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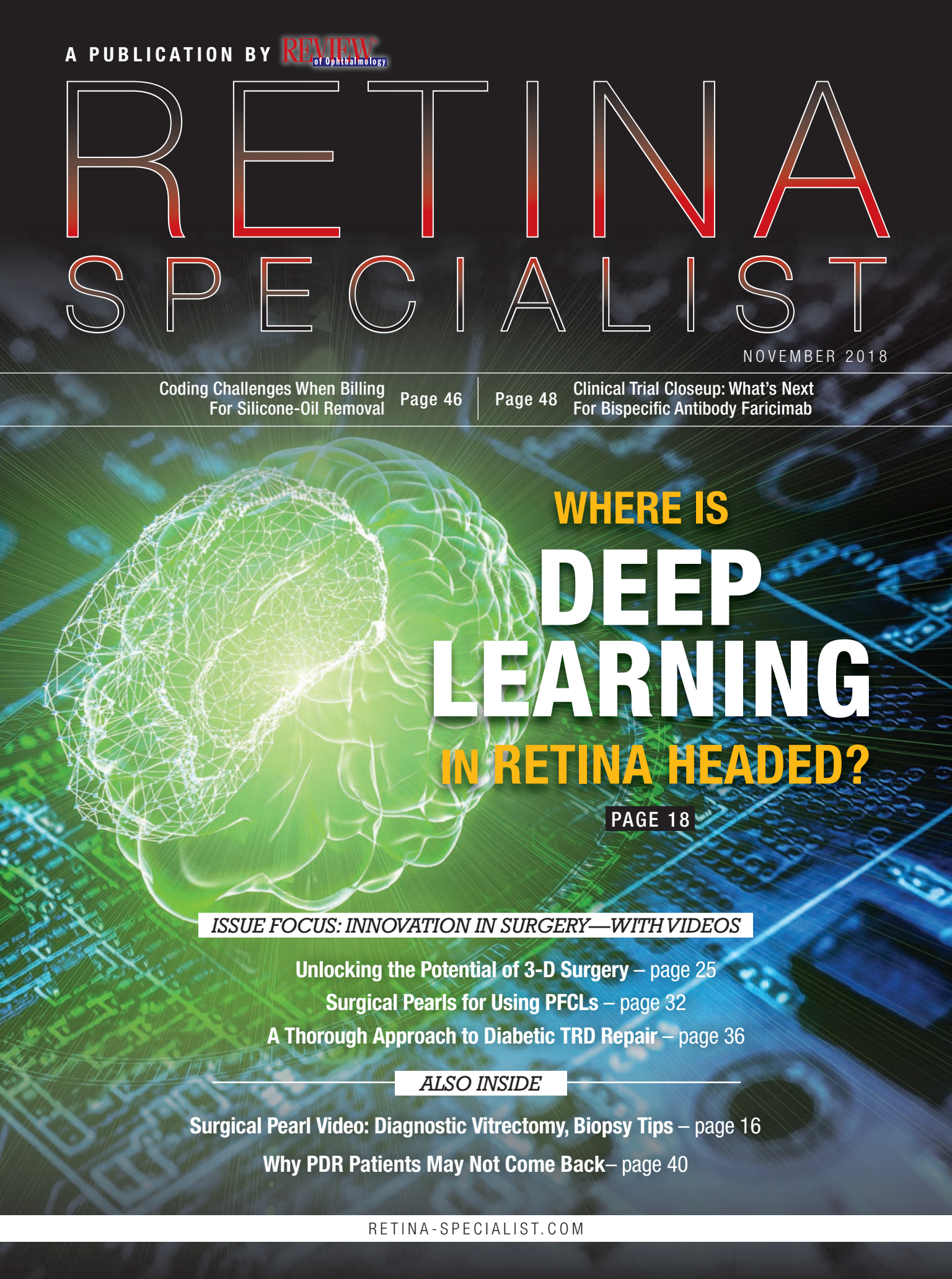
RETINA SPECIALIST

NOVEMBER 2018



WHERE IS DEEP LEARNING IN RETINA HEADED?

PAGE 18

ISSUE FOCUS: INNOVATION IN SURGERY—WITH VIDEOS

ALSO INSIDE

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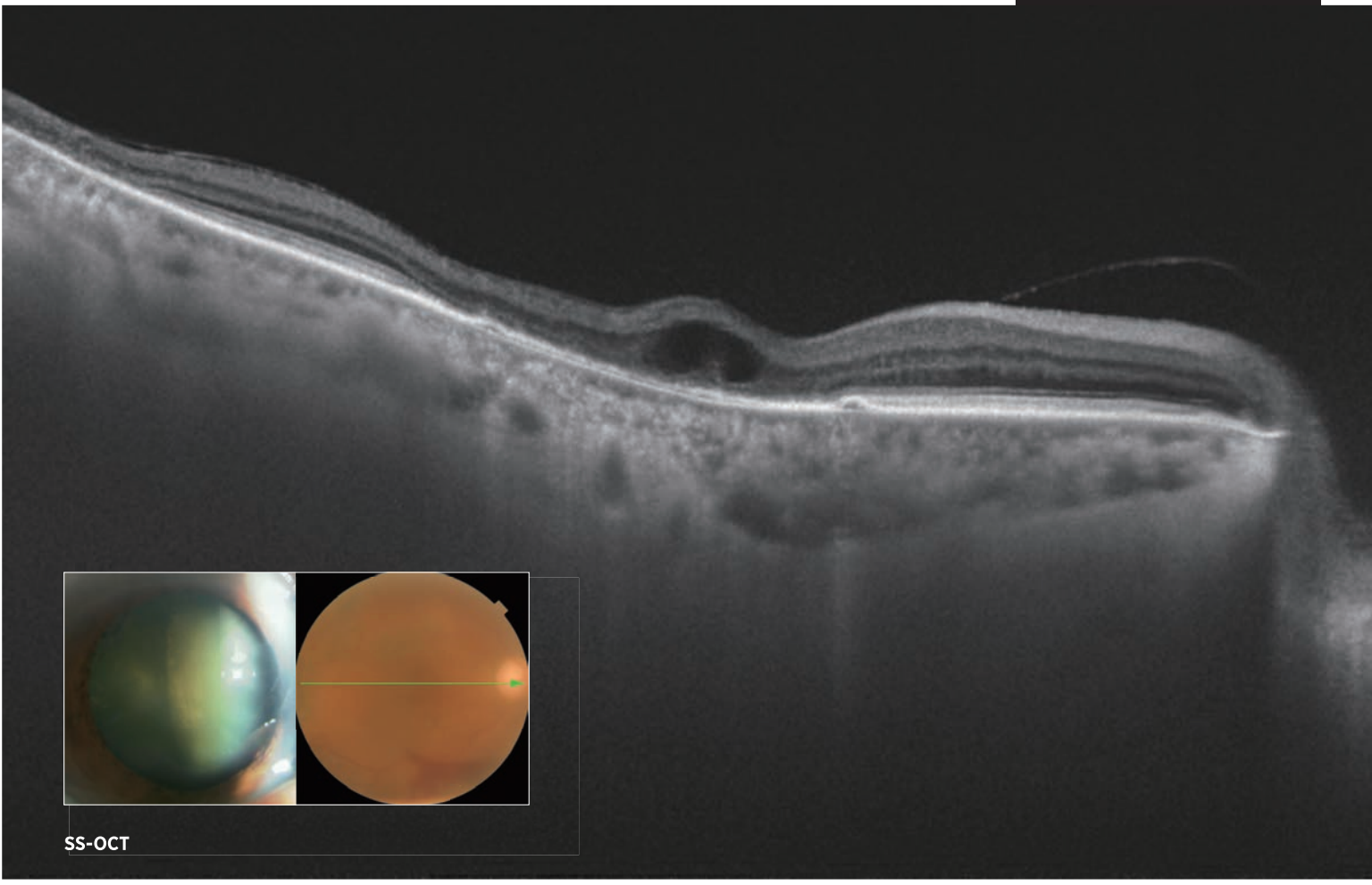

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By Charles C. Wykoff, MD, PhD

The Dawn Of AI in Retina

The 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 in 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," from a single fundus image.[2] It used isolated fundus images to deduce a subject's age, gender, blood pressure, smoking status and history of a major adverse cardiac event with remarkable accuracy. It appears a deep-learning system can tell if a fundus image belongs to a male or a female with astonishing consistency. Extrapolating from such deductive abilities hints at an incredible opportunity for retinal imaging to serve as a biomarker for systemic diseases.

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. RS

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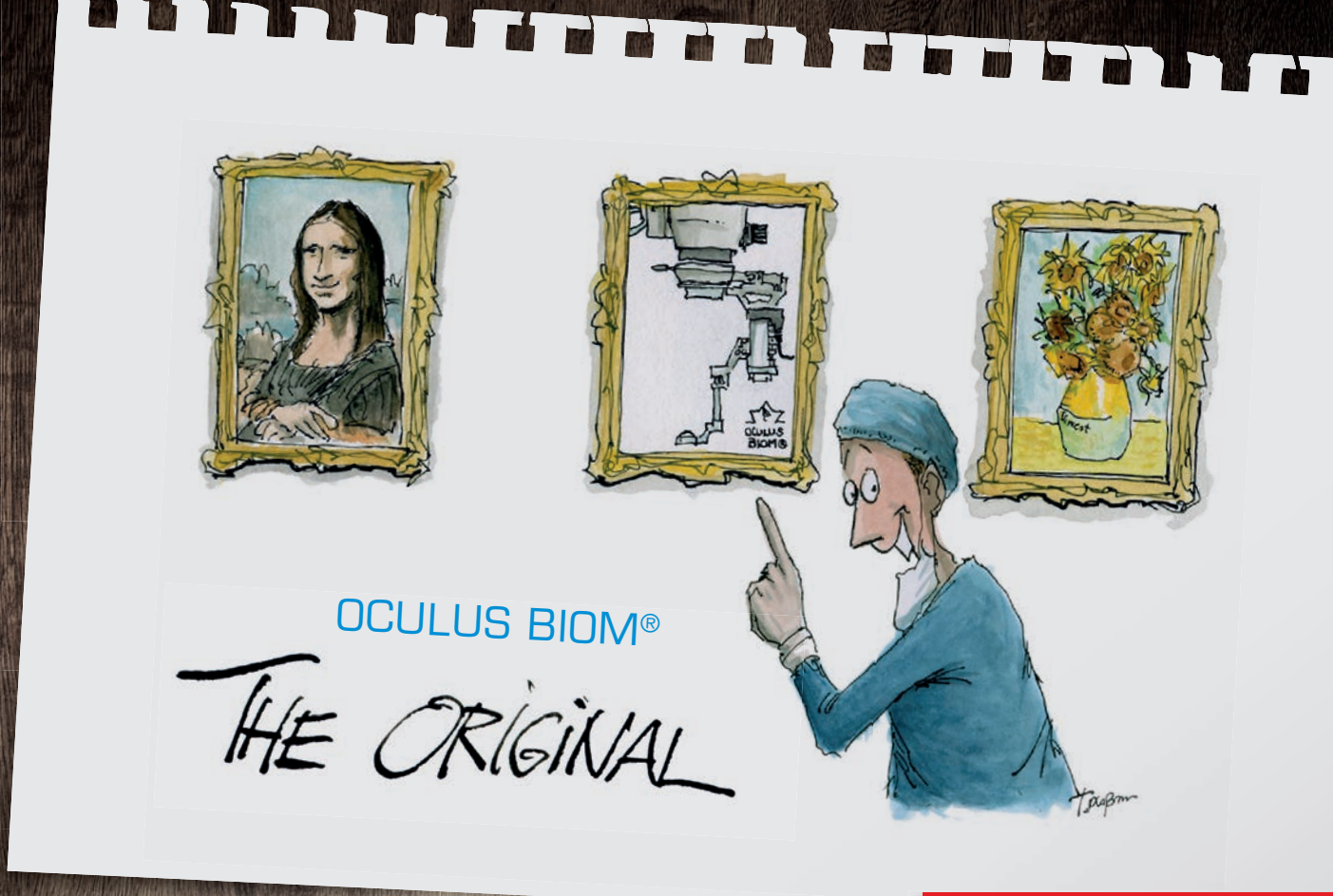
1. Marr B. 28 best quotes about artificial intelligence. Forbes. July 25, 2017. Available at: https://www.forbes.com/sites/bernardmarr/2017/07/25/28-best-quotes-about-artificial-intelligence/#5247b3664a6f. Accessed October 11, 2018.
2. Poplin R, Varadarajan AV, Blumer K, et al. Prediction of cardiovascular risk factors from fundus photographs via deep learning. Nat Biomed Engineer. 2108;2:158-164.



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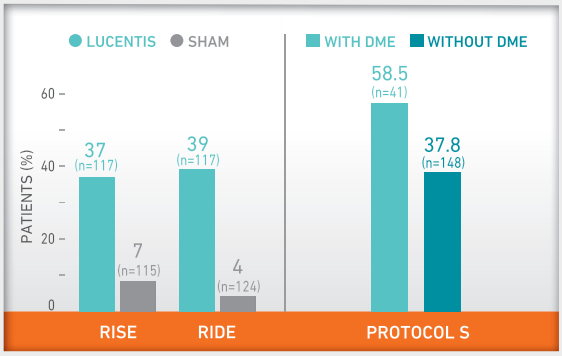
SIGNIFICANT REGRESSION IN DIABETIC RETINOPATHY

≥2-STEP IMPROVEMENTS AT 2 YEARS[1]*



≥3-STEP IMPROVEMENTS AT 2 YEARS[1]:

RISE AND RIDE

- LUCENTIS 0.3 mg: 9% (n=117) and 17% (n=117), respectively
- Sham arms: 0% (n=115) and 2% (n=124), respectively

PROTOCOL S

- Patients without DME: 28.4% (n=148)
- Patients with DME: 31.7% (n=41)

Confidence intervals (95%): ≥2-step—RISE: 31% (21%, 40%); RIDE: 35% (26%, 44%). Protocol S (DR with DME): 58.5% (43.5%, 73.6%); (DR without DME): 37.8% (30%, 45.7%). ≥3-step—RISE: 9% (4%, 14%); RIDE: 15% (7%, 22%). Protocol S (DR with DME): 31.7% (17.5%, 46%); (DR without DME): 28.4% (21.1%, 35.6%).[1]

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.[2,3]

LUCENTIS 0.3 mg is recommended to be administered by intravitreal injection once a month (approximately 28 days).[1]

VEGF, vascular endothelial growth factor.

0.3 MG LUCENTIS PREFILLED SYRINGE

REGRESSION DELIVERED[1]

HELP PATIENTS TURN BACK TO AN EARLIER STAGE OF DIABETIC RETINOPATHY (DR)[1]

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]

REFERENCES: 1. LUCENTIS [package insert]. South San Francisco, CA: Genentech, Inc; 2018. **2.** Brown DM, et al; RISE and RIDE Research Group. *Ophthalmology*. 2013;120:2013-2022. **3.** Gross JG, et al; Writing Committee for the Diabetic Retinopathy Clinical Research Network. *JAMA*. 2015;314:2137-2146.

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LUCENTIS®
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LUCENTIS®
RANIBIZUMAB INJECTION

Brief summary–please see the LUCENTIS® package insert for full prescribing information.

1 INDICATIONS AND USAGE
LUCENTIS is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
LUCENTIS is contraindicated in patients with ocular or periocular infections.

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

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored following the injection to permit early treatment should an infection occur *[see Dosage and Administration (2.6, 2.7) in the full prescribing information and Patient Counseling Information (17)]*.

5.2 Increases in Intraocular Pressure
Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately *[see Dosage and Administration (2.7 in the full prescribing information)]*.

5.3 Thromboembolic Events
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).

Neovascular (Wet) Age-Related Macular Degeneration
The ATE rate in the three controlled neovascular AMD studies (AMD-1, AMD-2, AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 of 441) in patients from the control arms *[see Clinical Studies (14.1 in the full prescribing information)]*. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8-7.1))).

Macular Edema Following Retinal Vein Occlusion
The ATE rate in the two controlled RVO studies during the first 6 months was 0.8% in both the LUCENTIS and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 of 260 in the control arms) *[see Clinical Studies (14.2 in the full prescribing information)]*. The stroke rate was 0.2% (1 of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 of 260) in the control arms.

Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

In a pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, 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.

5.4 Fatal Events in Patients with DME and DR at baseline
Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

A pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, 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.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Endophthalmitis and Retinal Detachments *[see Warnings and Precautions (5.1)]*
- Increases in Intraocular Pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Fatal Events in patients with DME and DR at baseline *[see Warnings and Precautions (5.4)]*

6.1 Injection Procedure
Serious adverse reactions related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis *[see Warnings and Precautions (5.1)]*, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

6.2 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3; in 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg LUCENTIS in 250 patients with DME and DR at baseline *[see Clinical Studies (14 in the full prescribing information)]*.

Safety data observed in Study AMD-4, D-3, and in 224 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.

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

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

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
Adverse Reaction	LUCENTIS 0.3 mg n=250	Control n=250	LUCENTIS 0.5 mg n=379	Control n=379	LUCENTIS 0.5 mg n=440	Control n=441	LUCENTIS 0.5 mg n=259	Control n=260
Conjunctival hemorrhage	47%	32%	74%	60%	64%	50%	48%	37%
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritus	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions
Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving LUCENTIS for DR, DME, AMD, and/or RVO and which occurred at a ≥ 1% higher frequency in patients treated with LUCENTIS compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

Table 2 Non-Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
Adverse Reaction	LUCENTIS 0.3 mg n=250	Control n=250	LUCENTIS 0.5 mg n=379	Control n=379	LUCENTIS 0.5 mg n=440	Control n=441	LUCENTIS 0.5 mg n=259	Control n=260
Nasopharyngitis	12%	6%	16%	13%	8%	9%	5%	4%
Anemia	11%	10%	8%	7%	4%	3%	1%	1%
Nausea	10%	9%	9%	6%	5%	5%	1%	2%
Cough	9%	4%	9%	8%	5%	4%	1%	2%
Constipation	8%	4%	5%	7%	3%	4%	0%	1%
Seasonal allergy	8%	4%	4%	4%	2%	2%	0%	2%
Hypercholesterolemia	7%	5%	5%	5%	3%	2%	1%	1%
Influenza	7%	3%	7%	5%	3%	2%	3%	2%
Renal failure	7%	6%	1%	1%	0%	0%	0%	0%
Upper respiratory tract infection	7%	7%	9%	8%	5%	5%	2%	2%
Gastroesophageal reflux disease	6%	4%	4%	6%	3%	4%	1%	0%
Headache	6%	8%	12%	9%	6%	5%	3%	3%
Edema peripheral	6%	4%	3%	5%	2%	3%	0%	1%
Renal failure chronic	6%	2%	0%	1%	0%	0%	0%	0%
Neuropathy peripheral	5%	3%	1%	1%	1%	0%	0%	0%
Sinusitis	5%	8%	8%	7%	5%	5%	3%	2%
Bronchitis	4%	4%	11%	9%	6%	5%	0%	2%
Atrial fibrillation	3%	3%	5%	4%	2%	2%	1%	0%
Arthralgia	3%	3%	11%	9%	5%	5%	2%	1%
Chronic obstructive pulmonary disease	1%	1%	6%	3%	3%	1%	0%	0%
Wound healing complications	1%	0%	1%	1%	1%	0%	0%	0%

6.3 Immunogenicity
As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%-5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-9% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in patients with DME and DR at 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 of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.
- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS
Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve (12) of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (± 2 days) after verteporfin PDT.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels [C_{max}]) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose *[see Animal Data]*.

Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab *[see Clinical Pharmacology (12.1 in the full prescribing information)]*, treatment with LUCENTIS may pose a risk to human embryofetal development.

LUCENTIS should be given to a pregnant woman only if clearly needed.

Data
Animal Data
An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted C_{max} levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

8.2 Lactation
Risk Summary
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/excretion.

Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUCENTIS and any potential adverse effects on the breastfed child from ranibizumab.

8.3 Females and Males of Reproductive Potential
Infertility
No studies on the effects of ranibizumab on fertility have been conducted. and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity.

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

8.5 Geriatric Use
In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 75 years of age *[see Clinical Studies (14 in the full prescribing information)]*. No notable 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 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

17 PATIENT COUNSELING INFORMATION
Advise patients that in the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5.1)]*.

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RETINA SPECIALIST

NOVEMBER 2018

FEATURES

DEPARTMENTS

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.

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

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 Durasert 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.

- 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.

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-lower drugs.[1]

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-lower drugs at baseline.

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 bezafibrate 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.

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What Lurks Beneath the RPE

Are polypoidal choroidal vasculopathy and exudative macular degeneration distinct entities?

By Nicholas K. Chan, MD, Steven S. Saraf, MD, and Ryan Yanagihara

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)

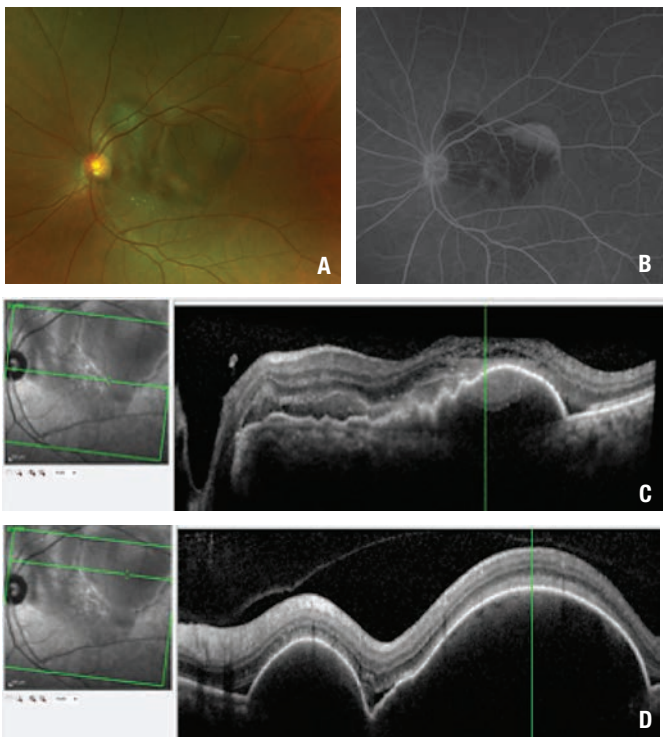

Figure 1. Color fundus photography at presentation (A) shows multiple pigment epithelial detachments (PED) associated with subretinal hemorrhage. The initial fluorescein angiogram of the left eye (B) shows blockage in the macula from the subretinal hemorrhage, late pooling within the PED in the temporal 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.

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(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.

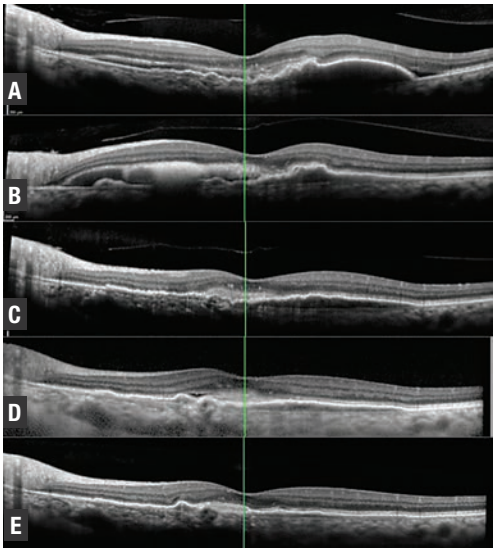


Figure 2. Progression of optical coherence tomography raster scans through the fovea at (A) presentation before treatment in our clinic; (B) one month after presentation and after one injection of bevacizumab; (C) four months after presentation, after three bevacizumab and one aflibercept injections; and (D) 12 months after the initial visit, after three bevacizumab and five aflibercept injections and one photodynamic therapy session. Thirteen months after presentation and an additional aflibercept injection, the most recent image (E) showed flattening of the shallow pigment epithelial detachment central macula, and resolution of the subretinal fluid.

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 (cholesteryl 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.[5]

How to Differentiate PCV

Although AMD and PCV may be on the same spectrum of disease, it is important to differentiate them

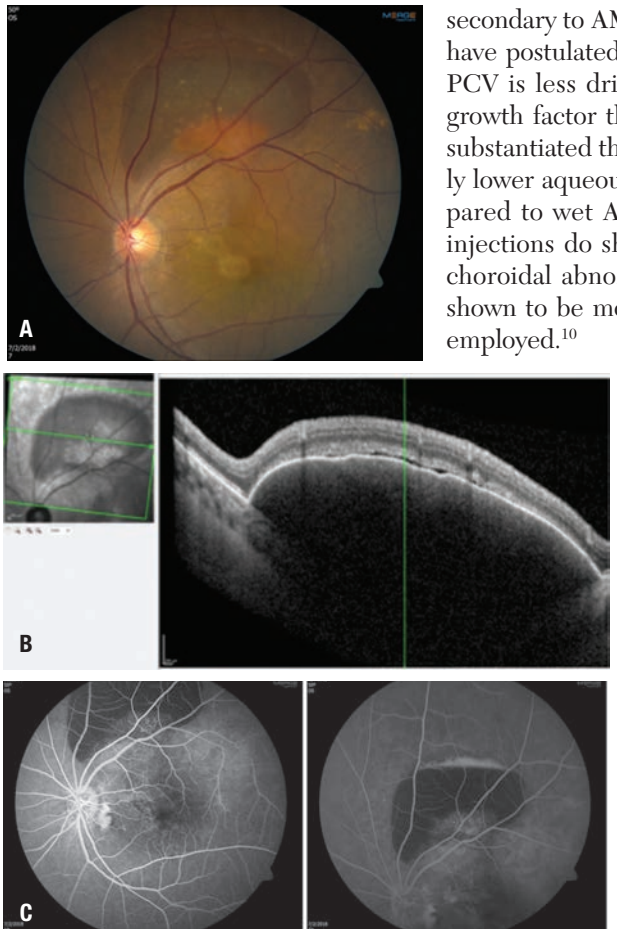


Figure 3. The patient returned after being lost to follow-up for seven weeks with worsening retinal pigment epithelial detachments in the macula and along the superior arcade of the left eye (A). The pigment epithelial detachment superiorly is associated with underlying hemorrhage and a gray subretinal structure along the inferior border consistent with a choroidal neovascular membrane. Optical coherence tomography (B) through the retinal pigment epithelial detachment show tense sub-RPE accumulation of hemorrhage and overlying subretinal fluid. Fluorescein angiography of the left eye (C) shows extensive leak points at the inferior border of the hemorrhagic pigment epithelial detachment. There is blockage from the sub-RPE hemorrhage and pooling in the serous component along the superior border.

because demographics, natural history, visual prognosis and management differ significantly.[6] 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.[6]

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.[7]

Several studies have evaluated the treatment of PCV. The efficacy of anti-VEGF agents is well known for CNV secondary to AMD.[8] 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.[9] Although anti-VEGF injections do show efficacy, the underlying choroidal abnormalities in PCV have been shown to be more responsive when PDT is employed.[10]

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.[11] The combination arm achieved the best visual and angiographic outcome, with the highest proportion of complete polypoidal lesion regression (78 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.[12]

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-

By Paul Hahn, MD, PhD »

Diagnostic Vitrectomy, Biopsy Tips

These steps before and during the procedure can improve your chances of obtaining sufficient samples. ***With Ananth Sastry, MD and Dilraj S. Grewal, MD***

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.[1] Alternatively, the undiluted sample can be harvested through a standard vitrectomy setup (i.e., with the aspiration line connected to the vitrectomy machine), followed by either reflux of the obtained sample into a collection tube or aspiration with a syringe from the aspiration line that is disengaged after the sample is collected. This latter technique is probably the simplest, but risks some loss of the precious sample.
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

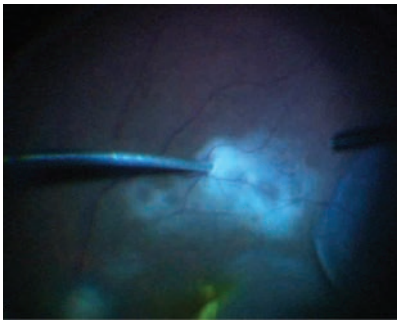


Figure 1. Retinal biopsy is obtained by inserting the tip of a 27-gauge cutter into the lesion.

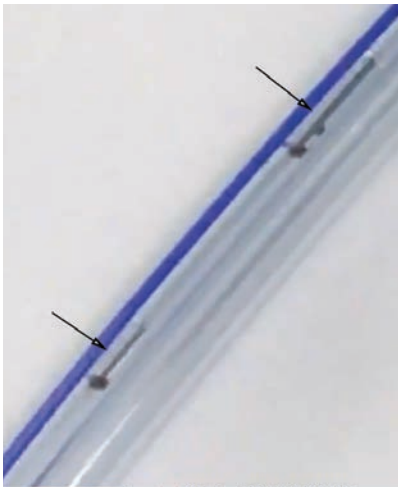
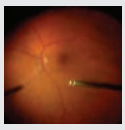


Figure 2. Retinal tissue is aspirated into the vitreous cutter tubing confirmed on visualization (black arrows).

View the Video



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 barricaded 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. Grewal is an associate professor of ophthalmology, specializing in vitreoretinal surgery and uveitis, at the Duke Eye Center, Durham, N.C.

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What Lurks Beneath the RPE

(Continued from page 15)

therapy may also be an effective approach.

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Dr. Olmos 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.

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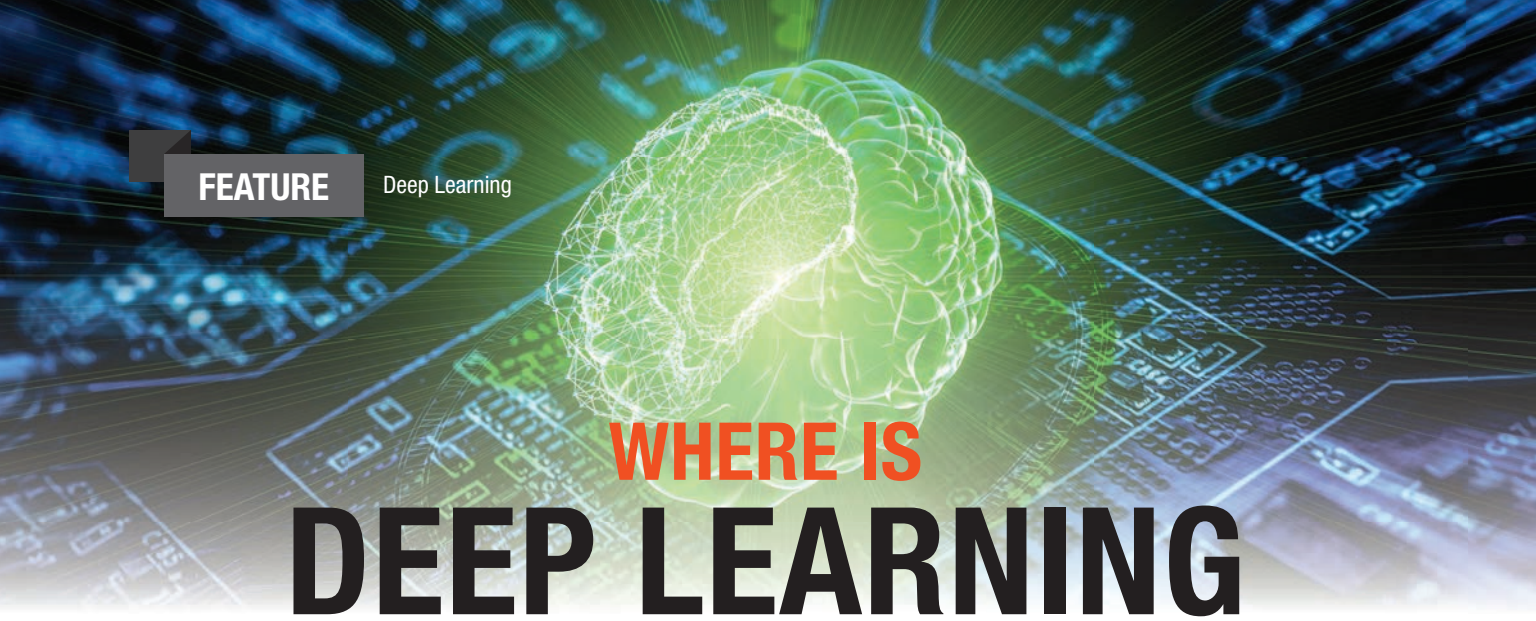

WHERE IS DEEP LEARNING IN RETINA HEADED?

A close look at four ways deep learning may change clinical practice — and a word of caution.

By Ehsan Rahimy, MD

Nearly 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

ABOUT THE AUTHOR

Dr. Rahimy is a vitreoretinal specialist in the San Francisco Bay Area. He has a research interest in the interplay between technology and medicine, notably with emerging artificial intelligence and deep learning platforms, and how ongoing advancements and further integration will transform health-care delivery in the future.

Disclosures: Dr. Rahimy is a consultant for Google.

cameras being deployed in various settings (primary-care-physicians' vs. endocrinologists' offices).

As this infrastructure continues to develop, deep learning overlay may augment remote imaging diagnostic capabilities by reducing the degree of human involvement needed. That is, shifting from requiring direct human interpretation of every image to primarily human oversight with grading/affirmation needed only for referable abnormals. Deep learning-based screening programs offer at least four potential benefits (*box*).

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.[2] 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).[6] The investigators 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.[7]

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 0.958, 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 0.889 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.[12] 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.[13]

A separate study from the same

Potential Benefits of Deep Learning-based Screening

- Increase efficiency and coverage (i.e., algorithms programmed to withstand repetitive image processing can work in parallel and do not fatigue).
- Reduce barriers to access in areas where an eye-care provider may not be available.
- Provide earlier detection of referable eye disease.
- Decrease overall health-care costs through earlier intervention in treatable disease rather than resorting to more costly interventions in more advanced pathology.

Take-home Point

This article defines the terms artificial intelligence, deep learning and machine learning and elaborates on four areas in which machine learning, and especially deep learning, are poised to have the greatest impact on retina practice: teleretinal screening; systemic disease assessment; clinical efficiency; and precision medicine. The author also issues a word of caution about deep-learning applications in the clinic going forward.

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.[14] 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.[15] 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.

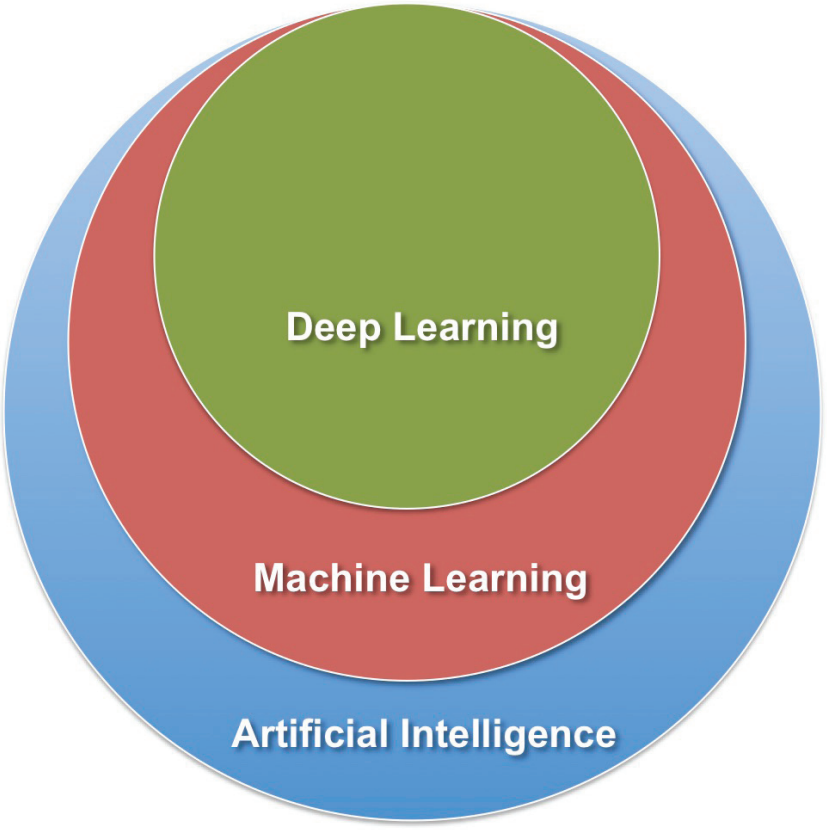

Figure. The terms "deep learning," "machine learning" and "artificial intelligence" can be thought of concentric circles: AI is the largest circle, machine learning a smaller circle within the subset of AI, and deep learning the smallest circle within the subset of machine learning

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 abnormals. 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.

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.

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."[23,21] 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. For

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.[24,25] 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.[24] 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 *pro re nata* arm of the HARBOR trial could be predicted based on OCT scans at baseline and months one and two.[25] 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.[5]

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.[27,28] This phenomenon is known as deskilling, 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.[27,28]

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.[29] 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.[30]

In other words, the question remains: Are patients directly benefiting 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.

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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. [26]

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 photocoagulation 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. RS

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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

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.[1,2] 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.

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.

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.[3,4] 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,[5] 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.[6] Despite slow initial progress

(Continued on page 29)

ABOUT THE AUTHORS

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

IMPORTANT SAFETY INFORMATION

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.

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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.

Reference: 1. LUXTURNA [package insert]. Philadelphia, PA: Spark Therapeutics, Inc; 2017.

P-RPE65-US-360005 April 2018

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Brief Summary of US Full Prescribing Information for LUXTURNA (voretigene neparvovec-rzyl)

1 INDICATIONS AND USAGE
LUXTURNA (voretigene neparvovec-rzyl) is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physicians.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis
Endophthalmitis may occur following any intraocular surgical procedure or injection. Proper aseptic injection technique should be used when administering LUXTURNA. Following the injection, patients should be monitored to permit early treatment of any infection. Advise patients to report any signs or symptoms of infection or inflammation without delay.

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

5.5 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.

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

6 ADVERSE REACTIONS
The most common adverse reactions (incidence ≥5%) were conjunctival hyperemia, cataract, increased intraocular 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 1.5×10^{11} vg; 9 eyes were exposed to lower doses of LUXTURNA. Study 1 (n=12) was an open-label, dose-exploration safety study. Study 2 (n=29) was 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 pediatric 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)

Adverse Reactions	Subjects n=41	Treated Eyes n=81
Any ocular adverse reaction	27 (66%)	46 (57%)
Conjunctival hyperemia	9 (22%)	9 (11%)
Cataract	8 (20%)	15 (19%)
Increased intraocular pressure	6 (15%)	8 (10%)
Retinal tear	4 (10%)	4 (5%)
Dellen (thinning of the corneal stroma)	3 (7%)	3 (4%)
Macular hole	3 (7%)	3 (4%)
Subretinal deposits*	3 (7%)	3 (4%)
Eye inflammation	2 (5%)	4 (5%)
Eye irritation	2 (5%)	2 (2%)
Eye pain	2 (5%)	2 (2%)
Maculopathy (wrinkling on the surface of the macula)	2 (5%)	3 (4%)
Foveal thinning and loss of foveal function	1 (2%)	2 (2%)
Endophthalmitis	1 (2%)	1 (1%)
Foveal dehiscence (separation of the retinal layers in the center of the macula)	1 (2%)	1 (1%)
Retinal hemorrhage	1 (2%)	1 (1%)

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

Immunogenicity
At all doses of LUXTURNA evaluated in Studies 1 and 2, immune reactions and extra-ocular exposure were mild. In Study 1 (n=12), the interval between the subretinal injections into the two eyes ranged from 1.7 to 4.6 years. In Study 2, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days. No subject had a clinically significant cytotoxic T-cell response to either AAV2 or RPE65.

Subjects received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye. The corticosteroids may have decreased the potential immune reaction to either vector capsid (adeno-associated virus serotype 2 [AAV2] vector) or transgene product (retinal pigment epithelial 65 kDa protein [RPE65]).

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 reproductive 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
Risk Summary: 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
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
Advise 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 floaters, eye pain, or any change in vision.

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

Expansion of intraocular air bubbles: Advise 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. A change in altitude while the air bubble is still present may cause irreversible damage.

Cataract: Advise patients that following treatment with LUXTURNA, they may develop a new cataract, or any existing cataract may get worse.

Shedding of LUXTURNA: Transient and low-level shedding of LUXTURNA may occur in patient tears. Advise patients and/or their caregivers on proper handling of waste material generated from dressing, tears, and nasal secretion, which may include storage of waste material in sealed bags prior to disposal. These handling precautions should be followed for up to 7 days following LUXTURNA administration.

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Spark Therapeutics, Inc.
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(Continued from page 25)
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 keratoprosthesis or "blind vitrectomy."[7-10]

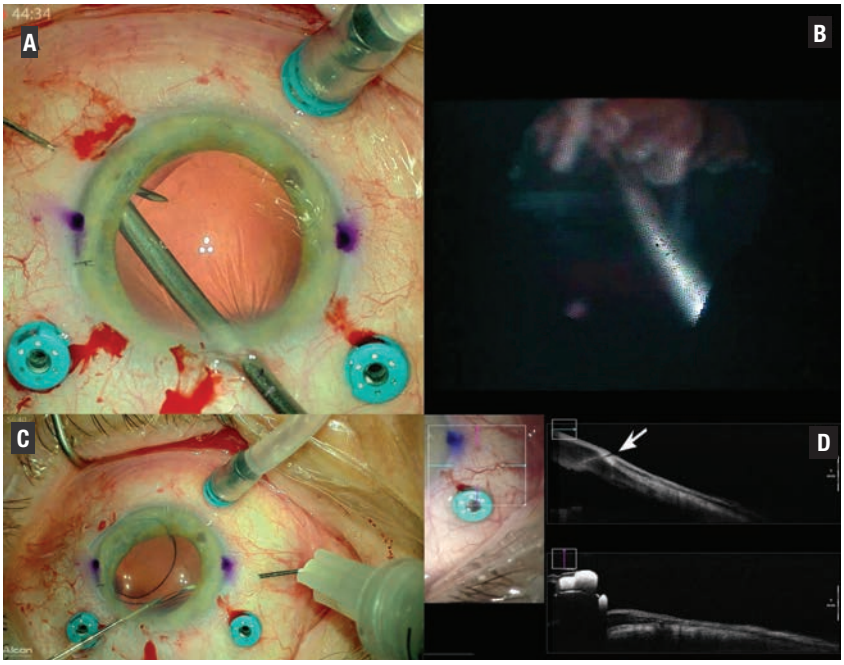


Figure 1. Images show secondary intraocular lens implantation with sutureless intrascleral IOL fixation. The split screen from the Ngenuity 3D Visualization System combines wide-field visualization (A) and endoscopic view (B) using a 19-gauge endoscope through the corneal wound in an aphakic eye. During needle insertion, the endoscope confirms the intraocular entrance posterior to the ciliary processes. The first haptic is externalized with the 27-ga needle (C). Intraoperative optical coherence tomography (D) confirms the position of the intrascleral haptic (arrow).

Surgeons unfamiliar with endoscopy may be unaware of the advantages of visualizing structures between the ora serrata and the retro-iridial space. Scleral depression or other technologies, such as the Topcon OMS-800 OFFISS microscope visualization system available in some countries, allow us to access the far periphery of the retina up to the ora serrata for shaving the vitreous base or peeling membranes. But they poorly visualize more anterior anatomical structures, which could aid in recognizing and diagnosing underlying pathology. We don't know what we don't know.

The availability of small-gauge endoscopy probes represented a big step forward. One of the advantages of a small-gauge endoscope is that it allows the surgeon to switch hands and reposition from superior to temporal trocars when he/she needs to address pathology in different locations.

In addition, valved small-gauge trocars also help maintain the fluidics control in more complex cases, representing an advantage over the larger-gauge trocars (19- and 20-ga) that glaucoma specialists use for endocyclophotocoagulation. The indications in clear media further extend the indications when media opacity is present (*Table*).[11-17]

Besides the limitations of straight small-gauge instruments when working in the far periphery, endoscopic visualization does pose some challenges for the newcomer. They include poor image resolution and limited

Table. Indications for Endoscopic Vitrectomy

Media Opacity
- Corneal opacity/edema
- Endophthalmitis
- Globe rupture
- Intraocular foreign body

Clear Media
- Anterior proliferative vitreoretinopathy
- Fibrotic posterior synechiae/small pupil
- Giant retinal tears: trimming of the anterior flap
- Large retinectomies
- Hypotony
- Intraocular lens instability/subluxation/fixation
- Proliferative diabetic retinopathy and neovascular glaucoma
- Retained lens fragment/chronic cystoid macular edema
- Retained silicone oil
- Secondary intraocular lens implantation

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.

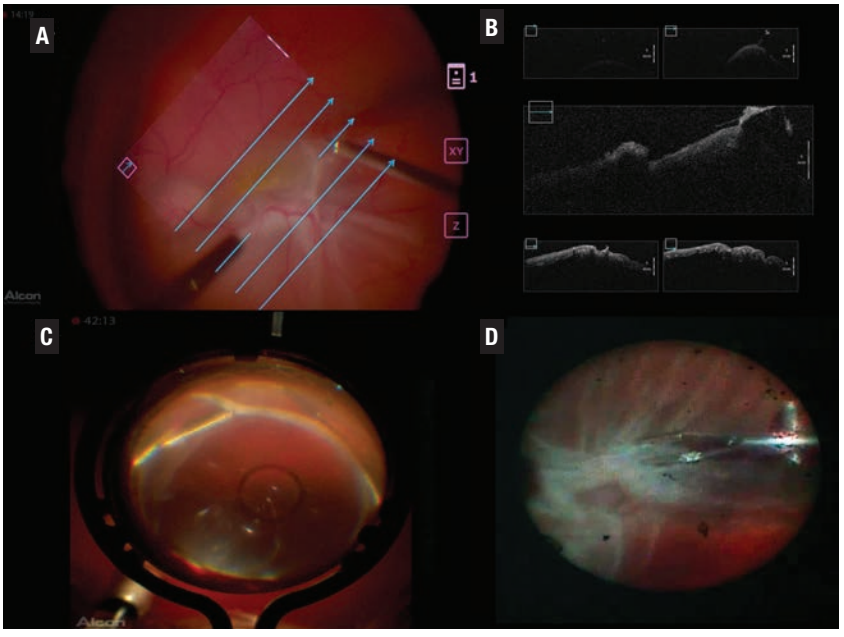


Figure 2. Images show treatment of a recurrent retinal detachment with hypotony and proliferative vitreoretinopathy C-1 and C-5 that involves macular star fold peeling with intraocular forceps assisted with intraoperative optical coherence tomography (A). Intraoperative OCT (B) shows real-time PVR peeling. Ngenuity split screen combines wide-field visualization (C) and endoscopic view (D) using a 23-gauge endoscopy probe and 25-ga adjustable chandelier to peel the anterior PVR causing traction and hypotony.

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 endoilluminator (*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.

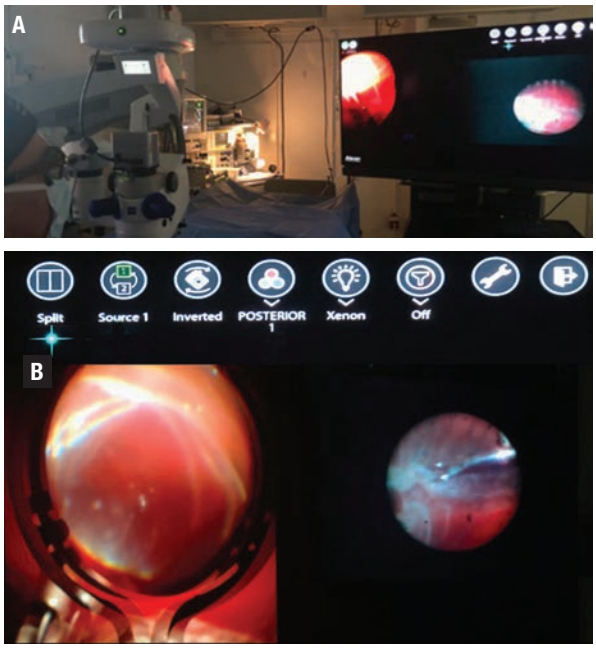


Figure 3. Operating-room setup of the Ngenuity 3D Visualization System (A) with monitor showing split screen function during endoscopic surgery. Screen settings (B) show the split-screen function selected (star cursor). To the left is a three-dimensional wide-field image that allows the surgeon to confirm the intraocular position of the instruments during anterior proliferative vitreoretinopathy peeling assisted by endoscopy, shown on the right image.

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

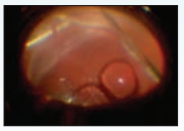
The application of a 3-D digitally assisted imaging system to vitreoretinal surgery is one of the latest and most promising advances in our field. Combining improved image performance with technologies such as endoscopic vitreoretinal surgery, intraoperative OCT and video overlay features should help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

Endoscopic Surgical Pearl

For small-gauge endoscopy, the use of adjustable fiber chandeliers (Bausch + Lomb Surgical) improves lighting and better identification of tissue planes.

View the Video

Drs. Rezende and Vila demonstrate 3D digitally assisted vitreoretinal surgery for a recurrent rhegmatogenous retinal detachment. Available at: bit.ly/RetSpec_3DSurgery_112018.



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Focus on Innovation in Surgery

SURGICAL PEARLS FOR USING PFCLS

A perspective on when we can use perfluorocarbon liquids and how we can avoid their pitfalls.

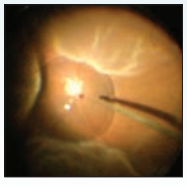
Nicolas Yannuzzi, MD, James Lin, MD, and Jayanth Sridhar, MD

Since they first emerged in retinal surgery in the late 1980s,[1] perfluorocarbon liquids have become an integral part of our management of complex rhegmatogenous retinal detachments with proliferative vitreoretinopathy[2] or giant retinal tears.[1–4] 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.[1] 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.

View the Video

Drs. Yannuzzi, Lin and Sridhar demonstrate their technique for filling the eye with perfluorocarbon liquid in a retinal detachment repair. Available at: bit.ly/RetSpec_PFCL_112018.



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, Alimera Sciences and Allergan.

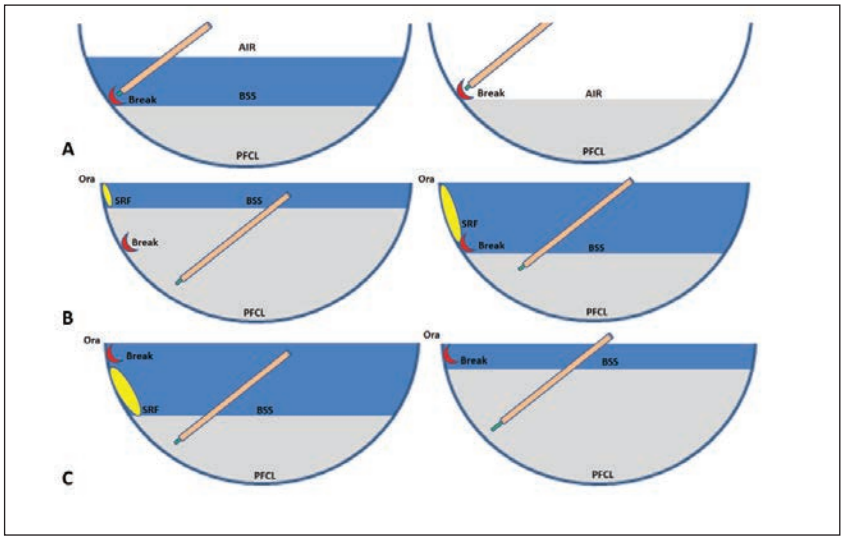


Figure 1. Our technique for perfluorocarbon liquid-assisted drainage in rhegmatogenous retinal detachment involves the following steps: A) Fill the PFCL to the most posterior retinal break then perform a fluid-air exchange while draining from the break, "sandwiching" any residual fluid between the air 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.

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 to 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."[6]

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

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]

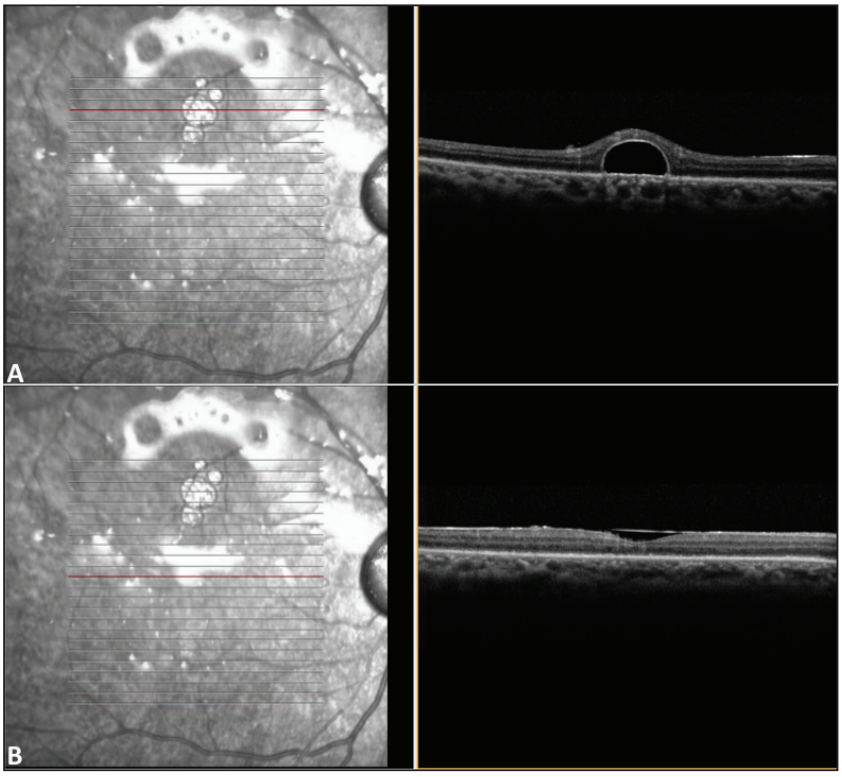


Figure 2. Spectral-domain optical coherence tomography scans of retained subretinal perfluorocarbon fluid in a 52-year-old man with rhegmatogenous retinal detachment repaired by pars plana vitrectomy show two different pictures. Through the superior macula (A), the scan shows several adjacent PFCL bubbles that collected in the subretinal space, as identified by the omega sign on the cross sectional image. Through the fovea (B), the scan shows no evidence of subfoveal PFCL.

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. RS

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Focus on Innovation in Surgery

A THOROUGH APPROACH TO DIABETIC TRD REPAIR

This careful approach to surgery covers all the steps, from preoperative use of PRP and bevacizumab to postoperative use of triamcinolone.

Sidney Schechet, MD, and Dimitra Skondra, MD, PhD

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 pre-vitrectomy 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

View the Video

A video that shows before and after images of Dr. Schechet's and Dr. Skondra's operative approach is available at bit.ly/RetSpec_TRDSurgery_112018

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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.[6] 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.[7] It has also been shown to reduce operative times.[8,9]

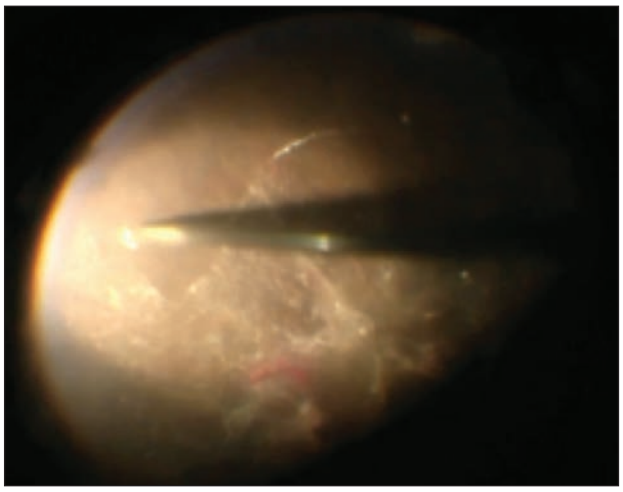

Figure 1. Repeated staining of residual hyaloid with triamcinolone after membrane peeling helps to visualize any residual hyaloid remaining after peeling.

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.[10]

• ***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 (*Figure 1*). Residual hyaloid left behind postoperatively can contract and be a scaffold for FVM reproliferation.

• ***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

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[11] and "lift and shave."[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.

• ***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.

• ***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*).

Managing Potential Problems During Surgery

• ***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.

• ***Avoiding and managing iatrogenic breaks.*** In nonrhegmatogenous diabetic TRDs, avoiding iatrogenic breaks is crucial, because

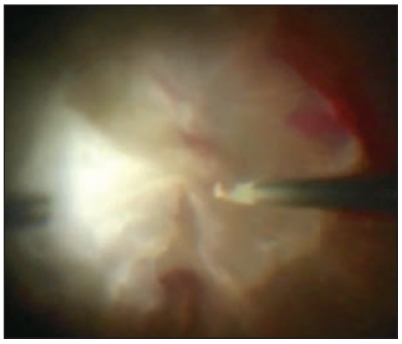

Figure 2. Vertical pneumatic membrane peeler-cutter scissors aid in the dissection of the fibrovascular membrane.

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.

• ***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, endoilluminated laser probes because they allow us to deliver anterior PRP while performing scleral depression.

• ***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:[13] an approximately 98-percent primary reattachment rate with a single surgery, and less than 2 percent secondary retinal detachments in complex cases.

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.[14]

Postoperative Care

• ***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

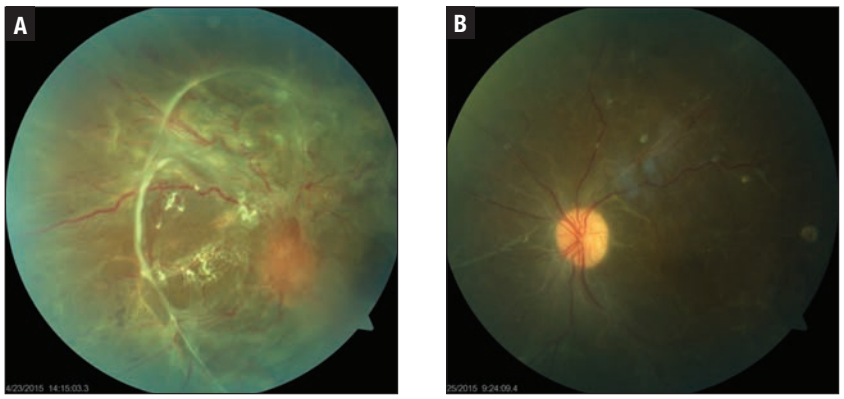

Figure 3. Preoperative visual acuity in this patient was counting fingers (A), but tractional retinal detachment repair restored VA to 20/80 (B).

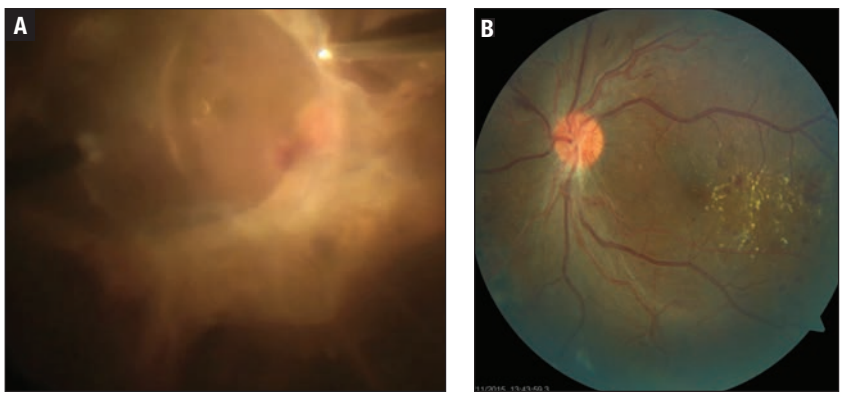

Figure 4. In this patient, preoperative visual acuity was counting fingers (A). Postoperative VA was 20/40 after tractional detachment repair (B).

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.

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WHY PDR PATIENTS MAY NOT COME BACK

A closer look at risk factors of patients who are lost to follow-up after treatment for proliferative diabetic retinopathy.

Anthony Obeid, MD, MPH, Jason Hsu, MD

The advent of panretinal photocoagulation has helped to significantly reduce the risk of vision loss secondary to proliferative diabetic retinopathy.[1] Recent trials have shown that intravitreal anti-VEGF therapy has a comparable, if not superior, treatment effect on PDR compared to PRP.[2,3] However, both therapies require consistent post-treatment follow-up.

Although studies have evaluated adherence to dilated fundus examination regimens established for diabetic patients,[4] 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*,[5] 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

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DISCLOSURES: Dr. Obeid has no relationships to disclose. Dr. Hsu disclosed receiving grants from Roche/Genentech, Santen and Ophthotech. He also receives personal fees from Ophthotech.

Risk Factors of Loss to Follow-up

- **Type of procedure.** Patients who undergo panretinal photocoagulation have higher rates of loss to follow-up (LTFU) than those who have intravitreal anti-VEGF treatments.
- **Age.** Patients younger than age 65 have higher rates of LTFU.
- **Race.** African Americans have higher rates of LTFU.

declines after adjusting for the various socio-demographic factors in the multivariate model (*Table*).

However, LTFU may also be secondary to other factors, such as pain level differences that patients experience between the two treatments. One study has shown that patients receiving PRP experience pain levels approximately 60 times higher on average than intravitreal injections when quantified on a visual analog scale.[6] Moreover, complications, such as diabetic macular edema and vitreous hemorrhage, which are more often associated with PRP, may also discourage patients from returning for follow-up.[2,3]

• ***Age.*** Rates of LTFU also decreased as age increased, with rates of 28.1 percent, 27 percent and 20.9 percent for patients ages ≤55, 56 to 65 and >65 years old, respectively (p=0.002). Interestingly, it appears the major decline in LTFU rates occurs after the age of 65.

We theorize that this may be related to insurance coverage as individuals age 65 and older are Medicare eligible. If this is true, we would expect patients of lower incomes to

Table. Logistic Regression Models of Potential Risk Factors for Loss to Follow-up in PDR Patients[5]

Variable	LTFU, n (%)	Univariate Model		Multivariate Model	
		Odds Ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Procedure					
Intravitreal injection	228 (22.1%)	Reference		Reference	
Panretinal photocoagulation	356 (28.0%)	1.37 (1.13–1.66)	0.001	1.24 (1.02–1.52)	0.03
Age (years)					
>65	161 (20.9%)	Reference		Reference	
56–65	187 (27.0%)	1.40 (1.10–1.78)	0.007	1.28 (1.01–1.64)	0.046
≤55	236 (28.1%)	1.48 (1.17–1.86)	0.001	1.26 (0.99–1.59)	0.06
Gender					
Male	307 (25.8%)	Reference			
Female	277 (25.0%)	0.96 (0.79–1.16)	0.66	---	---
Race					
White	229 (19.4%)	Reference		Reference	
African-American	179 (30.2%)	1.80 (1.43–2.26)	<0.001	1.52 (1.18–1.95)	0.001
Asian	15 (19.7%)	1.02 (0.57–1.83)	0.94	1.01 (0.56–1.81)	0.98
Hispanics, Native Americans and Pacific Islanders	30 (38.0%)	2.54 (1.58–4.10)	<0.001	2.09 (1.28–3.41)	0.003
Unreported	131 (34.9%)	2.23 (1.73–2.88)	<0.001	1.95 (1.49–2.55)	<0.001
Regional average adjusted gross income					
>$80,000	91 (19.7%)	Reference		Reference	
$41,000–80,000	317 (24.0%)	1.28 (0.99–1.67)	0.06	1.17 (0.89–1.52)	0.26
≤$40,000	176 (33.9%)	2.09 (1.56–2.80)	<0.001	1.51 (1.10–2.07)	0.01
Distance from clinic (miles)					
≤20	512 (25.4%)	Reference			
>20	72 (24.9%)	0.97 (0.73–1.29)	0.85	---	---

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

(***Used with permission Elsevier Science and Technology Journals. Obeid A, Gao X, Ali FS, et al. Ophthalmology. 2018;125:1386-1392.***)

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.

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 ≤$40,000 ($p$=0.02) and $41,000 to $80,000 ($p$=0.04), but not for incomes of over $80,000 ($p$=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) (p <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 health-care 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 health-care system. We need further studies to understand this cohort and the true etiology contributing to high LTFU rates.

Finally, all significant risk factors in the univariate model were retained in the multivariate model as significant independent predictors of LTFU (*Table, page 41*).

Role of Visual Acuity

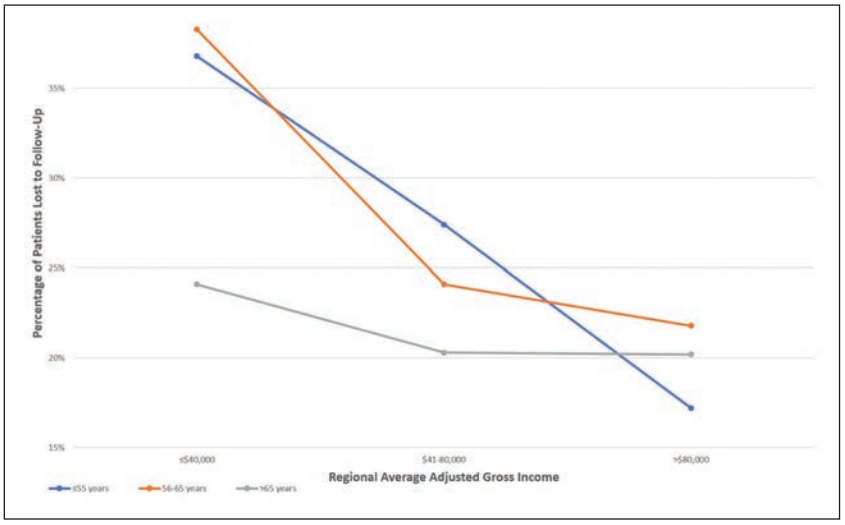

Figure. Change in loss to follow-up (LTFU) rates by age over approximately four years stratified for regional average adjusted gross income. (*Used with permission Elsevier Science and Technology Journals. Obeid A, Gao X, Ali FS, et al. Ophthalmology. 2018;125:1386-1392.*)

Study Design

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.

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 (p=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.

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.

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),[14] more than a fourth of patients have a year or less with a documented dilated fundus exam over four consecutive years of follow-up.[7]

Patients with DME have also shown high noncompliance with follow-up rates in Europe.[15] 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.[15] 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-intravitreal anti-VEGF therapy fare much worse, both anatomically and functionally, when compared to eyes that received PRP.[16]

A final important point to consider is the limited life expectancy of patients with PDR. Studies have shown high mortality rates in the patients that received PRP in the original Early Treatment Diabetic Retinopathy Study.[17] Moreover, these patients are expected to have numerous additional medical check-ups for other pathology secondary to the diabetes. Given the durability differences between the two treatments, with PRP demonstrated to have long-lasting effects, it becomes important to carefully evaluate each patient before selecting treatment.

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.

Future Directions

Although our study has identified several risk factors associated with LTFU, much remains to be done. Models evaluating social behavior are less robust than models evaluating physiological factors, given the numerous factors and complex confounders involved.

Although we assume we understand the factors most important in bringing back patients to our clinics, our current data demonstrates that this might not necessarily be true. This becomes particularly relevant in designing screening protocols that identify high-risk patients and interventions that aim to reduce LTFU rates. Models that have good predictive potential can help in achieving both these goals and provide a much better understanding on what contributes most to LTFU in our population. RS

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By Efrem D. Mandelcorn, MD, FRCSC »

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 underresearched condition that is becoming ever more prevalent as the population ages and people live longer. It causes intricate, lifelike 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.

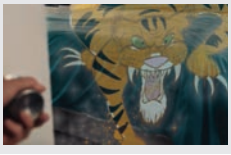
Hallucinations of Charles Bonnet patients can range from simple images, such as colored patterns, to complex scenes, such as children playing. Patients are often able to vividly describe and recall the images, which is highly characteristic of Charles Bonnet syndrome (*Figure*).[1]

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

The Macular Society has posted a video about Charles Bonnet Syndrome, available at: http://bit.ly/Bonnet_Syndrome .

"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.[6] The prevalence of this syndrome is astonishing, with an estimated 49 to 88 percent of amputees having experienced it.[7]

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.[8-11]

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. RS

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By Kirk A. Mack, COMT, COE, CPC, CPMA »

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)

By Richard Mark Kirkner »

DRI OCT Triton: One Doctor's Experience

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

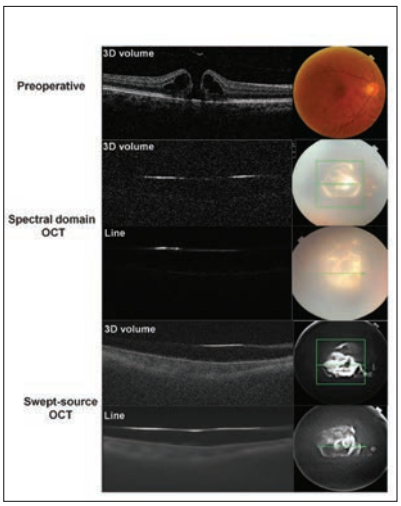
The Food and Drug Administration cleared the DRI OCT Triton imaging platform from Topcon almost a year ago, but at his clinic in Brazil, Daniel Lavinsky, MD, has been using the device for some time, and reports that it has helped to improve his workflow and decision-making by providing "almost every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



A readout from the DRI OCT Triton showing spectral domain vs. swept source optical coherence tomography scans, and the device itself (below) showing the operator screen.

"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 epitheliopathy through to choroidal neovascularization, with precision and without the need of intravenous contrasts." RS

Dr. Lavinsky disclosed he is a consultant to Topcon.

What's Next for Bispecific Antibody Faricimab

With the Phase II BOULEVARD trial completed, this dual-action, single-molecule agent for DME heads into Phase III trials. ***By Richard Mark Kirkner***

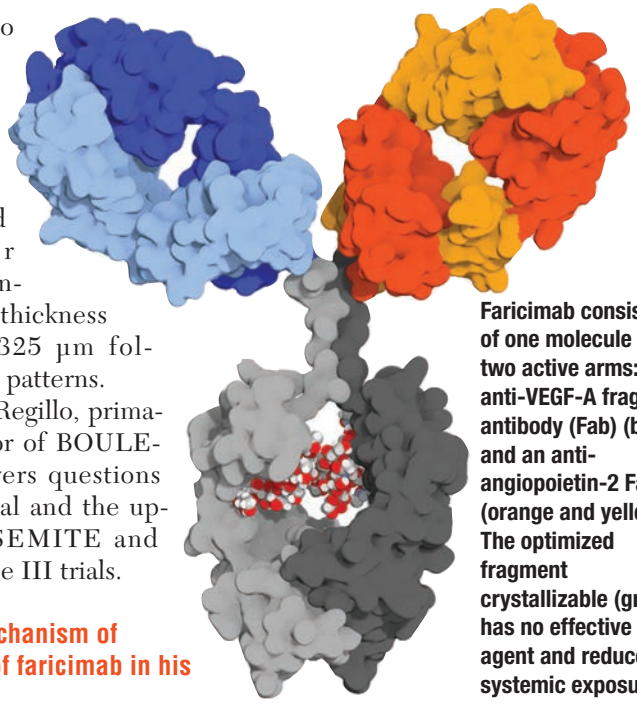
Faricimab—the generic name for what was once known as RG7716—is the first bispecific antibody for intravitreal administration that targets two key factors that contribute to diabetic retinopathy and diabetic macular edema: vascular endothelial growth factor and angiopoietin-2, otherwise known as Ang-2.

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- mg 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.



Faricimab consists of one molecule with two active arms: an anti-VEGF-A fragment antibody (Fab) (blue) and an anti-angiopoietin-2 Fab (orange and yellow). The optimized fragment crystallizable (gray) has no effective agent and reduced systemic exposure.

Q The mechanism of action of faricimab in his own words:

A 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.

Q More specifically, what role does Ang-2 play in the pathogenesis of DR/DME?

A Elevated levels of Ang-2 in the vitreous lead to vascular pericyte dropout with blood-retinal barrier breakdown and exudation, along with retinal microvascular inflammation.

Q How does faricimab differ from existing anti-VEGF agents?

A 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

could even exceed that.

Q What are the most telling findings of the BOULEVARD trial?

A 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.

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

A 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.

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Challenges With Silicone Oil Removal

(Continued from page 46)

ERM may have developed regardless of the oil.

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-postsurgical-modifier-confusion).

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EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments. Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. 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 [*see Dosage and Administration (2.7) and Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure. Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.7)*].

5.3 Thromboembolic Events. 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.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

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 other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

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

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Ocular hyperemia	4%	8%
Corneal epithelium defect	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Intraocular inflammation	2%	3%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

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

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

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

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

6.2 Immunogenicity. As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept [*see Clinical Pharmacology (12.1)*], treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.

Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation

Risk Summary

There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility

There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use. The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use. In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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

Issue Date: June 2017
Initial U.S. Approval: 2011

Based on the May 2017 EYLEA® (aflibercept) Injection full Prescribing Information.

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MAXIMIZING SURGEON CONTROL

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POWER TO PREVAIL

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 outcomes[1]

AMD = Age-related Macular Degeneration; DME = Diabetic Macular Edema;
DR = Diabetic Retinopathy; RVO = Retinal Vein Occlusion.

Dosing driving efficacy outcomes across all indications.[1]
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EYLEA®
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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.
- 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.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

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.

Reference: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. May 2017.

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