

# Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

## Ophthalmology

Selected by Stephen D. McLeod, MD

### Deep Learning for Identifying Eyes at Risk for Glaucomatous Optic Neuropathy

December 2019

Phene et al. developed an algorithm based on deep learning and tested its effectiveness for photographic features of the optic nerve head (ONH) that would prompt referral for further evaluation of glaucomatous optic neuropathy (referable GON). They found that a deep learning algorithm trained solely on fundus images has greater sensitivity than eye care providers for detecting referable GON; specificity was comparable for the two methods of detection.

The fundus images used in this research were obtained from screening programs, published studies, and a glaucoma clinic. The algorithm was trained using 86,618 images that also were graded by eye care providers for glaucomatous ONH features and referable GON. Of the 43 graders, 14 were fellowship-trained glaucoma specialists, 26 were comprehensive ophthalmologists, and three were optometrists.

The algorithm was validated using three datasets: 1) Dataset A included 1,205 images (one per patient; 18.1% referable) adjudicated by panels of glaucoma specialists; 2) dataset B consisted of 9,642 images (one per patient; 9.2% referable) from a diabetic teleretinal screening program; and 3) dataset C comprised 346 images (one per patient; 81.7% referable) from

a glaucoma clinic. Outcome measures were area under the receiver operating characteristic curve (AUC), sensitivity, and specificity for referable GON and glaucomatous ONH features.

The algorithm's AUC for referable GON was 0.945 in dataset A (95% confidence interval [CI], 0.929-0.960), 0.855 in dataset B (95% CI, 0.841-0.870), and 0.881 in dataset C (95% CI, 0.838-0.918). AUCs for glaucomatous ONH features ranged from 0.661 to 0.973. The sensitivity of the algorithm was significantly higher than that of seven of 10 graders not involved in determining the reference standard, including two of three glaucoma specialists. The specificity of the algorithm exceeded that of three graders (including one glaucoma specialist) and was comparable to that of other graders. The algorithm performed favorably across independent datasets. According to specialists and the algorithm, crucial features of referable GON were vertical cup-to-disc ratio  $\geq 0.7$ , notching of the neuroretinal rim, abnormality of the retinal nerve fiber layer, and barring of the circumlinear vessels.

The authors suggested that algorithms such as this one may improve the effectiveness of glaucoma screening

in settings without clinicians who can interpret ONH features.

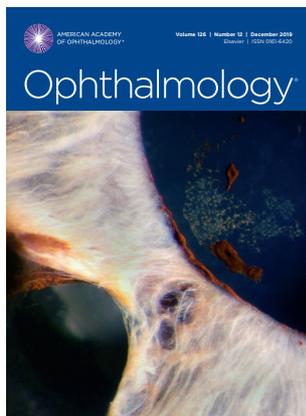
### OCT Predictors of DR Progression and DME

December 2019

Sun et al. assessed the relationship between metrics of optical coherence tomography angiography (OCTA) and the progression of diabetic retinopathy (DR) and development of diabetic macular edema (DME) in patients with diabetes. They identified key predictors of DR progression and DME development, thus supporting the predictive value of OCTA.

This prospective study included 129 patients (205 eyes) with diabetes who were monitored for at least two years. OCTA images of the superficial and deep capillary plexuses were generated by digital software. After a quality check, automated measurements were obtained of the foveal avascular zone (FAZ) area, FAZ circularity, vessel density, and fractal dimension of the superficial and deep capillary plexuses. Main outcomes were progression of DR and development of DME.

During follow-up (median, 27.14 months), DR progressed in 28 (13.7%) of the 205 eyes. Of the 194 eyes without DME at baseline, 17 (8.8%) developed the condition during the study. After adjustment for established risk factors (DR severity, HbA<sub>1c</sub> levels, age, diabe-



tes duration, and mean arterial blood pressure), significant predictors of DR progression were larger FAZ area, lower vessel density, and lower fractal dimension of the deep capillary plexus. With regard to DME development, lower vessel density of the superficial capillary plexus proved to be the significant prognostic factor.

In summary, better predictions of DR progression and DME can be attained by combining OCTA metrics with traditional risk factors, said the authors. Additional studies are needed to determine whether such metrics could identify subgroups of patients with DR who might benefit from more intensive workups or proactive treatment.

### **Imaging Nonperfusion in Patients With DME: Comparing Techniques**

December 2019

**Couturier et al.** compared retinal nonperfusion observations for two imaging modalities after anti-VEGF treatment of diabetic macular edema (DME). They found that swept-source widefield optical coherence tomography angiography (SS-WF OCTA) performed better than ultra-widefield fluorescein angiography (UWF FA) in detecting nonperfusion. However, after three treatment sessions, neither modality demonstrated reperfusion of arterioles or venules in areas of nonperfusion, despite improvement in the severity of diabetic retinopathy (DR).

This study was performed in nine patients (10 eyes) who had proliferative or severe nonproliferative DR. All received three intravitreal anti-VEGF injections for their DME, and all eyes were imaged with UWF color fundus photographs, UWF FA, and SS-WF OCTA. Imaging took place at baseline and one month after the third injection. The images were aligned and then divided into 16 identical boxes for analysis by two masked retina specialists. Main outcome measures included discrepancies in detection of nonperfusion between the two imaging modalities; assessment of DR severity by UWF fundus photographs; and changes in each area of nonperfusion between baseline and follow-up. (For the latter,

this included the number of 1) boxes per eye with at least one area of nonperfusion, 2) arterioles or venules that disappeared or reappeared, and 3) areas of nonperfusion in which capillaries disappeared or reappeared.)

Results showed that DR severity improved by at least one stage in eight of the 10 eyes. Evidence of this included a decrease in the mean number of microaneurysms and retinal hemorrhages on UWF photography at follow-up ( $40 \pm 28$  vs.  $121 \pm 57$  at baseline;  $p = .0020$ ) and by regression of fundus neovascularization if it had been present. All areas of nonperfusion identified by UWF FA also were observed with SS-WF OCTA, but the latter detected additional areas at baseline in 29% of boxes. Neither modality showed reperfusion of arterioles or venules at follow-up, even when a reduction in dark areas was apparent by UWF FA. Retinal capillaries were visible only with SS-WF OCTA.

The authors concluded that the unchanged number of areas of nonperfusion implies that neovascular complications may persist even if DR improves. Absence of reperfusion following anti-VEGF therapy highlights the risk of visual loss in patients who miss scheduled treatments.

—*Summaries by Lynda Seminara*

### **Ophthalmology Glaucoma**

Selected by Henry D. Jampel, MD, MPH

#### **RNFL Maps and Deep Learning**

November/December 2019

**Wang et al.** used full retinal nerve fiber layer (RNFL) thickness maps from patients with glaucoma and healthy controls to evaluate the diagnostic accuracy of four different machine learning algorithms. They found that all four models achieved similarly high diagnostic accuracies.

For this case-control study, the researchers evaluated 69 patients (93 eyes) with glaucoma and 128 healthy controls (128 eyes) from the Los Angeles Latino Eye Study (LALES). There was no significant difference in age, sex, best-corrected visual acuity, or axial

length between the two groups.

RNFL maps centered on the optic nerve head were supplied to two conventional machine learning algorithms and two convolutional neural nets, one of which was a custom-made deep learning network. AUC (area under the curve) values for the four models were greater than 0.90 (range, 0.91-0.92). In contrast, the AUC for mean circum-papillary RNFL thickness was 0.76 in the same patient population.

The findings support the importance of the spatial structure of RNFL thickness map data in diagnosing glaucoma, the researchers said. They cautioned that as the study participants were from the LALES, the results may not be applicable to other ethnic populations. —*Summary by Jean Shaw*

### **Ophthalmology Retina**

Selected by Andrew P. Schachat, MD

#### **Treatment of Retinal Tears and ERM Formation**

December 2019

Retinal tears can be treated with laser retinopexy or cryoretinopexy. Is one method more likely than the other to lead to formation of an epiretinal membrane (ERM)? **Blackorby et al.** set out to evaluate this issue and found no difference in the incidence, timing, or severity of ERM formation between the two treatments.

For this study, the researchers evaluated the charts of patients treated at a single surgical site over a 11-year period. Data were available on 2,257 eyes (2,257 patients). Of these, 1,655 were treated with laser retinopexy, and 602 were treated with cryoretinopexy.

All told, 74 patients (3.2%) experienced an ERM after treatment for a retinal tear. Of these, 26 had undergone cryoretinopexy, and 48 had been treated with laser retinopexy. The average time to ERM development was 11.5 months for those in the cryoretinopexy group and 12 months in those who had received laser retinopexy ( $p = 0.878$ ). Seven ERMs required surgical treatment; of these, two were in the cryoretinopexy group.

Given the lack of a statistically sig-

nificant difference in the incidence of macular ERM formation between the two groups, the researchers recommend that the choice of treatment for retinal tears rest on such issues as media clarity, retinal tear position, and extent of pathologic features.

—Summary by Jean Shaw

## American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

### Predicting POAG Progression With Machine Learning

December 2019

Can data-trained machine learning be used to identify glaucoma cases at high risk of progression? In addressing this question, **Baxter et al.** used a discrete event captured in the electronic health record (EHR)—surgical intervention—as a marker for progressive disease in patients with primary open-angle glaucoma (POAG). They found that some details in the EHR may have predictive value even if eye-specific data are lacking; pertinent information included blood pressure findings and certain classes of medication.

The authors collected EHR data for 385 patients with POAG who were treated at the same academic institution. The data were integrated into three models: multivariable logistic regression, random forests, and artificial neural networks. Leave-one-out cross-validation was applied. The performance of each model was tested by calculating mean area under the receiver operating characteristic curve (AUC) as well as sensitivity, specificity, accuracy, and the Youden index.

The analysis showed that multivariable logistic regression was the most effective model for predicting progressive disease that would require surgery (AUC, 0.67). The other models were close behind (AUC, 0.65 for both). In the logistic regression model, higher mean systolic blood pressure was found to significantly increase the likelihood of glaucoma surgery (odds ratio [OR], 1.09;  $p < .001$ ). Conversely, lower likelihood of surgery was linked to use of ophthalmic medications (OR, 0.28;  $p <$

.001), nonopioid analgesics (OR, 0.21;  $p = .002$ ), antihyperlipidemic medications (OR, 0.39;  $p = .004$ ), macrolide antibiotics (OR, 0.40;  $p = .03$ ), and calcium blockers (OR, 0.43;  $p = .03$ ). The authors acknowledged that the favorable findings for nonophthalmic drug classes may support the exploration of possible new therapeutic targets.

Accuracy was similar for the three models, ranging from 0.60 (artificial neural networks) to 0.62 (logistic regression and random forests). The best Youden index was achieved with logistic regression (0.26). The random forests model had the lowest sensitivity and the greatest specificity.

This type of machine learning provides additional groundwork for developing automated risk predictions from systemic EHR data, which could improve clinical decision-making, the researchers said.

### Quality of Life and Noninfectious Uveitis

December 2019

**Niemeyer et al.** set out to determine the time trade-off (TTO) utility values associated with noninfectious uveitis. They found that noninfectious uveitis is linked to modestly reduced quality of life (QoL), which correlated with long-term use of oral corticosteroids and poor visual acuity (VA) in the worse eye.

For this study, the researchers enrolled 104 consecutively treated adults with noninfectious uveitis. TTO utility values were calculated from responses to an interviewer-guided survey on QoL. The researchers also collected information about general health, ocular symptoms, and religion. Medical records were reviewed to determine anatomic location of uveitis, disease activity, VA, and treatments provided. Multivariable regression analysis with backward selection was used to identify factors associated with TTO scores.

Findings showed a median TTO value of 0.975 for the study population (interquartile range [IQR], 0.8-1.0), which corresponded to trading 1.28 years (median) of remaining life for healthy eyes (IQR, 0-6.29). According to regression analysis, controlled for

age and sex, lower TTO scores were linked to poorer VA in the worse eye, taking oral corticosteroids for more than six months, and current use of antidepressants ( $p = .008$ ,  $p = .006$ , and  $p = .008$ , respectively). Patients who had been taking oral corticosteroids for more than six months, regardless of the dose, were 10.5 times more likely to trade 20% or more years of remaining life (TTO  $\leq 0.8$ ) than were those who did not take oral corticosteroids ( $p = .002$ ). Patients who were legally blind in at least one eye had a median TTO score of 0.8 and were willing to trade a median of 4.3 years of remaining life.

Overall, 73% of patients were willing to trade time from their life for healthy eyes. The backward stepwise analysis showed that the greatest contributors to this willingness were college education (odds ratio [OR], 5.12;  $p = .008$ ) and Catholic religion (OR, 0.27;  $p = .03$ ).

To the authors' knowledge, this study is the first to investigate TTO utility values among patients with noninfectious uveitis. The results highlight the negative effect of long-term use of corticosteroids on QoL, regardless of dosage. The TTO tool had favorable test-retest reliability and thus may be useful to study QoL for patients with ocular disease, the authors concluded.

—Summaries by Lynda Seminara

## JAMA Ophthalmology

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

### Sex and the Ophthalmic Literature

November 2019

Is there a gap with regard to the sex of authors of ophthalmic studies? **Kramer et al.** performed a bibliometric analysis of published ophthalmic literature to compare authorship by sex and gain understanding of women's and men's preponderance and position in article bylines. The results showed that women represented roughly 35% of authorships and were less likely than men to have key roles in the research. However, in recent years, the percentage of women whose names appear first or last in the byline has increased.

For this study, the researchers looked at more than 10 years' worth of original English-language articles published in ophthalmology journals that are indexed in the Web of Science. Data were acquired in August 2018. Given names were used to determine the sex of each author. Articles originating from China, South Korea, and Taiwan were excluded because of the high number of unisex names. A prestige index, reflecting byline position, was calculated.

Outcome measures included the proportion of female authorships, odds ratios of women being listed first and last in bylines, rates of citation, and transnational female representation within ophthalmic research.

Overall, 87,640 original articles were published among 248 ophthalmologic journals. Of the 344,433 authorships, 120,305 were by females (34.9%). Women represented 37.1% of first-listed authors, 36.7% of coauthors, and 27.1% of authors listed last. The female-to-male odds ratio was 1.12 for first authorships, 1.20 for coauthorships, and 0.63 for last authorships. The annual rate of increase in authorship by females was 1.6% overall, 1.6% for first authorship, 1.3% for coauthorship, and 2.5% for last authorship. Women were underrepresented in prestigious authorships (prestige index,  $-0.22$ ). Articles with women in key authorship roles were cited slightly less frequently than those with men in key roles. On average, females were less prolific than males: 42.5% of female authors were responsible for the 34.9% of all authorships. No particular journal or country provided better chances for women to be in prestigious authorship roles.

The authors forecast that female authorship will grow to 44.1% by 2028, accompanied by sex-neutral distribution of prestigious roles. (*See also related commentary by Irena Tsui, MD, in the same issue.*)

### Assessing Online Information on Diabetic Retinopathy

November 2019

Kloosterboer et al. took a close look at various websites that contain patient information on diabetic retinopathy

(DR) and found that the content was generally poor in quality, difficult to interpret, and not suitable to help patients make sound medical decisions.

For their study, the authors developed a 26-item survey that addressed questions of relevance to patients and applied it to 11 websites with DR content to assess accuracy and completeness of freely available material. Included were news sites, WebMD, All About Vision, EyeWiki, Mayo Clinic, and national ophthalmic associations and societies. Readability was analyzed with an online tool, and each website was evaluated independently by a vitreoretinal surgeon and two vitreoretinal fellows. *JAMA* benchmarks were used to determine the quality of each site's content.

The mean (standard deviation [SD]) questionnaire score among the 11 sites was 55.76 (13.38) of 104 possible points. The quality of content varied among the sites ( $H = 25.811$ ,  $p = .004$ ). The mean (SD) reading grade for all websites was 11.30 (1.79), which equates to the 11th-grade reading level; however, 6th grade is the level recommended by the U.S. Department of Health and Human Services. WebMD was found to have the lowest degree of complexity. There was no correlation between content accuracy and the mean reading grade or the Google rank. No website achieved all four *JAMA* benchmarks, and only one site achieved three of the four. Four sites did not meet any *JAMA* benchmarks. No correlation was found between content accuracy and the number of *JAMA* benchmarks achieved. Reproducibility was similar among the three observers.

Given the uneven accuracy of online DR information, the authors emphasized the importance of directing patients to reliable sources. (*See also related commentary by Rahul N. Khurana, MD, in the same issue.*)

### Anti-VEGF Comparison in RCT for CRVO-Related Macular Edema

November 2019

Hykin et al. compared the clinical effectiveness of ranibizumab, aflibercept, and bevacizumab for managing

macular edema due to central retinal vein occlusion (CRVO) in a randomized clinical trial. They found that, at 100 weeks, aflibercept outcomes were noninferior (not worse) to ranibizumab outcomes; results for the comparison of bevacizumab versus ranibizumab were inconclusive, that is, they could not determine if the outcomes were worse or not worse with bevacizumab. In a post hoc analysis, they also noted the comparison of bevacizumab versus aflibercept were inconclusive.

The authors' main objective was to determine whether intravitreal administration of either aflibercept or bevacizumab, in comparison to ranibizumab, results in a noninferior mean change in vision at 100 weeks for eyes with CRVO-related macular edema. For this prospective study, they enrolled 463 adults treated at 44 ophthalmology departments of the U.K. National Health Service. The mean age of the study population was 69.1 years; 57.2% were male.

All participants had visual impairment of less than 12 months' duration caused by CRVO-related macular edema. Best-corrected visual acuity (BCVA) in the study eye ranged from approximately 20/32 to 20/400. Central subfield thickness according to spectral-domain optical coherence tomography was at least 320  $\mu\text{m}$  in the study eye.

The patients were assigned randomly to receive repeated intravitreal injections of ranibizumab (0.5 mg/0.05 mL), aflibercept (2.0 mg/0.05 mL), or bevacizumab (1.25 mg/0.05 mL) during a 100-week period. The main outcome was the adjusted mean change in BCVA in the study eye at week 100. Noninferiority was concluded if the lower bounds of 95% confidence intervals (CI) for both the intent-to-treat and per-protocol analyses were above  $-5$  letters.

At week 100, the mean (standard deviation) gain in BCVA letter score was 12.5 (21.1) for ranibizumab, 15.1 (18.7) for aflibercept, and 9.8 (21.4) for bevacizumab. Aflibercept was found to be noninferior to ranibizumab (intent-to-treat adjusted mean BCVA difference, 2.23 letters; 95% CI,  $-2.17$  to 6.63

letters;  $p < .001$ ). Bevacizumab was not found to be noninferior to ranibizumab (intent-to-treat adjusted mean BCVA difference,  $-1.73$  letters; 95% CI,  $-6.12$  to  $2.67$  letters;  $p = .07$ ). In a post hoc analysis, bevacizumab also was not found to be noninferior to aflibercept (adjusted mean BCVA difference,  $-3.96$  letters; 95% CI,  $-8.34$  to  $0.42$ ;  $p = .32$ ). Results of the per-protocol analysis were similar.

The mean number of injections was lower for the aflibercept group (10.0) than the ranibizumab group (11.8). There was a mean of 11.5 injections (95% CI, 10.7-12.4) in the bevacizumab group.

The authors cautioned that their results must be interpreted in the context of the eligibility criteria and treatment protocols used in this study.

—Summaries by Lynda Seminara

## OTHER JOURNALS

Selected by Deepak P. Edward, MD

### Multimodal Imaging to Detect Melanoma-Prone Choroidal Nevi

*British Journal of Ophthalmology* 2019;103(10):1441-1447

With multimodal imaging, subtle details of choroidal nevi can be observed, potentially leading to earlier detection of incipient melanoma and better prognosis. Dalvin et al. used high-resolution ultrasonography, fundus autofluorescence (AF), and spectral-domain optical coherence tomography (OCT) to examine choroidal nevi. They found that certain combinations of previously identified risk factors signal a high risk of progression to melanoma.

This retrospective study included 3,806 choroidal nevi (in 3,584 eyes of 3,334 patients), diagnosed consecutively during a 10-year period. In a prior study, these cases were evaluated by clinical examination and multimodal imaging, and six risk factors for transformation to melanoma were identified:

- tumor thickness  $>2$  mm on ultrasonography
- presence of subretinal fluid on OCT
- visual acuity loss to 20/50 or worse
- orange pigment by AF

- hollow acoustic density on ultrasonography
- largest basal tumor diameter  $>5$  mm by photography

In this study, a total of 2,355 nevi (2,211 eyes; 2,075 patients) were monitored for an average of three years (range,  $<1$ -11 years). No nevi had all six risk factors. The five-year Kaplan-Meier estimated risk of a choroidal nevus transforming to melanoma was 1% with no risk factor (hazard ratio [HR], 0.1), 11% with one factor (range, 9-37%; HR, 2.1-7.8), 22% with two factors (range, 12%-68%; HR, 1.8-12.1), 34% with three factors (range, 21%-100%; HR, 4.0-24.4), and 55% with four or five factors (range, 0%-100%; HR, 4.6-170.0 and 12.0-595.0, respectively). The highest-risk combination of three factors included decreased visual acuity, orange pigment, and hollow acoustic density (HR, 29.0). Among nevi with four risk factors, the most concerning combination was tumor thickness  $>2$  mm, subretinal fluid, visual acuity loss, and orange pigment (HR, 170). Risk factors responsible for the highest HR, in any set of two to five factors, were visual acuity loss and orange pigment.

The authors recommend multimodal imaging to guide choroidal nevi management. Detecting high-risk features may prompt referral to an ocular oncologist, whereas observation may be adequate for lower-risk nevi.

### Methotrexate Versus Mycophenolate Mofetil for Uveitis

*JAMA* 2019;322(10):936-945

Corticosteroids are standard first-line treatment for noninfectious uveitis, but local and systemic side effects are common with these drugs. Alternatively, patients may receive antimetabolite treatment with methotrexate or mycophenolate mofetil, sparing them the adverse effects of steroids. In the FAST (First-line Antimetabolites as Steroid-sparing Treatment) trial, Rathinam et al. compared the efficacy of these two agents in patients with active noninfectious uveitis and found methotrexate to be noninferior to my-

cophenolate mofetil.

FAST was a randomized, parallel, observer-masked clinical trial conducted in six diverse countries. Patients with noninfectious intermediate uveitis, posterior uveitis, or panuveitis were assigned randomly to receive methotrexate (25 mg weekly) or mycophenolate mofetil (1.5 g twice daily); both agents were administered orally. Patients also were given oral prednisone, with the goal of tapering to 7.5 mg daily by six months. Topical corticosteroids were allowed if needed, and they were to be reduced to  $<2$  drops/day of 1% prednisolone acetate.

The primary outcome, treatment success, was determined at months 6 and 12. Treatment success was defined as inflammation control, achievement of the target corticosteroid dosage, and acceptable safety and tolerability. Patients with treatment failure at month 6 received the other antimetabolite for the next six months.

Of the 216 patients enrolled, 194 had follow-up through six months, at which time the treatment success rate was 66.7% for methotrexate (64 of 96 patients) and 57.1% for mycophenolate mofetil (56 of 98 patients). Subgroup analysis of patients with posterior uveitis or panuveitis showed that methotrexate was more effective.

The 12-month evaluation was completed by 163 patients. About three-fourths of those with treatment success at six months continued to have control of inflammation at 12 months, and approximately half discontinued prednisone by this time. Among the 49 patients who switched treatment after the initial six months, those who transitioned to methotrexate had greater treatment success. Relatively few patients in either group had intolerability or safety issues, although liver function tests were more likely to be abnormal in those patients given methotrexate.

In summary, methotrexate was noninferior to mycophenolate mofetil as steroid-sparing immunosuppressive therapy for uveitis. Anatomic subtype may affect the success of either treatment; this possibility warrants further exploration, said the authors.

—Summaries by Lynda Seminara