Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Treat-and-Extend for Wet AMD Garners More Support

January 2018

Monthly injections of ranibizumab can improve best-corrected visual acuity (BCVA) outcomes in patients with neovascular age-related macular degeneration (AMD), but the frequency of dosing can be inconvenient. **Silva et al.** compared monthly and treat-and-extend (T&E) protocols in patients with wet AMD and concluded that T&E was statistically noninferior and clinically comparable to monthly treatment for improving visual acuity.

This 12-month phase 3 trial was conducted at 90 centers in 18 countries. The main objective was to demonstrate noninferiority of ranibizumab T&E, as measured by change in BCVA from baseline to study endpoint.

Secondary outcome measures were safety, treatment exposure, and changes in retinal central subfield thickness (CSFT).

Patients ≥ 50 years of age (mean age, 75.2 years; 55.4% women; 91.8% white) with newly diagnosed wet AMD were assigned randomly to receive ranibizumab 0.5 mg either according to a T&E regimen (n = 323) or monthly (n = 327). Demographics and baseline ocular characteristics were similar for the study groups.

Approximately 90% of each group completed the study. At 12 months, the least-squares mean BCVA change from baseline reflected improvement of 6.2 letters with T&E and 8.1 letters with the monthly regimen (p < .001 for non-inferiority). Both groups had rapid gains in BCVA, primarily during the first 6 months, which continued throughout the study. Mean changes in CSFT were similar: 169.2 µm in the T&E group and 173.3 µm in the monthly group.
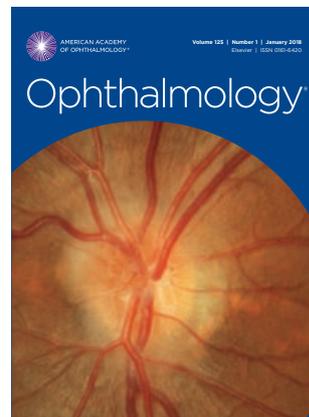
The mean number of ranibizumab injections was lower in the T&E group (8.7, vs. 11.1 for those treated monthly), as was the mean number of post-baseline visits (8.9 and 11.2, respectively). Types and rates of adverse events were similar.

The authors concluded that the T&E approach is not inferior to the monthly regimen. Advantages of T&E include treatment individualization, fewer injections, less-frequent visits, and lower costs.

Using Art Observation to Improve Medical Students' Ophthalmology Skills

January 2018

Although observation and description are crucial for practicing ophthalmology and other medical specialties, medical education does not include specific training in these areas. **Gurwin et al.** studied the effect of formal training in visual arts on the observation skills of medical students and found that just 6 sessions markedly improved the students' skills.

This study included 36 first-year medical students who were assigned randomly (1:1) to receive either art education at the Philadelphia Museum of Art or a free membership to the museum. During a 3-month period, the training group participated in 6 customized 1.5-hour sessions. The art educators used the "Artful Thinking" approach, which emphasizes introspection and observation before interpretation.

Before and after the 3-month period, all participants underwent testing, which entailed writing descriptions of works of art, retinal pathology images, and external photographs that depicted eye diseases.

Reviewers graded each description according to an a priori rubric for the type of image presented. Descriptions of works of art were graded by museum educators, while those of retinal and external eye images were graded by 2 ophthalmologists and a fourth-year medical student.

The assessments showed that overall observational skills improved significantly in the training group, and results were similar for each image category. In a follow-up questionnaire, the students trained in art observation stated that they were applying their new knowl-

edge in clinically meaningful ways.

The authors concluded that art observation training can improve the observational skills of medical students. Such training may be vital for specialties in which diagnosis and treatment are based mainly on direct observation, such as ophthalmology, dermatology, and radiology.

Additional research is warranted to document the durability of this effect and determine the impact on clinical care, the authors noted. *(Also see related commentary by David Epstein and Malcom Gladwell in the same issue.)*

Predicting Vision-Related Disability for Patients With Glaucoma
January 2018

The results of visual field assessments and self-reported questionnaires can help physicians assess the overall degree of vision-related disability in patients with glaucoma. However, translating the findings from these tools into clinical practice can be challenging. To help classify and analyze changes that occur with glaucoma, **Abe et al.** developed a novel methodology, which demonstrated that the risk of disability is associated with disease severity at baseline and the rate of deterioration over time. In addition, their method also may help determine how aggressive the treatment must be to slow visual decline and avoid disability.

For this prospective observational study, vision-related quality of life (QoL) was assessed at baseline and the end of follow-up using portions of the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25). A latent transition analysis (LTA) model was used to characterize NEI VFQ-25 results and to evaluate the probability of disability occurrence during follow-up. Standard automated perimetry (SAP) was conducted at 6-month intervals, and mean sensitivity (MS) of the integrated binocular visual field was used to determine rates of change. Predictors of future disability that were investigated included baseline glaucoma severity and rate of visual field loss.

At baseline, 67 (28%) of 236 patients
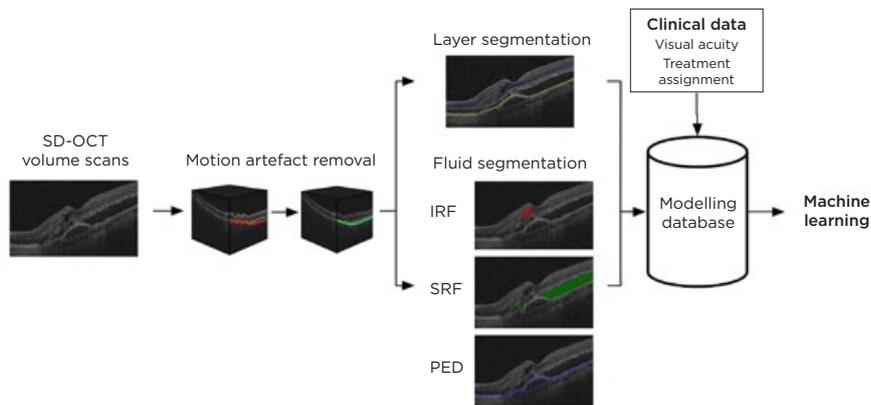
MACHINE LEARNING. *This diagram of the computational image analysis image pipeline illustrates the steps in data assessment. IRF = intraretinal fluid; SRF = subretinal fluid; PED = pigment epithelial detachment.*

with glaucoma were categorized as disabled and 169 (72%) as nondisabled based on NEI VFQ-25 results. According to the LTA model, nondisabled participants had a 14.2% likelihood of transitioning to the disabled state during follow-up (mean, 4.3 years). Binocular MS data showed that visual field loss occurred nearly 4 times faster in patients who became disabled. With adjustments for age, baseline visual acuity, and follow-up duration, each 1-dB lower baseline binocular MS was associated with 34% higher odds of future disability. Each 0.5-dB/year faster rate of loss of binocular MS increased the risk of developing disability more than 3.5 times.

—*Summaries by Lynda Seminara*

Ophthalmology Retina
Selected by Andrew P. Schachat, MD

Artificial Intelligence Predicts Visual Outcomes in Neovascular AMD
January 2018

Schmidt-Erfurth et al. set out to evaluate the ability of machine learning to predict functional outcomes in patients treated with ranibizumab for neovascular age-related macular degeneration (AMD).

They found that, according to their artificial intelligence (AI) algorithms, best-corrected visual acuity (BCVA) at month 3 was the strongest predictive factor of functional outcomes at the 1-year mark. In addition, they found

that currently used morphological features were of limited value in predicting BCVA outcome.

For this post hoc analysis of a clinical trial database, the researchers evaluated data from 614 patients who participated in the HARBOR trial. (During HARBOR, patients received intravitreal injections of ranibizumab monthly or on a pro re nata basis for 12 months; in addition, they were evaluated monthly via spectral-domain optical coherence tomography [SD-OCT] imaging.) The researchers used AI algorithms to first correlate OCT parameters observed at baseline to the corresponding visual function at months 1, 2, and 3 and then to predict the patients' final BCVA at 1 year.

They found that the correlation between predicted and final 12-month BCVA scores was loose at baseline—but by month 3, individual BCVA levels reached a solid predictive power for month 12.

However, fluid-based morphological features proved to be largely irrelevant for predicting therapeutic response, the researchers said.

The latter finding implies that classic exudative features—such as fluid within and underneath the retina—may be of limited value in explaining visual function in wet AMD and in providing individual patients with a visual prognosis, the authors said, and they added that this should prompt researchers to search for additional markers, such as a disruption of the external limiting membrane. —*Summary by Jean Shaw*

American Journal of Ophthalmology

Do Normal Eyes Follow the ISNT Rule?

January 2018

Neuroretinal rim loss and thinning of the retinal nerve fiber layer (RNFL) are hallmark features of glaucoma. As a result, eyes that deviate from the ISNT rule may need close monitoring for glaucoma—but research findings on the utility of this rule for establishing glaucoma are conflicting. **Poon et al.** sought to determine the percentage of normal eyes that follow the ISNT rule and found that, contrary to traditional teaching, the rule applies to less than 45% of rim assessments and RNFL measurements.

The authors' cross-sectional study included 110 normal eyes (110 participants). Neuroretinal rim assessments were made from disc photographs, and measurements of RNFL thickness were obtained from spectral-domain optical coherence tomography. The main outcomes were the percentages of eyes that obeyed the ISNT rule and its variants.

The researchers found that the ISNT rule was valid for only 37% of rim assessments and 43.8% of RNFL measurements.

For both types of assessments, variance of the nasal sector from the expected ISNT pattern was a major reason for deviation. Nasal rims were wider than inferior rims in 11% of subjects and wider than superior rims in 29%. Nasal rims were narrower than temporal rims in 15%. RNFL thickness was greater in the nasal quadrant than the temporal quadrant in 43%. Exclusion of the nasal quadrant from the ISNT rule significantly increased validity of the ISNT variants: 71% and 76% of disc photographs followed the IST rule and the IS rule, respectively. For RNFL thickness, 71% and 72% coincided with IST and IS rules, respectively.

As a result of these findings, the authors advocate use of IST and IS rules for distinguishing glaucomatous from nonglaucomatous eyes.

Corneal Changes in Pregnancy Linked to Fluctuating Thyroid Hormone Levels

January 2018

Tabibian et al. documented corneal changes that occur during pregnancy and evaluated their association with simultaneous hormonal changes. They found that the changes they observed correlated with fluctuating thyroid hormone levels rather than altered estradiol levels.

This prospective single-center observational study involved 24 pregnant women (48 eyes). Biomechanical and topographic properties of the cornea were measured with the Ocular Response Analyzer (ORA) and a Scheimpflug imaging system at 4 time points: once during each trimester and 1 month after delivery. During the same 4 visits, the blood plasma level of estradiol (E2) was determined, as were thyroid hormone levels (TSH, T3t, T4t). One-way multivariate analysis of covariance was used to detect interactions between hormonal plasma levels and changes in corneal biomechanical/topographic parameters.

Biomechanical and topographic data for the 4 time points were comparable. Although the level of E2 did not affect corneal parameters, TSH levels affected the maximal keratometry and vertical keratometry readings as well as the index of height asymmetry (these results remained unchanged after excluding

EXCEPTION TO THE ISNT RULE. *In this example, the RNFL thickness (bottom left) in the nasal quadrant is thinner than the temporal quadrant. This violates the ISNT rule, which holds that the inferior (I) rim is the widest, followed in turn by the superior (S), nasal (N), and temporal (T) rims.*

patients with hypothyroidism from the analysis). Moreover, differences in corneal biomechanical and topographic parameters were found in relation to T3t and T4t as well as the T3t/T4t ratio.

Further research is needed to determine the potential role of thyroid diseases in the development and progression of corneal disorders, the authors said.

—*Summaries by Lynda Seminara*
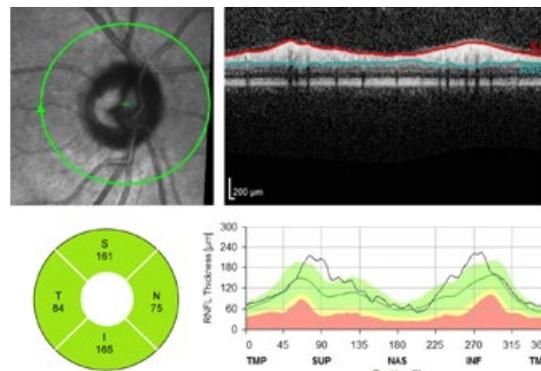
JAMA Ophthalmology

Prevalence and Features of CPR-Type Diplopia in Epiretinal Membrane

December 2017

Veverka et al. sought to determine the prevalence of central-peripheral rivalry (CPR)–type diplopia among patients with epiretinal membrane (ERM) and to describe the common clinical features. They found that CPR-type diplopia is not uncommon in patients with ERM and is linked to greater severity of metamorphopsia.

This study included 31 adults with ERM treated at clinics specializing in retinal disease in addition to a retrospective cohort of 25 adults with ERM treated at strabismus clinics. Diplopia was established by patient history and responses to questionnaires. CPR type was defined as diplopia associated with evidence of retinal misregistration in the absence of other causes of diplopia. Visual acuity (VA) and ocular alignment findings were documented. Metamorphopsia was assessed qualitatively and quantitatively. Aniseikonia was determined by subjective description and the Awaya new aniseikonia test. Testing for retinal misregistration also was performed. Clinical findings of patients with and without CPR-type diplopia were compared to detect differentiating factors.

Among the group of 31 patients, the prevalence of any type of diplopia was 23% (n = 7) and that of CPR-type diplopia was 16% (n = 5). In the entire series of 56 patients, 12 (21%) had CPR-type diplopia, and 37 (66%) had no diplopia. The other 7 had another type of diplopia and were excluded from subsequent analyses.

Relative to patients who did not have CPR-type diplopia, those with the disorder had better VA in their worse eye (mean difference of –0.23; p = .003) and more severe quantitative metamorphopsia (mean M-score difference of 0.6; p = .01). Rates of aniseikonia misregistration were similar for those with and without the disorder.

Although results indicate that patients with CPR-type diplopia generally have better worse-eye acuity and more metamorphopsia than those without the disorder, individual variability is considerable. Coexistence of retinal misregistration and metamorphopsia appears necessary for the development of CPR-type diplopia, but many patients without this diplopia may exhibit those features.

Generational Differences in AMD Incidence
December 2017

Cruickshanks et al. set out to determine whether the 5-year risk of AMD is changing as longevity increases and found that the risk has declined over time.

For their assessment, the authors obtained longitudinal data from 2 Beaver Dam eye studies in which the 5-year incidence of AMD was measured. A total of 4,819 participants (baseline mean age, 54 years) were at risk for AMD based on findings from the fundus images obtained at baseline. Fundus images were graded for AMD using the Wisconsin age-related maculopathy grading system, and AMD incidence was determined from 5-year follow-up results.

AMD was identified by the presence of pure geographic atrophy, exudative macular degeneration, any type of drusen with pigmentary abnormalities, or soft indistinct drusen without pigmentary abnormalities.

The 5-year incidence of AMD, adjusted for age and sex, was 8.8% for those born from 1901-1924, 3% for those born from 1925-1945, 1% for those born 1946-1964, and 0.3% for those born 1965-1984.

Each generation was > 60% less likely to experience AMD than the preceding generation, and this association remained significant after adjusting for age, sex, smoking status, education level, amount of exercise, selected lipid levels, and high-sensitivity C-reactive protein levels, and use/nonuse of non-steroidal anti-inflammatory drugs, statins, and multivitamins.

Although the 5-year risk of AMD declined throughout the 20th century, factors responsible for the decline were not apparent from this study. However, the results do suggest that modifiable factors contribute to the etiology of AMD and that the current epidemic of AMD among the oldest generation may diminish with time. Prospective epidemiologic studies are warranted to confirm the findings. *(Also see related commentary in the same issue by Raphael R. Goldacre, MSc, and Tiaran D.L. Keenan, PhD.)*

Does Cornea Preservation Time Affect DSAEK Success?
December 2017

Although donor corneas can be preserved in FDA-approved solutions for up to 14 days, many surgeons will not use cornea tissue that has been preserved for more than 7 days. To examine the effect of preservation time on graft success, **Rosenwasser et al.** compared 3-year outcomes of Descemet stripping automated endothelial keratoplasty (DSAEK) among corneas preserved for varying periods. They found that preservation time of < 12 days was linked to better success rates.

This double-masked randomized trial was conducted at 40 U.S. clinical sites (70 surgeons) from April 2012 to June 2017.

Eligible patients scheduled to undergo DSAEK for Fuchs endothelial corneal dystrophy (94.4% of participants) or pseudophakic or aphakic corneal edema received donor corneas preserved for ≤ 7 days (675 eyes) or 8-14 days (655 eyes). The median participant age was 70 years (range, 42-90 years), and 60.2% were female. Demographics of the study groups were similar.

The 3-year cumulative probability of graft success was 95.3% for donor corneas preserved for ≤ 7 days and 92.1% for those preserved 8-14 days. The upper limit of the 1-sided 95% confidence interval of this difference was 5.4%, which surpassed the noninferiority limit of 4% and was attributed to more primary donor failures in the group with longer preservation time (conditional probability of failure after the first month: 3.1% vs. 2.4%).

A secondary analysis showed that the likelihood of graft success decreased as preservation time increased. The success rate was lower for a period of 12-14 days (89.3%) than for ≤ 4 days (96.5%), 5-7 days (94.9%), or 8-11 days (93.8%).

The comparable success rates attained for corneas that had been preserved for up to 11 days should reassure surgeons. The high 3-year success rates with DSAEK for Fuchs dystrophy, regardless of preservation time, suggest that corneas that have been preserved for a longer time period can be used when necessary.

—*Summaries by Lynda Seminara*

Other Journals
Selected by Deepak P. Edward, MD

Spironolactone Effective for Acute Central Serous Chorioretinopathy
British Journal of Ophthalmology
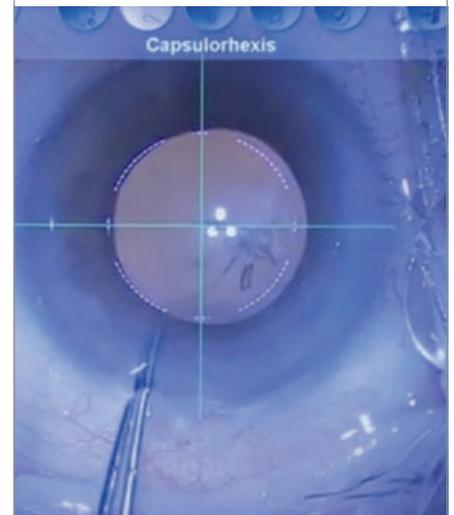Published online Oct. 31, 2017

Previous studies have shown the promise of mineralocorticoid-receptor antagonists in the treatment of chronic or recurrent central serous chorioretinopathy (CSC). Building on this premise, **Sun et al.** studied the efficacy of oral spironolactone among patients with acute CSC and found that, compared with observation alone, the treatment was much more effective and resulted in fast absorption of subretinal fluid (SRF).

For this prospective trial, the authors evaluated 30 patients (30 eyes) with acute CSC. The patients were assigned randomly either to the treatment group (spironolactone 40 mg orally, twice daily for 2 months; n = 18) or to the control group (observation alone; n = 12). Main outcome measures were the proportion of eyes with complete resolution of SRF by 2 months and the changes in central macular thickness (CMT), SRF height, best-corrected visual acuity (BCVA), and subfoveal choroidal thickness (SFCT) during the same period.

By 2 months, complete resolution of SRF had occurred in 10 of the 18 treated eyes and in only 1 of the 12 control eyes. Both groups experienced a significant decline in mean CMT and mean SRF height ($p < .05$), with significant between-group differences apparent at 2 months ($p < .05$ and $p < .05$, respectively). Mean BCVA improved in both groups by 2 months ($p < .05$). In the treatment group, mean SFCT decreased significantly, from 502.50 ± 87.38 μm at baseline to 427.44 ± 74.37 μm at 2 months ($p < .01$), whereas the change from baseline in the control group was not significant. Spironolactone did not produce any adverse effects in this study, perhaps because of the short duration of treatment.

Due to the multifactorial nature of CSC, the mineralocorticoid receptor may play a role in some patients but not others. Findings of this study may help to guide early intervention for acute CSC. In addition, the authors suggested that patients with CSC be given a medication guide to treatment of the disease.

Retinal Scanning May Help Detect Alzheimer Disease in Living Patients
JCI Insight
2017;2(16):e93621

Retinal examination may be a noninvasive method of detecting Alzheimer disease (AD). The retinas of deceased patients with AD exhibit myriad retinal pathologies, including the hallmark amyloid-β (Aβ) protein. **Koronyo et al.,** in a proof-of-concept study, demon-strated that such evidence also exists in the retinas of living patients. According to the retinal amyloid index (RAI) developed by the investigators, index scores were more than twice as high for patients with AD than in cognitively normal controls.

The authors first examined the burden, distribution, cellular layer, and structure of retinal Aβ plaques in donor tissue (eyes and brain) of patients with definitive AD (n = 23) and cognitively normal controls (n = 14). An amyloid probe curcumin formulation was derived from histologic findings, and a protocol for retinal amyloid imaging was established and applied to living patients (10 with AD, 6 healthy controls).

Histologic examination showed that patients with AD had classic and neuritic-like Aβ deposits, with increased retinal Aβ42 plaques (4.7-fold; $p = .0063$) and neuronal loss ($p = .0023$) relative to matched controls. The retinal Aβ plaque presentation mirrored brain pathology, particularly in the primary visual cortex. Retinal deposits often were associated with blood vessels and occurred in hot-spot peripheral regions of the superior quadrant and innermost layer of the retina. Transmission electron microscopy showed the assemblage of retinal Aβ into protofibrils and fibrils.

The authors then demonstrated the ability to image retinal amyloid deposits with solid-lipid curcumin and a modified scanning laser ophthalmoscope in living patients. A fully automated calculation of the RAI, a quantitative measure of increased curcumin fluorescence, was devised. Analysis of RAI scores showed that scores for patients with AD were 2.1 times higher than those of controls.

The geometric distribution and increased burden of retinal amyloid pathology in AD, coupled with the feasibility to noninvasively detect retinal amyloid deposits in living patients, may lead to a practical approach for large-scale diagnosis and monitoring of AD. Such imaging technology may prove to be sensitive and inexpensive for screening people at risk for AD.

—*Summaries by Lynda Seminara*