Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. Mcleod, MD

Deep Learning Model Predicts Glaucomatous Changes

March 2021

Medeiros et al. developed and trained a deep learning algorithm to analyze fundus photographs and predict global retinal nerve fiber layer (RNFL) thickness from images obtained by spectral-domain optical coherence tomography (SD-OCT). Their model produced objective and quantitative estimates of glaucomatous changes.

For this retrospective study, the authors used a 50% sample gathered from a large glaucoma registry that included patients with confirmed or suspected glaucoma. Participants had at least two longitudinal photographs from follow-up visits. Overall, there were 33,466 pairs of fundus photographs and corresponding SD-OCT images, collected from 717 patients (1,147 eyes). Average follow-up per eye was 5.3 ± 3.3 years. The main outcome was the relationship between changes in RNFL predicted from photographs and the changes seen over time by SD-OCT.

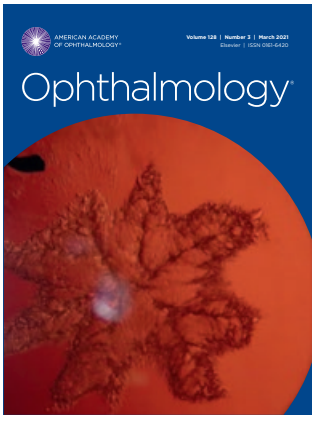
The mean global RNFL thickness estimated from the fundus photographs was 84.6 ± 14.4 µm, versus 84.5 ± 17.0 µm observed from corresponding SD-OCT scans, denoting a strong correlation between the two methods (R^2 = 63.6%; p < .001). The average change in RNFL thickness identified by the algorithm throughout the follow-up period was –4.3 ± 5.8 µm, whereas that observed by SD-OCT was –4.8 ± 5.3 µm. There was a strong correlation between the RNFL and SD-OCT changes (r = 0.76; 95% CI, 0.70-0.80; p < .001).

As this model provided objective and accurate estimates of RNFL thickness that correlated well with SD-OCT data, it may have a role in monitoring glaucoma progression, the authors said. They also noted its potential utility in settings where SD-OCT is not available or feasible.

Cataract Surgery Volume and Risk of Capsular Complications

March 2021

Although cataract extraction is a relatively safe and routine procedure, sight-threatening complications can occur. Using data from Swedish patients who underwent cataract surgery in a 10-year period, **Zetterberg et al.** looked at case mix in relation to capsular complications, possible associations between case mix and surgeon volume, and changes in case mix over time. They found that capsular complications were significantly associated with best-corrected visual acuity (BCVA) ≤0.1 logMAR units at baseline as well as with the presence of pseudoexfoliation (PEX), the use of Trypan blue, and placement of iris hooks at the rhexis margin.



The authors calculated a composite risk score from the data of 118,493 patients in the 2016 cohort (mean age, 74.2 years). Parameters included age, sex, BCVA, ocular comorbidity (excluding glaucoma, age-related macular degeneration, diabetic retinopathy, and cornea guttata), intraoperative difficulties, and whether communication with the vitreous occurred during surgery. Some data were not available for every year, and the analyses were modified accordingly. Single regression analyses of possible pre- and intraoperative risk factors were conducted, and any factor that significantly raised the risk for capsular complications in that analysis was evaluated subsequently by logistic binary regression. Case mix and surgeon volume were stratified by category. The main outcome measure was risk of capsular complication (adjusted and composite odds ratios) in relation to surgery volume.

Results showed that various pre- and intraoperative factors were linked to capsular complications in the single-factor and logistic regression analyses; these included pre-op BCVA ≤0.1, PEX, other ocular comorbidity, Trypan blue use, mechanical pupil dilation, and iris hooks at the rhexis margin. The composite risk score was significantly lower for

high-volume surgeons (≥500 procedures per year) than for those with low or medium case volumes (mean risk scored: 1.28, 1.34, and 1.49, respectively).

Case mix may contribute to the overall decline in capsular complications from 2007 to 2016, the authors said. Moreover, as time passed, there were decreases in the percentage of oldest patients (>88 years), those with poor baseline BCVA, and cases with intraoperative difficulties. Further work is planned to explore the effect of clinical setting on complication rates and case mix.

Impact of IOLs That Filter Blue Light on AMD

March 2021

Although early evidence suggested that IOLs which filter blue light can protect the retina and mitigate the occurrence or progression of neovascular age-related macular degeneration (AMD) after cataract surgery, results of recent studies have been equivocal. In a large registry-based study, **Achiron et al.** added to the debate. Their analysis showed no clear advantage to blue light–filtering (BLF) lenses with respect to incidence or progression of neovascular AMD or in secondary clinical outcomes such as best-corrected visual acuity (BCVA) or foveal thickness.

For this retrospective study, the investigators studied consecutive cases of uneventful cataract surgery performed in Finland since September 2007. Patients received BLF or standard IOLs per the surgeon's discretion. The main outcome measure was wet AMD development over time. Secondary outcomes were BCVA, foveal thickness, treatment interval, and total number of intravitreal injections. To assess the effect of BLF lenses on progression, the authors conducted a separate analysis among patients with preexisting disease.

Altogether, the researchers evaluated one eye of 11,397 patients (mean age, 75.4 years). Of these, 5,425 eyes (47.6%) had received a BLF lens, and 5,972 eyes (52.4%) had a standard IOL. Follow-up was somewhat longer for BLF users (55.2 vs. 50.5 months), and the incidence of new-onset AMD was higher in this group (88 vs. 76 patients).

AMD-free survival rates did not differ significantly between the cohorts. In a regression analysis controlled for age, sex, and AMD diagnosis, BLF lens use did not affect AMD development (hazard ratio, 1.075; p = .652). One year after diagnosis of AMD, secondary clinical outcomes were comparable for the BLF and non-BLF groups: BCVA (0.57 vs. 0.45 logMAR), foveal thickness (285 vs. 299 µm), number of anti-VEGF injections (6.5 vs. 6.2), and treatment interval (7.5 vs. 8.1 weeks), respectively. Secondary outcomes were comparable for patients with preexisting AMD.

The authors noted that the lack of preventive effect of BLF lenses on wet AMD was supported by results of the multivariate analysis, which accounted for possible confounders. They acknowledge that these findings are specific to neovascular AMD and may not be applicable to other forms of AMD. —*Summaries by Lynda Seminara*

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

VA Variability: Snellen Versus ETDRS Outcomes

March 2021

The Snellen visual acuity (VA) chart is routinely used in clinical practice, while that developed in the Early Treatment Diabetes Retinopathy Study (ETDRS) is the gold standard for ophthalmic clinical trials. In a retrospective chart review, **Yu et al.** set out to compare the variability between the two measurements of best-corrected visual acuity (BCVA). They found that the ETDRS visual acuity scores were significantly better—and that the difference was more pronounced among eyes with worse visual acuity. The findings suggest that caution must be taken when comparing clinical trial VA results with routine clinical outcomes.

For this study, the authors assessed data from 12 prospective clinical trials conducted at a large urban retina practice in the United States. Eyes were included if a Snellen VA measurement was performed at the visit preceding the initial trial screening and VA was better than counting fingers. All Snellen and ETDRS VA measurements were converted to logMAR units for direct comparison, and the variability between measurements was calculated.

All told, 413 patients (773 eyes) met the inclusion criteria for this study. Mean patient age was 62.8 years (range, 25-93 years), and there was a mean of 27.2 days between measurements. Outcome measures included absolute VA and VA variability among disease states.

Mean Snellen VA was 0.40 logMAR (20/50 Snellen equivalent), and mean ETDRS measurement was 0.27 logMAR (20/40 Snellen equivalent). Overall, 76.6% of eyes correctly identified more letters with the ETDRS chart. When VA was assessed by subgroups, eyes with worse vision had a greater difference between Snellen and ETDRS scores: Eyes 20/25 or better were a mean +1.9 letters better on ETDRS testing, and eyes 20/160 or worse were a mean +12.6 letters better on ETDRS testing ($p < .05$ for both).

The authors also conducted a subgroup analysis by disease state. Of the five conditions evaluated—diabetic retinopathy (DR) with diabetic macular edema (DME), DR without DME, wet age-related macular degeneration (AMD), dry AMD, and retinal vein occlusion—only those eyes that had DR without DME did not show a significant difference between VA scores. Thus, the authors said, the specific retinal disease state and extent of edema may play a role in the variability between the measurements. *(Also see related commentary by Andrew P. Schachat, MD, and Marco A. Zarbin, MD, in the same issue.)*

—*Summary by Jean Shaw*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

New WHO System Boosts Ability to Classify Conjunctival Lesions

March 2021

Accurate diagnosis of conjunctival melanocytic intraepithelial lesions (CMILs) is important both prognostically and therapeutically. **Milman et al.**

looked at interobserver agreement and accuracy of the new World Health Organization (WHO) classification system for CMILs and compared the findings with two commonly used classification schemes. They found that accuracy was comparable for the three systems. Interobserver agreement for distinguishing high- and low-grade lesions was greatest for the WHO system.

For this study, the authors reviewed pathology and other records for patients who underwent a primary biopsy procedure for conjunctival primary acquired melanosis (PAM) at Wills Eye Hospital from 1974 to 2002 and had follow-up for at least three years. Collected data included demographics and clinical findings such as disease course. The authors created virtual digital histopathology slides from actual slides to ensure uniformity of appearance for the 12 ophthalmic pathologists who assessed them. Three classifications systems were applied for each slide: WHO (fourth edition), PAM, and C-MIN (conjunctival melanocytic intraepithelial neoplasia).

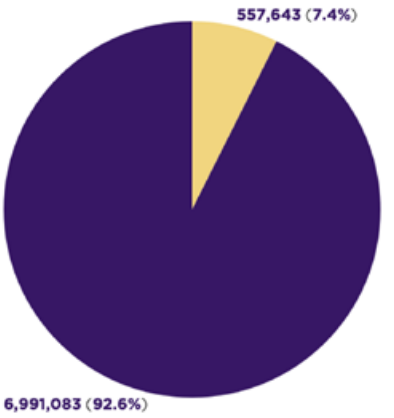
Overall, 64 patients (83 primary excision procedures) had tissue that was adequate for histopathologic evaluation. Interobserver agreement for differentiating low- and high-grade lesions was 81% for WHO, 76% for PAM, and 67% for C-MIN. With all three systems, low-grade lesions were the most difficult type to interpret. Average accuracy for identifying lesions with recurrence potential was 83% for WHO and C-MIN and 81% for PAM. Assessment by C-MIN took slightly longer than the other systems.

Although the new WHO scheme is viable in the context of pathology, the authors emphasized the clinical importance of identifying specific types of conjunctival epithelial acquired pigmentation, as outlined in the PAM classification system. With additional refinements in digital pathology, artificial intelligence, and molecular genetics, the authors stated that they are confident that "an integrated morphologic–molecular classification system will emerge that will further improve our ability to accurately diagnose these challenging lesions."

IRIS Registry Snapshot: Cataract Surgery

Analyzing statistically de-identified electronic health record data from the Academy's IRIS Registry, Verana Health assessed the number of cataract surgeries in the United States from 2016 through 2019.

The study included 7,548,726 total eyes from 4,537,122 unique patients. The number of normal (purple) and complex (yellow) cataract surgeries are shown in the pie chart. During the study period, trends in rates of normal versus complex cataract surgery remained stable year over year. The average rate of complex cataract surgery was 7.4% (range, 7.3%-7.6%).



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

Using the Eyecatcher to Monitor Glaucoma at Home

March 2021

In a pilot study, **Jones et al.** looked at the accuracy and adherence associated with at-home visual field (VF) monitoring by the tablet perimeter known as Eyecatcher. They found strong concordance between tablet data and conventional clinical data, and nearly all home tests were completed successfully.

In this study, 20 adults (median age, 71 years) with established glaucoma were issued an Eyecatcher. The patients were asked to conduct one VF home assessment per eye, per month, for six months (12 tests overall). As with conventional tests for glaucoma, patients looked at a central cross displayed on the device and pressed a button when they noticed a flash of light. The light appeared in different positions, and its intensity varied. To evaluate the tool's accuracy, VF assessment also was done in the clinic, using standard automated perimetry, both before and after home testing (four total tests per eye).

All 20 participants were able to perform monthly monitoring at home. One person stopped after four months, for an overall adherence rate of 98%. The median duration of an Eyecatcher test was 4.5 minutes. At-home VF findings coincided with data obtained in the clinic ($r = 0.94$, $p < .001$). In 21 (9%) of the 236 tests, mean deviation varied by more than 3 dB from the median. When combined with clinical results, home-monitoring data helped to reduce measurement error (by >50% in 90% of eyes), indicating that use of the Eyecatcher may detect rapid sight loss earlier than usual.

Substantial variations in ambient illumination had no observable effect on VF measurements.

Many studies have shown that patients with glaucoma would benefit from monitoring more often than is customary, and technology such as Eyecatcher could make this possible. Additional work is needed to determine whether home monitoring of glaucoma is sustainable for longer periods and is capable of detecting rapid progression.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Impact of State Legislation on Opioid Prescribing

February 2021

Do statewide laws designed to curb opioid prescribing have an impact on the number of such prescriptions for

surgical procedures? **Xie et al.** set out to assess this issue in the wake of the enactment of the Michigan Opioid Laws in 2017 and 2018. They found a significant reduction in postoperative opioid prescriptions for selected oculoplastic and orbital procedures after the new laws were in place.

For this cross-sectional study, the authors reviewed clinical data on 3,781 patients who underwent one of 10 common oculoplastic and orbital procedures at the University of Michigan between June 1, 2016, and Nov. 30, 2019. They also collected data on all outpatient opioid prescriptions ordered for each surgery and calculated morphine milligram equivalents (MMEs) to characterize the amount of opioids prescribed prior to, on the day of, and immediately after surgery.

Acetaminophen-hydrocodone was the most commonly prescribed opioid (87% of prescriptions); others included tramadol and oxycodone.

The patients' mean age was 63.3 years, and 1,614 (42.7%) were male. Of 2,026 patients who underwent surgery before June 1, 2018, 1,782 (88%) were prescribed post-op opioids. Of the 1,755 who underwent surgery after June 1, 2018, 878 (50%) were prescribed opioids postoperatively. Similarly, the MMEs given in the prescriptions declined by 36.2% during the same time frame.

The mean prescription amount in the full study period was equivalent to 80.1 MMEs. With regard to specific surgical procedures, the mean amounts of opioids prescribed were highest for three orbital procedures—periorbital approach to orbital floor fracture repair (117.1 MMEs), enucleation with orbital implant (108.1 MMEs), and orbitotomy for decompression with bone flap (91.5 MMEs). The lowest mean MME amounts were observed with entropion repair (61.9 MMEs) and blepharoptosis repair (64.7 MMEs). No prescribers provided opioid refills for any prescriptions.

The authors noted several limitations of the study, including a lack of data on patient-initiated refill requests and the inability to track whether patients obtained prescriptions from other providers outside the university system. Nonetheless, they said, the findings provide support for similar legislative efforts to curb the opioid crisis. *(Also see related commentary by Anton M. Kolomeyer, MD, PhD, and Bryan L. VanderBeek, MD, MPH, MSCE, in the same issue.)*

Glaucoma After Treatment for Infant Aphakia

February 2021

In a secondary analysis of data from a randomized clinical trial, **Freedman et al.** assessed the 10-year cumulative incidence of glaucoma and glaucoma-related adverse events in children who were enrolled in the Infant Aphakia Treatment Study (IATS). They found that the risk of glaucoma-related adverse events continues to increase with longer follow-up of these children.

Of the 114 infants treated in the IATS, 110 had completed a clinical exam at age 10.5 years, with a mean postsurgical follow-up of 10.4 years (range, 9.3-11.5 years).

By the 10-year mark, glaucoma status was available for 106 children; of these, 25 eyes had developed glaucoma, and 21 eyes were diagnosed as glaucoma suspects.

According to results of Kaplan-Meier analysis, the risk of glaucoma in all study eyes rose from 9% at one year following cataract removal to 17% at the five-year mark and to 22% at 10 years. When glaucoma suspect status was added, the combined risk rose from 12% at one year to 31% at five years and 40% at 10 years after cataract removal.

As part of this 10-year assessment, the authors also evaluated the retinal nerve fiber layer (RNFL) and optic nerve head (ONH) health of the children's eyes.

They found that eyes with glaucoma at 10 years had longer axial lengths than did unaffected eyes and those diagnosed as glaucoma suspect. However, the RNFL was relatively preserved in eyes with glaucoma, and their ONH appearance, visual acuity, and IOP were similar to those of glaucoma suspect and unaffected eyes.

The results of this study indicate that lifelong surveillance is necessary in children who undergo cataract surgery in infancy, the authors said.

Use of Novel Analytic Method to Predict DSAEK Graft Failure

February 2021

The machine-learning technique known as random survival forest (RSF) has emerged as a promising alternative to traditional analytic methods. **O'Brien et al.** used an RSF model to rank multiple variables associated with Descemet stripping automated endothelial keratoplasty (DSAEK) graft failure in the Cornea Preservation Time Study (CPTS). They found that intraoperative complications were highly predictive of graft failure in the CPTS.

For this cohort study, the authors evaluated data on 1,090 CPTS participants (1,330 eyes) who underwent DSAEK for Fuchs dystrophy (1,255 eyes; 94.4%) or for pseudophakic or aphakic corneal edema (75 eyes; 5.6%). All told, 81 eyes experienced graft failure in the first four years after DSAEK.

For their analysis, the authors selected 50 baseline donor, recipient, eye bank, and intraoperative variables and used RSF to analyze the data and rank the variables. The final RSF model, which comprised five variables, identified DSAEK intraoperative complications as the third most predictive factor of graft failure, after surgeon and eye bank. History of diabetes in the donor was the fourth most predictive factor, and preservation time ranked fifth.

With regard to graft survival time, in the first 47 months after DSAEK, grafts that experienced an intraoperative complication survived between 70 and 352 fewer days than those that did not.

To date, RSFs have been used successfully to predict survival in selected cardiology and oncology scenarios; however, their use in ophthalmology has been limited. These findings support the hypothesis that the RSF method is a promising alternative to standard analytic methods in ophthalmology. *(Also see related commentary by Joelle A. Hallak, MS, PhD, in the same issue.)* *—Summaries by Jean Shaw*

OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

Gabapentin Reduces Dry Eye Pain in Some Patients

Journal of Clinical Medicine
2020;9(11):3765

Oral gabapentin is a first-line treatment for chronic systemic neuropathic pain. Although it has been used for ocular discomfort after refractive surgery and in severe, painful dry eye syndrome (DES), it can depress the central nervous system. As a result, some physicians are reluctant to prescribe it for neuropathic ocular pain (NOP) that doesn't respond to topical treatment. **Yoon et al.** assessed the response to gabapentin among patients with DES who had signs of NOP. They found that some patients may benefit from gabapentin.

For this study, the authors reviewed medical records for 35 patients with DES plus NOP. Patients underwent clinical exams of the tear film, ocular surface, and meibomian glands, and they completed the Ocular Pain Assessment Survey (OPAS). One month into topical treatment with eyedrops, the decision to add gabapentin was made in accordance with ratings on an additional pain rating scale.

Patients were grouped by response to treatment: Group 1 responded to eyedrops alone (n = 11), group 2 responded to eyedrops plus gabapentin (n = 13), and group 3 did not respond to either regimen (n = 11).

With regard to clinical findings, while those in group 1 had no history of systemic comorbidity, ocular surgery, or trauma, they had the poorest corneal staining scores. Those in group 2 had the highest incidence of systemic comorbidities (defined as rheumatologic, neurologic, and psychological). Both groups 2 and 3 included patients who had a history of ophthalmic procedures such as cataract surgery or LASIK. Finally, those in group 3 were more likely than those in group 2 to experience pain in response to mechanical or chemical stimuli. Only one patient experienced an adverse effect from gabapentin (mild tremor).

The growing prevalence of DES has emphasized the need for effective management strategies, the authors said.

Findings of this study demonstrate that certain subsets of patients with DES and NOP may benefit from add-on gabapentin treatment, particularly if they have systemic comorbidities, healthy corneas, and no history of surgery or other trauma.

Myopia Progression in Children: Racial and Ethnic Differences

Investigative Ophthalmology & Visual Science
2020;61(13):20

Studies of myopia usually involve ethnically homogeneous cohorts. The minimal research in diverse populations has revealed little about the role of race in the development or progression of myopia or the subsets of children at greatest risk for advanced disease. To shed light on these issues, **Luong et al.** looked at myopia progression in a large, racially diverse population of children who had early onset myopia. They found that race/ethnicity was a major predictor of myopic progression and that meaningful differences exist between Whites and East/Southeast Asians based on age at onset.

For this retrospective study, the authors reviewed medical records of patients aged 4 to 11 years, whose documented refraction ranged from –6 to –1 D.

Excluded from the study were children with a history of amblyopia, strabismus, retinopathy of prematurity, or ocular surgery. The authors used growth-curve and linear mixed-effects modeling to track spherical equivalents (SEs) over time, modeled by race/ethnicity. They also adjusted for potential confounders, including body mass index, screen time, and physical activity.

Overall, 11,595 patients met the inclusion criteria. The mean age at initial refraction was 8.9 years, and 53% were female. The racial/ethnic breakdown was 55% Latino, 15% White, 9% Black, 9% East/Southeast Asian, and 2% South Asian. The average follow-up time was 3.1 years (range, 1.8-5.9 years).

The mean number of refractions during the study period was 3.4, including the baseline assessment. In mixed-effects models, no significant differences were noted for screen time or level of physical activity. A three-way interaction model to explore the effects of age at baseline, time since baseline, and race/ethnicity showed that myopia progressed fastest in children of East/Southeast Asian descent ($p < .001$) and that trajectories varied significantly by age at onset. SE declines were steeper in East/Southeast Asians than in Whites in all age groups except those with onset at 6 or 7 years of age, for whom the progression rate was similar.

Based on these real-world findings in a large study population, the authors proposed that race and ethnicity be considered in future myopia clinical trials and prevention programs. They noted that children of East and Southeast Asian descent require special attention because of their high risk of rapid progression. They also recommend more refined studies of the effects of screen time and physical activity on myopia progression.

—Summaries by Lynda Seminara

OPHTHALMOLOGY SCIENCE

Ophthalmology Science, the Academy's first gold open access journal, is publishing its inaugural issue this month (March 2021). The online journal will focus on preclinical developments, phase 1 and 2 clinical trials, laboratory-based work, ophthalmology informatics, and clinical science.

Ophthalmology Science is now open for submission. For information on submissions guidelines, contact the journal office at aaojournal@aao.org.