

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Using Machine Learning to Forecast Visual Outcomes in Wet AMD

July 2018

Rohm et al. established a comprehensive data warehouse and applied machine-learning algorithms to predict visual acuity (VA) outcomes of patients who received 3 intravitreal injections for neovascular age-related macular degeneration. They were able to predict VA at 3 months, and results were comparable to actual measured VA (called ground truth in this study). Moreover, the study showed that the 3-month predictions of VA were more accurate than were the 12-month forecasts.

Five algorithms were used in the study (AdaBoost.R2, Lasso, Gradient Boosting, Random Forests, and Extremely Randomized Trees). Clinical data obtained from the data warehouse included VA measurements drawn from electronic health records and findings from optical coherence tomography. To provide a quality measure, both mean absolute error (MAE) and root mean square error (RMSE) were calculated for each algorithm. (RMSE penalizes outliers, allowing selection of the most robust algorithm.)

Three-month forecasts were made for 653 patients (738 eyes). Mean VA before the first injection of an anti-vascular endothelial growth factor (anti-VEGF) drug was 0.54 logMAR (± 0.39). Of these patients, 456 (508

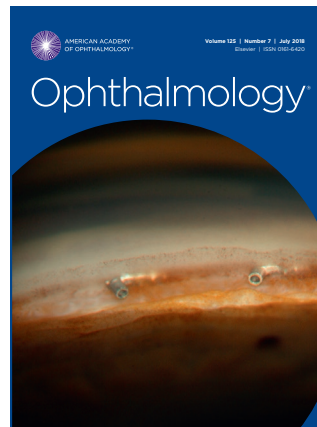
eyes) had sufficient follow-up data for the 12-month assessment. Among the 508 eyes, mean VA before the initial injection was 0.56 logMAR (± 0.42). The main outcome measure was the difference in predicted versus ground-truth logMAR VA at months 3 and 12 after the start of anti-VEGF therapy.

Analyses showed that the MAE of predicted VA over ground truth was 0.11 logMAR (5.5 letters) for the 3-month prediction and 0.16 logMAR (8 letters) for the 12-month prediction. The 12-month RMSE was lowest (0.2 logMAR; 10 letters of change) if data from the 4 visits before the third injection were taken into account, but this was not demonstrated for the MAE. The best-performing algorithm was the Lasso L1 regularized linear model. Although 12-month forecasts were not as accurate as their 3-month counterparts, they may be helpful for encouraging patients to stay on their therapy, the authors said.

Predicting Refractive Outcomes of Cataract Surgery

July 2018

Accurate measurement of axial length (AL) and corneal power (K) is essential for achieving good visual outcomes from cataract surgery. Surgeons often compare biometry between the 2 eyes



to check for discrepancies. However, data are lacking to describe the relationship between the degree of discrepancy and the refractive outcomes. Kansal et al. aimed to determine whether interocular differences in AL or K are predictive of refractive outcomes. They found that an AL

difference of just 0.2 mm is linked to greater likelihood of refractive errors exceeding 0.5 D from the target value and to poorer uncorrected visual acuity (UCVA). An interocular difference in K correlated with poorer UCVA but not with substantial refractive error.

This retrospective study included 729 patients (1,458 eyes) who underwent bilateral phacoemulsification at a laser eye center in Canada. The primary outcome was the incidence of biometry prediction error, defined as a difference of >0.5 D between the target and postoperative refractive power. Secondary outcomes included postoperative UCVA >0.3 logMAR and differences of >0.25 D and >1.0 D between target and postoperative refractive powers. The primary predictors were the absolute value of the interocular AL difference and absolute values of interocular K differences (steep, flat, and average).

Results showed that approximately 79% of eyes had outcomes within 0.5 D of target values, 47% were within

0.25 D, and 97% were within 1.0 D. The odds ratios for a refractive outcome >0.5 D from target for the 0.2-mm, 0.3-mm, and 0.4-mm cutoffs for interocular AL difference were 1.4 (95% confidence interval [CI], 1.1-1.8), 1.6 (CI, 1.2-2.1), and 1.8 (CI, 1.3-2.5), respectively. This translates to 70.0% being within target for interocular AL difference >0.4 mm versus 80.7% for that of <0.4 mm. For eyes that fell outside the target threshold, twice as many were below 0.5 D as above 0.5 D.

Interocular differences in K generally were not associated with prediction errors, but increasing steepness or flatness was linked to greater odds of UCVA >0.3 logMAR.

The authors suggested that these cutoff points be considered in preoperative planning, including discussions with patients. Further research is warranted to determine whether certain methods could reduce refractive error, such as repeating measurements, using adjunct measuring tools, or attempting to separate true differences from artifact based on preoperative refractive characteristics.

Quantifying Quality of Life in Cases of Good Unilateral Vision

July 2018

Utility data are important for performing reliable cost-utility analyses. By convention, normal health is assigned a utility value of 1, and death a utility value of 0. Ophthalmic vision utilities vary depending on whether 1 or both eyes have limited vision. For example, bilateral vision of 20/20 to 20/25 in conjunction with ocular disease has been associated with a utility of 0.97, whereas 20/40 vision bilaterally has a utility of 0.80. In a study for the Ophthalmic Utility Research Study Group, Brown et al. looked at patient time-tradeoff vision utilities for quantifying vision-related quality of life among patients with good vision in at least 1 eye. Their research showed utilities ranging from 0.94 to 0.79, depending on visual acuity in the fellow eye.

All told, 586 patients participated in the study, which included complete eye exams, personal interviews, and

validated methodology. The common 2-question interview was used to measure time-tradeoff vision utilities for patients with good vision in 1 eye (20/20-20/25) and vision that ranged from no light perception to 20/20 in the fellow eye. Participants were asked how long they expected to live and how much of that time they would be willing to trade for an intervention that would permanently return their vision to normal. The utility was calculated by subtracting the proportion of remaining hypothetical time traded from 1.0. The anchors were death (0.00) and normal vision bilaterally (1.00).

The mean time-tradeoff vision utility was 0.79 for patients whose fellow-eye vision had no light perception and 0.87 for those with fellow-eye vision ranging from counting fingers to light perception. Fellow-eye vision of 20/200 to 20/400, 20/60 to 20/100, 20/30 to 20/50, and 20/20 to 20/25 yielded time-tradeoff utilities of 0.88, 0.88, 0.87, and 0.94, respectively.

This study demonstrated a vision utility of 0.88 when 1 eye has good vision and the fellow eye has vision between 20/30 and light perception. If visual acuity in the fellow eye returns to 20/20 to 20/25, the utility improves. Similarly, if fellow-eye vision declines to no light perception, the utility worsens. The authors noted that this information may improve estimations of actual gains in quality-adjusted life-years because it is based on patient preferences.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

U.S. Experience: Real-World Outcomes in Wet AMD

July 2018

Ciulla et al. set out to assess the outcomes of “real-world” U.S. patients who receive intravitreal injections for neovascular age-related macular degeneration (AMD). They also sought to assess the impact that loss to follow-up has on visual outcomes. They found that—as previously noted in studies conducted outside the United States—patients treated with anti-vascular endothelial

growth factor (anti-VEGF) agents in clinical practice receive fewer injections and have worse visual outcomes than do those treated according to a strict protocol in a randomized clinical trial.

For this retrospective study, the researchers evaluated electronic health records from a geographically and demographically diverse sample of patients treated by U.S. retina specialists. At the time of the analysis (January 2011 to July 2013), there were 77,985 patients with neovascular AMD in the database; after inclusion criteria were applied, records of 2,213 treatment-naïve patients were evaluated.

The researchers divided the patients into 3 mutually exclusive cohorts, depending on whether they were considered lost to follow-up after 6, 12, or 24 months of treatment. Overall, anti-VEGF use by agent was 13% for aflibercept, 17% for ranibizumab, and 70% for bevacizumab; the 6-month cohort had a higher percentage of aflibercept use (20%), while 15% received ranibizumab, and 65% received bevacizumab.

Patients in the 6-month cohort received a mean of 5.4 injections, versus 7.3 and 12.1 injections, respectively, in the 12- and 24-month cohorts. No change in VA from baseline was noted in either the 6- or 12-month cohort; in contrast, patients in the 24-month cohort experienced a net gain of 3.1 letters. Individual patients with better VA at presentation tended to be particularly vulnerable to vision loss. In addition, patients lost to follow-up tended to have poorer VA at their final visit, the researchers noted.

Taken together, these real-world outcomes highlight an unmet need for better treatment of neovascular AMD, the researchers said.—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Treating Exudative AMD With Bevacizumab Is Highly Cost-Effective

July 2018

In a cost analysis of bevacizumab, ranibizumab, and aflibercept, Rosen-

feld et al. estimated the relative savings associated with bevacizumab in the treatment of exudative age-related macular degeneration (AMD) in the United States. The authors projected that the substitution of bevacizumab for the other treatments could yield savings of 80% for Medicare and 20% for patients.

The main outcome measure in this retrospective review was Medicare spending on bevacizumab, ranibizumab, and aflibercept from 2008 through 2015. Spending was tracked using the CPT code for intravitreal injections (67028) and treatment-specific J codes (J0178, J2778, J9035, J3490, J3590) for anti-vascular endothelial growth factor (anti-VEGF) agents. Associated claims were identified from Medicare Provider Utilization and Payment Data files from the Centers for Medicare & Medicaid Services among fee-for-service Medicare beneficiaries and from the 100% fee-for-service Part B Medicare Claims File. Bevacizumab claims unrelated to ophthalmology were excluded.

The average cost of a dose of bevacizumab ranged from \$60.86 in 2008 to \$73.03 in 2015. The average cost of a dose of ranibizumab exceeded \$2,000 in all years of the study, as did that of aflibercept once it became available. From 2008 to 2015, bevacizumab use resulted in overall savings of approximately \$17.3 billion: \$13.8 billion for Medicare and \$3.5 billion for patients. The savings for Medicare represent an underestimation because roughly 30% of Medicare-eligible people are enrolled in Medicare Advantage plans, which were not included in the study. Even more savings would have been realized by including eye disorders other than AMD that are treated with anti-VEGF agents, such as diabetic macular edema and retinal vein occlusion.

Off-label bevacizumab use is expanding because of its low cost, widespread availability, and effectiveness for exudative and neovascular ocular conditions. Concern has arisen in the United States and elsewhere regarding improper compounding of bevacizumab. In light of the drug's substantial cost savings and dominant position as the treatment of choice for exudative AMD,

emphasis should be placed on ensuring a safe and readily available supply.

Parents of Preterm Infants Have Limited Knowledge of ROP

July 2018

Lack of parental knowledge about retinopathy of prematurity (ROP) may lead to delays in screening and treatment of infants. Eneriz-Wierner et al. assessed parents' knowledge and education relating to ROP and found that many parents had not been aware of the condition, particularly those with limited English proficiency and low health literacy.

The authors' cross-sectional study included English- or Spanish-speaking parents of very low-birth-weight infants (<1,500 g). The infants were treated at 1 of 4 high-acuity neonatal intensive care units from September 2013 to April 2015. Parents were asked if they knew about ROP and, if so, how they had learned about the disease. They also were asked about their experiences in obtaining outpatient ROP follow-up care for their infants. Multivariate analysis was used to determine whether parents' knowledge of ROP correlated with factors such as English proficiency, health literacy, education modality (verbal, written, online, video), and the occurrence (or not) of a hospital transfer before discharge.

Of the 194 parents who consented to participate, 131 (68%) completed the survey. Overall, 18% had limited English proficiency as well as low health literacy; 26% had limited English proficiency only; and 37% had low health literacy only. Among respondents, 17% did not know that ROP is an eye disease, and 38% did not know that major risk factors are prematurity and very low birth weight. Sixty-two percent received verbal information about ROP, and 56% received written information. Few parents used online resources (12%) or videos (3%). Half of the parents reported that they received information about their infant's retinopathy status at discharge. Limited English proficiency (vs. proficiency) and low health literacy (vs. higher literacy) correlated with less knowledge of ROP.

No particular modality of education was associated with greater knowledge of ROP.

This study demonstrates that many parents lack knowledge of ROP and thus are unaware of the risks and consequences of this disease. Popular passive learning tools such as verbal or written information may not be effective for people with language or health literacy barriers; however, active learning techniques that employ visual imagery, video, or interactive web-based applications may be suitable. Future research should include active learning methods and address best practices for teaching parents about ROP.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Type of Health Insurance and Access to Eye Care

June 2018

Lee et al. compared eye appointment rates and waiting periods for Medicaid members versus individuals with private insurance. They found that those with Medicaid had more difficulty getting appointments, although the time between the request for an appointment and the appointment date was similar.

In this prospective study, trained researchers called the offices of randomly selected eye care providers in 2 states to request the first-available appointment for 2 types of patients: an adult needing a diabetic eye exam and a child requiring a routine exam after a screening had indicated declining vision. The study included 330 eye care professionals in Maryland (53%) and Michigan (47%), stratified by neighborhood (urban vs. rural) and profession (ophthalmologist vs. optometrist). Each practice was called twice, once for a patient with Medicaid and once for a patient with Blue Cross Blue Shield (BCBS). Main outcome measures were the rates of successfully made appointments and the mean waiting periods from phone calls to appointments.

Overall, 603 calls were made to eye care providers (303 ophthalmologists,

300 optometrists; 69% male) from Jan. 1, 2017, to July 1, 2017. Appointment booking rates for adults were 61.5% among Medicaid members and 79.3% among those with BCBS ($p < .001$). For children, the respective rates were 45.4% and 62.5% ($p < .001$). No significant differences in waiting periods were identified between adults and children or between insurance groups.

The primary reason that patients with Medicaid could not obtain appointments was that their insurance plan was not accepted by the practice. Adults with Medicaid were significantly less likely than their BCBS counterparts to secure an appointment (odds ratio [OR], 0.41; $p < .001$); the odds were better if they resided in Michigan rather than in Maryland (OR, 2.40; $p < .001$) or sought appointments with optometrists rather than ophthalmologists (OR, 1.91; $p < .001$). Similarly, children with Medicaid had lower odds of obtaining appointments (OR, 0.41; $p < .001$), and the odds were better for residents of Michigan than of Maryland (OR, 1.68; $p = .03$) and for care by optometrists versus ophthalmologists (OR, 8.00; $p < .001$).

Difficulty obtaining appointments may help to explain lower usage rates for recommended eye care services among Medicaid members. Understanding the apparent insurance-related disparity may help guide policy makers in programs to improve eye health, the authors said.

Unverifiable Publications on Ophthalmology Residency Applications

June 2018

Tamez et al. looked at rates of unverifiable publications among applicants offered an interview for ophthalmology residencies. They found that among candidates who listed published works, just over 9% had at least 1 unverifiable citation. As a result, they recommended that ophthalmology residencies require applicants to supply reference identification numbers or copies of publications.

For this retrospective review, the authors evaluated 322 ophthalmology residency applications (San Francisco

Match) submitted to Vanderbilt University School of Medicine during a 6-year period. Various search engines were used to verify publications listed by the applicants, including PubMed, Google, Google Scholar, and journal websites. Publications were deemed unverifiable if no record was found by any search attempt or if substantial discrepancies were detected, such as errors in authorship, incorrect journal names, or meaningful differences in the publication title or length (e.g., abstract vs. full length). Entries with small errors such as incorrect page numbers were not considered unverifiable.

Of 322 applications, 239 listed at least 1 published work. Of these, 22 (9.2%) cited an unverifiable publication. Two applicants had 2 unverifiable publications. Two of the 22 applicants with unverifiable publications (9.1%) had completed medical school outside the United States.

Specific problems included no verifiable location of a publication (54%), incorrect type of publication (20.8%), incorrect author position (16.7%), applicant not listed as an author (4.2%), and substantial differences in the title (4.2%). One entry contained both an incorrect author position and journal.

In light of these findings, the authors are changing their review process for applicants to Vanderbilt's ophthalmology residency program. Candidates may be asked to bring copies of published works to interviews or to list DOI (digital object identifier) and PubMed identification numbers in a brief supplemental application. The authors also noted that, given the persistence of this problem, making appropriate modifications to the San Francisco Match application may help to ensure recruitment of highly ethical individuals. (See related commentary by Neil R. Miller, MD, in the same issue. Also see a response from San Francisco Match on page 10 of this issue of EyeNet.)

Lampalizumab Ineffective for Geographic Atrophy

June 2018

A phase 2 trial of lampalizumab for geographic atrophy (GA) secondary

to age-related macular degeneration (AMD) suggested that this investigational compound might reduce the rate of GA enlargement. This result led to a pair of phase 3 trials, in which Holz et al. compared outcomes for intravitreal lampalizumab and a sham procedure. In the phase 3 trials, however, lampalizumab did not appear to slow lesion progression, nor was there a link between faster GA progression and presence of the complement factor I (CFI) biomarker.

The phase 3 trials, known as Chroma and Spectri, were double-masked, randomized, sham-controlled studies of identical design. Enrollees were at least 50 years old and had bilateral GA without previous or active choroidal neovascularization in either eye. Altogether, 275 sites participated, representing 23 countries. At baseline, GA lesions measured 2.54 mm² to 17.78 mm² and displayed banded or diffuse fundus autofluorescence patterns.

Participants were randomized (2:1:2:1) to receive 1 of the following regimens: 10-mg intravitreal injection of lampalizumab every 4 weeks, sham procedure every 4 weeks, 10-mg injection of lampalizumab every 6 weeks, or sham procedure every 6 weeks. Efficacy was assessed by calculating mean changes in GA lesion area from baseline to week 48, determined from centrally read fundus autofluorescence images and by the presence or absence of the CFI biomarker. The Chroma study included 906 patients (553 women; mean age, 78.1 years), and Spectri included 975 patients (578 women; mean age, 77.9 years). Overall, 1,732 (92%) of the combined study population completed treatment through week 48.

Adjusted mean increases in GA lesion area ranged from 1.93 mm² to 2.09 mm² across study groups. Differences in adjusted mean change in GA area (lampalizumab minus sham) for lampalizumab at 4-week intervals were -0.02 mm² ($p = .80$) in Chroma and 0.16 mm² ($p = .048$) in Spectri. The corresponding differences in lesion area for lampalizumab at 6-week intervals were 0.05 mm² and 0.09 mm². No benefit of lampalizumab was observed among prespecified subgroups, in-

cluding CFI subsets. Through week 48, endophthalmitis occurred after 5 of 12,447 injections (0.04%); all 5 occurred in participants receiving active treatment. Approximately 3% of subjects who received lamlalizumab experienced intraocular pressure increases that were considered serious.

To date, these are the largest randomized clinical trial studies of GA secondary to AMD. These results highlight the rapid substantial loss of retinal tissue and the risk of vision decline in patients with GA. Further analyses of the study data may provide new insights into the pathophysiology of AMD, which may guide the design of future trials.

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Refractive Error After Cataract Surgery: New Risk Factors Identified

Journal of Cataract & Refractive Surgery

Published online April 20, 2018

In a large multicenter study, Lundström et al. documented risk factors for refractive error after cataract surgery. In addition to previously reported risk factors, they identified several new indicators, including poor preoperative visual acuity, corneal opacities, and surgical complications such as vitreous loss and capsular break.

The authors gathered data from consecutive cases of cataract extraction reported to the European Registry of Quality Outcomes for Cataract and Refractive Surgery (EUREQUO) in 2014 and 2015. All told, 100 clinics and 12 countries were represented. Collected information included demographics, preoperative corrected distance visual acuity (CDVA), target refraction, coexisting eye disease, previous eye surgery, type of surgery and any surgical difficulties, and type of intraocular lens (IOL) implanted.

Of the 548,392 reported cases, follow-up data were available for 282,811 (mean age of patients, 74 years). The absolute mean biometry prediction

error was 0.42 D. The prediction error was within 1.0 D for 93% of eyes and within 0.50 D for 72%. Strong indicators of poor refractive outcome were target refraction (negative or absolute), poorer preoperative CDVA, coexisting eye disease, and surgical difficulty and complications. The odds ratios of refractive error in the presence of a surgical complication were 2.55, 5.57, and 13.8 for >0.5 D, >1.0 D, and >2.0 D, respectively.

The authors found that older age (>60 years) was associated with biometry prediction errors >0.5 D, while younger age was linked to prediction errors >2.0 D. There were no significant differences in refractive outcomes between men and women. The absolute mean biometry prediction error was 0.43 ± 0.55 D in 2014 and 0.41 ± 0.48 D in 2015 ($p < .001$).

The number of risk factors for refractive error is larger than expected. Results of this study may aid in updating evidence-based guidelines. The authors suggest lowering the absolute biometry prediction error from ≤ 0.6 D (as stated in 2012 guidelines based on the EUREQUO data) to ≤ 0.45 D, to more closely resemble their findings. They also propose increasing the benchmark percentage of error within 1.0 D from $\geq 87\%$ (per the 2012 guidelines) to at least 90%. Moreover, the authors recommend that all risk factors be considered during preoperative planning, including selection of the most appropriate IOL.

Off-Label Use of Juvéderm Voluma XC in Infraorbital Hollows

JAMA Facial Plastic Surgery

Published online April 5, 2018

Hyaluronic acid (HA) fillers for infraorbital hollows include Restylane and Belotero. Another HA-based filler, Juvéderm Voluma XC, has higher viscosity and longer duration than Belotero, Restylane, and several other Juvéderm products. The G' value (a measure of firmness) of Juvéderm Voluma XC is lower than that of Perlane, Radiesse, and Restylane, giving it a softer feel that may make it suitable for the lower eyelids. However, it has a higher G' than

other Juvéderm products, allowing it to better maintain its shape and resist spreading. In a study of Voluma XC for infraorbital hollowing, Hall et al. experienced acceptable safety and high patient satisfaction.

This observational study was conducted at a private practice for facial surgery. Participants (age range, 21-85 years) underwent injection of Juvéderm Voluma XC to the tear trough, nasojugal fold, and/or palpebromalar groove. Injection sites varied according to anatomy and volume loss. Main outcome measures were patient-reported FACE-Q scores, adverse events, and the need for additional treatment.

Overall, 101 patients (202 eyes) were treated; mean follow-up time was 12 months. The mean injection volume per patient was 1.0 mL. Most patients received 0.5 mL on each side, disbursed evenly throughout the orbital rim and zygomaticomalar depression, with some gel placed toward the septal confluence. All injections were in the supraperiosteal or submuscular plane. To minimize swelling, the authors generally do not inject more than 1.0 mL of HA gel in a sitting. Therefore, it is expected that some patients will require additional treatment, which is explained before the initial injection.

Most patients (89%) were female, had Fitzpatrick skin type 1 to 4 (98%), and had infraorbital hollow scores of 2 to 4 before injection (88%). Adverse events after injection were bruising (10%), contour irregularities (2%), swelling (3%), and the Tyndall effect (1%); most were mild and transient. Administration of hyaluronidase was required in 3 patients (3%). Eighteen patients (18%) needed more product within 3 months. Satisfaction rates for patients who completed the FACE-Q Satisfaction With Eyes or Satisfaction With Decision survey were 71% and 66%, respectively.

A familiar criticism of Juvéderm Ultra and Ultra Plus in the infraorbital region is the propensity for excessive swelling and the Tyndall effect. The authors reported that, in their experience with Juvéderm Voluma XC, these problems were not common.

—Summaries by Lynda Seminara