# Journal Highlights

## *Ophthalmology*

Selected by Stephen D. McLeod, MD

### CXL Halts Keratoconus Progression in Children
November 2021

**Larkin et al.** assessed the efficacy and safety of corneal cross-linking (CXL) in slowing keratoconus progression in children. They found that, compared with standard care alone, adjunctive CXL resulted in flatter corneas and better visual acuity (VA).

For this study, known as Keralink, the researchers included patients aged 10 to 16 years who were experiencing progressive keratoconus. One eye of each patient was designated as the study eye. Each study eye was assigned randomly to receive CXL plus standard care (CXL group) or standard care only (control group). Standard care was defined as spectacle or contact lens correction to improve vision. The primary outcome measure was steep keratometry (K2) in the study eye 18 months after randomization. Key secondary outcomes included keratoconus progression (defined as an increase of 1.5 D in K2) as well as uncorrected and corrected VA.

Overall, 58 eyes (58 patients) were analyzed, with 28 in the control group and 30 in the CXL cohort. Mean K2 at 18 months was 49.7 D in the CXL group (standard deviation [SD], 3.8 D) and 53.4 D in controls (SD, 5.8 D). The adjusted mean K2 difference was −3.0 D (p = .002), favoring CXL treatment. Similarly, the adjusted between-group differences in uncorrected and corrected VA favored CXL: −0.31 logMAR and −0.51 logMAR, respectively (both p = 0.002). Keratoconus progressed in two CXL-treated eyes (7%) and in 12 control eyes (43%). The unadjusted odds ratio (0.1) suggests that the likelihood of disease progression was 90% lower in the CXL group (p = .004).

In light of these findings, CXL may merit consideration as a first-line treatment option for young patients with progressive keratoconus, the authors said.
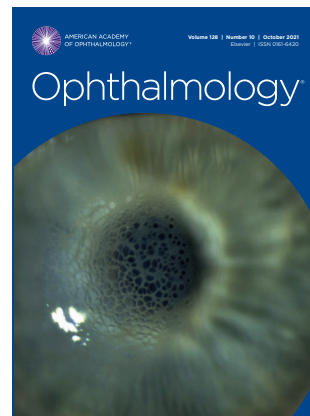
Additionally, the authors hypothesized that if "the arrest of keratoconus progression induced by CXL is sustained in longer follow-up, particular benefit may be derived from avoiding a later requirement for contact lens wear or corneal transplantation."

### Deep Learning Provides Insight Into Visual Function in Glaucoma
November 2021

**Christopher et al.** developed combination deep learning (DL) models that improve the estimates of visual function obtained from macula-centered spectral-domain OCT (SD-OCT). They found that these models may help physicians devise appropriate treatment plans for their patients with glaucoma.

The researchers set out by training DL models on thickness maps from SD-OCT macular images to estimate 10-2 and 24-2 visual field (VF) mean deviation (MD) and pattern standard deviation (PSD). They trained separate and combined DL models using data for six layers: retinal nerve fiber layer, ganglion cell layer, inner plexiform layer (IPL), ganglion cell-IPL (GCIPL), ganglion cell complex, and the retina itself. Combination models that incorporated data for all six layers were constructed using linear regression. Each model was equipped only with thickness maps or mean measurements derived from SD-OCT, not with labels of disease status or severity.

Findings for these models were compared with VF measurements. SD-OCT images of each study eye were paired with 10-2 and 24-2 VF findings. Primary outcome measures were $R^2$ and mean absolute error.

Altogether, the researchers assessed 2,408 SD-OCT/10-2 VF pairs and 2,999 SD-OCT/24-2 VF pairs. Images and data were obtained for healthy participants and for patients with suspected or confirmed glaucoma. The 10-2 cohort included 1,051 eyes (563 subjects), and the 24-2 cohort included 1,205 eyes (641 subjects); 1,037 eyes (560 subjects) were common to both cohorts.

The combined DL models estimating 10-2 achieved $R^2$ of 0.82 for MD and

0.69 for PSD; mean absolute error was 1.9 dB for MD and 1.5 dB for PSD. These findings were significantly more accurate than thickness estimates for 10-2 MD (0.61 $R^2$, 3.0 dB) and 10-2 PSD (0.46 $R^2$, 2.3 dB). The combined DL models estimating 24-2 achieved $R^2$ of 0.79 for MD and 0.68 for PSD; mean absolute error was 2.1 dB for MD and 1.5 dB for PSD. The DL models outperformed mean thickness estimates for 24-2 MD (0.41 $R^2$, 3.4 dB) and 24-2 PSD (0.38 $R^2$, 2.4 dB). Among the individual models, data were most accurate for GCIPL (0.79 $R^2$) and ganglion cell complex (0.75 $R^2$).

The authors concluded that DL models provide good estimates of functional status. They emphasized that SD-OCT images contain abundant information that has yet to be tapped; adding DL to the mix could lead to new biomarkers and better personalized treatment plans.

### Pneumatic Vitreolysis for Vitreomacular Traction
November 2021

If proven safe and effective, pneumatic vitreolysis (PVL) would be an alternative to vitrectomy that is less invasive and more economical. **Chan et al.** conducted two multicenter trials to assess the safety and efficacy of PVL for symptomatic vitreomacular traction (VMT), with or without macular hole (MH). Although PVL induced release of the hyaloid membrane in most study eyes, leading to hole closure in about one-third of eyes with full-thickness MH (FTMH), both trials were terminated early due to safety concerns.

The two trials involved 28 study sites. Both studies included adults with central VMT (vitreomacular adhesion ≤3,000 μm) but otherwise proceeded as follows:
• Protocol AG enrolled 46 patients (46 eyes) without FTMH who were assigned randomly to receive PVL (n = 23) or observation plus sham injection (n = 22). Visual acuity (VA) of the eyes in this study ranged from 20/32 to 20/400.

The main outcome was VMT release by 24 weeks; this was achieved without vitrectomy in 18 eyes treated with PVL

and in two eyes in the sham group (adjusted risk difference, 66%; p < .001). The mean VA change from baseline to week 24 was 6.7 letters in the PVL arm and 6.1 letters in the sham arm (adjusted difference, –0.8; p = 0.77).
• Protocol AH enrolled 35 patients (35 eyes) and was a single-arm study of PVL for FTMH. Treated eyes had an FTMH measuring ≤250 μm at the narrowest point, and VA in this group ranged from 20/25 to 20/400. PVL was performed with perfluoropropane ($C_3F_8$) gas.

The main outcome was FTMH closure by eight weeks; this was attained in 10 (29%) of the 35 eyes, without need for rescue vitrectomy. The mean change in VA from baseline to week 8 was –1.5 letters.

Rates of rhegmatogenous retinal detachment (RRD) or tear were higher than expected in both studies, leading to early termination. Overall, seven eyes (two in Protocol AG and five in Protocol AH) treated with PVL had an RRD (n = 6) or retinal tear (n = 1).

It is plausible that the risk of RRD and the indications for PVL may differ for VMT and MH, the authors said. Whether any modification of the PVL injection technique could reduce the risk of retinal detachment is not known and may be a topic of future research.
—*Summaries by Lynda Seminara*

## Ophthalmology Retina
Selected by Andrew P. Schachat, MD

### Genetics of Geographic Atrophy
November 2021

Can geographic atrophy (GA) secondary to age-related macular degeneration (AMD) be separated into two or more partially distinct subtypes? Moreover, do these subtypes have different genetic associations? Using phenotypic cluster analyses, **Keenan et al.** found defined subtypes of GA. However, no significant genotype-phenotype associations were observed.

For this study, the researchers analyzed data from 598 participants (598 eyes) who had incident GA during follow-up in AREDS2 (Age-Related Eye Disease Study 2). Phenotypic features

from fundus photographs were subjected to cluster analysis in cross-sectional and longitudinal analyses. Identified clusters were compared by four pathway-based genetic risk scores. The analyses were then repeated in reverse (i.e., clustering by genotype and comparison by phenotype).

Main outcome measures were the characteristics and quality of cluster solutions and the genotype-phenotype associations.

In clustering by phenotype, k-means identified two clusters (labeled A and B), while hierarchical clustering identified four (C-F). A-E membership differed principally by GA configuration but in relatively few other ways. In longitudinal phenotypic analyses, k-means identified two clusters that differed principally by smoking status (G, H). These three sets of cluster divisions were not similar to each other (r ≤ .20).

Moreover, pairwise cluster comparison by the four genetic risk scores demonstrated no significant differences (p > .05 for all).

In clustering by genotype, k-means identified two clusters (I, J). These differed principally at *ARMS2*, but no significant genotype-phenotype associations were observed (p > .05 for all).

Thus, the researchers concluded, "GA phenotypes may vary continuously across a spectrum, rather than consisting of distinct subtypes that arise from separate genetic etiologies." This suggests that, for any eye with GA, clinicians are "unlikely to infer the main genetic driver of GA from these phenotypic characteristics alone."
—*Summary by Jean Shaw*

## Ophthalmology Science
Selected by Emily Y. Chew, MD

### Calcified Deposits and Drusen Biogenesis
September 2021

In previous research, small spherules formed of hydroxyapatite or whitlockite have been found within deposits that accumulate in the sub–RPE-BL space, which is located between the

basal lamina (BL) of retinal pigment epithelium (RPE) and the inner collagenous layer of Bruch membrane. As it has been theorized that these calcified deposits play a role in drusen biogenesis, **Pilgrim et al.** set out to gain a better understanding of the spherules' morphology, structure, and distribution in human eyes with and without signs of age-related macular degeneration (AMD). They found that eyes with clinical signs of AMD had more spherules—and larger spherules—than did those without the disease.

For this experimental study, the researchers obtained five cadaveric eyes with varying degrees of sub–RPE-BL deposits. Two of the five eyes were reported as having clinical indications of AMD, while three were considered healthy. The eyes had been enucleated from older patients (range, 69-91 years).

The researchers used three high-resolution imaging methodologies (scanning electron microscopy, energy-dispersive X-ray spectroscopy, and time-of-flight–secondary mass spectrometry) to evaluate the tissue samples. Main outcome measures included the spherules' surface topography, internal structure, distribution, and average diameter.

Results indicated that the spherules' surface topography and internal structure varied significantly, and they were ubiquitous across the central axis and mid- and far-peripheral axis of the eyes. Two eyes with signs of AMD had more spherules, and the median diameter of the spherules noted in those eyes was larger than those noted in the healthy eyes (1.64 µm vs. 1.16 µm, respectively).

Understanding the differences in the microenvironment that might exist between healthy and affected eyes could potentially shed light on disease onset or progression, the authors said. This study's small sample size presented several limitations, they noted, and future research should include a larger cohort of eyes. In addition, better tissue preservation methods are needed, to facilitate better detection of the spherules' anatomical features.

*—Summary by Jean Shaw*

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

### Predictors of Keratoplasty for Keratoconus
November 2021

**Thanitcul et al.** conducted a review to uncover factors linked to higher or lower odds of a patient receiving keratoplasty for keratoconus. They found that young adults, patients with corneal hydrops, and residents of western regions of the United States were more likely to undergo keratoplasty. In contrast, the likelihood of keratoplasty was lower in individuals who had used contact lenses, had a history of glaucoma, or resided in the Northeast.

For this cross-sectional study, the authors reviewed medical records of patients with keratoconus who were <65 years of age. They obtained these records from the IBM MarketScan Database and focused on inpatient and outpatient claims made from 2010 through 2018. They developed a model, which was adjusted for potential confounders, to identify sociodemographic and comorbid factors associated with lower and higher likelihood of keratoplasty.

Of the 42,086 patients identified, 1,282 (3%) had undergone keratoplasty. According to the fully adjusted analysis, the likelihood of keratoplasty was lower for women (odds ratio [OR], 0.87) and for patients in metropolitan areas (OR, 0.75). The authors surmised that the regional trends may relate to access to fitting services for specialty contact lenses and to the effects of different climates on contact lens tolerability. With respect to age, patients in their 20s or 30s were more likely to receive keratoplasty than were younger patients (OR, 1.77 and 1.61, respectively). There was no difference between the youngest and oldest patients (10-19 and 50-64 years, respectively). Keratoplasty was less common among those who had worn contact lenses (OR, .61) or had a history of glaucoma (OR, .60). It was more common in patients with hydrops (OR, 4.87), Leber congenital

amaurosis (LCA; OR, 2.41), sleep apnea (OR, 1.46), diabetes (OR, 1.32), or depression (OR, 1.22).

Several predictors of keratoplasty noted in this study had not been identified previously, including LCA, depression, and diabetes. According to the authors, this information may help clinicians identify patients who need frequent monitoring or may be candidates for early interventions such as corneal cross-linking.

### Povidone-Iodine for Adenoviral Conjunctivitis
November 2021

Although there is no FDA-approved treatment for adenoviral conjunctivitis, in vitro testing has shown that povidone-iodine (PVP-I) has virucidal activity against adenovirus. Although PVP-I has been used off-label for many years to treat adenoviral conjunctivitis, there have been few clinical trials of its use as monotherapy. In a pilot, double-masked, randomized study, **Than et al.** compared safety and efficacy for 5% PVP-I and artificial tears in the treatment of patients with adenoviral conjunctivitis. They found that 5% PVP-I was well tolerated and that it reduced viral load for patients who presented within several days of symptom onset.

For this study, the authors recruited patients presumed to have adenoviral conjunctivitis who were screened at one of nine participating clinics in the United States. Candidates were required to be at least 18 years old, with symptoms lasting four or more days and a positive AdenoPlus test result. Excluded from participation were patients with iodine allergy, thyroid disease, recent ocular surgery, and ocular findings that did not suggest early-stage adenoviral conjunctivitis.

Study participants were assigned randomly to receive a single administration of 5% PVP-I or artificial tears (control) in one eye. They were examined within two days of treatment and again on days 4, 7, 14, and 21. Conjunctival swabs were obtained at each visit and analyzed by polymerase chain reaction. The main outcome measure was the percentage of reduction from peak

viral load. A key secondary outcome was improvement of clinical signs and symptoms of adenoviral conjunctivitis, as assessed by patients and clinicians. Evaluated symptoms included tearing, edema, redness, and mucoid discharge.

Among 212 screened participants, 56 met the inclusion criteria and were entered into the study. Half the enrollees (n = 28) had detectable viral titers at baseline. By day 4 following treatment, viral titers were 2.5% ± 2.7% of peak in the PVP-I group and 14.4% ± 10.5% of peak in the control group (p = .020). In addition, patient-reported symptoms were significantly milder for the 5% PVP-I group at this point (p < .05 vs. control group), and clinician-evaluated discharge, bulbar redness, and bulbar edema improved significantly by this time (all p < .05 vs. controls). After day 4, both groups had marked declines in viral titers and sign/symptom severity, and there were no meaningful differences between the groups.

The authors acknowledged that larger studies are needed to confirm these findings. Even so, they said, the data suggest that a single in-office administration of 5% PVP-I may speed viral-load reduction, leading to faster resolution of symptoms in patients who are treated promptly.

—*Summaries by Lynda Seminara*

## *JAMA Ophthalmology*
Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

### Medical Errors: Wrong Intravitreal Injections
October 2021

**Vora et al.** investigated a handful of medical errors involving intravitreal injections at their institution. Although they found that no long-term ocular morbidity occurred, they emphasized that these cases underscore the need to establish and consistently follow safety practices.

For this retrospective study, the authors identified four cases of wrong intravitreal injections that occurred between Jan. 1, 2019, and Dec. 31, 2020, at Kaiser Permanente Northern Califor-

nia. During that time frame, the institution's retina specialists performed more than 146,000 intravitreal injections.

Two of the four cases involved injection into the wrong eye; the others concerned medication errors (wrong medicine or wrong dosage). In evaluating the four cases, the authors noted that, in each instance, the surgical team did not review a preprocedure checklist. In addition, no surgical pauses or preprocedure timeouts took place, and the patient consent process was inconsistent.

The authors recommend that retina specialists develop a systematic process that 1) informs the staff of the injection plan; 2) ensures that patient consent and marking are handled properly; 3) includes a preprocedure checklist; and 4) incorporates a surgical pause or timeout to ensure that all information on patient, eye, medication choice, and medication dosage is correct before continuing.

### School-Based Vision Program and Academic Performance
October 2021

**Neitzel et al.** set out to assess the effect of a school-based vision program on academic achievement among students in grades 3 to 7. They found that the program had a positive impact on reading scores over one year. However, a sustained benefit was not observed through a second year.

This cluster randomized study was conducted in the Baltimore City Public School system. Participating schools were randomized 1:1:1 into one of three study cohorts, with cohorts 1, 2, and 3 receiving interventions in 2016-2017, 2017-2018, and 2018-2019, respectively.

All told, 2,304 students received eye examinations and eyeglasses. Of these, 1,260 (54.5%) were girls; the mean age was 9.4 (± 1.4) years. Students were provided replacement eyeglasses as needed within one year of their initial prescription. The primary outcome was the one-year intervention impact, measured by effect size (ES), defined as the difference in reading and mathematics test scores at the end of the year. The secondary outcome was the two-year

intervention impact, measured by ES.

Over the course of one year, students receiving eyeglasses achieved better reading scores (ES, .09; p = .02). A greater effect was noted in girls (ES, .15; p < .001) than in boys (ES, .01; p = .48), and students in special education classes and those at the lowest achievement quartiles at baseline also experienced improvement in reading scores (ES, .25 and .28, respectively; p < .001 for both). Mathematic test scores improved in elementary school grades (ES, .03; p < .001) but not in middle school grades (ES, −.21; p ≥ .99).

The improved academic achievements seen in the first year were not sustained at two years—although positive intervention impacts were noted in both reading and mathematics, these impacts were not statistically significant. In discussing this, the authors noted that students who receive eyeglasses in school-based vision programs may wear their eyeglasses less over time.

Refractive error findings and visual acuity change with eyeglasses in relation to academic outcomes will be reported separately.

### Preventing Macular Thickening After Cataract Surgery
October 2021

Which regimen is most effective at preventing postoperative thickening of the central macula following cataract surgery? **Erichsen et al.** compared a combination of NSAID and corticosteroid eyedrops, NSAID monotherapy, and a sub-Tenon depot of dexamethasone (dropless surgery). They also evaluated whether starting eyedrops three days before surgery was superior to starting them on the day of surgery. They found that combination therapy was not superior to NSAID monotherapy or dropless surgery.

For this single-center trial, 470 patients were randomized to 1 of 5 regimens: 1) preoperative combination drops (prednisolone plus NSAID); 2) post-op combination drops; 3) pre-op NSAID monotherapy; 4) post-op NSAID monotherapy; or 5) dropless surgery. Eyedrops were administered three times per day until three weeks

postoperatively. The main outcome measure was central subfield thickness (CST) at the three-month mark.

Three months after surgery, the mean CST was 250 μm in both the pre- and post-op combination groups, 251.3 μm in the pre-op NSAID monotherapy cohort, 249.2 μm in the post-op NSAID monotherapy group, and 255.2 μm in the dropless surgery cohort.

With regard to other outcomes, more than half of the patients in the sub-Tenon group required anti-inflammatory eyedrops following surgery. Mean IOP decreased in all groups postoperatively, but it was lower in those who did not receive prednisolone in the early post-op period. There were no elevations of greater than 25 mm Hg at any postoperative visit. There were no differences in visual acuity between groups at any post-op time point, but adverse events and unscheduled visits took place more often among those in the dropless surgery cohort.

Given these findings, NSAID monotherapy with initiation on the day of surgery may be preferred as an anti-inflammatory regimen for patients undergoing uncomplicated cataract surgery, the authors said.

—*Summaries by Jean Shaw*

# OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

**Changing Trends in Emergency Ocular Trauma**
*British Journal of Ophthalmology*
Published online Aug. 20, 2021

In an effort to understand the effect of the COVID-19 pandemic on ocular trauma, **Halawa et al.** compared the quantity and type of eye injuries that presented to emergency departments (EDs) in 2020 with those during 2011-2019. They found that while the proportion of ED-treated ocular wounds was substantially lower in 2020, the severity of these injuries was more profound.

For their study, the authors gathered data from the National Electronic Injury Surveillance System (NEISS) of the U.S. Consumer Product Safety Com-

mission. Their sample represented 100 hospitals that each had at least six ED beds and 24-hour service. To estimate the annual number of eye injuries in 2020, the authors used patient demographics and injury-related details. To calculate the incidence for prior years, they used NEISS database estimates along with U.S. Census Bureau population data. Statistical analyses were conducted to compare variables for the two study periods, including injury location and diagnosis.

Overall, 4,236 ocular injuries were seen in the selected hospitals' EDs in 2020, compared with a yearly average of 4,959 in the previous period. Probability sampling weights indicated that ED-treated eye injuries declined by 21.2% in 2020. This coincided with a 25.9% reduction in the estimated annual incidence, from 62 per 100,000 in 2011-2019 to 46 per 100,000 in 2020 (p < .001). Comparisons of annual incidence showed that 2020 had far fewer injuries relating to sports and recreation products (p < .001) and occurring in schools or (p < .001) or sports facilities (p = .002).

Despite the low rate of ocular trauma in 2020, the injuries were more severe than in previous years. The frequency of ruptured globe, hyphema, laceration, and orbital fracture was much greater in 2020 than in 2011-2019 (all p < .001).

The authors surmised that shifts in living and working environments prompted by the pandemic, including stay-at-home orders, led to the decreased incidence and different mix of ocular injuries seen in 2020 than in previous years.

**The Ocular Surface and Immunity**
*Investigative Ophthalmology & Visual Science*
2021;62(10):8

The Human Microbiome Project characterized the microbiomes of various body sites, but the eye was not among them. **Zysset-Burri et al.** conducted a study to better understand the microbial composition of the ocular surface and its relationship to the tear proteome. They found a crucial immune-defense link between these systems.

For this study, the authors collected lid swabs, conjunctival swabs, and tear fluid from 20 patients (20 eyes). The mean age of participants was 69.7 years; 75% were male. Swabs were processed, and DNA was isolated and underwent whole-metagenome shotgun sequencing. The tear proteome was identified using chromatography in tandem with mass spectrometry. Linear modeling was applied to explore interactions between the microbial or functional features of the microbiome and the functional features of the tear proteome.

Altogether, 229 taxa were found in ocular surface microbiomes. The majority (93.15%) were bacteria, 6.83% were viruses, and 0.02% were eukaryotes. The ocular microbiome was dominated by the phyla *Actinobacteria* and *Proteobacteria*. The most abundant class was *Actinobacteria* (63.1%), and the most prevalent genera were *Propionibacterium* (31.9%), *Agrobacterium* (22.4%), and *Corynebacterium* (21.2%). *P. acnes* and *Staphylococcus epidermidis* were much more common in lid samples than conjunctiva (p = .015 and .020, respectively). Lid microbiomes were enriched in genes of stage 3 glycolysis as well as de novo adenosine and L-isoleucine biosynthesis pathways. More than 2,100 protein groups were identified from human tear proteome. The most prevalent proteins were lactotransferrin, albumin, lipocalin-1, lysozyme, and immunoglobulin A. All of these except albumin have antimicrobial activity. Gene ontology terms were assessed for correlation with tear and lid findings. Positive correlations were found for the *Firmicutes* phylum and the term fatty-acid binding; for the *Agrobacterium* genus and vitamin B1 synthesis and the term upregulated antimicrobial activity; and between the term sensory perception of chemical stimus and the biosynthesis of heme, L-arginine, and L-citrulline.

These findings highlight the integral interplay of the ocular surface microbiome and tear proteome in ocular health, said the authors. They believe this knowledge could lead to new strategies to prevent and treat diseases of the ocular surface.

—*Summaries by Lynda Seminara*