Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Myopia Rate Increasing in Taiwanese Children

February 2021

Tsai et al. analyzed population-based data to better understand myopia rates among schoolchildren in Taiwan. They found that myopia prevalence has risen rapidly in this group since 1983. Major risk factors are older age and heavy involvement in near-work activities.

For this study, the authors looked at findings of eight population-based surveys on myopia that were conducted from 1983 through 2017 in children between the ages of 3 and 18. The number of participants per survey ranged from 5,019 to 11,656. Comprehensive ophthalmic evaluations were performed, and tropicamide 0.5% was applied to obtain cycloplegic refractive status. Myopia and high myopia were defined as spherical equivalents at or below –0.25 D and –6.0 D, respectively. Multivariate analyses were used to determine risk factors.

Results showed that myopia prevalence climbed steadily in all age groups during the study period. For example, the weighted prevalence rose from 5.37% to 25.41% among 7-year-olds and from 30.66% to 76.67% for 12-year-olds during this period (p = .001 for both trends). The prevalence of high myopia grew from 1.39% to 4.26% among 12-year-olds (p = .008) and from 4.37% to 15.36% among 15-year-olds (p = .039). In the 2005 and 2016 population surveys, children who spent <180 minutes/day on near work were less likely to develop myopia. The 2016 data showed that spending more than one hour a day on electronic devices increased the likelihood of myopia and high myopia (OR, 2.43 and 2.31).

The authors noted that their definition of myopia and choice of cycloplegic agent may have contributed to the relatively high prevalence of myopia in their study, especially in the assessment of the youngest children. Other experts reported that up to four drops of 1% cyclopentolate may be needed to accurately measure refractive error in some young children. These issues require exploration in carefully designed multicenter studies, said the authors. They recommend that eye care specialists and policymakers be cognizant of the increase in near-work time that stems from greater use of electronic devices.

The Downside of Pre-Op Testing for Cataract Surgery

February 2021

Patients scheduled for cataract surgery have a higher risk of falls if their surgery is delayed, but the effect of delays due to preoperative testing is not known. **Chen et al.** reviewed nine years of claims data to explore whether testing practice leads to harm for those patients who are awaiting cataract surgery. They found that pre-op medical testing often is overused and thereby may increase the likelihood that fall-related harm will occur before cataract surgery takes place.

This study included a 5% sample of Medicare beneficiaries (>65 years of age) who had undergone ocular biometry in the period 2006-2014. The authors gathered data and calculated the mean and median number of days between biometry and cataract surgery, as well as the proportion of patients who waited ≥30 days and ≥90 days for their surgery and the number who had a fall within 90 days of biometry.

Physicians were categorized as "high testing" or "low testing" according to the percentage of their patients who underwent biometry (≥75% or <75%, respectively), and the number of "delay days" was estimated for each group. Main outcomes were the incidence of falls between biometry and surgery, the odds of falling within 90 days of biometry, and the delay time associated with high and low testing levels.

Among the 248,345 beneficiaries in the study, 16.4% were patients of high-testing physicians. Of these 31.4% waited ≥30 days and 25% waited ≥90 days for their surgery, versus 8.2% and 5.5%, respectively, of those treated by
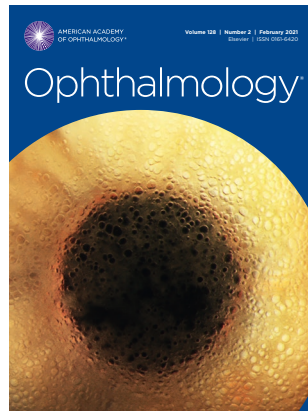
low-testing physicians. Among patients of high-testing physicians, a 43% increase in "fall events" occurred prior to surgery in the 90 days following biometry (1.0% vs. 0.7%; p < .0001). The adjusted odds ratio for falling within 90 days of biometry in patients of high-testing versus low-testing physicians was 1.10 (95% confidence interval [CI], 1.03-1.19; p = .008). After adjusting for surgical wait time, the odds ratio became 1.07 (95% CI, 1.00-1.15; p = .06). The delay for patients of high-level testers was 7.97 days longer than for patients of low-level testers (95% CI, 6.40-9.55 days; p < .0001).

Other factors linked to surgical delay included patient race (non-White), Northeast U.S. location, younger ophthalmologist (≤40 years of age), and lower surgical volume.

What Drives Noncompliance to AMD Treatment?
February 2021

In a literature review, **Okada et al.** examined factors that result in departure from clinical trial regimens (nonadherence) and lack of persistence in following recommended regimens (nonpersistence) in anti-VEGF injection therapy for neovascular age-related macular degeneration. They found myriad complex reasons for noncompliance, with the greatest overall barrier being treatment burden. Additional contributing factors included low baseline vision, poor treatment response, and concerns about COVID-19.

The authors evaluated publications that mention factors for nonadherence or nonpersistence to anti-VEGF therapy, as well as reports of strategies to address this matter. Cochrane review methods were applied to determine eligibility and to extract data, which were collated descriptively. Bias risk was estimated with the mixed-method assessment tool, and certainty of evidence was assessed using the GRADE tool.

Among the 37 full-text articles that met inclusion criteria, definitions of nonadherence and nonpersistence varied or were not stated. Up to 50% of patients stopped treatment within 24 months of starting it. Rates of nonad-

herence were high, ranging from 32% to 95%. However, the certainty of this finding was deemed only moderate because of the differing definitions of nonadherence. Although many factors contributed to nonadherence and nonpersistence, the most significant barrier to regimen compliance was treatment burden, including visit frequency and travel time. Condition-level factors with moderate evidence for nonadherence/nonpersistence were lower baseline vision and poorer response to treatment.

Although some factors cannot be changed (such as comorbidities), others are potentially modifiable, the authors said. Evidence of strategies to improve treatment compliance is minimal, but what evidence there is shows such efforts to have been successful.

—*Summaries by Lynda Seminara*

Ophthalmology Glaucoma
Selected by Henry D. Jampel, MD, MPH

Endothelial Cell Loss After Baerveldt Implant Surgery
January/February 2021

Hau et al. set out to assess changes in corneal endothelial cell density (ECD) following insertion of a Baerveldt glaucoma implant and to determine prognostic factors for ECD loss. They found

that ECD loss is greatest close to the tube. Moreover, they found that short tube length and tube insertion in the vicinity of—or anterior to—Schwalbe line (SL) were predictive of greater ECD loss over time.

For this prospective study, 72 patients (72 eyes) were recruited from a single clinic. All implants were placed in the superotemporal quadrant via a limbal conjunctival peritomy. Primary outcomes were central and peripheral corneal ECD loss at five years. Secondary outcomes included tube parameters as noted on optical coherence tomography, tube position relative to SL, anterior chamber flare, and clinical factors such as intraocular pressure (IOP).

No intraoperative surgical complications were noted. Postoperatively, six instances of hypotony without shallowing of the anterior chamber, one case of diplopia, and one case of hyphema occurred. In addition, three patients required further surgical procedures within the next three years.

All told, 64 patients (64 eyes) completed the study. The researchers observed a steady loss of ECD with time. At the five-year mark, the percentage of cell loss from baseline was 36.8% (range, 32.3% to 41.3%) for central corneal ECD and 50.1% (range, 45.3% to 54.9%) for peripheral corneal ECD. This equates to an average rate of loss

IRIS Registry Snapshot: Uveitis Dx and Tx

Verana Health analyzed statistically de-identified electronic health record (EHR) data from the Academy's IRIS Registry to assess the number of uveitis diagnoses in the United States, the location of the uveitis, and the location of steroid injections for treatment. The results include newly diagnosed cases.

Results. All told, 662,925 eyes were diagnosed with uveitis from Jan. 1, 2016, to Nov. 6, 2020, and 193,432 eyes received a steroid injection.

Disease location. Anterior uveitis was diagnosed in 523,120 eyes (78.9%), and posterior disease was diagnosed in 163,678 eyes (24.7%). (Percentages add up to more than 100%, as some eyes had both anterior and posterior disease.)

Injection type. Intravitreal injections took place in 123,210 eyes (63.7%), while 86,664 eyes (44.8%) received sub-Tenon injections. (Percentages add up to more than 100%, as some eyes received injections in both locations.)

Trend rates. During the study period, trends in rates of anterior versus posterior uveitis remained stable, as did the injection site and the number of diagnoses.

Note: The Academy has partnered with Verana Health to curate and analyze IRIS Registry data.

of 7.4% per year for central corneal ECD and 10% per year for peripheral corneal ECD in the area of the tube.

With regard to secondary outcomes, tube placement was the strongest predictor of cell loss: The fastest rate of cell loss was associated with tube location in the vicinity of SL or anterior to it. In addition, a shorter tube length was a strong predictor for a lower peripheral corneal ECD at five years.

The researchers noted that, in conjunction with evidence provided from other recent studies, the tube distance from the cornea and the insertion site of the tube into the drainage angle appear to be key predictors of ECD loss. Thus, they concluded, placing the tube entry site posterior to SL and placing a longer tube, positioned away from the cornea, may be preferable surgical strategies. —*Summary by Jean Shaw*

Ophthalmology Retina
Selected by Andrew P. Schachat, MD

Scleral Buckling Plus PPV for Retinal Detachment Repair
February 2021

Scleral buckling (SB) plus pars plana vitrectomy (PPV) for repair of rhegmatogenous retinal detachments (RRDs) remains controversial. **Echegaray et al.** compared the outcomes of primary uncomplicated RRD repair using PPV alone with those achieved via the combination of SB and PPV. They found that SB + PPV resulted in greater single-operation anatomic success (SOAS), particularly among phakic eyes.

This retrospective observational study of 488 patients (mean age, 59.2 years) was conducted at the Bascom Palmer Eye Institute from June 1, 2014, through Dec. 31, 2017. Patients younger than age 18 were excluded, as were those with advanced proliferative vitreoretinopathy, giant retinal tear, trauma, or secondary forms of RRD.

With regard to preoperative lens status, 288 of the patients (59%) were phakic, 188 (38.5%) had a posterior chamber IOL, and eight (1.6%) were aphakic. The extent of the RRD involved 3 clock hours or more in 447 patients (91.6%), and inferior RRD location was found in 265 patients (54.3%).

After a mean follow-up of 14.3 months, SOAS (defined as adequate retinal reattachment with only one procedure) and final anatomic success were achieved in 425 eyes (87.1%) and 487 eyes (99.8%), respectively. SOAS occurred in 90 of 111 eyes (81.1%) treated with PPV alone, compared with 345 of 374 eyes (92.2%) that underwent the combined procedure. In addition, in those treated with SB + PPV, greater SOAS occurred in phakic eyes (p < .0001) than in those with a posterior chamber IOL. In addition, SOAS was correlated with greater improvement in best-corrected visual acuity.

A retinal redetachment occurred in 63 patients (12.9%). Of these, 50 were affected within the initial three months following surgery (mean, 1.5 months), while the remaining 13 patients experienced redetachment after the three-month period (mean, 9.3 months). The authors noted that this bimodal distribution may inform optimal follow-up regimens. —*Summary by Jean Shaw*

American Journal of Ophthalmology
Selected by Richard K. Parrish II, MD

Respiratory Droplets Transmitted During Slit-Lamp Exams
February 2021

Shah et al. constructed a simulated slit-lamp examination to evaluate the effectiveness of personal protective equipment worn during the exam. They found that wearing a mask reduced the spread of simulated respiratory droplets—and that adding a slit-lamp shield provided extra protection.

For this study, the researchers used a pressurized spray canister to simulate both patient breathing and coughing. The canister contained fluorescent material, which was sprayed and then viewed using a handheld ultraviolet flashlight. The researchers measured the velocity and distance of particle emissions for "breathing" and "coughing"—and then assessed the ability of surgical masks and slit-lamp shields to block the droplets. (Model 3D printed heads served as stand-ins for human patients and clinicians.)

Without a slit-lamp shield or masks in place, the fluorescent droplets were widely dispersed. With both the coughing and breathing simulations, droplet dispersion was lowest when both patients and clinicians wore masks; however, particles still escaped from the top of the patient's mask, lateral to the nose. Although the slit-lamp shield blocked most of the dispersed particles, a substantial amount reached the slit-lamp joystick and table.

Subtyping Idiopathic Uveitis by Gene Expression
February 2021

Rosenbaum et al. set out to test the hypothesis that idiopathic uveitis may have subtypes, based on gene expression. They found that gene expression profiling was 85% accurate when uveitis was associated with one of four systemic diseases.

The authors used RNA sequencing to characterize the gene expression profile in peripheral blood collected from patients with uveitis associated with axial spondyloarthritis (n = 17), sarcoidosis (n = 13), inflammatory bowel disease (n = 12), or tubulo-interstitial nephritis (n = 10). They also determined gene expression levels for 18 healthy control subjects.

In addition, peripheral blood gene expression was characterized for 38 patients with idiopathic uveitis to determine if a likely diagnosis could be established from the transcriptional signature. A high-dimensional negative binomial regression model was used to compare each disease group with the control subjects, and the 20 most distinctive genes for each diagnosis were extracted. All told, 80 genes were extracted; of these, 75 were found to be unique. From these unique genes, the authors devised a classification algorithm by fitting a gradient boosting tree with fivefold cross-validation. They assessed the algorithm's utility by calculating diagnostic probability for each case of idiopathic uveitis.

Overall, gene expression profiling was 85% accurate when the uveitis was ascribed to one of the four diseases.

Although many patients with idiopathic uveitis may not have one of these systemic diseases, the gene expression profile helped determine the probable diagnosis in 11 of the 38 idiopathic cases (29%). —*Lynda Seminara*

JAMA Ophthalmology

Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

Retinal Vascular Occlusion and Hormone Therapy in Women
January 2021

Does taking an oral contraceptive or estrogen replacement therapy raise a woman's risk of retinal vascular occlusion (RVO)? **Song et al.** set out to determine whether filling a prescription of female hormone therapy (FHT) is associated with an increased risk of RVO or retinal artery occlusion (RAO) in women. They found no increase in risk.

For this study, the authors used an administrative claims insurance database. Multiple cohorts were created based on whether a FHT prescription was filled for all women 18 years or older. Patients were excluded if they had less than two years in the plan, had not undergone a previous ophthalmic exam, or had a history of RAO or RVO. They also were excluded if they had a systemic disease or took medications that affected their estrogen levels or if they had a disease associated with an increased risk for thromboembolism.

A total of 205,304 women who filled a prescription for FHT were matched to 755,462 control patients. The primary outcome was the incidence of a new diagnosis of RAO or RVO. Cox proportional hazard regression modeling with inverse probability of treatment weight (IPTW) was used to assess the hazard ratio (HR) for a new diagnosis of RAO or RVO relative to filling an FHT prescription. The researchers also conducted subanalyses to stratify by age, race/ethnicity, and the presence of diabetes and hypertension.

All told, there were 41 cases of RAO (.01%), 68 cases of RVO (.02%), and 111 combined RAO/RVO outcomes (.03%) in the FHT prescription group,

versus 373 RAO cases (.05%), 617 RVO cases (.08%), and 1,003 combined cases (.13%) in the control cohort. With IPTW analysis, no difference was seen in the likelihood of developing RAO (HR, 1.17; 95% confidence interval [CI], 0.83-1.65; p = .36), RVO (HR, 1.07; 95% CI, 0.82-1.39; p = .65), or the combined outcome (HR, 1.10; 95% CI, 0.89-1.36; p = .37) when those who took FHT were compared with controls. Moreover, after stratification by age, diabetes, and hypertension, no significant difference was found between those who took FHT and controls with regard to incidence of RAO, RVO, or RAO/RVO.

The authors pointed out that this study has several limitations, including the inability to confirm that patients consistently took their FHT after filling their prescriptions.

Glaucoma Macular Damage Patterns and Visual Disability
January 2021

Hirji et al. evaluated the link between diffuse and focal patterns of glaucomatous macular damage and visual disability experienced by patients with glaucoma. They found that diffuse macular damage was more likely to be associated with impairments in both contrast sensitivity (CS) and facial recognition. They noted that although diffuse damage may be more difficult to identify than focal damage, it is an important determinant of visual function.

For this prospective cohort study, the researchers evaluated 72 patients (144 eyes) with glaucoma and visual acuity of 20/40 or better in each eye. They excluded patients with visually significant cataract, posterior capsular opacification, severe dry eye, macular disease, or miotic pupils.

Glaucomatous eyes were categorized as having focal, diffuse, or mixed macular damage, based on optic disc and macular spectral-domain optical coherence tomography (SD-OCT) scanning and 10-2 visual field (VF) testing. Better- and worse-acuity eyes were determined by 10-2 VF mean deviation (MD). Facial disability was defined as facial recognition scores at the 2% level

of normal participants. Primary outcomes were monocular threshold and binocular facial recognition.

Of the 72 better-seeing eyes, 44 (61%) had macular damage. Of those, 22 (50%) had focal damage, 15 (34%) had diffuse damage, and the remaining seven (16%) had mixed focal and diffuse damage. Of the 72 worse-seeing eyes, 63 (88%) had macular damage. Of those, 26 (41%) had focal damage, 19 (30%) had diffuse damage, and the remaining 18 (29%) had mixed damage.

After the researchers adjusted for a number of potential confounding factors, the results indicated that eyes with diffuse damage had greater CS impairment than did those with focal damage (b = –0.5; 95% confidence interval [CI], –0.7 to –0.3; p < .001). With regard to facial recognition scores, better-seeing eyes with focal damage recognized 10 more faces than did those with diffuse damage (95% CI, 2-18.2; p = .001). Worse-seeing eyes with focal damage recognized 5.5 more faces than did those with diffuse damage (95% CI, 0.8-10; p = .02).

Given the impact of macular damage on patients' quality of life, the researchers said that careful evaluation of the macular OCT and 10-2 VF and early detection of diffuse macular damage are critical to minimize glaucoma-related visual disability.

FDA Conference Report: Ophthalmic Laser-Based Imaging
January 2021

In April 2019, the FDA convened a forum on optical coherence tomography (OCT) and other laser-based imaging, including adaptive optics (AO) and scanning laser ophthalmoscopy (SLO). Highlights of the forum, as summarized in a special report by **Brodie et al.**, include the following:
• Overview: OCT has become a valuable tool, furthering the diagnosis, management, and understanding of eye disease. FDA officials noted that efforts to streamline premarket evaluation of OCT devices are underway.
• Clinical applications: Applications of OCT technology to anterior segment disease include the use of intraopera-

tive OCT (iOCT) during surgery and the use of OCT to provide prognostic information on intraocular pressure changes following surgical procedures and to aid in intraoperative assessment of challenging corneal transplant cases. For posterior segment disease, presenters emphasized that the influence of OCT is impossible to overstate, as it has revolutionized the evaluation and management of many vitreoretinal diseases.

• Emerging technologies: Advances in OCT angiography, visible-light OCT, and iOCT were discussed, as was the use of artificial intelligence in conjunction with OCT in both the anterior and posterior segments.

• Current challenges: On the clinical side, the pursuit of greater accuracy and precision continues, as does the need for greater understanding of normal variance across age, race, and sex as well as variance that can be attributed to a particular device or to environmental factors. On the nonclinical side, imaging reimbursement continues to present a considerable challenge.

• Adaptive optics: At present, AO remains in the vision research domain. It can be used with OCT as well as with SLO. AO allows for dynamic sensing and correction of the optical aberrations in an individual's eye as well as aberrations that may arise in an individual imaging system. Although AO shows potential for tracking disease progression and treatment response, more research is needed on accuracy and safety, the presenters said.

—*Summaries by Jean Shaw*

Other Journals

Selected by Prem S. Subramanian, MD, PhD

Teprotumumab for Inactive TED
Eye
Published online Nov. 21, 2020

Teprotumumab, an insulin-like growth factor 1 receptor (IGF-1R) inhibitor, has been found to reduce proptosis and inflammation in active thyroid eye disease (TED). **Ugradar et al.** investigated whether the drug also could clinically benefit patients with inactive TED characterized by progressive strabis-

mus, proptosis, or optic neuropathy but no inflammation—a group for whom there is no accepted medical treatment. They found that teprotumumab reduced IGF-1R expression in patients with inactive disease relative to controls. They also determined that overexpression of IGF-1R was significantly more pervasive in cases of inactive and active TED than in controls.

In this clinical series, consecutive patients who had noninflammatory TED for at least four months (clinical activity score [CAS] ≤1) received a full course of teprotumumab (eight infusions total; 10 mg/kg initially, followed by 20 mg/kg every three weeks). The primary outcome measure was proptosis response at week 24. In addition, orbital tissues from patients with either stage of TED and healthy controls were histologically analyzed for expression of IGF-1R α and β.

A total of four patients (age range, 21-47 years) met the study's eligibility criteria. Before treatment, their mean (standard deviation [SD]) CAS was 0 (0). After treatment, their mean (SD) proptosis value decreased by 2.6 mm (1.2; p < .01), but their CAS and diplopia scores remained at 0.

For the histological analysis, samples were obtained from five patients with noninflammatory TED, five patients with inflammatory TED, and five controls (age range, 29-70 years). The mean numbers of regions staining positive for IGF-1R α and β antibodies differed significantly between noninflammatory and inflammatory TED (both p < .01) and between noninflammatory TED and controls (both p < .01).

Despite the small sample size, the significant reduction in proptosis attained with teprotumumab in noninflammatory TED suggests its potential as medical therapy, said the authors.

Do Structural Changes Truly Precede Functional Changes in Glaucoma?
Investigative Ophthalmology & Visual Science
2020;61(13):5

Some evidence suggests that structural changes occur before functional decline

takes place. Using structural equation models (SEMs) and biannual testing, **Gardiner et al.** explored whether a lag exists between true change in structure (retinal nerve fiber layer thickness [RNFLT]) and function (standard automated perimetry [SAP]) in patients with glaucoma. They found that the rate of functional change in a given interval was predictive of the rate of structural change in the subsequent interval, whereas the converse was not true—even though more eyes showed detectable changes in RNFLT than in SAP.

Data were collected for 164 patients diagnosed as having open-angle glaucoma or likelihood of developing glaucoma from the Portland Progression Project, an ongoing longitudinal study of progression and diagnostic testing in glaucoma. Rates of change were calculated for 318 eyes during 1,135 pairs of consecutive visits, with a mean of 207 days (range, 161-364 days) between visits. SEMs were applied to determine whether the rate of change in structure (RNFLT) or function (mean linearized total deviation [AveTDLin]) could be predicted by the concurrent or previous rate for the other modality after adjustment for its own rate in the preceding period.

Analyses showed that the rate of change in AveTDLin was predicted by its own rate in the previous interval but not by the rate of RNFLT change in the concurrent or previous interval (both p > .05). Similarly, the rate of RNFLT change was not predicted by concurrent AveTDLin change after adjustment for its own previous rate. However, the rate of AveTDLin change in the previous interval was significant for predicting the current rate of RNFLT change (p = .005) and suggested a period of about six months between AveTDLin and RNFLT changes.

Despite the lag observed in this study, the authors cautioned that the finding does not invalidate previous research suggesting that RNFLT may be detectable sooner. They encouraged the development of less variable functional tests, along with use of alternative structural measures, to improve damage detection and disease prognosis.

—*Summaries by Lynda Seminara*