Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Russell N. Van Gelder, MD, PhD

A Strict Low-Fat Diet May Raise Glaucoma Risk

June 2023

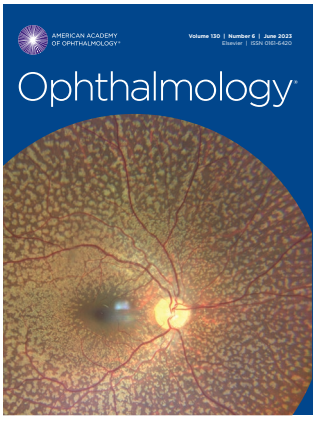
Using data from the Women's Health Initiative (WHI) Dietary Modification Trial, **Mehta et al.** explored glaucoma risk among women who followed a low-fat diet that was high in fruits, vegetables, and grains. They found that incident glaucoma was more common when fat consumption was very low.

For this research, prospective WHI data for women ≥50 years of age were linked to Medicare Part B claims. Participants were assigned randomly to adhere to their usual diet (control group) or follow the dietary modification (20% of energy from fat, ≥5 servings of fruits/vegetables, and ≥6 servings of grains per day). The diagnosis of primary open-angle glaucoma (POAG) was determined by the first medical claim that included relevant ICD-9 or ICD-10 codes. Participants completed a food-frequency questionnaire, and their responses were analyzed. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for POAG risk. Subgroup analyses by fat intake level also were conducted.

After excluding patients with glaucoma present before randomization, 23,217 participants remained (13,877 in the control arm, 9,340 in the intervention arm). Baseline characteristics were similar for the two groups. The overall incidence of POAG was 11.1 per 1,000 woman-years (mean follow-up time, 11.6 ± 7.4 years; mean duration of dietary modification, 5.2 ± 3.2 years). The data analysis did not show lower POAG risk in the modified-diet group (HR, 1.04; 95% CI, 0.96-1.12). Neither race nor age altered the findings. The quartile subgroup analysis by nutrient intake showed that the group with the lowest daily consumption of fat (≤33.8%) had the highest risk of POAG (HR, 1.22; 95% CI, 1.05-1.41; p = .007 for interaction).

To reduce glaucoma risk, the investigators concluded that "a careful design of future lifestyle and diet modifications is needed," including a healthy balance of fat intake. *(Also see related commentary by Emily Y. Chew, MD, in the same issue.)*

ALL SUMMARIES BY LYNDA SEMINARA.



Global Trends in Childhood Vision Loss

June 2023

In a trend analysis of demographics, **Liu et al.** looked at global, regional, and national burdens of vision loss in the pediatric population. They found that worldwide prevalence declined over the 30-year timeline, due mainly to reductions in refractive disorder. The number of years living with disability (YLD) due to vision loss decreased from 44.5 in 1990 to 40.2 in 2019. However, the prevalence of near-vision loss climbed significantly in nearly all age groups.

For this work, the authors gathered 1990-2019 data on the burden of vision loss and blindness from the Global Burden of Diseases, Injuries, and Risk Factors Study 2019 (GBD 2019). The relevant GBD category includes vision loss due to refractive errors, near-vision loss, and other eye diseases. The GBD 2019 definition of vision loss (Snellen VA <6/18) was used for the analysis. Severity was classified as 1) blindness, defined as VA <3/60 or <10% visual field around central fixation; 2) severe vision loss, defined as VA ≥3/60 and <6/60; 3) moderate vision loss, defined as VA ≥6/60 and <6/18; or 4) near-vision loss, defined as near VA <6/12 distance equivalent. Parameters used to estimate the burden of vision loss were case numbers, rates per 100,000 population, and average annual percentage changes (AAPCs) in prevalence rates and YLD. Data also were analyzed by sex and age group (<5, 5-9, 10-14, and 15-19).

According to the trend analysis, the prevalence of vision loss declined globally over time, from 1,091.4 per 100,000 in 1990 (95% uncertainty interval [UI],

895.2-1,326.1; AAPC, –0.3) to 1,036.9 per 100,000 in 2019 (95% UI, 847.8-1,265.9; AAPC, –0.2). YLD decreased from 44.5 in 1990 (95% UI, 28.1-66.5; AAPC, –0.5) to 40.2 in 2019 (95% UI, 25.1-60.7, AAPC: –0.4). On the contrary, near-vision loss became much more prevalent in all age groups except the youngest. Globally, boys fared better than girls. In countries with a low or mid sociodemographic index, the prevalence rate and YLD declined greatly. In higher-income countries, there were large increases in both parameters.

Global efforts in recent decades have markedly decreased the burden of childhood vision loss, said the authors, who noted that expanding screening coverage and boosting quality control should reduce the burden further. They stressed the need to address the growing prevalence of near-vision loss.

OPT-302: A VEGF C/D Inhibitor for Wet AMD

June 2023

Neovascular age-related macular degeneration (nAMD) is driven by VEGF A, C, and D, all of which promote angiogenesis and vascular permeability. The standard of care for nAMD is intravitreal injection of anti-VEGF A drugs, but this treatment does not affect the VEGF C or D pathway. This may explain why the response to traditional therapy is incomplete in many cases. **Jackson et al.** studied the efficacy and safety of OPT-302, a biologic inhibitor of VEGF C and D, given intravitreally in combination with ranibizumab. They also compared the dual-treatment strategy with ranibizumab monotherapy and found that the combination achieved superior VA gains.

This phase 2b, double-masked trial included patients with treatment-naïve nAMD who were enrolled among 109 sites. They were assigned randomly to one of three groups: ranibizumab alone (sham control), ranibizumab + 0.5 mg OPT-302, or ranibizumab + 2.0 mg OPT-302. The ranibizumab dose was the same (0.5 mg) for all study arms. Each participant received six injections, at four-week intervals. The main outcome was the mean change in BCVA from baseline to week 24, according to criteria of the Early Treatment Diabetic Retinopathy Study (ETDRS). Other outcomes were changes from baseline to week 24 in the proportion of patients who gained or lost ≥15 ETDRS BCVA letters; area under the ETDRS BCVA curve over time; and change in central subfield thickness (CST), intraretinal fluid, and subretinal fluid observed by SD-OCT.

Overall, 366 participants were recruited from December 2017 through November 2018: 122 received combination treatment with 0.5 mg OPT-302, 123 received combination treatment with 2.0 mg OPT-302, and 121 were given ranibizumab only. The mean (±SD) VA gain with 2.0 mg OPT-302 was significantly better than with ranibizumab alone (+14.2 ± 11.61 letters vs. +10.8 ± 11.52 letters; p = .01). Visual outcomes did not differ significantly between the 0.5-mg OPT-302 and ranibizumab-only groups. Secondary BCVA outcomes were superior with 2.0 mg OPT-302. Compared with ranibizumab treatment alone, structural outcomes were better with either dose of OPT-302. The incidence and type of adverse events were similar in all study arms. A serious adverse event occurred in 16, seven, and 10 recipients of 0.5 mg OPT-302, 2.0 mg OPT-302, and ranibizumab monotherapy, respectively. There were two deaths (both in the ranibizumab-only group); neither was deemed related to the study treatment.

The potential to enhance visual outcomes for patients with nAMD could translate to meaningful improvement in their quality of life, said the authors. They acknowledged that longer studies are needed to determine whether the visual benefits are sustained and to explore the long-term safety of OPT-302.

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Boosting Patient Engagement in the MI-SIGHT Program

May/June 2023

The Michigan Screening and Intervention for Glaucoma and Eye Health Through Telemedicine (MI-SIGHT) program is aimed at improving glaucoma detection rates. This approach to screening and care navigation is geared to high-risk, medically underserved communities. **Elam et al.** explored the effectiveness of methods to recruit MI-SIGHT participants and found that recruitment beyond the clinic increased participation significantly.

The study was conducted among the initial participants of the MI-SIGHT program, who were asked "How did you hear about the MI-SIGHT program?" Their responses were summarized (overall and per clinic) to compare clinic-based and community-based recruitment strategies. The main outcome measure was the proportion of recruits who became engaged in the clinic setting versus elsewhere.

The initial 647 patients were recruited in the first 11 months of the study; their average age was 54.4 years. Nearly 61% were female, approximately 46% were Black, and roughly 10% were Hispanic. Two clinics were involved: a federally qualified health center (FQHC) in Flint and a free clinic in Ypsilanti. Responses were missing for two patients from the free clinic. Overall, 168 participants (26%) learned of the MI-SIGHT program via a phone call from either clinic. Another 112 (17%) were informed by a friend, and 100 (16%) were notified by nonmedical clinic staff. Other participants discovered the program through a doctor (n = 77 [12%]), an in-clinic brochure or flyer (n = 51 [8%]), a community flyer (n = 44 [7%]), the clinic website or social media (n = 28 [4%]), or another means (n = 65 [10%]). By extending recruitment efforts beyond the clinic, as recommended by the MI-SIGHT Community Advisory Board, program participation increased by 265% at the free clinic and 46% at the FQHC.

These findings corroborate existing evidence of community-based research being most successful when it reflects the unique needs of community members. This type of outreach boosts the potential to reach diverse and specific subgroups, which often is challenging in medical research.

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

A Simple Phone Survey to Assess PVD Risk

June 2023

Balikov et al. aimed to create a brief telephone questionnaire for patients who report symptoms of posterior vitreous detachment (PVD) to gauge the risk of a retinal tear (RT) or retinal detachment (RD). Among the initial set of 23 questions and 70 possible answers considered for the questionnaire, the authors determined that RT/RD risk could be derived from just seven questions and 15 possible answers. "The simplified questionnaire can be administered quickly by telephone operators without any reference to physical examination or the patient's chart," they said.

Their research was based on conversations with patients who called the Kellogg Eye Center during a four-month period to report symptoms of PVD, such as flashes, floaters, or curtain/veil. During each call, a triage staff member administered a comprehensive survey to assess risk factors for RT/RD. Using multivariable logistic regression, the researchers identified risk factors that were most predictive of RT/RD at the follow-up visit, which occurred within 1.5 months of the phone call.

Of 193 callers, approximately 74% were established patients of the retina clinic or the comprehensive clinic, and 26% were new patients. At the follow-up visit, RT or RD was observed in 7%. The answers to seven questions were key to determining RT/RD risk:

- Are your symptoms in one or both eyes? (one eye = 5 points, both eyes = 1 point)
- When did your symptoms start? (<24 hours ago = 6 points, 24-72 hours ago = 3 points, >72 hours ago = 1 point)
- Do you have a nonmoving curtain, veil, or shadow in the side of your vision, or have you experienced blurred vision (aside from floaters)? If so, would you characterize it as constant or intermittent? ("yes" or "constant" = 14 points, "no" and "none" or "intermittent" = 1 point)
- When you were a young adult (before any procedure to the affected eye), did you need glasses to see to drive? ("yes" = 3 points, "no" = 1 point)
- Have you had a prior tear or detachment of either retina? ("yes" = 10 points, "no" = 1 point)
- Are you diabetic? ("yes" = 1 point, "no" = 5 points)
- Have you ever gone to the OR for retinal surgery in either eye? ("yes" = 10 points, "no" = 1 point)

A total score of at least 17 denoted an increased risk for RT or RD. The higher the score, the greater the risk. In the final multivariable analysis, area under the curve exceeded 0.90 for the risk-scoring model. Using a conservative risk score, the researchers estimated that about 50% of the callers could be safely seen nonurgently.

This risk-scoring system can help determine the urgency of a clinic visit, said the authors. They concluded that this tool "will simplify scheduling decisions about one of the most common triage questions that ophthalmology practices face." To their knowledge, this is the first PVD-related triage tool for use by nonphysicians.

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

blinq Vision Screener for Amblyopia and Strabismus

June 2023

The blinq (Rebion) scanner was designed for young children and uses retinal polarization scanning to detect amblyopia and strabismus. It has advantages over photo-screening tools that identify only amblyopia risk factors and have high false-positive rates. Whether blinq is as effective or practical as a full eye exam was the focus of work by **Monahan et al.** They compared blinq and clinical findings and found that blinq was highly sensitive for detecting both conditions.

This clinical validity study involved 267 children (age range, 1-12 years; mean, 6.3 years) who visited the Storm Eye Institute for an ophthalmic exam between June and November of 2021. The patients received blinq screening first; they were asked to focus on a smiley face while a 2.5-second simultaneous scan of both retinas detected the position of nerve fibers surrounding the fovea. Depending on the fixation results, blinq generated a "pass" (good binocular fixation) or "refer" result for complete scans or a "time-out" or "inconclusive" result for scans that could not be completed. After blinq scanning, each child had a comprehensive eye exam by a pediatric ophthalmologist who was unaware of the blinq results.

Altogether, blinq generated a pass for 106 (39.7%) of 267 children. Forty-four children (mean age, 3.21 years) whose test timed-out after multiple tries and eight others with inconclusive readings were subsequently considered automatic referrals. The overall sensitivity and specificity of blinq for detecting amblyopia or any constant strabismus was 87.5% and 51.3%, respectively, with a disease prevalence rate of 30%. When children with intermittent strabismus and/or high refractive error were included as true positives, the sensitivity and specificity rose to 91.3% and 63.2%, respectively, with disease prevalence of 43.1%.

Even though blinq readings were complete for many 1- and 2-year-olds in the study, the device is most suitable for children who are at least 3 years of age, said the researchers. They hope the findings will help care providers and communities design programs to further improve vision in young patients.

Robotic CyberKnife Radiosurgery for Choroidal and Ciliary Body Melanoma

June 2023

As experience with stereotactic radiosurgery has grown, treatment algorithms have been modified to optimize outcomes. However, the literature has not always kept pace with these changes, especially for choroidal melanoma. To close the gap, **Liegl et al.** reviewed 15 years of experience treating choroidal and ciliary body melanomas with the CyberKnife (Accuray). They found good rates of local control and eye retention through five years post-op and affirmed that these rates have improved

in the past decade.

Patients enrolled in this interventional case series had been referred to the department of ophthalmology of Ludwig-Maximilians University and European CyberKnife Center in Munich for the treatment of choroidal or ciliary body melanoma during a 15-year period, ending in 2019. Patients treated before 2012 usually received a radiation dose below 21 Gy, whereas those treated after 2012 typically received 21 Gy at the 70% isodose.

Altogether, 594 patients and tumors were included (22.7% stage I, 57.9% stage II, 18.9% stage III, 0.5% stage IV). Median apical tumor height was 5.8 mm, and median base diameter was 11.4 mm. The mean follow-up time was 41.7 months. Rates of local tumor control varied significantly by radiation dose. Among patients who received 21 to 22 Gy, local control was observed for 92.0% at three years and 84.3% at five years. For those who received ≤20 Gy, the rate of local control was 86.9% at year 3 and 77.7% at year 5. Three- and five-year rates of eye retention also varied by radiation dose: 89.9% and 81.0% (respectively) in the higher dose group and 85.9% and 80.0% (respectively) in the lower dose group. The main reasons for enucleation were tumor recurrence (59%) and secondary glaucoma (38%). Overall disease-specific survival rates were 93.1% at three years, 89.8% at five years, and 87.8% at seven years. Tumor size had little effect on outcomes.

The authors noted that the rate of local control achieved with 21 Gy—an adjustment made based on their experience—is similar to that with other treatments such as brachytherapy. They consider CyberKnife therapy to be a viable option for small and large melanomas of the choroid or ciliary body.

JAMA Ophthalmology

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

Azithromycin Versus Doxycycline for MGD

May 2023

The typical medical management for moderate or severe meibomian gland dysfunction (MGD) is a six-week course of doxycycline, which often causes adverse events (AEs) that hinder compliance. Although azithromycin has been explored as a treatment option for MGD, study designs have been limited. It is plausible that oral azithromycin, dosed at 1 gram weekly for three weeks, may result in adequate tissue levels of medication for at least one month—perhaps leading to better patient compliance than is possible with drugs that require daily dosing. In a double-masked, randomized controlled trial, **Upaphong et al.** compared this regimen of azithromycin with daily doxycycline dosing for six weeks and found comparable efficacy. Gastrointestinal AEs were less common with azithromycin.

The trial occurred at an ophthalmology referral center in Thailand and included patients with moderate or severe MGD that did not respond to conservative therapy. The participants were assigned randomly to receive oral azithromycin (1 g weekly for three weeks) or oral doxycycline (200 mg daily for six weeks). MGD score and ocular surface disease index (OSDI) were documented at the initial study visit (treatment inception), as well as six and eight weeks later. The prespecified equivalence margins for MGD score and OSDI were ±2 and ±9, respectively. To evaluate safety, AEs were recorded at weeks 6 and 8.

All told, 137 eyes (137 patients) underwent randomization: 68 received azithromycin, and 69 received doxycycline. The adjusted mean difference in total MGD score between the groups was −0.33 at six weeks (95% CI, −1.70-1.03; p for equivalence = .01) and 0.13 at eight weeks (95% CI, −1.59-1.84; p for equivalence = .02). The adjusted mean difference in OSDI between the groups was −1.20 at six weeks (95% CI, −5.31-2.91; p for equivalence < .001) and −1.59 at eight weeks (95% CI, −5.73-2.55; p for equivalence < .001). The rate of gastrointestinal AEs was lower for azithromycin (4.4% vs. 15.9%; risk difference, 11.5%; 95% CI, 1.6%-21.4%; p = .03).

The investigators concluded that "the reduced dosing and potentially fewer gastrointestinal AEs associated with azithromycin support its use as an alternative to doxycycline for at least six weeks" in the management of moderate or severe MGD. They noted that longer follow-up of both study groups would be required to determine if efficacy and safety will be sustained. *(Also see related commentary by B. Michele Melia, ScM, in the same issue.)*

mRNA Covid-19 Vaccines and RVO Risk

May 2023

Retinal vascular occlusion (RVO) has occurred following mRNA Covid-19 vaccination, but whether the incidence is higher than after influenza or Tdap vaccination is unclear. To learn more, **Dorney et al.** reviewed health records for several million people who received an mRNA Covid-19 vaccine. They compared RVO incidence among the three types of vaccines and found that the relative risk (RR) of new-onset RVO was not more common with the mRNA vaccine.

For this work, the authors gathered information from the TriNetX Analytics platform, a federated, aggregated EHR research network, which includes deidentified data for more than 103 million patients. Data for all EHRs in TriNetX were searched for vaccination CPT codes, and the instances of RVO newly diagnosed within 21 days of mRNA vaccination were recorded. Propensity-score matching was performed, based on demographics and comorbidities, to assess RR in relation to historical cohorts of patients who received the influenza or Tdap vaccine. The primary outcome was de novo RVO within 21 days after mRNA Covid-19 vaccination.

Among 3,108,829 patients (mean age, 50.7 years) who received the mRNA Covid-19 vaccine, 104 (0.003%; 95% CI, 0.003%-0.004%) had a new RVO diagnosis in the next 21 days. After propensity-score matching, the risk for new RVO after the first dose of mRNA vaccine did not differ significantly from that after the influenza shot (RR, 0.74; 95% CI, 0.54-1.01) or the Tdap vaccine (RR, 0.78; 95% CI, 0.44-1.38). How-

ever, compared with mRNA dose 1, the risk of new-onset RVO was higher after mRNA dose 2 (RR, 2.25; 95% CI, 1.33-3.81).

The authors concluded that "RVO diagnosed acutely after mRNA Covid-19 vaccination occurs extremely rarely, at rates similar to those of two different historically used vaccinations." Although they found no link between the mRNA vaccine and new-onset RVO, they affirmed that "detailed research on patients experiencing RVO after vaccination is necessary to elucidate risk factors for this vision-threatening condition." *(Also see related commentary by Lee M. Jampol, MD, and Maureen G. Maguire, PhD, in the same issue.)*

P. aeruginosa Keratitis Caused by Artificial Tears: Case Report

May 2023

Pseudomonas aeruginosa, a rare bacterium that resists treatment, had not been detected in the United States until 2022, when it caused multidrug-resistant (MDR) keratitis in dozens of users of EzriCare Artificial Tears, leading to enucleation in some cases. **Shoji et al.** shared a case study to highlight the gravity of this phenomenon and the importance of culturing corneal infiltrates, as well as contact lenses, their storage cases, and drop bottles containing eye- and lens-care solutions.

Case Report. A 72-year-old man arrived at Bascom Palmer Eye Institute in Miami, having experienced pain and reduced vision in his right eye for the past day. His medical history included diabetes, coronary artery disease, and chronic obstructive pulmonary disease. He reportedly wore contact lenses but did not sleep in them or overuse them. He had not undergone ocular surgery or been exposed to vegetation, but he was using EzriCare Artificial Tears for eye dryness. At presentation, his BCVA was hand motion in the right eye and 20/20 in the left eye. IOP was 29 mm Hg in the right eye and 14 mm Hg in the left eye. Slit-lamp examination of the right eye showed diffuse conjunctival hyperemia, a 6- × 5-mm corneal infiltrate with an overlying epithelial defect, and a 2-mm hypopyon. Ultrasound findings were normal. In light of recent concerns about contaminated eyedrops, the patient received hourly treatment (when awake) of topical fortified vancomycin, fortified tobramycin, and trimethoprim-polymyxin drops. His corneal infiltrate culture was positive for *P. aeruginosa,* which resisted fluoroquinolones, aminoglycosides (including amikacin and tobramycin), and cephalosporins. Resistance to carbapenem was moderate (minimum inhibitory concentration [MIC] = 4). The EzriCare solution also was positive for *P. aeruginosa,* which did not respond to fluoroquinolones, aminoglycosides, and cephalosporins. Resistance to carbapenem was higher than in the cornea (MIC = 8). Based on these findings, trimethoprim-polymyxin was continued hourly, and imipenem-cilastatin was given every two hours. At the most recent follow-up visit, the infection and visual loss persisted. Treatment and close monitoring were continued.

Risk factors for MDR *P. aeruginosa* include eye lubricants, compromised ocular surface, and bandage contact lenses. Contaminated products can cause severe infections. Until recently, artificial tears were considered relatively benign. Per the CDC, at least 10 brands of artificial tears have been implicated.

The authors hope to raise awareness of this vision-threatening contamination so that potentially blinding sources of infection can be eliminated. They concluded that "concern for contamination ideally should lead to prompt reporting to the CDC and U.S. Food and Drug Administration." *(Also see related commentary by Christina R. Prescott, MD, PhD; and Kathryn A. Colby, MD, PhD; in the same issue.)*

Other Journals

Selected by Prem S. Subramanian, MD, PhD

PRS + Retinal OCT Predict Cognitive Performance

British Journal of Ophthalmology
Published online March 28, 2023

Can the combination of retinal OCT findings and polygenic risk scores (PRS) improve the ability to predict cognitive decline? This question was the subject of research by **Sekimitsu et al.** The investigators examined OCT images for more than 50,000 people and found a significant link between retinal measurements and the genetic risk of neurodegenerative disease.

OCT images used in this study were obtained from U.K. Biobank participants and were tested for possible links between retinal layer thickness and the genetic risk for neurodegenerative disease. These metrics were combined with PRS of patients with Alzheimer or Parkinson disease to predict baseline cognitive status and future cognitive deterioration. Multivariate Cox proportional-hazard models were used to predict cognitive performance. Probability values for thickness analyses were adjusted for the false discovery rate.

The analysis showed that higher Alzheimer disease PRS were associated with increased thickness of the inner nuclear layer (INL), the chorioscleral interface (CSI), and the inner plexiform layer (IPL) (all $p < .05$). Higher Parkinson disease PRS corresponded to a thinner outer plexiform layer ($p < .001$). Poor baseline cognitive performance coincided with a thin retinal nerve fiber layer (adjusted odds ratio [aOR] = 1.038, $p < .001$), thin photoreceptor segment (aOR = 1.035, $p < .001$), and thin ganglion cell complex (aOR = 1.007, $p = .004$), as well as a thick ganglion cell layer (aOR = .981, $p = .009$), thick IPL (aOR = .976, $p = .003$), thick INL (aOR = .923, $p < .001$), and thick CSI (aOR = .998, $p < .001$). Future cognitive decline was linked to a thicker IPL (aOR = .945, $p = .045$) and CSI (aOR = .996, $p = .014$).

Given these findings, the authors believe that OCT data could serve as biomarkers of cognitive decline. To their knowledge, this is the first study of the OCT/PRS combo approach to cognitive evaluation. The findings "may help to inform future research, risk assessment, diagnostic, and disease surveillance strategies," said the authors.

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