

# Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

## Ophthalmology

Selected by Stephen D. McLeod, MD

### Treatment Patterns for Myopic Choroidal Neovascularization

July 2017

Willis et al. used data from the IRIS Registry to characterize treatment patterns and outcomes for patients with myopic choroidal neovascularization (mCNV) in the United States. They found that the most common treatment for mCNV was injections of anti-vascular endothelial growth factor (VEGF) drugs, and that one-fourth of patients who received no treatment experienced a decline in vision.

This retrospective cohort study included 185 adults with treatment-naïve mCNV (in at least 1 eye) who were seen in clinics participating in the Academy's IRIS Registry during a 3-year period. The type of initial treatment for mCNV (within 365 days of diagnosis) was categorized as either observation, intravitreal anti-VEGF injection, verteporfin photodynamic therapy (vPDT), or laser photocoagulation. The difference in visual acuity between the diagnosis date and 1 year afterward was documented. For that same 1-year period, the frequency of anti-VEGF injection per treated eye was estimated.

Active treatment within 1 year of diagnosis was reported for 73% of the patients ( $n = 135$ ); all other patients were observed ( $n = 50$ ). Of those treated actively, 134 (99%) received anti-VEGF injections, and 1 underwent vPDT. The mean number of anti-VEGF injections

per affected eye during the year following diagnosis was 2.8. In addition, anti-VEGF treatment was associated with significant improvement in visual acuity by 1 year of therapy (mean logMAR improvement, 0.17 units; 95% confidence interval [CI], 0.12-0.20;  $p < .01$ ). Eyes that were not treated during the first year showed significant visual decline (mean logMAR decline, 0.03 units; 95% CI, 0.008-0.05;  $p < .01$ ).

In conclusion, the most common treatment for mCNV in the United States is intravitreal injections of anti-VEGF medications. This strategy is highly effective for improving visual acuity, and many untreated patients experience visual decline. Additional studies are warranted to understand the barriers to delivering anti-VEGF therapy to patients with mCNV.

### Automated Identification of Diabetic Retinopathy Using Deep Learning

July 2017

As many cases of diabetic retinopathy (DR) are undiagnosed and untreated, improvements in screening and detection are needed. Gargeya and Leng developed technology to automate



DR screening and found that a data-driven grading algorithm based on artificial intelligence (AI) and fundus photography can help identify patients with diabetes who require further evaluation and treatment.

The authors obtained 75,137 publicly available fundus images from patients with diabetes. The images were used to develop and test an AI model capable of differentiating healthy

fundi from those with DR. For external validation, the model was tested using images from the Messidor 2 and eOphtha databases. The information gleaned via the automated screening was then displayed through an automatically generated abnormality heatmap, and specific subregions of each fundus image were highlighted for further clinical review.

The testing procedure trained 5 separate models, each holding out a distinct validation pool of approximately 15,000 images. Average metrics were derived from 5 test runs on respective held-out data by comparing the model's predictions with the gold standard determined by the panel of retina specialists. Area under the receiver operating characteristic curve (AUC) was selected as the metric to measure the precision-recall trade-off of the algorithm. Sensitivity and specificity also were calculated.

The model achieved an AUC of 0.97, with 94% sensitivity and 98% specificity

on 5-fold cross-validation using the local data set. Testing against the independent Messidor 2 and eOphtha data yielded AUC scores of 0.94 and 0.95, respectively.

The authors concluded that their algorithm is a reliable tool for automated detection of DR. It also offers ease of use, as it can be run on personal computers and smartphones.

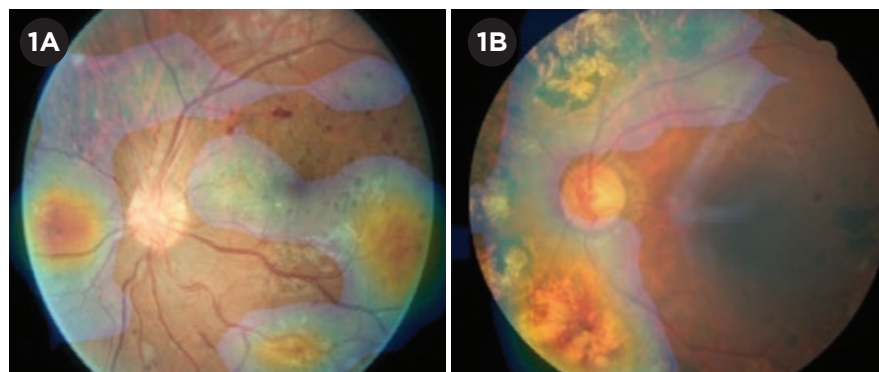
## Temporal Relation Between mGCIPL and pRNFL Loss in Glaucoma

July 2017

In a longitudinal study of patients with glaucoma, Kim et al. confirmed that thinning of the inferior macular ganglion cell–inner plexiform layer (mGCIPL) can be detected before defects are apparent in the peripapillary retinal nerve fiber layer (pRNFL). However, they cautioned that this finding may relate to high sensitivity of the mGCIPL map.

This 3-year retrospective study involved 151 patients (mean age, 51 years) with primary open-angle glaucoma and a visual field mean deviation of  $-1.5$  to  $-5.5$  decibels. Spectral-domain optical coherence tomography (OCT) mGCIPL and pRNFL deviation maps, obtained at baseline and follow-up, were superimposed onto RNFL photography using vascular landmarks to produce an integrated map. The pRNFL changes were further subdivided by location (i.e., macular vulnerability zone and inferoinferior portion). The primary outcome was temporal sequence of inferior mGCIPL loss with a corresponding pRNFL defect observed on the integrated deviation map.

At baseline, 99 (66%) of the 151 eyes showed inferior mGCIPL loss. Inferoinferior pRNFL defects were more common than pRNFL defects in the macular vulnerability zone (MVZ; 112 eyes [74%] and 5 eyes [3%], respectively). Three years later, 112 eyes (74%) demonstrated inferior mGCIPL loss, 123 eyes (82%) had inferoinferior pRNFL defects, and 25 eyes (17%) had pRNFL defects in the macular vulnerability zone. Among the 94 eyes that initially exhibited inferior mGCIPL thinning but no MVZ-pRNFL defect,



**DEEP LEARNING VISUALIZATION MAPS.** Fundus heatmaps overlaid on fundus images, highlighting pathologic regions (1A) in the nasal and temporal quadrants and (1B) in the upper and lower left quadrants.

19 (20%) showed this defect at follow-up. Of the 52 eyes without evidence of mGCIPL loss at baseline, only 1 (2%;  $p < .001$ ) subsequently demonstrated an MVZ-pRNFL defect.

Although inferoinferior pRNFL defects could be detected before inferior mGCIPL changes on the OCT deviation map in some eyes, no MVZ-pRNFL defects were identified before inferior mGCIPL changes. The authors deduced that change in the macular retinal ganglion cells precedes change in the corresponding pRNFL. They recommended adding macular OCT imaging when assessing structural loss in patients with early-stage glaucoma.

—Summaries by Lynda Seminara

## Ophthalmology Retina

Selected by Andrew P. Schachat, MD

### Sensitivity and Specificity of OCT-A to Detect Choroidal Neovascularization

July/August 2017

Faridi et al. set out to determine the sensitivity and specificity of optical coherence tomography angiography (OCT-A) when used to detect choroidal neovascularization (CNV) in eyes with age-related macular degeneration (AMD). They found that a combined approach—en face OCT-A plus cross-sectional OCT-A—is not only superior to that of en face OCT-A alone but also approaches the accuracy of the gold standard, fluorescein angiography.

The researchers evaluated 72 eyes. Of these, 32 had treatment-naïve CNV,

20 had dry AMD, and the remaining 20 had no pathology. All eyes were assessed via spectral-domain OCT (SD-OCT), and the 3D angiogram was segmented into separate en face views, including the inner retinal angiogram, the outer retinal angiogram, and the choriocapillaris angiogram. Two masked graders then reviewed the following sets of images: en face OCT-A alone, SD-OCT alone, and en face OCT-A plus cross-sectional OCT-A.

In evaluating the 32 eyes with CNV, both graders identified 26 true positives with en face OCT-A alone, for a sensitivity of 81.3%. SD-OCT alone had a sensitivity of 100%, as did the combination of en face OCT-A and cross-sectional OCT-A. The specificity results were 92.5% for grader A and 97.5% for grader B for en face OCT-A alone; 97.5% for grader A and 97.5% for grader B for SD-OCT alone; and 97.5% for grader A and 100% for grader B for the combination of en face OCT-A and cross-sectional OCT-A.

The researchers noted that larger clinical studies are needed to validate the use of OCT-A in determining whether any visualized fluid is related to CNV or to other retinal diseases, such as diabetic macular edema or retinal vein occlusion. In the interim, they said, the process of reviewing cross-sectional OCT-A scans should help clinicians both confirm the presence of CNV and distinguish between pathology and artifact.

—Summary by Jean Shaw

(See page 15 for Ophthalmology Retina subscription information.)

## American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

### Anterior Chamber Angle and Segment Structure in ROP

July 2017

Chang et al. compared structural aspects of the anterior chamber angle (ACA) and related optic components among children with and without retinopathy of prematurity (ROP). They observed that eyes with ROP had a narrower ACA, a more anteriorly curved iris, a steeper cornea, and thicker lenses.

This prospective cross-sectional study included 29 children (54 eyes) with a history of ROP and 67 healthy, aged-matched controls (134 eyes). Mean gestational ages were 26.7 and 38.4 weeks, respectively. Children with ROP had undergone laser therapy prior to study entry.

The ACA structures of all participants were evaluated by gonioscopy. The primary outcome measure was angularity of the anterior chamber and related anatomic changes.

Compared with healthy controls, children with ROP exhibited a narrower ACA ( $p < .001$ ), steeper iris curvature ( $p = .002$ ), and a more anteriorly inserted iris ( $p = .08$ ). ROP-affected eyes also had steeper corneas, shallower anterior chamber depth, thicker lenses, and greater refractive errors (all  $p < .001$  vs. control eyes). The mean ( $\pm$  standard deviation) best-corrected visual acuity was  $0.1 \pm 0.2$  in the ROP group and  $0.01 \pm 0.04$  in the control group ( $p < .001$ ). Mean spherical powers were  $-3.5 \pm 5.2$  D and  $-0.8 \pm 2.3$  D, respectively ( $p < .001$ ). Axial length was similar for the 2 study groups.

The authors concluded that more research is needed to explore associations between the abnormal structural findings and the development of other ocular diseases, including glaucoma.

### Stem Cell Tx for Retinal Disease

July 2017

In a review-based perspective article, Rao et al. recommended that clinicians

exercise caution when considering stem cell therapies for patients with retinal diseases. The authors emphasized that rigorous safety and efficacy analyses are lacking for these treatments and that federal regulations for trials involving stem cells may not be sufficiently stringent.

In theory, stem cell therapies may restore visual acuity in patients with age-related or inherited retinal degeneration. In practice, no patient has had improvement in visual acuity or retinal electrophysiology after transplantation of pluripotent fetal or adult stem cells. Autologous induced pluripotent stem cells (iPSCs), prepared from somatic cells, can be differentiated to yield retinal pigment epithelium with low immunogenicity. However, cancer-driver mutations may be incorporated during preparation of iPSCs, and the process of ensuring that cells are free of these mutations is a costly one. Presently, the aim of most stem cell therapies for retinal disease is to support survival of the patient's existing retinal cells by trophic stimulation, not to replace these cells.

Approximately 30 trials of stem cell-based treatments for retinal diseases are listed at [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov), but no treatment has been approved by the U.S. Food and Drug Administration. Although the 21st Century Cures Act allows for expedited approval of certain regenerative techniques, this law may allow treatments to be approved before long-term safety or efficacy data are available. Currently, most trials involve transplanting adult stem cells, which may be harvested from nonocular sites such as bone marrow or adipose tissue. Preclinical results have shown adverse effects and no benefits of applying adipose-derived stem cells to treat retinal disease.

Despite the promise of these therapies and some early data suggesting acceptable safety profiles, serious complications have occurred, including hemorrhage, proliferative vitreoretinopathy, retinal detachment, and blindness. The authors concluded that ophthalmologists should use caution when considering stem cell interventions for patients with retinal disease.

—Summaries by Lynda Seminara

## JAMA Ophthalmology

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

### RVO-Related Macular Edema: Baseline Factors and Outcomes

June 2017

Declining visual acuity is a common complication of macular edema secondary to retinal vein occlusion (RVO). The Study of Comparative Treatments for RVO 2 (SCORE2) provided valuable data on bevacizumab versus aflibercept for treatment of vision loss and central subfield thickness (CST) on optical coherence tomography (OCT) in eyes with RVO-related macular edema. An additional analysis of data by Scott et al. revealed that younger age and poorer vision at baseline correlated with better visual acuity (VA) results at 6 months and that aflibercept produced more favorable CST (but not VA) outcomes.

In SCORE2, 304 patients with central RVO (CRVO) and 58 patients with hemi-RVO were assigned randomly (1:1) to receive 6 monthly treatments with repackaged (compounded) bevacizumab or aflibercept (1.25-mg and 2-mg intravitreal injections, respectively). VA assessments and spectral-domain OCT were performed monthly. For the primary outcome results, the mean change in VA from baseline in the bevacizumab group was noninferior to (not worse than) than in the aflibercept group.

Subsequent multivariate analyses demonstrated that, regardless of treatment, younger age and lower (worse) baseline VA were associated with a 6-month gain of  $\geq 15$  letters. Compared with bevacizumab, aflibercept was more likely to result in resolution of macular edema and CST below 300  $\mu\text{m}$ . The odds of edema resolution were lower for eyes that received intravitreal injections before study entry than for treatment-naïve eyes.

The authors noted that the association of younger age and worse baseline vision with greater improvement in VA was consistent with outcomes in previously published research. These



findings, coupled with the greater efficacy of aflibercept in reducing retinal thickness and resolving edema, may help clinicians predict responses to short-term therapy for macular edema caused by CRVO or hemi-RVO. However, the authors cautioned that SCORE2 results were based on excellent patient adherence to treatment and that the primary finding that bevacizumab was noninferior to aflibercept with respect to VA improvement at 6 months should be kept in mind. (*Also see related commentary by Jennifer K. Sun, MD, MPH, in the same issue.*)

### **Portable Brain-Computer Device for Detecting Glaucoma**

June 2017

Nakanishi et al. conducted a case-control study to evaluate the utility of the nGoggle—a portable, wireless brain-computer interface device—in assessing loss of visual function in patients with glaucoma. The authors determined that the nGoggle enables discrimination of glaucomatous eyes from healthy eyes and has good test-retest reliability.

The nGoggle is a head-mounted unit that records and processes multifocal, steady-state, visual-evoked potentials (mfSSVEPs). In the study, 33 patients (62 eyes) with glaucoma and 17 healthy controls (30 eyes) were evaluated by standard automated perimetry and the nGoggle. The capacity of these modalities to distinguish glaucomatous eyes from healthy eyes was compared in terms of global and sectoral parameters. Diagnostic accuracy was expressed as area under the receiver operating characteristic curve (AUC). An AUC of 1.0 denotes perfect discrimination, whereas an AUC of 0.5 indicates chance discrimination.

Repeatability of nGoggle measurements was determined by testing 20 glaucomatous eyes (10 patients) in 3 weekly sessions and computing intraclass correlation coefficients (ICCs) and coefficients of variation. A canonical correlation analysis (CCA) was performed as a spatial filter to yield mfSSVEP-CCA parameters that were robust to artifacts.

In nGoggle tests, the mean global mfSSVEP of eyes with glaucoma was lower than that of healthy eyes (0.289 vs. 0.334, respectively). The AUC for nGoggle global mfSSVEP was 0.92; this exceeded global parameters obtained by standard automated perimetry, including mean deviation (AUC, 0.81), mean sensitivity (AUC, 0.80), and pattern standard deviation (AUC, 0.77). The modalities did not differ significantly in accuracy of sectoral measurements. For the nGoggle, the mean coefficient of variation of the mfSSVEP-CCA global parameter was 3.03%, and the average ICC was 0.92. (An ICC of  $\geq 0.75$  was considered indicative of good reproducibility.)

The authors concluded that this device can differentiate glaucomatous eyes from unaffected eyes. The adequate repeatability suggests that the device may be suitable for objective longitudinal assessment of glaucoma progression.

### **Cost-Effectiveness of Ranibizumab or PRP for Proliferative DR**

June 2017

Hutton et al. conducted a preplanned cost analysis of data from a randomized clinical trial in which ranibizumab had noninferior visual acuity (VA) outcomes at 2 years when compared to panretinal photocoagulation (PRP) for treating proliferative diabetic retinopathy (PDR). The authors noted that ranibizumab appears more cost-effective than PRP if the PDR is accompanied by vision-impairing diabetic macular edema (DME) for which anti-VEGF treatment would be given for the DME. That is, ranibizumab given for both the PDR and DME appears more cost-effective than giving ranibizumab for the DME and PRP for the PDR.

In a secondary analysis of the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol S trial, data were evaluated for 213 adults with PDR who had undergone unilateral therapy in the initial study. Study participants had been randomly assigned to receive intravitreal ranibizumab (administered monthly or less frequently) or PRP (performed at baseline and, if

needed, at follow-up). Any participant with concomitant vision-impairing DME received ranibizumab, regardless of initial treatment assignment.

In the original study, ranibizumab was deemed noninferior to PRP for the primary outcome of mean change in VA from baseline to 2 years. Furthermore, there were advantages to the anti-VEGF arm, including better VA over 2 years, fewer vitrectomies, less peripheral field loss, and decreased chance of developing DME with vision loss among eyes without vision-impairing DME at baseline. However, 1 injection of ranibizumab costs nearly 6 times more than a session of PRP. In the cost analysis, 2-year data of costs of treatment and complications (in dollars) and effectiveness (in quality-adjusted life-year, or QALY, based on VA outcomes) for ranibizumab and PRP were compared for the patients with ( $n = 46$ ) and without ( $n = 167$ ) vision-impairing DME at baseline.

The results, expressed as incremental cost-effectiveness ratios of ranibizumab versus PRP during the 2-year period, were \$55,568 per QALY for patients with DME and \$662,978 per QALY for those without DME. (In the United States, \$50,000 to \$150,000 per QALY typically is considered cost-effective.)

The authors cautioned that cost-effectiveness beyond 2 years of follow-up is not known, nor is the effectiveness of other anti-VEGF agents, such as aflibercept or compounded bevacizumab. The authors recommended weighing the pros and cons of ranibizumab and PRP on a case-by-case basis. (*Also see related commentary by Steven M. Kymes, PhD, in the same issue.*)

—Summaries by Lynda Seminara

## **OTHER JOURNALS**

Selected by Deepak P. Edward, MD

### **Adalimumab Plus Methotrexate for JIA-Associated Uveitis**

*New England Journal of Medicine* 2017;376(17):1637-1646

Ramanan et al. evaluated the efficacy of adalimumab for uveitis associated with juvenile idiopathic arthritis (JIA) and found that the combination of

adalimumab and methotrexate controls inflammation and results in fewer treatment failures than does methotrexate alone. However, they also found that adverse events are more common in patients treated with adalimumab.

In this placebo-controlled study, the efficacy and safety of adalimumab were assessed among 90 children and adolescents ( $\geq 2$  years of age) who had active JIA-associated uveitis. All patients were on a stable dose of methotrexate at study entry and were assigned randomly (2:1) to receive either adalimumab (20 mg or 40 mg, according to body weight) or placebo every 2 weeks by subcutaneous injection. The trial regimen was continued until treatment failure or until 18 months had elapsed. The primary endpoint was time to treatment failure.

During follow-up of  $\leq 2$  years, treatment failure occurred in 16 (27%) of the 60 children who received adalimumab and in 18 (60%) of the 30 who received placebo (hazard ratio, 0.25; 95% confidence interval, 0.12-0.49;  $p < .0001$ ). With regard to adverse events, 10.07 events occurred per patient-year in the adalimumab arm, versus 6.51 events per patient-year in the placebo group. The frequency of serious adverse events also was greater in the adalimumab group: 0.29 events per patient-year versus 0.19 events per patient-year in the placebo group. The most common adverse effects associated with adalimumab were minor infections, respiratory disorders, and gastrointestinal conditions. The follow-up time was insufficient to detect events such as cancer or demyelinating diseases.

### **Retinal Architecture, Intrathecal Immunity, and Clinical Course in Multiple Sclerosis**

*JAMA Neurology*

Published online May 1, 2017

**Knier et al.** assessed potential relationships between retinal volume, immunologic variables in the cerebrospinal fluid, and the course of disability in patients with relapsing-remitting multiple sclerosis (MS). They found that atrophy of the retinal ganglion cell layer correlates with elevated intrathecal B-cell fractions and is a strong independent

risk factor for worsening disability. In addition, a thicker inner nuclear layer indicated enhanced brain activity on magnetic resonance imaging (MRI).

For this observational study, the researchers evaluated 312 adults who were treated at the same hospital. Patients in cohort 1 ( $n = 72$ ) had very early disease (i.e., first relapse within 3 months of study entry). Patients in cohort 2 ( $n = 240$ ) had disease duration of at least 12 months at study baseline. All underwent optical coherence tomography (OCT) and MRI. The primary outcome variable was confirmation of worsening disability.

For cohort 1, volumes of the common ganglion cell-inner plexiform layer (GCIPL) and the inner nuclear layer (INL) were compared with immunoglobulin indices and the frequency of immune cells in cerebrospinal fluid to detect potential associations. Volume of the GCIPL itself (for both cohorts) or the GCIPL corrected for intrathecal B-cell frequencies (cohort 1) was examined in relation to disability course.

In cohort 1, low GCIPL volume was associated with greater frequency of intrathecal B cells and with intrathecal immunoglobulin G synthesis. INL volume correlated with the quantity of intrathecal CD56<sup>bright</sup> natural killer cells ( $r = 0.28$ ;  $p = .007$ ). Low GCIPL volume ( $\leq 1.99 \text{ mm}^3$ ) denoted a 6.4-fold risk for worsening disability in cohort 1 and a 2.4-fold risk in cohort 2 (versus higher volumes). For both cohorts, INL volume correlated with subsequent increases in gadolinium-enhancing lesions and the T2 lesion load.

In conclusion, GCIPL loss is an independent risk factor for worsening disability in relapsing-remitting multiple sclerosis. OCT of the retina may help determine the most appropriate treatment for each patient.

—*Summaries by Lynda Seminara*

### **Evidence-Based Screening for DR in Type 1 Diabetes**

*New England Journal of Medicine*  
2017;376(16):1507-1516

**Nathan et al.** used retinal photographs from 2 long-running studies of type 1 diabetes to develop an evidence-based

fundus photography screening program for diabetic retinopathy (DR). They found that their program, which takes patients' retinopathy status and glycated hemoglobin level into account, could reduce the frequency of eye examinations without delaying the diagnosis of clinically significant disease.

For this study, the authors used data and fundus photographs from the Diabetes Control and Complications Trial (DCCT), which ran from 1983 to 1993, and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study, which started in 1994 and is still ongoing. All told, the researchers were able to draw upon approximately 24,000 ophthalmologic assessments with 7-field fundus photography that were performed at intervals of 6-48 months during almost 30 years of follow-up. They then employed Markov modeling to determine the likelihood of progression to proliferative DR or clinically significant macular edema (ME).

The Markov models provided estimates of 5 states of DR progression, from preclinical (state 1) to proliferative DR or vision-threatening ME (state 5). State 1 patients or those with mild DR (state 2) were unlikely to progress to state 5 disease over a period of  $\geq 4$  years. However, those who had moderate (state 3) or severe (state 4) DR were highly likely to experience progression within a short time frame.

Overall, the data suggest that a practical, evidence-based screening schedule for time to next examination would be 4 years for state 1, 3 years for state 2, 6 months for state 3, and 4 months for state 4 disease. More frequent screening would be required for patients with higher glycated hemoglobin levels, as elevated mean glycated hemoglobin was strongly associated with a higher risk of progression. For instance, state 1 patients with a glycated hemoglobin level of 6% had a 1% risk of progressing to state 5 disease over a 5-year period. In contrast, the risk of progression from state 1 to state 5 for those with a glycated hemoglobin level of 10% was 4.3% over 3 years.

—*Summary by Jean Shaw*