Supplement to July/August 2021

MODERNOPTOMETRY

DIABETIC RETINOPATHY
UPDATE: BEST
PRACTICES IN
REFERRALS, SCREENING,
AND TREATMENTS

A CE activity administered by Evolve Medical Education LLC.

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ANDREW A. MOSHFEGHI, MD, MBA - MODERATOR

Associate Professor of Clinical Ophthalmology Director of Clinical Trials University of Southern California Keck School of Medicine Los Angeles, CA



MARK DUNBAR, OD, FAAO

Director of Optometric Services University of Miami Miller School of Medicine Bascom Palmer Eye Institute Miami, FL



ROGER A. GOLDBERG, MD, MBA

Partner, Bay Area Retina Associates Faculty, Sutter-CPMC Ophthalmology Residency Walnut Creek, CA



VEERAL S. SHETH, MD, MBA, FACS

Partner and Director of Clinical Trials University Retina Chicago, IL



FRANK G. ZHENG, OD, MS

Partner and Principle Optometrist Lafayette Optometric Group Lafayette, CA



Diabetic Retinopathy Update: Best Practices in Referrals, Screening, and Treatments

CONTENT SOURCE

This continuing education activity captures content from a virtual roundtable discussion.

ACTIVITY DESCRIPTION

The overwhelming majority (85%) of comprehensive eye exams are conducted by optometrists. Diabetic retinopathy (DR) is the most common ocular complication of diabetes and is currently responsible for more than 10,000 new cases of blindness each year in the United States alone. This supplement highlights discussion topics among experts in the field and provides important education on caring for this patient demographic.

TARGET AUDIENCE

This certified CE activity is designed for optometrists who manage patients with diabetic eye conditions.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- Summarize the rise of diabetes and DR in the US population and the related impact on ocular health.
- Understand effective screening strategies and imaging tools for diagnosing DR and diabetic macular edema (DME).
- **Identify** which patients need early referral to a retina specialist based on their behavioral patterns, disease state, and/ or other risk factors.
- Identify and discuss how imaging devices may be able to provide earlier diagnosis of disease or disease progression.
- Explain the latest treatment approaches to DR/DME.
- **Describe** novel developments in DR screening.

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PRETEST QUESTIONS

PLEASE COMPLETE PRIOR TO ACCESSING THE MATERIAL AND SUBMIT WITH POSTTEST/ACTIVITY **EVALUATION/SATISFACTION MEASURES FOR CE CREDIT.**

- 1. Please rate your confidence in your ability to identify which patients need early referral to a retina specialist based on their behavioral patterns, disease state, and/or other risk factors (based on a scale of 1 to 5, with 1 = "Not at all confident" and 5= "Very confident").
 - a. 1
 - b. 2
 - c. 3
 - d. 4 e. 5
- 2. Please rate how often you apply advances in treating diabetic eye disease to "real-world" patient management (based on a scale of 1 to 5, with 1 being never and 5 being always).
 - a. 1
 - b. 2
 - c. 3
 - d. 4 e. 5
- 3. A 65-year-old patient with type 2 diabetes returns for annual follow up. The patient's last HbA1c was 9.1%, blood pressure was 140/93 mm Hg, and the patient had dyslipidemia. The patient's VA on presentation was 20/20 and intraocular pressure was 14 mm Hg OU. The anterior segment examination was nonsignificant except for bilateral cataracts. The posterior segment examination was significant for severe nonproliferative diabetic retinopathy (NPDR). There is no sign of diabetic macular edema (DME) in both eyes.

Action	Consistent	Nonconsistent
Widefield fundus photography		
Electroretinogram/electrooculography measurements		
Repeated exam in 3-6 months		
Referral to endocrinology for better glucose control		
Early cataract extraction		
Anti-VEGF treatment for severe nonproliferative disease		
Intravenous fluorescein angiography (FA)		
Indocyanine green (ICG)-angiography		
Optical coherence tomography angiography (OCT-A)		
Relaxed control of blood pressure		
Control of lipids		

- 4. A 42-year-old Black man presents to an optometry practice complaining of blurry vision. He has been in treatment for type 2 diabetes for 7 years, which was well-controlled until stay-at-home orders began for the COVID-19 pandemic. He is on insulin once a day. He missed his annual diabetic eye exam due to fear of medical exams during the pandemic. He noticed blurry vision about 8 months ago, but was too nervous of COVID-19 exposure to come in. He says he feels better about the pandemic now and has been vaccinated, but is wary and nervous, based on his body language. His HbA1c is 12%. He has a history of hypertension and obesity. His BCVA is 20/50 OU. The exam showed moderate NPDR with several hemorrhages, cotton-wool spots, thickening and noncenter-involved DME. What are the next steps for this patient?
 - a. Correct the refractive error and follow the patient closely for the next 3 months to see if disease progresses.
 - b. Refer the patient to a retina specialist immediately for anti-VEGF injections and use the opportunity to explain that he will receive injections in his eye on a monthly basis for the rest of his life. Explain to the patient that you will correct the refraction after they've been seen and treated by the retina specialist.
 - c. Correct the refractive error and explain to the patient that you'd like to refer them to a retina specialist colleague for further evaluation and possible treatment; emphasize the importance of follow-up.
 - d. Correct the refractive error and schedule the patient for their yearly diabetic eye exam in a year. They do not need a referral.
- of patients will develop DR within 15 years 5. Approximately of diabetes diagnosis.
 - a. 50%
 - b. 80%
 - c. 60%
 - d. 75%
- 6. The phase 3 PANORAMA results suggest that diabetic patients may be at an elevated risk of vision threatening complications at what point in their diabetic eye disease?
 - a. When they progress to more than moderate NPDR
 - b. When they progress to proliferative DR (PDR)
 - c. When they progress to center-involved DME (CI-DME)
 - d. When they progress to mild NPDR

PRETEST QUESTIONS

PLEASE COMPLETE PRIOR TO ACCESSING THE MATERIAL AND SUBMIT WITH POSTTEST/ ACTIVITY EVALUATION/SATISFACTION MEASURES FOR CE CREDIT.

7. The American Optometric Association's guidelines for treating	
patients with diabetes notes some studies have found	of
patients with moderate NDPR without DME will progress to PDR in	1 year.

- a. 10% 25%
- b. 12% 27%
- c. 15% 30%
- d. 50% 75%
- 8. A 56-year old white female with type 2 diabetes was referred to a retina practice by an optometrist for DME treatment. She's had well-controlled diabetes for 20 years. Her HbA1c is 7%, and she has complained of decreased vision OS, specifically, for the last 6 months. Her vision is 20/25 OD and 20/40 OS. In addition to DME, you note that she needs cataract surgery in her left eye. What is the most appropriate next for this patient?
 - a. The retina specialist should refer her to cataract surgery and opt not to treat the DME until the cataract surgery is completed.
 - b. The retina specialist should treat her with intravitreal anti-VEGF therapy and call the referring optometrist to discuss how to comanage the cataract.
 - c. The retina specialist should treat her with an intravitreal anti-VEGF agent and defer cataract surgery altogether.
 - d. The retina specialist should treat her with panretinal photocoagulation and defer cataract surgery altogether.

9. What imaging is now considered standard of care for evaluating patients with DME?

- a. OCT-A
- b. Autofluorescence imaging
- c. Retinal Fundus Photography
- d. OCT

Because of the risk of cystoid macular edema in patients with diabetic eye disease who are undergoing cataract surgery,

- a. Never use corticosteroids postoperatively.
- b. Only use anti-VEGF agents before cataract surgery.
- c. Using either an anti-VEGF or a corticosteroid implant before or after cataract surgery is acceptable.
- d. It is common to insert a corticosteroid implant at the time of cataract surgery.

11. One takeaway from the Protocol W trial was that:

- a. Proactive anti-VEGF treatment can reduce the chance of developing CI-DME with vision loss by 16%.
- b. Proactive anti-VEGF treatment does not reduce the chance of developing CI-DME, but has significant visual benefit in patients who progress to CI-DME.
- c. Proactive anti-VEGF treatment can reduce the chance of developing CI-DME with vision loss by 16% and improve vision in patients who do progress to CI-DME.
- d. Proactive anti-VEGF treatment has no impact on risk of progression and does not provide a visual benefit in patients who progress to PDR.

12. Patients with diabetes are _____ times more likely to develop cystoid macular edema after cataract surgery compared with patients with diabetes.

- a. 2 times
- b. 3 times
- c. 4 times
- d. 5 times

13. Based on the ETDRS Research Group, what is the approximate risk for progression to PDR from severe NPDR in just 1 year?

- a. 20%
- b. 30%
- c. 40%
- d. 50%
- e. 60%

Diabetic Retinopathy Update: Best Practices in Referrals, Screening, and Treatments

Diabetes is a public health crisis, affecting almost 30% of the US population over the age of 65. Patients with diabetes require lifelong management and multidisciplinary care to mitigate its wide range of microvascular and macrovascular complications that include potentially blinding diabetic eye diseases such as diabetic retinopathy (DR) and diabetic macular edema (DME). Optometrists are often the first line of defense in screening patients for diabetic eye disease and need to know when to refer patients to a retina specialist for treatment, as research has shown that patients can maintain good vision if treated early and consistently with anti-VEGF therapy.²

However, there remains a debate as to when to refer patients with DR to an ophthalmologist for treatment, as well as the best point in the disease process to initiate treatment. Many of these decisions are nuanced and based on specific patient characteristics and the treating optometrist's comfort level. Clinicians must be able to accurately predict which patients are at risk for progression to DME in order to provide timely referral. The following roundtable convenes optometrists and retina specialists for a robust discussion on the comanagement of patients with diabetic eye disease.

-Andrew A. Moshfeghi, MD, MBA, Moderator

US PREVALENCE OF DIABETES AND DIABETIC RETINOPATHY

Andrew A. Moshfeghi, MD, MBA: Diabetes, DR, and DME are becoming more and more of a problem in the United States. Diabetes is a growing public health crisis, affecting 1 in 10 Americans. It's estimated that 75% of diabetic patients will develop DR within 15 to 20 years of diagnosis; 11% of those patients will develop DME.^{3,4} We see this increase in both rural and urban populations, and it's affecting every level of society.

I'm based at an academic medical center in Los Angeles, and I work out of three locations. At the main office in the heart of Los Angeles, I see a lot of DR and DME. At the suburban Pasadena location, I see fewer cases of DR and DME and more age-related macular degeneration (AMD). At the Los Angeles County location, nearly all my patients have DR and DME. Although every location has diabetic eye disease, different settings have varying prevalence. Do you see similar trends in your areas?

Frank G. Zheng, OD, MS: I practice in a private optometry office in Lafayette, California. I'd say up to 40% of our patients have diabetes. Most patients are prediabetic or have some degree of metabolic syndrome.

Veeral S. Sheth, MD, MBA, FACS: I'm in private practice in Chicago and have an academic affiliation with the University of Illinois. We see more diabetic eye disease in the urban area and more AMD in the suburbs and rural Illinois. I see patients with either type 1 and type 2 diabetes and patients with severe diabetic eye disease.

Roger A. Goldberg, MD, MBA: I'm in private practice as well, but in the San Francisco Bay Area. We have eight offices and incredible diversity in our patient populations, from the very wealthy to people experiencing homelessness. There's a large medically underserved community in the Bay Area. My patients run the gamut. I have patients with advanced diabetes and diabetic eye disease who are undiagnosed, and other patients who are the "worried well" with 20/20 VA and some mild dot hemorrhages but no DME.

Mark Dunbar, OD, FAAO: I practice at the University of Miami's Bascom Palmer Eye Institute. My practice is a typical hospital-based practice in which I see a good mix of patients with primary and secondary eye care problems. A significant percentage of my patients are geriatric. I see lots of patients with diabetes as well as other medical conditions such as dry eye disease, glaucoma and cataract. I'd say about one-third of my patients have diabetes in addition to other chronic conditions.

NUANCES IN REFERRALS

Dr. Moshfeghi: The American Academy of Ophthalmology recommends anti-VEGF treatment and retina specialist referral for patients with center-involved DME (CI-DME), regardless of the nonproliferative DR (NPDR) level (Table).5 From an optometry perspective, how do you decide when to refer a

TABLE. AMERICAN ACADEMY OF OPHTHALMOLOGY MANAGEMENT RECOMMENDATIONS FOR PATIENTS WITH DIABETES ⁵					
Severity of Retinopathy	Presence of Macular Edema	Follow-up (Months)	Panretinal Photocoagulation Laser	Focal and/or Grid Laser	Anti-VEGF Therapy
Normal or minimal NPDR	No	12	No	No	No
Mild NPDR	NO	12	No	No	No
	NCI-DME	3-6	No	Sometimes	No
	CI-DME	1*	No	Rarely	Usually
Moderate NPDR	NO	6-12	No	No	No
	NCI-DME	3-6	No	Sometimes	Rarely
	CI-DME	1	No	Rarely	Usually
Severe NPDR	NO	3-4	Sometimes	No	Sometimes
	NCI-DME	2-4	Sometimes	Sometimes	Sometimes
	CI-DME	1	Sometimes	Rarely	Usually
Non-high-risk NPDR	NO	3-4	Sometimes	No	Sometimes
	NCI-DME	2-4	Sometimes	Sometimes	Sometimes
	CI-DME	1	Sometimes	Sometimes	Usually
High-risk NPDR	NO	2-4	Recommended	No	Sometimes
	NCI-DME	2-4	Recommended	Sometimes	Sometimes
	CI-DME	1	Recommended	Sometimes	Usually
	red include intravitreal corticosteroids or anti-VEGF a dothelial growth factor; CI-DME, center-involved diab		er-involved diabetic macular edema; NPDR, nonproliferative diabe	tic retinopathy; PDR, proliferative diabetic ret	inopathy.

patient to a retina specialist for diabetic eye disease? Are you comfortable following a little bit of DR and DME or do you send those patients over right away?

Dr. Zheng: I am really fortunate to have access to an optical coherence tomography (OCT), a fundus camera, and an Optos ultra-widefield retinal scanner with autofluorescence capability in my office. With this technology, I am more comfortable following mild DR and mild NPDR instead of referring immediately to the retinal specialist. However, after the disease advances to moderate stage NPDR, I would refer. I am a lot more conservative with CI-DME and cystoid macular edema (CME). I'll refer these patients immediately because early treatment has been shown to provide better prognosis.

Dr. Dunbar: It's interesting how my practice patterns and referrals have evolved over the past 10 years. Traditionally, we would follow patients until they developed proliferative diabetic retinopathy (PDR) or clinically significant macular edema, and then refer at that time because that was the indication for treatment and we didn't want to overburden the retina specialists if they weren't going to treat. But now, we're referring patients to retina specialists much earlier based on clinical data that have come out over the past few years.

The data from the PANORAMA study showed that earlier treatment with anti-VEGF therapy may be beneficial in patients with moderately severe to severe NPDR. PANORAMA study investigators enrolled 402 patients with Diabetic Retinopathy Severity Scale (DRSS) scores of 47 and 53.6 The primary endpoint was the number of patients who had at least a 2-step reduction in DRSS with two different dosing

intervals of aflibercept compared with placebo. Patients were treated either every 8 weeks after five monthly loading doses or treated every 16 weeks after three monthly loading doses. At 52 weeks, 65% and 80% of patients in the aflibercept 8-week and 16-week arms, respectively, had at least a 2-step DRSS improvement compared with 15% in the placebo group. At 100-week follow-up, 62% of patients who continued 16-week aflibercept maintained at least a 2-step DRSS improvement rate compared to baseline. Treatment with aflibercept at 2 years also reduced the likelihood of vision-threatening events, including progression to PDR, by at least 75%.7

Multiple post-hoc analyses of the phase 3 RIDE and RISE trials have illustrated that anti-VEGF treatment improves disease in patients with moderately severe NPDR, further adding to the evidence that patients with DR and DME should be referred to retina specialists earlier in the disease process to maximize visual outcomes.8,9

The message now is that we need to refer patients with anything more than moderate NPDR. Since the advent of widefield imaging, we carefully scrutinize the level of retinopathy a patient has and realize that it's much harder to determine the extent of the retinopathy without the use of widefield imaging. Certainly, all patients with CI-DME should be referred, regardless of their visual acuity.

Dr. Moshfeghi: Before we had imaging platforms such as OCT and OCT angiography (OCT-A), and before we had anti-VEGF therapy, the decision to refer was a bit easier. There was less urgency. But now with anti-VEGF treatments and data showing that patients who receive treatment early do better,

it's made referral decisions more challenging. For our retina specialist panelists, when you receive a referral from an optometrist, what are your impressions? Do you wish the patient was referred earlier or are you wondering why they were referred?

Dr. Sheth: If you asked me this question a couple of years ago, I'd say I was referred patients earlier than needed. That is no longer the case. I'm now seeing patients with moderate to severe NPDR without DME. We've improved our understanding of the disease state and now know that these moderate and severe NPDR cases can worsen quickly. Patients with moderate NPDR without macular edema can rapidly progress to PDR before their next evaluation; 12% to 27% of patients with moderate NPDR without macular edema will progress to PDR within 1 year. 11 Managing these patients isn't about necessarily intervening, but watching them more closely. There are other important variables, too, such as hypertensive status, HbA1c levels, and cholesterol profiles. 12 We need to monitor their overall medical status. 13,14 We've done a a great deal to educate referring doctors, which has improved referrals, because there was a time when people weren't referred early enough.

Dr. Zheng: Also keep in mind it depends on the type of practice and diagnostic tools different practices have. In some settings, optometrists don't have access to all the imaging technologies retina specialists do, such as OCT or fundus cameras. This may also impact when an optometrist should refer.

Dr. Goldberg: I'm glad you brought that up, Dr. Zheng. Many corporate optometrists, because they're seeing patients on a vision plan and not a medical plan, don't have advanced imaging capabilities. I don't know if we would call an OCT an advanced imaging capability anymore; it should be standard of care. Large clinical trials, such as RIDE and RISE, rely on OCT imaging over stereoscopic photographs or a clinical exam because it allows for an objective measurement of retinal thickening. 2,15 But because these corporate practices aren't billing medical insurance, they aren't reimbursed for OCT and don't always have an OCT in the office.

Dr. Dunbar: That's exactly right. I'd say about 50% of optometrists have OCTs. In those practices, an optometrist may be comfortable monitoring mild and even moderate disease. Many will refer if it's anything more than mild just to be on the cautious side. If a patient has any sign of macular edema, they'll also refer, but many will monitor early-stage DR.

Dr. Goldberg: I think that strategy is appropriate. According to the DRCR.net Protocol V, patients with CI-DME can be observed as long as the patient has good vision; anti-VEGF injections are only needed if vision deteriorates.¹⁶

A total of 702 patients with CI-DME and VA of 20/25 or better were enrolled in Protocol V across 91 clinical sites. Patients were randomly assigned to treatment with monthly aflibercept injections (n = 226), laser photocoagulation (n = 240),

or observation (n = 236). Patients in the laser group were retreated at 13 weeks, if needed. Patients in both the laser and observation groups were monitored closely and switched to aflibercept if they lost 2 or more lines of VA at two consecutive visits. At 2 years, the number of patients who lost 5 or more letters of VA did not significantly differ between groups, with the average VA of 20/20.

Protocol V has a strict observation protocol, which needs to be established at baseline with the retina specialist. We not only need to talk to the patient about controlling their blood sugar and blood pressure, we need trackable baseline imaging so we know when to intervene.

Dr. Zheng: In your communities, how fast can the optometrist contact the retina specialist and get the patient in for an appointment? Do you find many delays in referrals because of the retina specialist's availability?

Dr. Goldberg: I certainly hope patients don't have a problem getting in. Retina specialists are used to seeing patients in an emergency. Access isn't a problem, at least not where I practice. It could be an issue in rural communities where patients have to travel several hours for a retina appointment. In those cases, I suspect the challenge isn't necessarily on the retina specialist side, it's logistical challenges on the patient side. Patients in rural communities face many barriers to follow-up appointments and treatment adherence including infrequent use of health care, long travel distances, poverty, distrust of health care providers, anxiety, and the overall burden of diabetes management.¹⁷

Dr. Sheth: There are many variables at play here. Geography matters. The optometrist's relationship with the retina specialist matters. I had a situation just this week where a patient called a different retina specialist because he converted to PDR and could not get an appointment for another month. The optometrist called our office and we saw the patient within 2 days. There are often many reasons why referral appointments are delayed. To me, the take-home point is that if you know a patient with moderate disease has a 27% chance of progressing within 1 year, refer them earlier before they progress, so it doesn't become an emergency.

Dr. Goldberg: I do a lot of clinical research in my practice. In studies such as PANORAMA, which looked for various levels of DR, there was a high screen failure rate. I think what happens is what looks clinically like moderate NPDR on imaging is actually scored by these reading centers as the moderately severe and severe levels 47 and 53, which we know is the highest risk group. Then we're surprised by how fast the supposedly "moderate" NPDR progressed. It actually wasn't fast at all; the patient already had severe disease. Most of us aren't there looking at the photo, counting dot blot hemorrhages in each quadrant, and comparing them to standard reference photographs like

they do at reading centers in clinical trials. The disease is often more severe than you think.

Dr. Sheth: I agree. We're involved in many of these clinical trials and I am still surprised at my inability to read these perfectly like the reading centers. Taking that one step further, you do widefield angiographies on these patients and you're not expecting to see the level of ischemia or capillary drop out that you do. These are important factors in how you decide to manage patients and how closely you're going to follow them.

Dr. Moshfeghi: We've discussed that optometrists in commercial retail settings do not have access to OCT. Do they have any imaging diagnostic tools to use, like a widefield or a nonmydriatic camera?

Dr. Dunbar: A lot of them have an Optos device.

Dr. Moshfeghi: Optometrists are sending diabetic patients for referrals based upon their clinical exam. Would you say that the majority of optometrists will go to a general ophthalmologist and then the general ophthalmologist will send the patient to the retina specialist?

Dr. Dunbar: No, not at all. Most optometrists are good about referring directly to the retina specialist. That is, unless you're in a rural setting where access to a retinal specialist may be a challenge. In these settings, a comprehensive ophthalmologist may be administering intravitreal injections. I think optometrists recognize the importance of sending patients directly to a retina specialist.

Dr. Goldberg: I've found that if the optometrist doesn't have an OCT, they reach for other diagnoses like cataract as the reason why the patient won't refract to 20/20. They send the patient to a general ophthalmologist who has an OCT, who will then find swelling in the retina. OCT-A is another advanced imaging technique that has proven useful for diagnosis and monitoring of DR.¹⁸ OCT-A can detect more subtle microvascular changes before clinically significant DR develops.¹⁹

MAINTAINING COORDINATED CARE BETWEEN OPTOMETRY AND OPHTHALMOLOGY

Dr. Moshfeghi: Have you had success comanaging patients after they have been introduced to the retina specialist?

Dr. Dunbar: I don't know that there are many opportunities to co-manage these patients because many patients who undergo treatment are often seen and followed by the treating ophthalmologist for extended periods. These patients are watched very carefully by the retina specialist. As a result, they don't always make it back to their primary eye care doctor—or, if they do, it's usually to update a glasses prescription. With many ODs having OCT in their offices, you would hope that would create an opportunity for better comanagement.

Dr. Zheng: I think comanaging works very well. I have had many patients with moderate case of DR who I referred to my retinal colleagues. They had their anti-VEGF injections from the retina specialist and would come back to me for their annual eye exam and get their updated glasses prescription.

Dr. Moshfeghi: When you see that patient back, do you repeat the OCT on that visit?

Dr. Zheng: I do, but I might not bill for it because insurance most likely will not cover it. I often repeat the OCT because I want to know how their macula is doing, and it helps guide the refraction. One of the reasons I like working with Dr. Goldberg is because he's really good about sending us the report. Many times, when we send patients out to retina specialists, we don't receive any communication.

Dr. Goldberg: Another point I want to make regarding comanagement is that we're not simply comanaging the DR, we're comanaging the patient. The retina specialist does not do frontline eye care work. If the patient is a glaucoma suspect, for example, I'm sending them back to their referring doctor to manage that. Oftentimes, if an optometrist sends me a patient with DME or DR, they've held the glasses prescription because the optometrist wants my diagnosis first. That's where communication becomes really important. It's up to me to come back to the optometrist and communicate my management plan so the patient has their refraction corrected properly. We also know that cataract progresses more quickly in diabetic patients; diabetes is associated with a 5-fold higher prevalence of cataract. 20,21 Before they need cataract surgery, they might need to have their refraction updated once or twice.

Dr. Moshfeghi: When I treat a patient for DR or DME, and then recognize their cataracts are worsening, it's easy for me to send the patient to a cornea specialist or a comprehensive ophthalmologist at my academic center. It's easy to forget that the referring doctor who referred that patient may prefer to make that decision about cataracts or have that conversation with the patient. Does anyone have tips for managing this?

Dr. Sheth: I document who referred each patient in their electronic health record. I want to make sure we keep that line of communication open with the referring physician so we can send the patient back when the time comes for their yearly refraction or quarterly glaucoma check. Keeping the referring physician at the top of my notes helps me remember where the patient needs to go.

Dr. Goldberg: I'm also very mindful of this because referrals are the life blood of private practice. If I see that a cataract is getting worse, I'll call the referring optometrist and ask what they'd like to do. Do they want to comanage the patient or should I refer them to a cataract specialist? It works well because it's another touchpoint. It helps build the relationship and connection between retina specialists and optometrists.

Dr. Zheng: When optometrists take care of patients, we often have a particular surgeon in mind in anticipation of referring the patient for cataract, cornea, or retina care. When I send a referral over, I'll list the known issues of the patient in my letter to outline my plan for the next couple of years. We can estimate what's going to happen. For example, if a patient has an epiretinal membrane, the optometrist knows they're going to need cataract surgery after the peel. You might as well lay it out for the patient and the referring doctor. It really helps with patient education.

CASE 1: MANAGING A PATIENT WITH PDR AND DME

Dr. Moshfeghi: Our first case is of a 36-year-old white male who was diagnosed with type 2 diabetes at age 24. He has hypertension, kidney disease, and obesity, and presented with decreased vision in both eyes. The patient was being followed annually by his optometrist, who never noted DR, according to the patient. He was referred to retina for new, extensive retinal hemorrhages in both eyes that were not there during his previous annual exam. His latest HbA1c is 7.6%. His VA is 20/50 OD and 20/40 OS. His intraocular pressure is 16 mm Hg. The dilated fundus exam showed a clear vitreous but nearly 360° neovascularization of the disc in both eyes. His vessels are dilated and tortuous, with arteriovenous nicking and silver wiring OU. The macula has scattered intraretinal hemorrhages, cotton wool spots, and macular edema in both eyes. He has scattered intraretinal hemorrhages in all four quadrants, mostly in the mid-periphery, and neovascularization elsewhere OU. The exam is consistent with a diagnosis of PDR and DME, in both eyes. How would you treat this patient?

Dr. Goldberg: This patient has advanced diabetic retinopathy with DME, and needs prompt treatment. He has already lost a significant amount of vision, some of which may not be recoverable and is a ticking time bomb for massive vision loss, either from a vitreous hemorrhage or diabetic tractional retinal

detachment. I would certainly treat this patient with a series of anti-VEGF agents in both eyes. Given the disease severity and the results of DRCR Protocol T,^{22,23} which compared the three most commonly used agents head-to-head-to-head, I would likely initiate treatment with aflibercept. This was shown to have better outcomes in the first year for patients with 20/50 or worse VA. Based on my sense of the patient's reliability, I would have a low threshold to apply panretinal photocoagulation (PRP)—not the scorched earth laser of our predecessors, but targeted to ischemic retina, generally anterior to the equator—to prevent the worst outcomes if the patient were to be lost to follow-up.

Dr. Sheth: I agree with Dr. Goldberg's plan for this patient. I think using monthly anti-VEGF injections to "cool" this eye off are critical for short-term stabilization of these eyes. I don't do a lot of angiograms, but these are cases where I believe they play an important role in assessing disease activity. After the neovascularization has regressed and the DME is under better control, I would add PRP. To Dr. Goldberg's point, I don't do heavy 360° PRP. I use the angiogram to guide my PRP application and focus on areas that are poorly perfused. The hope is that, with PRP, we are able to achieve better long-term control of the disease and decrease the likelihood of vision loss from complications such as vitreous hemorrhage or traction retinal detachment.

Dr. Moshfeghi: Recently published results from Protocol S address how to treat this patient.²⁴ Protocol S compared PRP with ranibizumab 0.5 mg in 394 diabetic eyes (305 patients) with PDR. Patients received either one to three sessions of PRP or ranibizumab every 4 weeks for 12 weeks, then as needed. Patients could receive rescue PRP if needed. Patients in the PRP arm could also receive ranibizumab for concomitant DME. The primary outcome was mean change in BCVA at 2 years.

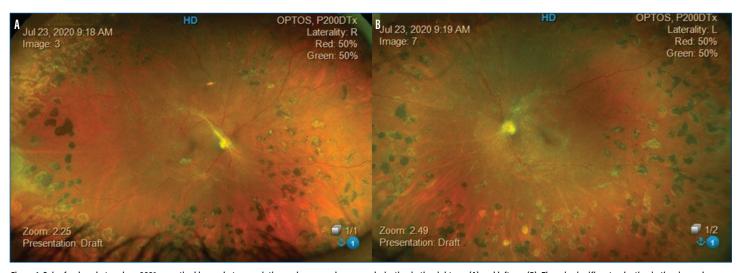


Figure 1. Color fundus photos show 360° panretinal laser photocoagulation and regressed neovascularization in the right eye (A) and left eye (B). There is significant reduction in the size and quantity of intraretinal hemorrhages OU.

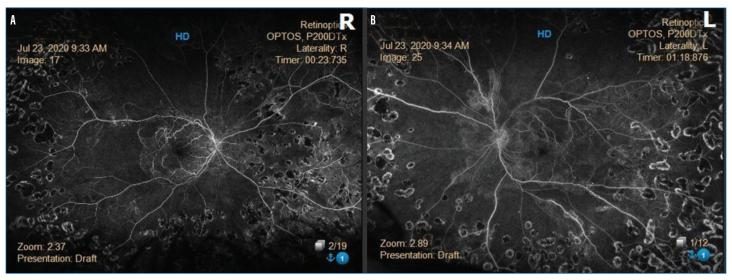


Figure 2. The most recent (ie, July 2020) fundus autofluorescence imaging in this patient's right (A) and left (B) eye shows the absence of leakage and persistent peripheral nonperfusion.

At 2 years, ranibizumab was noninferior to PRP with a mean BCVA improvement of 2.8 letters in the ranibizumab arm and 0.2 letters in the PRP arm. More patients in the ranibizumab arm gained 10 or more letters than patients in the PRP arm.²⁵

This patient received two injections of ranibizumab and two rounds of PRP OU. He had an excellent response to medical management, with VA improvement to 20/25 OD and 20/20 OS. Figure 1 shows his imaging a year and a half after treatment. Figure 2 shows his latest fluorescein angiography (FA) from July 2020. Figure 3 shows his latest OCT in December 2020, 2 years posttreatment.

With the approval of anti-VEGF therapy for DR (regardless of whether DME is also present), retina specialists now have more therapeutic options in managing the patient with PDR. Often times, we don't use one therapy or another, but integrate both anti-VEGF therapy and PRP. Many retina specialists will start a new PDR patient with intravitreal anti-VEGF agents (as was done in this case) to calm the ischemic drive down initially and then follow that up with consolidating and lasting PRP laser therapy.

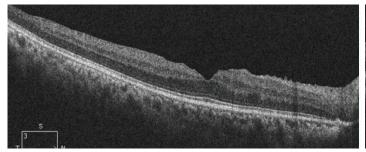
With this approach, there is less urgency to get the laser completed quickly and there may potentially be an opportunity to do a "less-than-full" PRP pattern, although rigorous data are lacking to support these intuitive assertions.

CASE 2: HOW PENDING CATARACT SURGERY AFFECTS DME MANAGEMENT

Dr. Moshfeghi: How do you manage a patient with DME who is already scheduled for cataract surgery? Does the pending cataract surgery affect your treatment plan compared with those who already had cataract surgery or won't be having cataract surgery anytime soon?

Dr. Sheth: As long as I know when they're having their cataract surgery, we can plan a pre- and postsurgical visit depending on how stable they are. Are we actively treating them? Are they getting treatments every 2 or 3 months? There's a lot that goes into the scheduling. I don't delay the cataract surgery; we work around it in these scenarios.

Dr. Goldberg: I'm not as stringent on injections before cataract surgery. I usually treat them 1 to 2 weeks before cataract surgery because I want to concurrently control any postoperative CME. Diabetic patients are 4 times more likely to develop CME after cataract surgery compared with nondiabetic patients. ²⁶ I



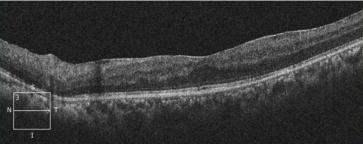


Figure 3. The most recent (ie, December 2020) OCT imaging in this patient shows evidence of mild epiretinal membrane and resolution of CME, subretinal fluid, and hard exudates in both eyes. The excellent appearance of his OCT corresponds to his excellent visual acuity. The patient's VA remained stable at 20/25-1 OD and 20/20 OS.

like to time an injection in advance of cataract surgery, targeting 1 to 2 weeks beforehand. That said, I have injected 3 days before. Postoperatively, I like to give the corneal incision time to heal (ie, at least 2 weeks) before administering an injection.

Dr. Moshfeghi: Because of the CME risk in diabetic patients. nonsteroidal anti-inflammatory drugs and corticosteroids are needed to manage postoperative inflammation.^{27,28} The dexamethasone intravitreal implant, a sustained-release implant containing 700 µg of dexamethasone, has been approved by the US Food and Drug Administration for DME based on the findings of the MEAD trial.^{29,30} How does cataract surgery impact the timing of administering the dexamethasone implant? Do you wait longer after cataract surgery, or is it within the same timeframe?

Dr. Goldberg: I would wait a little bit longer before injecting a dexamethasone implant both before and after surgery. Its efficacy peaks at about 6 to 8 weeks after treatment, so I like to pretreat eyes with a dexamethasone implant about 3 to 4 weeks prior to cataract surgery. You want to dampen any CME that might occur in addition to the DME.

CASE 3: TREATING A PATIENT WITH HIGH-RISK PDR AND UNCONTROLLED DIABETES

Dr. Moshfeghi: Our next case comes from a colleague, and it concerns a 42-year-old man with type 2 diabetes who presented for a comprehensive eye examination. He has no visual complaints, but his last eye exam was 10 years ago. He is on insulin and his diabetes is poorly controlled. He does not check sugars regularly, and his last HbA1C was 10.0%. He has a history of hypertension. His VA is 20/20 uncorrected, and his intraocular pressure is 15 to 16 mm Hg.

Anterior segment examination is unremarkable. FA late frames reveal nonperfusion and late leakage in the right eye consistent with a diagnosis of high-risk PDR with neovascularization of the disc and elsewhere (Figure 4). FA late frames of the left eye reveal nonperfusion and less prominent leakage consistent with neovascularization elsewhere and a diagnosis of PDR.

Figure 5 shows the OCT-A imaging and large fronds of neovascularization. Although they were visible on FA, they were much easier to view on OCT-A. What is your treatment plan for this patient?

Dr. Sheth: Unfortunately, these cases are all too common. There are a couple of features that I would highlight here. First, we often see this type vision/disease mismatch, especially as our imaging modalities improve. This patient came in with 20/20 uncorrected VA yet clearly has severe disease in both eyes. The OCT-A here is quite impressive. The red flags here are that this patient has not had an eye exam in over a decade and presents with a very high HbA1c. These are patients that I treat aggressively as their disease can progress rapidly and we are never sure how long a window of opportunity we will get with these patients. I would start this patient on anti-VEGF therapy immediately and quickly add PRP to the areas of nonperfusion as I am worried that they could disappear again.

Dr. Goldberg: This is a great case with excellent imaging. While the ultra-widefield FA is critical at the time of diagnosis, I find OCT-A can be used to monitor flow through the neovascularization, which can help guide treatment. In terms of treatment, this patient has a clear history of noncompliance, with a 10-year gap in eye exams, and poor sugar control. I would start with anti-VEGF injections, but again, I have a low threshold to add PRP, especially if I was concerned about the patient getting lost to follow-up. There's still some art to medicine, and treatment plans need to be tailored to each individual patient.

Dr. Moshfeghi: I believe the optimal treatment for a patient like this is to get the systemic disease and comorbidities under control while simultaneously managing the acute intraocular aspect of his diabetes. The important thing here is to control the neovascularization with anti-VEGF therapy and/or PRP while aiming for euglycemia and blood pressure control. In a case like this, I like to use intravitreal anti-VEGF therapy to get things stabilized quickly from an ocular standpoint and then to add PRP.

This next question is for our optometry colleagues. Let's say we see a patient that we believe has either a very severe NPDR or possibly an early-stage or high-risk PDR patient. Do you talk to that patient about some of the newer ways of managing PDR? Or do you refer to the retina specialist to talk about therapies?

Dr. Dunbar: I wrestle with this question a lot. Obviously, I let the patient know that they have vision-threatening disease and they have to be seen regularly given the risk of vision loss. I try to make sure they understand while also being encouraging about the treatment options. Treatments are effective to preventing progression to PDR. Data from Protocol W showed that aflibercept reduced the progression of diabetic eye disease; patients who received preventative affibercept had a 16% chance of developing CI-DME with vision loss or PDR compared with 43% of patients in the control arm.31 However, there was no visual benefit from preventative treatment with aflibercept at 2 years compared with observation after PDR or CI-DME developed, so the results were mixed.

When counseling patients on their treatment options, I often avoid describing the treatment as a needle in the eye because I don't want them to dwell on that and not show up. There are some patients who would rather go blind then get a shot in their eye, all because of unfounded fears. However, other patients need to hear exactly what the treatments entail so they can prepare. You have to read the patient a bit and gauge what you think their reaction will be. It's also not entirely clear to many optometrists how the patient will be treated. Will the patient get some degree of combination therapy of PRP and an injection? Or are they going to get injections only?

Protocol S found that anti-VEGF injections do a bit better than traditional PRP, but most retina specialists I work with seem to do a combination of PRP and anti-VEGF.25 So I try to avoid a discussion about what the treatment entails, specifically.

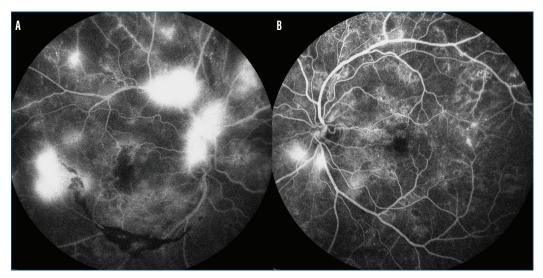


Figure 4. FA late frames of the patient's right (A) and left (B) eye. Nonperfusion and late leakage was observed in right eye, which was consistent with a diagnosis of high-risk PDR with neovascularization of the disc and elsewhere. Nonperfusion and less prominent leakage consistent with neovascularization elsewhere and a diagnosis of PDR was observed in the left eye.

Dr. Zheng: I agree: I don't talk about the intravitreal injection, and I don't talk about PRP. I leave that up to the retina specialist. I don't know what the best treatment is for the patient. I don't want to tell them one thing and have it end up being something else. I also don't want to discourage them from seeing the retina specialist. Instead of speculating, I focus on what I can show the patient. I focus on the imaging in front of me. I point out the bleeding. I tell them they need a referral and educate them on the importance of HbA1c control. The patient may be aware that their HbA1c is high and that their vision is blurry. When you're able to validate that, and tell them they need a referral, it's almost a sigh of relief for them.

Dr. Moshfeghi: Severe NPDR or early PDR is a very different scenario from CI-DME. Many of these patients are asymptomatic and view it as a pain to go see yet another doctor. They think their vision is fine and don't understand why they need a referral. When you explain that they could go blind, they don't believe you. With DME, the patient notices the decline in vision and want you to help them.

Dr. Goldberg: I have found that when a patient knows about the treatment in advance, it makes the conversation easier for me. Of course, I have patients who are referred and never come into the office. But I've found that if the optometrist has gone over the treatment options before the patient comes to me, then it saves me some chair time.

Dr. Sheth: Patients with DME and patients with NPDR and good vision have different expectations. I agree with Dr. Goldberg that it is nice when a patient comes in and knows an injection is a possibility because you're not the one breaking this news to them. I treat many DME patients the same day because I don't want to tell them they have to get an injection in their eye, then have them go home and let them dwell on that and the surrounding fear for a week or two. Unplanned treatments like this can throw a wrench into the clinic, but we have to get the patient over this hump. After the first injection, the patient will realize it's not as bad as they thought and their vision will improve. That's what brings them back for additional treatment.

For patients with NPDR, my approach is a bit different. I'm less aggressive with them in these initial visits, and I spend a

lot of time educating them. I show them the pictures of nasty, scary bleeding in the eye. I follow them closely and show them whether it's changing or not. After they've bought into the fact that they have a diseased eye, I'll discuss potential therapies. I'm a little more hands off in the very beginning with the treatment standpoint for those patients because I feel I have time.

Dr. Zheng: One of the most common things my patients tell me is that they're scared of getting that injection in their eye. But after the first shot, most patients say it's not that bad. I've had patients who refused to get the shots and say they'd rather go blind. They can't get a shot in the eye, they think it will kill them. If we can get them over that initial reaction, they'll say it wasn't as bad as they thought, and compliance is significantly improved.

Dr. Moshfeghi: Every retina doctor will tell you the exact same experience from when we're describing informed consent with the patient. The patient is looking at you like you're crazy, sticking a needle in their eye. And then afterward, they realize it is no big deal.

Dr. Dunbar: From an optometrist perspective, it's one of the most difficult discussions that we have. Do we tell them, or do we not tell them? It's one of the hardest decisions we have to make.

Dr. Goldberg: A lot of it, I think, comes down to the art of medicine. I want the optometrist to do whatever they feel is necessary at the time. What does this patient, specifically, need to know? How anxious are they? Some patients don't want to know anything, and other want to know about every single study that's been published. I rely on your good judgement on how much, or how little, to communicate.

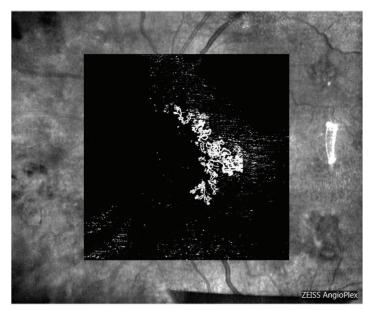


Figure 5. Neovascularization of the disc as depicted on OCT-A at baseline.

Dr. Moshfeghi: This has been an exceptionally informative discussion. I always learn something when we have a panel discussion like this, and this is no exception. Thank you for taking the time to discuss best practices and future developments in the management of DR.

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DIABETIC RETINOPATHY UPDATE: BEST PRACTICES IN REFERRALS, SCREENING, AND TREATMENTS

INSTRUCTIONS FOR CE CREDIT

To receive credit, you must complete the attached Pretest/Posttest/Activity Evaluation/Satisfaction Measures Form and mail or fax to Evolve Medical Education LLC; 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950. To answer these questions online and receive real-time results, please go to https://evolvemeded.com/course/2012-supplement-2. If you experience problems with the online test, please email us at info@evolvemeded.com. Certificates are issued electronically; please be certain to provide your email address below.

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		LEARNING	OBJECTIVES			
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• •	oatients need early referral patterns, disease state, and	to a retina specialist based o l/or other risk factors.	n			
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Explain the late	st treatment approaches t	o DR/DME.				
Describe novel	develonments in DR scree	ninσ				

PLEASE COMPLETE AT THE CONCLUSION OF THE PROGRAM.

- 1. Based on this activity, please rate your confidence in your ability to identify which patients need early referral to a retina specialist based on their behavioral patterns, disease state, and/or other risk factors (based on a scale of 1 to 5, with 1 = "Not at all confident" and 5= "Very confident").
 - a. 1
 - b. 2
 - c. 3
 - d. 4 e. 5
- 2. Based on this activity, please rate how often you intend to apply advances in treating diabetic eye disease to "real-world" patient management (based on a scale of 1 to 5, with 1 being never and 5 being always).
 - a. 1
 - b. 2
 - c. 3
 - d. 4
 - e. 5
- 3. A 65-year-old patient with type 2 diabetes returns for annual follow up. The patient's last HbA1c was 9.1%, blood pressure was 140/93 mm Hg, and the patient had dyslipidemia. The patient's VA on presentation was 20/20 and intraocular pressure was 14 mm Hg OU. The anterior segment examination was nonsignificant except for bilateral cataracts. The posterior segment examination was significant for severe nonproliferative diabetic retinopathy (NPDR). There is no sign of diabetic macular edema (DME) in both eyes.

Action	Consistent	Nonconsistent
Widefield fundus photography		
Electroretinogram/electrooculography measurements		
Repeated exam in 3-6 months		
Referral to endocrinology for better glucose control		
Early cataract extraction		
Anti-VEGF treatment for severe nonproliferative disease		
Intravenous fluorescein angiography (FA)		
Indocyanine green (ICG)-angiography		
Optical coherence tomography angiography (OCT-A)		
Relaxed control of blood pressure		
Control of lipids		

- 4. A 42-year-old Black man presents to an optometry practice complaining of blurry vision. He has been in treatment for type 2 diabetes for 7 years, which was well-controlled until stay-at-home orders began for the COVID-19 pandemic. He is on insulin once a day. He missed his annual diabetic eye exam due to fear of medical exams during the pandemic. He noticed blurry vision about 8 months ago, but was too nervous of COVID-19 exposure to come in. He says he feels better about the pandemic now and has been vaccinated, but is wary and nervous, based on his body language. His HbA1c is 12%. He has a history of hypertension and obesity. His BCVA is 20/50 OU. The exam showed moderate NPDR with several hemorrhages, cotton-wool spots, thickening and noncenter-involved DME. What are the next steps for this patient?
 - a. Correct the refractive error and follow the patient closely for the next 3 months to see if disease progresses.
 - b. Refer the patient to a retina specialist immediately for anti-VEGF injections and use the opportunity to explain that he will receive injections in his eye on a monthly basis for the rest of his life. Explain to the patient that you will correct the refraction after they've been seen and treated by the retina specialist.

- c. Correct the refractive error and explain to the patient that you'd like to refer them to a retina specialist colleague for further evaluation and possible treatment; emphasize the importance of follow-up.
- d. Correct the refractive error and schedule the patient for their yearly diabetic eye exam in a year. They do not need a referral.
- 5. Approximately _____ of patients will develop DR within 15 years of diabetes diagnosis.
 - a. 50%
 - b. 80%
 - c. 60%
 - d. 75%
- 6. The phase 3 PANORAMA results suggest that diabetic patients may be at an elevated risk of vision threatening complications at what point in their diabetic eye disease?
 - a. When they progress to more than moderate NPDR
 - b. When they progress to proliferative DR (PDR)
 - c. When they progress to center-involved DME (CI-DME)
 - d. When they progress to mild NPDR
- 7. The American Optometric Association's guidelines for treating patients with diabetes notes some studies have found ______ of patients with moderate NDPR without DME will progress to PDR in 1 year.
 - a. 10% 25%
 - b. 12% 27%
 - c. 15% 30%
 - d. 50% 75%
- 8. A 56-year old white female with type 2 diabetes was referred to a retina practice by an optometrist for DME treatment. She's had well-controlled diabetes for 20 years. Her HbA1c is 7%, and she has complained of decreased vision OS, specifically, for the last 6 months. Her vision is 20/25 OD and 20/40 OS. In addition to DME, you note that she needs cataract surgery in her left eye. What is the most appropriate next for this patient?
 - a. The retina specialist should refer her to cataract surgery and opt not to treat the DME until the cataract surgery is completed.
 - b. The retina specialist should treat her with intravitreal anti-VEGF therapy and call the referring optometrist to discuss how to comanage the cataract.
 - c. The retina specialist should treat her with an intravitreal anti-VEGF agent and defer cataract surgery altogether.
 - d. The retina specialist should treat her with panretinal photocoagulation and defer cataract surgery altogether.
- 9. What imaging is now considered standard of care for evaluating patients with DME?
 - a. OCT-A
 - b. Autofluorescence imaging
 - c. Retinal fundus photography
 - d OCT
- 10. Because of the risk of cystoid macular edema in patients with diabetic eye disease who are undergoing cataract surgery, _____.
 - a. Never use corticosteroids postoperatively.
 - b. Only use anti-VEGF agents before cataract surgery.
 - c. Using either an anti-VEGF or a corticosteroid implant before or after cataract surgery is acceptable.
 - d. It is common to insert a corticosteroid implant at the time of cataract surgery.

11. One takeaway from the Protocol W trial was that:

- a. Proactive anti-VEGF treatment can reduce the chance of developing CI-DME with vision loss by 16%.
- b. Proactive anti-VEGF treatment does not reduce the chance of developing CI-DME, but has significant visual benefit in patients who progress to CI-DME.
- c. Proactive anti-VEGF treatment can reduce the chance of developing CI-DME with vision loss by 16% and improve vision in patients who do progress to CI-DME.
- d. Proactive anti-VEGF treatment has no impact on risk of progression and does not provide a visual benefit in patients who progress to PDR.
- 12. Patients with diabetes are _____ times more likely to develop cystoid macular edema after cataract surgery compared with patients with diabetes.
 - a. 2 times
 - b. 3 times
 - c. 4 times d. 5 times
- 13. Based on the ETDRS Research Group, what is the approximate risk for progression to PDR from severe NPDR in just 1 year?
 - a. 20%
 - b. 30%
 - c. 40%
 - d. 50%
 - e. 60%

ACTIVITY EVALUATION/SATISFACTION MEASURES
our responses to the questions below will help us evaluate this CE activity. They will provide us with evidence that improvements were lade in patient care as a result of this activity.
ate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low
ate your knowledge/skill level after participating in this course: 5 = High, 1 = Low
his activity improved my competence in managing patients with this disease/condition/symptom Yes No
robability of changing practice behavior based on this activity: Yes No No change needed
you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)
Change in pharmaceutical therapy Change in diagnostic testing Change in diagnostic testing Change in current practice for referral My practice has been reinforced Change in nonpharmaceutical therapy Choice of treatment/management approach Change in differential diagnosis I do not plan to implement any new changes in practice
ease identify any barriers to change (check all that apply):
CostLack of experienceLack of resources (equipment)Lack of consensus orLack of time to assess/counsel patientsPatient compliance issues professional guidelinesLack of opportunity (patients)No barriersLack of administrative supportReimbursement/insurance issuesOther. Please specify:
he design of the program was effective
he content supported the identified arning objectives. Yes No You were satisfied overall with the activity. Yes No You were satisfied overall with the activity.
he content was free of commercial bias. ———————————————————————————————————
ease check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through our participation in this activity:
Patient Care Medical Knowledge Practice-Based Learning and Improvement Interpersonal and Communication Skills System-Based Practice
dditional comments:
I certify that I have participated in this entire activity. his information will help evaluate this CE activity; may we contact you by email in 3 months to see if you have made these changes? If so, plear rovide your email address