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The Dawn Of AI in Retina

T
he eyes may be well known as the, “window to the soul,” but an appreciation for the information contained within them is just beginning to dawn in our space. The images that retina specialists pore through daily are untapped treasure troves, holding far more potential than previously predicted.

In 2016, Google published a deep-learning algorithm capable of detecting diabetic retinopathy as accurately as trained ophthalmologists. Such data seems predictable now, and authors have described similar systems for interpreting skin lesions and dermatology.

Since then, the field has moved quickly. As Elon Musk recently surmised, “The pace of progress in AI is incredibly fast … you have no idea how fast.”1 In 2018, Google again advanced the AI ball in retina and demonstrated that deep learning can extract information “not previously thought to be present or quantifiable in retinal images.”2

The images that retina specialists pore through daily are untapped treasure troves, holding far more potential than previously predicted.

On the whole, retina specialists seem vaguely aware that advanced machine-learning platforms have impacted medical fields such as radiology and cardiology, but many in our field think the technology is not yet ready to penetrate it.

On page 18, Ehsan Rahimy, MD, astutely outlines the current landscape of AI within retina and predicts where we’re headed. In the near future, such advances promise to improve access to disease screening and augment our clinical capabilities through improved prognostication and more specific application of precision medicine.

AI will also extend into our clinics beyond image interpretation. Consider AI systems serving as medical scribes, both for patient intake and for improved physician documentation. Imagine a system that continuously improves based on your direct feedback until it is incredibly fine-tuned to your voice and documentation desires.

It could alleviate administrative costs and burden tremendously, and greatly enhance the quality of the exam and discussion documentation.

As our profession continues to evolve, I see a bright future for AI in retina. I encourage you to engage with me in creating this future for the betterment of our patients.

REFERENCES
BIOM® Optic Set –
Single-use Lens for BIOM® Systems

• Perfect view in every case
  Single-use means no scratches or opacities

• Maximum precision
  Superb depth of field even under high magnification

• Cost effective
  No reprocessing costs and reduced O.R. turnaround time

Compatible with all OCULUS BIOM® 3/4/5
INDICATIONS
LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with:
• Diabetic retinopathy (DR)
• Diabetic macular edema (DME)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
• LUCENTIS is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

WARNINGS AND PRECAUTIONS
• Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. Proper aseptic injection technique should always be utilized when administering LUCENTIS. Patients should be monitored following the injection to permit early treatment, should an infection occur.
• Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately.
• Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).
• In a pooled analysis of Studies DME-1 and DME-2, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.
• Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. A pooled analysis of Studies D-1 and D-2, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

ADVERSE EVENTS
• Serious adverse events related to the injection procedure that occurred in <0.1% of intravitreal injections included endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.
• In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough.
• As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The clinical significance of immunoreactivity to LUCENTIS is unclear at this time.

Please see Brief Summary of LUCENTIS full Prescribing Information on following page.

*The following clinical trials were conducted for the DR & DME indications: RISE & RIDE—Two methodologically identical, randomized, double-masked, sham injection–controlled, Phase III pivotal trials (N=759) that studied the efficacy and safety of LUCENTIS 0.3 mg and 0.5 mg administered monthly to patients with DR and DME at baseline. The primary outcome was the proportion of patients gaining ≥15 letters at 2 years. Protocol S—A randomized, active-controlled study that evaluated LUCENTIS 0.5 mg vs panretinal photocoagulation in DR patients with and without DME. All eyes in the LUCENTIS group (n=191) received a baseline 0.5 mg intravitreal injection followed by 3 monthly injections. Further treatments were guided by prespecified retreatment criteria. FDA approval was based on an analysis of the LUCENTIS arm of Protocol S. The primary outcome was mean change in visual acuity from baseline to 2 years.1,2

LUCENTIS 0.3 mg is recommended to be administered by intravitreal injection once a month (approximately 28 days).3

VEGF, vascular endothelial growth factor.
The efficacy and safety of LUCENTIS in DR, studied in 3 clinical trials, available in a prefilled syringe. LUCENTIS is the only anti-VEGF approved for DR with or without diabetic macular edema (DME).1

6.2 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared with rates observed in other clinical trials and may not reflect the rates observed in practice.

The data below reflect exposure to 0.5 mg LUCENTIS in 446 patients with neovascular AMD in Studies A1-MD-1, A2-MD-2, and A3-MD in 238 patients with macular edema following retinal vein occlusion. The data also reflect the exposure to 0.3 mg LUCENTIS in 252 patients with diabetic macular edema (see Clinical Trials (7.1) in the full prescribing information).

Safety data observed in DME A1-MD-4, D-3, and in 234 patients with mCNV were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen (Adverse Reactions).

Table 1 shows frequently reported adverse ocular reactions in LUCENTIS-treated patients compared with the control group.

Table 1: Ocular Reactions in the DME and OR, AMD, and RVO Studies

<table>
<thead>
<tr>
<th>Reaction</th>
<th>DME 2 and 4 week</th>
<th>OR 1 year</th>
<th>AMD 1 year</th>
<th>AMD 1 year</th>
<th>RVO 1 year</th>
<th>RVO 2 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central retinal vein occlusion</td>
<td>5% (n=250)</td>
<td>37% (n=65)</td>
<td>11% (n=150)</td>
<td>-</td>
<td>12% (n=25)</td>
<td>-</td>
</tr>
<tr>
<td>Central retinal vein occlusion</td>
<td>4% (n=250)</td>
<td>37% (n=65)</td>
<td>11% (n=150)</td>
<td>-</td>
<td>12% (n=25)</td>
<td>-</td>
</tr>
</tbody>
</table>

6.3 Immunogenicity

As a full-length therapeutic, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the potential for immune responses in patients treated with LUCENTIS who were not pretreated with other drugs for antibodies to LUCENTIS in immunocross and are highly dependent on the type of tissue and specificity of the antibody.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0.5%–5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-5% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, no adverse events were reported. No antibodies were detected in patients with DME or on baseline, or RVO patients with the highest levels of immunoreactivity.

6.4 Postmarketing Experience

The following adverse reaction has been identified during post approval use of LUCENTIS. Because this reaction was reported voluntarily from a population on an uncontrolled basis, it is not possible to reliably estimate the frequency or estimate a causal relationship to drug exposure.

★ Ocular Thick (retinal pigment epithelial) changes in patients with neovascular AMD.

7. DRUG INTERACTIONS

No drug interactions have been conducted with LUCENTIS. LUCENTIS intravitreal injection has been used adjunctively with photodynamic therapy (PDT) (see 12.1) or with anti-vascular endothelial growth factor (VEGF) neovascular AMD drug developed serious intraocular inflammation, in 10% or the 12.5% level of LUCENTIS when administered 7 days (7 or 2 days) after phototherapies.

8. USE IN SPECIFIC POPULATIONS

Pediatric Use

There are no adequate and well-controlled studies of LUCENTIS in pediatric patients. Administer of LUCENTIS to pediatric patients under 18 years of age, patients with neovascular AMD

9.6. Lactation

There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/secretion.

Because many drugs are excreted in human milk, and because the potential for adverse effects to infants of harm to infant in the long-term growth and development, caution should be considered when administering LUCENTIS to a nursing woman. The developmental and health benefits of breast milk feeding should be considered along with the mother’s medical need for LUCENTIS and any potential adverse effects of the drug to the nursing infant.

9.3 Females and Males of Reproductive Potential

9.4. Pediatric Use

The safety and effectiveness of LUCENTIS in pediatric patients have not been established.

9.5. Genetic Use

In the clinical studies, approximately 7% (924 of 12,272) of patients randomized to treatment with LUCENTIS were > 60 years of age and approximately 5% (464 of 12,272) were > 70 years of age (see Clinical Trials (7.1) in the full prescribing information). No apparent differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

10. OVERDOSAGE

More concentrated doses as high as 2 mg ranibizumab in 0.1 mL have been administered to patients. All additional unexpected adverse reactions were observed.

17. PATIENT COUNSELING INFORMATION

Advise patients that the time between LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, system develops a change in vision, advise the patient to seek immediate care from an ophthalmologist (see Warnings and Precautions (5.7)).

LUCENTIS (ranibizumab injection)

Manufactured by: Genentech, Inc.
A Member of the Roche Group
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AAO, ASRS Join 170 Medical Groups Opposing Proposed CMS Payment Rule

The American Academy of Ophthalmology and American Society of Retina Specialists joined with the American Medical Association and about 170 other medical groups in sending a letter to Centers for Medicare and Medicaid Administrator Seema Verma voicing their opposition to the Trump administration’s proposal to collapse payment rates for office visit services for new and established patients from eight to two. Now, CMS is weighing whether to implement those changes for the 2019 fiscal year or hold off until 2020.

The AMA sent the letter before the comment period closed on September 10. CMS has proposed adopting the new rules for January 1, 2019, but solicited comments on delaying their implementation for a year. The proposed rules are part of a larger CMS initiative called “Patients Over Paperwork” aimed to streamline providers’ documentation requirements and modernize Medicare payment policies to accommodate access to virtual care.

CMS claims the proposed changes to the Physician Fee Schedule (PFS) would save individual clinicians an estimated 51 hours per year if 40 percent of their patients are in Medicare, and changes in the Quality Payment Program would collectively save clinicians an estimated 29,305 hours and approximately $2.6 million in reduced administrative costs in 2019.

The American Society of Interventional Pain Physicians—one of the medical organizations that signed the letter to Ms. Verma—reports the change in the payment structure for evaluation and management (E/M) services would mimic the United Kingdom system, using one payment for most levels of services, aiming to avoid upcoding and downcoding.

Among the changes CMS has proposed are:

- Blend payment for five levels of new patient office visits (99202 to 99205) into one payment of $135 instead of $76 for Level II to $172 to Level V. Established patient office visits (99212 to 99215) would be blended to be paid at $93 instead of $45 for Level II and $148 for Level V.
- Create new codes to provide add-on payments to office visits for specific specialties ($9) and for primary care physician ($5).
- Allow practitioners from the same group and specialty to bill for same-day visits if medically necessary, ICD-10 Monitor reports. Office visits on the same day as a procedure with no global period would be paid at a 50-percent discount when billed with modifier -25.
- Pay physicians for their time when they check in with patients via telephone or online, and pay physicians for their time to review a video or image sent by a patient to assess whether a visit is needed.
- On the documentation side, change the required documentation of the patient’s history to focus only on the interval history since the previous visit.

IN BRIEF

EyePoint Pharmaceuticals has received Food and Drug Administration approval of its YUTIQ implant for treatment of chronic, posterior non-infectious uveitis. YUTIQ utilizes the Duraset non-bioerodible intravitreal micro-insert and contains 0.18 mg of fluocinolone acetonide, designed to release the drug over three years. It is supplied in a sterile single-dose preloaded applicator.

Heidelberg Engineering has received approval from the FDA for its optical coherence angiography module for the Spectralis OCT platform. The OCTA module is available for new and existing Spectralis upgradable devices.

REGENXBIO Inc. has completed dosing of the fourth cohort of six patients in a Phase I clinical trial evaluating the gene therapy RGX-314 for treatment of wet age-related macular degeneration, bringing the total to 24 subjects dosed in the trial. The company said it will report updated results at the American Academy of Ophthalmology annual meeting.

Quotable

“There are a number of unanswered questions and potential unintended consequences,” and the proposed rates “could hurt physicians and other health care professionals in specialties that treat the sickest patients.”

— Medical Groups’ Letter
• No longer require practitioners to personally document patient history, but allow them to review history entered by staff or the patient and indicate they verified it.
• Remove the need to justify a home visit vs. an office visit.

The AMA and medical societies support the proposed documentation rules. “Implementation of these policies will streamline documentation requirements, reduce note bloat, improve workflow and contribute to a better environment for health care professionals and their Medicare patients,” the letter notes.

However, the medical groups aren’t so warm to the proposed payment rates, noting “there are a number of unanswered questions and potential unintended consequences” and that “it could hurt physicians and other health care professionals in specialties that treat the sickest patients.” Another argument they invoked against the rule change: CMS factored the issue of multiple same-day services into prior valuations of the affected codes. “The proposal also has significant impact on certain services, such as chemotherapy administration, that may be an unintended consequence of altering the current practice expense methodology to accommodate the proposal,” the letter states.

The signature organizations expressed their support for an AMA-led working group to the E/M coding and payment issues in time to implement the 2020 Medicare PFS.

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**Large Study Adds to Evidence That Lower Cholesterol Means Lower DR Risk**

The evidence that statins and fenofibrate to treat high cholesterol in patients with type 2 diabetes may have a protective effect against diabetic retinopathy received a significant boost with the publication of a large study in Japan that found a 23-percent reduction in risk among patients on lipid-lowering drugs.

The study, led by Ryo Kawasaki, PhD, of Yamagata University in Japan, evaluated two cohorts of about 85,000 patients with type 2 diabetes who were taking glucose-lowering drugs. In the first cohort of 69,070 patients without DR at baseline, 49,744 (72 percent) were on some form of lipid-lowering therapy. In the second cohort of 15,738 patients with DR at baseline, 10,499 (66.6 percent) were on such therapy. Among the types of statins used, 20.9 percent were on standard statins (simvastatin, pravastatin and fluvastatin) and 79.1 percent on strong statins (atorvastatin, rosuvastatin and pitavastatin). The proportion of prescriptions for fenofibrate and fenofibrate was 54.4 and 45.5 percent, respectively.

In the first cohort, the rate of developing DR in three years among those on lower-lipid therapy was 7.4 percent (n=1,423) vs. 11.4 percent (n=5,5687) for those not taking the drugs. Among the second cohort, the treatment burden for DR was about one-third lower for the group on lipid-lowering drugs, 1.9 percent (n=98) vs. 3 percent (n=320).

Novartis and Pfizer Japan provided research grants to support the study.

**REFERENCE**

A 54-year-old Asian woman presented to the University of Washington Eye Institute with a one-day history of blurry vision and metamorphopsia in the inferonasal visual field of the left eye. Her ocular history was significant for central serous chorioretinopathy (CSCR) affecting the left eye, diagnosed in Los Angeles four months before her visit. At that time, she was noted to have submacular fluid in the left eye, treated initially with two intravitreal injections of bevacizumab (Avastin, Roche/Genentech).

She reported the first treatment was not effective, but the second treatment led to a modest reduction in the subretinal fluid. She was subsequently treated with verteporfin photodynamic therapy (PDT) without complete resolution of the fluid in the left eye. The patient noted increased stress recently from moving to Seattle and starting a new job one month before her visit. She works as a physician-scientist researcher.

**Examination Findings**

Best-corrected visual acuity was 20/20 and 20/40 in the right and left eyes, respectively. Intraocular pressures were normal, as were pupils, extraocular movements and confrontational visual fields. The anterior segment examination was only notable for trace nuclear sclerosis cataracts in both eyes.

The dilated fundus examination of the right eye showed a posterior vitreous detachment and a mild epiretinal membrane. In the left eye, the dilated fundus exam was notable for large-diameter, highly elevated pigment epithelial detachments (PEDs) with adjacent subretinal hemorrhage (SRH) concentrated in the superonasal macula (Figure 1A). No drusen, geographic atrophy, or pigment mottling were present in either eye.

**Ancillary Testing**

Fluorescein angiography with transit in the left eye showed normal transit time and vascular filling. However, there was blockage throughout the macula due to the subretinal hemorrhage. Late pooling was noted superiorly within the most temporal part of the PED. Diffuse and pinpoint leakage was also observed in the macula (Figure 1B). Optical coherence tomography of the left eye showed large serous PEDs with shallow surrounding SRH in the macula and along the superior arcade. Subretinal fluid (SRF) was also noted (Figure 1C).

**Diagnosis and Management**

The patient’s acute hemorrhage was suspicious for a choroidal neovascular membrane (CNVM). Additionally, the leakage on FA was suggestive of CNVM vs. chronic CSCR. The differential diagnosis included wet age-related macular degeneration, polypoidal (Continued on page 14)

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**Figure 1.** Color fundus photography at presentation (A) shows multiple pigment epithelial detachments (PED) associated with subretinal hemorrhage. The initial fluorescein angiogram of the left eye (B) shows blockage in the macula from the subretinal hemorrhage, late pooling within the PED in the temporal macula and diffuse and pinpoint leakage in the central macula. Optical coherence tomography (C) shows a central macular PED with adjacent subretinal hemorrhage. Raster scans through the superior macula (D) show large PEDs and small pockets of subretinal fluid.
Performing LIV tests allow you to objectively evaluate retinal health now and over time for tailored treatment and more precise disease management.

Objective clarity. Functional insights. Illuminating results.


That’s LIV-ing.
(Continued from page 12) choroidal vasculopathy (PCV) or CSCR with secondary CNVM.

We treated the hemorrhage and macular fluid with additional intravitreal bevacizumab injections. One month after the first injection, the subretinal hemorrhage displaced inferiorly just nasal to the fovea. She had three more monthly bevacizumab injections with near resolution of the subretinal hemorrhage, then we switched to intravitreal aflibercept (Eylea, Regeneron). With ongoing treatments, the patient achieved excellent anatomic recovery with flattening of the macular PED and stable visual acuity (Figure 2A to D).

After her third monthly aflibercept injection, the patient was lost to follow-up for seven weeks. She returned with enlargement of the PED in the central macula and an enlarged hemorrhagic PED along the superior arcade of the left eye (Figure 3A). Her visual acuity had decreased to 20/50.

At this point, we restarted aflibercept on a monthly basis, resulting in improvement of the macular PED, but with persistence of the PED along the superior arcade. We also prescribed oral eplerenone up to 50 mg daily for four months, but ultimately discontinued the medication because it did not appear to be helpful.

One month later, we treated the PED along the superior arcade with PDT followed by an aflibercept injection. The combination resulted in flattening of the shallow PED in the central macula (Figure 2D). Her visual acuity recovered to 20/30 in the left eye. The PED along the superior arcade persisted, but ultimately decreased in size.

The patient had OCT angiography approximately one year into treatment so we could characterize the choroidal neovascular membrane. The right eye appeared normal, but the left eye showed two large branching networks of neovascular vessels in the sub-RPE space (Figure 4, page 17). One focus was located in the central macula and another at the inferior border of the PED along the superior arcade.

Are PCV, Wet AMD Distinct?

Given this patient’s demographics, imaging characteristics and response to the combination of anti-VEGF and PDT, our leading diagnosis is PCV. Debate remains whether PCV represents a subtype of neovascular AMD or a completely separate entity. Both diseases share similarities, such as the presence of CNVM and associated predisposing genes such as HTRA1 (HtrA Serine Peptidase 1) and variants in CETP (cholestereryl ester transfer protein).1

Patients with PCV are mostly Asian or African-American. Many cases of wet AMD manifest with features of PCV in these populations. PCV occurs in Caucasians less frequently than wet AMD.2 Studies suggest that 54.7 percent of Japanese patients with neovascular AMD also have PCV, in contrast to 9.8 percent of Caucasians.3 PCV patients are also younger than AMD patients—usually age 50 to 65 years. PCV is more often unilateral in Asians and bilateral in Caucasians.1

The etiology of PCV is poorly understood. However, it is characterized by serosanguinous detachments of the pigmented epithelium, exudation and subretinal fluid. Other findings include subretinal fibrosis and atypical branching vascular networks with terminal aneurysmal dilatations referred to as polyps, often localized to the peripapillary region.4 In PCV, drusen are few and rare, or even absent; in AMD, drusen are the characteristic sign.1 Although PCV has been associated with multiple recurrent serous retinal detachments, it results in much less fibrous proliferation compared to end-stage neovascular AMD.3

How to Differentiate PCV

Although AMD and PCV may be on the same spectrum of disease, it is important to differentiate them
because demographics, natural history, visual prognosis and management differ significantly. On FA, PCV lesions resemble occult CNVM lesions and can be mistaken for AMD when localized in the central macula.

Indocyanine green angiography, with its ability to highlight choroidal vasculature, is the standard for diagnosis of polypoidal lesions. The polyps present as focal hyperfluorescent spots. In the later stages of the disease, the dye pattern reverses as the center of the lesion becomes hypofluorescent with surrounding hyperfluorescence. OCT can also show double reflective layers that consist of retinal pigment epithelium and another highly reflective layer beneath the RPE—known as “double-layer sign” — in the area of the branching network vessels. OCT can also show a notch in the margin of large PED, indicating the site of polypoidal lesions.

Several studies have evaluated the treatment of PCV. The efficacy of anti-VEGF agents is well known for CNV secondary to AMD. However, some authors have postulated that the pathophysiology of PCV is less driven by vascular endothelial growth factor than wet AMD. Studies have substantiated this claim, showing significantly lower aqueous VEGF levels in PCV compared to wet AMD. Although anti-VEGF injections do show efficacy, the underlying choroidal abnormalities in PCV have been shown to be more responsive when PDT is employed.

**Combination Therapy**

The combination therapy of PDT and an anti-VEGF agent has shown superior results, including improved vision, reduced SRH and reduced recurrence of polyps compared to either alone. The EVEREST trial compared PDT combined with ranibizumab vs. monotherapy of either treatment in patients with macular PCV. The combination arm achieved the best visual and angiographic outcome, with the highest proportion of complete polypoidal lesion regression (75 percent) and highest mean gain in vision (+10.9 letters).

Recently, the PLANET trial compared intravitreal aflibercept monotherapy to aflibercept with adjunctive PDT in 318 older adults with symptomatic PCV. The study showed aflibercept monotherapy was noninferior to aflibercept plus PDT. However, the study could not elucidate the benefits of adding PDT because most participants responded to intravitreal aflibercept alone.

In summary, PCV can occur in any sex or race. It is more commonly seen in the peripapillary area, without associated drusen, and in nonwhite patients. PCV is diagnosed with ICGA showing leakage from a vascular network of polyps and visible exudation associated with PED. OCTA may allow excellent visualization of these structures both for diagnosis and to assess therapeutic response. Lastly, evidence shows that PDT may serve as an effective adjunct to traditional anti-VEGF medications used for wet AMD, but that aflibercept mono-
Diagnostic vitrectomy or a retinal biopsy is sometimes essential to identify the etiology of suspected infection or malignancy such as intraocular lymphoma. Here, Ananth Sastry, MD, and Dilraj S. Grewal, MD, of the Duke Eye Center share their approach to this daunting procedure.

Preoperative Evaluation, Prep

Prior to surgery, it is imperative to communicate with the cytopathologist, flow cytometry laboratory and any outside laboratories to determine their preferences for specimen processing, handling and transport. It is also important to have a differential diagnosis to appropriately allocate the higher-quality, undiluted sample to higher-yield studies.

On the day of surgery, it’s helpful to pre-label the collection tubes and have them ready on the sterile field. The surgeon personally aliquotes the obtained samples into the tube.

Surgical Technique

1. Connect infusion line. The procedure begins with the infusion line connected to the eye but clamped to avoid premature intraocular dilution. At the Duke Eye Center, where a fellow or other skilled assistant is consistently available, a 10-cc syringe is connected to the disengaged aspiration line of the cutter for manual aspiration.

2. Reduce cut rate. Reducing the cut rate to ~1,000 cpm may minimize morphological alterations in the sample. As you initiate vitreous cutting in the mid-vitreous cavity, an assistant gently aspirates the vitreous using the attached syringe. Undiluted vitrectomy continues until the eye becomes hypotonous. Alternatively, the infusion can be opened to air, which may maximize the volume of an undiluted sample and prevent hypotony.

3. Harvest the sample. In the absence of a skilled assistant, a “vitreous trap” uses a vacutainer to provide a simple, surgeon-controlled method for obtaining undiluted samples. Alternatively, the infusion can be opened to air, which may maximize the volume of an undiluted sample and prevent hypotony.

4. Open infusion line. Following harvesting of the undiluted sample, the infusion line is opened to fluid, and a diluted sample is obtained with a fresh 10-cc syringe. Drs. Sastry and Grewal prefer to aspirate all the diluted sample in 10-cc syringes, which simplifies processing by the lab vs. sending the vitrectomy cassette.

5. Aspirate tissue for biopsy. If a retinal biopsy is indicated, a 27-gauge cutter can be directly introduced into the retina or subretinal space (Figure 1) and the tissue aspirated using high vacuum (~600 mmHg) and low cut rate (~300 to 500 cpm). Once you visualize the specimen in the infusion line (Figure 2), withdraw the cutter and reflux engaged after the sample is collected. This latter technique is probably the simplest, but risks some loss of the precious sample.

Drs. Sastry and Grewal demonstrate their technique for diagnostic vitrectomy and retinal biopsy. Available at: http://bit.ly/VideoPearl_008
Figure 3. Sample is refluxed from the vitreous cutter tubing directly into the microcentrifuge tube and then sent for analysis.

the sample into the collection tube (Figure 3). Alternatively, a larger piece of retinal tissue may be harvested using scissors and carefully extracted through an enlarged sclerotomy. In such cases, the retinotomy is barrierced with endolaser. Intraocular tamponade is usually used.

While diagnostic vitrectomy and retinal biopsy are the preferred techniques for tissue diagnosis, it’s important to recognize that the yield is dependent upon obtaining a sufficient volume of cells/tissue, choosing appropriate tests and communicating appropriately with the laboratory.

Dr. Sastry is a vitreoretinal surgery fellow and Dr. Greco is an associate professor of ophthalmology, specializing in vitreoretinal surgery and uveitis, at the Duke Eye Center, Durham, N.C.

REFERENCES

What Lurks Beneath the RPE (Continued from page 15)

therapy may also be an effective approach.

REFERENCES

Dr. Ohmura de Koo is an associate professor of ophthalmology and director of the retina fellowship program at the University of Washington in Seattle, where Dr. Chan is a second-year ophthalmology resident and Dr. Saraf is a second-year retina fellow. Mr. Yanagihara is a visiting fourth-year medical student from the University of Hawaii John A. Burns School of Medicine.

Figure 4. Optical coherence tomography angiography (from the outer retina to the choriocapillaris layer) reveals extensive vascular networks in the subretinal pigment epithelium space and within the pigment epithelial detachments of the left eye.

early two years have passed since the Google Brain team presented data showing that a deep-learning algorithm is capable of detecting signs of diabetic retinopathy at least as accurately as a cohort of ophthalmologists.1 While this was certainly not the first exploration of artificial intelligence or machine learning applications in medicine, it had a profound impact in terms of capturing the collective attention and imagination of researchers, clinicians, industry and mainstream media. Deep learning had announced its arrival in ophthalmology, although many were unsure of how, when, why and to what extent it would help reshape the way we deliver care.

Since then, numerous studies have validated deep-learning models in the detection and diagnosis of diseases afflicting the posterior segment of the eye, with extremely high accuracy.1-7 In April 2018, the Food and Drug Administration granted breakthrough device designation to the cloud-based software IDx-DR (IDx Technologies) as the first artificial intelligence-based medical device to detect referable DR from color fundus photographs.2 This is the first approved instrument to provide a screening decision without clinician input.

Moving forward, ongoing advances in machine learning, and especially deep learning, offer the potential to help expand patient access to care, increase efficiency, reduce errors and improve overall quality of care. Here, we elaborate on four areas in which this revolutionary technology is positioned to impact our day-to-day clinical practice as retina specialists.

1. Deployment of Large-Scale Teleretinal Screening Programs

Diabetes is a growing epidemic both domestically and internationally. Current estimates show that more than 30 million Americans have diabetes; this number exceeds 400 million worldwide.8,9 Both of these figures continue to rise at staggering rates that surpass most predictive models. Despite well-established guidelines for screening and potential early detection of DR by an eye-care provider, 30 to 50 percent of people with diabetes do not adhere to these recommendations for a multitude of reasons.10,11 Teleretinal screening programs for DR may help close this gap, and are already demonstrating success in select regional markets with nonmydriatic...
Disease Study dataset (Institutes of Health Age-related Eye classification problem, categorizing age-related macular degeneration ing algorithms to solve a two-class applied two different deep-learn- M. Burlina, PhD, and colleagues detecting various posterior segment algorithms have shown promise in Deep Learning in AMD and president of IDx.)

FDA approval of the IDx-DR device was based on a prospective study that assessed the software performance on retinal images from 900 diabetic patients at 10 primary-care offices. In the study, Michael Abràmoff, MD, PhD, and colleagues showed that IDx-DR’s sensitivity and specificity for detecting greater-than-mild DR were 87 and 90 percent, respectively. Notably, existing staff at the primary-care physician sites received a one-time standardized four-hour training program on operating the system, after which they were able to successfully image patients and transfer information to the platform 96 percent of the time. (Dr. Abràmoff is founder and president of IDx.)

Deep Learning in AMD

Beyond diabetes, deep-learning algorithms have shown promise in detecting various posterior segment diseases. For example, Philippe M. Burlina, PhD, and colleagues applied two different deep-learning algorithms to solve a two-class age-related macular degeneration classification problem, categorizing fundus images from the National Institutes of Health Age-related Eye Disease Study dataset (n>130,000 images) as either disease-free/early stage AMD (for which dietary supplements are not considered) or intermediate or advanced stage (for which supplements and monitoring are considered). The investiga- tors found that both deep-learning methods yielded accuracy that ranged between 88.4 and 91.6 percent, while the area under the curve (AUC) was between 0.94 and 0.96. These findings were promising and indicated performance levels comparable to physicians.

Furthermore, a group of international researchers reported on a deep-learning system that, in addition to detecting referable DR and vision-threatening DR (defined as severe nonproliferative DR or proliferative DR), was also trained to identify AMD and referable glaucoma. The investigators commented that screening for other vision-threatening conditions should be mandatory for any clinical diabetic screening program. In the primary validation dataset (n=71,896 images), the AUC of the algorithm for referable DR was 0.936, with sensitivity of 90.5 percent and specificity of 91.6 percent. For vision-threatening DR, the AUC was 0.955, with sensitivity of 100 percent and specificity of 91.1 percent. For possible glaucoma, the AUC was 0.942, with sensitivity of 96.4 percent and specificity of 87.2 percent. Finally, for AMD, the AUC was 0.931, with sensitivity of 93.2 percent and specificity of 88.7 percent. Among the additional 10 datasets used for external validation (n=40,752 images), the AUC range for referable DR was between 0.859 and 0.983.

Wide-Field Imaging Potential

Equally as important as the disease screened for is the imaging modality used to do the screening. Numerous nonmydriatic fundus camera systems are currently available, but limited investigations have been conducted thus far using wide-field imaging, which may offer unique advantages for future teleretinal screening programs. The collaboration between Nikon’s Optos subsidiary and Google’s Verily (formerly Google Life Sciences) in late 2016 is evidence. Researchers in Japan reported on their deep learning algorithm to detect rhegmatogenous retinal detachment using Optos ultra-wide-field fundus images, which demonstrated a high sensitivity of 97.6 percent with an AUC of 0.988.

A separate study from the same...
group aimed to use Optos ultra-wide-field images for the detection of neovascular AMD. Similarly, they reported a high sensitivity of 100 percent with an AUC of 0.998. The single greatest limitation of both studies was the low number of images used for training in each study (n<500), as deep learning requires a large number of data sets for optimal training. Moving forward, larger sets of classified, labeled wide-field images will need to be procured for more optimal deep-learning algorithm development.

2. Systemic Disease Assessment

Retina specialists routinely assess for ocular involvement of various systemic disease states, ranging from vascular (diabetes, hypertension) to infectious (tuberculosis, syphilis) to inflammatory (sarcoidosis, Behçet’s). However, deep learning offers the potential to identify subclinical findings and patterns from retinal images that extend beyond the discernible threshold of a human interpreter. This may one day enable fundus photography to be used as a supplemental biomarker for overall systemic morbidity/mortality assessment, rather than for just identifying retinal pathology.

Retinal Imaging in CVD

This exciting possibility was recently explored by Google researchers working with a Stanford University cardiologist. They used a deep-learning algorithm trained on retinal fundus images (n=284,335 patients) to predict associated cardiovascular risk factors. Their algorithm accurately predicted cardiovascular risk factors not previously thought to be detectable in retinal images, such as patient age (within 3.26 years), gender (AUC=0.97), smoking status (AUC=0.71), systolic blood pressure (within 11.23 mmHg) and major adverse cardiac events (AUC=0.70). This performance approached the accuracy of other cardiovascular risk calculators, which typically require a blood draw to measure cholesterol levels.

While this is a new and evolving area of study, future directions may also investigate associations with subclinical retinal findings and neurodegenerative conditions such as Alzheimer’s, Parkinson’s and multiple sclerosis.

3. Improving Clinical Efficiency and Daily Workflow

The widespread use and success of intravitreal agents for the management of retinal diseases has not only revolutionized patient care, but also dramatically increased the burden of treatment for retina specialists. The ever-expanding indications for these medications (e.g., anti-VEGF for any stage of DR), as well as the promise of new targeted therapies for conditions without current treatment (e.g., dry AMD), are likely to challenge and further strain the day-to-day clinical practice of retina specialists as patient...
office visits and diagnostic testing only increase.

Given how optical coherence tomography imaging is the single most common diagnostic test performed on a daily basis in retina clinics, this task potentially lends itself to automation with deep-learning techniques. Several groups have successfully utilized deep learning in segmentation of OCT scans for the detection of morphological features such as intraretinal fluid (IRF) or subretinal fluid (SRF) from various retinovascular diseases.16-19

Taking Deep-Learning One Step Further

Researchers in Germany proposed a deep-learning model with the goal of predicting the need for intravitreal anti-VEGF retreatment rather than just detecting the presence of IRF or SRF.20 In their study, 183,402 OCT images from patients receiving ongoing anti-VEGF therapy were cross-referenced with the electronic institutional intravitreal injection records. The trained algorithm reached a prediction accuracy of 95.5 percent on the images in the validation set. For single retinal B-scans in the validation dataset, a sensitivity of 90.1 percent and a specificity of 96.2 percent were achieved, with an AUC of 0.968.

Taken together, deep learning in this setting may one day be used for more rapid, automated evaluation and assessment of images and monitoring of disease activity, only necessitating human verification for abnormalities. Similar protocols have been implemented in the field of radiology to improve efficiency. Furthermore, these methods may additionally offer the clinician support in decision-making on a given patient’s need for treatment.

Deep Learning and EHR

Deep learning appears poised to impact clinical workflow efficiency beyond tasks pertaining to just image recognition and classification. For example, some of the earlier applications of deep learning were in the fields of voice/speech recognition and language processing. Accordingly, Deep Scribe, Robin and other companies are developing deep learning-based digital medical scribing platforms to augment and improve the physician’s documentation process into the electronic health record.21,22

Having a system, rather than a live/remote human scribe, that can reliably produce clinic notes up to the physician’s standards while constantly evolving and improving over time may help to increase direct face-time with patients, alleviate administrative and clerical burden, reduce administrative practice costs and, ultimately, improve day-to-day clinic efficiency.

4. Precision Medicine in Retina

The Precision Medicine Initiative had defined precision medicine as “an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.”23 An individualized approach to medicine may enable physicians to more accurately predict which treatment strategies may be most effective for certain patient groups based on inherent individual differences.

Inferring Disease Patterns

Looking further down the road, deep learning offers the potential to help solve a number of our overburdened health-care system’s growing problems. As of now, these algorithms have been mostly used for the detection and diagnosis of disease. However, as efforts grow toward acquiring sequential datasets from the same patients over an extended period of time, deep learning may unlock the potential to start inferring patterns of disease progression, and, from that, make treatment and prognostic predictions.

We may one day be able to tailor treatments and interventions to patients at highest risk of disease progression at an earlier stage.

AI, Machine Learning and Deep Learning Defined

Due to ever-increasing popularity and integration into popular culture, the terms artificial intelligence, machine learning and deep learning are frequently used interchangeably. However, it is important to differentiate and distinguish amongst the three. Generally speaking, these can each be viewed as concentric circles: AI is the largest circle, machine learning a smaller circle within AI and deep learning the smallest circle within the subset of machine learning (Figure).

- **Artificial intelligence** is defined as the ability of computer systems to perform complex, independent tasks that require human-like intelligence, such as visual processing, speech recognition or decision-making.
- **Machine learning** is employed when computer programs have the ability to improve their own decision-making by learning from data provided to them without being given explicit rules.
- **Deep learning**, an increasingly popular and powerful model of machine learning, utilizes layers upon layers of neural networks to enhance the software’s ability to independently extract features data.
example, DR could potentially be reclassified along a scale where a numeric grade denotes a patient’s risk of developing diabetic macular edema or progressing to proliferative disease. Once a certain numeric threshold is crossed, treatment would then be indicated, even if center-involving DME or neovascularization has not yet developed.

Conversely, deep learning may also elucidate for whom and when treatment can be selectively withheld; that is, where there may not be any added functional visual benefit, thus avoiding overcommitment of expensive and finite resources.

**Predicting Treatment Outcomes**

Research groups are currently investigating deep-learning methodologies to identify OCT structural biomarkers in hopes of predicting clinical treatment outcomes. Austrian investigators have applied deep learning techniques to OCT images from 614 clinical patients in the HARBOR trial, aiming to predict functional response to intravitreal anti-VEGF therapy. HARBOR was a 24-month, Phase III dose-response trial of ranibizumab (Lucentis, Roche/Genentech) for treatment of wet AMD.

One of their studies applied a deep-learning algorithm to delineate retinal layers and the CNV-associated lesion components, IRF, SRF and pigment epithelial detachment. These were extracted together with visual acuity measurements at baseline, months one, two and three, and then used to predict vision outcomes at month 12 by using “random forest” machine learning. The group found that the most relevant OCT biomarker for predicting the corresponding visual acuity was the horizontal extension of IRF within the foveal region, whereas SRF and pigment epithelial detachment ranked lower.

With respect to predicting final visual acuity outcomes after one year of treatment, the accuracy of the algorithm increased in a linear fashion with each successive month of data included from the initiation phase. The most accurate predictions were generated at month three (R2=0.70).

In a separate study, the same researchers applied their deep-learning techniques to assess whether low and high ranibizumab injection requirements from the *pre nata arm* of the HARBOR trial could be predicted based on OCT scans at baseline and months one and two. Of 317 eligible patients, 71 had low injection requirements (≤five), 176 had medium (five to 16) and 70 had high (≥16) injection...

**Looking Ahead and A Word of Caution**

Although a rapidly growing body of literature supports a role for deep learning applications within ophthalmology, significant work remains as the next steps are taken toward its clinical validation and eventual implementation. Numerous challenges exist. Many studies of deep learning retrospectively used training sets from relatively homogenous patient populations. Moving forward, the goal will be to continue training on larger image sets that are diverse across not only patient demographics, but also the types of images obtained (i.e., different fundus cameras, wide-field imaging, mydriatic vs. nonmydriatic images, etc.).

A separate area of concern is the “black box” nature of deep learning, whereby neither the physicians nor the engineers who programmed them entirely understand the rationale for the outputs the algorithms generate. This has created some apprehension in the public eye, and raises an ethical dilemma of how to build public trust for a technology we do not fully comprehend. Nevertheless, groups have been attempting to fill in these knowledge gaps by generating heat maps highlighting regions of influence on each image that contribute to the algorithm’s conclusion.

**The Risk of ‘Deskilling’**

Should we arrive at a future where automated image analysis has been integrated into clinical practice, there are concerns over whether this may eventually lead to a reduction in physician skills and clinical acumen due to an over-reliance on technology. This phenomenon is known as deskillling, where the skill level required to complete a task is reduced when components of the task become automated, leading to inefficiencies whenever the technology fails or breaks down.

At the recent Human Intelligence and Artificial Intelligence in Medicine Symposium, numerous speakers cautioned about the lack of published, prospective, peer-reviewed data, and the potential for patient harm if this technology is rushed into the clinic without first enduring sufficient testing and regulation. Even with the pivotal IDx-DR results from Michael Abràmoff, MD, PhD, and colleagues, which were used to form the basis for Food and Drug Administration approval of the IDx-DR system, there still remains the unknown issue of clinical effectiveness. Two thought leaders of AI in medicine made this point in a recent editorial—Pearse A. Keane, MD, MSc, leader of the Google DeepMind research team and Moorfields Eye Hospital in London, and Eric J. Topol, MD, a cardiologist at Scripps Clinic-Scripps Health and founder and director of the Scripps Research Translational Institute in La Jolla, Calif.

In other words, the question remains: Are patients directly benefitting from the use of these systems and demonstrating at least non-inferior visual outcomes with these screening algorithms as opposed to traditional screening measures? Only time will tell.
INNOVATION THAT’S WITHIN EASY REACH.

The I-OPS™ Instrument Delivery System

The I-OPS Instrument Delivery System from Reliance Medical Products is designed to eliminate inefficiencies associated with traditional injection procedures. Injection workflows with I-OPS allow for efficient movements, easy reach to supplies and secure, customizable instrument layouts.

“We designed I-OPS to offer vitreoretinal surgeons improved efficiency and enhanced safety, and superior ergonomics.”

Christopher Riemann, M.D.
Cincinnati Eye Institute, Cincinnati, OH

requirements during the PRN phase of treatment extending from three to 23 months.

The authors found that classification within low or high treatment demonstrated AUCs of 0.7 and 0.77, respectively. Additionally, the most relevant OCT biomarker for prediction of injection burden was volume of SRF within the central 3 mm at month two.

Analyzing Massive Datasets
On a larger scale, deep-learning algorithms are being applied to analyze substantial quantities of electronic health records with the goal of making predictive assessments regarding certain high-risk populations. Predictive modeling with EHR data is anticipated to further advance personalized medicine and improve overall health-care quality. A Google-led study recently demonstrated that deep-learning methods using patients’ entire raw EHR records are capable of accurately predicting multiple medical events.

In the study, de-identified EHR data from two U.S. academic medical centers with 216,221 adults hospitalized for at least 24 hours was unrolled into a total of 46 billion data points. The deep-learning models achieved high accuracy for tasks such as predicting in-hospital mortality (AUC=0.93 to 0.94), 30-day unplanned readmission (AUC=0.75 to 0.76), prolonged length of stay (AUC=0.85 to 0.86), and all of a patient’s final discharge diagnoses (AUC=0.90).

This type of research may be of unique interest given the patient demographic retina specialists care for are typically elderly (i.e., AMD) or vasculopathic (i.e., diabetes). Thus, both groups may be at higher risk for systemic adverse events necessitating hospitalizations. Extrapolating the results of this study, being able to identify patients at highest risk for experiencing secondary events beforehand could theoretically influence our future treatment paradigms.

For example, in managing PDR, a more definitive panretinal photoacoagulation may be indicated over anti-VEGF injections for a patient whom an algorithm denotes as having a high risk of inpatient hospitalization. That may potentially mean a higher risk of missing clinic appointments.

REFERENCES


Three-dimensional, digitally assisted visualization systems are enhancing optical microscope-based approaches to vitreoretinal surgery. Besides the clear advantages of the 3-D technology over the traditional approach—4,000-pixel (4K) monitor, decreased light phototoxicity, digital enhancements, improved depth of field, digital filtering and high-dynamic range—these platforms can be integrated with other commercially available visualization systems. Available 3-D systems include:

- Ngenuity 3-D Visualization System (TrueVision Systems and Alcon);
- Trenion 3-D HD (Carl Zeiss Meditec); and
- RV800 Viewing System (Leica Microsystems).

Currently, Ngenuity offers all the described features, including integration of endoscopy and intraoperative optical coherence tomography.

At a debate during the American Academy of Ophthalmology’s Retina Subspecialty Day last year, the audience voted on whether 3-D digitally assisted vitreoretinal surgery is ready to become the new standard. Although the audience voted largely no, the arguments were based only on image quality and teaching advantages. The digital integration with other technologies, though, is something unprecedented in our field, especially with regards to endoscopic vitrectomy. Here, we report on the state of the art of 3-D digitally assisted platforms in vitreoretinal surgery.

**Evolution of Endoscopy**

Harvey Thorpe, MD, first described endoscopic ocular surgery in 1934, well before pars plana vitrectomy became the gold standard in vitreoretinal surgery. In the early 1990s, Martin Uram, MD, at New York Eye and Ear Infirmary, introduced endoscopy to the vitreoretinal world. Despite slow initial progress here, we report on the state of the art of 3-D digitally assisted platforms in vitreoretinal surgery.

**Take-home Point**

It’s a propitious time to incorporate endoscopy as a tool in vitreoretinal surgery. New three-dimensional technologies offer the possibility of integrating multiple visualization systems. Combined with the latest technologies, these systems should encourage experienced surgeons that have tried endoscopy in the past to try it again and younger surgeons to adopt it as well. This article reviews the advantages of endoscopy with a 3-D digitally assisted visualization system.

**Focus on Innovation in Surgery**

**UNLOCKING THE POTENTIAL OF 3-D SURGERY**

Digitally assisted visualization can make endoscopy more accessible for vitreoretinal surgery.

**By Flavio Rezende, MD, PhD, and Natalia Vila, MD, PhD, FEBO**

ABOUT THE AUTHORS

Dr. Rezende is a vitreoretinal surgeon at Maisonneuve-Rosemont Hospital and associate professor of ophthalmology at the University of Montreal.

Dr. Vila is a consultant vitreoretinal surgeon at Royal Liverpool University Hospital, Liverpool University, U.K.

DISCLOSURES: The authors have no relevant financial relationships to disclose.
Warnings and Precautions

• **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.

• **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

• **Retinal abnormalities** may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. Do not administer LUXTURNA in the immediate vicinity of the fovea. Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.

• **Increased intraocular pressure** may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.

• **Expansion of intraocular air bubbles** instruct patients to avoid air travel, travel to high elevations or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.

• **Cataract** Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

Adverse Reactions

• In clinical studies, ocular adverse reactions occurred in 66% of study participants (57% of injected eyes), and may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.
A New Vision
for your patients with an inherited retinal disease (IRD)

LUXTURNA (voretigene neparvovec-rzyl) is a one-time gene therapy that improves functional vision in individuals with an IRD who have confirmed biallelic RPE65 gene mutations and viable retinal cells.¹

With LUXTURNA, patients experienced a clinically meaningful improvement in the ability to navigate at lower light levels.¹

IMPORTANT SAFETY INFORMATION (CONT’D)

• The most common adverse reactions (incidence ≥5% of study participants) were conjunctival hyperemia (22%), cataract (20%), increased intraocular pressure (15%), retinal tear (10%), dellen (thinning of the corneal stroma) (7%), macular hole (7%), subretinal deposits (7%), eye inflammation (5%), eye irritation (5%), eye pain (5%), and maculopathy (wrinkling on the surface of the macula) (5%).

Immunogenicity
Immune reactions and extra-ocular exposure to LUXTURNA in clinical studies were mild. No clinically significant cytotoxic T-cell response to either AAV2 or RPE65 has been observed. In clinical studies, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days and 1.7 to 4.6 years. Study participants received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye, which may have decreased the potential immune reaction to either AAV2 or RPE65.

Pediatric Use
Treatment with LUXTURNA is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during the cell proliferation. The safety and efficacy of LUXTURNA have been established in pediatric patients. There were no significant differences in safety between the different age subgroups.

Please see a brief summary of the US Full Prescribing Information on the following pages.


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P-RPE665-US-360005 April 2018

LEARN MORE AT www.LUXTURNAHCP.com
5.2 Permanent decline in visual acuity

Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

5.3 Retinal abnormalities

Retinal abnormalities may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. LUXTURNA must not be administered in the immediate vicinity of the fovea. [See Dosage and Administration (2.3) in full prescribing information]

Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.

5.4 Increased intracocular pressure

Increased intracocular pressure may occur after subretinal injection of LUXTURNA. Monitor and manage intracocular pressure appropriately.

5.5 Expansion of intracocular air bubbles

Instruct patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.

5.6 Cataract

Cataract: Advise patients that following treatment with LUXTURNA, they may develop a cataract. Increased incidence of cataract development and/or progression of existing cataract may occur.

6. ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5%) were conjunctival hyperemia, cataract, increased intracocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other products and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to LUXTURNA in two clinical trials, consisting of 41 subjects (81 eyes) with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Forty of the 41 subjects received sequential subretinal injections of LUXTURNA to each eye. One subject received LUXTURNA in only one eye. Seventy-two of the 81 eyes were exposed to the recommended dose of LUXTURNA at 1.5 x 10^11 vg. 9 eyes were exposed to lower dose of LUXTURNA. Study 1 (n=12) with open-label, dose-expansion safety study. Study 2 (n=29) was on an open-label, randomized, controlled study for both efficacy and safety [see Clinical Studies (14) in full prescribing information]. The average age of the 41 subjects was 17 years, ranging from 4 to 44 years. Of the 41 subjects, 25 (61%) were pediactric subjects under 18 years of age, and 23 (56%) were females. Twenty-seven (27/41, 66%) subjects had ocular adverse reactions that involved 46 injected eyes (46/81, 57%). Adverse reactions among all subjects in Studies 1 and 2 are described in Table 1. Adverse reactions may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

Table 1. Ocular Adverse Reactions Following Treatment with LUXTURNA (N=41)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Subjects n=41</th>
<th>Treated Eyes n=81</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ocular adverse reaction</td>
<td>27 (66%)</td>
<td>46 (57%)</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>9 (22%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>8 (20%)</td>
<td>15 (19%)</td>
</tr>
<tr>
<td>Increased intracocular pressure</td>
<td>6 (15%)</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Retinal tear</td>
<td>4 (10%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Dellen (thinning of the corneal stroma)</td>
<td>3 (7%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Macular hole</td>
<td>3 (7%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Subretinal deposits*</td>
<td>3 (7%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Eye inflammation</td>
<td>2 (5%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>2 (5%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>2 (5%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Maculopathy (wrinkling on the surface of the macula)</td>
<td>2 (5%)</td>
<td>3 (4%)</td>
</tr>
</tbody>
</table>

*Transient appearance of asymptomatic subretinal precipitates inferior to the retinal injection site 1-6 days after injection.

6 USE IN SPECIFIC POPULATIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary: Adequate and well-controlled studies with LUXTURNA have not been conducted in pregnant women. Animal reproduction studies have not been conducted with LUXTURNA. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Lactation: There is no information regarding the presence of LUXTURNA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for LUXTURNA and any potential adverse effects on the breastfed infant from LUXTURNA.

8.3 Females and Males of Reproductive Potential

No nonclinical or clinical studies were performed to evaluate the effect of LUXTURNA on fertility.

8.4 Pediatric Use

Pediatric Use: Treatment with LUXTURNA is not recommended for patients younger than 12 months of age because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during cell proliferation. The safety and efficacy of LUXTURNA have been established in pediatric patients. Use of LUXTURNA is supported by Study 1 and Study 2 [see Clinical Studies (14) in full prescribing information] that included 25 pediatric patients with biallelic RPE65 mutation-associated retinal dystrophy in the following age groups: 21 children (age 4 years to less than 12 years) and 4 adolescents (age 12 years to less than 17 years). There were no significant differences in safety between the different age subgroups.

8.5 Geriatric Use

The safety and effectiveness of LUXTURNA have not been established in geriatric patients. Clinical studies of LUXTURNA for this indication did not include patients age 65 years and over.

17 PATIENT COUNSELING INFORMATION

Advises patients and/or their caregivers of the following risks:

Endophthalmitis and other eye infections: Serious infection can occur inside of the eye and may lead to blindness. In such cases, there is an urgent need for management without delay. Advise patients to call their healthcare provider if they experience new eye pain, eye pain, or any change in vision.

Periorbital edema in visual acuity: Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Advise patients to contact their healthcare provider if they experience any change in vision.

Retinal abnormalities: Treatment with LUXTURNA may cause some defects in the retina such as a small tear or hole in the area or vicinity of the injection. Treatment may cause thinning of the central retina or bleeding in the retina. Advise patients to follow up with their healthcare provider on a regular basis and report any symptoms, such as decreased vision, blurred vision, flashes of light, or floaters in their vision without delay.

Increased intracocular pressure: Treatment with LUXTURNA may cause transient or persistent increase in intracocular pressure. If untreated, such increases in intracocular pressure may cause blindness. Advise patients to follow up with their healthcare provider to detect and treat any increase in intracocular pressure.

Proper aseptic injection technique should be used when administering LUXTURNA. Following the injection, patients should be monitored to permit early treatment of any infection that may develop.

Any ocular adverse reactions that involved 46 injected eyes (46/81, 57%) included 27 (66%) subjects who had adverse reactions that involved 46 injected eyes (46/81, 57%). Adverse reactions among all subjects in Studies 1 and 2 are described in Table 1. Adverse reactions may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.
in the developing this technology, it evolved toward the higher-resolution (17,000 pixels) and smaller-gauge probes (23-gauge in North America [Endo Optiks E2 endoscope platform, Beaver-Visitec International Inc.] and 25-ga in Japan [FiberTech Co. Ltd.]). This advance in technology made endoscopy more attractive to vitreoretinal surgeons. However, endoscopic vitrectomy is still only being adopted by a few retina specialists. The learning curve can be steep, and a misconception exists that endoscopic vitrectomy has only a limited number of indications.

**Advantages of Endoscopy**

The advantages of endoscopy in cases of media opacity, such as cloudy cornea, trauma or endophthalmitis are well known, and it’s accepted as an alternative to temporary keratopros-
field of view in a 2-D environment (lack of stereopsis), making it harder to find instruments inside the eye, which may discourage adoption. Consequently, few reports support its use. In addition, terminology used in both clinical scenarios (media opacity or clear media) should be reappraised.

**Integration of Endoscopy, 3-D**

The integration of endoscopy into 3-D visualization systems offers a new perspective to surgeons with little to no endoscopy experience, helping them to overcome the learning curve faster and allowing them to work simultaneously in a familiar wide-field environment.

The new 3-D monitors with split screen combine endoscopic and wide-field view simultaneously during endoscopic vitrectomy. Traditionally, the use of the endoscope requires a monitor. The surgeon works heads up, looking at the screen (2-D) instead of through the microscope. The 3-D, heads-up technology eliminates the need for a second monitor because the probe is connected to the 3-D system through a coaxial output from the endoscopy console to the 4K monitor.

Alternatively, other devices are available to convert S-Video output from the endoscope into HDMI. The Ngenuity split-screen feature simplifies the surgical setup. The endoscopy probe simultaneously provides at the same time the endoscopic image and the wide-field 3-D viewing as an endilluminator (Figure 2).

The most challenging aspects in learning endoscopic vitrectomy include having the right orientation,

**How 3-D Endoscopic Vitrectomy Can Fit in Three Practice Scenarios**

**For Experienced Surgeons.** Many experienced surgeons have tried endoscopy in the past and given up because of its difficulties. Now seems to be a friendlier time to give it another try. The more experienced surgeons embrace the technology, the more companies will be willing to invest on the field, and the more likely that endoscopy becomes a routine procedure in university-based hospitals. And the better the technology gets, the safer and more efficient it becomes, even for ambulatory surgical centers.

**For Teaching Surgeons.** The 3-D digitally assisted systems are ideal for teaching institutions. Attendings can control the cursor on the monitor and show exactly where he/she wants the fellows/residents to be. For the fellows first trying endoscopic vitreoretinal surgery, we recommend starting with silicone oil removal. Many times after we remove silicone oil, even after sequential fluid-air exchanges, multiple residual oil bubbles remain trapped behind the iris and on the anterior vitreous base. Endoscopy facilitates complete removal of all remaining droplets. Another clear advantage of this system is the video quality. What you see on the screen is what will appear in your video, always in focus.

**For Rising Stars.** If you are starting a vitreoretinal career or still in training, the surgical world is significantly better than it has been. Multiple high-quality vitrectomy machines and viewing systems are changing our field. This allows endoscopic vitrectomy to improve as well. The more frequently you get exposed to endoscopy, the more likely you are to learn during training or early in your vitreoretinal career. Many glaucoma services have endoscopy consoles for endocyclophotocoagulation, so the added cost is low.
being aware of the distance from ocular tissues and positioning the intraocular instruments. Traditionally during endoscopy, if the surgeon is struggling to find where the instruments are during the endoscopic view, one has to go back to the microscope to confirm the position or feel comfortable with the view. This takes a few seconds and annoys surgeons because of the need to readjust when they switch from the microscope to the endoscopy monitor and back.

However, the split-screen feature can allow the surgeon to skip this step because this information is readily available at any time during the surgery. Using the Ngenuity cursor, you can activate the split-screen feature, allowing simultaneous viewing of endoscopy and a wide-field 3-D image (Figure 3). In addition, new Ngenuity Datafusion software integrates the Constellation Vision System (Alcon), which allows surgeons to track key data parameters (intraocular pressure, flow rates, infusion pressure and laser power) in real-time, and offers additional functionality that allows for customization.

Using 2-D viewing in a 4K, 3-D platform substantially improves image quality and allows a better detection of tissue planes despite the inherent limitations of fiber optics in a small-gauge probe, although the stereopsis doesn’t change. The lighting systems in endoscopy tend to cause glare, although digital image enhancement can reduce the glare and confer additional advantages to this system.

Looking Ahead

The application of a 3-D digitally assisted imaging system to vitreoretinal surgery is one of the latest and most promising advances in our field. Combining improved image performance with technologies such as endoscopic vitreoretinal surgery, intraoperative OCT and video overlay features should help improve surgical precision and, ultimately, outcomes for our patients.

REFERENCES

Since they first emerged in retinal surgery in the late 1980s, perfluorocarbon liquids have become an integral part of our management of complex rhegmatogenous retinal detachments with proliferative vitreoretinopathy or giant retinal tears. More recently, PFCLs have acquired additional, versatile roles in retinal surgery. Here, we provide pearls that we have picked up in training fellows to use PFCLs safely and effectively, and then also explore alternative uses of this versatile fluid.

PFCLs are optically clear and have a specific gravity greater than balanced salt solution (BSS) as well as tensile properties similar to silicone oil but with lower viscosity. These properties enable flattening of the retina, unrolling of folds, drainage of subretinal fluid, manipulation of tissues under the liquid and application of endolaser while maintaining good visualization, stabilization of the peripheral retina, and easy injection and removal.

**PFCL Pearls for Retinal Detachment Repair**

**How to Fill**

Prior to filling, we make sure that all traction, especially over breaks, has been relieved. We prefer to use a dual-bore cannula to inject PFCL while maintaining a constant intraocular pressure. Alternatively, a single-bore cannula can be used while aspirating fluid through the second trocar with the vitrector or soft tip.

We begin by filling the eye over the attached retina and then fill toward the detached retina (Video). We make sure to aim the cannula away from the fovea when starting the PFCL bubble because too vigorous of an infusion can cause damage to the photoreceptors and commotio retinae, or can open a macular hole.

**ABOUT THE AUTHORS**

Drs. Yannuzzi (top) and Lin are vitreoretinal surgery fellows at Bascom Palmer Eye Institute at the University of Miami School of Medicine.

Dr. Sridhar is an assistant professor of clinical ophthalmology at Bascom Palmer Eye Institute.

**DISCLOSURES:** The authors have no relevant financial relationships to disclose. Dr. Sridhar is a consultant for Alcon, Allergan Sciences and Allergan.
We try to maintain the cannula in the center of the PFCL bubble when enlarging it to avoid fish eggs. After filling with PFCL, a nice surgical plane may develop to complete a shave of the vitreous base if it hasn’t been performed already. Authors have described accomplishing this by staining with preservative-free triamcinolone acetonide after instilling PFCL to create a vitreous sandwich between a plane of PFCL posteriorly and BSS anteriorly.5

How to Drain
We prefer to fill the PFCL to the most posterior retinal break. Next, we perform a fluid-air exchange while draining from the break. This technique “sandwiches” any residual fluid between the air meniscus and PFCL meniscus (Figure 1). Once the break is dry, we completely remove the PFCL and laser under air. Another option is to fill the PFCL up to the ora serrata and then laser under the PFCL. However, this maneuver requires an anterior break (or a more anterior edge cut to a posterior break) to prevent retained subretinal fluid (Figure 1). It’s important to note that PFCL drainage may result in trapped subretinal fluid, especially if the SRF is chronic. To facilitate maximal drainage, we rotate the eye to allow the break to assume the most gravity-dependent area.

How to Minimize Risk Of Subretinal PFCL And Safely Remove It
Breaks with active traction can act as a sink for PFCL, so we also make sure to relieve any traction before filling and shaving the vitreous gel alongside the bubble. An ophthalmic viscoelastic device (OVD) can also be used to cover retinal breaks while instilling PFCL to prevent subretinal migration in the so-called “soft-shell technique.”

Fish eggs are a risk factor for subretinal migration, and we try to avoid them in several ways. First, in the case of large retinal breaks we prefer to instill the PFCL through the trocar on the contralateral side to avoid inadvertently introducing bubbles directly into the break. While having an assistant apply depression during shaving at the edge of PFCL, we begin and end the depression slowly and gently to avoid turbulence from rapid changes in the infusion that can cause movement of PFCL into a break.

When removing PFCL, place the tip of the aspirating instrument just within the edge of the PFCL bubble. We teach fellows to maintain a negative pressure gradient on the syringe after filling and after extrusion when exiting the eye to prevent inadvertent dripping of PFCL bubbles from the instrument, especially over the break. During removal of PFCL, this can also be achieved by using a back flush under passive aspiration when entering and exiting the eye. After removing PFCL at the end of the fluid-air exchange, instilling a few drops of BSS over the optic nerve

Figure 1. Our technique for perfluorocarbon liquid-assisted drainage in rhegmatogenous retinal detachment involves the following steps: A) Fill the PFCL to the most posterior retinal break then perform a fluid-air exchange while draining from the break, “sandwiching” any residual fluid between the air meniscus and PFCL meniscus. B) In the case of a posterior break with extension of anterior fluid, filling PFCL over the break may result in trapping anterior fluid, so one option is to make another retinotomy more anteriorly and then fill to the most anterior iatrogenic break and drain from it. C) In the case of an anterior break located near the ora serrata, PFCL can be filled up to the break without trapping anterior fluid.

Take-home Point
Perfluorocarbon liquids are a wonderful surgical tool. When applied safely in the proper situation, their use can result in favorable surgical outcomes. First used in surgery for rhegmatogenous retinal detachments with proliferative vitreoretinopathy or giant retinal tears, PFCLs have taken on more versatile uses ranging from silicone-oil exchange to macular hole repair. This article provides tips that will help the retinal surgeon maximize efficiency and reduce complications.
as a “rinse” helps to ensure that no retained vitreous bubble occurs.

**Retained PFCL; Now What?**

PFCLs can become retained in the anterior chamber and subretinal space (Figure 2). PFCL that has migrated to the anterior chamber can cause visual symptoms, corneal failure and glaucoma. To remove it, a 27-gauge needle can be inserted through the limbus inferiorly and aspirated. Within the retina, PFCL remnants may cause intraocular toxicity, chronic inflammation and decreased retinal sensitivity.7

Histopathologic studies have documented macrophages engorged with intracellular vacuoles containing PFCL.8 Subretinal PFCL, when left in the eye for a long duration, may also lead to formation of a retinal hole.9,10 When seen postoperatively and visually significant, submacular PFCL may be displaced by making an inferior retinotomy and injecting BSS through it to form a focal retinal detachment. This allows the fluid to communicate with the retained PFCL. You can then perform a fluid-air exchange to remove the bubble followed by upright head positioning.11

Alternatively, authors have also described direct aspiration of the subretinal PFCL bubble using a 41-gauge needle transretinally.12 Intraoperatively, optical coherence tomography can be used to assist in visualization of retained PFCL and to insure its complete removal.13

**Alternative Uses of PFCL**

**Direct PFCL-to-Silicone Oil Exchange**

You may use direct PFCL-to-silicone oil exchange in certain situations with retinal instability, such as a giant retinal tear and retinectomy. To reduce the likelihood of retinal slippage, you can instill PFCL to flatten the retina, after which the infusion line may be connected to a 25-ga oil-infusion cannula and inserted by an assistant, while using the light pipe in one hand and the extrusion line under passive aspiration in the other hand to remove the PFCL as the oil infuses. If operating without an assistant, you can use a chandelier and the 25-ga oil-infusion kit in one hand with the extrusion in the other.14

**Lens Fogging**

You may encounter lens fogging following the air-fluid exchange, particularly in silicone intraocular lenses. Filling the eye with PFCL to the lens can remove fogging, and laser can be added directly under PFCL.

**Ocular Trauma**

You can use PFCL to float up a dislocated crystalline lens, dislocated intraocular lens or nonmetallic intraocular foreign bodies.15 PFCL can also help to stabilize metallic foreign bodies, making removal easier.

A cushion of PFCL can also deflect foreign bodies from damaging the posterior pole if dropped during removal.16 A dislocated crystalline lens can be floated anteriorly using PFCL, allowing for a cushion to pro-
tect the posterior pole from damage that ultrasound energy, dissipated from the fragmatome, can cause—and also to inhibit subretinal migration of lens fragments. PFCL can also provide countertraction to allow for extraction of foreign bodies enveloped by retina.

**Macular Holes**

PFCLs can provide a useful interface for endolaser and peeling. However, certain situations may present challenges. For instance, in cases of rhegmatogenous retinal detachment with concurrent macular holes (MH), regrasping an inner limiting membrane flap that is raised and peeled may be difficult because the PFCL bubble will flatten the flap as soon as it is dropped.

Recently, Chirag D. Jhaveri, MD,17 described a novel approach in which a perfluorooctane marble is injected and moved over the macular hole, then the ILM is peeled around it under BSS. This prevents the PFCL bubble from inhibiting flap regrasping but still provides adequate countertraction.

**REFERENCES**

When we encounter a tractional retinal detachment in a patient with diabetes, we must consider if and when to proceed with surgery. Here, we explain our technique.

Performing macular optical coherence tomography is invaluable in assessing the foveal status and membrane extent. Ongoing OCT imaging during follow-up is efficient and can detect TRD progression. Extramacular/extrafoveal TRDs can be observed closely because only about 15 percent of cases progress to the macula in one year, and 21 to 24 percent do so in two years.1 However, very close monitoring is vital because even transient macular detachments may result in permanent visual loss,2,3 and progression to a combined tractional-rhegmatogenous retinal detachment will reduce surgical success rates and visual outcomes.4

Planning the Operation
When deciding upon surgery, the surgeon must consider the status of the fellow eye, paying particular attention to potentially progressive TRD. In eyes with diabetic TRDs that have undergone vitrectomy, approximately one-third of fellow eyes will also require a vitrectomy for worsened TRD by three years.5 Finally, while considering and discussing with the patient any potential surgery, it’s important to convey the realistic goals and expected outcomes, including risks of complications. While an operation may be technically and anatomically successful with retinal reattachment, preexisting macular ischemia may prevent vision from improving postoperatively.

- Low threshold for previtrectomy cataract surgery. A good surgical view is crucial for these complex cases, given that close peeling to the retina is necessary. Thus, we have a low threshold for cataract surgery prior to vitrectomy, and we try to avoid combined phacoemulsification/vitrectomy for...

**ABOUT THE AUTHORS**

Dr. Skondra is an assistant professor of ophthalmology, specializing in vitreoretinal diseases and surgery, at the University of Chicago department of ophthalmology and visual science. She is also the director of the J. Terry Ernest Ocular Imaging Center at the University of Chicago.

Dr. Schechet is a second-year surgical vitreoretinal fellow at the University of Chicago department of ophthalmology and visual science.

DISCLOSURES: The authors have no financial relationships to disclose. The article discusses off-label use of bevacizumab (Avastin, Roche/Genentech), triamcinolone and systemic steroids.
long, complex TRD cases. We ask the cataract surgeon to make a large capsulorhexis, place a three-piece intraocular lens in the bag to ensure stability under air and with gas tamponade, do a thorough posterior capsule polish and suture the main wound.

- **Evaluate systemic status.** It’s important to assess and optimize the systemic status of these often-ill diabetic patients before surgery. The mean survival from time of TRD diagnosis is 2.7 years with a 48.7-percent mortality rate at 10 years. These long and complex surgeries frequently require general anesthesia, so preoperative clearance from the primary-care provider and anesthesia are necessary. Also, pre- and perioperative control of diabetes and hypertension decreases the risk of ocular and systemic complications.

- **Preoperative PRP, bevacizumab.** Planned preoperative panretinal photocoagulation and intravitreal bevacizumab (Avastin, Roche/Genentech) can aid in surgical success. Applying PRP in an attached peripheral retina a few weeks before surgery is helpful as it prevents TRD progression and vascularity, decreases operative time and reduces postoperative inflammation.

We also routinely use intravitreal bevacizumab two to four days before surgery to minimize intraoperative bleeding. One should be prudent and first obtain preoperative medical clearance. A meta-analysis found that pretreatment with anti-VEGF was associated with decreased intraoperative bleeding, iatrogenic retinal breaks, silicone-oil use and need for relaxing retinotomies. It has also been shown to reduce operative times.

### Figure 1
Repeated staining of residual hyaloid with triamcinolone after membrane peeling helps to visualize any residual hyaloid remaining after peeling.

### Intraoperative Steps

- **Location of the port.** Small-gauge vitrectomy (23-, 25- or 27-gauge) is now the norm for diabetic TRD repair. The proximity of the port to the tip allows better maneuverability and cutting ability of these very adherent fibrovascular membranes (FVMs) to the retina. A recently described hybrid system works very well using a 27-ga vitrector handpiece with 23-ga sclerotomies.
- **Maintain a clear view.** Maintaining a clear view during the case is vital. We apply 50% dextrose on the cornea followed by a layer of viscoelastic. We find this keeps the cornea clear much longer than using conventional viscoelastic alone. Contemporary wide-angle, noncontact viewing systems provide excellent peripheral visualization. A high-magnification macular contact lens can be useful when performing delicate macular peeling.
- **Triamcinolone to visualize FVM dissection.** Following the core vitrectomy and releasing 360 degrees of anterior-posterior vitreous traction, attention is directed to the posterior pole. Inducing a posterior vitreous detachment (PVD) is almost always impossible due to extensive and tightly adherent FVMs, so the posterior hyaloid is peeled and separated during FVM dissection and can be visualized better with triamcinolone staining. If you don’t look for residual hyaloid, you won’t find it. So, near the end of the surgery, after membrane peeling, we recommend repeat staining of any potential residual vitreous with triamcinolone.
- **Removal of FVMs.** Patience and persistence are required for meticulous removal of FVMs. The ultimate goal is to relieve all tractional forces from the retina using triamcinolone staining.

### Take-home Point
Diabetic tractional retinal detachments are severe and complex sequelae of proliferative diabetic retinopathy. Diabetic TRDs are among the most technically challenging scenarios for a vitreoretinal surgeon. All diabetic TRDs, as well as diabetic patients, are not the same. Therefore, these cases require extra time for planning. In this article, the authors describe their approach when they encounter TRDs.
techniques such as segmentation and delamination\textsuperscript{11} and “lift and shave.”\textsuperscript{12} Leaving residual pegs of fibrovascular tissue is usually acceptable as long as the associated traction is relieved. Sometimes FVMs are too adherent and inseparable from the retina and traction cannot be released, so a focal retinectomy can be considered.

\begin{itemize}
  \item **Finding safe planes to begin FVM dissection.** Preoperative planning comes into play here. Analyzing the OCT may aid in finding safe potential planes to begin the FVM dissection. Starting by the optic nerve, move in an “inside-out” approach. Gently perform dissection of the fibrovascular tissue from the nerve.
  \item **Segmentation and delamination.** Once a plane is created, carry out segmentation and delamination with utmost care. Sometimes a bimanual approach, using lighting from a chandelier or lighted instruments, is helpful. Often more tools, in addition to the light and cutter, are needed. These can include the delaminating blunt spatula, internal limiting membrane forceps, flex loop and curved horizontal or vertical pneumatic membrane peeler-cutter scissors (Figure 2).
\end{itemize}

**Managing Potential Problems During Surgery**

\begin{itemize}
  \item **Bleeding.** Even with thorough preoperative planning, intraoperative bleeding can be cumbersome. Make sure to meticulously stop all bleeding foci as early as possible with gentle endodiathermy, endolaser and elevating intraocular pressure as needed.
  \item **Avoiding and managing iatrogenic breaks.** In nonrhegmatogenous diabetic TRDs, avoiding iatrogenic breaks is crucial, because these require a more aggressive approach and carry a worse long-term prognosis, including the possible development of proliferative vitreoretinopathy (PVR). If breaks occur, it’s imperative to relieve all surrounding traction and membranes, or make a focal retinectomy of surrounding inseparable plaques when peeling is not possible. In a few cases with large FVM plaques around breaks combined with PVR and vitreous base contraction, large (90 to 180 degrees) retinectomies and scleral buckle placement may be needed to release traction successfully. Demarcate all breaks with gentle endodiathermy to ensure they are found and lasered accordingly after air-fluid exchange.
  \item **Air-fluid exchange around breaks.** After completing membrane dissection and ruling out any residual hyaloid, perform an air-fluid exchange followed by PRP and laser retinopexy around breaks. It’s much easier to laser the peripheral anterior retina in the operating room as opposed to the clinic, so this is a great time to ensure good peripheral laser is completed all the way to the ora serrata. We like to use flexible, curved, endolitinated laser probes because they allow us to deliver anterior PRP while performing scleral depression.
  \item **Gas with face-down positioning.** At the end of the case, whether we encounter breaks or not, we like to use long-acting 14% or 16% perfluoropropane (C3F8) gas tamponade with prolonged face-down positioning of two to three weeks duration. We reserve silicone oil for very rare cases that need an extensive and large inferior retinectomy (about 5 percent of cases). This gas tamponade/face-down positioning approach has provided excellent results in one study of 89 consecutive, complex diabetic TRD cases amongst our team:\textsuperscript{13} an approximately 98-percent primary reattachment rate with a single surgery, and less than 2 percent secondary retinal detachments in complex cases.
  \item **Gas with face-down positioning provides tamponade of possible undetected iatrogenic or laser-induced microbreaks while PRP scars are forming.** Furthermore, in one study gas tamponade eliminated postoperative vitreous hemorrhage (VH) vs. a 17-percent VH rate in cases without it.\textsuperscript{14}
\end{itemize}

**Postoperative Care**

\begin{itemize}
  \item **Role of postoperative steroids.** At the conclusion of the case we frequently treat the patient with steroids to prevent postoperative fibrin and the inflammatory cascade, especially in cases with significant intraoperative PRP, membrane peeling and a long case duration. In addition to sub-Tenon’s triamcinolone, we ask anesthesia to give 125 mg of intravenous solumedrol if the patient’s blood-sugar levels are controlled, followed sometimes
by an oral dose of prednisone in the postanesthesia care unit.

- **Monitor for sequelae.** We follow these patients very closely postoperatively, monitoring for possible redetachment, recurrent VH, fibrinoid syndrome and anterior hyaloid proliferation, neovascular glaucoma and progressing cataract. Recurrent VH following diabetic TRD repair is a common complication occurring in 16 to 43 percent of cases, with approximately 5 to 10 percent requiring a vitrectomy washout.\(^{15,16}\)

- **Address patient expectations.** Lastly, the follow-up visits are important opportunities to maintain the patient’s expectations, because visual-acuity results can be highly variable.

### Extra Effort is Priceless

Repairing diabetic TRDs is extremely complex and time-consuming, but this carefully planned and executed surgical approach can result in excellent outcomes (Figures 3 and 4). While these cases all have the same underlying disease process, each TRD and patient is unique. A personalized care plan is necessary. Improvements in the evolution of small-gauge vitreoretinal instrumentation, along with a continually growing base of knowledge and novel techniques, keep improving the success rates of these difficult surgeries.

As we’ve described, managing and treating diabetic TRDs is a long-term process encompassing the preoperative, intraoperative and postoperative periods, but the extra effort is priceless for providing good vision and hope for these sick diabetic patients. 😊

### REFERENCES


The advent of panretinal photocoagulation has helped to significantly reduce the risk of vision loss secondary to proliferative diabetic retinopathy. Recent trials have shown that intravitreal anti-VEGF therapy has a comparable, if not superior, treatment effect on PDR compared to PRP. However, both therapies require consistent post-treatment follow-up.

Although studies have evaluated adherence to dilated fundus examination regimens established for diabetic patients, limited data exists on loss to follow-up (LTFU) after treatment among these patients. Therefore, we conducted a study, recently published in the journal Ophthalmology, that sought to evaluate LTFU after either PRP or anti-VEGF therapy for PDR and identify key independent predictors of LTFU. Here, we report on what the study revealed about patients who don’t return for follow-up after treatment.

**Study Findings**

Our final analysis included 2,302 patients, of whom 1,272 (55.3 percent) received PRP and 1,030 (44.7 percent) received anti-VEGF treatment. The mean (standard deviation [SD]) number of PRP sessions was two (+1.3), and the mean number of intravitreal anti-VEGF injections given was 3.8 (+4.5). There were 584 (25.4 percent) patients LTFU immediately post-treatment and 1,718 (74.6 percent) that followed up within 12 months.

**Risk Factors of LTFU**

We observed several risk factors that were significantly associated with LTFU.

- **Type of procedure.** The first risk factor observed was the type of procedure, with 356 patients (28 percent) who received PRP and 228 (22.1 percent) who received anti-VEGF therapy lost to follow-up post treatment ($p=0.001$).

  One can postulate the higher rate observed in the PRP group is secondary to selection bias, because physicians are more likely to attempt to select patients who they think would be compliant for anti-VEGF therapy. This appears to partially account for the disparity, as the effect of the procedure on LTFU odds...
Take-home Point

Both panretinal photocoagulation and anti-VEGF therapy have proved effective for treating proliferative diabetic retinopathy, but both require patients to return to the office for follow-up visits. However, about one-quarter of patients are lost to follow-up. In this article, the authors report on their recent published studies that identified potential risk factors among patients who tend to have higher rates of loss to follow-up.

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Cl = confidence interval; LTFU = loss to follow-up.

have a more pronounced disparity in LTFU rates when compared to higher incomes for patients younger than 65. Indeed, this is what the study observed, with significant differences in LTFU rates between age groups for regional adjusted gross incomes of ≤$40,000 ($=0.02) and $41,000 to $80,000 ($=0.04), but not for incomes of over $80,000 ($=0.62) (Figure). We also hypothesized that this may be due to the amount of time patients have available to see doctors; older individuals are much less likely to have a full-time job.

- **Race.** African-Americans had significantly higher LTFU rates (30.2 percent) than whites (19.4 percent) and Asians (19.7 percent) ($<0.001).

The evidence regarding the association of race and compliance with follow-up remains inconclusive, with conflicting findings from different studies.4,7,8 Underlying etiologies that contribute to the differences in LTFU rates may include distrust in the healthcare system,9 access to insurance coverage and time.10 However, the number of social and environmental factors involved may render such an evaluation difficult.

Interestingly, we also observed an increase in LTFU rates in patients who refused to identify their race (34.9 percent). We believe this may represent a psychosocial component, and these patients may be more skeptical of the healthcare system.11,12 Given that our analysis only included a subgroup of patients with accessible medical records, the lack of a difference may be secondary to sample size. However, other studies also appear to present conflicting findings on the role of VA in LTFU,11,12 although these studies evaluated different diseases and used different definitions of LTFU.

Moreover, there did not appear to be a difference in baseline VA by follow-up status in the Diabetic Retinopathy Clinical Research Network Protocol S five-year follow-up results.13 Therefore, we will need further studies to validate the true role of VA on LTFU rates.

Contrary to our expectations, VA did not appear to play a significant role in LTFU rates. LTFU rates for eyes with ≥20/40, 20/50 to 20/200, and <20/200 VA at the final procedure before LTFU were 15 percent, 18.8 percent and 16.5 percent, respectively ($=0.37, n=920).

Given that our analysis only included a subgroup of patients with accessible medical records, the lack of a difference may be secondary to sample size. However, other studies also appear to present conflicting findings on the role of VA in LTFU,11,12 although these studies evaluated different diseases and used different definitions of LTFU.

Our study was conducted as a retrospective cohort study at the Wills Eye Hospital Retina Service and Mid Atlantic Retina clinics located across Pennsylvania, Delaware and New Jersey. We identified patients receiving either panretinal photocoagulation or intravitreal anti-VEGF therapy between January 1, 2012, and April 20, 2016. The study excluded patients who:

- had received both treatments in the study period;
- lived outside of the tristate region of our practice; or
- had died.

The study gathered potential risk factors of patients who were lost to follow-up. They included: procedure type, age, gender, race (reported by the patient at clinical registration), regional adjusted gross income and distance to clinic.

For a subgroup of patients with accessible visual acuity measurements, VA was obtained on the first and final procedure. For patients with bilateral disease, the eye with better VA was used in the analysis.

## Role of Visual Acuity

Figure. Change in loss to follow-up (LTFU) rates by age over approximately four years stratified for regional average adjusted gross income. (Used with permission Elsevier Science and Technology Journals. Obeid A, Gao X, Ali FS, et al. Ophthalmology. 2018;125:1386-1392.)
Factors That Hinder Follow-up

Our study results demonstrated that more than 20 percent of patients with PDR were LTFU after at least one treatment session over a four-year period. Although limited evidence exists on LTFU rates in patients with PDR, previous studies have documented high rates of noncompliance with recommended guidelines in diabetic patients. For example, although patients with diabetes require at least one dilated fundus exam annually (as the practice guidelines recommend), more than a fourth of patients have a year or less with a documented dilated fundus exam over four consecutive years of follow-up. Patients with DME have also shown high noncompliance with follow-up rates in Europe. More recently, the five-year results of the Protocol S trial showed that approximately 40 percent of patients were LTFU from both groups over the duration of the trial. This is particularly concerning, as we would expect that patients who agree to take part in such trials are generally more concerned with their disease and more likely to be motivated to comply with follow-up recommendations.

LTFU rates become even more relevant when we consider the potential sequelae secondary to LTFU stratified by treatment selection. Another study we recently published reported that eyes LTFU post-panretinal photocoagulation therapy fare much worse, both anatomically and functionally, when compared to eyes that received PRP. A final important point to consider is that patients with PDR, Studies have shown high mortality rates in the patients that received PRP in the early

How the Study Defined Loss to Follow-up

To evaluate follow-up status, the study measured the interval between each procedure and the subsequent follow-up visit. Loss to follow-up (LTFU) was defined as more than 12 months between the two. Patients with multiple procedures required only one interval of greater than 12 months to be considered LTFU.

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When Blindness Induces Hallucinations

In Charles Bonnet syndrome, patients know the images they see are not real. Its prevalence is growing. By Haley Monson, Esther Gonzalez, PhD, Luminita Nister-Taroto, PhD, and Mark Mandelcorn, MD.

Charles Bonnet syndrome is a common although rather obscure and under-researched condition that is becoming ever more prevalent as the population ages and people live longer. It causes intricate, life-like and recurring hallucinations in patients who have significant vision loss, especially in those diagnosed with macular degeneration, diabetic retinopathy or glaucoma.

Charles Bonnet first described the syndrome that bears his name in the 18th century. He had observed such hallucinations in his 87-year-old grandfather, who had almost complete vision loss in both eyes due to glaucoma, and yet perceived women, children, buildings, geometric patterns, scenes and physically impossible circumstances. He saw that his grandfather was cognitively well, and concluded that the hallucinations were a result of his vision loss.1

Etiology of Bonnet Syndrome

Charles Bonnet syndrome can affect any person of any age. However, the affected population is predominantly older because vision loss is more common in this age group.

As causes of blindness became more clearly differentiated, cases of Charles Bonnet syndrome were separated into the group of macular disease. The prevalence of Charles Bonnet syndrome among patients with vision loss has been estimated at 10 to 38 percent.1 Differing definitions of the syndrome, as well as patients’ unwillingness to report symptoms for fear of being labeled as mentally incompetent, may explain the wide range in the reported incidence.

Charles Bonnet is by no means a mental illness, nor is it a symptom of neurological disease. The images Charles Bonnet sufferers see are nonpsychotic hallucinations. While the experience is involuntary, the person experiencing the phenomenon recognizes that it is not the product of external stimuli and is not real.2 This differentiates it from a hallucination experienced as a result of mental illness, in which the person does not perceive the images as imaginary.

Hallucinations of Charles Bonnet patients can range from simple images, such as colored patterns, to complex scenes, such as children playing. Patients are often able to vividly describe and recall the images, which is highly characteristic of Charles Bonnet syndrome (Figure).1

Brain ‘Sees’ What Eyes Don’t

Medical experts have speculated about the causes of Charles Bonnet syndrome hallucinations, but the consensus is that the brain is reacting to a lack of visual input. As one experiences vision loss, the brain will continue to interpret visual data, even without corresponding visual input. Lacking that input, the brain will invent images, and visual brain cells will begin to fire spontaneously in order to compensate for lack of visual data. As the brain adjusts to the vision loss, the frequency of the hallucinations will wane and eventually cease entirely.3

A study in which 13 normally sighted and mentally healthy subjects were blindfolded for five consecutive days supports this theory. After one day, 10 of the patients reported visual hallucinations, ranging from simple to complex.4

Similar effects to Charles Bonnet syndrome can be seen in a number of conditions affecting the elderly. An estimated 36 percent of those with Parkinson’s disease have experienced hallucinations. Parkinson’s patients experiencing hallucinations will also have insight into the nature of the images, suggesting that such hallucinations have aspects in common with Charles Bonnet syndrome.5

Hallucinations are also prominent in a number of psychiatric illnesses, such as bipolar disorder and psychosis. They can be triggered by drug or alcohol use. Patients in withdrawal often experience hallucinations. Those who have hallucinations that arise from a mental illness or drug use do not have insight into their nature, another characteristic that differentiates them from hallucinations in Charles Bonnet syndrome.

View the Video
“Everywhere I walk I see disembodied gargoyle heads,” is how one patient with Charles Bonnet Syndrome described her hallucinations. (Image courtesy of Macular Society)

‘Phantom Vision Syndrome’

Charles Bonnet syndrome is also known as “Phantom Vision Syndrome,” and can be grouped in with a number of other “phantom” conditions that occur when the body loses one of its parts or functions. The most famous of these is phantom limb syndrome, whereby the loss of a limb causes a patient to experience sensations in the lost appendage. The sensations can include light touch or even pain, and patients with this syndrome often have a sense of weight or movement in their phantom limb. The prevalence of this syndrome is astonishing, with an estimated 49 to 88 percent of amputees having experienced it. Perhaps the most parallel condition to Charles Bonnet Syndrome is paracusis, or auditory hallucination, in deaf or hearing-impaired people. These conditions have helped in determining the cause of Charles Bonnet syndrome. The same mechanism causes all of these conditions: the brain’s reaction to a lack of information from a sense or limb.

The literature on Charles Bonnet syndrome is meager. Most of the published research in this area has been primarily descriptive. Investigative studies of issues that relate to visual perception, generally a subject for experimental psychologists, have not been published.

Our Research In Visual Perception

Our research group, composed of several full-time experimental psychologists and clinicians, has published the results of a number of visual perception studies in the ophthalmic literature on topics such as fixation stability following successful macular disease treatment and binocular and monocular fixation behavior in AMD. Most recently, our group has followed a number of patients with Charles Bonnet syndrome to try to more rigorously define the nature of their visual hallucinations from the perspective of visual perception abnormalities. We’re attempting to determine if the observed visual images change in relative size, and what might be the determinants of this phenomenon, or if they display “size constancy.” We hope to be able to shed new light on this condition, which has been known for more than 200 years and yet is still poorly understood.

The authors are with University Health Network, Toronto.

REFERENCES

Challenges With Silicone Oil Removal

Four scenarios that can help you determine the right coding for complicated cases.

The process of removing silicone oil following a complex retinal detachment typically occurs one of two ways: via vitrectomy; or aspiration without a vitrectomy. We receive periodic questions about the correct coding for this procedure. We are also asked about what ICD-10 code applies and if a modifier is needed. Here, we review those issues and provide direction.

**The Correct CPT Code**

There is ongoing confusion regarding the correct code to use to describe the removal of silicone oil. Retina specialists use silicone oil in cases of a chronic retinal detachment, proliferative vitreoretinopathy (scarring), advanced cases of diabetic retinopathy; macular holes and other disease processes that require long-term tamponade of the retina following vitrectomy. Silicone oil is injected into the eye following the vitrectomy and left in the eye until the surgeon determines the retina is stable.

The two most common codes used for removal of oil, without treatment of other pathology, are 67036 and 67121. The Current Procedural Terminology (CPT) Manual defines the two codes as:

- **67036** – Vitrectomy; mechanical, pars plana approach; and
- **67121** – Removal of implanted material, posterior segment; intraocular.

The question we receive is “Which CPT code best describes the work performed to remove the silicone oil?” When the situation is straightforward and removing the oil is the only procedure completed, the coding is easily determined by examining the technique the surgeon describes in the operative report. If the surgeon employs a pars plana vitrectomy to remove the oil, CPT 67036 is used. Conversely, if the surgeon removes the oil with aspiration and does not use the vitrector, consider 67121.

**Coding Complicated Cases**

However, patients are often more complicated, and the answers can vary with respect to CPT, diagnosis coding and modifiers. The rationale and timing for oil removal can help determine what ICD-10 code to use and the need for a modifier. Consider the following questions:

- Is oil removal a second stage of the primary procedure?
- Does a new problem necessitate the oil removal?
- Did the oil cause a complication for which removal is the solution?
- Is there a secondary problem (comorbidity)? If yes, is it complicated by the oil?
- Is the oil being removed in the global period of the retinal detachment repair?

The following four examples will shed some light on the best ICD-10 code and the need for any modifiers.

**Example 1: Staged Procedure**

Surgeons often plan to remove the oil as the eye approaches stability. However, the eye doesn’t reach stability until completion of the final staged procedure—silicone oil removal. From the patient’s perspective, the presence of silicone oil causes poor vision and is undesirable. The appropriate diagnosis code for the staged vitrectomy (or aspiration) to remove the silicone oil is the original diagnosis from the primary procedure.

Conflict and misunderstandings arise when chart notes (during the postoperative period of the primary procedure) state “retina stable” or “retina flat,” as if a satisfactory endpoint has been reached. The retina appears flat with an imperfect view through the oil when, in actuality, the treatment of the primary problem is neither complete nor successful until the oil is removed.

If the oil removal occurs during the postoperative period, append modifier -58 (staged procedure) to the procedure code. This modifier is unnecessary if removal takes place outside the 90-day postoperative interval, although the concept of a staged procedure still applies. The appropriate CPT codes are likely 67036 or 67121.

**Example 2: New Condition**

The patient returns four months after vitrectomy of the right eye with placement of silicone oil. The patient has developed a new epiretinal membrane. The surgeon recommends vitrectomy with ERM stripping as well as removal of silicone oil. The ICD-10 code H35.371 (Puckering of macula, right eye) is used on the claim. The silicone oil is removed during the vitrectomy/membrane peel, which is reported by CPT 67041 (PPV with removal of preretinal cellular membrane), so no separate charge is made for removal of the oil.

If the ERM stripping occurred during the 90-day global period, modifier -79 would apply since the procedure and condition are unrelated to the initial procedure. In addition, the

(Continued on page 49)
DRI OCT Triton: One Doctor’s Experience

The imaging platform provides more detailed information and eases workflow in this retina specialist’s clinic.

The Food and Drug Administration cleared the DRI OCT Triton imaging platform from Topcon almost a year ago, but at his clinic in Brazil, Daniel Lavinsky, MD, has been using the device for some time, and reports that it has helped to improve his workflow and decision-making by providing “almost every crucial information necessary for my diagnosis and therapeutic decision.”

Dr. Lavinsky, who practices at the Federal University of Rio Grande do Sul in Porto Alegre, Brazil, explains that Triton has improved the way he images the retina, “because it incorporates color fundus imaging, high resolution wide-field optical coherence tomography and OCT angiography to my clinical practice in a quick and objective way.” He notes that previous technologies he’s used could acquire either high-resolution scans or fast scans, but lacked OCTA until recently.

DRI OCT Triton Features

The DRI OCT Triton features a 1-µm, 1,050-nm light source with a scanning speed of 100,000 A-scans/second. It incorporates a built-in retinal camera, eye tracking for selected scans, OCT imaging, color, red-free, fluorescein angiography and fundus autofluorescence imaging with swept-source OCT.

Topcon also notes the DRI OCT Triton can visualize deeper pathology, penetrating the choroid and even the sclera, without being obscured by media opacities or hemorrhage. The DRI OCT Triton can visualize from the vitreous through to the sclera with high sensitivity and speed, the company says. The instantaneous capture of a high-density data cube, composed of 512 B-scans, reduces interpolation between slices, revealing imagery. The instrument also features wide-field OCT scanning (12 x 9 mm) with a reference database.

“The most striking advantage of SS-OCT is speed and depth,” Dr. Lavinsky says. “With Triton OCT, we are able to quickly acquire wide-field OCT with high-quality scans. And we are able to analyze the optic disc, macula and retinal vasculature with just one cube.”

Going to Greater Depth

He also notes that, in his experience, the Triton achieves greater depth than other OCT platforms he’s used. “With SS-OCT we are capable of acquiring high-resolution images of the vitreous down to the sclera with details that we were not able to get previously with other technologies,” Dr. Lavinsky says.

The instrument has also had an impact on his workflow. “It hastens and improves my workflow, since it provides posterior and anterior high-quality OCT scans, performs OCTA, autofluorescence and fluorescein angiography in one instrument, quickly and precisely,” he says.

Dr. Lavinsky also uses the IMAGEnet 6 software that enables dynamic viewing of the OCT data, providing two- and three-dimensional and fundus images simultaneously.

Triton also enhances viewing through media opacities. “It is very important to be able to view and image through media opacities such as cataract and vitreous hemorrhages, especially for deciding treatment of macular edema and before cataract surgery,” Dr. Lavinsky says.

He’s found Triton to be particularly helpful in managing chronic central serous chorioretinopathy, “since we now are able to detect the pachychoroidal spectrum, from epitheliotropathy through to choroidal neovascularization, with precision and without the need of intravenous contrasts.”

Dr. Lavinsky disclosed he is a consultant to Topcon.
Faricimab—the generic name for what was once known as RG7716—is the first bispecific antibody for intravitreal administration that targets two key factors that contribute to diabetic retinopathy and diabetic macular edema: vascular endothelial growth factor and angiopoietin-2, otherwise known as Ang-2.

The BOULEVARD Phase II trial showed that in treatment-naïve patients with DME, faricimab (Roche/Genentech) demonstrated statistically significant visual acuity gains and has potentially maintained disease stability longer than ranibizumab (Lucentis, Roche/Genentech). BOULEVARD enrolled 229 patients, 168 who were treatment-naïve, in three treatment arms: 0.3-mg ranibizumab (n=59); and 1.5- and 6-mg faricimab (n=55 and 55, respectively).

In presenting the BOULEVARD results in September at the Retina Society annual meeting in San Francisco, Carl Regillo, MD, of Wills Eye Hospital, Philadelphia, reported that the 6-mg faricimab group had an adjusted mean improvement of 13.9 letters at 24 weeks vs. 10.3 for ranibizumab (p=0.03).1 Patients on faricimab, whether treatment naïve or previously treated with anti-VEGF, were more likely to gain 10 letters or more in vision: 70.5 and 61.2 percent in the 6- and 1.5-mg faricimab groups, respectively, vs. 57.1 percent for the ranibizumab patients in the treatment-naïve group; and 65.2 percent in the faricimab 6-mg group vs. 42.9 percent of ranibizumab patients who had previous anti-VEGF treatment.

Results for patients who achieved ≥15-letter gains and central subfield thickness (CST) of ≤325 µm followed similar patterns. Here, Dr. Regillo, primary investigator of BOULEVARD, answers questions about the trial and the upcoming YOSEMITE and RHINE Phase III trials.

The mechanism of action of faricimab in his own words:

Faricimab is a single-molecule but has a dual mechanism of action, in that it blocks VEGF-A, which works very well for DME and DR, but it also blocks Ang-2, which has been shown to be upregulated with increased vitreous levels in DR. Ang-2 works through the TIE-2 pathway and is potentially detrimental because it promotes vessel breakdown, which, in turn, leads to the leakage and proliferation in DR.

How does faricimab differ from existing anti-VEGF agents?

Blocking VEGF works well in treating DME, but blocking the VEGF and Ang-2 together appears to work even better. In the BOULEVARD trial, the faricimab 6-mg dose showed better visual-acuity outcomes and macular drying along with improvement of DR levels compared to the gold standard of monthly injections of ranibizumab 0.3 mg.

Protocol P of the Diabetic Retinopathy Clinical Research Network study reported that aflibercept (Eylea, Regeneron) had better VA outcomes and drying effects than ranibizumab at one year, but the degree that was seen in BOULEVARD with faricimab
What are the most telling findings of the BOULEVARD trial?

One, to achieve better visual acuity in DME, you have reduce the macular edema. At 24 weeks, the faricimab 6-mg group had better drying of the macula with a much greater proportion of patients having DME resolution which translated into statistically significantly better visual-acuity outcomes.

Two, more faricimab-treated patients maintained visual acuity and central subfield thickness for a longer time frame in the off-treatment observation period, suggesting greater drug durability compared to the ranibizumab group. In the faricimab 6-mg and ranibizumab 0.3-mg groups, respectively, rates of BCVA loss exceeding 5 letters were 45 and 53 percent, and CST increase ≥50 mm were 43 and 73 percent at 14 weeks posttreatment.

Third, faricimab treatment resulted in a much higher percentage of two-or-more-step improvement in diabetic retinopathy severity. This was particularly impressive in eyes with a baseline diabetic retinopathy severity scale (DRSS) of 53 or more in which 88 percent of patients in the faricimab 6 mg arm had 2 or more steps of DRSS improvement compared to only 25 percent with the ranibizumab 0.3 mg arm at week 24.

How will the BOULEVARD findings inform the structure of the Phase III trial?

BOULEVARD was a well-designed, good-size Phase II trial, and we’re going into Phase III with a good level of confidence that it will show faricimab to have a good effect on DME. The YOSEMITE and RHINE studies will have 900 patients each and compare faricimab and aflibercept head to head. The trials will consist of three treatment arms: faricimab 6 mg every eight weeks; faricimab 6 mg on a personalized treatment interval; and aflibercept 2 mg every eight weeks—all after monthly loading dosing.

The personalized, or variable, treatment interval arm, which is like treat-and-extend, was added to tell us more about the durability of the drug.

REFERENCE


Challenges With Silicone Oil Removal

Example 3: Recurrent Condition

The patient had a retinal detachment with proliferative vitreoretinopathy. The surgeon performed a vitrectomy with membrane stripping with injection of silicone oil (CPT 67113). The patient recovered nicely, although the oil remained in the eye. Now, the patient presents with a recurrent retinal detachment and proliferative vitreal retinopathy four months postoperatively. The surgeon recommends another vitrectomy with membrane stripping.

Use the appropriate RD ICD-10 code (H33.-) along with CPT 67113. As in the second example, there’s no additional charge for the oil removal. If the recurrent RD develops during the 90-day global period, modifier -78 applies since the procedure and condition are related and the coding for the initial procedure was 67113.

Example 4: Complication

The patient develops a complication from the silicone oil, such as a spike in intraocular pressure not controlled with medical therapy, so the oil needs to be removed. While it may be tempting to use the same diagnosis as the primary procedure, as in the first example, the reason for removing the oil is the IOP spike secondary to its appropriate use, not the aforementioned retinal problem. According to ICD-10, an ocular surgical complication from an implant is coded as T85.398 (Other mechanical complications of other ocular prosthetic devices, implants and grafts). Any applicable secondary ICD-10 codes would also apply.

Conclusion and Further Reading

If only oil is being removed, the CPT coding is obvious. However, when considering other factors, such as global periods, complications, recurrence, comorbidities and/or new problems, the answers become complicated. Take your time and consider these scenarios to reach the correct answer. For a more detailed discussion regarding reimbursement for surgical procedures during the postoperative period, see the article “Avoiding Post-Surgical Modifier Confusion” (Retina Specialist, December 2017; available at www.retina-specialist.com/article/avoiding-post-surgical-modifier-confusion).

Mr. Mack is a senior consultant with Corcoran Consulting Group. He can be reached at 1-800-399-6565 or at www.corcoranccg.com.
BRIEF SUMMARY—Please see the EYLEA package insert for full Prescribing Information.

1 INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR) in Patients with DME

2 CONTRAINDICATIONS

- EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA.
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3 WARNINGS AND PRECAUTIONS

- 3.1 Endophthalmitis and Retinal Detachments
- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments (see Adverse Reactions (6.7)). Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, and therapy should be managed appropriately (see Drug Administration (2.5)) and Pharmacodynamics and Pharmacokinetics (4.5).

- 3.2 Thromboembolic Events
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as non-fatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in AMD studies during the first year was 3% (8/262) in the EYLEA group and 1% (2/182) in the control group. The incidence in the DME studies (including deaths of unknown cause) was 0.2% (3/1624) in the EYLEA group compared with 0.1% (2/1824) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the IVO studies.

4 ADVERSE REACTIONS

- The following potentially serious adverse reactions are described after the labeling:
- Hypersensitivity (see Contraindications (4.3))
- Endophthalmitis and retinal detachments (see Warnings and Precautions (3.1))
- Intraocular pressure increased (see Warnings and Precautions (3.2))

5 Clinical Trials Experience

- In clinical trials, the incidence of adverse reactions related to the injection procedure was similar in the clinical trials of patients treated with EYLEA and those in the control group. The most common adverse reactions (≥1% reported in patients receiving EYLEA and corresponding percentage in the placebo group) were:

6 ADVERSE REACTIONS

- Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

7 Less common adverse reactions reported in ≥1% of the patients treated with EYLEA were:

8 Adverse Reactions in >2% of the Patients Treated with 2 mg EYLEA in the IVO Studies

9 Table 2: Most Common Adverse Reactions (≥1%) in IVO Studies

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11 Issue Date: June 2017

Manufactured by:
Regeneron Pharmaceuticals, Inc.
77 Old Saw Mill River Road
Tarrytown, NY 10591

EYLEA is also available from other manufacturers.

REGENERON

12 DATA

- Data in this summary may have been updated since approval and are indicative of the drug and may not reflect the rates observed in practice.

13 There was a 2.3% (74/3251) reported incidence of injection-site pain in patients treated with EYLEA compared with 1.5% (47/3000) in the control group. There were no reported clinical injection-site reactions in the DME studies. The incidence of reported injection-site reactions in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies was 0.6% (17 out of 287) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported injection-site reactions in the IVO studies.

14 Adverse Reactions EYLEA

- Adverse Reactions in >2% of the Patients Treated with 2 mg EYLEA in the IVO Studies

15 Intraocular inflammation 1% 1% 0% 0%

16 Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

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The TDC cutter has a cut speed of up to 8000 cpm and is designed to facilitate cutting tissue on the return of each stroke of the vitrectome, effectively doubling the cut speed.

MAXIMIZING SURGEON CONTROL

Revolutionary Fluidics: Vacuum & Flow
TDC Cutter: up to 16,000 cpm*
Extensive range of 27G instruments

* The TDC cutter has a cut speed of up to 8000 cpm and is designed to facilitate cutting tissue on the return of each stroke of the vitrectome, effectively doubling the cut speed.
As demonstrated in phase 3 clinical trials evaluating BCVA,* as measured by ETDRS letters, in patients with Wet AMD, Macular Edema following RVO, DME, and by ETDRS-DRSS† in DR in Patients with DME,1 as well as your clinical experience

Start with EYLEA for proven efficacy outcomes1

Dosing driving efficacy outcomes across all indications.1

Learn more at EYLEA.us/dose

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS
EYLEA® (aflibercept) Injection is indicated for the treatment of patients with
• Neovascular (Wet) Age-related Macular Degeneration (AMD): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).
• Macular Edema following Retinal Vein Occlusion (RVO): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly).
• Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in Patients with DME: The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

CONTRAINDICATIONS
• EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS
• Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.

ADVERSE REACTIONS
• Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
• There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

Please see adjacent Brief Summary.

*Best-corrected visual acuity.

†Early Treatment Diabetic Retinopathy Study—Diabetic Retinopathy Severity Scale: an established grading scale for measuring the severity of DR.


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