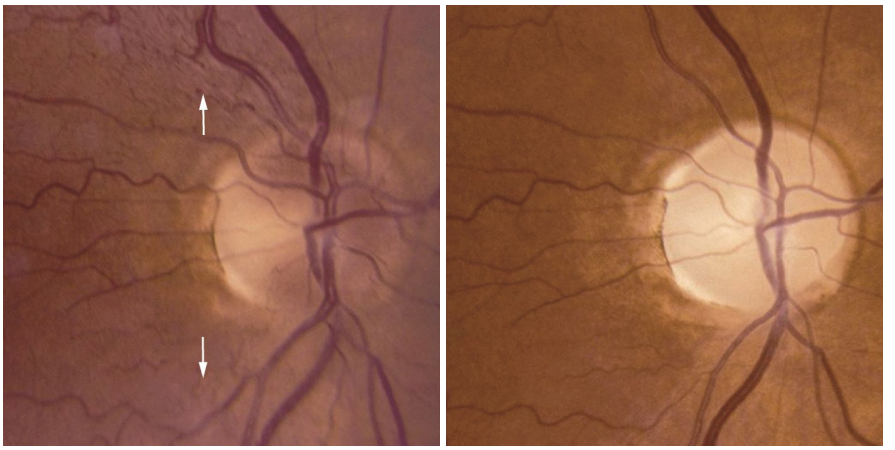


LHON. *Genetic tests confirmed a point mutation in this patient with LHON. (Left) Arrows indicate peripapillary telangiectasias observed in the acute phase of vision loss. (Right) Several months later, the optic disc is diffusely pale.*

GENETICS

Outcomes of LHON Gene Therapy Elucidated

IN A PAIR OF STUDIES, A TEAM OF Chinese researchers has reported on long-term outcomes of gene therapy for Leber hereditary optic neuropathy (LHON)[1] and elucidated some factors that predispose patients to better visual outcomes following treatment.[2]

Study No. 1: Seven years of follow-up. In a small study of nine patients who underwent gene therapy for LHON, two-thirds continue to have persistent, significant gains in their best-corrected visual acuity (BCVA) after seven years (range, 75-90 months).[1]

The scientists found that the improvement in BCVA in these patients was ≥0.3 logMAR, equivalent to 15 letters on the EDTRS chart, said principal investigator Bin Li, MD, PhD, at the Huazhong University of Science and Technology and Tongji Hospital, both in Wuhan, China. In addition, no adverse outcomes were noted. "This demonstrates the long-term safety and efficacy of gene therapy," Dr. Li said.

Protocol and results. All patients received a single unilateral intravitreal injection of a recombinant adeno-associated virus serotype 2 (AAV2) carrying the *ND4* gene, which is mutated in most LHON cases.

Of the six patients who maintained clinically significant improvement in BCVA, the vision of two improved enough that one was admitted to a high school and the other, who gained 8 lines of BCVA, was able to travel to Beijing to obtain a job one year after treatment, Dr. Li said.

Study No. 2: A look at treatment response. In the second study,[2] the researchers reported on early treatment responses from a large prospective trial (149 subjects, including seven from Argentina). "On average, responders convert from legally blind to low vision, with a good percentage of patients reaching normal vision," Dr. Li said. "We will publish the full results soon, and we are actively investigating why some patients responded significantly better than the others."

The initial results in this study showed that about a third of the patients (28.9%) had significantly improved vision within three days of treatment, including significant improvement in acuity in some (18.8%) uninjected fellow eyes. These results confirm the promising findings from the smaller study, Dr. Li said.

The subjects who experienced such rapid acuity gains were the youngest patients and those who had the best vision before treatment, Dr. Li said. In addition, female participants had better responses to treatment than did their male counterparts, he said.

Need for additional investigation. Might patients benefit even more from a second injection? Dr. Li said his team is moving cautiously on this, because the first patient they treated received two injections and the visual outcome was poor.

"Years of research has made us realize that gene therapy is very different from small molecule and antibody drug treatment," Dr. Li said. "The specific mechanism of action may extend beyond the simple gene replacement concept, and much more needs to be explored in order to fully unveil and leverage this new modality of therapy."

An overview of the field. The Chinese group's studies, which began with preclinical work in 2008, are the longest-running trials so far to report on using a recombinant AAV vector to deliver a normal *ND4* mitochondrial gene to patients who have a mutant form of the gene. This mutation, G11778A, accounts for most cases of LHON and the severest disease.[3]

Another group, based at the University of Miami, reported in 2017 on using their own AAV vector containing the *ND4* gene on 14 LHON patients, nine of whom had been followed for at least 12 months.[4]

A third AAV vector for delivering the *ND4* gene is being investigated by European researchers on behalf of GenSight Biologics, which is based in Paris. The group has completed phase 1/2 clinical trials,[3] and a phase 3 trial is ongoing. —*Linda Roach*

1 Yuan J et al. *Ophthalmolology*. Published online Feb. 25, 2020.

2 Liu HL et al. *Acta Ophthalmol*. Published online Feb. 24, 2020.

3 Bouquet C et al. *JAMA Ophthalmol*. 2019;137(4): 399-406.

4 Guy J et al. *Ophthalmolology*. 2017;124(11): 1621-1634.

Relevant financial disclosures—Dr. Li: Wuhan Neurophth Biotechnology: S.

RETINA

Consider Early Tx for DME When VA Is Good

WATCHFUL WAITING, ACCEPTED AS proper management of patients with diabetic macular edema (DME) and good baseline visual acuity (VA), may not be the best approach in a select subset of patients.

In patients who have hyperreflective foci (HRF), a disorganization of the inner retina layers (DRIL), or a disruption of the ellipsoid zone (EZ) on spectral-domain optical coherence tomography (SD-OCT), early treatment may reduce the risk of future VA loss, German researchers reported.[1]

It appears that "there are patients with a higher risk for VA loss during observation than others," said Catharina Busch, MD, at University Hospital Leipzig in Leipzig, Germany. "We might have to consider that the conclusion we got from Protocol V and the OBTAIN studies—that close observation is proper management—does not apply for all patients. There might be patients in which an immediate treatment might provide better long-term results."

Clues from SD-OCT. The current findings are based on a subanalysis of OBTAIN, a 12-month retrospective cohort study that considered charts of 210 patients (249 eyes) with baseline VA equal to or worse than 20/25 and center-involving DME.[2]

For this secondary analysis, the researchers included observed eyes and eyes that received anti-VEGF treatment at baseline. They focused on the observed eyes (n = 147), of which 21% (n = 32) experienced VA loss of 10 or more letters during 12 months of follow-up. In the presence of one SD-OCT feature—HRF, DRIL, or EZ disruption—the odds of experiencing VA loss of

GLAUCOMA

Novel Contact Lens Sensor Passes First Hurdle

A NOVEL CONTACT LENS THAT MEASURES INTRA-ocular pressure (IOP) continuously over 24 hours, including during undisturbed sleep, proved accurate and reliable in a first in-human feasibility assessment.[1]

The noninvasive pressure-measuring contact lens (PMCL) measures IOP in mm Hg as well as ocular pulsation. (The latter's role in glaucoma pathogenesis remains controversial.)

"A 24-hour IOP curve could positively impact management of patients with glaucoma, especially those with functional/structural signs of progression despite apparently well-controlled IOP," said Kaweh Mansouri, MD, MPH, at the Montchoisi Clinic in Lausanne, Switzerland. The potential beneficiaries of 24-hour monitoring include at-risk subjects with IOP in normal range during office hours, unstable glaucoma patients showing glaucoma progression despite low target IOP, and patients with normal tension glaucoma, he said.

Proof of concept. The device includes a silicone contact lens, pressure sensor, antenna, and a telemetry microprocessor embedded in the lens. In this prospective nonrandomized trial, it was placed on the eyes of eight subjects—four with glaucoma and four without—shortly after IOP was measured by Goldmann applanation tonometry (GAT) and dynamic contour tonometry (DCT). The lens remained in place for 24 hours, after which researchers compared its IOP values to those obtained via GAT and DCT.

As measured by the sensor, the mean IOP difference was within 5 mm Hg in 75% of subjects measured with GAT and in 87.5% of subjects measured with DCT. The IOP difference was within the requested 5 mm Hg limits for new tonometers.

Subjects also took a water drinking test, which perturbs the aqueous fluid system and may promote a rise in IOP. In the test, the PMCL detected an average IOP increase of 2.43 mm Hg, compared to 1.85 mm Hg with DCT. (GAT was not used for this test.)

Need for improvement. After the sensor was removed, 75% of eyes had transient corneal erosions; of these, 33.3% were mild, 50% were moderate, and 16.7% were severe. All resolved with or without medication after a mean of 3.1 days. Patients rated PMCL tolerability somewhere in the middle, with a mean score of 55.5 on a scale from 0 (no discomfort) to 100 (severe).

The next step is to test a second-generation device, which was designed to enhance safety and tolerability and increase accuracy of the measurements, Dr. Mansouri said. —*Miriam Karmel*

1 Wasilewicz R et al. *Br J Ophthalmol*. Published online Feb. 19, 2020.

Relevant disclosures—Dr. Mansouri: Implandata: C; Sensimed: C.

at least 10 letters during observation increased 2.7- to 3.2-fold.

When all three features were present, the risk for future VA loss of 10 or more letters during observation increased up to 47% over baseline. When patients were treated immediately at baseline, the risk of future VA loss was reduced to 26% during follow-up.

The presence of subretinal fluid was not a factor.

More study needed. It should be noted that these findings did not reach statistical significance, perhaps due to the small sample size. Moreover, as with the original OBTAIN study, this was a retrospective evaluation.

But the findings suggest the need for further studies in bigger cohorts of patients to evaluate whether an immediate treatment in these high-risk patients is superior to observation or not, Dr. Busch said.

In the meantime, she suggested that clinicians consider the presence or absence of DRIL, HRF, and EZ disruption when deciding whether to treat immediately or closely observe. "Our study changed my personal awareness. If risk features are present, I adapt my control intervals and decide for treatment earlier." *—Miriam Karmel*

1 Busch C et al. *Acta Ophthalmol.* Published online March 1, 2020.

2 Busch C et al. *Acta Diabetol.* 2019;56(7):777-784.

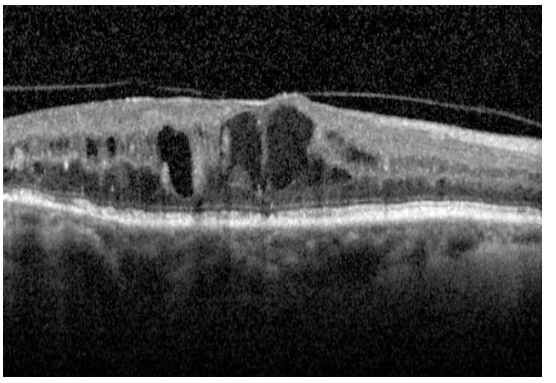
Relevant financial disclosures—Dr. Busch: None.

TELEMEDICINE

Cloud-Based Referral Platform Enables Rapid Triage

EACH MONTH, 22 INDIVIDUALS IN the United Kingdom lose vision because of hospital-initiated system delays, the Royal College of Ophthalmologists has estimated.[1] One potential solution to this dilemma: a cloud-based referral platform that was designed to improve communication between ophthalmologists and other providers and promote rapid triage.

The platform, developed by London-based Big Picture Medical, was put to the test in a pilot study involving three U.K. optometry offices and Moorfields Eye Hospital in London. The result: Of 103 patients initially classified into the referral pathway, 54 (52%) did not need to be referred to a specialist, 35 (34%) could be handled with a routine referral, and 14 (13.6%) needed urgent care.[2]



OCT MORPHOLOGY. *This patient had all three risk factors at baseline—DRIL, HRF, and EZ disruption.*

Catharina Busch, MD

For each case, it took the referring optometrist approximately 9 minutes to gather and send the pertinent clinical data—and it took the ophthalmologist an average of 3 minutes to review and triage the case.

Study rationale. "This study was the first of many steps taken to offer a more streamlined approach to eye care—a digital first encounter that may take the form of asynchronous telemedicine in a store-and-forward model—where a clinical history, eye scans, and visual fields may be reviewed remotely by a relevant specialist," said Dawn A. Sim, MBBS, FRCOphth, PhD, at Moorfields.

And while the study was conducted with referring optometrists, the platform could be put into place with general practitioners and urgent care facilities.

Well-suited to ophthalmology. The platform lends itself to "subspecialty areas with chronic diseases such as medical retina and glaucoma, which form a large proportion of outpatient consultations," Dr. Sim said.

In addition, it opens the door to synchronous telemedicine, she said, "in the form of video consultations with the patient at home or with doctors from the emergency department with the aid of a slit-lamp attachment." This could be useful for oculoplastic and strabismus patients, she said.

"Diagnostic drift" over time. The study has now been running for two years and currently includes nine optometry practices, Dr. Sim said. "The diagnostic drift of different eye conditions that were being referred demonstrates the efficacy of this shared learning [once it is] embedded into a referral workflow."

For example, she said, during the first year, most referrals were for suspected wet age-related macular degeneration. This shifted in the second year, when patients who had a wider variety and complexity of conditions were referred in.

Next steps. "Working with cloud-based telemedicine platforms has moved this field forward in ophthalmology" as the approaches aim to be "truly device-agnostic," Dr. Sim said. But while that represents improvement, real progress will depend upon electronic health records systems and major hardware vendors "opening their APIs and paying more than lip service to DICOM compliance," she said.

And a COVID-19 note. The current pandemic "has forced our hand in changing how we practice ophthalmology," Dr. Sim said. "In this digital age of high-definition eye scans, mobile devices, and high-speed networks, we must convince commissioners and insurers that specialist care does not always have to involve a slit-lamp exam."

—Jean Shaw

1 www.rcophth.ac.uk/wp-content/uploads/2019/01/RCOphth-A4-Census-Infographic.pdf. Accessed March 17, 2020.

2 Kern C et al. *Br J Ophthalmol.* 2020;104:312-317.

Relevant financial disclosures—Dr. Sim: Big Picture Eye Health: C.

See the financial disclosure key, page 8. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.