Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Cost-Effectiveness Comparison of DMEK and DSAEK

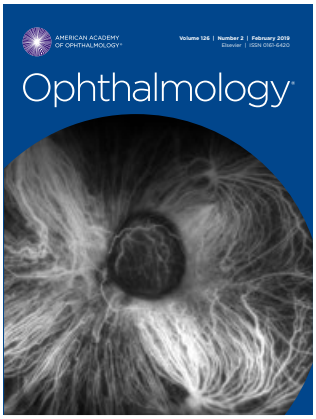
February 2019

Gibbons et al. studied the cost effectiveness of Descemet membrane endothelial keratoplasty (DMEK) and Descemet stripping automated endothelial keratoplasty (DSAEK) and found DMEK to offer superior cost effectiveness, with similar cost but greater utility.

The base case in this study was a 70-year-old man undergoing his first endothelial keratoplasty for bilateral Fuchs endothelial dystrophy. Costs were compared for a 15-year time horizon. The costs and incidences of complications were derived from Medicare reimbursement data, average wholesale prices, and PubMed literature in English. All costs were discounted 3% per annum and were adjusted for inflation to 2018 U.S. dollars. Uncertainty was assessed by deterministic and probabilistic sensitivity analyses. The primary outcomes were incremental cost-effectiveness ratios and incremental cost-utility ratios, measured in cost per quality-adjusted life-years (QALYs).

For the 15-year period, DMEK was superior to DSAEK with respect to QALYs, generating an extra 0.4 QALYs overall. DMEK also was more cost-effective for improving visual acuity, from the societal and third-party payer perspectives. Probabilistic sensitivity analyses, which included variations in costs and rebubble rates, showed that cost savings were greater with DMEK than DSAEK in 38% of iterations. Moreover, in 98% of the models, DMEK costs were within the societal willingness-to-pay threshold of $50,000/QALY.

Despite the favorable findings for DMEK, performing this procedure can be challenging because of the steep learning curve. The economic model in this study was designed for cases that were equally amenable to DMEK and DSAEK. However, the authors acknowledge that some patients are not suitable candidates for DMEK.



Pathologic Features of VA Decline in Patients With CNV: Five-Year Results

February 2019

In a cohort study of patients from the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), **Jaffe et al.** looked at associations between macular morphology and visual acuity (VA) through five years of anti-VEGF treatment. They also sought to determine the retinal anatomic features that contributed to the VA results. They found the relationships between VA and morphology that had been identified in year 1 were sustained or strengthened by year 5. Strong contributors to VA decline from year 2 to year 5 included new foveal scar, choroidal neovascularization (CNV), retinal thinning, and the presence of intraretinal fluid (IRF) or subretinal hyper-reflective material (SHRM).

The study cohort included CATT participants with active CNV secondary to age-related macular degeneration and with a VA of 20/25 to 20/320. During CATT, patients were assigned randomly to receive ranibizumab or bevacizumab for two years; after this, treatment was at the discretion of each patient's ophthalmologist. Outcomes of interest were VA, morphologic features on optical coherence tomography, and lesion size and foveal composition on fundus photography and fluorescein angiography.

Of the 914 participants alive at the five-year mark, image gradings and VA data were available for 523 (57%). At this time point, 66% of eyes had SHRM, 60% had IRF, 38% had subretinal fluid (SRF), and 36% had subretinal pigment epithelium (RPE) fluid. Mean foveal center thicknesses were 148 µm for the retina, 125 µm for the subretinal tissue complex, 103 µm for RPE + RPE elevation, 11 µm for SHRM, and 5 µm for SRF. Factors that were independently associated with poorer VA were SHRM ($p < .001$), thinner retina

($p < .001$), greater CNV lesion area ($p < .001$), foveal center pathology ($p < .001$), and IRF ($p < .05$). The adjusted mean number of VA letters was 65 for nongeographic atrophy; 64 for nonfibrotic scar; 62 for no pathology in the foveal center; 61 for CNV, fluid, or hemorrhage; 56 for fibrotic scar; and 53 for geographic atrophy (GA).

The presence or worsening of the following pathologic features in years 2 to 5 was linked to greater loss of VA from baseline to 5 years: GA area, foveal GA, foveal scar, foveal CNV, foveal IRF, SHRM, retinal thinning, and CNV lesion area. Such factors were present even in patients whose treatment remained aggressive.

Childhood Intermittent Exotropia Outcomes: PEDIG Report

February 2019

Donahue et al., of the Writing Committee for the Pediatric Eye Disease Investigator Group (PEDIG), reported comparative long-term outcomes for bilateral lateral rectus recession (BLRc) and unilateral lateral rectus recession plus medial rectus resection in the same eye (R&R) as primary treatment for intermittent exotropia (IXT). By the three-year mark, there were no substantial differences in the incidence of suboptimal surgical outcome between these approaches. As a result, the authors do not recommend one procedure over the other.

This randomized multicenter trial included 197 children (aged 3 to <11 years) with basic-type IXT. The largest deviation by prism and alternate cover test, at any distance, ranged from 15 to 40 prism diopters (PD), and near stereoacuity was at least 400 seconds of arc. Patients were assigned randomly to receive BLRc (n = 101) or R&R (n = 96). During follow-up visits, which occurred every six months until three years postoperatively, a study-certified examiner who was masked to treatment assignment obtained measurements of stereoacuity, exotropia control, and ocular alignment. The main outcome measure was suboptimal surgical outcome by three years, defined as any of the following: exotropia of ≥10 PD (distance or near) according to the simultaneous prism and cover test (SPCT); constant esotropia of ≥6 PD (distance or near) per SPCT; loss of ≥2 octaves of stereoacuity from baseline at any follow-up exam; or reoperation.

The cumulative probability of suboptimal surgical outcome within three years was 46% (n = 43) for the BLRc group and 37% (n = 33) for the R&R group (95% confidence interval [CI], –6% to 23%). Nine patients (10%) in the BLRc group (eight of whom had a suboptimal outcome) needed reoperation, as did four patients (5%) in the R&R group (three of whom had a suboptimal outcome). Six of the 9 reoperations in the BLRc group were for recurrent exotropia, whereas 3 of the 4 reoperations in the R&R group were for esotropia. Among participants with three full years of follow-up, 29% of the BLRc group (25 of 86) and 17% of the R&R group (13 of 77) underwent reoperation or had a suboptimal outcome by three years (95% CI, –2% to 13%). With respect to improving IXT control and reducing deviation magnitude, the benefits of the two procedures were similar.

The authors acknowledged that three years is a relatively short assessment period; follow-up will continue for another five years.

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Exfoliation Syndrome and Chronic Obstructive Pulmonary Disease

January/February 2019

Exfoliation syndrome (XFS) and chronic pulmonary obstructive disease (COPD) share some elements of pathophysiology, notably the process of elastin repair and extracellular matrix (ECM) modeling. Given this link, **Taylor et al.** set out to determine whether patients with XFS were at greater risk of having COPD and vice versa. They found that patients with XFS were more likely to be diagnosed with COPD, particularly if they were smokers, but that those with COPD were not at elevated risk of developing XFS. They also found that patients with both COPD and XFS had significantly better survival rates than did those with COPD alone.

The researchers evaluated 2,943 patients with XFS, 20,589 patients with COPD, and 162 patients with both illnesses. All were older than age 50 and had been treated between 1996 and 2015. Medical records were drawn from the Utah Population Database. Controls were selected and matched by sex and birth year to patients in a 5:1 ratio. Conditional multivariable logistic regression was used to calculate the odds ratio (OR) to estimate risk of COPD in patients with XFS. Model covariates included race, obesity, and tobacco use.

The results show that the risk of a COPD diagnosis was increased in XFS patients compared to that of non-XFS controls (OR = 1.41, 95% confidence intervals [CI] 1.17-1.70; $p < .0004$), with a subset of patients who used tobacco at a 2.2-fold increased risk (OR = 2.17, 95% CI 1.15-4.09; $p = .02$). Overall 10-year survival rates were better in COPD patients who had XFS than in those who did not (76% and 43%, respectively), perhaps because the diagnosis of XFS moved these patients into the health care system at an earlier point in their lives.

The findings add to the understanding that XFS is more than an ophthalmic disease, the researchers said. They also noted that the finding that COPD risk was particularly elevated in those XFS patients who used tobacco suggests that tobacco is the "insult" that leads to degradation of ECM metabolism, thus increasing COPD risk.

—Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

SS-OCT Angiography Imaging of Geographic Atrophy

February 2019

Thulliez et al. used two different swept-source optical coherence tomography angiography (SS-OCTA) scanning patterns to image geographic atrophy

(GA), with the goal of determining whether the patterns provided similar measurements in eyes affected by age-related macular degeneration (AMD). They found that the two patterns strongly correlated on measurements of area and enlargement rate (ER), and they suggest that all macular GA can now be imaged with 12 × 12 mm SS-OCTA scans, which provide a 40-degree field of view (FOV).

For this prospective case series, the researchers enrolled 25 patients (32 eyes) with GA secondary to dry AMD. They compared the area and ER measurements obtained when the same GA lesion was imaged using 6 × 6 mm and 12 × 12 mm scan patterns on the same SS-OCTA machine. Images were obtained at baseline and at the six- and 12-month marks—and at baseline, the atrophic lesions had to be fully contained within the 6 × 6 mm scan pattern.

The results showed that lesion area and ER measurements for both scan patterns were comparable for all eyes in all patients through the 12 months of the study. As a result, the researchers said, the 12 × 12 mm SS-OCTA scans can now be considered the ideal single imaging modality for the detection and follow-up of GA, as they provide a wider FOV and provide information on both structure and flow. The researchers cautioned, however, that it is not possible to assess hyperautofluorescence patterns at the margins of GA with this technology.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Sarcoidosis-Related Uveitis: Progression to Systemic Disease

February 2019

Ma et al. studied the clinical course and disease characteristics of sarcoid uveitis with the goal of understanding the timing and potential risk factors of its progression to systemic sarcoidosis. They found that concurrent undiagnosed systemic sarcoidosis is common at the time of uveitis onset and recommended that clinicians maintain a high degree of suspicion for systemic disease during and after the detection of uveitis.

This study was a single-center retrospective review of records for 113 patients with concomitant uveitis and presumed (n = 69) or biopsy-proven (n = 44) sarcoidosis. Gathered data included the rate and timing of the development of symptomatic systemic sarcoidosis in relation to the onset of uveitis. The authors compared and contrasted demographics, uveitis characteristics, treatments, and visual outcomes between patients who remained systemically asymptomatic and those in whom symptomatic systemic sarcoidosis developed.

In 89 patients (79%), uveitis was the initial presenting sign of sarcoidosis. Among patients with presumed sarcoidosis, 23 had symptoms of concurrent undiagnosed systemic sarcoidosis at uveitis onset, such as a dry cough, exertional dyspnea, or erythema nodosum. Over time, symptomatic sarcoidosis developed in 29 patients in an organ that was not involved at uveitis onset. The median time from uveitis detection to the development of symptomatic systemic sarcoidosis was 12 months. All patients received topical corticosteroids for intraocular inflammation, and more than half also received regional treatment. Neither group had substantial deterioration of visual function, nor were there meaningful associations between any uveitis characteristic and the progression to extraocular sarcoidosis.

Diabetes Itself May Not Impair Recovery After Cataract Surgery

February 2019

Although studies suggest that the risk of pseudophakic cystoid macular edema (PCME) after routine cataract surgery is higher for patients with diabetes, this may relate more to diabetic retinopathy than to diabetes alone. In a post-hoc analysis of data from two double-blind randomized controlled trials, **Danni et al.** compared outcomes of uneventful cataract surgery between nondiabetic patients and those with diabetes but no retinopathy. For nearly all outcomes assessed, there were no substantial differences between the groups.

This study included 276 eyes (266 patients) that underwent routine cataract surgery. Patients with type 1 or 2 diabetes (56 eyes) were compared with nondiabetic patients (220 eyes). Clinical evaluation was performed by the operating physician, and a research technician recorded data attained before surgery and on postoperative day 28. Demographics and baseline ophthalmic and surgical parameters were comparable for the study groups.

The following outcomes were similar for patients without and with diabetes, respectively: increase in aqueous flare (6.3 ± 16.4 vs. 3.7 ± 8.9 photon units/ms; p = .282), increase in central retinal thickness (CRT; 12.0 ± 38.2 vs. 5.9 ± 15.8 µm; p = .256), and improvement in corrected distance visual acuity (0.57 ± 0.31 vs. 0.53 ± 0.35 decimals; p = .259).

In eyes that received steroid monotherapy (n = 64), the increase in CRT was 38.1 ± 72.8 µm for those without diabetes and 7.8 ± 6.6 µm for those with diabetes (p = .010). In eyes of patients on nonsteroidal anti-inflammatory drug (NSAID) monotherapy (n = 157), the increase in CRT was 5.7 ± 18.4 µm for nondiabetic patients and 6.2 ± 20.5 µm for diabetic patients (p = .897). Among the 55 eyes that received steroid and NSAID therapy, CRT increased 3.6 ± 4.1 µm in nondiabetic patients and 2.9 ± 3.2 µm in patients with diabetes (p = .606). Within 28 days of the surgery, PCME was reported for eight eyes; of these, seven were in the nondiabetic group. On day 28, intraocular pressure was nearly identical for the study groups.

The only outcome with a significant between-group difference was the change in CRT among patients on steroid monotherapy. Therefore, patients with optimally managed diabetes may not be at greater risk of PCME. In light of the relatively small sample size, the authors urged caution in drawing conclusions from their study. Longer follow-up may shed light on differences in macular edema kinetics between patients with and without diabetes.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Association of Cataract Outcomes With Surgical Experience

January 2019

Some evidence suggests that the quality of patient care may be lower in the latter stages of a physician's career. Of particular concern is the technical proficiency of surgeons, given the neurophysiologic changes that occur naturally with aging. In a large population-based study that addressed this matter for cataract surgery, **Campbell et al.** found no correlation between late career stage and the risk of adverse surgical events.

The study included data for 499,650 cataract operations performed in Ontario, Canada, from 2009 through 2013, which represented all ophthalmologists who performed the surgery in the province during this period. Linked health care databases were used to study cataract surgery complications while controlling for patient-, surgeon-, and institution-level covariates. The authors focused on four serious adverse events: dropped lens fragments, posterior capsular rupture, suspected endophthalmitis, and retinal detachment. Surgeons were grouped by career level, with early-, mid-, and late-career phases defined as <15 years of experience, 15-25 years of experience, and >25 years of experience, respectively.

Random-effects logistic regression models were used to evaluate the association between late-career stage and the risk of adverse events, controlling for both patient-level and surgeon-level covariates and for institution type. In a secondary analysis, surgeon age was the variable of interest. Analyses were adjusted for secular trends.

During the study period, late-career surgeons performed 143,108 (28.6%) of the surgeries, and their work was not associated with higher overall risk of surgical adverse events (odds ratio [OR], 1.06 vs. midcareer surgeons). In a sensitivity analysis in which surgeon volume was removed from the model, the result was similar (OR, 1.10). An association was observed between late career stage and the risk of suspected endophthalmitis (OR, 1.41) and dropped lens fragment (OR, 2.30).

The authors noted that, in future studies, it may be worthwhile to consider the frequency of secondary surgery as another indicator of the quality of primary surgical care.

Ultrawide-Field Imaging for Assessing Diabetes Severity

January 2019

Substantial retinal pathology can exist beyond the 7 standard fields of the Early Treatment Diabetic Retinopathy Study (ETDRS), which include only about two-thirds of the retinal surface. Ultrawide-field (UWF) imaging allows for evaluation of up to 82% of the retinal surface in a single image. **Aiello et al.** looked at a large body of evidence to evaluate the reliability of UWF imaging relative to that of 7-field ETDRS for assessing the severity of diabetic retinopathy (DR). The authors observed exact agreement for 59% of eyes and agreement within 1 step for 97%—findings that may justify using UWF in future clinical trials.

For this cross-sectional study, the investigators included modified ETDRS 7-field images and UWF images captured with the Optos 200Tx system. All images were from adults with type 1 or type 2 diabetes (mean age, 62.2 years). Images were evaluated by trained graders who were masked to the clinical data. κ statistics were used to measure agreement among ETDRS 7-field images, UWF images, and UWF images masked to include only the ETDRS 7-field area.

Among the 742 eyes with graded ETDRS 7-field and UWF images, 359 (48.4%) initially had exact agreement and 653 (88.0%) had agreement within 1 step (weighted κ, 0.51). After open adjudication by an independent senior grader who examined all images that had a discrepancy of more than 2 steps, there was perfect agreement for 435 eyes (59.0%) and agreement within 1 step for 714 eyes (96.9%). Hence, concordance between the two imaging modalities was substantial (weighted κ, 0.77).

Of eyes that were 2 or more steps discrepant, 116 were available for adjudication. The ability of ETDRS and UWF masked images to accurately detect DR was considered similar for 59 eyes (50.9%), better with 7-field ETDRS for 22 eyes (19.0%), and better with UWF masked images in 31 eyes (26.7%). For 12.5% of eyes, the severity grade was at least 1 step higher with UWF unmasked versus UWF masked images. Predominantly peripheral DR lesions were present in 41.0% of eyes, indicating that the actual DR severity was at least 2 steps higher for 11.0% of eyes. Disparity for individual eyes was similar for these imaging modalities. *(Also see related commentary by Stephen S. Feman, MD, in the same issue.)*

iStent May Reduce the Need for Glaucoma Drugs After Cataract Surgery

January 2019

Wang et al. compared postoperative use of ocular antihypertensive drugs among patients who had cataract surgery alone and those who underwent cataract surgery and received the iStent Trabecular Micro-Bypass (Glaukos). They found that, by 20 to 24 months following surgery, the standalone group needed substantially more glaucoma medications.

For this retrospective longitudinal study, the authors included patients enrolled in a U.S. managed care network who had cataract surgery plus the iStent (n = 1,509 bilateral; n = 1,462 unilateral) as well as a control group that received bilateral cataract surgery only and was matched (1:1) to patients who had bilateral iStent/cataract surgery. All procedures were performed between 2012 and 2016. The main outcome measure was the number of topical ocular antihypertensive agents used postoperatively versus preoperatively (baseline).

Diagnoses of those who underwent iStent/cataract surgery were primary open-angle glaucoma (78.4%), narrow angles (12.8%), and secondary glaucoma (8.8%). At baseline, 41.2% of this group were not receiving a topical glaucoma agent, and 29.5%, 14.7%,

and 14.6% were receiving 1, 2, or ≥3 agents, respectively. Among the 22.8% of iStent/cataract surgery participants who completed at least two years of postoperative follow-up, the authors observed an increase (to 64.7%) in the number who required no drops by 20 to 24 months postoperatively ($p < .001$, χ^2 test). Patients using at least one topical agent at baseline had a mean reduction of 1.01 and 0.61 in the number of medications by 20 to 24 months after bilateral or unilateral surgery, respectively (both $p < .001$, paired t test). Sustained reduction in medication use was more common for patients who had at least three medications at baseline versus only one medication (hazard ratio, 1.68).

Compared with matched controls who underwent cataract surgery alone, those with the combination procedure had a greater reduction in the mean number of drops used by month 20 to 24 (0.99 vs. 0.49; $p < .001$, paired t test). Moreover, a larger percentage of the iStent/cataract surgery group were receiving no drops by the 20- to 24-month mark (73.5% vs. 55.3%; $p < .001$; χ^2 test).

These findings support those of smaller studies showing that the iStent in combination with cataract surgery reduces dependence on ocular antihypertensive drugs following surgery.

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Ocular and Brain Injury in Pediatric Trauma Patients

Journal of AAPOS
2018;22(6):421-425

In a large retrospective study, **Gise et al.** evaluated the relationship between traumatic brain injury (TBI) and sight-threatening ocular injury. They found that nearly 55% of pediatric trauma patients with ocular comorbidity were found to have TBI. The most common ocular injuries in patients with TBI were orbital fractures and contusions of the eye or adnexa.

For their research, the authors used the U.S. National Trauma Data Bank registry to review records of pediatric patients who were hospitalized for trauma from 2008 through 2014. Ocular injuries were categorized by type and location. TBI was identified by relevant ICD-9 codes (for skull fracture; intracranial injury; shaken baby syndrome; injury to the optic chiasm, optic pathway, or visual cortex; and head injury not otherwise specified).

Of the 58,765 pediatric patients (< 21 years of age) with concomitant trauma and ocular injury upon admission, 32,173 (54.8%) were diagnosed as having TBI. The majority were 12-18 years of age (41.3%), and 69.8% were boys. The most common ocular injuries associated with TBI were contusions of the eye/adnexa (39.1%) and orbital fractures (35.8%). Globe ruptures were not significantly associated with TBI and occurred in only 5.1% of cases.

With regard to age distribution, younger children were more likely to be injured at home, particularly during a fall, while adolescents were more likely to be injured as a result of a motor vehicle accident. With regard to racial distribution, blacks and Hispanics were most likely to be injured during an assault, while whites were more likely to have self-inflicted or unintentional wounds. Whites also were more likely to be injured in a motor vehicle accident. Firearm-inflicted trauma was highest among blacks, and Hispanics had the greatest risk of being injured because of being struck by a motor vehicle.

These findings demonstrate that TBI is common among trauma patients with concurrent ocular injury. Demographic patterns may help to identify patients with the greatest risk of TBI, leading to earlier diagnosis and treatment.

RNFL Thickness and Brain Neurodegeneration

JAMA Network Open
2018;1(7):e184406

In a study of elderly patients without dementia, **Méndez-Gómez et al.** explored the relationship between thickness of the retinal nerve fiber layer (RNFL) and alterations in brain regions that are prone to neurodegeneration. The authors found that greater RNFL thickness correlated with better findings during magnetic resonance imaging (MRI), not only in the brain's visual pathways but also in areas linked to Alzheimer disease processes.

For this investigation, the authors conducted a cross-sectional analysis of participants in the population-based Three-City Study in France. Brain volume was evaluated for 104 patients, and diffusion tensor imaging was analyzed for 79 patients. The mean age of the 104 participants was 80.8 years; 56.7% were women.

Global RNFL was assessed by spectral-domain optical coherence tomography. T1-weighted MRI images were used for measurement of global white and gray matter fractions and the hippocampal fraction. Microstructural brain alterations were determined from diffusion tensor imaging at various locations, including the level of posterior thalamic radiations, limbic system tracts (the fornix and cingulum bundles), and the posterior limb of the internal capsule (control region). Linear regression models were applied, and adjustments were made for relevant confounders.

Results of these assessments showed that a thicker global peripapillary RNFL was associated with better diffusion tensor imaging variables in the global and hippocampal part of the cingulum, a region of the brain associated with neurodegeneration noted in Alzheimer disease. No significant associations were found between the RNFL and the diffusion tensor imaging variables in the control region located outside the visual pathway, nor were any significant associations found with global MRI variables.

Axonal thickness of the retina, which can be measured quickly and easily, may allow for early-stage detection of neurodegeneration in the brain. The authors acknowledged that more research is needed to confirm the potential utility of RNFL thickness as an indicator of early degeneration of the brain in presymptomatic elderly adults.

—Summaries by Lynda Seminara