News in Review

COMMENTARY AND PERSPECTIVE

PEDIATRICS

New ROP Screening Criteria Validated

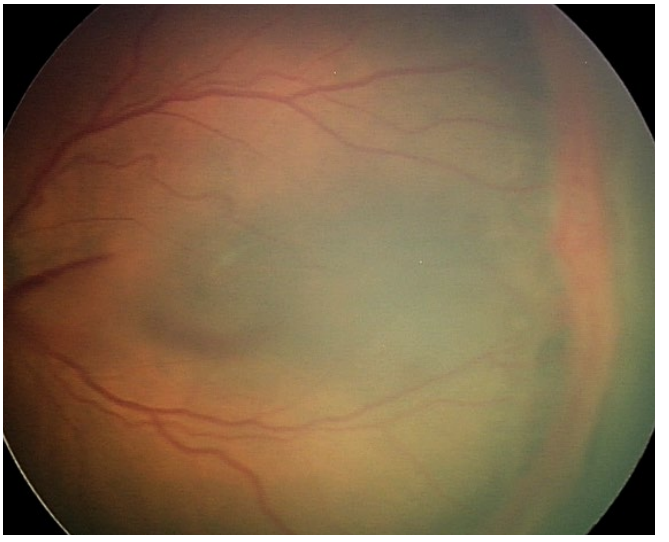
NEW CRITERIA FOR EXAMINING premature infants for retinopathy of prematurity (ROP) have been found to be more sensitive and specific than current screening guidelines.[1] The study group known as G-ROP reaffirmed that the new criteria are 100% sensitive for predicting type 1 ROP. Moreover, the new guidelines have the potential to reduce the number of infants receiving examinations by a third.

The new screening criteria have both clinical and cost-saving implications. Fewer at-risk babies will have to endure stressful retinal examinations in the neonatal ICU, and those who would benefit from an examination are less likely to slip through the cracks.

"We were happy that the criteria maintained such high sensitivity," said study group chair Gil Binenbaum, MD, MSCE, at the Children's Hospital of Philadelphia. "Even though they were developed using data from a very large cohort, there was still a chance that some overfitting could have occurred or that changes in neonatal care, such as oxygen saturation targets, may have resulted in changes in the characteristics of infants who developed severe ROP. Fortunately, the G-ROP criteria still performed well."

Expanding the criteria to improve screening. Currently recommended guidelines are based on birth weight (BW) of less than 1,501 g or a gestational age (GA) of 30 weeks or less.

The new G-ROP guidelines use six criteria, any one of which leads to an examination for ROP. These criteria include a BW of less than 1,051 g; a GA of less than 28 weeks; three measures of slow postnatal weight gain; or the presence of hydrocephalus.



Gil Binenbaum, MD

ROP. *The now validated G-ROP criteria include measures of slow growth as well as birth weight and gestational age.*

The postnatal weight gain measures capture infants with higher BW and older GA who develop type 1 ROP. Weight gain is a proposed surrogate measure for factors that result in decreased VEGF activity and poor retinal vessel development.

Generalizability of the G-ROP criteria. The validation study applied the G-ROP criteria to a new cohort of premature babies (N = 3,981), who were examined between 2015-2017 at 25 of the original G-ROP hospitals and 16 new hospitals in the United States and Canada.

In the current study, the criteria predicted 219 of 219 cases of type 1 ROP (100% sensitivity). And the percentage of infants undergoing exams fell by 35.6% (n = 1,418). In a pooled cohort of 11,463 infants from this study and an earlier cohort, the criteria predicted 677 of 677 cases of type 1 ROP (100% sensitivity) and yielded a 32.5% reduction in examinations (n = 3,730).

A caveat. The validation study applies only to countries with highly developed neonatal care systems. It is not generalizable to countries in which excessive oxygen supplementation is the primary cause of ROP and postnatal weight gain is not reliably predictive of ROP. Dr. Binenbaum said that each new setting will require separate validation.

Toward a new standard. The case for adopting a new set of national guidelines is strong, Dr. Binenbaum said. In the pooled cohort analysis, for example, currently recommended guidelines predicted 674 of 677 type 1 cases (99.6% sensitivity), compared to 100% sensitivity screening with the newer G-ROP criteria.

"Even a 0.4% decrease in sensitivity is not acceptable," Dr. Binenbaum said, as this represents about 25 babies a year nationally being missed and possibly going blind.

"If the difference were reversed and the G-ROP criteria had the slightly lower sensitivity, there would be no chance anyone would use them to decide who to examine. But the situation is not reversed. So, the argument to keep using

the current criteria is not a strong one, because the G-ROP criteria are actually more sensitive," he said.

"With validation, we now have criteria with higher sensitivity and much greater specificity than the current guidelines, so we think it is appropriate to use these criteria for screening decisions." —*Miriam Karmel*

1 Binenbaum G et al. *JAMA Ophthalmol.* Published online Nov. 14, 2019.

Relevant financial disclosures—Dr. Binenbaum: None. *This study was funded by the NIH and by an endowed chair at the Children's Hospital of Philadelphia.*

RESEARCH

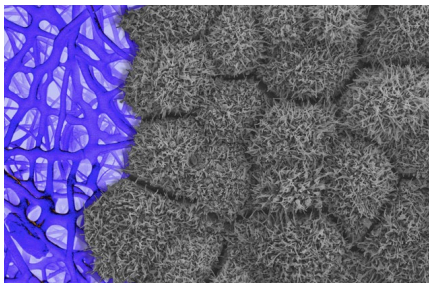
AI Used to Assure Quality of Cell Therapy

RESEARCHERS AT THE NEI HAVE DEV-eloped a simple method using artificial intelligence (AI) to assure quality control of a cell therapy for patients with age-related macular degeneration (AMD).[1] In a proof-of-principle study, they confirmed that their methodology reliably, quickly, and noninvasively evaluated their autologous cell therapy product.

Their approach should increase tissue production and speed its delivery to the clinic for replacement of degenerated retinal pigment epithelial (RPE) cells.

"This AI-based method of validating stem cell-derived tissues is a significant improvement over conventional assays, which are low-yield, expensive, and require a trained user," said Kapil Bharti, PhD, at the NEI Ocular and Stem Cell Translational Research Section. "The current technology brings the autologous cell therapy a step closer to AMD patients."

Seeking confirmation. With a garden-variety microscope programmed with deep learning algorithms, a technician will be able to verify that the replacement RPE cells are correctly manufactured just prior to transplantation in patients. Specifically, the AI methodology allows validation of "patches" of stem cell–derived RPE cells. The RPE "patch" is made from induced pluripotent stem cells (iPSCs) that are made from the patient's blood.



MICROGRAPH. *This image shows the fiber-based scaffold (blue) and cultured iPSC-RPE cells (gray). The hair-like structures on top of each cell are their apical processes that confirm their polarity and maturity.*

The need for validating healthy replacement cells. This need was underscored by the researchers, who noted that at least 11 investigations

NEURO-OPHTHALMOLOGY

Dry Eye, Migraine, and Visual Quality of Life

DRY EYE SEEMS TO BE THE MOST IMPORTANT SYMPTOM that reduces visual quality of life (QoL) and worsens headache impact in patients who experience migraines. That finding emerged from a cross-sectional study conducted at the University of Utah in Salt Lake City.[1]

"We knew from previous research that patients with chronic migraine have reductions in visual QoL that can be as substantial as those reported for neuro-ophthalmic diseases such as multiple sclerosis with optic neuritis and idiopathic intracranial hypertension," said neurologist Seniha Ozudogru, MD. Coauthor and neuro-ophthalmologist Kathleen B. Digre, MD, added, "The purpose of this investigation was to attempt to determine which ocular symptom(s) were driving the observed reductions in visual QoL."

Methods. Patients were recruited from the Headache Clinic and General Neurology Clinic in Salt Lake City. They completed several validated questionnaires, including the NEI visual functioning questionnaire-25 (VFQ-25), the headache impact test (HIT-6), the visual aura rating scale (VARS), the ocular surface disease index (OSDI), and the Utah photophobia symptom impact scale (UPSIS-17).

Results. Of the 62 patients who completed all questionnaires, 17 had episodic migraine and 45 had chronic migraine. Twenty-three patients experienced aura.

The most striking correlations were observed between VFQ-25 and the OSDI (–0.678; $p < .001$), between the HIT-6 and UPSIS-17 (0.489: $p < .001$), and between the HIT-6 and OSDI (0.453; $p < .001$). The strongest of these correlations was between VFQ-25 and OSDI, indicating that as symptoms of dry eye increase, visual QoL also worsens.

Among the ocular symptoms tested, dry eye seemed to be the only symptom that correlated with reductions in visual QoL in migraine patients. Also, the statistically significant correlation between HIT-6 and OSDI supports the researchers' hypothesis that dry eye symptoms may be both a significant and underappreciated problem for migraine patients. Photophobia had a modest influence on headache impact.

A form of allodynia? The researchers speculated that dry eye symptoms in migraine may be a form of allodynia, pain from usually painless stimulation, a well-known feature of chronic migraine. Their hope is that future investigations will help determine if dry eye treatments are helpful—and, if so, will pinpoint those treatments that are the most effective. —*Arthur Stone*

1 Ozudogru S et al. *Headache*. 2019;59(10);1714-1721.

Relevant financial disclosures—Drs. Digre and Ozudogru: None.

NEI / Nathan Hotaling

are underway using RPE cells to treat AMD.[2] In fact, they are awaiting FDA approval of a phase 1 trial to transplant RPE cells in AMD patients. Pending approval, they will begin manufacturing patient cells, likely this year.

A two-step methodology. Dr. Bharti's team first had to validate the ability of quantitative bright-field absorbance microscopy (QBAM) to make a precise, reproducible measurement of tissue quality. Next, they had to employ AI to analyze QBAM images for predicting multicellular function.

To that end, Dr. Bharti's team trained deep neural networks (DNNs) to assess QBAM images of iPSC-RPE created from both healthy and diseased donors. They found that deep learning could determine the sensitivity of QBAM to biological variation. The DNNs also identified borders of cells in QBAM images. And DNNs determined if the cells came from the same donor.

Confirming the identity of each patient's dose is essential, because the lab will be manufacturing cells from multiple patients simultaneously. "For every patient, we need to manufacture this product over and over again, and functionally validate it every time," Dr. Bharti said. "This will be a live and noninvasive method to confirm identity of given donor's cells."

Toward a clinical application. While awaiting the green light from the FDA, the team has begun implementing its deep learning software onto microscopes that they plan to install in their manufacturing facility. "Once that's completed, we are ready to go," Dr. Bharti said. "With our new AI-based method to functionally validate patient cell–derived transplants, we are more confident that we are manufacturing the correct, safe, and functional clinical product." —*Miriam Karmel*

1 Schaub NJ et al. *J Clin Invest.* Published online Nov. 12, 2019.

2 Aijaz A et al. *Nat. Biomed Eng.* 2018;2(6):362-376.

Relevant financial disclosures—Dr. Bharti: None.

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RETINA

OCT Provides Fuller Picture of Tamoxifen Retinopathy

TAMOXIFEN RETINOPATHY MAY BE more of an issue than previously recognized, researchers in South Korea have found—and optical coherence tomography (OCT) may be needed to diagnose the earliest signs of the condition.[1]

Previous studies have found a prevalence rate of 1.5% to 11.8% in patients being treated for breast cancer. But in this study, the researchers found a prevalence rate of 12%.

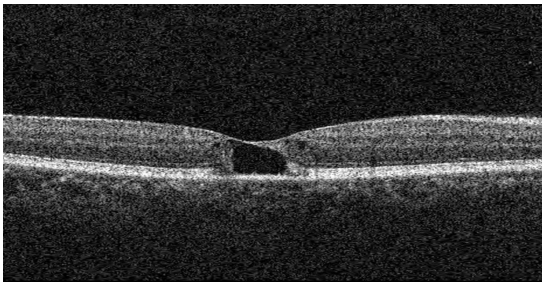
Findings. For this retrospective study, the researchers evaluated the medical records of 251 female breast cancer patients who had undergone both fundus photography and OCT scanning after taking tamoxifen for at least two years. Of these, 19 patients had bilateral tamoxifen retinopathy, and 11 had unilateral disease. Twelve patients had foveal cavitations only, four had refractive crystalline deposits, and 14 had both. Eight of the 30 patients had decreased visual acuity or metamorphopsia.

Breast cancer stage, type of chemotherapeutic agent, history of hormone replacement therapy, and menopausal status were not associated with tamoxifen retinopathy. All patients were on low-dose tamoxifen (20 mg per day).

Surprises. "My institute is the biggest hospital in Korea, and so it has a huge cancer unit," said Young Hee Yoon, MD, at the University of Ulsan College of Medicine's Asan Medical Center in Seoul. Even with this case load, she said, the researchers were surprised that the incidence of retinal toxicity was higher than previously reported. They were also surprised that the patients were never advised of the potential ocular risk of tamoxifen by their breast surgeons or oncologists.

OCT the key? In an earlier study, Dr. Yoon and her colleagues evaluated OCT angiography findings of tamoxifen retinopathy.[2] In that study, they realized that "some patients no longer had crystalline deposits even if they had typical OCT findings of pseudocystic cavitation or photoreceptor depletion," Dr. Yoon said.

In addition, she said, because most previous studies of tamoxifen retinopathy used fundus findings alone, "we decided to conduct this study to find out the real incidence of tamoxifen retinopathy" based on both fundus photography and OCT scanning.



TAMOXIFEN IMPACT. *This 50-year-old patient with breast cancer had noticed a gradual decrease in vision. She was diagnosed with pseudocystic foveal cavitation; OCT of her left eye shows cystic cavitary alterations and a large outer hole.*

And indeed, evaluating OCT scans may have been the key to the results of the current study, Dr. Yoon said. She explained that they might have missed the early retinal changes if they had not checked the OCT scans.

Looking ahead. The ophthalmology and breast cancer teams are currently conducting a prospective study to evaluate the incidence of tamoxifen retinopathy, Dr. Yoon said. She added, "Both patients and doctors should be aware of this toxicity—and, in order to diagnose the retinopathy and manage it properly, teamwork is necessary between breast cancer and retina specialists." —*Jean Shaw*

1 Kim HA et al. *Ophthalmology.* Published online Nov. 7, 2019.

2 Lee S et al. *Ophthalmol Retina.* 2019;3(8):681-689.

Relevant financial disclosures—Dr. Yoon: None.

See the financial disclosure key, page 10. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.