sealing sclerotomies, reduction in post-operative inflammation and hypotony, and more precise manipulation of tissue in smaller dissection planes. However, there is limited data regarding its use in the pediatric population. The authors retrospectively reviewed the records of 56 eyes from 47 patients that underwent 27-G vitrectomy for treatment of various pediatric retinal pathologies. There were no cases of intraoperative complications, infusion issues, or post-operative endophthalmitis, though there was one case of instrument bending during surgery. There were 67/145 (45%) sclerotomies that were sutured, though 51 of those were sutured out of precaution and only 16 were sutured due to leakage. Four cases (7.1%) required conversion to a larger gauge, and 3 cases (5.3%) developed post-operative hypotony. Anatomic success was achieved in 96.4% of eyes. The authors concluded that 27-G vitrectomy is safe and feasible in the pediatric population, though further study is warranted.

#### Laser prophylaxis in Stickler syndrome: the Manchester protocol

Linton E, Jalil A, Sergouniotis P, et al.

Retina. 43(1):88-93, January 2023.

Patients with Stickler syndrome have high risk of giant retinal tears and retinal detachment, but there is presently no consensus about the optimal prophylactic approach. The authors retrospectively reviewed the records of all patients treated for Stickler syndrome at their institution, excluding patients who presented with retinal detachment. They divided patients into two groups: those who underwent prophylactic 360° retinal laser, and those who didn't. Overall, 113 eyes of 63 patients met criteria. 82 of those eyes (72.6%) received prophylactic laser at an average age of 14.6 years, while the remaining 31 did not. Of the patients who received prophylactic laser, 7 (9%) eyes went on to develop retinal detachment at an average age of 19.7 years and none developed giant retinal tears. Of the 31 eyes that did not receive prophylaxis, 7 (23%) eventually developed retinal detachment at an average age of 21.9 years and 3 developed giant retinal tears. Though the study was limited by its retrospective nature, lack of randomization, and lack of matching patient characteristics between the two groups, the authors conclude that 360° retinal laser prophylaxis is a safe and effective approach for people with Stickler syndrome.

#### Efficacy of inner wall retinectomy for bullous schisis cavity hanging over or threatening the macula in patients with congenital x-linked retinoschisis

Iwahashi C, Matsushita I, Kuniyoshi K, Kondo H, Kusaka S.

Retina. 43(1):64-71, January 2023.

There are several indications for vitreoretinal surgery in children with X-linked retinoschisis, one of which is bullous schisis hanging over or threatening the macula. However, the optimal surgical procedure for this situation remains controversial. The authors sought to investigate the role of vitrectomy in these patients by retrospectively reviewing the records of all patients undergoing vitrectomy for this indication at 3 hospitals in Japan over an 8-year period. Twelve eyes of 9 patients met study criteria, with age at vitrectomy ranging from 4 months to 103 months (median 14 months). Eight eyes initially underwent inner wall retinectomy, with one of those eyes later requiring additional surgery for postoperative complication. The other four eyes did not undergo initial inner wall retinectomy, and all 4 required subsequent retinal surgeries due to post-operative complications. The authors concluded that inner wall retinectomy is beneficial in eyes with bullous cavity hanging over or threatening the macula in patients with congenital X-linked retinoschisis.

#### Topical carbonic anhydrase inhibitors in the long-term treatment of juvenile X-linked retinoschisis

Schmitt MA, Wang K, DeBenedictis MJ, Traboulsi E. Retina. 42(11):2176-2183, November 2022.

Treatment for X-linked retinoschisis is limited, but carbonic anhydrase inhibitors (CAI) have shown some promise. The authors present a case series of 18 eyes of 10 patients treated with topical dorzolamide 2% 2-3 times daily for an average of 8.38 years. Two eyes were excluded due to presence of retinal detachments. Mean patient age at baseline visit was 12.22 years. The mean central subfield thickness decreased from 429.88 µm at baseline to 372.28 µm at final exam. The mean LogMAR best-corrected

visual acuity improved from 0.45 to 0.34. None of the patients experienced any side effects from topical dorzolamide. The study was limited by its small sample size, retrospective nature, and absence of a control group, but it does provide encouraging evidence that topical CAI may be beneficial for patients with X-linked retinoschisis.

Macular microvasculature in x-linked retinoschisis: optical coherence tomography and optical coherence tomography angiography study

Kwon HJ, Kim YN, Min CH, et al.

Retina. 42(10):1939-1949, October 2022.

The recent retinal imaging modality of optical coherence tomography angiography (OCTA) has been rarely used in patients with x-linked retinoschisis. The authors aimed to evaluate the macular microvasculature of X-linked retinoschisis (XLRS) and identify correlations between vascular changes, structural changes, and functional outcome. They performed OCTA and optical coherence tomography on 17 eyes of 9 patients with XLRS and 22 eyes of 11 controls. Flow density in the deep capillary plexus at foveal and parafoveal area decreased in XLRS patients compared with control subjects, whereas foveal avascular zone area and perimeter increased. Although outer and total retinal layers were significantly thicker in XLRS, inner retinal layer was thinner with reduced photoreceptor layer thickness and shortened photoreceptor outer segment length. Foveal flow loss in deep capillary plexus, foveal avascular zone enlargement, thinner inner retina and photoreceptor layer thickness, and shortened photoreceptor outer segment length correlated with best-corrected visual acuity. The authors concluded that OCTA provides the detection of significant microvascular alteration in eyes with XLRS exhibit decreased flow density in the deep capillary plexus and variable foveal avascular zone with enlarged perimeter. Structural deterioration of the photoreceptor best reflects the degenerative changes, whereas microvascular alteration shows considerable correlation with functional outcome in XLRS.

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Treatment of Advanced Coats' Disease With Combination Therapy of Laser Photocoagulation, Intravitreal Ranibizumab, and Sub-Tenon Methylprednisolone Acetate.

Petroni S, Catena G, Iarossi G, et al.

J Pediatr Ophthalmol Strabismus. 2022;59(3):187-191. doi:10.3928/01913913-20211110-02

This single-center retrospective study sought to investigate the efficacy of combination therapy with laser photocoagulation, intravitreal ranibizumab, and sub-Tenon methylprednisolone acetate in patients presenting with advanced Coats' disease. The authors reported outcomes of 16 patients aged  $5.12 \pm 2.7$  years (range: 3 to 10 years) with mean follow-up time  $45.43 \pm 29.01$  months (range: 12 to 108 months). Of the 16 patients (16 eyes), 6 patients had stage 3A and 10 patients had stage 3B Coats' disease. Laser was applied to all areas of avascular retina, telangiectasias, and adjacent to exudative detachments w/ fluorescein guidance. As exudative detachments resolved, additional laser was applied over the previously detached areas, and treatments were continued until there was complete anatomic resolution of exudation and telangiectasias. The mean number of laser applications was 10 (range: 4 to 18). Globe preservation was achieved in all patients. Final visual acuity outcomes were satisfactory: 20/20 to 20/50 in 2 patients, 20/60 to 20/100 in 1 patient, and 20/200 or worse in 13 patients. The authors concluded that the combined therapy achieved anatomical success, globe preservation, and reasonable visual acuity outcomes w/ some benefit over intravitreal steroid injections in reduced risk of adverse complications.

Optical coherence tomography angiography findings of retinal vascular structures in children with celiac disease,

Ishak Isik, MD, Lutfiye Yaprak, MD, Asli Yaprak, MD, and Ulas Akbulut, MD.

J AAPOS 2022; 26:69.e1-4.

Celiac disease (CD) is an autoimmune disorder that is most associated with the small intestine; however, it can also affect the liver, skin, nervous system, eyes, reproductive, and musculoskeletal systems. The purpose of this study was to investigate the effect of autoantibodies against tissue transglutaminase 2 (TG2) on the vasculature of the retina and choroid in children with CD using optic coherence tomography angiography (OCTA). A total of 131 children were included in the study (60 in the celiac group, 71 in the control group). There were no differences in vascular density between the two groups. There were

differences seen in the mean subfoveal choroid thickness (lower in the celiac group) and foveal avascular zone size (larger in the celiac group); however, these differences did not meet statistical significance. While the authors hypothesized that TG2 autoantibodies might affect retinal microvasculature and choroid plexus, this study did not support this. The authors felt it may be possible that greater difference would be seen with longer follow-up. This study lays a framework for future studies trying to ask this same questions with a larger study population and longer follow-up.

Analysis of optical coherence tomography angiographic findings of prematurely born children and its relationship with macular edema of prematurity.

Ersan Cetinkaya, MD, Mehmet Fatih K€uc€uk, MD, Elcin S€uren, MD, Mustafa Kalayci, MD, Muhammet Kazim Erol, MD, Fulya Duman, MD, Berna Dogan, MD, and Ozdemir Ozdemir, MD.  
J AAPOS 2022; 26:73.e1-6.

In addition to having the vascular changes commonly associated with ROP, 30-60% of premature infants have cystoid macular edema (CME) that can be seen on portable spectral domain optical coherence tomography (SD-OCT). This edema disappears spontaneously by postmenstrual age (PMA) of 52 weeks; however, little is known about the long-term effects of this edema. This paper aims to compare foveal characteristics in pre- and full-term children and to evaluate their relationship with CME in the prematurity period using SD-OCT angiography (SD-OCTA). OCTA was performed on 70 children aged 4-6 years old (45 premature, 25 term) who were split into 3 groups: premature with CME (group 1), premature without CME (group 2), and term (group 3). Foveal avascular zone (FAZ), foveal vascular density (VD), and foveal thickness (FT) were compared amongst the 3 groups. This is the first study to evaluate these variables. The most notable finding was that the FAZ area was significantly large in group 3 compared to groups 1 and 2. FAZ area also correlated with gestational age and birth weight. Interestingly, there was no correlation between FAZ area and visual acuity or axial length. There were no significant differences in any of the parameters between groups 1 and 2. This study is important as it gives additional prognostic information that can be shared with the parents of premature infants. It is limited by the cross-sectional study design and small sample size.

Retinal hemorrhage after pediatric neurosurgical procedures.

Caroline W. Chung, MD, Alex V. Levin, MD, MHS Brian J. Forbes, MD, PhD, and Gil Binenbaum, MD, MSCE.

J AAPOS 2022; 26:74.e1-5.

A subset of children undergoing evaluation for non-accidental trauma require urgent neurosurgical intervention, which can delay ophthalmic examination for retinal hemorrhages. If retinal hemorrhage is identified following the neurosurgical procedure, questions may arise as to whether the procedure itself may be responsible for the findings. The effects of neurosurgery on the retina and possible associated patterns of retinal hemorrhage are unknown, so this study sought to determine the prevalence and patterns of retinal hemorrhage attributable to neurosurgical intervention in children. The study included 267 children who underwent a variety of neurosurgical procedures (craniotomies, burr-hole procedures, ventricular cerebrospinal fluid drain implantations, spinal surgeries, and others). Retinal hemorrhage was seen in 32 cases (12%); however, in every case they were seen pre-operatively or matched the pattern of coexistent known cause of retinal hemorrhage. Overall, the prevalence of retinal hemorrhage definitively attributable to neurosurgery was 0%. Since the authors found no clear evidence that neurosurgery itself causes retinal hemorrhage in children, they propose that neurosurgery is not likely to cause retinal hemorrhage. Since neurosurgery independently is unlikely to procedure retinal hemorrhage, needing neurosurgical intervention prior to a dilated eye exam should not be a confounding factor in the interpretations of findings on the dilated exam. This study provides support to pediatric ophthalmologists who screen for abusive head trauma that their findings should not be altered by neurosurgical procedures performed prior to their dilated eye examination.

Fundus Changes in the Offspring of Mothers with Confirmed Zika Virus Infection During Pregnancy in French Guiana, Guadeloupe, and Martinique, French West Indies

Harold Marle MD PhD, Maxime Chassery MD, Laurence Beral MD PhD, et al.

JAMA Ophthalmol. Published online September 1, 2022.

This study sought to identify the ocular lesions found in children exposed to the Zika Virus (confirmed by PCR testing) during pregnancy in the French West Indies. This is a cross-sectional multicentric study which screened 330 children between August 1, 2016, and April 30, 2019. To date, this is the largest cross-sectional multi centric study of fundus screening of an entire population exposed to Zika Virus. Eleven children (3.3%) had perivascular retinal hemorrhages, and 3 (0.9%) had lesions compatible with congenital ZIKV infection: 1 child had torpedo maculopathy, 1 child had a chorioretinal scar with iris and lens coloboma, and 1 child had a chorioretinal scar. Retinal hemorrhages were found at childbirth during early screening. Microcephaly was not associated with lesions compatible with congenital ZIKV infection (odds ratio [OR], 9.1; 95% CI, 0.8-105.3;  $P = .08$ ), but severe microcephaly was associated with an OR of 81 (95% CI, 5.1-1297.8;  $P = .002$ ). Overall, this study suggests that ocular lesions are rare in the Zika Virus exposed population of French Guiana. When lesions are present, they mostly affect the choroid and retina possibly due to choroiditis related scarring. This is in contrast to other studies of affected children in other parts of the world (Brazil, Colombia, Venezuela), which showed higher percentages of affected patients.

Kurultay I, Sancakli O. Evaluation of choroidal thickness in children with acute asthma attack by optical coherence tomography.

Eur J Ophthalmol. 2022 May;32(3):1424-1429.

This prospective study was conducted between March 2020 and October 2020 in children with mild to moderate persistent asthma between 5-17 years of age to evaluate the change in central choroidal thickness before and after treatment with  $\beta_2$  agonists. It has been suggested in other studies that sympathetic activity and noradrenaline that provide bronchodilation reduce choroidal flow while parasympathetic activity causes bronchoconstriction and increases choroidal blood flow.  $\beta_2$  agonists are the first-choice treatment for an acute asthma attack and are presumed to decrease choroidal blood flow and thereby possibly decrease choroidal thickness. About 100 eyes of 50 patients with visual acuity of 20/20 who had no retinal, choroidal, and systemic comorbidity were examined by enhanced depth optical coherence tomography (EDI-OCT) before and after asthma attack treatment. Sixty eyes of 30 healthy children of similar age and gender were evaluated as the control group. The central choroidal thickness, peak expiratory flow (PEF), forced expiratory volume 1 (FEV<sub>1</sub>), oxygen saturation, and heart rate were evaluated. The mean age of the study patients was  $9.2 \pm 3.1$  years, and the mean saturation values of patients was  $97.2 \pm 1.3$  before treatment, and it increased to  $98.3 \pm 0.9$  after treatment with a statistically significant difference. The mean FEV<sub>1</sub> values were  $80.8 \pm 15.2$  before treatment and  $92.7 \pm 12.9$  after treatment, and PEF values were  $75.9 \pm 18.6$  before and  $89.3 \pm 18.9$  after treatment. These differences were statistically significant ( $p < 0.001$ ). The average choroidal thickness before the treatment was  $310.4 \pm 34.2 \mu\text{m}$  and decreased to  $302.7 \pm 34.4 \mu\text{m}$  after the treatment, and this decrease was statistically significant ( $p < 0.001$ ). The mean choroidal thickness of the control group was  $303.0 \pm 7.3 \mu\text{m}$ , which was similar to the post-treatment values, although this was not a statistically significant difference. The authors conclude that standard  $\beta_2$  agonist treatment for asthma attacks caused a significant decrease in choroidal thickness in pediatric patients. While there was also a statistically significant increase in oxygen saturation, PEF, and FEV<sub>1</sub> values after asthma attack treatment, there was no correlation between these values and the decrease in choroidal thickness.

Optical coherence tomography angiography in healthy children: A comparison of macular structure.

Plaitano C, Periti F, Guagliano R, Bertone C, Barillà D, Arpa C, Tinelli C, Gallo FG, Bianchi A, Magli A. Eur J Ophthalmol. 2022 Jul;32(4):2005-2010.

The purpose of this study was to investigate the perfusion density (PD) of macular superficial (SCP) and deep capillary plexus (DCP), the size of foveal avascular zone (FAZ), and central macular thickness (CMT) in healthy children using optical coherence tomography angiography (OCT-A). About 206 eyes of 111 healthy, Caucasian children were analyzed in this prospective observational cross-sectional comparative study. Inclusion criteria of the study were: age between 4 and 16 years old, refractive error between  $-5$  D (diopters) and  $+5$  D, absence of congenital disorders affecting visual system, good patient cooperation. The study sample included 63 girls and 48 boys; the mean age was 9.4 (SD: 3) years.

The correlation of gestational age (GA), birth weight (BW), age, sex, refractive errors, and visual acuity (VA) with OCT-A parameters were investigated. The mean PD of the fovea and the mean FAZ area of SCP were 17.1% (DS: 4.26) and 234.47 (DS: 106.39)  $\mu\text{m}^2$ . The mean PD of the fovea and the mean FAZ

area of DCP were 13.5% (DS: 5.23) and 298.32 (DS: 112.37)  $\mu\text{m}^2$ . Superficial and deep FAZ areas were not correlated with sex, age, BW, refractive errors, or VA. FAZ area of SCP was correlated with foveal PD ( $r = -0.76$ ) and with CMT ( $r = -0.68$ ). FAZ area of DCP was correlated with foveal's PD ( $r = -0.61$ ). There was no correlation between CMT and refractive errors. OCT-A may provide a non-invasive and reliable approach to evaluate macular perfusion in children. As the FAZ area, PD, and CMT change during the growth period, the authors established a reference range for different ages.

Changes in ocular pulse amplitude and choroidal thickness in childhood obesity patients with and without insulin resistance.

Aydemir GA, Aydemir E, Asik A, Bolu S.

Eur J Ophthalmol. 2022 Jul;32(4):2018-2025.

This prospective, cross-sectional study aimed to compare choroidal thickness (CT) and ocular pulse amplitude (OPA) in childhood obesity with insulin resistance (IR) and without IR. Ocular pulse amplitude (OPA), representing the pulsatile waveform that forms with the passage of blood through the eye, is an indirect choroidal perfusion marker. Sixty-two healthy patients (control group) and 73 cases with childhood obesity (study group) comprised the study population. The groups were both age-matched and gender-matched. Obesity was determined as having a body mass index (BMI) – standard deviation (SD) score that was  $> 2$  SD. Intraocular pressure (IOP) and OPA were measured using a dynamic contour tonometer. The CT measurements were performed using enhanced depth imaging optical coherence tomography at three locations, comprising at the fovea, at a position 500  $\mu\text{m}$  nasal, and also at a position 500  $\mu\text{m}$  temporal to the fovea. Mean BMI value was  $28.72 \pm 4.85$  in the patients with childhood obesity and  $21.47 \pm 1.14$  in the control group. The mean IOP and OPA values were determined to be  $15.90 \pm 2.30$  and  $14.10 \pm 2.16$  mm Hg,  $1.50 \pm 0.28$  and  $1.74 \pm 0.32$  mm Hg in the patients with childhood obesity and the control group, respectively ( $p < 0.001$ ,  $p < 0.001$ ). The mean subfoveal CT value was  $350.50 \pm 81.51$   $\mu\text{m}$  in the eyes with childhood obesity and  $390.02 \pm 71.50$   $\mu\text{m}$  in those of the control group ( $p = 0.003$ ). When the patient groups with and without IR were compared, no significant difference was found between CT, OPA and IOP values ( $p > 0.005$ ). The study results suggest that both OPA and CT values were significantly decreased in childhood obesity patients. Further studies to verify longitudinal changes in OPA and CT, and also the evaluation of these parameters in other populations, is necessary for correlation.

Pediatric choroidal neovascularization: Etiology and treatment outcomes with anti-vascular endothelial growth factors.

Ranjan R, Salian R, Verghese S, Manayath GJ, D'Souza P, Kanakath AV, Shah PK, Saravanan VR, Venkatapathy N.

Eur J Ophthalmol. 2022 Jul;32(4):2355-2367.

This retrospective, single-center, interventional case series studied a total of 26 eyes of 23 consecutive pediatric patients with choroidal neovascularization (CNV) of various etiologies that were treated with intravitreal injection of anti-VEGF agents. The authors aimed to evaluate the etiology of CNV and treatment outcomes with anti-VEGF treatment in this patient group. There were 15 males (65.2%) and eight females (34.8%) under 18 years of age diagnosed with CNV during the study period from 2011 to 2021. The mean age at presentation with CNV was  $11.7 \pm 3.3$  years, (range 4-16 years) and the mean follow was  $28.1 \pm 18$  months, (range 8-72 months). Inflammatory CNV was the most common etiology. The mean best corrected visual acuity (BCVA) and mean central macular thickness (CMT) at presentation, were logMAR  $0.8 \pm 0.3$  and  $367.6 \pm 134.8$   $\mu\text{m}$  respectively. At the final visit, CNV in all eyes remained regressed with significant improvement in mean BCVA to logMAR  $0.4 \pm 0.4$  ( $p < 0.0001$ ) and mean CMT to  $242.5 \pm 82.4$   $\mu\text{m}$  ( $p < 0.0001$ ). A mean of two intravitreal injections per eye was required for CNV regression. The authors assert that this is the largest single-center study on pediatric CNV (26 eyes of 23 children), in which intravitreal anti-VEGF monotherapy was used for the treatment of active CNV (19 eyes of 18 children). They conclude that the use of anti-VEGF agents in a wide variety of active pediatric CNV cases is an effective and safe treatment modality. Earlier diagnosis of CNV with prompt treatment results in good anatomical and functional outcomes. CNV in children carries a favorable prognosis and requires a fewer number of anti-VEGF injections, with a lower tendency for recurrence compared to the adult population.

Interocular differences in subfoveal choroidal thickness in monocular intermittent exotropia.

Na JH, Lee SJ

*J AAPOS*. 2022 Jun;26(3):127.e1-127.e5.

The authors used retrospective review to determine whether subfoveal choroidal thickness and central foveal thickness measured using OCT differ according to the presence of fixation preference in patients with intermittent exotropia without anisometropia or amblyopia. There has been differing study results concerning retinal and choroidal thickness in amblyopic eyes and no studies prior to the current study examining these parameters according to fixation preference alone. The authors controlled for assessing for fixation preference by including only patients without amblyopia and no significant refractive error. The patients were divided into the monocular exotropia group (46 patients) and alternating exotropia group (35 patients) for measurement of subfoveal choroidal thickness and central foveal thickness. The interocular difference in central foveal thickness showed no significant difference between the groups. The difference in subfoveal choroidal thickness between eyes in the monocular group was significantly greater than that between eyes in the alternating group. The choroid of the nondominant eye tended to be thicker than the choroid of the dominant eye. The authors speculate that this difference may be the result of increased metabolic demand associated with reduced use of one eye. Limitations of this study include small recruitment size and manual measurement of choroid thickness. This study is important in reminding pediatric ophthalmologists that there is still a tremendous amount to learn about why children have strabismus and the relationship between structure and function.

Impact of ocular dominance on circumpapillary and macular retinal nerve fibre layer thickness and ganglion cell layer thickness in a healthy pediatric population.

Jimenez-Santos M, Cifuentes-Canorea P, Ruiz-Medrano J, Felipe-Marquez G, Valverde-Megias A, Gomez de Liano R.

*Can J Ophthalmol*. Jun 2022;57(3):201-206. doi:10.1016/j.jcjo.2021.03.012

This is a cross-sectional study of 89 children (178 eyes) in a Hispanic pediatric population in Spain. The study aims to evaluate the difference in segmented macular layers and circumpapillary retinal nerve fibers to identify ocular dominance as a factor in the interocular difference. The authors determined ocular dominance using the hole in the card and convergence near point tests. Only included children who had the same eye dominance with both tests. Children born at term from 5 to 16 years old were recruited. UCVA, BCVA, stereo test, subjective refraction, and cycloplegic refraction were performed. Optical Biometry and SD-OCT of the posterior pole map centered on the fovea and peripapillary RNFL circle scan were obtained. 67.4% showed right eye dominance. The retinal ganglion cell layer in the central 1 mm in the dominant eye was significantly thinner than in nondominant eyes, but it failed significance statistically after the Bonferroni correction. There was no difference in RNFL. The authors concluded there was no difference between dominant and nondominant eyes. This study was carried out in a Hispanic population; therefore, cannot be extrapolated to other ethnicities.

Retinopathy of prematurity incidence and treatment modalities in moderate and late preterm infants: a study from two tertiary centers.

Comez A, Celemler P, Ozmen MC, et al.

*Can J Ophthalmol*. Jun 2022;57(3):195-200. doi:10.1016/j.jcjo.2021.03.014

This is a retrospective cohort of 4156 preterm infants with a GA between 32 to 36w6d in two tertiary referral centers in Turkey. The aim is to evaluate the incidence, severity, and treatment modalities of ROP in these infants. Turkey's screening guidelines include infants born GA  $\leq$  32 weeks or BW  $\leq$  1500g. Infants were divided into two groups, moderate preterm (32w to 33w6d) and late preterm (34-36w6d). Infants were also classified into three groups based on their weight  $<$ 1500, 1500-2000,  $>$ 2001. Infants with APROP, type 1, and type 2 were defined as having severe ROP. The overall incidence of any ROP was 22%, and severe ROP was 2.5%. The rate of severe ROP was 5.3% in moderate preterm and 0.9% in late preterm. The mean BW and GA of infants with severe ROP were significantly lower than those with mild ROP. 2.5% required treatment. APROP was detected in 22 infants (21.5%) requiring treatment. The mean treatment time was at the fifth postnatal week. Partial retinal detachment was detected in 2 infants with BW  $>$ 2000. The authors conclude that severe ROP, especially treatment-requiring ROP is still a public health issue in Turkey, likely from excessive or inappropriate oxygen therapy, insufficient nursing care, or an inadequate number of neonatologists. The authors could not determine the risk factors

associated with the development of treatment requiring ROP in these infants as most were being referred from outside institutions.

X-Linked Retinoschisis: Deep Phenotyping and Genetic Characterization.

Georgiou M, Finocchio L, Fujinami K, Fujinami-Yokokawa Y, Virgili G, Mahroo OA, Webster AR, Michaelides M.

Ophthalmology. 2022 May;129(5):542-551. doi: 10.1016/j.ophtha.2021.11.019. Epub 2021 Nov 23. PMID: 34822951.

This study describes the genetic, clinical, and imaging characteristics of 132 male patients with molecularly confirmed XLRs. It is the largest cohort study to date and includes data on multimodal imaging and genotype-phenotype investigation. 66 variants of the RS1 gene were identified of which 7 were novel. There was significant phenotypic variability and the BCVA and frequency of complications was more associated with null vs missense mutation. The most common retinal finding was macular schisis (82.4%.) Peripheral schisis was found in about 40% of patients and only 11% had macular atrophy. The patients with schisis were younger than those with atrophy. BCVA appeared to have slow modest progression over time. Structural changes were found on FAF of varying patterns along with variable layers affected. For the purposes of clinical trials OCT was the most available modality that could provide metrics for study endpoints. In addition, it could be able to detect early disease changes before the development of overt atrophy, however the slow disease progression may make quantifiable changes in OCT difficult to detect within study timeframes. The authors conclude that XLRs has a wide spectrum of clinical characteristics but given that it is a monogenic disorder it is a prime target for the possibility of gene therapy. Given the slow progression there may also be a wide window of opportunity for treatment. This study is interesting in characterizing the genetic and phenotypic appearance of XLRs.

Optical coherence tomography angiography of subclinical ocular features in pediatric Behçet disease  
Yılmaz Tuğan, Büşra et al.

Journal of American Association for Pediatric Ophthalmology and Strabismus {JAAPOS}, Volume 26, Issue 1, 24.e1 - 24.e6

This is a prospective cross-sectional study of pediatric patients diagnosed with Behçet disease (BD) without ocular involvement was evaluated using an optical coherence tomography angiography (OCTA) and compared with age and sex matched healthy controls. 22 eyes of 22 pediatric patients were analyzed. Vessel density of the whole image, fovea, parafovea, and perifovea in DCP were significantly lower in the nonocular pediatric BD group. There was no significant difference between the groups in vascular density (VD) parameters of both superficial capillary plexus (SCP) and optic nerve head (ONH), as well as foveal avascular zone (FAZ) parameters. Although outer retina and choriocapillaris flow area at 1 mm, 2 mm, and 3 mm radius were lower in the nonocular pediatric BD group than in the control group, the difference was statistically significant only in the outer retina flow area at 3 mm radius. The BD patients had decreased vessel density in the deep capillary plexus (DCP) and decreased outer retinal flow. In this cohort the OCTA can detect microvascular changes in patients without detectable ocular involvement.

Foveal hypoplasia grading in 95 cases of congenital aniridia: correlation to phenotype and PAX6 genotype.

Daruich A, Robert MP, Leroy C, de Vergnes N, Beugnet C, Malan V, Valleix S, Bremond-Gignac D. American Journal of Ophthalmology. 2022 May 1;237:122-9.

A well-established manifestation of aniridia is foveal hypoplasia, though data about genotype-phenotype correlation in this condition is limited. The goal of this retrospective study was to characterize foveal hypoplasia in children with congenital aniridia and assess for a genotype-phenotype correlation. This was a retrospective single center study of 95 children with aniridia. All children underwent optical coherence tomography of the macula and foveal hypoplasia was graded using a standardized scale. The authors report several interesting findings. First, they found that foveal hypoplasia was more severe in those with PAX6 genetic changes. Among the genetic changes in PAX6, nonsense variants were associated with higher degrees of foveal hypoplasia. Deletions in the 3' regulatory regions flanking PAX6 were associated with less severe foveal hypoplasia and better vision. Additionally, the extent of the iris defects correlated

to the severity of the foveal hypoplasia. As expected, visual acuity was better in children with thicker outer retinal layers. A specific genetic change (deletions in the 3' regulatory regions flanking PAX6) was associated with best outcomes in terms of foveal hypoplasia and visual acuity. This has implications for visual prognosis counseling for children with aniridia and genetic testing.

Macular thickness by using spectral domain optical coherence tomography in children and adolescents  
Hashemi H, Khabazkhoob M, Heydarian S, Emamian MH, Fotouhi A.

*Retina*. 2022 Aug 1;42(8):1599-1607. doi: 10.1097/IAE.0000000000003484. PMID: 35384933.

Assessment of macular morphology is important in diagnosis of many conditions affecting the retina, with many disorders starting in childhood. The authors sought to use spectral domain OCT to determine normal central macular thickness (CMT) in a population of 5043 Iranian school-children aged 9 to 15. Average CMT was  $239 \pm 19.35 \mu\text{m}$ . The authors determined the normal range to be between 200 and  $278 \mu\text{m}$ , as 5% of children had a CMT less than 200 and 5% had a CMT thicker than 278. Central macular thickness was significantly higher in boys and rural children. There was a positive association between axial length and CMT, but no significant correlation with refractive error. This study helps to establish normative values for macular morphology in the pediatric age range, in particular for children of Persian descent.

Evidence against a contralateral Coats phenotype by optical coherence tomography angiography  
Daruich A, Zola M, Elalouf M, Munier FL.

*Retina*. 2022 Jun 1;42(6):1184-1188. doi: 10.1097/IAE.0000000000003438.

Coats disease has generally been considered a unilateral disease process; but with the advent of ultrawide-field imaging, it has been suggested that Coats disease could be considered a bilateral condition due to the presence of peripheral vascular changes in the fellow eyes of some children with Coats disease. The authors sought to evaluate the laterality of Coats disease by analyzing optical coherence tomography angiography (OCTA) features in affected, fellow, and control eyes. OCTA images were retrospectively reviewed from 34 children with Coats disease, with 13 of those children having OCTA images taken of both eyes and 21 having images only taken in the fellow eye. The unaffected eyes of 24 children with unilateral retinoblastoma or unilateral congenital cataracts were used as a control group. The foveal avascular zone was enlarged and the vascular density was decreased in affected eyes of children with Coats disease when compared to the fellow eyes of the same children, but no differences were seen between fellow and control eyes. These findings support the long-held assertion that Coats disease is a unilateral disease process. Children diagnosed with presumed bilateral Coats disease should undergo a thorough work-up to rule out other potential etiologies of their retinopathy.

Evaluation of macular flow voids on optical coherence tomography angiography [OCT-A] as potential biomarkers for silent cerebral infarction in sickle cell disease

Thangamathesvaran L, Ong SS, Wang J, Lance E, Tekes A, Scott AW.

*Retina*. 2022 Feb 1;42(2):340-347. doi: 10.1097/IAE.0000000000003309. PMID: 34608107.

Silent cerebral infarction (SCI) is the most common neurologic complication of sickle cell disease (SCD) in children, and it is diagnosed when MRI of the brain is abnormal in the setting of a normal neurologic exam and with no known history of an overt stroke. While fluorescein angiography has generally been considered the gold standard for diagnosing retinal vascular changes in SCD, the advent of optical coherence tomography angiography (OCT-A) now allows for more convenient and less invasive imaging of the retinal vasculature. The authors sought to determine whether there is an association between retinal abnormalities found on OCT-A and the presence of SCI in children with SCD. They retrospectively reviewed imaging of 28 eyes of 14 children with SCD who had undergone both OCT-A and MRI of the brain. Eight children had been found to have SCI on their MRI, while the other six did not. Deep capillary plexus vessel density was lower in the temporal hemifield of patients with SCI, but no other OCT-A parameters were found to be statistically between the two groups. The study was limited by its small sample size, but it suggests that reduced deep capillary plexus vessel density as measured by OCT-A could potentially represent a biomarker for SCI in children with SCD.



Asymptomatic Retinal Vein Occlusion in a 13-Year-Old with Heterozygous Deletion of the PMP22 Gene and a Diagnosis of Hereditary Neuropathy with Liability to Pressure Palsies

Saffra NA, Emborgo TS, Laureta EC, Kirsch DS, Guarini L

*J Neuroophthalmol.* 2022;42(1):e367-e370

Hereditary neuropathy with liability to pressure palsies (HNPP) is a disease caused by a mutation in the PMP22 Gene and is typically characterized by muscular weakness, muscular atrophy, and numbness secondary to mechanical stress. The authors present a rare case of a 16-year-old female, diagnosed with HNPP 3 years previously, who was found to have a, asymptomatic retinal vein occlusion (RVO) in the left eye on routine ophthalmologic exam. Extensive hematologic, cardiac, and inflammatory/autoimmune work-up revealed no sign of hypercoagulability or vascular abnormality. The authors suggest it is possible that the PMP22 mutation – which, in addition to its involvement in myelination, has also been reported to be associated with cerebral microvasculature – may be the underlying cause of the RVO in this case. Of course, further study of this potential association is required. For now, ophthalmologists should simply be aware of potential retinal vascular complications in children with HNPP.

X-Linked Retinoschisis: Novel Clinical Observations and Genetic Spectrum in 340 Patients.

Hahn LC, van Schooneveld MJ, Wesseling NL, Florijn RJ, Ten Brink JB, Lissenberg-Witte BI, Strubbe I, Meester-Smoor MA, Thiadens AA, Diederens RM, van Cauwenbergh C, de Zaeytijd J, Walraedt S, de Baere E, Klaver CCW, Ossewaarde-van Norel J, van den Born LI, Hoyng CB, van Genderen MM, Sieving PA, Leroy BP, Bergen AA, Boon CJF.

*Ophthalmology.* 2022 Feb;129(2):191-202. doi: 10.1016/j.ophtha.2021.09.021. Epub 2021 Oct 6. PMID: 34624300.

This is a retrospective cohort study describing the natural course, genotype, and phenotype of 340 patients with X-linked retinoschisis (XLRS). Patient data were gathered from the Delleman archive, a large database for hereditary eye diseases of the Amsterdam University Medical Centers and from various Dutch centers within the RD5000 consortium, a nationwide collaborative registry for patients with retinal dystrophies. Data were collected by extensively reviewing all medical records for medical history, age at onset, symptoms, age at diagnosis, XLRS-associated complications, familial history, VA, refractive error, dilated fundus examination findings, full-field electroretinography findings, spectral-domain (SD) OCT images, fundus autofluorescence images, and color fundus photography. Note that every one of these pieces of data was not available for every patient in the cohort, which is a limitation of this study. The median age of onset of symptoms was 4.0 years and the median age of diagnosis was 7.0 years. Median age to reach mild visual impairment (<20/40 and >20/70) was 12 and low vision was 25 (<20/70 and >20/200). Median age of severe visual impairment (<20/200 and >20/400) or blindness (<20/400) could not be calculated due to lack of data. Severe visual impairment and blindness were observed predominantly in patients older than 40 years, with a predicted prevalence of 35% and 25%, respectively, at 60 years of age. The annual rate of visual decline was ~0.4%. The most common clinical findings included cystic changes in the macula, spoke wheel appearance on funduscopy, and peripheral retinal schisis. In patients with electroretinogram data, the most common findings were reduced b-to-a wave amplitude (72.2%). On OCT, the integrity of the ellipsoid zone and the photoreceptor outer segment (PROS) length in the fovea correlated significantly with VA. There was large variability in the clinical course and visual function among patients. Genetically, 53 different RS1 variants were identified, the most common being c.2146->A (38.7%) and a deletion of exon 3 (14.6%). There was no clear genotype-phenotype correlation identified.

## 19. RETINOBLASTOMA / INTRAOCULAR TUMORS

Association of choroidal invasion with retinoblastoma survival rates

Loya A, Ayaz T, Gombos DS, and Weng CY

J AAPOS 2023;27:32.e1-8

A retrospective nationwide analysis of retinoblastoma cases diagnosed between 2004-2016 using the Surveillance, Epidemiology, and End Results database was conducted to assess survival, cause-specific survival and all-cause mortality risks. A total of 393 retinoblastoma patients were included, of whom 268 (68.2%) had no choroidal invasion, 91 (23.2%) had focal choroidal invasion, and 34 (8.7%) had massive choroidal invasion on enucleation. A total of 6 deaths occurred throughout an average follow-up period of 72.2 + 47.1 months: 4 deaths were cancer related. All cancer-related deaths occurred in patients with massive choroidal invasion. Adjusted Cox regression analysis revealed that patients with massive choroidal invasion had higher all-cause mortality in comparison to patients with no choroidal invasion; in contrast, those with focal choroidal invasion showed no difference in all-cause mortality. On further stratification by level of optic nerve invasion (ONI), all cancer-related deaths (4/4) were found to have occurred in patients with massive choroidal invasion and concomitant postlaminar ONI (PLONI). All retinoblastoma-related deaths occurred in patients with both massive choroidal invasion and PLONI. This study could not establish massive choroidal invasion as an independent risk factor for mortality.

Quantity and duration of exposure to general anesthesia for pediatric patients with retinoblastoma

Kerri McInnis-Smith, Kelsey Chen, Molly Klanderma, Todd Abruzzo, Aparna Ramasubramanian .

J AAPOS. 2022 Dec;26(6):313.e1-313.e5.

Long-term effects of prolonged general anesthesia during young childhood became a concern in 2016 when the FDA gave advice suggesting limiting repeated or lengthy general anesthesia in children younger than age 3 years and pregnant women because of possible developmental concerns. The authors used retrospective review to quantify the duration of anesthesia required for optimal management of retinoblastoma (Rb) stratified by clinical factors. The article is important to pediatric ophthalmologists since Rb is a disease of children less than 5 years of age. Diagnosis, management, and surveillance often include repeated need for general anesthesia. Nonhuman studies suggest general anesthesia has long-lasting functional effects. These findings have been more difficult to make same conclusions from human studies. Some studies indicate single, brief exposures likely have no long-term effects. Other studies show exposure to multiple procedures requiring general anesthesia is associated with increased risk for learning disabilities and attention-deficit/hyperactivity disorder. Some argue risk may be due to underlying disorder. Authors found that patients with bilateral RB had significantly higher frequency and duration of general anesthesia compared to children with unilateral RB. Patients with bilateral Rb underwent a median of 1,659 minutes of total anesthesia, compared with 397 minutes for those with unilateral disease. Patients who received IAC as their primary treatment had the highest median anesthesia duration (2,100 minutes), followed by systemic chemo (654 minutes) and enucleation (289 minutes). Patients with more severe unilateral disease were subjected to lower anesthesia due to quicker movement to enucleation being a more definitive treatment with less need for repeated anesthesia. The authors find that optimal treatment of RB requires prolonged and repeated anesthesia. They suggest that further studies are necessary to assess neurocognitive ramifications of these repeated anesthesia and determine any correlation between the two.

Wide-field Fundus Imaging and Fluorescein Angiography Findings in Various Pseudoretinoblastoma Conditions.

Gündüz AK, Mirzayev I, Tetik D.

J Pediatr Ophthalmol Strabismus. 2023;60(1):60-74. doi:10.3928/01913913-20220228-01

This retrospective review reported the clinical and imaging records of 28 patients (36 eyes) with various pseudoretinoblastoma disorders: Coats disease (9 eyes), congenital glaucoma (3 eyes), persistent fetal vasculature (3 eyes), familial exudative vitreoretinopathy (2 eyes), retinopathy of prematurity (2 eyes), myelinated retinal nerve fibers (2 eyes), optic nerve hypoplasia (2 eyes), oculocutaneous albinism (2 eyes), meridional fold (2 eyes), combined hamartoma of retina and retinal pigment epithelium (2 eyes), grouped congenital hypertrophy of the retinal pigment epithelium (1 eye), retinal astrocytic hamartoma (1

eye), morning glory syndrome (1 eye), optic glioma (1 eye), giant choroidal nevus (1 eye), vasculitis (1 eye), and chorioretinitis (1 eye). RetCam imaging and fluorescein angiography demonstrated telangiectasias, microaneurysms, submacular exudation/fibrosis, capillary non-perfusion, and exudation posterior to telangiectasias in Coats disease. Hypofluorescent optic discs, peripheral non-perfusion, and vascular leakage were observed in congenital glaucoma. Large areas of capillary non-perfusion, poor foveal morphology/formation, elongated ciliary processes with hyperfluorescent central core, and hyperfluorescent fibrovascular stalk at the posterior pole were hallmarks of persistent fetal vasculature. The authors concluded that widefield fundus imaging and FA played an important role in the diagnosis of pseudoretinoblastoma conditions.

Mirzayev I, Gündüz AK, Özalp Ateş FS, Tetik D. Pseudoretinoblastoma: Distribution based on gender, age, and laterality.

Eur J Ophthalmol. 2023 Jan;33(1):104-111.

This study retrospectively evaluated the clinical records of 607 patients (851 eyes) who were referred for diagnosis of retinoblastoma or simulating conditions (pseudoretinoblastoma, PSRB) between October 1998 and May 2021. Patients were stratified by age as follows:  $\leq 1$  year,  $>1$ -3 years,  $>3$ -5 years, and  $>5$  years. Of 190/607 PSRB patients, 129 (67.9%) were males and 61 (32.1%) females ( $p = 0.001$ ). The 3 most common diagnoses in males were Coats disease (20.2%), persistent fetal vasculature (PFV, 14.0%), and chorioretinal coloboma (6.2%). In females, the most common diagnoses included PFV (21.3%), retinal dysplasia, congenital glaucoma, and combined hamartoma (each 6.6%). PFV was the most common diagnosis in the  $\leq 1$  year old patient group (26.6%). Coats disease and PFV were the most common diagnoses in the  $>1$ -3 years old patient group (each 16.7%). Coats disease was the most common diagnosis in the  $>3$ -5 years old (30.8%) and  $>5$  years old patient groups (13.1%). PSRBs were unilateral in 121/190 (63.7%) patients. Coats disease most often presented unilaterally ( $p < 0.001$ ) while PFV, optic nerve head drusen, and retinopathy of prematurity as bilateral diseases ( $p = 0.019$ ,  $p = 0.001$ , and  $p = 0.001$  respectively). PSRB diagnoses show differences depending on gender, age, and laterality. In our study, the most common PSRB lesions were Coats disease in males and PFV in females. PFV was the most frequent diagnosis in  $\leq 3$  years and Coats disease in  $>3$  years of age groups. Coats disease and PFV were the most common unilateral and bilateral PSRB diagnoses respectively.

Changing trends in pseudoretinoblastoma diagnoses: A 10 year review from the United Kingdom.

Badhwar V, Yeo DC, Joshi S, Clifton C, Fraser M, Naeem Z, Sagoo MS, Reddy MA.

Eur J Ophthalmol. 2023 Jan;33(1):129-135.

The authors were interested in the frequency of conditions mimicking retinoblastoma (pseudo-retinoblastoma) of cases referred to a retinoblastoma specialty center for evaluation. They performed a retrospective chart review of 341 patients presenting to the Royal London Hospital from January 2009 to December 2018. Of these, 220 patients (65%) were confirmed to have retinoblastoma, while 121 (35%) had pseudoRB. There were 23 differential diagnoses in total. The top 3 differential diagnoses were Coats' disease (34%), Persistent Fetal Vasculature (PFV) (17%) and Combined Hamartoma of Retina and Retinal Pigment Epithelium (CHR-RPE) (13%). PseudoRBs differed with age at presentation. Under the age of 1 ( $n = 42$ ), the most likely pseudoRB conditions were PFV (36%), Coats' disease (17%) and CHR-RPE (12%). These conditions were also the most common simulating conditions between the ages of 1 and 2 ( $n = 21$ ), but Coats' disease was the most common in this age group (52%), followed by CHR-RPE (19%) and PFV (14%). Between the ages of 2 and 5 ( $n = 32$ ), Coats' disease remained the most common (44%) pseudoRB lesion followed by CHR-RPE (13%), or PFV, Retinal Astrocytic Hamartoma (RAH), familial exudative vitreoretinopathy (FEVR) (all 6.3%). Over the age of 5 ( $n = 26$ ), pseudoRBs were most likely to be Coats' disease (35%), RAH (12%), Uveitis, CHR-RPE, FEVR (all 7.7%). The authors conclude that 35% of suspected retinoblastoma cases are pseudoRB conditions. Overall, Coats' disease is the most common pseudoRB condition, followed by PFV. Hamartomas (CHR-RPE & RAH) are more prevalent in this cohort, reflecting improvements in diagnostic accuracy from referring ophthalmologists.

Targeted chemotherapy in retinoblastoma: A step forward from patient survival to globe survival.

Naseripour M, Sedaghat A, Mirshahi R, Abdolalizadeh P, Koushki A, Faranoush M, Ghorbani M, Kashkouli MB, Sadeghipour A, Chaibakhsh S, Mehrvar A.

Eur J Ophthalmol. 2023 Jan;33(1):574-586.

Despite being the most common intraocular malignancy in childhood, there is a substantial disparity between developing and developed countries in terms of patient and globe survival in retinoblastoma (Rb). This study intends to determine patient and globe survival before and after the introduction of the new targeted treatment modalities in a developing country. Medical records of 350 patients (516 eyes) with retinoblastoma referred to a tertiary referral center for Rb in Tehran, Iran, were reviewed. In order to compare patient and globe survival before and after the availability of the new treatment modalities, including intra-arterial and intravitreal chemotherapy, the patients were divided into group 1 (2001-2007) and group 2 (2008-2018) based on the calendar period of diagnosis. Two-hundred-twenty-three eyes of 149 patients and 293 eyes of 201 patients were categorized into groups 1 and 2, respectively. The 5-year patient survival was 97% across the current survey, and the overall survival rate was 96% in group 1 and 99% in group 2 ( $P = 0.08$ ). Overall, 50% of eyes with retinoblastoma underwent enucleation, which was the primary treatment in 63% (116/184) of the unilateral and 30% (99/322) of the bilateral cases. Primary enucleation was significantly lower in group 2 (35%) in contrast to group 1 (50%) ( $P < 0.001$ ). In addition, globe survival improved significantly in the International Classification of Retinoblastoma Groups D (17% in group 1 vs. 66% in group 2,  $P < 0.001$ ) and E (1% in group 1 vs. 23% in group 2  $P < 0.001$ ) during the two timelines. In enucleated eyes, despite the increased rate of prelaminar involvement in group 2 (13% vs. 2% in group 1,  $P = 0.003$ ), the rate of high-risk histopathologic findings was similar between the two groups. Similar to developed countries, the application of new targeted treatment modalities, including intra-arterial and intravitreal chemotherapy, has been associated with significantly improved globe survival in Rb patients. However, it should be noted that even with the availability of these novel treatment options, the decision for timely enucleation should not be deferred.

Bioinformatics Analysis and Experimental Identification of Immune-Related Genes and Immune Cells in the Progression of Retinoblastoma.

Shuilian Chen; Xi Chen; Ping Zhang; et al.

Investigative Ophthalmology & Visual Science October 2022, Vol. 63, 28.

While the prognosis and treatment of RB has dramatically improved over the years, some patients do develop invasive RB and little is known about the differences between invasive vs non invasive RB. As early diagnosis and treatment is critical for survival in these patients, distinguishing the differences between the two is important for clinical treatment. The goal of this study was to investigate mutations in immune-associated genes and cells related to RB invasion, as a growing amount of literature has shown that immune genes and cells play a critical role in tumor progression. They used two public datasets to analyze the immune genes and cells that could indicate the risk of progression from noninvasive to invasive RB. They found 8 unregulated genes and 6 down regulated genes in invasive RB. They also have found a higher proportion of myeloid-derived suppressor cells in invasive RB. Decreased SHGL2 expression also appears to promote the migration of RB cells in vitro and lead to increased tumor size and weight. This data suggests that SH3GL2 and MDSCs play a critical role in RB progression and invasion, and could be candidates for treatment targets in RB.

Magnetic Resonance Imaging Can Reliably Differentiate Optic Nerve Inflammation from Tumor Invasion in Retinoblastoma with Orbital Cellulitis.

Jansen RW, van der Heide S, Cardoen L, Sirin S, de Bloeme CM, Galluzzi P, Göricke S, Brisse HJ, Maeder P, Sen S, Biewald E, Castelijns JA, Moll AC, van der Valk P, de Jong MC, de Graaf P; European Retinoblastoma Imaging Collaboration.

Ophthalmology. 2022 Nov;129(11):1275-1286. doi: 10.1016/j.ophtha.2022.06.013. Epub 2022 Jun 22. PMID: 35752210

The authors examined the prevalence and MRI phenotype of retinoblastoma associated orbital cellulitis. Postlaminar optic nerve invasion (PLONI) is a risk factor for developing metastatic disease which can be detected on MRI as postlaminar optic nerve enhancement. This has become an increasingly important tool as emerging eye sparing treatment without needing histopathologic material. When there is retinoblastoma associated orbital cellulitis the metastatic risk factor assessment may be complicated because of the inflammation in the orbit. The purpose of the study was to investigate the MRI prevalence of retinoblastoma associated orbital cellulitis (RAOC) and assess concomitant intraocular MRI features. In addition, it aimed to assess sensitivity and specificity of PLONE for predicting PLONI in retinoblastoma with orbital cellulitis. Finally, the study aimed to identify specific optic nerve enhancement patterns

differentiating between inflammation and tumor invasion. This is a combined consecutive cohort and retrospective case-control study. The first part looked at the prevalence of RAOC on MRI. The second part took the patients in Part I and supplemented with orbital cellulitis retinoblastoma from referral centers. 10 cases of histopathologically proven PLONI were selected to look at the diagnostic accuracy of PLONE for predicting PLONI. The results showed that the prevalence of RAOC on MRI was 6.8%. All of these cases were staged as Group E eyes and underwent enucleation. On MRI RAOC more often had globe filling, total detachments and buphthalmos. The authors concluded that Rb presenting with orbital cellulitis showed MRI findings of larger eyes, extensive tumor necrosis, uveal abnormalities and lens luxation. MRI findings looking at the post laminar optic nerve can differentiate between tumor invasion and inflammatory changes and thereby improve metastatic risk classification. This paper is important because it may help to elucidate which patients require more aggressive treatment with enucleation and patients that may be able to preserve the globe in cases of retinoblastoma.

Risk factors for ophthalmic artery stenosis and occlusion in patients with retinoblastoma treated with intra-arterial chemotherapy.

Zhou M, Wen X, Jia S, Han Y, He X, Han M, Xu W, Fan J, Jia R, Fan X.

Br J Ophthalmol. 2022 Nov;106(11):1581-1586. doi: 10.1136/bjophthalmol-2021-319118.

This was a retrospective case-control study of Chinese patients with unilateral or bilateral retinoblastoma treated with IAC 2016-2019. Cases were patients who suffered ophthalmic artery stenosis and/or occlusion; controls were patients who did not develop OA stenosis/occlusion. There were 352 attempted ophthalmic artery catheterization (OAC) infusions in 107 retinoblastoma tumors of 105 consecutive patients, 346 of which were successful. The total incidence of OA occlusion was 15.89%. OA diameter prior to IAC, the ratio of OA orifice diameter differences between first and last IAC to the initial OA orifice diameter and total number of IAC treatments may be three predictors of OA stenosis and occlusion after this procedure. OA diameters < 0.65mm are specifically at risk. Limitations include retrospective design, single center data, and specific Chinese population that may not be generalizable. However, this study can help the process of clinical evaluation and risk stratification when making treatment decisions.

American Joint Committee on Cancer Ophthalmic Oncology Task Force. Retinoblastoma seeds: impact on American Joint Committee on Cancer clinical staging.

Tomar AS, Finger PT, Gallie B, Kivelä T, et al.

Br J Ophthalmol. 2023 Jan;107(1):127-132. doi: 10.1136/bjophthalmol-2021-318892.

Since the last update on RB staging by the American Joint Committee on Cancer Ophthalmic Oncology Task Force in 2017, new evidence has emerged on the topic of focal vs diffuse seeding. The committee therefore sought to examine if clinical characteristics and intraocular distribution of RB seeds at presentation can be used to predict local treatment failure and improve RB staging. 18 RB centers from 13 countries contributed data from RB patients diagnosed between January 2001 and December 2013. 2190 total patients were included in the registry, 2085 of which had sufficient data for study purposes. This study specifically analyzed 1054 eyes with clinically visible seeds assigned as category cT2b. Of these, 40% underwent primary enucleation. Of the remaining 59% who had an attempt at eye salvage, 40% were successfully salvaged. RB eyes with diffuse seeds were more commonly treated with primary enucleation. By far the most common treatment strategy for eye salvage was systemic chemotherapy (93%) vs IAC in 6% and EBRT in 0.5%. Intraocular chemotherapy was used in 5% and periocular chemotherapy in 6% of eyes. The distribution of seeds among globe salvage eyes was focal in 143 (24.2%) and diffuse in 449 (75.8%) eyes. Diffuse seeds, and specifically spherical seed types, were associated with an increased risk of local treatment failure. Subclassification of AJCC RB category cT2b into focal vs diffuse seeds can improve prognostication for eye salvage.

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Iodine-125 Plaque Radiotherapy for Retinoblastoma Recurrence Following Intra-arterial Chemotherapy.

Ruben M, Eiger-Moscovich M, Yaghy A, Tadepalli S, Shields CL.

J Pediatr Ophthalmol Strabismus. 2022;59(3):164-171. doi:10.3928/01913913-20210903-01

This single-center retrospective study sought to assess the efficacy and toxicity of Iodine-125 (I-125) plaque radiotherapy for retinoblastoma following intra-arterial chemotherapy (IAC). The authors reported the outcomes of 41 eyes with Rb in 41 patients treated with I-125 plaque radiotherapy after IAC at a

median age of 32 months. The indication for plaque radiotherapy was solid tumor recurrence with or without overlying subretinal/vitreous seeds (n = 33, 80%), subretinal seeds alone (n = 6, 15%), and vitreous seeds alone (n = 2, 5%). The median irradiated basal diameter and thickness was 9 and 4 mm, respectively. Mean radiation dose to tumor apex was 3,483 centigray (cGy) delivered at mean rate of 35 cGy/hr. The irradiated site was controlled in 39 eyes (95%) at a median of 20 months after plaque radiotherapy for solid tumor (31 of 33, 94%), subretinal (6 of 6, 100%), and vitreous seeds (2 of 2, 100%). A subgroup of tumors occurring within an ischemic retinal/choroidal field was identified on fluorescein angiography (n = 24) and demonstrated control in 22 of 24 (92%). The authors reported that radiation complications at 2 years included vitreous hemorrhage (37%), retinopathy (28%), papillopathy (18%), and cataract (18%). Five eyes (12%) were enucleated for recurrence outside the irradiated area, chronic vitreous hemorrhage, and/or total retinal detachment. The authors concluded that I-125 plaque radiotherapy provided 95% control for Rb tumors that failed IAC, including those in ischemic fields untreatable with further chemotherapy, and that radiation complications should be anticipated in eyes exposed to substantial chemotherapy.

Recurrence and new tumor development after frontline intravenous chemotherapy for retinoblastoma: Risk factors and treatment results.

Gündüz AK, Mirzayev I, Dinçaslan H, Özalp Ateş FS.

Eur J Ophthalmol. 2022 May;32(3):1795-1803.

Intravenous chemotherapy (IVC) has been employed to avoid enucleation and external beam radiotherapy (EBRT) for retinoblastoma (RB). However, recurrence and new tumors (NT) can still develop after IVC. The authors analyze the factors affecting recurrence and NT formation in RB patients who underwent primary IVC and focal treatments and report the results of secondary treatments for recurrent and NTs over a 20-year period. The clinical records of 246 eyes of 166 intraocular RB patients, who received IVC as primary treatment between October 1999 and August 2020 were reviewed. The mean ages at presentation were 9.0 (median: 8.0) and 9.2 (median: 8.5) months in cases with recurrence and NTs respectively. Recurrence was detected in 40 (16.3%) eyes, NTs in 29 (11.8%), and both recurrence/NTs in 24 (9.8%). The mean time elapsed until recurrence and NT was 10.7 months. Multivariable analysis showed that the factors predictive of recurrence were largest tumor base diameter (LTBD) >12 mm ( $p = 0.039$ ) and presence of subretinal seeds at diagnosis ( $p = 0.043$ ). Multivariable risk factors for the development of NTs were bilateral familial retinoblastoma ( $p = 0.001$ ) and presence of subretinal seeds at diagnosis ( $p = 0.010$ ). Mean follow-up was 80.1 (median: 72.5) months. By Kaplan-Meier analysis, the 1-, 3-, and 6-year recurrence and NT rates were 21.2%, 28.1%, and 28.7% and 14.9%, 22.6%, and 23.9% respectively. The most common treatment methods used for recurrent and/or NTs included cryotherapy, transpupillary thermotherapy, and intra-arterial chemotherapy. Enucleation was eventually required in 24/93 (25.8%) eyes. No patient developed metastasis. Development of recurrence and/or NT after IVC was noted in 38% of all retinoblastoma eyes. Bilateral familial disease, LTBD >12 mm, and presence of subretinal seeds at baseline were risk factors for recurrence and NTs in this study.

Health related quality of life of patients treated with bilateral enucleation for retinoblastoma.

Al Qahtani M, AlMasfer S, Khandekar R.

Eur J Ophthalmol. 2022 Jul;32(4):1960-1965.

The authors evaluated the health-related quality of life (HQL) and associated factors among patients who underwent bilateral surgical enucleation for retinoblastoma. Using a retinoblastoma registry, 58 patients who fit the criteria within the past 33 years (1989 to 2019) were interviewed via telephone in January 2020. Collected data included age, gender, literacy, occupation, marital status, and health issues. Patients were asked eight questions on HQL. The responses were graded as 0-10, with a "0" score denoting "not at all satisfied" while "10" meant "fully satisfied" regarding the status mentioned in the question. Twenty-one out of 24 participants were interviewed (median age, 23 years). Fourteen participants answered the HQL question themselves, and 7 patients had their parents answer the questionnaire. Twenty patients (95%) had an ocular prosthesis. The median HQL score was 58 (out of a maximum score of 80) (interquartile range (IQR): 49; 70; minimum, 0 and maximum, 74). Age at enucleation of the second eye ( $p = 0.001$ ), students ( $p < 0.001$ ), and self-responders ( $p < 0.001$ ) were independent predictors of a high HQL score. A high HQL score correlated to higher education levels and

better opportunities as students in special schools and education programs. Those with other disabilities in addition to visual limitations were dependent on their caregivers and subsequently had a lower HQL score. The authors conclude that the HQL of individuals having bilateral eye enucleation for retinoblastoma was reasonably good and positively correlated to self-reporting, learning as students to cope with their condition, and age at the removal of the second eye. Anaplasty services to improve cosmetics seem to benefit these patients.

Pediatric pilomyxoid astrocytoma - ophthalmic and neuroradiologic manifestations.

Mbekeani JN, Abdel Fattah M, UI Haq A, Al Shail E, Ahmed M.

Eur J Ophthalmol. 2022 Sep;32(5):2604-2614.

Pilomyxoid astrocytomas (PMA) are a rare primary central nervous system (CNS) tumor. The authors identified twenty-two histopathology-proven cases of PMA and sought to supplement the literature by adding details of the spectrum of presentations, neuro-radiologic manifestations, histopathology, and clinical course. This study was designed as a retrospective chart review of consecutive patients, histologically determined to have pilomyxoid astrocytoma (PMA), conducted from January 1, 2001 to January 31, 2021. Nineteen of 22 patients identified to have pilomyxoid astrocytomas had complete medical records and MRI studies and were included in this study. Nine males and ten females presented at a mean (SD) age of 2.1 (1.2) years, (range: 2 months-8 years). Nine (47.3%) patients overall had ophthalmic symptoms at presentation including decreased vision, strabismus, eye movement abnormalities, and proptosis. Nine patients (52.9%) with suprasellar tumors were documented to have diencephalic syndrome (DS) while 88.2% had documented symptoms/signs of DS. Six (35.3%) had both DS and ophthalmic presentations. Snellen visual acuities varied from 20/20 to no light perception. All patients had surgical excision or debulking procedures with additional ventriculoperitoneal shunting for cases associate with ventriculomegaly. Eight cases (42.1%) had documented growth of residua or local recurrences. Fifteen (78.9%) required adjuvant chemotherapy and eight (42.1%) had additional salvage radiation therapy. Histopathology of the tumors revealed spindle-shaped, piloid astrocytes within a rich myxoid matrix. Monophasic cellular clumps with peri-vascular rosettes and, without Rosenthal fibers or eosinophilic bodies and were observed. With respect to MRI findings, the hypothalamic-chiasmatal (suprasellar) region was the most common location comprising seventeen (89.5%) PMA tumors. Six tumors (35.3%) involved the third ventricle with consequent hydrocephalus and most of the larger suprasellar tumors impinged on neighboring lobar, and diencephalic tissue. This study confirms the propensity of PMA to occur in infants with preference for the suprasellar region. Histopathologic confirmation of PMA should prompt appropriate neurosurgical intervention, early institution of adjuvant therapy, and close follow up that should include ophthalmic evaluations and visual rehabilitation.

Aqueous humor as a surrogate biomarker for retinoblastoma tumor tissue.

Raval V, Racher H, Wrenn J, Singh AD.

J AAPOS. 2022 Jun;26(3):137.e1-137.e5

The authors sought to demonstrate the feasibility of identifying a germline RB1 pathogenic variant in retinoblastoma (RB) from an aqueous humor (AH) sample using a pilot case series of 3 patients. All patients were slated for enucleation secondary to extensive tumor burden and peripheral blood, fresh tumor and AH were obtained for each patient. RB1 germline status is important because of its association with risk for additional tumors and second malignancies requiring a different level of surveillance. Trends in RB treatment show increasing globe salvage which results in less fresh tumor tissue for analysis. The authors show pathogenic RB1 variant results from AH in all 3 eyes tested were concordant with direct tumor sampling, suggesting the possibility that AH can be used as a surrogate source for tumor tissue. Previously AH was avoided in order not to cause seeding of tumor. Recent studies show an excellent safety profile and no increased risk of tumor dissemination with AH aspiration. The authors suggest that AH should be performed prior to treatment. The authors call for further research to ensure accuracy, reproducibility, limits of detection and false positive rate by using a larger patient pool. Although further research is needed to validate this concept, it is important to pediatric ophthalmologists to be aware of changes in in the diagnosis and treatment of RB.

Evaluation of intravitreal topotecan dose levels, toxicity and efficacy for retinoblastoma vitreous seeds: a preclinical and clinical study.

Bogan CM, Kaczmarek JV, Pierce JM, Chen SC, Boyd KL, Calcutt MW, et al.

Br J Ophthalmol. 2022 Feb;106(2):288-296. doi: 10.1136/bjophthalmol-2020-318529.

The authors have developed a rabbit xenograft model of RB with vitreous seeds and retinal tumors in order to study the toxicity of various IAC drugs. They also have a complete platform to assess functional and structural retinal toxicity associated with local delivery of various chemotherapeutic agents. They use this rabbit model and toxicity evaluation platform to determine the dose of intravitreal topotecan which is effective and non-toxic when delivered as monotherapy, and then corroborate this evidence of non-toxicity with clinical experience treating RB patients with vitreous seeds with intravitreal topotecan. The patient portion of the study was a retrospective cohort of 235 patients receiving 990 intravitreal injections of topotecan or melphalan. Intravitreal topotecan 30 $\mu$ g (equals 60 $\mu$ g in humans) achieved the IC90 (inhibitory concentration, or how much of a drug is needed to inhibit a given biological process by 90%) across the rabbit vitreous. Three weekly topotecan injections (either 15 $\mu$ g or 30 $\mu$ g) caused no retinal toxicity in rabbits, whereas melphalan 12.5 $\mu$ g (equals 25 $\mu$ g in humans) reduced ERG amplitudes 42%–79%. In the clinical study, patients received 881 monotherapy injections (48 topotecan, 833 melphalan). Patients receiving 20 $\mu$ g or 30 $\mu$ g topotecan demonstrated no significant ERG reductions, whereas melphalan caused ERG reductions of 7.6  $\mu$ V for every injection of 25 $\mu$ g ( $p=0.03$ ) or 30 $\mu$ g ( $p<0.001$ ). It's important to note that most patients treated with intravitreal topotecan in the clinical setting also received intravitreal melphalan at some point during their treatment course. Among those eyes treated exclusively with topotecan monotherapy, all eyes were salvaged. These early experiments suggest that topotecan monotherapy is effective and non-toxic and are paving the way for future clinical trials.

Primary laser therapy as monotherapy for discrete retinoblastoma.

Soliman S, Feng ZX, Gallie B.

Br J Ophthalmol. 2022 Jun;106(6):878-883.

This study is a single-institution retrospective noncomparative interventional case series 2004-2018 looking at the safety and efficacy of laser as primary monotherapy for discrete retinoblastoma with well-defined borders and attached retina. Tumors were primarily treated by laser therapy if <3mm, noncentral, and when primary systemic chemotherapy was not required for larger tumors in the other eye and used either 532 or 810 wavelength per surgeon preference. A total of 112 tumors in 55 eyes of 44 children who received primary photocoagulation were reviewed. After one laser session, 35 tumors (24 eyes) showed initial remission designated as absence of tumor activity on 2 follow-ups; 68 tumors (38 eyes) showed variable degrees of regression while 9 tumors (8 eyes) showed progression. Additional laser sessions at 3–4 weeks interval were continued for 67 tumors and 57/67 (85%) achieved initial remission. The median number of laser sessions was 2 (range, 2–10 sessions) for tumors in group A/B eyes and 4.5 (range 4–5 sessions) for tumors in group C eyes. Based on their results, the authors identified a threshold of largest basal diameter of 3 disc diameters (DD) for successful laser monotherapy, where 92/106 (87%) of tumors  $\leq 3DD$  and 0/6 >3DD achieved long-term stability with laser monotherapy.

Pediatric Cataract Surgery Following Treatment for Retinoblastoma: A Case Series and Systematic Review.

Kletke SN, Mallipatna A, Mireskandari K, Gallie BL, Ali A.

American Journal of Ophthalmology. 2022 Feb 13.

Cataract development in children with retinoblastoma has become increasingly common as globe salvage therapies such as external beam radiotherapy have gained popularity. The goal of this case series and systemic review was to summarize the current literature regarding cataract surgery in children with a history of treatment for retinoblastoma. The case series contains 15 eyes of 15 children with underwent cataract surgery over a 20 year period at a single center. 73% of children has improvement in vision following surgery and all children had improvement in posterior pole visualization following surgery. Over mean follow up of 76 months, there was no instance of extraocular tumor extension. The systemic review included 18 articles (220 children) and showed similarly low rates of extraocular extension and metastasis (<1%). The authors discuss several issues related to cataract surgery in this population including intraoperative considerations and systemic complications. This review serves as a good overview for ophthalmologists considering cataract surgery in a child with a history of retinoblastoma.

UBE2T/STAT3 Signaling Promotes the Proliferation and Tumorigenesis in Retinoblastoma.



Xu N, Cui Y, Shi H, Guo G, Sun F, Jian T, Rao H.

*Invest Ophthalmol Vis Sci* 2022;63(2).

This study investigated the expression and function of Ubiquitin-conjugating enzyme 2T (UBE2T), a human E2 ubiquitin-conjugating enzyme, in human retinoblastoma. The expression of UBE2T in normal retina and retinoblastoma was analyzed using the Gene Expression Omnibus (GEO) databases, and its expression was immunohistochemically evaluated in 29 retinoblastoma sections and 5 normal retinas. Then CCK-8, flow cytometry, RNA-sequencing analysis, and in vivo assays were performed to explore the exact role of UBE2T in retinoblastoma. Retinoblastoma showed higher UBE2T expression than normal retina in GEO datasets and tissues. The immunoreactive score of UBE2T  $\geq 4$  was associated with group E in IIRC, T2-T4b in pTNM staging, poorly differentiated retinoblastoma, and high-risk histopathological factors. Knockdown of UBE2T reduced the cell viability, increased the apoptosis cells and G0/G1 cells, and inhibited subcutaneous tumor growth in vivo. Mechanistic studies showed that UBE2T knockdown induced down-regulation of phosphorylation of STAT3 and its downstream genes in vitro and in vivo. Rescue assays confirmed that STAT3 signaling pathway was involved in the effect of reduced cell viability, elevated apoptosis cells, and G0/G1 cells mediated by UBE2T knockdown. This data is important because it indicates that UBE2T significantly participates in the proliferation of retinoblastoma via the STAT3 signaling pathway, suggesting the potential of UBE2T as a therapeutic target for retinoblastoma treatment.

American Joint Committee on Cancer Ophthalmic Oncology Task Force. Metastatic Death Based on Presenting Features and Treatment for Advanced Intraocular Retinoblastoma: A Multicenter Registry-Based Study.

Tomar AS, Finger PT, Gallie B, Kivelä TT, Mallipatna A, Zhang C, Zhao J, Wilson MW, Brennan RC, Burges M, Kim J, Berry JL, Jubran R, Khetan V, Ganesan S, Yarovoy A, Yarovaya V, Kotova E, Volodin D, Yousef YA, Nummi K, Ushakova TL, Yugay OV, Polyakov VG, Ramirez-Ortiz MA, Esparza-Aguilar E, Chantada G, Schaiquevich P, Fandino A, Yam JC, Lau WW, Lam CP, Sharwood P, Moorthy S, Long QB, Essuman VA, Renner LA, Semenova E, Català-Mora J, Correa-Llano G, Carreras E;

*Ophthalmology*. 2022 Aug;129(8):933-945. doi: 10.1016/j.ophtha.2022.04.022. Epub 2022 Apr 30.

This is a multicenter registry-based case series, investigating the risk of metastatic mortality in patients with advanced retinoblastoma based on presenting clinical features, intraocular tumor size, and treatment modalities. Advanced RB was defined as 8<sup>th</sup> edition American Joint Committee on Cancer (AJCC) stage cT2 or cT3 categories. The study included 1841 patients from a pooled registry data base across 18 RB centers from 13 countries. High-risk clinical features for advanced RB were stratified in cT2 and cT3 subcategories: retinal detachment with risk of subretinal tumor cells (cT2a); seeding (cT2b); phthisis bulbi (cT3a); anterior segment tumor invasion (cT3b); rubeosis iridis with neovascular glaucoma (cT3c); hyphema, massive vitreous hemorrhage, or both (cT3d); and aseptic orbital cellulitis (cT3e). Tumor size was divided into 4 groups: 1= <50% of globe volume, 2= >50% but <2/3 globe volume, 3= >2/3 globe volume, and 4= diffuse infiltrating RB. Five and 10-year cumulative probabilities of survival by clinical AJCC categories were 98% for cT2a (subretinal fluid), 96% for cT2b (RB seeds), 88% for cT3a (phthisis), 95% for cT3b (anterior chamber involvement), 92% for cT3c (glaucoma), 84% for cT3d (intraocular hemorrhage), and 75% for cT3e (orbital cellulitis). In general, increasing subcategory translated to an increased risk of metastasis related death. By treatment modality, the 5-year cumulative probability of survival was 96% for primary enucleation, 89% for systemic chemotherapy followed by secondary enucleation, and 90% for systemic chemotherapy with eye salvage. In terms of the size groups, 5-year cumulative probability of survival decreased with larger size: 99%, 96%, 94%, and 83% for Size Groups 1, 2, 3, and 4, respectively. In summary, this study found that higher AJCC stage, treatment attempts at eye salvage with systemic chemotherapy, and larger tumor size increase the risk of mortality by metastasis in patients with advanced RB. The 8<sup>th</sup> edition AJCC staging seems to be an effective tool to assess the risk of metastatic death in these patients.

American Joint Committee on Cancer Ophthalmic Oncology Task Force. High-risk Pathologic Features Based on Presenting Findings in Advanced Intraocular Retinoblastoma: A Multicenter, International Data-Sharing American Joint Committee on Cancer Study.

Tomar AS, Finger PT, Gallie B, Kivelä TT, Mallipatna A, Zhang C, Zhao J, Wilson MW, Brennan RC, Burges M, Kim J, Berry JL, Jubran R, Khetan V, Ganesan S, Yarovoy A, Yarovaya V, Kotova E, Volodin D, Yousef YA, Nummi K, Ushakova TL, Yugay OV, Polyakov VG, Ramirez-Ortiz MA, Esparza-Aguilar E,

Chantada G, Schaiquevich P, Fandino A, Yam JC, Lau WW, Lam CP, Sharwood P, Moorthy S, Long QB, Essuman VA, Renner LA, Semenova E, Català-Mora J, Correa-Llano G, Carreras E; Ophthalmology. 2022 Aug;129(8):923-932. doi: 10.1016/j.ophtha.2022.04.006. Epub 2022 Apr 15. This is a multicenter registry-based case series, investigating the strength of the association of high-risk clinical features of advanced retinoblastoma with high-risk pathologic features in eyes after primary enucleation. The 8<sup>th</sup> edition American Joint Committee on Cancer (AJCC) staging criteria were used to stratify the advanced RB by clinical features: retinal detachment with risk of subretinal tumor cells (cT2a); seeding (cT2b); phthisis bulbi (cT3a); anterior segment tumor invasion (cT3b); rubeosis iridis with neovascular glaucoma (cT3c); hyphema, massive vitreous hemorrhage, or both (cT3d); and aseptic orbital cellulitis (cT3e). The AJCC Ophthalmic Oncology Task Force also developed a size group stratification: 1= <50% of globe volume, 2= >50% but <2/3 globe volume, 3= >2/3 globe volume, and 4= diffuse infiltrating RB. The AJCC high-risk pathologic features corresponding to the pT3 category were defined as histopathologic evidence of massive choroidal invasion, post-laminar invasion of the optic nerve head with or without a positive margin, and scleral invasion, and those corresponding to the pT4 category were defined as extraocular extension. High-risk pathologic features were evaluated in only eyes classified as cT2 or cT3. The study included 942 primarily enucleated eyes with from a pooled registry data base across 18 RB centers from 13 countries. cT3c, cT3d, and cT3e were predictive factors for high-risk pathologic features when compared with cT2a with an odds ratio of 2.3 (P = 0.002), 2.5 (P = 0.002), and 3.3 (P = 0.019), respectively. Size Group 3 and 4 were the best predictive factors with an odds ratio of 3.3 and 4.1 (P < 0.001 for both), respectively, for high-risk pathologic features when compared with Size Groups 1. This data shows that elevated intraocular pressure from iris neovascularization, hyphema, massive vitreous hemorrhage, tumor size >2/3 of the globe or diffuse infiltrating tumors are important predictive factors for high-risk pathologic factors in RB. The AJCC retinoblastoma cT stratification and Size Groups appear to be an effective tool to stratify clinical risk factors that can be used to predict the presence of high-risk pathologic factors in advanced RB, which may help with treatment decision.

Eye-Preserving Therapies for Advanced Retinoblastoma: A Multicenter Cohort of 1678 Patients in China. Zhou C, Wen X, Ding Y, Ding J, Jin M, Liu Z, Wang S, Han M, Yuan H, Xiao Y, Wu L, Wang J, Li Y, Yu J, Wen Y, Ye J, Liu R, Chen Z, Xue S, Lu W, Liao H, Cui J, Zhu D, Lu F, Tang S, Wu Y, Yangkyi T, Zhang G, Wubuli M, Guo H, Wang X, He Y, Sheng X, Wang Q, Luo Y, Fan J, Qi J, Yu Z, Tan J, Liang J, Sun X, Jin L, Yang X, Zhang J, Ji X, Zhao J, Jia R, Fan X. Ophthalmology. 2022 Feb;129(2):209-219. doi: 10.1016/j.ophtha.2021.09.002. Epub 2021 Sep 15. PMID: 34536465.

This is a retrospective cohort study evaluating the impact of eye-preserving therapy on long-term prognosis of overall survival and ocular salvage in patients with advanced retinoblastoma. Subjects include 1678 patients diagnosed with group D or group E retinoblastoma from January 2006 through May 2016 from 38 retinoblastoma centers in mainland China. After diagnosis, patients underwent enucleation or eye-preserving therapies, which included intravenous chemotherapy, intra-arterial chemotherapy, intravitreal chemotherapy, periocular chemotherapy, and vitrectomy. In patients with unilateral RB, 10% from the primary enucleation group and 9.3% from the eye preserving group died. Multivariate analysis showed no significant difference in overall survival between the 2 groups. Among surviving patients, 29% achieved final eye preservation, 44% for group D and 15% for group E. In patients with bilateral RB, 13% from the primary enucleation group and 17% from eye-preserving group died. Primary salvage treatment was also not an independent risk factor for overall survival. In those whose worse eye was classified as group E, patients who underwent enucleation showed better overall survival, but this advantage was not evident until after 22.6 months from diagnosis. In surviving patients, the eye preservation rate was 72% overall, 83% in group D and 62% in group E. Limitations of this study include its retrospective nature, lack of ethnic diversity, known heterogeneity of treatment among different referral centers, and a substantial number of patients that had to be excluded due to lack of follow-up or lack of clinical information. This study shows that the choice of primary treatment should be weighed carefully in patients with advanced RB, in particular those with bilateral disease with the worse eye being group E.

## 20. ORBIT

Influence of corneal biomechanical properties on intraocular pressure measurement in different types of Graves' orbitopathy.

Pérez-López M, Ting DSJ, Lanzagorta-Aresti A, Montolio-Marzo S, Davó-Cabrera J, Cid-García I. *Eur J Ophthalmol.* 2023 Jan;33(1):567-573.

This was a cross-sectional study that included patients with inactive Graves orbitopathy (GO) and healthy controls who underwent complete ocular examination, including Goldmann applanation tonometry (GAT), corneal biomechanical analysis using Ocular Response Analyser (ORA), and corneal epithelial thickness analysis using Optovue. Patients with inactive GO were classified based on the severity and orbital phenotype (predominantly myogenic or lipogenic). Comparison among groups was performed. 60 eyes from 30 inactive GO patients and 30 healthy eyes were examined. Corneal hysteresis (CH) was significantly lower in inactive GO patients (9.6 [p25 8.1; p75 11.2]) compared to controls (10.4 [9.8; 11.5]) ( $p = 0.012$ ). In GO patients, cornea compensated intraocular pressure (IOPcc) was significantly higher than Goldman applanation tonometry IOP (IOP-GAT) ( $p = 0.001$ ). A total of 13.3% GO patients were initially classified as having ocular hypertension (OHT; defined as IOP > 21 mmHg with no signs of glaucomatous optic neuropathy) based on IOP-GAT measurement. According to IOPcc, 27.8% of GO patients were classified as OHT. In GO patients, no differences were found in corneal biomechanical properties according to the disease severity or orbital phenotype. CH is significantly lower in inactive GO patients compared to healthy subjects. ORA corrected IOP was significantly higher in GO patients compared to IOP measurements by GAT. No differences in corneal biomechanical properties between mild and moderate-to-severe GO disease and between myogenic and lipogenic orbitopathy were found.

Ophthalmological findings in children with unicoronal craniosynostosis.

Touzé R, Paternoster G, Arnaud E, Khonsari RH, James S, Bremond-Gignac D, Robert MP. *Eur J Ophthalmol.* 2022 Nov;32(6):3274-3280.

Unicoronal craniosynostosis (UCS) presents the highest rate of ophthalmic manifestations requiring close monitoring of vision, due to the high risk of amblyopia. After birth or during childhood, children with UCS have a high risk of presenting with aniso-astigmatism and strabismus. The aim of this study was to characterize clinical ophthalmologic findings associated with UCS in a pediatric cohort. This retrospective study included children admitted and treated at the hospital unit for isolated UCS between 2015 and 2021, who had undergone complete ophthalmological assessment comprising visual assessment, refractive status and oculomotor examination. Children with associated craniofacial disorders were excluded. A total of 28 children met the inclusion criteria. Median age was 62 [13-192] months with a large proportion of girls (86%) and 71% of right-sided UCS. The mean best corrected visual acuity was 0.07 ( $\pm 0.13$ ) LogMAR, including 10 (36%) children with an amblyopia or history of amblyopia. Astigmatism was significantly higher on the contralateral side of the UCS than on the ipsilateral side, with a refractive cylinder error of 0.97 ( $\pm 1.06$ ) vs 0.56 ( $\pm 0.68$ ) diopters, respectively ( $p = 0.03$ ). Strabismus was observed in 20 patients (71%) with a main pattern of esotropia with a vertical component. A pseudo-superior oblique palsy was found in 13 children (65%) with a median cyclodeviation of 8.7° [-5,4°-20.6°]. This study suggests that children with UCS experience a high rate of various visual manifestations. This study highlights the need for these patients to have strict ophthalmological follow-up, in order to diagnose and treat amblyopia risk factors as early as possible and prevent long-term visual complications.

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The Management of Congenital Microphthalmia With Orbital Cyst: A Case Series.

Gutkovich E, Zahavi A, Man Peles I, et al.

*J Pediatr Ophthalmol Strabismus.* 2022;59(3):192-199. doi:10.3928/01913913-20210929-01

This single-center retrospective study sought to describe the cases of 6 patients (7 eyes) treated for congenital microphthalmia associated with orbital cyst. Six cysts were located inferiorly and one superiorly. Two patients had a visual potential of light perception or better in the affected eye. In 4 eyes, the cyst was initially retained and the eye was fitted with a custom-made conformer. In 1 eye, the fornices were too shallow for a conformer, warranting fornix reconstruction and cyst excision. Early surgery was required in 1 eye for an expanded cyst and large orbit volume, and in another eye the cyst had overgrown

the orbit, causing bone erosion and remodeling. Cosmetic results were good in 3 of the eyes in which the cyst was retained in early childhood, stimulating orbital growth. The authors note that cyst retention combined with ocular conformers may stimulate socket expansion, and that if treated early, enucleation was avoidable during cyst excision. Although this is a very limited case series, the condition is itself rare and thus, this study provides some valuable insight into management.

Ophthalmic features of craniosynostosis: A Malaysian experience.

Rafique Ali AA, Ismail F, May May C, Mohd Abdullah AA, Khaliddin N, Hariri F, Abdul Rahman ZA, Iqbal T.

Eur J Ophthalmol. 2022 May;32(3):1417-1423.

This is a retrospective study of patients with craniosynostosis who were evaluated at the Combined Craniofacial Clinic (CFC) at University Malaya Medical Centre (UMMC) from 2014 to 2020. Out of 37 patients, 29 had syndromic craniosynostosis, and 8 had non-syndromic craniosynostosis. Visual impairment was present in 32.1% of patients. Causes for visual impairment included amblyopia (25.0%), exposure keratopathy (3.6%), and optic atrophy (3.6%). Hypermetropia and myopia were each seen in 20.6% of patients. Astigmatism was seen in 47.1% of patients, and 29.1% of patients had anisometropia. Proptosis was present in 78.6% and lagophthalmos in 53.3% of patients. Strabismus in primary position occurred in 51.7% of patients. Thirty-one percent of the patients had exposure keratopathy. Optic disc atrophy was seen in 13.7% of patients, and 8.3% had optic disc swelling. Optic disc swelling was resolved in all patients who underwent craniofacial surgery. These findings in the Malaysian craniosynostosis population are consistent with previously reported data on ophthalmic features of craniosynostosis patients. Additionally, the authors found that non-syndromic craniosynostosis patients are equally at risk of ocular complications as their syndromic counterparts. Appropriate treatment of amblyogenic risk factors, ocular complications, and timely detection of papilledema, and prompt surgical intervention are crucial in preserving long-term visual function in these patients.

## 21. OCULOPLASTICS

Socket expansion with conformers in congenital anophthalmia and microphthalmia.

Watanabe A, Singh S, Selva D, Tong JY, Ogura T, Kajiyama S, Sotozono C.

J AAPOS. 2022 Dec;26(6):318.e1-318.e6.

The authors used a noncomparative, interventional case series (18 patients with 24 eyes) to report outcomes of acrylic conformer-assisted socket expansion in congenital anophthalmia and microphthalmia. Traditional socket reconstruction is often performed using static acrylic conformers or dynamic hydrogel tissue expanders. Suturing the expander to the conjunctiva and performing a tarsorrhaphy requires general anesthesia in children. Socket reconstruction can also be performed using progressively larger acrylic conformers placed and removed with topical anesthesia in clinic. The authors achieved good outcomes in 75% of orbits and fair outcomes in 25% of cases. All were able to wear a prosthesis with good cosmesis. This article is important for pediatric ophthalmologist because it demonstrates obtaining a good result while conserving resources and decreasing risks to the patient.

Epidemiologic Differences and Management of Eyelid Lesions in the Pediatric Population.

Sheng J, Joshi M, Williams KJ, Herce HH, Allen RC.

J Pediatr Ophthalmol Strabismus. 2022;59(6):405-409. doi:10.3928/01913913-20220210-02

This retrospective analysis reported the findings of 137 consecutive pathology-confirmed eyelid lesions at a single quaternary children's hospital. Benign non-cystic epithelial lesions comprised 48.2% of all excised lesions, followed by mesenchymal (14.6%) and cystic (10.2%) lesions. The most common lesions were molluscum contagiosum (21.9%) and verruca vulgaris (19.0%). Hispanic White race represented 62.0% of cases, followed by non-Hispanic White (23.3%) and Black (8.8%). There were no malignant lesions. A specific preoperative clinical diagnosis was attempted in 70.1% of cases. Of these, 60.4% had a matching histopathology. The authors concluded that there was a higher proportion of molluscum and verruca vulgaris than prior literature suggested and that malignancy in typical pediatric eyelid tumors is rare. This was a small, but clinically meaningful report.

Frontalis suspension by a minimally invasive "harvesting-stripping technique" for congenital blepharoptosis in children under 3-years-old.

Evereklioglu C.

Eur J Ophthalmol. 2023 Jan;33(1):161-170.

The authors describe a minimally invasive "harvesting-stripping technique" on a small segment of autogenous fascia lata (AFL) in small children with severe blepharoptosis under 3-years-old. A single-surgeon, uncontrolled surgical trial was designed for 25 eyelids of 18 small children (5 girls, 13 boys) with severe blepharoptosis. Single- and short-skin incisions (2-cm) were made on the thigh and a final 3X0.6-cm or 3.5X1-cm AFL segment was excised according to the ptosis laterality. The surface area of the harvested AFL was calculated and dissected for a final 9-cmX2-mm-long fascial strip for each eye. Functional and aesthetic outcomes of the upper eyelids were evaluated and the feasibility, effectiveness, and advantages of this novel approach in younger patients were assessed. The mean age was 28.3 months (17-35) with a mean follow-up of 34.3 months (6-96). All eyelids achieved good or excellent functional and aesthetic results (except one), with no peri- or post-operative severe complications such as hemorrhage, wound infection, hypertrophied thigh scar, muscle prolapses, eyelid contour abnormalities, ptosis recurrence or overcorrection. The authors conclude that the "harvesting-stripping technique" with the AFL may be an alternative approach to correct severe upper blepharoptosis in small children under 3-years-old, which offers various benefits over conventional methods with non-autogenous materials.

Assessment of Lacrijet monocanalicular intubation for congenital nasolacrimal duct obstruction.

Hamed Azzam S, Hartstein M, Dolmetsch A, Mukari A.

Eur J Ophthalmol. 2022 Nov;32(6):3340-3345.

This study assessed the success rate and complications of Lacrijet monocanalicular stent (FCI S.A.S, Paris, France) intubation in children treated for congenital nasolacrimal duct obstruction (CNLDO). This retrospective review included 20 eyes with a mean age of  $26.25 \pm 11.25$  months. 17 eyes (85%) had undergone probing previously. Mean operation time of Lacrijet intubation was 8.5 min (95% CI 7.04-9.95). The mean follow-up period was  $204.65 \pm 105.27$  days. Lacrijet intubation resulted in statistically

significant improvements in tear meniscus height ( $P < .001$ ), FDDT ( $P < 0.001$ ) and MUNK scores to rate the severity of epiphora ( $P < 0.001$ ) in all children. Two different sizes of Lacrijet intubations were used. Complete success was obtained in all cases. No complications were observed. Based on the findings of this study, the authors conclude that Lacrijet lacrimal intubation has a high rate of success, shortens surgical time and has a low rate of complications in children with CNLDO.

#### Outcomes of Patients With Thyroid Eye Disease Partially Treated With Teprotumumab.

Ho TC, Maamari RN, Kossler AL, Sears CM, Freitag SK, Reshef ER, Shinder R, Rootman DB, Diniz SB, Kahana A, Schlachter D, Do TH, Kally P, Turner S, Mokhtarzadeh A, Harrison AR, Hwang CJ, Kim HJ, Avila SA, Thomas DA, Magazin M, Wester ST, Lee WW, Clauss KD, Holds JB, Sniogowski M, Compton CJ, Briggs C, Malik AI, Lucarelli MJ, Burkat CN, Patel LG, Couch SM.  
Ophthalmic Plast Reconstr Surg. 2022 Sep 9. PMID: 36095848.

Teprotumumab has shown success treatment of thyroid eye disease. The standard protocol for teprotumumab is an 8-dose regimen. During the pandemic, production of this medication was halted. This study's purpose is to assess the outcomes of patients treated with fewer doses. This is an observation cross-sectional cohort study that included 74 patients with active (62 patients) and minimal or no clinical activity (12 patients) treated with teprotumumab. Patients completed an average of 4.2 infusions before interruption. There was still a significant reduction in proptosis in both patient groups and this was maintained after interruption. For active patients, there was a reduction of clinical activity score and ocular motility restriction that was maintained after interruption. Diplopia resolved in 17.7% of patients and 3.2% reported a return in diplopia during the interruption. Given the limited long term follow up and other limitations of this study, it did show patients partially treated maintained reduction in their proptosis, CAS score and EOM restriction. Further studies would need to be done before a reduction in treatment can be advised.

#### Psychosocial and mental health disorders among a population-based, case-control cohort of patients with congenital upper eyelid ptosis.

Hendricks TM, Griepentrog GJ, Hodge DO, Mohny BG.

Br J Ophthalmol. 2023 Jan;107(1):12-16. doi: 10.1136/bjophthalmol-2021-319276.

This is population-based cohort study of 81 children diagnosed with simple congenital ptosis over a 40-year period and their sex- and age-matched controls. All subjects were <19 years of age and residents of Olmsted County, Minnesota. The authors sought to describe the prevalence and types of psychiatric and psychosocial abnormalities diagnosed by early adulthood. The medical records of both cases and their controls were reviewed for psychosocial and mental health parameters. An adverse psychosocial development was diagnosed in 41 (51%) patients with simple congenital ptosis compared with 26 (33%) controls ( $p=0.02$ ), and mental illness was diagnosed in 38% of ptosis patients compared to 20% of controls ( $p=0.02$ ). Children with ptosis were 2.5 times more likely than controls to develop a mental illness and 2 times more likely to develop a psychosocial maladjustment. Patients with ptosis were also significantly more likely to have a greater number of mental health disorders ( $p=0.02$ ) and a longer duration of psychotropic medication use ( $p=0.007$ ). Generalized anxiety, mood disorders and alcoholism were the most common types of disorders among children with ptosis. Social deficits or anxiety, anger issues, developmental delay, behavior problems at home, poor self-esteem and lack of motivation were significantly more prevalent among children with ptosis compared with controls. Neither the relative asymmetry between the height of the two upper eyelids nor the amount of ptosis measured by the MRD correlated positively with the rate of mental illness or psychosocial difficulty. Interestingly, neither having ptosis surgery nor the age at which surgery occurred influenced the rate of mental illness or psychosocial burden. However, among the 34 children who underwent ptosis repair, those displaying a greater change in fissure height had less mental illness or psychosocial burden. Maybe we should be fixing ptosis even if not amblyogenic? Or maybe we should refer our ptosis patients for early psychosocial intervention?

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#### Parent-provided photographs as an outcome measure for childhood chalazia.

S. Ayse Erzurum, MD, Rui Wu, MS, B. Michele Melia, ScM, Zhuokai Li, PhD, Robert W. Arnold, MD, David I. Silbert, MD, John W. Erickson, OD, Nicholas A. Sala, DO, Raymond T. Kraker, MSPH, Jonathan

M. Holmes, BM, BCh, and Susan A. Cotter, OD, MS, on behalf of the Pediatric Eye Disease Investigator Group.

J AAPOS 2022; 26:60.e1-5.

Monitoring of chalazia is traditionally done over several visits in the outpatient setting. This study sets out to determine if smartphone photos taken by parents could be used as an alternative to these in person examinations. Children were evaluated in person to determine if they had at least one chalazion measuring 2 mm or larger in diameter. Parents then took 4 photographs of their child's eyelids that were evaluated by a masked eyecare professional to look for the presence of a chalazion. No clinical history was given to the masked readers. A total of 240 eyelid photographs were available; 85 with at least one chalazion, 155 without a chalazion. The masked reader correctly identified 68 of 85 eyelids with a chalazion (sensitivity 80%) and 151 of 155 eyelids without a chalazion (specificity 97%). Sensitivity increased to 89% for lesions >5 mm in diameter and to 94% for superficial lesions. This paper is important as it demonstrates a possible excellent use for tele-ophthalmic care. Parent submitted photographs could help increase care in underserved areas and decrease wait times for clinical visits. They may be particularly useful for monitoring resolution in clinical practice and future clinical trials looking at the treatment of chalazia.

The significance of primary monocanalicular silicone tube intubation in late surgical treatment in children. Sahar B, Ciftci F.

Eur J Ophthalmol. 2022 May;32(3):1464-1468.

The authors evaluated the outcomes of monocanalicular silicone tube intubation as an initial surgical treatment in children older than 1 year old with primary nasolacrimal obstruction. Isolated probing was performed on 53 eyes of 43 patients and silicone tube intubation on 45 eyes of 39 patients. Treatment was considered successful after improvement in patient complaints, the presence of normal tear meniscus, and normal results of fluorescein disappearance dye test. Treatment outcomes were retrospectively compared between the two groups according to age groups. Treatment success was 79.1% in the probing group and 92.3% in the silicone tube intubation group. Patients with successful outcomes were further stratified into age groups of 12 to <24 months, 24 to <36 months, and 36 to <48 months. Although the success rate of the silicone tube intubation group was consistently found to be higher, the difference was not statistically significant. Treatment success decreased statistically significantly in the isolated probing group with increasing age of the patients, especially after 24 months. There was no such statistically significant decrease treatment outcomes in the silicone tube intubation group with increasing patient age. The study results lead the authors to conclude that the choice of monocanalicular silicone tube intubation for primary surgical treatment in children with primary nasolacrimal obstruction may be superior to isolated probing in children older than 24 months.

Functional metagenomic profile of the lacrimal sac microbial communities in primary acquired nasolacrimal duct obstruction: The Lacriome paper 2.

Ali MJ.

Eur J Ophthalmol. 2022 Jul;32(4):2059-2066.

This prospective study evaluated the functional metagenomic profile of the microbes isolated from the lacrimal sac of patients with primary acquired nasolacrimal duct obstruction. Ten consecutive lacrimal sac samples were obtained for the metagenomic analysis from patients with primary acquired nasolacrimal duct obstruction who underwent endoscopic dacryocystorhinostomy at a tertiary care center. The samples were collected intraoperatively soon after a full-length lacrimal sac marsupialization and immediately transported on ice to the laboratory. Following DNA extraction and library preparation, a whole shotgun metagenome sequencing was performed on the Illumina NOVASEQ 6000™ platform. The downstream processing and bioinformatics of the samples were performed using multiple software packaged in SqueezeMeta™ pipeline and functional analysis using the MG-RAST™ pipeline. The microbial gene mapping and protein prediction models demonstrated proteins with known functions to range from 66.41% to 84.03% across the samples. The functional category distribution of Kyoto Encyclopedia of Genes and Genomes ortholog (level 1 data) showed metabolism to be the most commonly involved function followed by environmental information processes, genetic information processes and cellular processes. The functional subsystem profiling demonstrated genes associated with carbohydrate, protein and RNA metabolism, amino acids and their derivatives, cofactors and

prosthetic groups and factors involved in cell structure regulation and cell cycle control. This is the first functional metagenomic profile of the lacrimal sac microbiota from patients with primary acquired nasolacrimal duct obstruction. Functional analysis has provided newer insights into the ecosystem dynamics and strategies of microbial communities inhabiting the lacrimal sac. Further Lacriome studies may provide clues for better understanding of the disease pathogenesis.

Teprotumumab reduces extraocular muscle and orbital fat volume in thyroid eye disease

Jain AP, Gellada N, Ugradar S, Kumar A, Kahaly G, Douglas R.

Br J Ophthalmol. 2022 Feb;106(2):165-171.

This is a retrospective review of 6 patients enrolled in the phase III teprotumumab clinical trial (OPTIC, NCT03298867) with active TED who received 24 weeks of teprotumumab and had pre- and post-treatment orbital imaging (CT or MRI). Twelve non-TED patients (24 orbits) were analyzed as a comparative control group. Three-dimensional volumetric analyses of four orbital rectus muscles, orbital fat and the orbital cavity were performed using the previously validated 3D image analysis software. The hypothesis was that inhibition of the IGF-1R pathway with teprotumumab results in decreased orbital soft tissue volumes of EOM and orbital fat, correlating with the clinical findings of a reduction in the CAS, diplopia and proptosis. A single orbit was designated as the study orbit, which was based on the more severely affected orbit, in accordance with previous clinical trial protocols. The study orbit demonstrated a 36% mean decrease in total EOM volume (range 17%–45%) over the 24 week period ( $p < 0.01$ ). The inferior rectus demonstrated the greatest reduction in muscle size in 4/6 patients with a 48% mean reduction in muscle volume (range 29%–68%; study orbit). The mean fat volume (FV) in the study orbit prior to therapy was 12,391 mm<sup>3</sup>. Post-therapy, there was a reduction of 4387 mm<sup>3</sup> to a mean of 8004 mm<sup>3</sup> ( $p < 0.03$ ), resulting in a 30% average FV reduction in the study orbit (range–12% to 44%). There was a mean proptosis reduction as measured by Hertel exophthalmometry of 5 mm (range 3–7 mm) in the study eye. At baseline, 8/12 orbits had a CAS of 5 or 6. At the end of the clinical trial (week 24), the CAS reduced to 0 or 1 in all 6 patients. The difference between the total EOM volume in post-therapy patients and non-TED controls was not significant ( $p = 0.09$ ), demonstrating that post-treatment EOM volume returned to normal volumes. However, there was a statistically significant difference between post-therapy patients and controls regarding orbital FV measurements ( $p < 0.05$ ), indicating that post-treatment orbital FV was reduced, but did not return to a normal when compared to controls. This study is limited in its small number of participants and retrospective nature, but it helps demonstrate the soft tissue changes resulting from teprotumumab therapy and the associated clinical benefits.

Outcomes of enucleation and porous polyethylene orbital implant insertion in patients with pediatric retinoblastoma: a long-term follow-up study.

Yang MK, Lee MJ, Kim N, Choung H, Khwarg SI.

Br J Ophthalmol. 2022 Apr;106(4):502-509.

This was a retrospective single-center cohort study of pediatric patients who underwent enucleation and simultaneous insertion of unwrapped porous polyethylene (PP) spherical orbital implant for advanced retinoblastoma 1998-2014. The cohort was divided into four groups according to the development in surgical techniques and PP implant. Group A) 1998- 2001 classic enucleation and PP spherical implant insertion were performed. Group B) 2001-2011, anterior closure of the posterior Tenon's (ACPT) capsule in front of the PP implant was added to classic enucleation procedures. Group C) 2001-2007, free orbital fat grafts combined with PP implant insertion and ACPT were performed in some patients. Group D) 2004-2014 SST PP implant insertion, instead of PP implant insertion, and ACPT were performed. 198 eyes of 196 patients were included in the cohort and the mean follow-up time was 13 years. Orbital recurrence was identified in three patients at 2, 7 and 8 months after enucleation and was successfully treated by additional chemotherapy followed by autologous peripheral blood stem cell transplantation. Implant infection, extrusion and migration were not observed in any patient during the follow-up period. The rates of conjunctival thinning and implant exposure were the highest in group A (78.4% and 56.8% at 10 years, respectively). Excluding patients in group A, the postoperative 10-year exposure rate was 2.9% (3/102). Further analyses revealed that only ACPT was associated with a significant reduction in implant exposure. The overall success rate of dermis-fat grafts (86.7%) was higher than the success rate of scleral grafts (45.5%) when treating exposure. The rates of upper eyelid ptosis and lower eyelid retraction



were 24.2% and 15.2%, respectively, during the 13.0- year median follow-up period. A 20mm-sized implant was beneficial for the prevention of cosmetic complications after enucleation.

Spontaneous resolution rates in congenital nasolacrimal duct obstruction managed with massage or topical antibiotics compared with observation alone.

Mohney BG, Sathiamoorthi S, Frank RD.

Br J Ophthalmol. 2022 Sep;106(9):1196-1199.

The medical records of 1998 consecutive patients younger than 5 years diagnosed as having CNLDO while residing in Olmsted County, Minnesota, 1995-2004, were retrospectively reviewed to determine if nasolacrimal massage or topical antibiotics are associated with higher rates of resolution compared with observation alone. 11.3% of births during the study period were diagnosed with CNLDO at a mean age of 5.2 weeks. Approximately 9/10 cases were diagnosed by a pediatrician or primary care physician. The management of the 1958 with two or more examinations was as follows: 516 (26.4%) were merely observed, 506 (25.8%) were prescribed nasolacrimal massage only, 485 (24.8%) were prescribed at least one course of topical antibiotics, 397 (20.3%) were prescribed both topical antibiotics and nasolacrimal massage, and 54 (2.8%) had no recommended therapy recorded within the medical record. 85% spontaneously resolved at a median age of 2.4 months (range: 0–87 months) while the remaining 14.8% required surgical intervention. Among those who spontaneously resolved without surgery, 89.1% resolved within 3 months of their diagnosis and an additional 6.1% by 6 months. Non-surgical resolution was 74.6% for the merely observed, 89.7% for those prescribed digital massage, 87.0% for those prescribed antibiotics and 90.7% for those treated with both, and this comparison was significant in both unadjusted and multivariable comparisons. This study does report a significantly higher rate of spontaneous resolution among CNLDO patients using massage, topical antibiotics, or a combination of both therapies, although it's important to note the very high rate of spontaneous resolution in the observation group too.

The Evolving Story of CNLDO: Serial Photographic Documentation and Parental Perspectives.

Singh S, Ali MJ.

Ophthalmic Plast Reconstr Surg. 2022 Jul 13. Epub ahead of print. PMID: 35829659.

Epiphora is a common symptom in nasolacrimal duct obstruction (NLDO). This is a perspective observational report on the evolution of NLDO in one infant. The authors of this study both had a newborn child with NLDO and documented the clinical findings on a daily basis. Data collected included epiphora, discharge, tear meniscus level, matting of lashes, difficulty in eye-opening upon awakening, conjunctival congestion, cutaneous hyperemia of eyelids, etc. Photographic documentation was also performed daily. Lacrimal massage was performed (10 strokes for 4-6x/day). The results were reported on a weekly basis. Peak symptoms were reported about 4 weeks after onset. In summary, initial symptom was epiphora, followed by discharge. There was excoriation of the periocular skin. Key points from this report include wet wipes were more effective than moist cloth to remove discharge and lacrimal massage was comfortable to the infant.

Microdebridement of Intranasal Cysts Associated With Congenital Dacryocystoceles.

Magoon K, Landau Prat D, Guo M, Revere K, Katowitz WR.

Ophthalmic Plast Reconstr Surg. 2022 Jul-Aug 01;38(4):401-403. Epub 2022 Jul 5. PMID: 35170563.

The treatment of congenital dacryocystoceles has evolved in recent decades. This is a retrospective case series examining patients with congenital dacryocystocele treated with endoscopic examination and powered microdebridement of nasal cysts over a 12 year period. 37 procedures of 29 patients were included in the study. Mean age of diagnosis was 15 +/- 28 days and surgical intervention was done at 1.4 +/- 1.7 months of age. Mean follow up was 7.5 mo. Intranasal cysts were observed in 86% of lacrimal drainage systems. The authors reported 97% surgical success with one patient requiring a DCR due to persistent symptoms. This report highlights the use of a powered microdebrider as a surgical intervention for dacryocystocele.

Echographic Assessment of Extraocular Muscle Response to Teprotumumab.

Tran C, Pham CM, Simmons BA, Warner LL, Fuhrmeister LJ, Shriver EM.

Ophthalmic Plast Reconstr Surg. 2022 Jul-Aug 01;38(4):336-339. Epub 2022 Oct 13. PMID: 34652310.

Patients with thyroid eye disease (TED) can have enlarged extraocular muscles (EOM). Teprotumumab is a novel medication that can successfully treat patients with TED. This is a retrospective study to evaluate the EOM response via orbital echography in patients with TED. Adult patients with TED had exams and documentation of clinical activity score, Gorman diplopia score, ocular motility, and recti muscle diameters measured via ultrasound pre- and post-teprotumumab. The patient's more proptotic eye was designated as the study orbit. Six patients were included in the study. There was an improvement in the proptosis in 11/12 eyes after treatment. In addition, there was an improvement in ocular motility and Gorman diplopia score. The mean EOM diameter reduced from 27.4 to 23.4mm ( $p < 0.001$ ). This study shows the reduction in size of EOM after teprotumumab treatment with echography. Limitations of the study include small sample size, single center, and geographic region. A specified timeline to obtain echography would also be helpful. This can be helpful in counselling patients and potential need of adjusting prisms during treatment.

#### Predictive Modeling of New-Onset Postoperative Diplopia Following Orbital Decompression for Thyroid Eye Disease.

Nair AA, Ediriwickrema LS, Dolman PJ, Law G, Harrison AR, Mokhtarzadeh A, Stewart K, Men C, Lucarelli MJ, van Landingham S, Wingelaar M, Verma R, Chen A, Selva D, Garrity J, Eckel L, Kazim M, Godfrey K, Baxter SL, Korn BS, Kikkawa DO.

Ophthalmic Plast Reconstr Surg. 2022 May 13. Epub ahead of print. PMID: 35551414.

Clinical manifestations of thyroid eye disease (TED) can include strabismus and diplopia. The purpose of this multi-center retrospective study was to identify risks factors for the development of new post-operative diplopia following orbital decompression. The study was conducted over a 16 year period from 2002-2017. Exclusion criteria was  $< 18$  years of age, prior radiation or surgical decompression, preoperative diplopia in the primary position,  $< 3$  mo of follow up, and incomplete data/imaging. 331 patients and 563 orbits were included in this study. The average length of follow up was 21.9 months. At 3 months post-operative, 82 patients developed diplopia. Preoperative clinical risk factors included older age, proptosis, use of peribulbar or systemic steroids, high CAS score, and the presence of compressive optic neuropathy. Imaging findings of a large cross-sectional area of EOM in patients also had a high risk of postoperative diplopia. Surgical risk factors included medial wall decompression, bilateral orbital surgery, and balanced decompression. Endoscopic medial wall decompression was found to be protective. In summary, risk factors identified in the study are all signs of a more severe TED. This study highlights the need for preoperative counselling of the potential need for diplopia care and perhaps a pre-operative assessment by an adult strabismus specialist.

#### Primary Monocanalicular Stent Intubation for Children With Congenital Nasolacrimal Duct Obstruction: Surgical Outcome and Risk Factors.

Katowitz WR, Prat DL, Munroe CE, Revere K, Khatib L, Hua P, Ying GS, Binenbaum G.

Ophthalmic Plast Reconstr Surg. 2022 May 3 Epub ahead of print. PMID: 35502807.

Congenital nasolacrimal duct obstruction is the most common cause of epiphora in infants. The use of primary monocanalicular stent intubation is being done but not well studied. The purpose of this paper is to determine the risk factors impacting success of primary monocanalicular stent intubation for CNLDO. This is a retrospective chart review of all subjects  $< 18$  years of age who underwent monocanalicular stent intubation as a first and only procedure by a single surgeon over a 12 year period at CHOP. Exclusion criteria included prior canalicular surgery, acquired tearing after the age of 1, nasolacrimal trauma, Down syndrome, dacryocystocele/dacryocystitis, and craniofacial abnormalities. Patients who were lost to follow up were also excluded. Stents were removed at the three month follow up appointment. 1001 patients were included in this study. The average age at surgery was 1.86 years of age. The avg follow up was 35 months. The overall success rate was 92.6%. Bilateral surgery, severe duct stenosis, and early stent loss were significantly associated with higher risk of surgical failure. The procedure has a high success rate and low rate of reoperation. A comparative analysis evaluating the success rate between primary NLDO probing and irrigation and primary monocanalicular stent intubation would be useful.

#### Congenital Nasolacrimal Duct Obstruction Update Study (CUP Study): Paper 4-Infantile Acute Dacryocystitis (InAD)-Presentation, Management, and Outcomes.

Bothra N, Ali MJ.

Ophthalmic Plast Reconstr Surg. 2022 May-Jun 01;38(3):270-273. Epub 2021 Oct 13. PMID: 34652315.

Acute dacryocystitis (AD) in infants is a medical urgency with rapid onset of pain, erythema, and edema. The treatment of infantile AD includes broad-spectrum antibiotics followed by early decompression of the lacrimal system with probing and marsupialization of intranasal cysts. Preoperative bacteremia is a significant risk in infants and reported to be close to 23%. Thus is a retrospective single center study to evaluate the presentation, management, and outcome of infantile AD. Data collected included patient demographics, history, presenting features, management, complications, and outcomes. Successful outcome was defined as resolution of infection and subjective improvement of epiphora. 27 infants were analyzed during the study period of June 2016-Dec 2019. Mean age of infants was 3.26 months. Mean duration of symptoms was 4.66 weeks. 96% of patients had redness, epiphora, discharge and edema. 74% of patients had preseptal cellulitis. Endoscopy-guided probing was performed on 21 infants (5 were lost to follow up). Intranasal cysts were found in 33% of patients. One patient required a DCR. 3 infants had infections with staph aureus, 2 with pseudomonas, and one each with staph epi and strep pneumonia. Average follow up was 7.95 months. 90.4% of patients who had a surgical intervention had no epiphora or delay on dye disappearance test. This study shows the importance of early detection and treatment. Early management of patients have successful outcomes. The need for pre probing prophylactic antibiotic administration remains controversial and further studies are needed for firm guidelines.

#### Facial Asymmetry in Children With Unilateral Congenital Ptosis.

Tenzel PA, Brown K, Zhou B, Itani KM, Mancini R.

Ophthalmic Plast Reconstr Surg. 2022 Mar 30. Epub ahead of print. PMID: 35353779.

Unilateral congenital ptosis is a disease of both functional and cosmetic importance. Patients can develop amblyopia and vision impairment depending on the degree of ptosis. Surgical treatment is often considered to minimize amblyopia and improve cosmetics. Studies have shown that pre-existing facial asymmetry may contribute to patient dissatisfaction with surgical outcome. The purpose of this study is to analyze facial asymmetry in children with unilateral congenital ptosis. This is a retrospective review of pediatric patients undergoing unilateral ptosis repair at a single center. Gender, age, lateraling, MRD1, LF, and surgical intervention were analyzed. Preoperative photos were assessed using ImageJ software. Measurements from this software were used in symmetry analysis. 44 patients were included in this study. 20% of patients had mullerectomy, 34% had levator resection, and 46% had frontalis suspension. The side of the face with blepharoptosis had smaller MRD1, smaller horizontal palpebral fissure, shorter mid face height and a more inferiorly displaced lateral canthus. There are limitations to this study including retrospective nature, use of only one photograph at one point in time per patient, and incomplete standardization of photograph. Further studies should include further imaging analysis such as MRI/CT and postoperative photos. A larger cohort of patients and a standardization of patients without ptosis would be helpful. This is however important for surgeons to know to help patients have realistic expectations of surgical outcome.

#### Hypolacrimia and Alacrimia as Diagnostic Features for Genetic or Congenital Conditions (Review).

Willems M, Wells CF, Coubes C, Pequignot M, Kuony A, Michon F.

Invest Ophthalmol Vis Sci 2022;63(2).

As part of the lacrimal apparatus, the lacrimal gland participates in the maintenance of a healthy eye surface by producing the aqueous part of the tear film. Alacrimia and hypolacrimia, which are relatively rare during childhood or young adulthood, have their origin in a number of mechanisms which include agenesis, aplasia, hypoplasia, or incorrect maturation of the gland. Moreover, impaired innervation of the gland and/or the cornea and alterations of protein secretion pathways can lead to a defective tear film. In most conditions leading to alacrimia or hypolacrimia, however, the altered tear film is only one of numerous defects that arise and therefore is commonly disregarded. Here, the authors systematically review all of those genetic conditions or congenital disorders that have alacrimia or hypolacrimia as a feature. Where it is known, they describe the mechanism of the defect in question. It has been possible to clearly establish the physiopathology of only a minority of these conditions. As hypolacrimia and alacrimia are rare features, this review could be used as a tool in clinical genetics to perform a quick diagnosis, necessary for appropriate care and counseling.

## 22. INFECTIONS

None in the last 6 months

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Survey of state conjunctivitis policies for school-age students.

Lee T, Kuo IC.

J AAPOS. 2022 Jun;26(3):115.e1-115.e5.

The authors conducted a survey to examine state policies on conjunctivitis in students for completeness of information and for internal consistency. A previous similar study in 2007 showed variation in policies and called for standardization. The authors searched state health department websites and education department websites if necessary to find the information concerning management of students with conjunctivitis. They additionally contacted the head of a state's department of health by email if need to obtain information. The following parameters were recorded: policy and electronic link, date of policy, information on types of conjunctivitis, criteria for exclusion, and criteria for return to school. Policies were reviewed for recommendation internal consistency, information that treatment is based on etiology, reference to an "expert" resource, and definition of outbreak. The authors found little progress in standardization from the previous study in 2007. The authors found that state policies on conjunctivitis vary widely. None of the states included American Academy of Ophthalmology as a reference. The authors also recommend discouraging blanket rules requiring antibiotics prior to return to school and emphasize that such policies may have a greater impact on communities of color and lower socio-economic status. The authors were also concerned about a lack of information on identification of an adenoviral outbreak and methods to curtail an epidemic which is much more serious than random individual cases. The authors conclude requesting consideration of collaboration of the American Academy of Pediatrics, American Association of Pediatric Ophthalmology and Strabismus, and American Academy of Ophthalmology that could advise state policy makers on methods of constructing policies should be easily accessible and have as a goal preventing spreading of infection while minimizing school exclusion/missed work and honoring principles of antibiotic stewardship. The authors acknowledge limitations of not verifying current state of revisions of online policies and that there is no evidence that the current situation has resulted in harm. The authors highlight the difficulty that the medical community faces in dealing with the care of school age children with conjunctivitis when there are mandates in school policies for exclusion, treatment, and return to school.

A qualitative evaluation of pediatric conjunctivitis medical decision making and opportunities to improve care.

Sebastian T, Frost HM.

J AAPOS. 2022 Jun;26(3):113.e1-113.

Acute infectious conjunctivitis is a common pediatric disease impacting the everyday life of children and their parents. Treatment indications and return to school parameters are unclear. The authors used semi-structured interviews with 20 providers who volunteered after email and newsletter solicitation to describe the indications for treatment used, identify factors that reduce unnecessary antibiotic prescribing, and to review COVID-19 pandemic effect on antibiotic prescribing frequency. Interviews were transcribed and evaluated for major themes using deductive and inductive content analysis methods. Interviews were stopped when no new themes were elicited (data saturation). The study demonstrated key drivers influencing antibiotics prescribing decisions: clinical presentation, family expectations, antibiotics stewardship concerns, inability to confirm diagnosis, and school/daycare requirements for return. Factors identified that could reduce unnecessary ophthalmic antibiotic use: increasing family education, reliable validated diagnostic test to confirm diagnosis, standardizing return to school/daycare policies and national clinical management guidelines. Providers acknowledged higher rates of prescribing ophthalmic antibiotics during COVID-19 pandemic coinciding with increased use of nurse-line visits guided by protocols. The authors acknowledge several limitations with the study qualitative design. The design may have sample and selection bias. Accuracy of prescribing patterns could not be verified and being interviewed by a fellow physician may have influenced responses. This article is important to pediatric

ophthalmologists in calling for further attention to creating a national guideline for management of infectious conjunctivitis as well as standardizing school/daycare exclusion policies.

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### 23. PEDIATRICS / SYNDROMES / SYSTEMIC DISEASE

Abnormalities of the contralateral eye in unilateral congenital anophthalmic or blind microphthalmic patients

Ma L, Li Y, Zhang H, Li L, Deng G, Xu J, Li D

J AAPOS 2023;27:34.e1-4.

The medical records of patients with unilateral congenital anophthalmia and blind microphthalmia at Beijing Tongren Hospital from January 2017 to December 2021 were reviewed retrospectively to investigate abnormalities of the fellow eye. A total of 168 patients were included. 28 (16.7%) of these fellow eyes had abnormalities. The most common finding was a coloboma (7.7%), followed by optic nerve dysplasia (3.0%), familial exudative vitreoretinopathy (FEVR) (1.8%), morning glory disc (1.8%), and retinal fiber layer defect (1.2%). High myopia fundus changes, retinal folds, maculopathy, peripapillary staphyloma, and bergmeister optic disc were also noted. This hospital-based study has the potential for referral bias. Nevertheless, this is noteworthy as the fellow eye abnormalities are potentially vision threatening and monitored closely.

Choroidal Vascular Index in Patients With Attention-Deficit/Hyperactivity Disorder and Methylphenidate

Kiziltoprak H, Kocabas DO, Aydemir GA, Kalınlı EM, Aydemir E, Oren B.

J Pediatr Ophthalmol Strabismus. 2022;1-6. doi:10.3928/01913913-20221026-01

This cohort study investigated choroidal vascularity in children with ADHD receiving therapy vs children with ADHD not receiving therapy, and healthy controls based on the hypothesis of neurovascular changes underpinning the development of ADHD. The authors measured both choroidal vascularity index (CVI) and choroidal thickness using an enhanced-depth imaging mode of spectral-domain optical coherence tomography (EDI OCT) (Spectralis; Heidelberg Engineering GmbH). They found that a significant difference in CVI and stromal area between groups: significantly lower in patients with ADHD treated with methylphenidate (MPH) compared with the other groups ( $P < .001$ , for each); however, there was no difference between the treatment-free ADHD group and controls ( $P = .305$ ). In contrast, stromal area was significantly higher in patients with ADHD treated with MPH than the other groups ( $P < .001$ , for each group). The correlation of CVI with MPH treatment duration in patients with ADHD treated with MPH showed a significant, moderate negative correlation ( $P = .01$ ,  $r = -0.66$ ). The authors conclude that CVI is reduced in patients with ADHD treated with MPH, and the decrease in CVI becomes significant with increasing duration of MPH treatment. This result reflects an indirect effect of MPH treatment on choroidal vascular structures. Of course, the clinical implications of this small, non-generalizable study are unclear.

Comparative study of laser flare photometry versus slit-lamp cell measurement in pediatric chronic non-infectious anterior uveitis.

Yalçındağ FN, Köse HC, Temel E.

Eur J Ophthalmol. 2023 Jan;33(1):382-390.

The authors were interested in evaluating the role of laser flare photometry (LFP) for monitoring the course of intraocular inflammation in children with chronic anterior uveitis. A retrospective chart review of seventy-six eyes in 43 children with non-infectious chronic anterior uveitis was conducted. The median follow-up was  $48.6 \pm 23.1$  months. Patients on immunosuppressive treatment at last follow-up showed significantly higher flare values than patients who discontinued treatment ( $20.47 \pm 15.49$  vs.  $6.33 \pm 4.87$   $p < 0.001$ ). The higher LFP values were correlated with the duration of immunosuppressive treatment, total duration of topical corticosteroid use and the risk for development of ocular complications at all follow-ups (all  $p < 0.001$ ). No significant correlation was found between the degree of AC inflammation and the duration of immunosuppressive treatment, topical corticosteroid use and the prevalence of complications. LFP measurements have a predictive value of monitoring the course of uveitis and the occurrence of ocular complications, and it should be considered as a primary modality to monitor intraocular inflammation in children with chronic anterior uveitis.

Ocular manifestations of COVID-19 in the pediatric age group.

Alnahdi MA, Alkharashi M.

Eur J Ophthalmol. 2023 Jan;33(1):21-28.

The authors aim to outline the various pediatric ocular manifestations of COVID-19 described in the literature. The manifestations may be divided into isolated events attributed to COVID-19 or occurring in

the newly described multisystem inflammatory syndrome in children (MIS-C), a novel entity associated with COVID-19 infection. Ocular manifestations are found in all age groups ranging from neonates, infants, children, and adolescents. Episcleritis, conjunctivitis, optic neuritis, cranial nerve palsies, retinal vein occlusion, retinal vasculitis, retinal changes, orbital myositis, orbital cellulitis were reported in the literature with this emerging viral illness. Conjunctivitis was the most common ocular manifestation in MIS-C, presenting in nearly half of the patients. Other ocular manifestations in MIS-C were anterior uveitis, corneal epitheliopathy, optic neuritis, idiopathic intracranial hypertension, and retinitis. The clinical outcome was favorable, and children regained their visual ability with minimal or no deficits in most cases. Further follow-up may be warranted to better understand the long-term effects and visual prognosis.

Corneal confocal microscopy identifies a reduction in corneal keratocyte density and sub-basal nerves in children with type 1 diabetes mellitus.

Gad H, Al-Jarrah B, Saraswathi S, et al.

Br J Ophthalmol. 2022 Oct;106(10):1368-1372. doi: 10.1136/bjophthalmol-2021-319057.

This study investigated whether clinical and metabolic alterations are associated with a change in corneal stromal keratocyte density and corneal nerve fiber morphology in children with type 1 diabetes (T1DM) vs age matched healthy controls. There were 20 children in each group with mean age 14 years and mean disease duration 4 years with average HbA1c 9.3%. Corneal confocal microscopy was undertaken using the Heidelberg Retina Tomograph Cornea Module and keratocytes were counted manually using CCMetrics. Anterior and mid keratocyte densities were lower with no difference in posterior keratocyte density in children with T1DM compared with controls. Corneal nerve fiber density was lower in children with T1DM. Age, disease duration, height, weight, and BMI did not correlate with keratocyte densities, but there was an inverse correlation between HbA1c and posterior keratocyte density. They did not find an independent association between keratocyte densities and corneal nerve parameters. Bilirubin has been found to be protective in diabetic neuropathy, however, they did not find any relationship between bilirubin levels and corneal nerve fiber parameters in this study which is limited by its cross-sectional design and small cohort size.

#### Retinopathy of Prematurity: A Global Perspective and Recent Developments

Kourosh Sabri, MB ChB, FRCOphth, FRCSC; Anna L Ells, MD, FRCSC; Elizabeth Y. Lee, MD; Sourabh Dutta, MD, PhD; Anand Vinekar, MD, FRCS, PhD

Pediatrics (2022) 150 (3): e2021053924. <https://doi.org/10.1542/peds.2021-053924>

Retinopathy of prematurity (ROP) is a significant cause of potentially preventable blindness in preterm infants worldwide. This is a nice summary article for pediatricians that gives a very comprehensive update. It provides a comprehensive review of pathophysiology, classification, diagnosis, global screening, and treatment of ROP. Key historical milestones as well as touching upon the very recent updates to the (international) ROP classification system and technological advances in the field of artificial intelligence and ROP are discussed.

Some new key points include the new definitions for plus and pre plus, and aggressive ROP “A-ROP”

Plus and preplus disease: Plus disease is defined by the dilation and tortuosity of the posterior retinal vessels. Preplus disease is defined by abnormal retinal vascular dilation and tortuosity insufficient for plus disease.

Introduction of description of plus disease as a spectrum: Posterior retinal vascular changes in ROP should represent a continuous spectrum from normal to preplus to plus disease. The plus disease spectrum should be assessed by vessels within zone I rather than from within the field of narrow-angle photographs and the number of quadrants of abnormality.

Aggressive ROP The term aggressive-posterior ROP describes a severe, rapidly progressive form of ROP located in posterior zones I or II. Introduction of the term “aggressive ROP” or “A-ROP” to replace aggressive posterior ROP: the new term aggressive ROP (A-ROP) is recommended as a severe, rapidly progressive form of ROP located in posterior zones I or II that may occur beyond the posterior retina, particularly in larger preterm infants and regions of the world with limited resources.

Evaluating for Suspected Child Abuse: Conditions That Predispose to Bleeding Shannon L. Carpenter, MD, MS, FAAP, Thomas C. Abshire, MD, Emily Killough, MD, FAAP, James D. Anderst, MD, MS, FAAP, and the AAP SECTION ON HEMATOLOGY/ONCOLOGY, THE AMERICAN SOCIETY OF PEDIATRIC HEMATOLOGY AND ONCOLOGY, and the AAP COUNCIL ON CHILD ABUSE AND NEGLECT PEDIATRICS Volume 150, number 4, October 2022:e2022059277 FROM THE AMERICAN ACADEMY OF PEDIATRICS Downloaded from [http://publications.aap.org/pediatrics/article-pdf/150/4/e2022059277/1374187/peds\\_2022059277.pdf](http://publications.aap.org/pediatrics/article-pdf/150/4/e2022059277/1374187/peds_2022059277.pdf)

Child abuse might be suspected when children present with cutaneous bruising, intracranial hemorrhage, or other manifestations of bleeding. In these cases, it is necessary to consider medical conditions that predispose to easy bleeding. In particular bleeding disorders are addressed in this article.

Early Postinjury Screen Time and Concussion Recovery, Molly Cairncross, PhD; Keith Owen Yeates, PhD; Ken Tang, PhD; Sheri Madigan, PhD; Miriam H. Beauchamp, PhD; William Craig, MDCM; Quynh Doan, MDCM, PhD; Roger Zemek, MD; Kristina Kowalski, PhD; Pediatrics (2022) 150 (5): e2022056835 <https://doi.org/10.1542/peds.2022-056835>

#### OBJECTIVES

To determine the association between early screen time (7–10 days postinjury) and postconcussion symptom severity in children and adolescents with concussion, as compared to those with orthopedic injury (OI).

#### METHODS

This was a planned secondary analysis of a prospective longitudinal cohort study. Participants were 633 children and adolescents with acute concussion and 334 with OI aged 8 to 16, recruited from 5 Canadian pediatric emergency departments. Postconcussion symptoms were measured using the Health and Behavior Inventory at 7 to 10 days, weekly for 3 months, and biweekly from 3 to 6 months postinjury. Screen time was measured by using the Healthy Lifestyle Behavior Questionnaire. Generalized least squares models were fit for 4 Health and Behavior Inventory outcomes (self- and parent-reported cognitive and somatic symptoms), with predictors including screen time, covariates associated with concussion recovery, and 2 3-way interactions (self- and parent-reported screen time with group and time postinjury).

#### RESULTS

Screen time was a significant but nonlinear moderator of group differences in postconcussion symptom severity for parent-reported somatic ( $P = .01$ ) and self-reported cognitive symptoms ( $P = .03$ ). Low and high screen time were both associated with relatively more severe symptoms in the concussion group compared to the OI group during the first 30 days postinjury but not after 30 days. Other risk factors and health behaviors had stronger associations with symptom severity than screen time.

#### CONCLUSIONS

The association of early screen time with postconcussion symptoms is not linear. Recommending moderation in screen time may be the best approach to clinical management.

#### Preterm Brain Injury and Neurodevelopmental Outcomes: A Meta-analysis

Philippa Rees, MPhil, MBChB; Caitriona Callan, MB BChir; Karan R. Chadda, MB BChir; Meriel Vaal, MBChB (Hons); James Diviney, MB BChir; Shahad Sabti, MBBS; Fergus Harnden, MBChB; Julian Gardiner, PhD; Cheryl Battersby, PhD; Chris Gale, PhD; Alastair Sutcliffe, PhD Pediatrics (2022) 150 (6): e2022057442. <https://doi.org/10.1542/peds.2022-057442>

Visual outcomes after IVH grade 3 to 4 were reported by 5 comparable studies that included 7203 infants. They highlighted a significantly increased crude risk of visual impairment OR 5.42, 95% CI (2.77–10.58) Neurodevelopmental Impairment

Neurodevelopmental impairment up to 3 years after preterm WMI (or IVH and WMI) was explored across 12 included studies. Included infants were born at less than 34 weeks' gestation or weighing less than 1500 g, between 1993 and 2015. Of these studies, 8 provided data on neurodevelopmental impairment after cystic periventricular leukomalacia (cPVL) and 4 of these were suitable for meta-analysis. They highlighted a significantly increased crude risk of moderate to severe neurodevelopmental impairment: OR 3.63, 95% CI (2.49–5.31) This effect was attenuated on pooling studies that adjusted for key covariates, such as antenatal steroid exposure, gestation, sex, race, education, and bronchopulmonary dysplasia: OR 2.38, 95% CI (0.73–7.7)  $I^2 = 94\%$  However, there was high statistical heterogeneity.



## Visual Impairment

Three studies explored visual outcomes after WMI. Broitman 2007 reported a higher crude risk of severe visual impairment after cPVL OR 13.45, 95% CI (5.8–31.18) and after PVL OR 7.15, 95% CI (3.54–14.42). Adams-Chapman 201 combine infants with IVH grade 3 to 4 and PVL (Periventricular Leukomalacia) and reported a higher adjusted risk of bilateral blindness.

IN SUMMARY: infants with PVL and cPVL have a significant higher risk of neuro/visual impairment.

## Efficacy of Medical Treatments for Vernal Keratoconjunctivitis: A Systematic Review and Meta-analysis I Roumeau, A Coutu, V Navel, et al..

J Allergy Clin Immunol. 2021;148(3):822–834 Mitchell R. Lester, MD Pediatrics (2022) 150 (Supplement 3): S13–S14 <https://doi.org/10.1542/peds.2022-059346R>

The authors conducted a literature search of interventional prospective studies measuring the efficacy of any treatment of VKC. Articles published in English, French, Spanish, or Portuguese that reported an activity score (symptoms and/or signs) of VKC before and after any treatment. Meta-analyses on the effects of treatment were conducted at the most frequent time of re-evaluation for each study as compared with baseline, or the closest time to the most frequent time and effect size (standardized mean difference) was calculated.

### RESULTS:

Over 1100 articles were identified in the initial search. 45 articles were included in the analysis. Of those, 27 were randomized control trials (14 placebo-controlled and 13 versus a comparator therapy), 2 were controlled studies, and 16 were single group cohort studies. A total of 1749 patients with VKC were included, nearly all of whom had both eyes studied. Of those, 1440 received active treatment in both eyes, 107 (6%) received active treatment in 1 eye and placebo in the other, and 202 (12%) were treated with placebo in both eyes.

All but 2 studies assessed local treatments. Cyclosporine was assessed in 16 (36%) studies, mast cell stabilizers (MCS) in 11 (24%) studies, and tacrolimus in 10 (22%) studies. Other treatments were represented in fewer than 3 studies each. For each of the medications assessed, a wide variety of concentrations were used in the included studies.

Overall meta-analyses show that total signs and symptoms scores improved globally with treatment. MCSs, cyclosporine, and tacrolimus each individually demonstrated a large beneficial treatment effect. Topical antihistamines, antihistamine and MCS combinations, topical nonsteroidal antiinflammatory drugs, and other less frequently studied treatments also resulted in large effect size, but because of the limited number of studies with these medications, it was difficult to make strong conclusions regarding their effects.

Meta-analyses for all the individual signs and symptoms studied also demonstrated strong effects. Results for all analyses were independent of age, sex, baseline activity score, atopic, type of treatment, and concentration of the calcineurin inhibitors used.

### CONCLUSIONS:

Clinical signs and symptoms of VKC improved with all treatments tested. The efficacy of MCSs in treating VKC was confirmed.

### PEDIATRIC REVIEWER COMMENTS:

VKC is more than just a bad springtime allergic conjunctivitis. Because it has potentially vision threatening complications (shield ulcers, keratoconus, and irregular astigmatism) it is important that practitioners recognize and treat this disorder. Although eye drops that have combination mast cell stabilizing and antihistaminic activity were only used in 2 of the studies, they were shown in this study to be effective, and there is no reason to suspect they would be less effective than MCSs alone. We are fortunate that 2 such medications (olopatadine and ketotifen) are now easily available over-the-counter, as is cromolyn (an MCS).

Corticosteroid eye drops are available by prescription and although representing just a few studies herein, corticosteroids were also effective in VKS. Inhibitors of calcineurin (cyclosporine and tacrolimus) were the most studied class in this meta-analysis. Neither currently has FDA approval for VKC but are approved for keratoconjunctivitis sicca (dry eye).

Although none were included in this meta-analysis, there are also studies showing the effectiveness of high-dose subcutaneous pollen immunotherapy in VKC with allergic rhinitis.

Vernal keratoconjunctivitis is highly treatable and must not be ignored.

URL: [www.pediatrics.org/cgi/doi/10.1542/peds.10.1016/j.jaci.2021.03.026](http://www.pediatrics.org/cgi/doi/10.1542/peds.10.1016/j.jaci.2021.03.026)

AAPOS REVIEWER COMMENT: VKC can be vision threatening and be managed with many modalities. The use of steroids, mast cell stabilizers, inhibitors of calcineuin (cyclosporin and tacrolimus) are effective. Off label use may be effective when many drugs are not approved or covered for pediatrics.

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### Knowledge, Attitude, and Practice Patterns Related to Digital Eye Strain Among Parents of Children Attending Online Classes in the COVID-19 Era: A Cross-sectional Study.

Kaur K, Kannusamy V, Gurnani B, Mouttapa F, Balakrishnan L.

J Pediatr Ophthalmol Strabismus. 2022;59(4):224-235. doi:10.3928/01913913-20211019-01

This cross-sectional, descriptive, questionnaire-based study sought to assess the prevalence of digital eye strain among children and extrapolate the association between knowledge, attitude, and practice patterns related to device use during the COVID-19 lockdowns. A total of 305 responses were obtained. The most common reason for device use was online classes (288 children; 94.4%) and the most common mode was smartphone (263 children; 86.3%). The prevalence of digital eye strain was 64.6%. The mean knowledge score was  $48.5 \pm 5.1$ , the mean attitude score was  $26.7 \pm 4.9$ , and the mean practice score was  $17.8 \pm 3.5$ . The difference between knowledge, attitude, and practice scores among parents of children with and without glasses was not statistically significant ( $P = .580$ ,  $.521$ , and  $.503$ , respectively). A direct correlation was found between the knowledge and practice scores ( $P = .002$ ), but attitude scores did not show a significant correlation ( $P = .712$ ). The authors concluded that there was a large knowledge gap among parents related to safe digital device use, indicating a need to spread awareness about the effects of excessive screen time in children in the form of digital eye strain and myopia and the corrective measures to avoid the same. One major limitation of the study is the framing of many of the questions in the survey ("Are you making sure..?" and "Are you taking care that your child...?" etc) which could predispose to recall bias.

### Ophthalmic involvement in PHACES syndrome: prevalence, spectrum of anomalies, and outcomes.

Soliman SE, Wan MJ, Pennal A, Pope E, Mireskandari K.

J AAPOS. 2022 Jun;26(3):129.e1-129.e7.

The authors used retrospective, noncomparative, single institution observational case series of 43 children with PHACES syndrome (posterior fossa malformations, infantile hemangiomas, arterial, cardiac, eye, and sternal anomalies) to highlight prevalence, spectrum of anomalies, and outcome of ophthalmic involvement. Prevalence of ocular involvement of 6-7% is based on case reports and case series of 8 patients. Vision may also be affected by periocular obstruction of the visual axis with amblyopia as well as intracranial anomalies causing cranial nerve palsies and papilledema. The authors report 12% of the cohort in their study had PHACES-specific ocular criteria which is almost double prevalence reported in a consensus statement on PHACES and other published reports. They suggest population differences and referral center bias may explain these differences. Some studies relied on imaging studies alone to diagnosis ocular involvement without an ophthalmologic exam which could have detected abnormalities that could not be detected on MRI imaging. Five children had PHACES-specific ocular abnormalities meeting diagnostic criteria. Posterior segment anomalies included peripapillary staphyloma, retinal vascular anomalies, and optic nerve hypoplasia. Anterior segment anomalies included cataract and corneal opacity. Four children had non-PHACES specific ocular anomalies. These included a dysmorphic optic nerve and anterior segment anomalies that did not meet criteria including Peters anomaly and persistent pupillary membrane. Ocular anomalies were ipsilateral to the facial hemangioma. All eyes with posterior involvement with major criteria had intracranial vascular anomalies. Periocular involvement of the eyelids by hemangioma was seen in 29 children (67%). Severe infantile hemangioma-related ophthalmic involvement was seen in 21/29 patients consisting of severe ptosis, proptosis, and strabismus. Amblyopia occurred in 67% of the children with severe ocular involvement at presentation. Poor vision was associated with a diagnostic structural anomaly. The authors propose that the term anterior segment dysgenesis be considered in the future as a minor diagnostic criterion. The authors emphasize that it is important to recognize and manage amblyopia as early as possible. They suggest ophthalmologic examination soon after diagnosis to detect ocular anomalies as well as risk factors for

amblyopia. Ophthalmic follow-up is guided by risk factors for amblyopia needing intervention. One limitation of the study is that the treatment protocol changed halfway through the study period from steroids to beta-blockers. Another limitation was small cohort size. Longer-term follow up may also be important in understanding outcome of ocular presentations. This study is important to pediatric ophthalmologists in highlighting the spectrum of disease seen in PHACES syndrome and as a reminder for the need to be ever vigilant about the detection and treatment of amblyopia.

Ocular manifestations of congenital insensitivity to pain: a long-term follow-up.

Elsana B, Gradstein L, Imtirat A, Yagev R, Barrett C, Ling G, Abu Tailakh M, Baidousi A, Tsumi E. *Br J Ophthalmol*. 2022 Sep;106(9):1217-1221.

Congenital insensitivity to pain with anhidrosis (CIPA) and congenital insensitivity to pain without anhidrosis (CIP) are rare autosomal recessive neuropathies characterized by the inability to sense noxious stimuli as pain and heat. The ocular manifestations of CIPA and CIP are related to impaired corneal innervation due to loss of nerve growth factor (NGF)-dependent neurons and may include dry eye syndrome, superficial punctate keratitis (SPK), corneal opacities, neurotrophic keratopathy and corneal ulcers. This retrospective chart review study describes the ocular findings including long-term sequelae in 39 patients with clinical or genetic diagnosis of CIPA (32 patients) or CIP (7 patients) followed at a single institution in Israel since 2008 and compares the natural histories of these diseases. Blink reflex to evaluate corneal sensitivity was assessed in 26 patients with CIPA and in 6 with CIP and was found positive in 52.0% and 33.3% of the eyes, respectively. Corneal opacities were found in 23.4% of the CIPA eyes vs 57% of the CIP eyes. There was a moderate negative correlation between preserved corneal sensitivity and the development of corneal opacities in the whole cohort and in the CIPA group specifically (CIP group is too small for analysis). Tear production analyzed by the Schirmer test in cooperative patients was normal in the majority of patients with CIPA and reduced in those with CIP. The authors stress the importance of early detection of this neuropathy and aggressive preventative treatment to minimize the risk of corneal opacities and associated vision loss.

Ocular and adnexal anomalies in Treacher Collins syndrome: a retrospective multicenter study  
Rooijers, Wietse et al.

*Journal of American Association for Pediatric Ophthalmology and Strabismus {JAAPOS}*, Volume 26, Issue 1, 10.e1 - 10.e6

This study looked at the prevalence of ocular and adnexal anomalies in TCS and to identify patients at risk of visual impairment. Medical records of patients at 4 craniofacial centers were retrospectively reviewed. Primary ocular anomalies were reported in 98.5% of cases, secondary anomalies in 34.5%, strabismus in 27.3%, refractive errors in 49.5%, and visual impairment in 4.6%. We found no association between ocular anomalies and visual impairment or between the severity of TCS and ocular anomalies or visual impairment, except for an increased prevalence of secondary ocular anomalies in patients with more severe manifestations of TCS. Primary ocular anomalies were described in almost all patients, mostly consisting of downslanting of the palpebral fissures (93.8%), colobomata of the lower eyelids (69.6%) and (partial) absence of lower lid eyelashes (42.8%). The most prevalent secondary ocular anomalies were epiphora (24.2%) and exposure keratopathy (14.4%). This study cohort suggests recommending a referral for ophthalmic examination in all TCS patients.

Vision and Concussion: Symptoms, Signs, Evaluation, and Treatment

Christina L. Master, MD, FAAP; Darron Bacal, MD, FAAP; Matthew F. Grady, MD, FAAP; Richard Hertle, MD, FAAP; Ankoor S. Shah, MD, PhD; Mitchell Strominger, MD, FAAP; Sarah Whitecross, MMedSci, CO; Geoffrey E. Bradford, MD, MS, FAAP; Flora Lum, MD; Sean P. Donahue, MD, PhD;

AAP SECTION ON OPHTHALMOLOGY; AMERICAN ACADEMY OF OPHTHALMOLOGY; AMERICAN ASSOCIATION FOR PEDIATRIC OPHTHALMOLOGY AND STRABISMUS; and AMERICAN ASSOCIATION OF CERTIFIED ORTHOPTISTS

*Pediatrics* (2022) 150 (2): e2021056047. <https://doi.org/10.1542/peds.2021-056047>

Concussion is a common injury in childhood, affecting an estimated 1.4 million children and adolescents annually in the United States. Blurred vision, light sensitivity, and double vision have been reported to occur in up to 40% of children and adolescents immediately after concussion. Additional symptoms may

include complaints of losing one's place or ocular fatigue while reading. Another consideration is that children are frequently unable to recognize or articulate specific visual complaints; thus, clinicians may need to have an appropriately elevated index of suspicion to identify vision-specific issues. Although concussion symptoms generally spontaneously resolve over the course of 4 weeks after injury in children and adolescents, up to one-third may have prolonged symptoms. Of those with prolonged symptoms, 69% had at least one associated vision disorder. This article summarizes ocular related findings associated with concussion. Tests necessary for evaluation include: Pursuits, Saccades, VOR (vestibular ocular reflex), Near point of convergence, accommodative amplitudes, strabismus. In general, treatment of the visual complications of concussion can be divided into 2 categories: symptom management with task modification and referral to specialists for targeted treatment of the observed oculomotor abnormalities. A summary of strategies to manage concussion-related vision disorders is provided.

#### Evaluation of the Visual System by the Primary Care Provider Following Concussion

Christina L. Master, MD, FAAP, CAQSM, FACS, FAMSSM; Darron Bacal, MD, FAAP; Matthew F. Grady, MD, FAAP, CAQSM, FAMSSM; Richard Hertle, MD, FAAO, FACS, FAAP; Ankoor S. Shah, MD, PhD; Mitchell Strominger, MD, FAAO, FANOS, FAPOS, FAAP; Sarah Whitecross, MMedSci, CO, OC(C); Geoffrey E. Bradford, MD, MS, FAAP; Flora Lum, MD; Sean P. Donahue, MD, PhD;

AAP Section on Ophthalmology; AMERICAN ACADEMY OF OPHTHALMOLOGY; AMERICAN ASSOCIATION FOR PEDIATRIC OPHTHALMOLOGY AND STRABISMUS; and AMERICAN ASSOCIATION OF CERTIFIED ORTHOPTISTS

Pediatrics (2022) 150 (2): e2021056048. <https://doi.org/10.1542/peds.2021-056048>

Concussion is a common injury in childhood and has the potential for substantial impact on quality of life. Visual issues have been increasingly recognized as a common problem after concussion. Many children initially seek care for concussion with their pediatrician, making it even more important for pediatricians to recognize, evaluate, and refer children with visual issues after concussion. This clinical report is intended to support the recommendations in the companion policy statement on vision and concussion and provides definitions of some of the physiologic aspects of the visual system as they relate to concussion. A description of clinically feasible testing methodologies is provided in more detail to aid the clinician in assessing the visual system in a focused fashion after concussion. This guidance helps direct clinical management, including support for return to school, sports, and other activities, as well as potential referral for subspecialty care for the subset of those with persistent symptoms.

#### Differences Between Viral Meningitis and Abusive Head Trauma

Danielle Horton, MD; Tanya Burrell, MD; Mary E. Moffatt, MD; Henry T. Puls, MD; Rangaraj Selvarangan, BVSc, PhD; Lindsey Hultman, MD; James D. Anderst, MD, MS

Pediatrics (2022) 150 (1): e2021054544. <https://doi.org/10.1542/peds.2021-054544>

Compared with viral meningitis subjects, abusive Head Trauma (AHT) subjects were >300 times more likely to be afebrile, >150 times more likely to have a mental status change, and nearly 60 times more likely to have at least 1 or more acute symptom. Though less acutely ill than the AHT group, the (Subdural Hemorrhage) SDH-only group was still 12 times more likely to require intubation and nearly 5 times more likely to require intensive care than the viral meningitis group. Fever was significantly less common in the AHT and SDH-only groups than the viral meningitis group. Among subjects with an abnormal WBC, AHT and SDH-only subjects were more likely to have a high WBC than viral meningitis subjects. The presence of combined features of a history of acute mental status change with lack of clinical fever on presentation had a positive predictive value for abuse of 95%. No SDH-only subjects had retinal hemorrhages characteristic of abuse; however, 6/31 examined did have retinal hemorrhages that were few in number and did not extend to the periphery

#### CONCLUSIONS

Viral meningitis is not supported as a mimic of AHT.

#### Differentiating Bell's Palsy From Lyme-Related Facial Palsy

Danielle Guez-Barber, MD, PhD; Sanjeev K Swami, MD; Jacqueline B Harrison, BA; Jennifer L McGuire, MD, MSCE

Pediatrics (2022) 149 (6): e2021053992. <https://doi.org/10.1542/peds.2021-053992>

#### BACKGROUND AND OBJECTIVES

To describe the etiology and clinical course of pediatric acute-onset unilateral peripheral facial palsy (FP), to define factors that distinguish Bell's palsy from Lyme-related FP (LRFP), and to determine if early corticosteroid use impacts facial strength recovery in Bell's palsy or LRFP.

#### METHODS

Retrospective cohort study of children 1 to 18 years old who received clinical care within our pediatric clinical care network (Lyme-endemic region) between 2013 and 2018 for acute-onset unilateral peripheral FP.

#### RESULTS

The study included 306 children; 82 (27%) had LRFP, 209 (68%) had Bell's palsy, and 15 (5%) had FP of different etiology. Most children with LRFP presented between June and November (93%), and compared with Bell's palsy, more often had a preceding systemic prodrome, including fever, malaise, headache, myalgias, and/or arthralgias (55% vs 6%,  $P < .001$ ). Neuroimaging and lumbar puncture did not add diagnostic value in isolated FP. Of the 226 children with Bell's palsy or LRFP with documented follow-up, FP was resolved in all but 1. There was no association between ultimate parent/clinician assessment of recovery and early corticosteroid use.

#### Health Supervision for Children and Adolescents With Down Syndrome

Marilyn J. Bull, MD, FAAP; Tracy Trotter, MD, FAAP; Stephanie L. Santoro, MD, FAAP; Celanie Christensen, MD, MS, FAAP; Randall W. Grout, MD, MS, FAAP;

#### THE COUNCIL ON GENETICS

Pediatrics (2022) 149 (5): e2022057010. <https://doi.org/10.1542/peds.2022-057010>

This clinical report is designed to assist the pediatrician in caring for the child, adolescent, and family in whom a diagnosis of Down syndrome has been confirmed by chromosome analysis or suspected by prenatal screening.

This paper reported the following:

Vision problems	60–80
Nystagmus	3–33
Glaucoma	<1–7
Nasolacrimal duct occlusion	3–36
Cataracts	3
Strabismus	36
Refractive errors	36–80
Keratoconus	1–13

Down syndrome is the most common chromosomal cause of intellectual disability, and there has been a significant improvement in quality of life for affected people. Awareness of the issues important to affected children, adolescents, and their caregivers can make a great difference in outcomes across the lifespan.

#### ABSTRACTS FROM ANNUAL MEETING:

##### ABSTRACT| FEBRUARY 23 2022

Accommodative Amplitude and Pupillary Light Reflex Metrics Before and After Exercise Among Adolescents with Sport-related Concussion

Eileen P. Storey, MD; Christina L. Master, MD; Rebekah C. Mannix, MD, MPH; Mohammad N. Haider, MD, PhD; John J. Leddy, MD, PhD; Barry S. Willer, PhD; William P. Meehan, MD; Nabin Joshi, PhD; Kenneth Ciuffreda, PhD; Kristy B. Arbogast, PhD; Matthew F. Grady, MD

Pediatrics (2022) 149 (1 Meeting Abstracts February 2022): 196.

Exercise intolerance is a manifestation of autonomic nervous system (ANS) dysfunction after concussion. Accommodative amplitude (AA) and pupillary light reflex (PLR) may be useful clinical proxies for ANS dysfunction

Conclusion: Adolescents with reduced exercise tolerance after concussion are more likely to have abnormal AA after exercise, suggesting that concussion-related autonomic dysfunction is precipitated by an aerobic exercise stress test. Abnormal AA and PLR metrics after exercise may provide prognostic utility in concussion. Since monocular accommodation is essential for successful participation in school, detecting deficits in AA that are due to ANS dysfunction and require targeted exercise rehabilitation rather than vision therapy may help with the return to school process after concussion.

### 3D Printed Adjustable Glasses: A New Model for Corrective Lens Delivery for Pediatric Refractive Error in Underserved Communities

Nathan Ostlie;Mari Ogino, ;James Hermsen, ;Gabe Linke;Suh W. Donny, MD  
Pediatrics (2022) 149 (1 Meeting Abstracts February 2022): 472.

This newly proposed, modular glasses design provides a one-size-fits-all frame with circular lens mounts to accommodate any axis of astigmatism. 3D printed materials allow these frames to be constructed at a fraction of the cost of conventional frames. Conclusion: While corrective lenses are made available through a variety of distribution models, the infrastructure to fit and deliver these glasses to remote and resource poor areas remains a major challenge leading to inequities in pediatric URE treatment. The flexibility of the new glasses design allows for these glasses to be distributed in rural and urban environments alike, with minimal training required to fit and assemble, at a low cost to patients.

### A Toddler with Unilateral Eye Swelling

Rasha Kazi, MD;Helene E. Tigchelaar, N/A, MD;Rajan Arora, MD  
Pediatrics (2022) 149 (1 Meeting Abstracts February 2022): 805

Pediatric eye swelling is a common emergency department (ED) presentation. Underlying etiology is mostly local (allergy, insect bite, trauma, and infection) but at times can be secondary to a systemic process (nephrotic syndrome, malignancy). This abstract presents an unusual case, initially felt to be cellulitis who presented with an acute onset atraumatic left eye swelling and was subsequently diagnosed with acute myeloid leukemia (AML).

### Association of Mood Disorders, Substance Abuse, and Anxiety Disorders in Children and Teens With Serious Structural Eye Diseases.

Meer EA, Lee YH, Repka MX, Borlik MF, Velez FG, Perez C, Yu F, Coleman AL, Pineles SL.  
American journal of ophthalmology. 2022 Aug 1;240:135-42.

Decreased visual acuity and visual impairment can affect quality of life as well as wellness and mental health. This cross-sectional study using a commercial insurance claims database aimed to describe the association between mental illnesses and 5 eye diseases (glaucoma, cataract, congenital optic nerve disease, congenital retinal disease, and blindness/low vision). Over the 11 year study period, the authors identified over 11.8 million children, of which over 180,000 had at least one of the ocular conditions of interest..The authors found that after adjusting for confounding variables such as age, sex, race and ethnicity, education, family net worth, and geographic region, there was a significant association between the eye conditions and schizophrenia, anxiety, depression, and bipolar disorders. Due to the nature of this study and data, it is not possible to establish a causal relationship. Additionally, the insurance database excludes Medicaid patients, ultimately limiting its generalizability outside of the study population. Despite these limitations, the findings of this study do demonstrate the importance of the overlap between ocular disease and mental health. The authors encourage consideration of multidisciplinary approaches to support children with eye conditions at risk for mental illness.

## 24. UVEITIS

Alternative Biologic Therapy in Children Failing Conventional TNF $\alpha$  Inhibitors for Refractory, Noninfectious, Chronic Anterior Uveitis.

Utz VM, Angeles-Han ST, Mwase N, Cassedy A, Hennard T, Lovell DJ, Lopper S, Brunner HI, Dosunmu EO, Grom AA, Henrickson M.

American Journal of Ophthalmology. 2022 Dec 1;244:183-95.

Biologics are being used with increasing frequency to manage children with uveitis, particularly those with chronic anterior uveitis, who may fail to respond to conventional therapy. Among biologics, the most commonly used are methotrexate, infliximab, and adalimumab. Others are often referred to as alternative biologic treatments (ABTs). The goal of this retrospective study was to describe the clinical outcomes and response of children with chronic anterior uveitis to ABTs. The study included 52 children (of which 75% had juvenile idiopathic arthritis). The majority of the children were being treated with conventional therapy, but 9 received ABT (1 abatacept, 3 tocilizumab, and 5 golimumab). Overall, children on ABT had a higher number of ocular complications compared to those on conventional therapy, but all 9 children demonstrated uveitis control. This study is a small study with non-randomized observation, thus limits the broader application, but it does serve as a small study demonstrating anecdotal response to ABT for children with chronic anterior uveitis.

Argon laser photocoagulation for treatment of presumed trematode-induced granulomatous anterior uveitis in children.

Alsmman AH, Abdalla A, Ezzeldawla M, Mossa EAM, Abozaid M.

Br J Ophthalmol. 2022 Dec;106(12):1667-1671. doi: 10.1136/bjophthalmol-2021-318796.

Presumed trematode-induced granulomatous anterior uveitis (PTGAU) is a relatively common anterior uveitis among pediatric patients from rural Egypt. It has been linked to swimming or bathing in the Nile river and freshwater canals. It is characterized by chronic granulomatous iridocyclitis with one or more pearl-like nodules within the anterior chamber. Current treatment options include topical and systemic steroids, antiparasitics, limbal cryotherapy and surgical excision. The authors report here a non-randomized clinical trial of 48 patients to assess argon laser photocoagulation of the pearl nodules compared to patients who received medical treatment. The AC nodule(s) disappeared in 96% of cases in the argon laser group with resolution of the AC reaction within 2–4 weeks and this response was maintained throughout the 3-month follow-up period. Initial response to medical therapy was also high, however, recurrence of AC cells and nodules was apparent in a significant number of patients by 3 months. This study demonstrates that argon laser is an effective treatment strategy for PTGAU but longer followup is needed to understand duration of results and any longer term complications.

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Long-Term Outcomes of Pediatric Idiopathic Intermediate Uveitis.

AlBloushi AF, Solebo AL, Gokhale E, Hayouti H, Ajamil-Rodanes S, Petrushkin H.

American Journal of Ophthalmology. 2022 May 1;237:41-8.

Uveitis in children is relatively rare, leading to a dearth of information regarding long-term outcomes. The goal of this retrospective study was to report clinical findings, complications, and long-term visual outcomes for children with idiopathic intermediate uveitis. This was a single center, retrospective study of 221 eyes of 125 children diagnosed with intermediate uveitis at less than 16 years of age with a median follow up on 57 months. The most common complications observed in their cohort were ocular hypertension (30%), cataract (18%), and macular edema (13%). One third of children were treated with corticosteroid-sparing agents, with methotrexate being the most common. In terms of visual acuity, the majority of children in this cohort had good vision at final follow up (93% with 20/40 or better vision). This study is slightly limited by the heterogeneity of the study population (disease severity, age of onset, etc), but does provide useful information confirming that generally, visual outcomes for children with intermediate uveitis are quite good despite the high incidence of vision threatening complications.

## 25. PRACTICE MANAGEMENT/ HEALTH CARE SYSTEMS / EDUCATION

Patient education in pediatric ophthalmology: a systematic review.

Frank T, Rosenberg S, Talsania S, Yeager L.

J AAPOS. 2022 Dec;26(6):287-293.

Poor parental comprehension of the disease process has been shown in the literature to be a key reason for failure in amblyopia therapy. The authors performed a systematic review of the PubMed database of peer-reviewed studies analyzing specific educational interventions in pediatric ophthalmology and their outcome impact. Studies meeting inclusion criteria resulted in 14 studies of which 9 were randomized controlled trials. Educational methods included: printed material alone, computer based, animated video, and multifactorial. Outcome measures included adherence, caregiver knowledge, psychological impact, visual outcome, and no-show rate. Conditions in pediatric ophthalmology can involve complicated treatment plans, some with urgency, to prevent a bad outcome (retinoblastoma, strabismus, amblyopia, retinopathy of prematurity). Literature shows that patients forget 40-80% of what they hear, written material improves recall and online material sought out may be sub-optimal. Educational interventions varied widely and were widely successful as measured by outcome measures. Subjects not receiving educational information were more likely to make errors such as patching the incorrect eye or not perform any patching. Some of the studies showed that both low and high resource utilization can result in improved adherence to treatment and clinical outcomes. Educational interventions are important in providing health equity for vulnerable populations, particularly non-native speaking groups. Limitations of this study include varied educational interventions with diverse outcomes making comparison difficult. Some studies used parent reported adherence which introduced subjectivity. Standardization of measurement of knowledge and psychological outcomes was challenging. This study shows that highly cost-effective educational interventions can improve patient knowledge, compliance and clinical outcomes.

A decline in the strabismus surgical experience of ophthalmology residents in the United States from 2010 to 2019.

Isdin Oke, MD, Gena Heidary, MD, PhD, Iason S. Mantagos, MD, PhD, Ankoor S. Shah, MD, PhD, and David G. Hunter, MD, PhD.

JAAPOS 2022;26:263-265.

This study compared the strabismus surgery numbers reported to the ACGME in the 2010-2011 academic year to those in the 2019-2020 academic year. They found a 26% decrease in strabismus surgeries over that time period. It was the only area of surgical exposure where there was a decrease in assistant cases, primary surgeon cases, and total cases. All other areas saw a decrease in assistant cases, but this was made up for with an increase in primary surgeon cases. Glaucoma and cataract cases saw an increase over the same time period. While surgical case numbers may not be a perfect proxy for overall pediatric ophthalmology exposure, this trend indicates that there is likely a decrease in the emphasis on pediatric ophthalmology in residency programs. This is concerning for 2 reasons: 1) this may lead to less residents considering a career in pediatric ophthalmology, 2) it means that general ophthalmologists will be less prepared to treat children, which will become more necessary if the number of pediatric ophthalmologists continues to decrease. There should certainly be more investigation into whether exposure to pediatric ophthalmology in residency increases the likelihood of pursuing a pediatric ophthalmology fellowship as that might then lead to increases in the ACGME minimums for strabismus surgery.

Carbon footprint of the 2021 and 2022 AAPOS annual meetings.

Constance E. West, MD, and David G. Hunter, MD, PhD.

JAAPOS 2022;26:255-257.

This paper endeavored to study the impact of converting the AAPOS meeting from an in-person format to a virtual format on carbon dioxide emissions. The cities and countries of origin were obtained for the 2021 AAPOS Annual Meeting (scheduled for Boston, MA) and the 2022 AAPOS Annual Meeting (Scottsdale, AZ). Driving emissions were calculated for those deemed close enough to drive to the meeting site and flight emissions were calculated for all other attendees. There was a total savings of 1,282 tonnes of CO<sub>2</sub> emissions due to the conversion of the 2021 AAPOS meeting to a virtual format. For the 2022 meeting in



Scottsdale, US attendees incurred 19% greater CO<sub>2</sub> emissions than if they had attended the 2021 meeting in Boston due to the meeting location relative to the population of attendees. This study likely underestimates the overall environmental impact of switching to virtual meetings as it only considers the CO<sub>2</sub> emissions associated with travel to the venues. It points out other benefits to a virtual format including gained time from lack of travel, ability to reach a more diverse group of attendees, and increased flexibility for participants with clinical or familial demands. At the same time, the benefits of in person meetings are also mentioned, including the ability to do hands-on courses and to foster comradery. Overall, I think this is an insightful paper and an important topic to consider. Likely the best arrangement for meetings will be a hybrid format or switching to every other year in person/every other year virtual. At the least, a conversation should be had on an organizational level discussing the environmental and inclusivity benefits that can come from a virtual format.

The socioeconomic effect of COVID-19 on pediatric ophthalmologists: data from the first 12 months. Lance M. Siegel, MS, MD, Brent A. Siegel, BS, Eric A. Packwood, MD, and Shira L. Robbins, MD, on behalf of the AAPOS Socioeconomic Committee. JAAPOS 2022;26:230.e1-6.

This paper assessed the financial burden of COVID-19 on the pediatric ophthalmology (PO) community 1 year after the pandemic started (April 2021). An initial study (done 1 month into the lockdown - April 2020) found that surgical revenue dropped by 82% and clinical revenue dropped by 77%. A follow-up study (17 weeks after initial lockdown – July 2020) showed persisting hardships but suggested improving trends. This study looked at the responses of 185 surveys from US practitioners. For the most recent month prior to the survey, POs reported their practices being 78% of normal surgical volume on average. Clinically, respondents' examination volume had improved to 78% of normal as well. Extrapolations were done showing that, over the course of the year, 65,000 surgeries were not performed, and 1,533,203 examinations were not performed. POs lost \$290,151 per physician practice (an estimated combine loss of \$303,188,097 for all AAPOS members). Private practices were the hardest hit when it came to salary loss. While this study is limited due to its nature as a survey, it is an important study for documenting the impact of COVID-19 on the viability of pediatric ophthalmology practices.

Time for effective cycloplegia in patients with brown iris.

Al-Omari, Rami, Atoum, Dema, Khader, Yousef, Al-Dolat, Wedad, Jammal, Hisham M., Al-Thawabieh, Wejdan, Asseidat, Ibrahim, Seetan, Khaled. Faculty of Medicine, Ophthalmology, Jordan University of Science and Technology, Irbid Strabismus, 30:1, 29-34

We aimed to evaluate the time needed for effective cycloplegia after instillation of cyclopentolate 1% in patients with brown irides. A prospective analytical study involving 161 patients (322 eyes) with a mean (SD) age of 9.0 (3.1) years (range: 3-16 years), who attended outpatient eye clinic. All had brown irides, cyclopentolate 1% was instilled two times, 10 minutes apart, spherical equivalent (SE) was calculated using readings taken by Nidek AR-1000 autorefractometer before the first drop and at 15, 30, 45 and 60 minutes after the first drop. The time for effective cycloplegia was determined from the time point at which the 95% confidence interval of the differences between the average spherical equivalent (SE) at each point and its final value at 60 minutes was reached and remained within  $\pm 0.25$  D. We found that maximum cycloplegia was reached 30 minutes after the instillation of first drop of cyclopentolate 1% in all refractive error categories (emmetropia, hyperopia and myopia) with the exception of high hyperopia subgroup (SE  $\geq +6.0$ D) where at least 45 minutes were needed to achieve cycloplegia. Additionally no clinically significant difference in the minimum time required to achieve maximum cycloplegia was noticed in subjects under 10 years old and those aged 10 years or older with both groups needed at least 30 minutes to achieve maximum cycloplegia after the instillation of first drop of cyclopentolate 1%. In this group of patients with brown irides, most children reached maximum cycloplegia after 30 minutes of instillation of cyclopentolate 1% eye drops.

The Economic Downturn of Pediatric Ophthalmology and Its Impact on Access to Eye Care.

Lee KE, Sussberg JA, Nelson LB, Thuma T.

J Pediatr Ophthalmol Strabismus. 2023;60(1):18-24. doi:10.3928/01913913-20221108-01 This survey reported the impact of the economic downturn in pediatric ophthalmology. The authors reviewed surveys

and articles examining impact of reimbursement cuts and practice pattern changes in the US. They found that these studies demonstrated a deteriorating economic situation marked by progression in reimbursement cuts, reductions in pediatric ophthalmologists accepting Medicaid patients, and dwindling numbers of residents pursuing pediatric ophthalmology fellowships. Provider-to-population relationships revealed that pediatric ophthalmologists are not evenly distributed to meet population demand, and that many states are suffering from a shortage of pediatric ophthalmologists. Furthermore, many states with high percentages of Medicaid coverage simultaneously have lower AAPOS members/million person ratios. They concluded that there was a crisis in access to pediatric eye and adult strabismus care, and that an interdisciplinary effort among health care providers and governmental officials is needed to revive the field of pediatric ophthalmology and improve access to eye care.

#### Is There a Path for an Economic Turnaround in Pediatric Ophthalmology?

Lee KE, Sussberg JA, Nelson LB, Thuma T.

*J Pediatr Ophthalmol Strabismus*. 2023;60(1):25-32. doi:10.3928/01913913-20221025-03

This survey sought to assess potential solutions for an economic turnaround in pediatric ophthalmology. The authors devised a 12-question survey which was completed by 301 pediatric ophthalmologists. Of these, 31 (10.3%) respondents used OCT in children with amblyopia, 81 (26.9%) were a partner in an ambulatory surgery center, 133 (44.2%) had an ROP financial contract arrangement with a NICU to examine premature children, and 95 (31.6%) had a financial contract arrangement with an optical shop in their office. Twenty-four (8.0%) respondents were currently in the process of being or had been bought out by a private equity investor, 52 (17.3%) owned a Spot Vision Screener (Welch Allyn) for refraction, 158 (52.5%) had hired a pediatric ophthalmology extender (pediatric optometrist, technician, or orthoptist), 87 (29.5%) had recently increased their marketing profile, and 90 (29.9%) owned the property that their practice occupied. The authors concluded that economic turnaround in pediatric ophthalmology could be done with several income-generating suggestions that simultaneously improve workforce and manpower issues, thus increasing access to pediatric eye care.

#### The Economic Factors Impacting the Viability of Pediatric Ophthalmology.

Lee KE, Sussberg JA, Nelson LB, Thuma T.

*J Pediatr Ophthalmol Strabismus*. 2022;59(6):362-368. doi:10.3928/01913913-20220817-01

This 12-question survey sought to assess the economic factors impacting the viability of pediatric ophthalmology. In the US. A total of 243 pediatric ophthalmologists completed the survey. One hundred seven (44.0%) respondents reported a surgical revenue decrease between 10% and 25%, 117 (48.1%) a clinical revenue decrease of less than 10%, 111 (45.6%) an overall income decrease of less than 10%, and 127 (52.2%) an overhead cost increase between 10% and 25%. Seventy-two (29.6%) respondents reported subsidizing income with pursuits outside of pediatric ophthalmology, 27 (11.1%) stopped operating due to reimbursement cuts, 75 (30.8%) limited the number of Medicaid or other public funded patients, 16 (6.5%) retired in the past 3 years, and 92 (37.8%) would not recommend a resident pursue a pediatric ophthalmology fellowship. The authors concluded that there was an impending upheaval coming for the field because of these factors, and a severe shortage of providers as a result.

#### Economic Impact of the COVID-19 Pandemic Post-Mitigation on Pediatric Ophthalmologists.

Thuma TBT, Sussberg JA, Nelson LB, Schnall BM.

*J Pediatr Ophthalmol Strabismus*. 2022;59(5):291-295. doi:10.3928/01913913-20220623-01

This 14 question survey sought to examine the economic impact of COVID19 and post-shutdown measures had on pediatric ophthalmologists. 129 pediatric ophthalmologists completed the survey: 84 (65.1%) respondents reported a clinical revenue decrease of greater than 10%, 83 (64.3%) a surgical decrease of greater than 10%, and 66 (51.2%) an income decrease of greater than 10%. Fifteen (11.6%) respondents reported limiting the number of Medicaid patients. This was more prevalent among those in private practice ( $P = .027$ ). Twenty-seven (20.9%) pediatric ophthalmologists responded that they planned to retire earlier than anticipated because of the pandemic and 2 (1.6%) responded that they have retired since the start of the pandemic. Six (4.7%) respondents reported that they have sold their practice since the start of the COVID-19 pandemic. The authors concluded that these economic pressures and further impending changes may create severe issues in recruiting new trainees, leading to a crisis in pediatric ophthalmology access in the US.

Gender Representation Among Presenters in Ophthalmology Subspecialties in 2019: A Retrospective Review.

Burton E, Jebaraj A, Eddington D, Brintz BJ, Simpson RG, Pettey JH.

American Journal of Ophthalmology. 2022 May 23.

Surgical sub-specialties including ophthalmology have historically been male-dominated with a significant gender gap and according to the American Academy of Ophthalmology (AAO), women represent only 24% of AAO members. The goal of this retrospective cross-sectional study was to describe gender representation at national ophthalmology conferences: AAO, American Society of Cataract and Refractive Surgery (ASCRS), American Glaucoma Society (AGS), American Society of Retina Specialists (ASRS), American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS), American Association for Pediatric Ophthalmology and Strabismus (AAPOS), North American Neuro-Ophthalmology Society (NANOS), and American Uveitis Society (AUS). They compared gender makeup by specialty based on American Board of Ophthalmology (ABO) estimates to corresponding gender makeup of presenters at the corresponding meetings. Overall, they found that the proportion of female presenters was less than expected for glaucoma, neuro-ophthalmology, and pediatric ophthalmology. When broken down by clinical versus surgical sessions, they found that women were underrepresented in surgical sessions. This paper is a call to action for subspecialties including pediatric ophthalmology to think critically and through an equity lens when considering practices for choosing and promoting speakers at the AAPOS annual meeting.

Leadership in Ophthalmology Professional Organizations: A Descriptive Analysis and Trends, 2002-2022.

Lee RH, Vinod K, Grajewski AL.

American Journal of Ophthalmology. 2023 Feb 1;246:155-62.

There has been increasing focus on the demographics of various stages of the ophthalmology pipeline: from medical school to national leadership. The goal of this study was to describe the trends in ophthalmology professional leadership over a 20-year period (2002 – 2022). Using a web based search, the authors of this study evaluated leadership of the following organizations: American Board of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, American College of Eye Surgeons, American Glaucoma Society, American Ophthalmological Society, American Society of Cataract and Refractive Surgery, American Society of Ophthalmic Plastic and Reconstructive Surgery, American Society of Retina Specialists, Association for Research in Vision and Ophthalmology, Cogan Ophthalmic History Society, Contact Lens Association of Ophthalmologists, Cornea Society, North American Neuro-Ophthalmology Society. The authors report several interesting findings. First, a large majority of leaders had subspecialty training (93%). Leaders were typically granted leadership positions more than 30 years after medical school graduation. Additionally, women accounted for only 22% of leaders. They found high levels of variability in number of publications at the time of appointment. Comparing the two 10-year periods 2002-2012 and 2012-2022, the number of female leaders doubled. Overall, 13% of leaders were pediatric ophthalmologists and this number decreased from 18.6% to 11.5% over the two 10-year periods. Overall, this study demonstrates some improvement in gender representation in ophthalmology society leadership, though further work is needed to clarify the systems in place that influence leadership demographics.

Ophthalmology Education Leadership Attitudes Toward Mentorship of Female Medical Students.

Paul M, Dweck M, Chadha N.

American Journal of Ophthalmology. 2022 Nov 1;243:149-57.

Several studies have addressed the role of gender-specific mentorship in medical student career decisions, though limited information is available regarding these trends in ophthalmology. To address this, a 22 question survey was administered to residency program directors and medical student educators, which resulted in a 30% and 41% response rate, respectively. There was no difference in the number of female mentees between male and female survey respondents (around 47% in each group). There were no statistically significant differences with regards to demographics including sub-specialty, age, self-reported race, or time in practice. Overall, female respondents felt that gender-specific mentoring was more important. This study is limited based on its status as a survey, which lends itself to selection bias (whereas those more interested in female mentorship may be more likely to respond), but

does provide interesting insight into how gender may play into mentorship and the next generation of ophthalmologists.

Qualification of non-pediatric ophthalmologists in examining children.

Mezad-Koursh D, Skaat A, Davidov B, Manaim T, Leshno A.

Eur J Ophthalmol. 2023 Jan;33(1):123-128.

This study evaluated the clinical approach of comprehensive ophthalmologists in managing pediatric patients and assessed referral patterns to pediatric ophthalmologists and orthoptists. An online survey was sent to all community ophthalmologists through national society and social media platforms. The questionnaire included questions regarding the responders' professional experience as well as management approaches to children younger than 8 years of age. 93 physicians working as general ophthalmologists completed the questionnaire. Most respondents were in practice for over 10 years (64/93, 68.8%) and over two-thirds were also hospital-affiliated (65/93, 69.1%). The responders estimated on average that  $35.1 \pm 29.6\%$  of patients under 8 years of age were referred to pediatric ophthalmology for further evaluation. The level of confidence of three aspects unique to pediatric ophthalmology including cycloplegic refraction, strabismus evaluation, and prescribing glasses was significantly lower ( $p < 0.01$ ) than the confidence level in performing a basic eye exam. The very high rate of referrals stands in contradiction to the reported low rate of ocular pathology in the pediatric population. These findings suggest that more pediatric-specific training is needed for most comprehensive ophthalmologists in order to reduce the referral burden to pediatric specialists.

Evaluation of the impact of childhood obesity on retrobulbar hemodynamics and retinal microvasculature.

Celik G, Gunay M, Ozcabi B, Gulturk U, Kizilay O, Vural A, Ozkul Saglam N, Papatya Cakir ED, Palabiyik F, Onal Gunay B, Yigit FU.

Eur J Ophthalmol. 2022 Nov;32(6):3556-3563.

The goal of this study was to evaluate changes in retrobulbar ocular blood flow parameters by using Colour Doppler Imaging (CDI) and changes in foveal microvasculature by using Optical Coherence Tomography Angiography (OCTA) in pediatric obese patients in comparison to non-obese children. Children diagnosed with obesity without hypertension and diabetes (39 subjects, obese group) and age-matched healthy controls (26 subjects, control group) underwent CDI and OCTA imaging. Peak systolic velocity, end-diastolic velocity and resistivity index from ophthalmic, central retinal and posterior ciliary arteries on CDI; superficial and deep capillary plexus vascular density and foveal avascular zone area on OCTA imaging were obtained in each group. Central foveal and subfoveal choroidal thicknesses were also measured. CDI and OCTA parameters were compared between two groups. Peak systolic and end-diastolic velocities were found to be significantly lower in obese children than in controls in all three examined arteries ( $p < 0.05$ ). Resistivity index values were similar between the groups. OCTA imaging did not reveal significant changes in superficial and deep capillary plexus vascular densities and foveal avascular zone area across analyzed retinal regions between the groups. The subfoveal choroid was thicker in the obese group compared to the control group ( $325.89 \pm 52.77 \mu\text{m}$  vs.  $304.52 \pm 21.76 \mu\text{m}$ ,  $p = 0.04$ ). These results suggest the possibility of early ocular macrovascular compromise rather than retinal microvascular impairment in childhood obesity.

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Practice Patterns of Pediatric Ophthalmologists During the COVID-19 Pandemic.

Bello NR, Nelson LB, Gunton KB.

J Pediatr Ophthalmol Strabismus. 2022;59(3):145-150. doi:10.3928/01913913-20210921-01

The purpose of this cross-sectional study was to report the use of protective personal equipment (PPE) during the coronavirus disease 2019 (COVID-19) pandemic among pediatric ophthalmologists using a 12-question multiple-choice survey. The authors reported the responses of 128 participants, of whom 87 (68.0%) were in private practice and 41 (32.0%) were in an academic setting. Of 128 respondents, 69 (53.9%) reported routinely using N95 respirators, 72 (56.3%) reported wearing medical scrubs, 41 (32.0%) reported using disposable gloves, 33 (25.7%) reported wearing goggles, and 12 (9.4%) reported using face shields during office examinations. Also, 121 (94.5%) reported having slit lamps with plastic shields and 52 (40.6%) reported having phoropters with plastic shields. In addition, 99 (77.3%) responded that they would see a patient older than 2 years who refused to wear a mask for a nonemergency visit. The authors concluded that PPE practice varied widely among pediatric ophthalmologists during the

COVID-19 Pandemic, but admitted that the survey design did not differentiate patterns before and after the availability of vaccines.

Income Disparities in Outcomes of Horizontal Strabismus Surgery in a Pediatric Population.

Zdonczyk AN, Gupte G, Schroeder A, Sathappan V, Lee AR, Culican SM.

J Pediatr Ophthalmol Strabismus. 2022;59(3):156-163. doi:10.3928/01913913-20210824-02

This single-center retrospective review sought to examine the potential impact of SES on pediatric patients undergoing horizontal strabismus surgery, using PEDIG surgical failure criteria: undercorrection w/ misalignment >10PD at near or distance, overcorrection with misalignment >6PD at near or distance, or undergoing a reoperation. The authors reported the outcomes of 284 subjects and found that there was no difference in failure rates between patients with Medicaid and patients with private insurance 24 months postoperatively (45.9% vs 50.5%, respectively,  $P = .46$ ). Patients with Medicaid were more likely to not follow up postoperatively (28.2% vs 9.6%, respectively,  $P < .01$ ), whereas patients with private insurance were more likely to complete more than three follow-up appointments in 24 months (21.5% vs 39.0%, respectively,  $P < .01$ ). Postoperative attendance was linked to Medicaid status ( $P < .01$ ) but not travel time, neighborhood income levels, or social deprivation index factors. The authors concluded that although there was no difference in failure rates between patients with Medicaid and patients with private insurance, Medicaid status was significantly predictive of loss to follow-up. The authors cited retrospective design and unequal group distributions as limitations, and although they addressed rationale for choosing 11 months as the minimum follow-up period for inclusion, they noted that only 62% of patients who ended up meeting failure criteria by 24 months did so by 11 months.

Is YouTube a Useful Tool for Trainees in Pediatric Cataract Surgery?.

Fouzdar Jain S, Eggleston C, Larson SA, Suh DW.

J Pediatr Ophthalmol Strabismus. 2022;59(3):200-203. doi:10.3928/01913913-20211111-01

This study sought to determine the utility of surgical videos published on YouTube (Google) as resources for trainee education in pediatric ophthalmology. The authors searched “congenital cataract surgery” and “pediatric cataract surgery” and then applied exclusion criteria to the most viewed videos, yielding a Top 10 list. These videos were independently reviewed by three separate board-certified, fellowship-trained, practicing pediatric ophthalmologists. Videos were assessed for surgical competency on a 5-point Likert scale in six key areas as outlined in the American Academy of Ophthalmology’s congenital cataract surgery guidelines. The teaching quality of the videos was also subjectively assessed based on multiple measures. The mean overall score was  $3.93 \pm 0.94$  (range: 2.67 to 4.67). Only one video failed to receive an overall score of greater than 3, indicating incompetent overall surgical performance. No other video failed to have a mean competent score for any single individual technique. One video demonstrated potential patient safety concerns. Eighty percent of videos had adequate or better picture quality. The authors concluded that if used correctly, YouTube could be a useful tool for trainee education, but caution must be exercised because of potential publication of unvetted or harmful content.

Comparing the diagnostic accuracy of telemedicine utilization versus in-person clinical examination for retinopathy of prematurity in premature infants: a systematic review.

Wanjin Li, BMSc, Ronald Cheung, BMSc, and Monali S. Malvankar-Mehta, PhD.

J AAPOS 2022; 26:58.e1-7.

ROP screening is important to limit visual impairment in premature infants; however, there are logistical challenges to in person screening. This study aimed to compare the accuracy of telemedicine to ophthalmic examination for ROP detection. Over 500 studies were identified and screened, 14 studies were deemed eligible and were included in the final qualitative review. Virtually every study found that telemedicine compared favorably with in-person examination in detecting ROP. Sensitivity and specificity ranged from 70-100%. The sensitivity for treatment-requiring disease was particularly high with several studies showing 100% sensitivity. This paper is important as it shows that telemedicine can be incorporated into ROP screening while still maintaining a high level of care.

Unmet needs for vision care among children with gaps in health insurance coverage.

Mufida Muhammad, BS, and Dmitry Tumin, PhD.

J AAPOS 2022; 26:63.e1-4.

Vision care for children can be impacted by availability and type of health insurance coverage. Prior studies have focused on differences in care based on type of insurance; however, this study aims to look at the increased risk of unmet needs for vision care related to gaps in coverage. The authors used the National Survey of Children's Health to analyze whether experiencing a gap in health insurance coverage was associated with a greater likelihood of caregiver-reported unmet needs for vision care. They also looked at whether gaps in insurance coverage were associated with lower likelihood of completing an annual vision screening. In the sample of 106,876 children, 3.8% had a recent gap in insurance coverage and 5% lacked insurance for the entire year. Compared with children who had year-round private insurance coverage, the odds of caregiver-reported unmet needs for vision care were nearly 19 times high among kids with gaps in coverage. Children with gaps in coverage had 40% lower odds of completing an annual vision screening exam when compared to children with year-round private coverage. This study highlights the negative impact that gaps in insurance coverage can have on children getting the eye care that they need. It should encourage public policy interventions that expand public health insurance, decrease requirements for enrollment/re-enrollment, and eliminate premiums.

Time for effective cycloplegia in patients with brown iris.

Al-Omari, Rami, Atoum, Dema, Khader, Yousef, Al-Dolat, Wedad, Jammal, Hisham M., Al-Thawabieh, Wejdan, Asseidat, Ibrahim, Seetan, Khaled. Faculty of Medicine, Ophthalmology, Jordan University of Science and Technology, Irbid  
Strabismus, 30:1, 29-34

We aimed to evaluate the time needed for effective cycloplegia after instillation of cyclopentolate 1% in patients with brown irides. A prospective analytical study involving 161 patients (322 eyes) with a mean (SD) age of 9.0 (3.1) years (range: 3-16 years), who attended outpatient eye clinic. All had brown irides, cyclopentolate 1% was instilled two times, 10 minutes apart, spherical equivalent (SE) was calculated using readings taken by Nidek AR-1000 autorefractometer before the first drop and at 15, 30, 45 and 60 minutes after the first drop. The time for effective cycloplegia was determined from the time point at which the 95% confidence interval of the differences between the average spherical equivalent (SE) at each point and its final value at 60 minutes was reached and remained within  $\pm 0.25$  D. We found that maximum cycloplegia was reached 30 minutes after the instillation of first drop of cyclopentolate 1% in all refractive error categories (emmetropia, hyperopia and myopia) with the exception of high hyperopia subgroup (SE  $\geq +6.0$ D) where at least 45 minutes were needed to achieve cycloplegia. Additionally no clinically significant difference in the minimum time required to achieve maximum cycloplegia was noticed in subjects under 10 years old and those aged 10 years or older with both groups needed at least 30 minutes to achieve maximum cycloplegia after the instillation of first drop of cyclopentolate 1%. In this group of patients with brown irides, most children reached maximum cycloplegia after 30 minutes of instillation of cyclopentolate 1% eye drops.

Reliability of telemedicine for real-time pediatric ophthalmology consultations.

Stewart C, Coffey-Sandoval J, Reid MW, Ho TC, Lee TC, Nallasamy S.

Br J Ophthalmol. 2022 Aug;106(8):1157-1163.

This study was a prospective, non-inferiority study assessing agreement in diagnosis and management plan between telemedicine and in-person examinations at a single institution conducted 2016-2018. A pediatric optometrist on the patient's side conducted the telemedicine examination, while a pediatric ophthalmologist watched in real time and counselled the family on her findings and plan. To determine the accuracy of the telemedicine examination, the pediatric ophthalmologist subsequently re-examined the patient in-person later the same day, but the participants did not know this second exam would take place at the time of recruitment and participation in the telemedicine visit. Noninferiority threshold was  $<1.5\%$  for management plan or  $<15\%$  for diagnosis discrepancies. The primary outcome measure was agreement in diagnoses and management plans between the telemedicine and in-person evaluations. Two hundred ten patients age 0-17 years (median age=6 years) participated with at least one parent. 62% of patients were primarily diagnosed with strabismus (n=131); other common primary diagnoses included eyelid abnormalities (n=12), glaucoma suspect (n=10) and conjunctival disorders (n=9). No primary diagnoses were changed between the telemedicine and in-person examinations, and no management plans, including surgical plans, were changed following in-person examination. 62 subjects

went on to have surgery, and 54/55 who consented for surgery at the initial visit did so during the telemedicine examination, while masked to receiving an in-person examination. Only 11.% of all exams experienced some sort of delay related to equipment challenges. Nearly all parents felt comfortable with the quality of the telemedicine examination (98.5%) and reported they would participate in another one in the future (97.1%). This study suggests that pediatric ophthalmic conditions can be reliably managed through real-time telemedicine , potentially addresses the specialist shortage, increases surgical volume, and improves access to care for underserved children.

Trends in Racial and Ethnic Diversity of Ophthalmology Residents and Residency Applicants.

Aguwa UT, Srikumaran D, Canner J, O'Rese JK, Scott AW, Green L, Woreta F.

American Journal of Ophthalmology. 2022 Aug 1;240:260-4.

Ophthalmology is significantly behind many medical and surgical sub-specialties with regards to racial and ethnic diversity of trainees. This is also reflected in the proportion of underrepresented in medicine (URiM) trainees compared to population proportions. This study evaluated the demographic data of all ACGME residency programs between 2011-2019 and compared this to data from ophthalmology residency applicants over the same time period. Overall, the authors found that the percentage of URiM ophthalmology residents increased from 4.7% to 5.8%. This is much lower than other surgical subspecialties, though other surgical subspecialties saw a decrease from 9.9% to 9.1% over this time period. The authors conclude that while some small strides have been made in terms of representation of URiM applicants and trainees in ophthalmology, work is needed to address the lack of diversity in our field. Specific programs and interventions, including the American Academy of Ophthalmology's Minority Ophthalmology Mentorship program, are discussed.