

# Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

## Ophthalmology

Selected by Stephen D. McLeod, MD

### Demographic and Clinical Features of MIGS Recipients

September 2021

Performing minimally invasive glaucoma surgery (MIGS) at the time of cataract extraction is becoming more routine. Understanding the demographic and clinical profile of patients who undergo these procedures together may improve candidate selection for MIGS. In a retrospective review of data from the IRIS Registry, **Olivier et al.** gathered information on patients who had cataract surgery with or without MIGS and found links between MIGS use and various features, including ethnicity, older age, higher cup-to-disc ratio (CDR), and moderate glaucoma severity.

The study included adults who were 40 years old or older with a diagnosis of open-angle glaucoma (OAG) and no history of MIGS or cataract surgery who underwent cataract extraction, with or without concurrent MIGS, in the United States from 2013 through 2017. The authors applied multivariable logistic regression to determine odds ratios (ORs) and 95% confidence intervals (CIs) for variables of interest.

Results showed that MIGS was more common in those older than 59 (OR, 1.10; 95% CI, 1.05-1.16), among Blacks (vs. Whites: OR, 1.11; 95% CI, 1.07-1.15), and in patients with Medicare (vs. private insurance: OR, 1.12; 95% CI, 1.10-1.15). Clinical features leading to MIGS use were moderate glaucoma

as opposed to mild (OR, 1.07) and higher CDR (OR, 1.24 for CDR 0.5-0.8 vs. < 0.5; OR, 1.27 for CDR > 0.8-1.0 vs. < 0.5). MIGS frequency was higher in the Midwest and Northeast than in the South (OR, 1.32 and 1.26, respectively). It was lower among women (vs. men: OR, 0.96), patients taking five or more glaucoma medications (vs. one or two: OR, 0.94), and cases of severe glaucoma (vs. mild: OR, 0.64).

These findings highlight the importance of capturing demographic and clinical factors in patients' health records, said the authors, who believe such data clarify current practice patterns and inform future directions, including candidate selection for MIGS. They concluded that making appropriate changes to practice patterns "could broaden population access to a group of safer procedures that can address intraocular pressure and reduce the cost and adherence issues related to glaucoma medications."

### Pegcetacoplan Carries Risk of New Exudation

September 2021

The pathogenesis of geographic atrophy (GA) is known to involve the complement pathway, but effective treatments



for GA have been elusive. In the phase 2 FILLY trial, investigators found that intravitreal pegcetacoplan, which inhibits cleavage of complement component C3, slowed progression of GA lesions but raised the risk of new exudative age-related macular degeneration (AMD). In a post hoc analysis of that study, **Wyckoff et al.** aimed to identify clinical factors that may signal the

onset of exudative AMD during treatment with pegcetacoplan. They found that double-layer sign (DLS) in the study eye and a history of exudative AMD in the fellow eye were indicators of new exudative disease.

For this analysis, the researchers evaluated 246 patients with GA secondary to AMD who received intravitreal pegcetacoplan (15 mg) or placebo monthly or every other month for 12 months or until new exudative AMD was found in the study eye. This was followed by six months without treatment. Primary outcome measures were time to new AMD onset, changes in visual acuity (VA), and findings on OCT and fluorescein angiography (FA).

During treatment, exudative AMD occurred in 26 (10.6%) of the 246 eyes, including 18 (21%) of 86 eyes that received pegcetacoplan monthly, 7 (9%) of 79 eyes that received pegcetacoplan every other month, and 1 (1%) of 81 eyes in the placebo group. The time to detection of new exudative AMD varied widely (mean, 256 days), and

strong indicators of new disease were exudative AMD in the contralateral eye at baseline and DLS in the study eye on OCT. All 21 patients who had OCT when the new AMD was detected were found to have subretinal fluid or intraretinal cysts. Ten of the 17 patients with FA at exudative AMD diagnosis also had occult macular neovascularization. Onset of AMD was not linked to loss of VA, and all new cases of exudative disease responded to anti-VEGF therapy.

This research indicates that intravitreal pegcetacoplan slows GA growth but carries an unexpected risk of new-onset AMD, which seems to be dose dependent. However, the risk-benefit profile of pegcetacoplan was deemed sufficiently favorable to retain the current enrollment criteria for subsequent studies. The conversion of nonexudative macular neovascularization may have an immunologic basis, said the authors. They are exploring this possibility and other hypotheses in a global phase 3 program.

## Eye Shields for NFL Players

September 2021

The Academy classifies football as a sport with moderate risk of eye injury and recommends that players wear a polycarbonate visor for eye protection. Despite this guidance, visor use remains optional for players. To assess the value of visors, Dhoot et al. reviewed five seasons of injury reports from the National Football League (NFL) website, which accounts for all 32 teams. They found that eye injuries are more common in players who do not use visors.

The authors looked at reports of injuries occurring in preseason, regular, and playoff games, and searched for terms relating to the eye (e.g., ocular, eye, orbit). Predictors of visor use were established from linear mixed-model regression analysis in which predictive factors had been prespecified. Continuous variables were scaled and centered (to allow for model fit), then transformed to produce adjusted odds ratios for clinical interpretation.

After 250 injury reports were reviewed, the event rate for football-related eye injuries ( $n = 16$ ) was deemed

too low for multilevel regression. Unadjusted analyses showed no significant difference in the incidence of eye injury between players who wore a visor ( $n = 4$ ) and those who did not ( $n = 12$ ). Gouges were the most common type of injury ( $n = 6$ ). Offensive and defensive players were affected equally ( $n = 8$  each). Visors were not worn by any kickers or punters. Of the 9,729 NFL players who participated in at least one regular season game during the study period, 3,049 (31.6%) wore a visor, and most visors were clear. Visor use increased with each season. Visor wear varied by team and ranged from 19.4% to 38.6%.

The fact that visor use has been climbing is encouraging, said the authors. However, many players feel that visors impede their performance. More research is needed to explore concerns about visor wear and to study eye injuries in amateur players, who may not have access to equipment and resources available in the NFL and thus might be susceptible to more severe injuries, said the authors.

—Summaries by Lynda Seminara

## Ophthalmology Retina

Selected by Andrew P. Schachat, MD

### MEWDS Misdiagnosis Is Common

September 2021

Using a large single-center cohort, Ramakrishnan et al. evaluated the clinical and imaging characteristics of multiple evanescent white dot syndrome (MEWDS). They reported that although a distinct set of clinical exam and imaging findings permit recognition of this rare condition, misdiagnosis often occurs.

For this retrospective study, the researchers assessed the medical records of 111 patients who were diagnosed with MEWDS in the Kaiser Permanente Northern California system between 2012 and 2019. Main outcome measures were patient characteristics, visual acuity (VA), clinical examination and imaging findings, and final diagnosis.

Of the 111 patients, 73 were confirmed to have MEWDS, nine were excluded for inadequate imaging, and

29 were classified as misdiagnosed. Of the 73 confirmed to have MEWDS, 58 were female, with a mean (standard deviation [SD]) age at presentation of 35.2 (14.2) years and a mean refractive error of  $-1.6$  D. Initial mean (SD) VA was logMAR 0.39 (0.31); this improved to mean (SD) logMAR 0.07 (0.15) at final follow-up. Presenting symptoms included blurred vision, scotomas, photopsias, and floaters. Nine patients had a previously diagnosed autoimmune disease, and two patients had been recently vaccinated (one for influenza, the other for the human papillomavirus).

Clinical exam and imaging results indicated that all of the correctly diagnosed patients had ellipsoid zone disruption. Other common findings were white fundus lesions (67 patients), foveal granularity (54 patients), and hyperfluorescence on fluorescein angiography (45 patients). Both optic disc edema and vitreous cell were noted clinically or from angiography in approximately half of cases. Of note, the authors pointed out that, in some cases, foveal granularity can be the only presenting feature of MEWDS. They also noted that although most patients were young, some were as old as 75 years.

Of the 29 patients who were initially misdiagnosed, the ultimate diagnosis was typically a different type of infectious or inflammatory chorioretinal disease, including punctate inner choroiditis, syphilis, and primary vitreoretinal lymphoma. This high rate of misdiagnosis reflects the diagnostic challenge that MEWDS presents, the authors said, and they urged clinicians to consider other sight- and life-threatening diagnoses when patients present with uncommon retinal findings.

—Summary by Jean Shaw

## American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

### Return to OR After RD Repair: Revisiting the 45-Day Metric

September 2021

Researchers are assessing unplanned returns to the OR as a quality measure of surgical care, especially returns within

45 days. To evaluate the appropriateness of the 45-day metric for surgical repair of retinal detachment (RD), **Grosinger et al.** reviewed medical records of patients who underwent the procedure. They found that risk-adjusted metrics and a longer post-op period may be warranted to adequately measure the caliber of surgical care.

The study included 268 patients (mean age, 58.6 years) and 270 primary repairs. Eighty-two detachments were considered complicated (trauma-related RD or proliferative vitreoretinopathy [PVR] history at presentation), and 188 were deemed uncomplicated. The minimum follow-up time was 90 days (mean, 1.5 years).

Altogether, 33 (12.2%) of the 270 primary procedures resulted in unplanned return to the OR during the follow-up period, and 17 (51.5%) of these reoperations occurred within 45 days. Among the complicated RD group, return to the OR was required in 12 (14.6%) of 82 cases, six of which (50%) occurred within 45 days. In the uncomplicated group, return to the OR was needed for 21 (11.2%) of 188 cases, 11 of which (52.4%) took place within 45 days. The mean time to return was 70.9 days overall, 75 days for complicated cases, and 68.6 days for uncomplicated cases.

Among the entire study population, factors significantly associated with greater risk of unplanned return to the OR were high myopia, pars plana vitrectomy requiring silicone oil tamponade, trauma-related detachment, and history of choroidal detachment or open globe. Overall, unplanned returns to the OR correlated with poorer visual outcomes, regardless of the time to reoperation. As only about half of the cases of return to the OR occurred within 45 days, the authors believe that longer follow-up may be warranted to properly evaluate the quality of RD surgery.

### **Screen Use and Meibomian Gland Atrophy in Children**

September 2021

During the COVID-19 pandemic, children increased their use of electronic screens for schoolwork as well as for

social and recreational purposes. Prolonged screen use is known to decrease blink rates and exacerbate the risk of dry eye disease in adults; **Cremers et al.** studied its effects on meibomian glands in children. They also explored autoimmune disease biomarker positivity as a possible independent risk factor for severe meibomian gland atrophy. Their findings suggest that excessive screen use is linked to severe gland atrophy in children and that an underlying autoimmune disease may exacerbate this effect.

For this retrospective cross-sectional study, the researchers included children 6 to 17 years of age whose meibomian gland atrophy grade was 2 or higher for at least one eyelid according to meibography. Age-matched controls had gland atrophy grades of 1 or less. Questionnaires were used to obtain information on dry eye symptoms, daily habits regarding use of electronic screens, diet, and time spent outdoors. Those with severe gland atrophy were assessed for autoimmune disease biomarkers if a positive rheumatoid factor was identified.

Forty-one children met the inclusion criteria (mean age, 11 years). Seventeen of them had severe gland atrophy (grade  $\geq 2$ ); the other 24 constituted the control group. All patients with severe atrophy had ocular signs or symptoms of dry eye disease, including corneal neovascularization (43%) and decline of best-corrected visual acuity (41%). Control patients had no clinically meaningful dry eye symptoms or signs. Among patients with severe atrophy, 86% reported 4 or more hours of cumulative screen use per day, and 50% reported 8 or more hours. No control participants used electronic screens more than 2 hours a day.

Patients with severe meibomian gland atrophy had significantly higher meibography scores, and cumulative screen use time correlated with increased meibography scores in adjusted and unadjusted analyses (odds ratios, 2.74 and 2.81, respectively). Among the 16 patients with severe gland atrophy who were tested for autoimmune biomarkers, 10 had a positive result, although they had no systemic symptoms.

The authors encourage more research to establish limits on the use of electronic screens based on meibography grade and to further explore the relationship between biomarkers of autoimmune diseases and meibomian gland atrophy. In the interim, they advise limiting screen use for children who have severe atrophy or relevant autoimmune diseases.

—Summaries by Lynda Seminara

## **JAMA Ophthalmology**

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

### **COVID-19's Potential Impact on Vision Scientists**

August 2021

What impact has COVID-19 had upon the next generation of vision scientists? Last September, the Alliance for Eye and Vision Research (AEVR) convened a panel of early-stage investigators to hear their concerns about the potential impact of COVID-19 disruptions on the next generation of vision scientists. As **Jorkasky et al.** report, the early months of the pandemic were associated with a substantial increase on the stress on the researchers, potentially threatening their productivity and, in some cases, their livelihood.

The panel comprised 22 vision scientists who had yet to be awarded their first independent funding. The investigators, who had been nominated by their institutions, covered bench to bedside vision research. AEVR's goal was to hear their concerns and prepare a video that would be distributed to members of the U.S. Congress.

Challenges reported by the investigators included the following:

- Patient-based clinical research: The shutdown stopped patient recruitment, enrollment, participation, and follow-up in its tracks. Other areas of clinical research—such as epidemiologic and artificial intelligence studies—also were affected.
- Access to animal colonies and cell cultures: Both animals and cell cultures were lost during laboratory shutdowns.
- Collaboration with other researchers: Research collaborations were stymied

by myriad factors, including meeting cancellations and work restrictions that forced non-U.S.-born personnel to return to their country of origin.

- Trainee education: This included reductions in training time as well as delays and limits affecting grants for training and career development.
- Career pathways: Cutbacks in research time, missed grant cycles, and loss of grant and institutional support raised anxiety about future employment.

Overall, the authors said, the prevailing mood was one of “punishing uncertainty.”

Federal and private granting agencies may need to take these factors into account to retain talented early-stage vision researchers, the authors noted.

## Sequential Bilateral Cataract Surgery and Refractive Outcomes

August 2021

Owen et al. evaluated visual acuity (VA) outcomes among patients who underwent immediate and delayed sequential bilateral cataract surgery. They found that immediate sequential surgery is associated with worse visual outcomes—but that the clinical relevance of these outcomes may depend on patients’ additional risk factors.

For this study, the researchers used population-based data from the Academy’s IRIS Registry. The patients were divided into three groups: 1) immediate sequential bilateral surgery, with both procedures occurring on the same day ( $n = 44,525$ ); 2) short-interval delayed sequential bilateral surgery (1-14 days between operations [mean, 11.4 days];  $n = 897,469$ ); and 3) long-interval delayed sequential bilateral surgery (15-90 days [mean, 34.6 days];  $n = 882,202$ ).

Patients in all three groups had similar rates of age-related macular degeneration, diabetic retinopathy, and glaucoma, as well as similar baseline VA in their worse-seeing eyes. Those in the immediate sequential bilateral surgery group had higher pre-op VA in their better-seeing eyes. Univariable and multivariable linear regression models were used to analyze refractive outcomes. Main outcomes were mean

uncorrected VA and best-corrected VA following the procedures.

Results of the analysis showed that patients who underwent immediate sequential bilateral cataract surgery had, on average, worse UCVA following surgery (2.8 fewer letters in first eyes and 1.7 fewer letters in the second eyes) than did those who had the longest intervals between procedures. Other results included the following:

- Post-op 20/20 UCVA in second eyes: Results were 21% for those in the immediate sequential surgery group, 24.2% in the short-interval delayed surgery group, and 21.7% in the long-interval delayed surgery group.

- Post-op 20/20 BCVA in second eyes: Results were 46.8% for those in the immediate surgery group, 56.9% in the short-interval delayed surgery group, and 53.4% in the long-interval delayed surgery group.

Ethnicity (specifically, self-reported ethnicity other than White), Medicaid coverage, and comorbid eye disease were independently associated with worse outcomes.

Given the small sample size of those who underwent immediate sequential surgery and other limitations of the data used in this analysis, further studies on the topic are warranted, the authors said. (*Also see related commentary by Fasika A. Woreta, MD, MPH, and Oliver D. Schein, MD, MPH, MBA, in the same issue. In addition, see “Update on Sequential Bilateral Surgery,” page 16.*)

## ICD-10 Codes for Uveitis: EHR Discrepancies

August 2021

McKay et al. set out to assess the degree of uniformity in uveitis diagnosis and ICD-10 coding among institutions that used the same electronic health record (EHR) system. They found that although uveitis-related ICD-10 code mapping was highly uniform among the institutions, some discrepancies did exist.

For this study, participants were drawn from ophthalmology departments of five institutions that use the Epic EHR system. The investigators recorded ICD-10 codes associated with 54 uveitis-

related diagnostic terms that made up a diverse anatomic and etiologic set of uveitic diseases. For each center, data were collected within a single day, with the exception of longitudinal analyses conducted at two centers to explore mapping discrepancies for intermediate uveitis.

The study was conducted between Sept. 14 and Oct. 9, 2020. The 54 uveitis-related diagnostic terms were queried within the Epic EHR system, and the corresponding ICD-10 codes were evaluated. The main outcomes were the degree of uniformity for uveitis clinical concepts and associated codes.

Among the five institutions, there was perfect agreement for 52 of the 54 diagnostic terms. Two terms—“juvenile idiopathic arthritis associated chronic uveitis” and “intermediate uveitis”—had coding differences. These discrepancies appear to be related to a recent update in diagnostic mapping in Epic, the authors said. In addition, a substantial number of commonly used diagnostic terms were not mapped to specific codes in Epic’s diagnostic dictionary.

Overall, the findings suggest that “efforts should be considered to standardize mapping, track and disseminate information regarding impactful changes with time, and improve precision and coverage for uveitic conditions,” the authors concluded. (*Also see related commentary by Karandeep Singh, MD, and Maria A. Woodward, MD, MSc, in the same issue.*)

—Summaries by Jean Shaw

## OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

### SARS-CoV-2: RNA Genomics in Ocular Specimens

*British Journal of Ophthalmology*  
Published online April 9, 2021

Casagrande et al. examined retinal and optic nerve biopsy specimens of deceased patients who had COVID-19. They found SARS-CoV-2 RNA in half of the retinal specimens and in most of the optic nerve specimens.

This study was performed in Germa-



ny and included 14 eyes of 14 deceased patients in whom COVID-19 had been confirmed. The researchers' objectives were to understand infectivity via virus isolation and to detect and quantify SARS-CoV-2 RNA by real-time reverse transcriptase polymerase chain reaction. They obtained postmortem throat swabs and biopsy specimens of the retina, vitreous humor, and optic nerve, which underwent further exploration by virus cultivation/isolation, molecular analysis, and immunohistochemistry.

Thirteen of the 14 patients died of COVID; the other died of unrelated hemorrhagic shock. No documentation of COVID-related ocular symptoms was found in the patients' medical records. SARS-CoV-2 RNA was observed in seven (50%) of 14 retinal specimens, 10 (77%) of 13 optic nerve specimens, and eight (57%) of 14 vitreous humor samples. SARS-CoV-2 viremia was found in six (55%) of 11 samples. Virus isolation failed in all vitreous humor, retina, and optic nerve specimens. Moreover, immunohistochemistry findings were negative for the SARS-CoV-2 spike protein. Subgenomic RNA was detected in 40% of retinal and 60% of optic nerve samples.

Although the presence of subgenomic RNA could denote SARS-CoV-2 invasion of neuronal tissue, said the authors, they believe this would be unlikely in the absence of virus isolation or spike protein detection. Hence,

subgenomic RNA itself does not definitively denote active replication. The authors recommend larger studies of the ophthalmic features and effects of SARS-CoV-2 infection.

### Outcomes of RRD Repair

*Graefe's Archive for Clinical and Experimental Ophthalmology*  
Published online July 3, 2021

Vounotrypdis et al. reviewed final outcomes for nonvitrectomized eyes that developed rhegmatogenous retinal detachment (RRD) following intravitreal injections. They found that anatomic results generally were acceptable after one surgical intervention, but visual outcomes were poor for most patients. In addition, they found that, when compared with anti-VEGF agents, the dexamethasone implant and ocriplasmin injections were linked to higher rates of incident RRD, recurrent RRD, and proliferative vitreoretinopathy (PVR).

For this retrospective review, the authors included all nonvitrectomized phakic and pseudophakic eyes of patients from two vitreoretinal centers in Europe. Eyes that developed RRD after intravitreal therapy were treated promptly with either 1) scleral buckling with cryopexy, 2) standard small-gauge pars plana vitrectomy (PPV) with laser retinopexy, or 3) a combination of these procedures. All cases of recurrent

RRD underwent PPV. Main outcomes were the rates of primary and secondary retinal attachment after surgery, the rate of PVR, and functional results. In one center, 10-year RRD incidence rates per injection were calculated.

Fifty-two eyes (52 patients) met the inclusion criteria. The success rates for primary and secondary anatomic repair were 83% (n = 43) and 96% (n = 50), respectively. PVR was noted in three eyes with uveitis, in two eyes with postoperative cystoid macular edema, and in eight of nine eyes that received a dexamethasone implant. The presence of PVR was unrelated to age, number of injections, duration of symptoms, or time from the last injection to the detachment. Mean best-corrected visual acuity improved in 28 eyes, remained stable in 16, and worsened in eight.

With regard to specific intravitreal medications, the 10-year RRD rates were 0.04% for ranibizumab, 0.109% for bevacizumab, and 0.214% for dexamethasone. Aflibercept and ocriplasmin were in use for seven of the 10 years and had RRD rates of 0.007 and 1.527%, respectively, during that time. The higher rate of detachment with dexamethasone may reflect the relatively large sclerotomy, wide needle, and/or underlying disease, said the authors, who recommend exploring the potential role of these factors in the development of PVR.

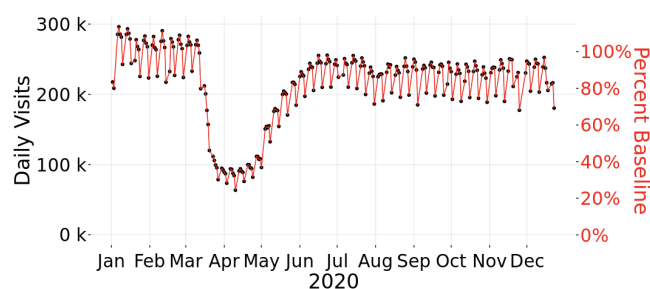
—Summaries by Lynda Seminara

## IRIS Registry Data Snapshot: Patient Visits During the Pandemic

On March 18, 2020, the Academy sent a recommendation to "cease providing any treatment other than urgent or emergent care immediately" via email to members. In the month following that email, patient visits declined by more than 70% compared with baseline.

To assess the impact of the COVID-19 pandemic on patient care and outcomes, Leng et al. evaluated data from the IRIS Registry. Their earlier analysis covered January through August 2020.<sup>1</sup> A new snapshot (right) updates their findings with data through December 2020. By mid-June, patient visits stabilized to 85%-95% of baseline, representing a substantial but not full recovery, possibly because vaccines were not available until the end of the year.

<sup>1</sup> Leng T et al. *Ophthalmology*. Published online June 15, 2021.



**COVID IMPACT.** Daily weekday (nonholiday) patient visit volume during 2020. Secondary y-axis shows visit volume compared to a baseline from Jan. 1 to March 17, 2020.

**Note:** The Academy has partnered with Verana Health to curate and analyze IRIS Registry data.