

# Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

## Ophthalmology

Selected by Russell N. Van Gelder,  
MD, PhD

### FLACS Versus Phaco: Efficacy, Safety, and Cost August 2022

For an Academy *Ophthalmic Technology Assessment*, Lin et al. reviewed and compared refractive outcomes, safety, and cost-effectiveness of femtosecond laser-assisted cataract surgery (FLACS) and conventional phacoemulsification cataract surgery (PCS). According to their review of published studies, both procedures are safe and have excellent refractive outcomes, but economic analyses showed that PCS is less costly.

The authors began this work by searching PubMed for randomized controlled trials in which the two types of surgery were compared. The search was conducted in August 2020 and was designed to capture all relevant studies published by then. Meta-analyses of primary literature were not considered. To qualify for inclusion, a study's primary objective must have been a comparison of refractive outcomes and/or safety for FLACS and PCS. Of the 727 abstracts identified for potential inclusion, 33 were suitable for full-text review. Twelve studies ultimately qualified for inclusion, all of which represented level 1 evidence. The minimum sample size for studies of

refractive outcomes was 322, the number needed to detect a 0.1 difference (5 letters) in logMAR VA between FLACS and PCS.

The results showed no significant differences between the procedures in mean uncorrected distance VA, mean best-corrected distance VA, or the proportion of eyes within .5 or 1 D of the refractive target.

Intraoperative and postoperative complications also were comparable:

in most studies, there was no difference in endothelial cell count at any assessment point through six months post-op. In large randomized studies conducted in France and the United Kingdom, FLACS was more costly than PCS.

This information helps to address some concerns that have surrounded FLACS since its inception in 2011. In the United States, most payers still do not cover FLACS, and its cost-effectiveness from a public health standpoint remains uncertain. The authors acknowledged that FLACS may be more beneficial in certain cases, such as those involving a trauma history, zonulopathy, narrow angles, and other conditions that make it crucial to preserve endothelial cells. They recommend comparing FLACS and PCS among patients with these conditions,

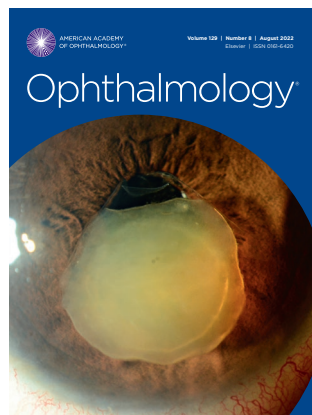
as well as exploring the potential value of femtosecond technology in correcting corneal astigmatism.

### Ophthalmology Residency Programs Still Lack Racial Diversity August 2022

Atkuru et al. assessed the racial makeup of ophthalmology residents and compared their findings with those for residents in other specialties. They found that diversity remains lower in ophthalmology residency programs than in all other specialties. The fields ranked highest for diversity in this study were public health/preventive medicine, obstetrics and gynecology, and family practice.

For this research, the authors gathered 10-year demographic data from the Accreditation Council for Graduate Medical Education and compared findings for ophthalmology residency programs with those of 17 other medical specialties. They applied a linear regression model to estimate trends over time.

Altogether, more than 1.1 million residents were identified among the 18 specialties, but only 1.1% were enrolled in ophthalmology programs. The lowest proportion of residents from underrepresented minority (URM) groups was in ophthalmology (5.4%), followed by other surgical specialties (9.9%) and nonsurgical specialties (10%). However, from 2011 to 2019, the URM growth rate was marginally higher for ophthalmology residencies (.24%) than for



other surgical (.01%) or nonsurgical (.20%) programs. URM represented only 6.3% of ophthalmology residents in the 2019-2020 academic year; however, URM representation among U.S. medical school enrollees was 18.4% in 2018-2019 and 22.5% in 2021-2022, according to the Association of American Medical Colleges.

Contributors to the low diversity in ophthalmology may be multifactorial, said the authors. Possible reasons include low level of interest, late exposure to ophthalmology in medical school, the competitiveness of residency programs, and the lack of racially diverse role models.

Although the current Minority Ophthalmology Mentoring program partnership between the Academy and the Association of University Professors of Ophthalmology is a step in the right direction, the authors emphasized that more efforts are needed to address implicit biases and clear other obstacles that deter URM students from pursuing a career in ophthalmology.

### **Pediatric Optic Neuritis: Two-Year Outcomes**

August 2022

Pediatric optic neuritis (ON) is a rare condition that is poorly understood. In a prospective study of outcomes through two years, Pineles et al. evaluated VA, recurrence risk, and final diagnoses. They found that even though vision was poor at presentation, recovery was possible for most patients, but associated neurologic conditions were common.

Twenty-three pediatric ophthalmology clinics in North America participated in the study, and treatments were chosen by participating investigators. At enrollment, a study-certified examiner tested monocular distance high-contrast VA (HCVA) and low-contrast VA (LCVA) in each patient's habitual refractive correction state, using the electronic Amblyopia Treatment Study HOTV protocol for those under 7 years of age or the electronic ETDRS protocol for older children. Magnetic resonance imaging (MRI) of the brain, with and without intravenous gadolin-

ium, was performed within two weeks of symptom onset.

Initial and two-year MRI images were reviewed by the masked examiner (who was unaware of demographic or clinical data) to determine presence/absence of optic nerve enhancement or white matter lesions. Follow-up assessments occurred at months 1 and 6 and years 1 and 2.

At each visit, the patients' HCVA and LCVA were tested, and the anterior and posterior segments were examined. MRI-detected white matter lesions were considered to represent an associated neurologic autoimmune diagnosis. If a masked MRI reading or antibody finding for myelin oligodendrocyte glycoprotein (MOG)—or aquaporin-4, if tested—was discordant with the initial diagnosis, study chairs reviewed all case data and adjudicated to a final diagnosis. The main outcome measure was the proportion of eyes with age-normal HCVA; secondary outcomes included LCVA, neuroimaging findings, and final diagnoses.

Of the 44 enrollees (median age, 10.3 years), 28 (63.6%) completed the two-year assessment. Final diagnoses were isolated ON (39%), MOG-associated demyelination (29%), multiple sclerosis (14%), neuromyelitis optica spectrum disorder (11%), and acute disseminated encephalomyelitis (7%). Five patients (18%) had ON recurrence during follow-up. Recurrence and neurologic conditions were less common with isolated ON. Mean VA improved from approximately 20/125 at presentation to approximately 20/25-2 by six months and was maintained through two years. Twenty-four children (79%) had age-normal VA at two years, and VA was 20/20 or better for 21 participants (66%). Mean LCVA improved from the presenting logMAR score of 1.45 to scores of .78 by six months and .68 by two years.

These data provide insight on the risk of ON recurrence and associated neurologic autoimmune disorders, which can affect VA, said the authors. They recommend comparing treatment strategies to further optimize VA outcomes.

—Summaries by Lynda Seminara

## **Ophthalmology Glaucoma**

Selected by Henry D. Jampel, MD, MHS

### **Electronic Monitoring Improves Adherence to Drop Regimen**

July/August 2022

McGlumphy et al. set out to electronically monitor the prescribed use of topical corticosteroid drops in patients who underwent glaucoma surgery and to compare measures of adherence to postsurgical outcomes. They found that they were able to remotely monitor patient adherence, which was high overall. In addition, they found that surgical success was greater among eyes with nearly ideal adherence rates and poorer in older patients and in those with more advanced glaucoma.

For this prospective cohort study, the researchers included 90 patients (90 eyes) with open-angle glaucoma (n = 86) or angle-closure glaucoma (n = 4). Patients had undergone trabeculectomy (n = 58), combined trabeculectomy and cataract surgery (n = 20), or tube shunt surgery (n = 12). All were provided with a Kali Drop device, which is a wireless, 3G-enabled plastic unit that encloses the eyedrop bottle and records the time and amount of drop administration. Adherence parameters were designed to capture both the number of drops a patient administered each day during waking hours and the time between each drop. Main outcome measures included adherence to the drop regimen during the first five post-op weeks as well as the achievement of target IOP at six weeks, six months, and one year.

Results indicated that adherence was  $89.7\% \pm 13.7\%$  overall and  $80.9\% \pm 15.8\%$  when the drop regimen required dosing every two hours. Seventeen patients had no follow-up examinations at six months or one year; for the remaining 73, target IOP was achieved at the final visit in 59 (80.8%). Factors associated with poorer adherence included older age and features suggestive of worse glaucoma disease, such as greater visual field loss in the operated eye. —Summary by Jean Shaw

## Ophthalmology Retina

Selected by Andrew P. Schachat, MD

### Using Federated Learning to Standardize ROP Diagnosis

August 2022

Federated learning (FL) is an approach used to train deep learning (DL) models across institutions without sharing data between them. Hanif et al. set out to determine whether FL could be used to delineate institutional differences in the diagnosis of retinopathy of prematurity (ROP). They found differences in the clinical diagnoses of plus disease and overall levels of ROP severity between institutions.

For this informatics study, a total of 867 patients (1,686 eyes) across seven institutions were represented by the 5,245 wide-angle retinal images from neonatal ICUs of the participating institutions. The images were labeled with the clinical diagnoses of plus disease (plus, preplus, and no plus), which were documented in the chart, and a reference standard diagnosis (RSD) was determined by three graders and the clinical diagnosis.

The researchers trained a DL model for plus disease classification, using the clinical labels. The three clinical probabilities were then converted into a vascular severity score (VSS) for each eye exam, as well as an “institutional VSS” (for the latter, the average of the VSS values assigned to patients’ worse eyes at each examination was calculated for each institution). Demographics, clinical diagnoses of plus disease, and institutional scores were compared using multiple analytic methods.

Overall, the proportion of patients who developed plus disease was 8.1% by clinical diagnosis and 8.2% by RSD. However, there were significant differences between the clinical diagnosis of plus and an RSD of plus at the institutional level, ranging from 0% at one site to 8.9% at another—and for preplus disease, this variance at the institutional level ranged from 2.08% at one site to 15.6% at another. Moreover, the researchers found that the institutional VSS varied significantly by site.

These findings suggest variability in diagnostic paradigms among clinicians, the researchers said, and they suggested that an FL approach holds promise for objectively assessing such variability as well as any differences in disease severity between individual institutions. (Also see related commentary by Daniel Shu Wei Ting, MD, PhD, in the same issue.)

—Summary by Jean Shaw

## Ophthalmology Science

Selected by Emily Y. Chew, MD

### Using AI to Grade Cataract Severity

June 2022

Young Son et al. aimed to develop and validate an automated platform for diagnosing and grading cataracts using slit-lamp and retroillumination lens photographs. They found that their deep learning (DL)-based artificial intelligence (AI) platform was able to accurately and precisely detect and grade nuclear opalescence (NO), nuclear color (NC), cortical opacity (CO), and posterior subcapsular opacity (PSC).

For this cross-sectional study, the researchers evaluated 596 patients (887 eyes) who were 14 to 94 years old and had nuclear sclerotic, cortical, or posterior subcapsular cataracts. The images were graded by two trained graders, using the Lens Opacities Classification System (LOCS) III, and were divided into training, validation, and test datasets. Main outcome measures were diagnostic and LOCS III-based grading prediction performance.

A total of 1,335 slit-lamp and 637 retroillumination lens images were obtained. Of the slit-lamp images, 918 were in the training dataset, 152 were in the validation dataset, and 265 were in the test dataset. For the retroillumination lens images, these numbers were 435, 71, and 131, respectively.

For nuclear sclerotic cataracts, the AI system’s diagnostic performance of NO and NC showed excellent results—area under the curve (AUC) of .9992 and .9994 and accuracy of 98.82% and 98.51%, respectively. Excellent results also were achieved for cortical and

posterior subcapsular cataracts: the AUC for CO and PSC was .9680 and .9465, while accuracy was 96.21% and 92.17%, respectively.

All told, the results show the platform’s potential for accurate detection and grading in LOCS III 6- and 7-level classifications for all types of cataracts, the authors said.

—Summary by Jean Shaw

## American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

### Abuse-Related Head Trauma May Raise IOP

August 2022

Minckler et al. investigated orthograde axonal transport of amyloid precursor protein (APP-A4) in the retina and the lamina cribrosa (LC) portion of the optic nerve in the eyes of children believed to be victims of abusive head trauma (AHT). They found that nearly all globes with nerve heads available for analysis were positive for LC accumulation of the APP-A4 marker, emphasizing the importance of measuring and monitoring IOP in victims of head trauma.

For this case-control study, 36 pairs of cadaveric eyes from infants and toddlers with and without AHT were obtained from the Los Angeles coroner. Shaken baby syndrome was suspected in the AHT cohort. All eyes underwent immunohistochemistry, and axonal transport was assessed by light microscopy after paraffin processing. A proprietary biomicroscopy imaging software was used to estimate LC APP-A4 blockage in a subset of patients who survived their head injuries (n = 21).

In AHT eyes, accumulation of APP-A4 was found in retinal ganglion cell (RGC) bodies, in nerve fiber layer axons around the ends of Bruch membrane, and in LC optic nerve axon bundles. These observations indicate that the obstruction of axonal transport likely was caused by elevated IOP. Most of the 21 AHT suspects who survived at least one day (range: 1-1,588 days) exhibited accumulation of APP-A4.

Although seldom recorded and

not previously reported in the literature, IOP may be elevated in AHT for various reasons, said the authors. These include frequent retinal and vitreous hemorrhages and possible clogging of outflow pathways by red cells, macrophages, or fibrin, as noted in other studies. Other contributors may be constriction of ocular venous outflow by subdural blood expanding the optic nerve sheath, inflammation from retinal trauma debris, vitreous hemorrhage, angle contusion injury, and tears in anterior segment structures or the retina. Despite substantial artifactual retinal fragmentation and detachment, APP-A4 labeling of RGCs was a consistent finding in most AHT suspects in this study, as was the accumulation of APP-A4 reaction product in the LC of the anterior optic nerve.

In light of these findings and evidence from previous studies, the authors advise IOP assessment of patients with suspected AHT. They also encourage further pathologic studies of AHT.

### Is DMEK Posturing Necessary?

August 2022

Graft detachment is a common complication of Descemet membrane endothelial keratoplasty (DMEK) that often requires rebubbling or regrafting. It is believed that placing the patient in a supine position postoperatively may reduce the risk of graft detachment, but patients may be uncomfortable maintaining this position for long periods. Moreover, there is no consensus on which posturing regimen (with regard to length of time) is best. Given the lack of data on DMEK without posturing, Roberts et al. performed a retrospective review to explore the risk of graft detachment when post-op posturing does not take place. They found that the rate of this complication was low.

This interventional case series included 134 consecutively treated eyes (101 patients) that required DMEK for endothelial failure of any cause. DMEK was performed with an intraoperative inferior peripheral iridotomy. After unscrolling and centration of the graft, the anterior chamber was filled almost completely with 20% sulfur hexaflu-

oride (SF6). After filling, there was no intraoperative tamponade period or postoperative posturing. Main outcomes were the rates of graft detachment, rebubbling, and rejection; rates of primary and secondary failure; intraoperative and postoperative complications; and VA at months 3 and 12.

Postoperatively, all patients received topical preservative-free moxifloxacin .5% or chloramphenicol .5% four times daily for seven days. Detachment occurred in more than a third of the graft area in five eyes (3.7%) and in less than a third of the graft area in 19 eyes (14.2%). Rebubbling was required in 19 eyes (14.2%), and primary failure occurred in six eyes (4.5%). Graft survival lasted through 12 months in 122 eyes (91%). Nine eyes (6.7%) had an episode of endothelial rejection, and the average time to rejection was 9.5 months (range, 1-20 months). Two eyes (1.5%) had pupil blockage that required partial evacuation of the bubble; both occurred within post-op day 1. Among the eyes without a visually significant comorbidity, 96.6% had VA of 20/40 or better by three months; 30.3% had VA of 20/20 or better at this time. Within one year, VA was 20/20 or better in 98.5% and at least 20/20 in 39.4%.

Rebubbling rates in published literature range from .2% to 76% (mean, 28.8%). The low rate of rebubbling in the present study suggests that routine postoperative posturing may not be necessary, but further research is needed, said the authors. They recommend prospective direct comparisons of postured and posture-less DMEK.

—Summaries by Lynda Seminara

## JAMA Ophthalmology

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

### Long-Term Outcomes of Revised AREDS2 Supplement

July 2022

Chew et al. set out to assess the 10-year risk of developing lung cancer and late age-related macular degeneration (AMD) in participants of the Age-Related Disease Study 2 (AREDS2). They found that while the development of

lung cancer nearly doubled in former smokers who took the supplement with beta carotene, participants who took the version with lutein/zeaxanthin were not at increased risk of developing lung cancer. In addition, the researchers found that lutein/zeaxanthin was associated with a reduced risk of progression to late AMD.

For this follow-up study, the researchers evaluated 3,882 participants (6,351 eyes) of the original 4,203 patients in the AREDS2 cohort. The participants' mean age at baseline was 72 years, and 2,240 (57.7%) were women. Most self-identified as White (97.1%) or non-Hispanic (98.1%) individuals.

During the original study, participants were randomized to receive lutein/zeaxanthin and/or omega-3 fatty acids or placebo and, secondarily, to beta carotene versus no beta carotene and to high versus low doses of zinc. In this follow-up study, all participants received the AREDS2 supplements that had no beta carotene but did have lutein/zeaxanthin, vitamins C and E, and zinc plus copper. Outcomes were assessed every six months via telephone calls, and analyses of AMD progression and lung cancer development were conducted using proportional hazards regression and logistic regression, respectively.

During the full 10-year study period, 117 participants developed lung cancer, and 2,040 of the study eyes (48%) developed late AMD (the subtypes were unknown). At the 10-year mark, the odds ratio of having lung cancer was 1.82 for those randomly assigned to beta carotene and .91 for those who received lutein/zeaxanthin. When outcomes of lutein/zeaxanthin were compared to no lutein/zeaxanthin, the hazard ratio (HR) for progression to late AMD was .91. An analysis of lutein/zeaxanthin to beta carotene found that the HR for late AMD was .85.

These results provide further support for the addition of lutein/zeaxanthin to—and removal of beta carotene from—the AREDS2 supplement, the researchers said. Not only did former smokers in the lutein/zeaxanthin group have a lower risk of lung cancer, but the addition of lutein and zeaxanthin



also appeared to be associated with a decreased risk of progression to late AMD.

### **Omega-3 Supplements Ineffective for Dry Eye**

July 2022

Christen et al. evaluated whether long-term daily supplementation with marine omega-3 fatty acids prevents the development of dry eye disease (DED). They found that long-term supplementation did not reduce either the incidence of diagnosed DED or the occurrence of severe dry eye symptoms.

For this ancillary study of VITAL (Vitamin D and Omega-3 Trial), the researchers evaluated 23,523 U.S. adults who were free of a previous diagnosis of DED and were not experiencing severe symptoms of dry eye. Participants' mean age was 67 years, and they took either 1 g of marine omega-3 fatty acids (n = 11,757) or placebo (n = 11,766) daily. Main outcome measures included the incidence of clinically diagnosed DED, as confirmed by a review of the medical records.

During a median of 5.3 years of treatment (range, 3.8-6.1 years), 472 participants (2%) were clinically diagnosed with DED. There was no difference in diagnosed DED by assignment to the omega-3 or placebo cohort. Similarly, there was no difference between groups with regard to the incidence of severe symptoms of DED.

As a result, the authors said, the results do not support recommending marine omega-3 fatty acid supplements to patients as a strategy for reducing the incidence of dry eye disease. (*Also see related commentary by Penny A. Asbell, MD, MBA, and Maureen G. Maguire, PhD, in the same issue.*)

### **Anti-VEGF Cost Analysis: Implant Versus Injections**

July 2022

How do costs of the ranibizumab port delivery system (PDS) compare with intravitreal injections of anti-VEGF agents for the treatment of neovascular age-related macular degeneration (AMD)? Sood et al. addressed this

question in a cost analysis study. They found that the PDS costs more than intravitreal injections of ranibizumab and aflibercept under certain treatment scenarios. Bevacizumab injections were less costly than the PDS under all scenarios studied.

The authors used data from two clinical trials of the PDS and Medicare reimbursement rates. Main outcome measures included the number of intravitreal ranibizumab, aflibercept, and bevacizumab injections needed to break even with the cost of the PDS.

Results showed that the mean number of anti-VEGF injections needed to break even with the PDS was as follows:

- It took a mean of 6.4 ranibizumab, 5.5 aflibercept, and 34.5 bevacizumab injections to break even with the cost of the initial implantation of the PDS with medication.
- It took a mean of 10.8, 9.3, and 58.1 injections of ranibizumab, aflibercept, and bevacizumab, respectively, to break even with the cost of the PDS and one refill.
- A mean of 15.2 ranibizumab, 13.1 aflibercept, and 81.6 bevacizumab injections were needed to break even with the cost of the PDS with two refills at six-month intervals.
- To break even with the cost of an additional PDS refill, a mean of 4.4 ranibizumab, 3.8 aflibercept, and 23.6 bevacizumab injections were needed.

The authors noted that use of the PDS will rest on "other factors than cost, including safety, preferred practice, and willingness to undergo a surgery with frequent clinic visits." (*Also see related commentary by Shrijj Patel, MD, MBA, and Paul Sternberg Jr., MD, in the same issue.*)

—Summaries by Jean Shaw

## **OTHER JOURNALS**

Selected by Prem S. Subramanian, MD, PhD

### **Longitudinal Study of Link Between Visual Impairment and Depression**

*British Journal of Ophthalmology*  
Published online May 12, 2022

Studies of the relationship between

depression and visual impairment (VI) have not yielded consistent findings. In a nine-year nationwide study conducted in South Korea, Seong et al. found that visually impaired patients had a higher than normal risk of depression both before and after the documentation of VI.

The researchers included 131,434 adults from the Korean National Health Information Database with VI identified by objective VA testing between 2005 and 2013. Using 1:1 propensity score matching, randomly selected patients matched by age, sex, residential area, and household income (control group) were compared with patients known to have VI (patient group). Patients' data were collected from at least three years before being registered in the national database as visually impaired through a minimum of five years thereafter. Korean Standard Classification of Diseases codes (F32 and F33) and insurance claims were used to identify cases of depression. The risk of depression was assessed using a conditional logistic regression model.

Among the study population, depression was experienced by 9,011 control participants and 16,451 members of the patient group. In the years leading to documentation of VI, the risk of depression gradually increased. The odds ratio (OR) of depression occurring three years prior to VI was 1.186, which increased to 1.925 by the time of VI documentation. In the subsequent five years, the risk of depression decreased slowly. By year 5, the OR was 1.128. Despite the decreasing trend, the risk of depression remained significant in the patient cohort throughout the five years. The risk of depression was highest for men, patients with severe VI, and younger individuals (18-29 years of age), with reduced self-esteem from VI being suggested as a driver of depression, particularly in the younger patients. The authors recommend earlier screening and intervention in patients at high risk.

—Summary by Lynda Seminara

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