

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by George H. Bartley, MD

Myocilin Genetic Testing for POAG Allows Early Identification in At-Risk Patients

March 2017

Souzeau et al. compared disease severity between 2 groups of patients with primary open-angle glaucoma (POAG) who had a *Myocilin* (*MYOC*) disease-causing variant: those who were diagnosed through normal clinical pathways (Clinical) versus those who were examined following positive results from genetic testing (Genetic). The researchers found that POAG was identified at an earlier stage in the Genetic group.

This study retrospectively examined records from the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG); 97 *MYOC* mutation carriers were identified in the database, of whom 73 had clinical details available from their initial presentation. Among these 73 participants, 43 were Clinical cases and 30 were Genetic.

All cases were classified into 4 groups (unaffected, glaucoma suspect, glaucoma, advanced glaucoma) according to disease severity at the time of their first examination by an ophthalmologist. The main outcome measures were glaucoma clinical parameters and age at presentation.

At the first examination, 83% of Genetic cases were unaffected, and 17% were glaucoma suspects. In contrast, among Clinical cases, 44% were glaucoma suspects, 28% had glaucoma, and

28% had advanced glaucoma. Genetic cases were significantly younger at presentation than were Clinical cases (40.6 vs. 47.5 years, respectively; $p = .018$). Glaucoma parameters for the Clinical and Genetic groups, respectively, included the following: mean highest intraocular pressure, 32.2 vs. 17.6 mm Hg ($p < .001$); cup-to-disc ratio, 0.65 vs. 0.48 ($p = .006$); and mean deviation on visual field testing, -10.0 vs. -1.2 ($p < .001$).

The researchers concluded that their findings demonstrate that *MYOC* cascade genetic testing for POAG allows identification of at-risk individuals at an early stage, even before signs of glaucoma are apparent. Further, they noted that, to their knowledge, this is the first study to demonstrate the clinical utility of predictive genetic testing for *MYOC* in glaucoma.

Anti-VEGF Use Among Privately Insured and Medicare Advantage Patients

March 2017

Parikh et al. characterized the trends during the first 10 years of ophthalmic usage of intravitreal anti-VEGF medications (bevacizumab, ranibizumab, and aflibercept). Their retrospective cohort study was based on administrative claims data for anti-VEGF injections from 2006 through 2015. They found that intravitreal anti-VEGF injections

increased annually throughout this period and that the most common use was for treatment of age-related macular degeneration (AMD).

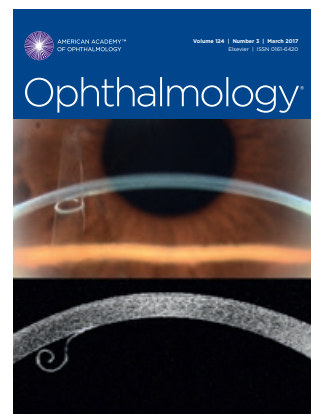
Using a data warehouse containing administrative claims data for more

than 100 million commercial-ly insured and Medicare Advantage patients, the researchers identified intravitreal anti-VEGF injections by means of Current Procedural Terminology codes. The main outcome measures were total and annual

numbers of intravitreal anti-VEGF injections, as well as injections per 1,000 enrolled patients per general category of ophthalmic disease.

A total of 959,945 anti-VEGF injections were given to 124,835 patients during the study period. Among all injections, 64.6% were bevacizumab, 22.0% were ranibizumab, and 13.4% percent were aflibercept. With regard to conditions treated, 62.7% of injections were for AMD, 16.1% were for diabetic retinal disease, 8.3% were for retinal vein occlusion, and 12.9% were for all other uses.

For treatment of AMD, the use of bevacizumab and ranibizumab rose from 58.8 and 35.5 injections/1,000 patients, respectively, in 2006; peaked in 2011-2012 (338.6 and 137.7 injec-



tions/1,000, respectively); and decreased thereafter (294.4 and 100.7 injections/1,000 in 2015, respectively). In contrast, aflibercept use increased every year (in 2011, 1.1 injections/1,000 AMD patients; in 2015, 183.0 injections/1,000).

For diabetic retinal disease, bevacizumab use increased each year (2.4 injections/1,000 patients in 2009 to 13.6/1,000 in 2015), while that of ranibizumab initially increased significantly and then declined after 2014 (0.1/1,000 in 2009, 6.3/1,000 in 2014, 4.0/1,000 in 2015). Aflibercept use increased each year for patients with diabetic retinal diseases and RVO (respectively, 0.001 and 0.05 injections/1,000 in 2011; 5.6 and 140.2 injections/1,000 in 2015).

The authors concluded that intravitreal injections of anti-VEGF medications increased annually from 2006 to 2015. Bevacizumab was most commonly used, despite its lack of FDA approval for ophthalmic indications, and AMD was the most common condition treated. Ranibizumab use declined after 2014, while both the absolute and relative use of bevacizumab and aflibercept increased.

Long-Term Posterior Capsule Opacification Reduction With Square-Edge PMMA IOL

March 2017

In a randomized controlled study, Haripriya et al. compared posterior capsule opacification (PCO) scores and rates of Nd:YAG capsulotomy for a modified square-edge (SE) PMMA intraocular lens (IOL) against 2 other types: round-edge (RE) PMMA or SE hydrophobic acrylic IOLs. They found that at the 9-year follow-up, both the PCO scores and the rates of capsulotomy were significantly lower in the SE-PMMA group.

Many patients in the developing world receive sutureless, manual small-incision cataract surgery, often in conjunction with nonfolding PMMA IOLs. These IOLs, however, are associated with a higher rate of PCO compared with foldable acrylic IOLs. This is a particular problem in areas with limited access to postop care and Nd:YAG. Animal studies suggested that

a sharp edge on the optic of a PMMA IOL reduced PCO; thus, the authors developed a modified SE-PMMA, which they evaluated in this study.

The study included 94 patients who were scheduled for bilateral phacemulsification. All patients had an SE-PMMA IOL implanted in 1 eye; in the fellow eye, 46 patients received an RE-PMMA IOL (group A) and 48 received an SE acrylic IOL (group B). Randomization was used to determine group assignment and which IOL was implanted in the first eye to undergo surgery. The main outcome measures were PCO scores and YAG capsulotomy rates. PCO score was determined objectively by image analysis software grading of standardized retroillumination photos taken annually for the first 5 postoperative years and at year 9.

In both groups A and B, the SE-PMMA IOL had significantly lower PCO scores at 9 years than either of the comparison groups. Moreover, 9-year Nd:YAG capsulotomy rates were 2% for SE-PMMA IOLs versus 37% for RE-PMMA IOLs in group A and 4% for SE-PMMA IOLs versus 10% for SE acrylic IOLs in group B.

The authors noted that creating a squared posterior PMMA optic edge adds approximately \$1 to the manufacturing cost of each IOL. However, given the long-term benefit in reducing PCO, they concluded that this modification is highly cost-effective and could significantly reduce the burden of vision-impairing secondary membrane in developing countries.

—*Summaries by Marianne Doran*

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Setting Priorities for Diabetic Retinopathy Clinical Research

March/April 2017

Le et al. sought to identify evidence gaps and set priorities for new systematic reviews and randomized controlled trials (RCTs) for managing diabetic retinopathy (DR), including diabetic macular edema (DME). They used a 2-round Delphi survey among Diabetic Retinopathy Clinical Research Network

(DRCR.net) investigators to rate the importance of research questions on the effectiveness of various interventions. Through this process, the authors identified 22 high-priority clinical questions.

The authors invited 410 DRCR.net investigators to participate (of whom 7.8% completed both rounds of the Delphi process). The authors provided recommendations from the American Academy of Ophthalmology's 2012 *Preferred Practice Patterns (PPP)* for Diabetic Retinopathy as 91 answerable clinical research questions about intervention effectiveness and asked the investigators to rate each question's importance from 0 (not important) to 10 (very important); further, they invited the DRCR.net investigators to suggest other questions (15 were added for a total of 106). Questions were deemed high priority if at least 75% of respondents assigned an importance rating of 5 or higher in Round 2.

The authors also extracted outcome measures relevant to DR and asked respondents to identify those that "must be measured in all studies." In addition, they mapped Cochrane reviews published up to March 2016 to the high-priority clinical research questions.

Among the final list of 106 clinical research questions, 22 met the definition of high priority: 9/22 concerned the effectiveness of anti-VEGF therapy, and 13/22 focused on frequency of follow-up and treatment effectiveness in patients with specific characteristics (e.g., DME). Outcomes that at least 75% of respondents marked as "must be measured in all studies" included visual acuity and visual loss, death of participants, and intraocular pressure. Only 1 of the prioritized questions was associated with conclusive evidence from a Cochrane systematic review.

Despite the limited response rate from DRCR.net members, the authors identified 22 high-priority clinical questions in the management of DR, including DME, but few were associated with Cochrane reviews. They concluded that their results support the need for further systematic reviews and RCTs to address the evidence gaps.

—*Summary by Peggy Denny*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Phakic ICL Implantation to Correct Myopia in Children With Special Needs

March 2017

Correcting high degrees of ametropia can be challenging in children with special needs, who may resist wearing glasses and may not be able to use contact lenses appropriately. Tychsen et al. prospectively studied a cohort of children with special needs and found that implantation of a phakic intraocular collamer lens (ICL) was safe and improved visual function.

Clinical course and outcome data were obtained for 40 implanted eyes (23 children aged 1-18 years). Before implantation of the Visian ICL device (Staar Surgical), myopia ranged from -3.0 D to -14.5 D (mean, -9.2 D). The correction goal range was plano to +1.0 D. The mean follow-up period was 15 months (range, 6-22 months).

Implantation of the lens resulted in correction within ± 1.0 D of the refractive goal for 35 eyes (88%). The other 5 eyes were corrected to within 1.5 D. Uncorrected distance visual acuity improved markedly for all eyes, from a mean of 20/1,050 to a mean of 20/42. Of the 13 children with a neurobehavioral disorder (such as Down syndrome, cerebral palsy, or autism), 11 experienced enhanced attentiveness, visual awareness, or social interaction after the surgery.

Of the 23 children, 2 were returned to the operating room on the first postoperative day for alleviation of pupillary block caused by a nonpatent iridotomy. No other complications occurred, and no patient experienced worsening visual acuity during the follow-up period.

The authors emphasized that the surgical and perioperative management of children with special needs differs from that of myopic adults who undergo similar refractive surgery; recommendations are provided in the article.

The authors concluded that implan-

tation of a phakic ICL into the ciliary sulcus appears to be effective and safe in children with special needs. Major advantages of this procedure include avoidance of marked refractive regression and corneal haze (concerns with excimer laser keratectomy of pediatric eyes) and reduction in the risk of accommodation loss and aphakic/pseudophakic retinal detachment (disadvantages of refractive lensectomy).

Insights Into Epiretinal Membranes and Staging

March 2017

Govetto et al. reviewed the records of 172 patients (194 eyes) diagnosed with epiretinal membranes (ERMs). Based on findings from spectral-domain optical coherence tomography (SD-OCT), they identified a novel clinical entity associated with substantial vision loss: ectopic inner foveal layers.

The authors also proposed a 4-stage classification system for ERMs. Stage 1 ERMs are thin, with a foveal depression, and have readily distinguishable retinal layers. Stage 2 membranes lack a foveal depression and exhibit retinal distortion, with stretching or widening of the outer nuclear layer, although retinal layers still are distinct. Stage 3 denotes emergence of continuous ectopic inner foveal layers and maintenance of observable retinal layers. Stage 4 ERMs are thick, with a disrupted macula, distorted and indistinguishable retinal layers, and continuous ectopic inner foveal layers.

The ERMs in this study were graded as follows: stage 1, 43 eyes (22.1%); stage 2, 88 eyes (45.4%); stage 3, 51 eyes (26.3%); and stage 4, 12 eyes (6.2%). Continuous ectopic inner foveal layers were detected in 63 eyes (32.5%).

Successive ERM stages were associated with progressively reduced best-corrected visual acuity (BCVA), thickening of the central fovea, and greater prevalence of tractional cystoid macular edema and ellipsoid disruption. The presence of ectopic inner foveal layers correlated with poorer BCVA, even when controlled for other potential causes of reduced BCVA.

Sixty-three eyes were scheduled for

surgery. During follow-up (mean, 22 months) of the nonsurgical eyes, 9 of 32 ERMs progressed from stage 1 to 2, 10 of 77 from stage 2 to 3, and 2 of 17 from stage 3 to 4. In all cases, progression was accompanied by a significant decline in BCVA. No progression was seen in 108 eyes.

The authors concluded that the presence of continuous ectopic inner foveal layers, as revealed on SD-OCT, is a prognostic factor for significant visual loss; and they proposed an OCT-based grading system for ERMs. Their study confirmed that the inner retinal layers of the macula may be particularly sensitive to tractional stress and demonstrated that ERM formation may significantly alter the microanatomy of the inner fovea.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Outcomes of the Veterans Affairs LOVIT II Trial

February 2017

The initial Veterans Affairs Low Vision Intervention Trial (LOVIT) evaluated the effectiveness of an intensive rehabilitation program for legally blind veterans with macular diseases. In the subsequent trial (LOVIT II), Stelmack et al. compared outcomes for 2 types of low vision (LV) interventions among veterans with less severe visual impairment (best-corrected distance visual acuity [BCDVA] in the better eye of 20/50-20/200): LV optical devices provided either (1) with no LV therapy or (2) in combination with LV rehabilitation with a therapist. Although both interventions were beneficial, the added rehab increased effectiveness only for patients with BCDVA of 20/63-20/200.

In the LOVIT II study, 323 veterans (314 men; mean age, 80 years) were randomized to receive LV devices with or without rehab therapy from a specialist who provided training and homework on the use of the devices.

In telephone interviews at baseline and 4 months, participants responded to questionnaires including the VA Low

Vision Visual Functioning Questionnaire, Short Form-36, EuroQoL-5D, and MNREAD; and the researchers evaluated changes in visual ability and quality of life. Visual ability was measured in dimensionless log odds units (logits), with a 0.14-logit change corresponding to the ability change expected from a 1-line change in visual acuity.

The authors found that both basic LV services and basic LV plus rehabilitation therapy improved visual ability and mobility in veterans with macular disease and better-eye BCDVA of 20/50-20/200. In the preplanned stratified analyses, individuals with BCDVA of 20/63-20/200 experienced greater improvement with LV rehab than with basic LV services. Among patients whose better-eye BCDVA was 20/50-20/63, there were no significant differences in outcomes between the 2 programs.

On the basis of their findings, the authors concluded that basic LV services alone may be adequate for most patients with mild visual impairment.

Transplant Suitability of Corneal Tissue From Donors With Diabetes

February 2017

As the prevalence of diabetes continues to grow, so does the pool of donor tissue from individuals with the disease. Margo et al. reviewed a large data set of donated eyes (including approximately 31% from donors with type 1 or type 2 diabetes) and found no correlation between the presence or severity of diabetes and the suitability of the corneal tissue for transplantation.

Donor information was obtained from the SightLife Eye Bank for the 3-year study period (2012-2015). Data included endothelial cell count, lens status, medical/surgical history, transplant suitability, and time from death until refrigeration and preservation of the cornea. The main outcome measures were endothelial cell density, suitability for transplantation based on tissue analysis, and technician-induced endothelial damage. The researchers stratified donors in categories of severe and nonsevere diabetes to assess the

effect, if any, of disease severity.

Among 14,532 donors (mean age, 58.6 years), the mean endothelial cell count was 2,732 cells/mm². Type 1 or 2 diabetes was listed in the medical history for 8,552 (30.6%) of 27,948 donor eyes; 5,242 eyes (18.8%) were from patients with severe diabetes. After adjusting for factors including sex, phakia versus pseudophakia, and time from death to tissue refrigeration/preservation, no correlation was found between the presence of diabetes (adjusted odds ratio [OR], 0.79; *p* = .28) or severe diabetes (adjusted OR, 0.86; *p* = .54) and suitability for corneal transplantation.

Contrary to findings from other studies, the endothelial cell counts of donors with diabetes (regardless of disease severity) were similar to those of the overall donor population. Technician-induced endothelial damage occurred in 59 corneas (0.2%) but was not associated with diabetes.

The authors concluded that diabetes, which is increasingly common among cornea donors, is not associated with lower endothelial cell counts or poor suitability for transplantation. Longitudinal studies are warranted to determine the long-term outcomes of transplanting corneal tissue from donors with diabetes.

Dry Eye Syndrome: Longitudinal Study of Frequency and Risk Factors

February 2017

Although risk factors for dry eye syndrome have been elucidated by cross-sectional studies, little information exists about symptom progression and persistence over time. In a longitudinal study, Ong et al. found that most patients who had severe symptoms of dry eye at baseline reported persistence of those symptoms 1 year later.

The study population comprised 120 patients (mean age, 64 years) recruited from Miami Veterans Affairs System eye clinic. At baseline, signs and symptoms of dry eye ranged from none to severe. Because the study focused on idiopathic dry eye, researchers excluded individuals with corneal or eyelid abnormalities; contact lens use; prior

refractive, glaucoma, or retinal surgery; ocular medication use (except artificial tears); and ocular or systemic conditions associated with dry eye.

At baseline, each participant provided information on demographics, ocular and medical history, and use of medications; they also self-reported their eye pain on a numerical scale and completed standardized questionnaires including the Dry Eye Questionnaire 5 [DEQ5]), Ocular Surface Disease Index, and the Neuropathic Pain Symptom Inventory modified for the eye. Ocular surface evaluation was also performed at baseline. The questionnaires were administered again at 1 year, to assess change from baseline and determine risk factors associated with severe dry eye symptoms at 1 year.

At baseline, 58 patients had absent, mild, or moderate symptoms of dry eye. Of these, 26 (45%) progressed to more severe symptoms at 1 year. Of the 62 patients who had severe symptoms (a score of ≥ 12 on the DEQ5) at baseline, 46 (74%) reported that their symptoms persisted during the follow-up year.

Baseline ocular risk factors for severe dry eye symptoms at 1 year included more severe dry eye symptoms, ocular pain, and neuropathic pain-like ocular symptoms. Nonocular risk factors included sleep disturbances (e.g., sleep apnea, insomnia), mental health status (e.g., depression, posttraumatic stress disorder [PTSD]), nonocular pain, and medication use (e.g., anxiolytics, analgesics). The most significant risk factors were found to be sleep apnea (odds ratio [OR], 3.80), DEQ5 score (OR, 1.15), and PTSD (OR, 1.04).

The authors concluded that patients with severe dry eye symptoms and ocular pain at baseline are more likely to experience continuation of those symptoms. Individual pain perception and severity are important considerations in the evaluation and management of patients with dry eye. Further, the authors recommended that dry eye assessment should be expanded to include questions about the time course, pain severity, and neuropathic qualities of dry eye symptoms.

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Resident Compliance With AAO Preferred Practice Patterns for POAG Suspects

Journal of Glaucoma
2016;25:963-967

Mihlstin et al. examined resident compliance with the American Academy of Ophthalmology Preferred Practice Patterns (PPPs) for primary open-angle glaucoma suspects (POAGS) in a resident ophthalmology clinic. After analyzing data from 200 patient charts, the authors found that compliance was high overall (73.8%), although the level of compliance varied markedly among the elements of the PPP.

The 200 charts were randomly selected from those of adult patients with the ICD diagnostic code for POAGS at their initial visit to the Kresge Eye Institute resident clinic. Electronic medical records were evaluated for documentation and compliance with 17 elements in the PPP, in the areas of history, examination, and patient education.

The overall mean compliance was 73.8% for all charts and was similar across training levels: 74.4% for first-year residents (n = 53), 74.5% for second-year residents (n = 38), and 73.3% for third-year residents (n = 109). For the 3 elements of history, overall compliance was 92%.

For the 10 elements in the examination category, the overall compliance rate was 88%. Although compliance was 99%-100% on the elements of best-corrected visual acuity, pupillary reaction, slit-lamp examination, and IOP measurement, there was moderate compliance (84%-85%) for the elements of optic nerve head/retinal nerve fiber analysis and visual field evaluation. Substantially lower compliance was found for 2 examination elements: gonioscopy (46%) and central corneal thickness (69%).

Compliance was lowest for the 4 elements of patient education, at 26% overall. Only 5% of charts included documentation of discussion of diag-

nosis, risk factors, management, and prognosis; while no charts documented discussion of the chronic nature of treatment and potential physical or emotional effects of long-term treatment.

The authors concluded that residents' compliance was high for most elements of the PPPs for POAGS, but they identified specific areas of poor compliance, especially concerning patient education. They noted that adherence to PPPs can be a helpful method of assessing resident performance.

FLACS vs. Standard Phacoemulsification Cataract Surgery

Journal of Cataract and Refractive Surgery
2016;42:1779-1790

In a multicenter case-control study, Manning et al. compared the visual, refractive, and adverse outcomes of femtosecond laser-assisted cataract surgery (FLACS) and conventional phacoemulsification cataract surgery. They found that FLACS did not yield better visual or refractive outcomes than conventional phaco.

The researchers matched 2,814 FLACS cases performed by experienced surgeons in Europe and Australia to 4,987 conventional phaco cases drawn from the European Registry of Quality Outcomes for Cataract and Refractive Surgery (EUREQUO). Matching criteria included baseline corrected distance visual acuity (CDVA), age, number of ocular comorbidities, and surgical risk factors. Intraoperative and postoperative complications and refractive outcomes were compared. Patient follow-up was 7 to 60 days.

Results obtained with FLACS and conventional phaco, respectively, were as follows: posterior capsule complications, 0.7% versus 0.4%; postoperative logMAR CDVA, 0.05 versus 0.03; postoperative CDVA worse at follow-up by 5 letters or more, 1.0% versus 0.4%; CDVA of 0.3 or better, 96.3% versus 97.1%; absolute biometry prediction error, 0.43 D versus 0.40 D; within ± 0.5 D of target, 72% versus 74.3%; and postoperative complications, 3.4% versus 2.3%.

The researchers concluded that both

FLACS and conventional phacoemulsification cataract surgery provided excellent visual outcomes, with few complications. However, they found no evidence to support claims that FLACS is superior to conventional phaco; in fact, postoperative complications were lower with the conventional surgery.

Schlemm's Canal Expansion After Uncomplicated Phacoemulsification Surgery

Investigative Ophthalmology & Visual Science
2016;57:6507-6512

Zhao et al. used swept-source optical coherence tomography (OCT) to evaluate the effects of uncomplicated phacoemulsification cataract surgery on Schlemm's canal (SC). They observed expansion of SC after surgery, which correlated with a reduction in intraocular pressure (IOP).

The study included 25 patients with a senile cataract. The SC area and diameter were measured by OCT at baseline and at 1 day, 1 week, 1 month, and 6 months after surgery. The researchers used multivariate linear regression analysis to identify predictors of change in the mean SC area and diameter.

After cataract surgery, the researchers found a significant increase in SC area and diameter and a decrease in IOP through the end of the study period. After multivariate analysis, the changes in the SC area and diameter 6 months after surgery were significantly correlated with the change in IOP (SC area, $\beta = -0.575$; SC diameter, $\beta = -0.576$) and the change in the anterior vault (SC area, $\beta = 0.359$; SC diameter, $\beta = 0.413$).

The authors concluded that after cataract surgery, the SC morphologic measurements increased significantly, and this increase was accompanied by a decrease in IOP. However, they added that further investigation is needed to determine whether such changes will continue to affect IOP in the longer term.

—Summaries by Marianne Doran



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