

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Russell N. Van Gelder,
MD, PhD

Low Corneal Hysteresis and Risk of Glaucoma Progression

April 2023

In an *Ophthalmic Technology Assessment* for the Academy, Sit et al. explored the utility of corneal hysteresis (CH) to assist clinicians in diagnosing glaucoma and assessing the risk of disease progression. Results of their analysis showed that CH is lower when glaucoma is present and that low CH signals faster disease progression, even in patients whose IOP is well controlled.

The researchers began by searching PubMed for relevant peer-reviewed articles published through July 2022. The search returned 423 abstracts, which were examined to rule out reviews and non-English articles. Studies that met the inclusion criteria were original research in adults, focused on CH measured by the Ocular Response Analyzer, and identified the risk of glaucoma progression or differentiated patients with glaucoma from healthy subjects. The final analysis set comprised four cohort studies, four cross-sectional studies, two case series, and three case-control studies.

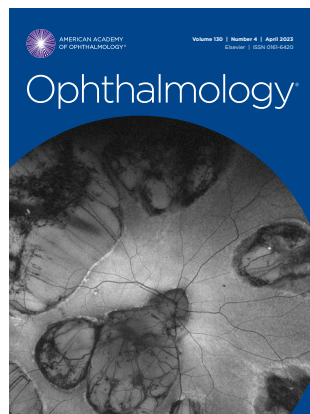
Relative to normal controls, most patients with primary open-angle glaucoma (POAG), primary angle-closure

glaucoma, pseudoexfoliative glaucoma, or pseudoexfoliation syndrome were found to have lower CH. However, the interpretation of low CH in patients who had high IOP or were using hypotensive medications was hindered by the influence of these parameters on CH measurements. Moreover, CH was lower in treatment-naïve patients with normal-tension glaucoma than in healthy controls whose IOP was similar. In patients with POAG, lower CH was linked to higher risk of glaucoma progression based on visual field

or structural markers, even for those with well-controlled IOP. Most of the findings suggest that measuring CH is a potential adjunct for identifying patients with glaucoma or gauging the risk of progression.

Further research is needed to explore any

causal relationship, said the authors. If low CH is found to be a causative factor for glaucoma and its progression, the alteration of ocular tissue properties to increase CH could become a new therapeutic target, independent of IOP reduction. The authors emphasized that measuring CH can complement the standard structural and functional assessments performed in patients with confirmed or suspected glaucoma.



Do HPSAs Apply to Eye Care?

April 2023

The U.S. government uses health professional shortage areas (HPSAs) to gauge patient accessibility to primary care, but whether these shortage areas apply to eye care is not known. Soares et al. conducted a cross-sectional retrospective study to explore this matter and found only a weak correlation between HPSAs and the availability of eye care.

For this work, the investigators gathered U.S. census data and documented practice locations of ophthalmologists and optometrists listed in the Medicare database, from which eye care provider (ECP) density per county was calculated. HPSA scores were determined from the publicly available HPSA dataset, and county-level data on visual impairment were derived from the CDC's Vision and Eye Health Surveillance System. The main outcome measure was the relationship between vision loss and ECP density. Sociodemographic factors linked to ECP shortage also were explored.

The study authors applied a two-step floating catchment area (FCA) method to newly identify areas of eye care shortage, based on patient accessibility score (PAS), with higher scores denoting lower access. For every U.S. county, they weighted the two-step FCA scores by prevalence of vision loss and ECP density.

Altogether, there were 72,735 census tracts. The authors found weak correlations between HPSA scores and visual impairment as well as ECP

density per county population. All told, 54% of census tracts with ECP density per county below the 25th percentile were HPSAs. Among the census tracts exceeding the 75th percentile for visual impairment, 58% were HPSAs ($p < .0001$). Multivariable regression showed higher odds of ECP PAS ≥ 75 th percentile (weaker accessibility) in rural counties (adjusted OR [aOR], 2.47; $p < .001$) and in counties with a high proportion of residents who lacked a high school education (aOR, 1.21; $p < .001$). Higher odds of ECP PAS also were more common in areas with a greater percentage of older adults (aOR, 1.10; $p < .001$) and people without health insurance (aOR, 1.04; $p < .001$). Lower odds of ECP PAS ≥ 75 th percentile were found for counties with larger percentages of men (aOR, .93; $p < .001$) and White residents (aOR, .99; $p < .001$).

Self-Reported Conflicts of Interest Are Largely Incomplete

April 2023

Incomplete self-reporting of financial relationships by authors of medical content can compromise transparency and undermine confidence in research and findings. Hwang et al. explored the completeness of disclosure reporting by ophthalmology researchers and looked for factors that correlate with complete reporting. They found that the level of complete self-reporting was low even for journals that require full disclosures. The completeness of reporting was greater for authors who received large amounts of compensation.

For this cross-sectional observation study, the disclosures stated by authors of articles in ophthalmology journals were compared with information in the Open Payments database (OPD). The study included all articles by U.S. authors published from January to June 2017 in *Ophthalmology*, the *American Journal of Ophthalmology*, *JAMA Ophthalmology*, and *Investigative Ophthalmology & Visual Science*. The latter two journals require disclosure of “relevant” financial relationships, whereas the other two require disclosure of all financial relationships. In accordance with journal guidelines, the conflict-of-interest

(COI) statement must include mention of each company that provided remuneration in the 36 months prior to manuscript submission. The proportion of OPD-specified relationships that were self-reported was calculated for each authorship. The main outcome measure was the proportion of authors who failed to state any company mentioned in their OPD record.

The researchers evaluated 660 studies that represented 486 unique authors. No OPD-documented financial relationship was self-reported by 413 (62.6%), some relationships were self-reported by 112 (17%), and all relationships were self-reported by nine (1.4%). The remaining 126 (19.1%) had no financial relationships according to the OPD. The percentage of COI statements that did not include any OPD-specified relationship did not differ significantly by journal requirement. In 115 disclosure statements (17.4%), authors reported relationships that were not found in the OPD. Although authors who received more than \$10,000 during the 36-month period had better self-reporting rates ($p < .001$ for trend), their proportion of complete reports was low (3.3%).

These findings suggest that some authors make good-faith efforts to comply with reporting requirements. “The high frequency of incomplete reporting in ophthalmology likely reflects a lack of awareness of current guidelines, as well as ambiguities within these guidelines,” the researchers wrote. They believe that a clear and consistent journal guideline for COIs, coupled with education and enforcement, could reduce ambiguity and improve the accuracy of financial information reported by authors.

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Successful Home Monitoring of Glaucoma With a Home Tonometer and VF Device

March/April 2023

Hu et al. assessed patients’ acceptance of—and ability to use—a home tonom-

eter and visual field device to monitor their glaucoma at home. They found that the patients found the two tools helpful and easy to use.

For this prospective feasibility and acceptability study, the researchers evaluated 20 patients (39 eyes) with primary open-angle glaucoma (POAG), ocular hypertension, or suspected glaucoma. Two-thirds of the patients were women, and their mean age was 55.4 years (range, 25–83). The participants were trained on the iCare Home tonometer (HT) and Virtual Field (VF) devices. They then took the HT and VF devices home for one week and were instructed to use the HT four times a day for four days and to use the VF three times during the week.

Feasibility was assessed by device usage and the quality of the test results. Acceptability was assessed via a 35-item satisfaction survey as well as by structured interviews with a thematic analysis.

The HT is a handheld rebound tonometer used for self-monitoring of IOP. Most of the participants (73.7%) found it easy to use, and all found it useful. The VF is a mobile visual field test that uses a head-mounted virtual reality headset. All of the patients found it easy to use, and the majority (94.4%) found it useful.

All patients obtained acceptable IOP measurements and successfully completed a VF test at home. During the interviews, the researchers identified four key themes:

- advantages of home monitoring, such as accessibility, convenience, and patient empowerment;
- challenges posed by home monitoring, including technology concerns and loss of patient-physician interaction;
- future considerations for home monitoring, including patient selection; and
- patient-reported experience of having glaucoma, including IOP anxiety, fear of blindness, and test anxiety.

The HT is already FDA-approved for home monitoring. Additional studies are needed to demonstrate the validity of the patient-administered VF device, the authors wrote.

—Summary by Jean Shaw

Delayed Retinal Tears After Acute PVD

April 2023

Jindachomthong et al. assessed the long-term incidence of and risk factors for delayed retinal tears in cases of acute, symptomatic posterior vitreous detachment (PVD) that initially occurred without retinal tears. They found that patients with lattice degeneration were at increased risk of developing a delayed tear—and that some tears occurred as long as 6.24 years following the initial PVD diagnosis.

For this retrospective observational case series, the researchers included all patients diagnosed with an acute, symptomatic PVD without concurrent retinal breaks seen at an academic tertiary medical center between Jan. 1, 2013, and Dec. 31, 2018. The main outcome measure was time to the development of a delayed retinal tear.

The final study analysis included 389 patients (389 eyes). Patients' mean age was 64.58 years (± 9.36 years). Mean follow-up was 1.83 years (± 1.48 years). Results of Kaplan-Meier analysis showed that 7.39% of eyes developed delayed retinal tears by 6.24 years after initial PVD diagnosis. Of these, 50% occurred within 4.63 months after the PVD, and 63.46% occurred by the one-year mark. Moreover, 55% of the delayed tears occurred after the routine six-week follow-up period for PVDs.

With regard to risk factors, results of multivariate analysis showed that the presence of lattice degeneration was significantly associated with delayed retinal tear. Younger age (<60 years) and myopia were not.

In their discussion, the authors noted that the results emphasize the need for continued and repeated long-term reevaluation after an acute, symptomatic PVD is diagnosed. In addition, they wrote, "patients should know that they may experience delayed retinal tears even after the common six-week follow-up period and be wary of new symptoms." —*Summary by Jean Shaw*

SCORE2 Report: VA, CST Outcomes, and Treatment Adherence

April 2023

Six-month results from the Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2) showed that improvement in the VA letter score was comparable for bevacizumab and aflibercept for treatment of macular edema (ME) and retinal vein occlusion. After month 12, improvements diminished when the SCORE2 protocol was replaced with treatment at the investigator's discretion. Although most patients continued anti-VEGF treatment during follow-up, one-third received no treatment in year 5.

In a subsequent study, Scott et al. sought to characterize the profile of patients who stopped treatment and determine whether outcomes for VA letter score and central subfield thickness (CST) played a role in the decision to halt or continue treatment. They found that patients who discontinued early were younger at baseline and more likely to be Black than were those who received uninterrupted treatment. Although the VA letter score generally did not differ between these groups over time, those who stopped treatment had a significantly lower mean CST and a higher proportion of complete ME resolution by month 60.

The investigators classified those who completed 60 months of participation in SCORE2 ($N = 150$) into one of three groups: early discontinuation of treatment ($n = 23$), intermittent treatment ($n = 41$), and continuous treatment ($n = 86$). Mean age at baseline was 60.9, 66.7, and 70.5 years, respectively, among the three groups.

There was little difference among the groups in VA or change in VA over time. The early-discontinuation group had a larger percentage of resolved ME relative to the other groups (69.6% vs. 15% or 15.7%; $p < .001$). Moreover, those who stopped treatment had lower

mean CST during follow-up (257 μm) than did those treated continuously (300 μm ; $p = .01$) or intermittently (303 μm ; $p = .02$). Blacks represented 17.4% of participants who discontinued treatment, 19.5% of patients treated intermittently, and 4.7% of those treated continuously.

The authors emphasized that these findings support the need for ongoing monitoring and personalization of anti-VEGF treatment for patients with ME caused by retinal vein occlusion.

PK Versus DALK for Advanced Keratoconus

April 2023

Feizi et al. studied patients with advanced keratoconus who underwent penetrating keratoplasty (PK) and deep anterior lamellar keratoplasty (DALK). In addition to confirming that both techniques vastly improved visual and refractive outcomes and had similar graft survival rates, they found that PK produced better overall VA and refraction and fewer suture-related complications, whereas DALK reduced risks of graft rejection and graft failure due to endothelial decompensation.

The analysis involved 378 patients treated consecutively (411 eyes with mean pre-op keratometry ≥ 60 D) with primary PK ($n = 218$) or DALK ($n = 193$). All procedures were performed in Iran, by the same surgeon, from September 1994 to June 2020. Main outcomes were post-op VA and refraction, procedure-related complications, and the need for additional surgery.

Baseline parameters and follow-up times were similar for the two groups. Consistent with previous research, uncorrected and corrected distance VA improved significantly from baseline after both procedures. The mean corrected distance VA was $.18 \pm .13$ logMAR after PK and $.26 \pm .19$ logMAR after DALK ($p < .001$). Spherical equivalent refraction was lower in both groups (-2.89 ± 2.89 D and -4.58 ± 3.62 D, respectively; $p < .001$). Final keratometric astigmatism findings were similar ($p = .82$).

Suture-related complications occurred in 48.6% of PK eyes and 72%

of DALK eyes ($p < .001$). In addition, 33.5% of PK eyes and 19.7% of DALK eyes had at least one episode of graft rejection ($p = .002$). Endothelial graft rejection occurred only in the PK group, whereas subepithelial and stromal rejections were more common in the DALK group, which may have been related to the definitions of graft failure used in the study. At the final follow-up exam, 98.2% of PK grafts and 94.8% of DALK grafts were clear ($p = .06$).

The superior VA outcomes of PK persisted even after adjustment for donor-graft quality, said the authors; however, they emphasized the importance of graft survival in assessing efficacy.

—*Summaries by Lynda Seminara*

JAMA Ophthalmology

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

Access to Pediatric Eye Care in the United States

March 2023

Where have all the pediatric ophthalmologists gone? Walsh et al. analyzed the number and geographic distribution of pediatric ophthalmologists in the United States. They found that geographic disparities in access to pediatric eye care have increased over the past 15 years and are associated with lower socioeconomic status.

For this study, the authors used public databases from the Academy and the American Association for Pediatric Ophthalmology and Strabismus to identify U.S. pediatric ophthalmologists in practice as of March 2022. Main outcomes were the geographic distribution of the pediatric ophthalmologists and any association between their geographic distribution and U.S. population demographic characteristics.

All told, 1,056 pediatric ophthalmologists were identified. Using 2020 U.S. Census population estimates, the researchers found that there was one pediatric ophthalmologist per 3.2 million persons in the United States, versus one per 2.8 million persons in 2007. At the state level, nearly one-third (32.5%) of pediatric ophthalmologists practiced in the four most populous states—Cal-

ifornia, Florida, New York, and Texas—while New Mexico, North Dakota, South Dakota, and Vermont had no practicing pediatric ophthalmologists listed at the time of the study. At the county level, nearly 90% of counties across the country were not served by any pediatric ophthalmologist.

The researchers also cross-referenced publicly available demographic data with clinicians' practice addresses. The results underscored disparities in access to health care: those counties with one or more pediatric ophthalmologists in practice had a higher median household income, were more likely to have children with health insurance, and were more likely to have a higher proportion of families with internet service and access to a vehicle. (Also see related commentary by Julius T. Oatts, MD; Maanasa Indaram, MD; and Alejandra G. de Alba Campomanes, MD, MPH, in the same issue.)

Cost-Effectiveness of Aflibercept or Bevacizumab Plus Aflibercept for DME

March 2023

Hutton et al. set out to assess the cost and cost-effectiveness of two anti-VEGF strategies for treating diabetic macular edema (DME). They found that, for eyes with vision loss from DME, treating with repackaged (compounded) off-label bevacizumab first and then switching to aflibercept as needed may confer substantial cost savings without sacrificing gains in VA.

For this study, the researchers analyzed cost data from the DRRC Retina Network Protocol AC, assessing the incremental cost-effectiveness ratio (ICER) in cost per quality-adjusted life-year (QALY) over two years.

Protocol AC involved 228 participants with center-involved DME and BCVA of 20/50 to 20/320. Per study design, 116 participants received aflibercept alone, while 112 were enrolled in the bevacizumab-first cohort. (Of these, nearly two-thirds were eventually switched to aflibercept because of suboptimal response to bevacizumab.)

The cost of aflibercept monotherapy was \$26,504 (95% CI, \$24,796-

\$28,212). In contrast, the cost of bevacizumab-first treatment was \$13,929 (95% CI, \$11,984-\$15,874), wherein 70% of the participants had been switched to aflibercept by two years. Those who received aflibercept only gained .015 QALYs using the better-seeing eye and had an ICER of \$837,077 per QALY gained compared with the bevacizumab-first group.

The researchers estimated that aflibercept monotherapy may be cost-effective if the per-dose price drops to \$300 or less—or the price of bevacizumab rises to \$1,307 per dose. Moreover, using 2022 prices for every 10,000 new patients starting therapy for DME, the bevacizumab-first strategy could lead to a cost savings of more than \$125 million in the United States.

Fungal Endophthalmitis After Cataract Surgery

March 2023

Kim et al. evaluated the features and outcomes of an outbreak of fungal endophthalmitis linked to a contaminated ophthalmic viscoelastic device (OVD) used in cataract surgery in South Korea. Based on their findings, they recommend performing vitrectomy in conjunction with IOL and lens capsule removal as a first-line treatment, especially when the causative agent is *Fusarium* species.

The outbreak of fungal endophthalmitis occurred between Sept. 1, 2020, and June 30, 2021. A contaminated OVD was withdrawn from the South Korean market. For this analysis, patient data were collected from members of the Korean Retinal Society. Main outcomes were the clinical features and causative species in addition to treatment outcomes for patients who underwent six months of follow-up.

A total of 310 eyes (282 patients) were reported by 100 retina specialists. Of these, 281 eyes (265 patients) were included in the study. The patients' mean age was 65.4 ± 10.8 years, and 153 (57.7%) were female. The mean time between the cataract surgery and diagnosis was 24.7 ± 17.3 days.

Initial clinical signs and symptoms included conjunctival injection (224 eyes; 79.7%), anterior chamber cell

counts approximately 2+ or greater (253; 90%); fluffy or feathery infiltration around the IOL periphery (143; 50.9%); and vitreous opacity (212; 75.4%). Cultures were performed in 260 (92.5%) of the eyes, and positive fungal culture results were noted in 103. The index species was *Fusarium*, which was detected in 89 (86.4%) of the culture-positive eyes; other fungal species included *Aspergillus* and *Candida*.

As initial treatment, 68 eyes (29.8%) received injections of an intravitreal antifungal agent, 59 (25.9%) underwent vitrectomy without IOL removal, and 101 (44.3%) underwent vitrectomy with IOL removal. All told, 91 eyes underwent more than two vitrectomies, and 31 eyes were treated with intravitreal injections alone. Overall, a mean of 13 antifungal injections (range, 1-56) were administered; patients also received systemic antifungal therapy.

With regard to treatment outcomes, mean BCVA improved from 20/120 at diagnosis to 20/45 at the six-month mark. Disease remission with no signs of fungal endophthalmitis was noted in 214 (93.9%) of the affected eyes.

—Summaries by Jean Shaw

Other Journals

Selected by Prem S. Subramanian, MD, PhD

Impact of Sustained Abnormal BP on the Optic Nerve

Translational Vision Science & Technology
2023;12(2):3

Pan-Doh et al. looked at the relationship between blood pressure (BP) patterns and OCT measures of optic nerve (ON) health late in a patient's life, including density of the ganglion cell complex (GCC) and peripapillary retinal nerve fiber layer (RNFL). They found that neither sustained hypertension nor late-life hypotension correlated with structural abnormalities of the ON.

For this community-based cohort study, the authors included White and Black participants of the Atherosclerosis Risk in Communities study and the nested Eye Determinants of Cognition

(EyeDOC) study. Each patient had six BP readings obtained from 1987 to 2017. Based on these readings, the patient was categorized as having:

- sustained normotension,
- midlife normotension plus late-life hypertension (systolic BP [SBP] >140 mm Hg or diastolic BP [DBP] >90 mm Hg or using antihypertensive medication),
- sustained hypertension,
- midlife normotension plus late-life hypotension (SBP <90 mm Hg or DBP <60 mm Hg), or
- midlife hypertension plus late-life hypotension.

Associations between each BP pattern and late-life OCT findings for GCC and RNFL thickness were assessed by linear regression modeling. Altogether, 931 patients (931 eyes) were included. Mean age at the EyeDOC study visit was 80 years. Sixty-three percent were women, and 45% were Black. With sustained normotension, the mean GCC and RNFL thickness was $90.8 \pm 10.3 \mu\text{m}$ and $89.9 \pm 11.2 \mu\text{m}$, respectively. With sustained hypertension, the GCC and RNFL measurements were $89.4 \pm 11.9 \mu\text{m}$ and $90.1 \pm 12.2 \mu\text{m}$, respectively (not significantly different from normotension). Similarly, there were no significant differences in GCC or RNFL thickness between the normotension pattern and any of the other three anomalous BP patterns.

According to the authors, these findings suggest that neither hypertension (even in midlife) nor late-life hypotension is a risk factor for late-life ON damage.

AI Outperformed Humans in Assessing Ophthalmic Images

British Journal of Ophthalmology
Published online Jan. 31, 2023

Pandey et al. trained an artificial intelligence (AI) algorithm to classify retinal disorders from fundus photographs alone, then compared the algorithm's performance with that of human experts. They found that their ensemble of deep convolutional neural networks (CNNs) was more accurate and reliable than image assessment by board-certified ophthalmologists.

The authors predetermined four

conditions to explore in their study: diabetic retinopathy (DR), glaucoma, age-related macular degeneration (AMD), and normal fundus appearance (no pathology). The CNN architecture was based on the InceptionV3 model, and initial weights were pretrained on the ImageNet dataset. Altogether, there were 43,055 fundus images, representing 12 public datasets. An ensemble of five trained CNNs was then tested on an "unseen" set of 100 images, and seven board-certified ophthalmologists were asked to classify these images. Evaluation metrics included overall accuracy, defined as the percentage of correct predictions among all test images, as well as the per-condition and overall (macro-averaged) F1-score, positive predictive value, sensitivity, and specificity. To understand the reliability of predictions, the authors looked for agreement between a classifier's confidence level and the accuracy of each prediction. They assumed that confidence would be higher for correct predictions.

According to the analyses, the overall mean accuracy rate was 72.7% for the ophthalmologists and 79.2% for the ensemble of deep CNNs ($p = .03$). The AI system also had significantly better mean F1-scores for identifying DR (76.8% vs. 57.5% for ophthalmologists; $p = .01$) and numerically higher F1-scores for recognizing glaucoma (83.9% vs. 75.7%; $p = .10$), AMD (85.9% vs. 85.2%; $p = .69$), and absent pathology (73% vs. 70.5%; $p = .39$). Moreover, the mean agreement between accuracy and confidence was higher for the CNN ensemble (81.6% vs. 70.3%; $p < .001$).

"This work provides proof-of-principle that an algorithm is capable of accurate and reliable recognition of multiple retinal diseases using only fundus photographs," the authors wrote. They believe that their AI model could be a cost-effective adjunct for decision-making in specialty ophthalmology clinics and in general health care settings, including family practice and emergency departments. They emphasized that automated AI classifiers may be helpful for community-based eye screening programs.

—Summaries by Lynda Seminara