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MODERN OPTOMETRY

DR & DME: ADDRESSING BARRIERS TO EARLY TREATMENT

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DR & DME: ADDRESSING BARRIERS TO EARLY TREATMENT

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CONTENT SOURCE

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

ACTIVITY DESCRIPTION

This supplement summarizes a roundtable discussion among retina specialists and optometrists on the topic of collaboration for improved care of patients with diabetes. The clinicians review the latest trial data and share their experiences related to the importance of imaging and how early treatment can preserve vision in patients with diabetes.

TARGET AUDIENCE

This certified CE activity is designed for optometrists.

LEARNING OBJECTIVES

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

- **Discuss** the benefits of telemedicine for continued screening of diabetic patients for diabetic retinopathy (DR) and diabetic macular edema (DME) in order to provide timely treatment.
- **Execute** appropriate referrals of patients with DR and DME by working with your network to understand the need for timely referrals to a retina specialist based on the latest clinical data.
- **Interpret** clinical data supporting the treatment of patients with moderate nonproliferative diabetic retinopathy (NPDR) without macular edema with anti-VEGF therapy.
- **Discuss** longer duration therapies for DME and NPDR that are currently under investigation.

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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 execute appropriate referrals of patients with diabetic retinopathy (DR) and diabetic macular edema (DME) by working with your network to understand the need for timely referrals to a retina specialist (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 for the past 10 years 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 the 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 DME in both eyes.

Action	Consistent	Nonconsistent
Early cataract extraction		
Optical coherence tomography angiography		
Intravenous fluoresceing angiography		
Referral to endocrinology for better glucose control		
Relaxed control of blood pressure		
Anti-VEGF treatment for severe nonproliferative disease		
Repeated exam in 3-6 months		
Indocyanine green angiography		
ERG/EOG measurements		
Control of lipids		
Widefield fundus photography		

4. What are the color photograph/ophthalmoscopy features of severe NPDR?

a. Severe hemorrhages in four quadrants, arteriovenous (AV) nicking in two quadrants, prominent intraretinal microvascular abnormalities (IRMA) in one quadrant
b. Severe hemorrhages in four quadrants, venous beading in two quadrants, prominent IRMA in one quadrant
c. Mild hemorrhages in four quadrants, AV nicking in two quadrants, prominent IRMA in one quadrant
d. Moderate hemorrhages in two quadrants, venous beading in two quadrants, prominent IRMA in one quadrant

5. Which one of these sets of features describe DRSS-defined high-risk PDR?

a. Neovascularization of the disc (NVD) greater than 1/3 disc area with vitreous hemorrhage
b. Neovascularization elsewhere (NVE) less than 1/2 disc area with vitreous hemorrhage
c. Isolated vitreous hemorrhage
d. NVE greater than 1/2 disc area without vitreous hemorrhage

6. All of the following are considered risks for the development of PDR EXCEPT:

a. Duration of diabetes
b. Level of baseline retinopathy
c. Severe obesity
d. Level of glycemic control or HbA1c level

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

a. 20%
b. 30%
c. 0%
d. 50%
e. 60%

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

8. You have a 37-year-old patient with type 1 diabetes for 20 years. She has well-controlled diabetes (insulin pump) and her last HbA1c was 7.0%. She has newly diagnosed PDR in both eyes with vitreous hemorrhage and an area of superotemporal traction and has been non-adherent with follow-up exams by her primary care physician. All of the following options would be reasonable next steps in the management of this patient EXCEPT:

a. Observation without treatment
b. Anti-VEGF
c. Panretinal photocoagulation (PRP)
d. Pars plana vitrectomy (PPV)

9. How much greater relative risk is there for a 36-year-old to develop DR having been diagnosed with diabetes 12 years ago versus 7 years ago?

a. 0.5x
b. 1x
c. 1.5x
d. 2x
e. 2.5x

10. Longer duration of diabetes _____ the risk of retinopathy.

a. Decreases
b. Increases
c. Has no affect on
d. Risk is unknown

11. A 35-year-old woman with a history of type 2 diabetes presents for her annual evaluation. She has marked hemorrhages in four quadrants, exudates and thickening with the macula, plus evidence of neovascularization elsewhere present in the left eye as well as neovascularization of the disc with mild inferior vitreous hemorrhage. All of the following are evidenced-based approaches to the patient EXCEPT?

a. The patient may benefit from an ultra widefield angiogram to evaluate in more detail her PDR
b. The patient likely has severe NPDR. Close observation is warranted
c. The patient has proliferative diabetic retinopathy and therefore anti-VEGF or PRP is indicated
d. The patient should be investigated for signs of neuropathy and nephropathy

12. A 58-year-old male with type 2 diabetes (HbA1c 7.7%) has been coming to you for annual eye examinations for the past 5 years. Previously, he had demonstrated no signs of retinopathy on examination, but this year you notice several microaneurysms, and multiple dot and blot hemorrhages in both eyes. You perform optical coherence tomography angiography. This imaging modality is limited by its inability to show _____.

a. Microvasculature
b. Leakage
c. Collateral vessels
d. Neovascularization

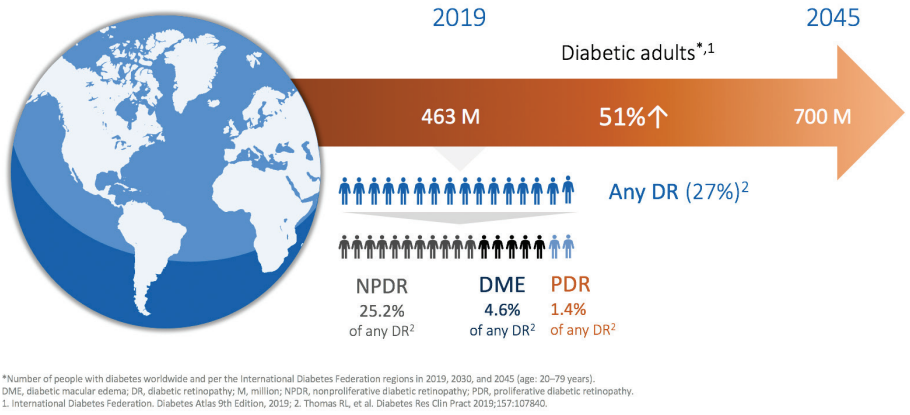
DR & DME: Addressing Barriers to Early Treatment

By 2035, it is estimated that close to 600 million people worldwide will be living with diabetes,[1] many of whom will be affected by vision-threatening diabetic retinopathy (DR) or diabetic macular edema (DME). We know from multiple large-scale studies that medical therapies have reduced the severity of DME and DR and timely treatment can reduce severe vision loss by 90%.[2] Among the clinical trials supporting the use of anti-VEGF agents that report improvements in both best-corrected visual acuity and decreased central retinal thickness are BOLT, DaVINCI, DRCR.net's Protocol I, S, T, and W, PANORAMA, RESOLVE, READ-2, RISE/RIDE, RESTORE, RETAIN, and VIVID/VISTA.[2-20] But the key to early treatment is early diagnosis and ensuring patients are appropriately referred in a timely manner. We've gathered experts from around the country to discuss techniques in screening and evaluating patients, how to incorporate telemedicine in our practices, and when to refer to a retinal specialist.

— Rishi P. Singh, MD, Program Chair

Q | Dr. Singh, MD: We know the population of patients with diabetes and diabetic eye disease is rapidly increasing. Today, there are about 100 million adults worldwide with DR, 10% of which is vision threatening.[21] Dr. Ferrucci, you work at a Veterans Affairs clinic. Are you seeing volumetric changes we keep hearing about? Are you seeing more pathology in the patients who present at your clinic? What—if anything—differentiates these patients from those in the past?

Steven G. Ferrucci, OD, FAAO: We've always had a high rate of patients with diabetes in our clinic, and I don't see any indication that will change. Unfortunately, because of the COVID-19 pandemic, some patients might have delayed routine care. We found this to be particularly true with our diabetic patients, especially if they had other comorbidities.[22] As California has eased some of the COVID-related restrictions and patients have started coming back to clinic more frequently, I've seen a few



*Number of people with diabetes worldwide and per the International Diabetes Federation regions in 2019, 2030, and 2045 (age: 20–79 years).
DME, diabetic macular edema; DR, diabetic retinopathy; M, million; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.
1. International Diabetes Federation. Diabetes Atlas 9th Edition, 2019; 2. Thomas RL, et al. Diabetes Res Clin Pract 2019;157:107840.

Figure 1. Worldwide impact of diabetes, 2019-2045.[26,27]

more train wrecks in the past couple months than I'd seen in quite some time.

Dr. Singh: That's resonating for me, too. I've seen a lot of patients who did not come in during the COVID-19 pandemic for the recommendations that were given, and more patients ignored the recommendations for evaluation. Now I'm seeing more patients who are coming in with tractional detachments and vitreous hemorrhages than I would have prepandemic. What about everyone else?

Jordana G. Fein, MD, MS: It's the same for our practice. We're seeing a lot more patients who are coming in after a vitreous hemorrhage who were lost to follow-up for more than a year. These were patients who were supposed to come back for a 3- or 4-month follow-up because they had severe nonproliferative DR (NPDR), but missed that window and are now returning with severe vision-threatening complications. I think one of the hardest populations to treat are our working-age adults with diabetes. They're trying to manage several different specialist visits and it can be difficult for them to make time to see all the physicians they need to on a regular basis. But to answer your overall question, Dr. Singh, yes, the number of people with diabetes who are presenting for eye exams in my practice seems to be growing exponentially.

Joseph J. Pizzimenti, OD, FAAO: San Antonio, Texas, has a high prevalence of diabetes that is rapidly rising. The pandemic has only amplified the challenges by increasing the barriers to care. Since the beginning of 2021, I've seen significantly more cases, percentage-wise, of center-involved DME, very severe NPDR and proliferative DR (PDR) with high-risk complications. This is no doubt due to the reasons proposed by my fellow panelists.

Jaya Badhwar Kumar, MD: I've also noticed that a lot of my patients lost medical insurance. Many lost jobs or were furloughed because of COVID, and as a result they were unable to come to appointments due to lack of transportation or limited resources. Numerous patients were hospitalized for long periods of time because they couldn't afford insulin or other medications for routine diabetic management. We offered telemedicine in our clinics, and for some patients it was helpful. However, many patients who required routine intravitreal injections or laser treatment were unable to get to our clinics. As a result, I have seen more vision-threatening diabetic complications, including tractional retinal detachment, vitreous hemorrhage, and worsening macular edema in all age groups, particularly the younger population. In the past year, I've seen a lot more diabetics between the ages of 30 and 50 who are now unfortunately legally blind.

Q | Dr. Singh: We've all seen a greater number of vision-threatening complications increasing, including PDR and DME. DR is now the leading cause of blindness in the United States for people between 20 and 74 years of age, and it is the leading complication associated with diabetes.[23] Figure 1 shows us these numbers are only going to increase. Dr. Ferrucci, which of these topics do you discuss with your patients when you see them? How do you address the patient with some level of DR? We know there are numerous modifiable factors,[24,25] but is there a preferred order when you're talking to the patient?

Dr. Ferrucci: Patient education for those with diabetes is extremely important. As clinicians, though, we have limited chair time. I concentrate on good blood sugar control, because we know from multiple studies that good glycemic control reduces the likelihood of DR progression and can help delay the onset.[28-36] I also concentrate on discussing hypertension, because concurrent hypertension can worsen DR.[28,37-40] But there are a multitude of modifiable factors we can also discuss, including smoking cessation, diet, weight, level of exercise, etc.

Dr. Fein: I begin by telling patients that what we're seeing in their eye is the result of what's been happening for years. One thing I've noticed with patients in our clinic is a level of frustration, particularly with patients who have been seen for several years with DME and they're improving, but they still need regular treatment. They're frustrated because they've improved their HbA1c levels and lowered their blood pressure, so they may not understand why they still need injections.

I reiterate that keeping their systemic diseases under control is the most important step in terms of both long-term health of their eyes and their whole body. The other points Dr. Ferrucci mentioned are equally critical. I'll also try to ensure they are seeing their primary care doctors and/or endocrinologists. During the COVID-19 pandemic, many patients had virtual visits. They may not have had a recent HbA1c or true blood pressure reading, so I'm doing my part to encourage them to get back to their regular doctor visits.

Dr. Kumar: I agree. I emphasize to patients that diabetes is not limited to the eye and that it's a systemic disease. I will review optical coherence tomography (OCT), fundus photos, and angiograms with patients. I explain that what's happening in the eyes is happening to other organs in the body as a complication of the systemic disease. I implore them to "work on their ABCs" —A1c, blood pressure, and "C" is both cholesterol management and cigarette smoking cessation. Florida has historically been a popular destination for "snowbirds," but now we are seeing an even larger influx of permanent residents from all around the country who may not have an established primary care physician and they end up seeing a retina specialist first. We are the ones often helping patients establish care with primary care physicians and endocrinologists.

Dr. Pizzimenti: I will add that patients with DR, no matter the stage, should see an endocrinologist at least once during their care for the proactive management of lifestyle and medications for optimal glycemic control. We've arranged for some of our patients to have virtual visits with an endocrinologist to stay on top of managing their systemic conditions.

Dr. Singh: All good points. We know the prevalence of some of these ocular conditions are affected by the level of retinopathy. And we know that DR is a multifactorial event between inflammation, vascular instability or degradation and neurodegenerative changes as well.[23,41-46] So, when you talk about patients with DR, is there an easy way to describe to the patient the changes that are occurring in their eyes?

Dr. Ferrucci: That's a good question. I think the response is dependent upon who is sitting in front of you. Generally speaking, though, I explain that diabetes causes the blood vessels inside the eyes to become weak, which can lead to bleeding or other fluid build-up in the eye.[38,43,47-51] It's this build up that can cause the vision issues. That may not be the best way to explain the pathogenesis, but it resonates with patients.

Dr. Singh: Dr. Fein, what tools do you use to educate the patients on their level of retinopathy?

Dr. Fein: I find color fundus photographs to be extremely valuable tool both from a documentation and educational perspective. I can point out to patients a microaneurysm or a cotton wool spot on those images. I think seeing these diabetic changes directly and understanding that even if they can see well and they feel fine, diabetes is affecting their entire body including their eyes, which is why we need to monitor them closely to prevent the development of a complication that may lead to permanent vision loss. Those same photographs are relevant clinically so we can monitor DME progression over time and/or DR improvement after anti-VEGF treatments.

IMPLEMENTING TELEMEDICINE

Q | **Dr. Singh:** Dr. Kumar, earlier you mentioned telemedicine. Can you share how you have implemented telemedicine into your practice?

Dr. Kumar: We offered a hybrid model of telemedicine with the goals of providing clinical care, allowing social distancing and minimizing wait times in the office. We scheduled patients 15 minutes apart. Once patients arrived they would interact with one receptionist at check-in, one technician who performed the work up (history, vision, intraocular pressure), and one photographer who performed OCT and wide-field imaging (without dilation). The patient then had the choice to connect virtually with the physician in the office live or from home. We found the live method to be more effective because many patients had difficulty with internet connection or challenges with using the Zoom interface. One advantage of using an advanced platform like Zoom allowed us to share our screen with the patient to highlight the images in our discussion. This model was more beneficial for routine eye exams like moderate NPDR or dry AMD, not for someone with established DME or proliferative changes that may need treatment.

Dr. Singh: Great. And what would you do if a patient had more advanced levels of retinopathy in that population?

Dr. Kumar: If we noted worsening DME on OCT or suspicious findings on the imaging, we would schedule these patients for a live exam and possible angiogram the next clinic day.

Dr. Singh: Dr. Ferrucci, the Department of Veterans Affairs (VA) has done this type of screening for years, with some very positive results. Tell us about your practice and how you integrate telemedicine as part of it.

Dr. Ferrucci: We've had this sort of thing for 10 or 15 years. We've stationed cameras in the primary care clinics, and in some satellite clinics that don't have an eye care provider on staff, other staff members take pictures of patients with diabetes and those images are then screened by our staff optometrist or staff ophthalmologist who will make a recommendation whether the patient should be seen in clinic for a more in-depth face-to face exam. If there was no meaningful retinopathy, we schedule them for the following year. Patients with meaningful retinopathy will be seen in 3 to 6 months or whatever is appropriate based on the imaging. This has worked very well at allowing us to identify patients that quite frankly would not have been seen otherwise and bring them into the clinic for further evaluation and the appropriate treatment.

Dr. Fein: We also have some remote imaging that is run through a few satellite primary care clinics. We rotate reading those images as part of our practice. Similar to what Dr. Ferrucci said, it is certainly helpful to flag some patients who might need to be seen by a specialist. Unfortunately, even with trained staff obtaining the photography, sometimes an image for one eye will

be gradable, but the contralateral eye may have had a flash go off or it's difficult to see the full macula to make an assessment. Those images worry me because they're difficult to interpret.

But overall, I think good quality images are very helpful for remote screening. When the pandemic started, we did try to do some retina-specific telemedicine, but to connect with patients who had an acute issue. We would screen them via a televisit and then bring them in if it sounded necessary (eg, loss of vision, worsening floater, etc).

Dr. Pizzimenti: It is impressive what some of the experts on this panel are doing with respect to telemedicine! The extent of my involvement thus far has consisted of virtual consultations centered around discussion and eliciting any "red flag" symptoms that would prompt an urgent in-office appointment. One helpful modification that we've made is to move our imaging technologies closer to the main patient care areas.

IMAGING ADVANCES AND THE IMPACT ON CLINICAL PRACTICE

Q | **Dr. Singh:** Let's move onto imaging. What impact have some of the latest technologies had in your practices?

Dr. Kumar: We are fortunate that even our satellite clinics have Optos widefield imaging available, and it has enhanced our diagnosis and treatment. For example, with telemedicine we can access the imaging software from home. We can zoom in pathology on the fundus photos and scroll through the fluorescein angiograms (FAs) to look at the early and late frames. In the regular clinical setting, I find ultra-widefield imaging helps identify peripheral pathology we may have otherwise missed. I recently had a young girl with sickle cell anemia, and I was able to identify neovascularization in the periphery that I would not have picked up on a traditional nonwidefield imaging. For DR, widefield imaging highlights areas of peripheral nonperfusion, leakage, and neovascularization.

Dr. Pizzimenti: Although I still rely on traditional examination methods and imaging modalities, it's hard to imagine providing care for patients with diabetes without the use of OCT. Although we can usually see DME funduscopically, the ability to characterize and quantify the edema with OCT has been a difference maker. OCT-angiography (OCT-A) is still in its relative infancy but is rapidly improving to the point where it has become useful in detecting areas of nonperfusion, macular ischemia, and subtle neovascularization of the disc (NVD), and neovascularization elsewhere (NVE).

Dr. Singh: Dr. Ferrucci, in the VA, has it been strictly nonmydriatic cameras or do you use ultra-widefield as well?

Dr. Ferrucci: We have a combination of both. We use nonmydriatic, but we also have both the Optos system and the EIDON (iCare). We've started to incorporate more widefield fluorescein into our practice.

Dr. Pizzimenti: I'm glad that Dr. Kumar mentioned earlier the importance of evaluating the retinal periphery in DR and other retinal vascular conditions. Our main clinic has the CLARUS 700 (Carl Zeiss Meditec), which has been a versatile, multimodal widefield system. As we know, DR is not limited to the central retina. Peripheral nonperfusion may also serve as a biomarker for impending center involved DME or neovascularization.

Q | **Dr. Singh:** Let's talk more about OCT-A. What, if any, benefits have you found with OCT-A?

Dr. Fein: OCT-A is very interesting to look at for diabetics, particularly in the setting of macular ischemia or vision loss that's not necessarily explained by what you're seeing on your exam or on traditional OCT. OCT-A, as well as FA, is very helpful. I like OCT-A to be more of an adjunctive component. I don't know that at this moment in time OCT-A directly affects my clinical management of my patients. But you can certainly see microaneurysms, macular ischemia, capillary dropout, etc. In some cases, the image quality is much better than traditional fluorescein.

Dr. Kumar: We don't have access to OCT-A in all of our clinics. But based on my experience, I definitely think it's a great tool to have, especially for our diabetic patients and dialysis patients who have challenging venous access.

RETINOPATHY SEVERITY

Q | **Dr. Singh:** Let's discuss severity of retinopathy. There have been multiple studies showing progression of proliferative diabetes, going back to the original Early Treatment of Diabetic Retinopathy Study (ETDRS). In one of its earlier reports, the ETDRS showed that 51% of patients with severe NPDR will progress to PDR within a year's time.[52] This has been replicated in some of the more recent trials, including PANORAMA.[8,9,53] In that study, the sham arm had a high risk of progression within the first year. What are your intervals for follow-up and interventions when screening these patients? Dr. Ferrucci and Pizzimenti, when you see someone with level 47 or higher (moderately severe NPDR), do you refer? Do you observe? In general, what do you think optometrists are most comfortable doing?

Dr. Ferrucci: We have a very busy retina practice, and before we had some of the more advanced imaging technologies, if the patient didn't need treatment the optometry department would not send them for referral to a retina specialist. But now, once a patient reaches the moderately severe to severe levels, as an optometrist I think it's a good idea to refer them to the retina specialist to at least consider treatment.[52,54,55]

We know that treatment with intravitreal anti-VEGF injections can help prevent NPDR from progressing to PDR and can help prevent some of the sight-threatening complications. As optometrists, I think the moderately severe to severe NPDR is the appropriate time to refer to retina colleagues for that second opinion on whether they should intervene.

Dr. Pizzimenti: I agree with Dr. Ferrucci. Evidence from some of the more recent trials and protocols supports initiating a retinal consultation for patients with moderately severe and very severe NPDR, regardless of whether there is DME. If timely treatment can reduce the rate of sight-threatening complications, such as neovascular disease and center-involved DME, why wait to make the referral? Even if the retina specialist elects to hold off on immediate treatment, it at least buys some time.

Dr. Fein: I was fortunate to be one of the principal investigators on the PANORAMA trial, and the numbers are really staggering when you think about the patients who progress to PDR.[8,9] In PANORAMA, 65% and 80% of 16-week and 8-week eyes, respectively, versus 15% of sham eyes had a 2-step or greater improvement on the Diabetic Retinopathy Severity Scale (DRSS) at year 1. At week 100, the same level was achieved by 62% and 50% of 16-week and 8-week eyes, respectively, versus 13% of sham eyes.[8] Before PANORAMA, I'd see patients every 6 or 9 months if they did not have PDR, but now I'm much more likely to follow them every 3 or 4 months and monitor them more closely because the risk is so high. To Dr. Ferrucci's earlier point, having the retina specialist involved when patients are at the NPDR level gives us a little bit more time—to get to know them as a patient to determine goals for care, and to have them get to know us before vision loss occurs. I like to see patients a few times to build up trust before I must talk to them about a specific treatment.

Dr. Kumar: Dr. Fein brings up some excellent points. Being able to establish a relationship with a patient before you start the conversation about treating the eye is really important. We also see patients referred from primary care providers, optometrists, or general ophthalmologists for mild or moderate NPDR. When we perform the FA, we see the proliferative changes that we may not have picked up on clinical exam.

To me, that's where advanced imaging is most helpful. I can think of numerous clinical scenarios in which the exam findings seemed so subtle that after FA I was fooled more than once. Referring patients earlier helps to monitor the disease and probably helps us pick up more patients with more advanced stages of disease. For me, if the patient has moderate NPDR, I follow up at 6 months. For severe NPDR, I usually follow closer to 3 months.

Q | **Dr. Singh:** Dr. Pizzimenti, when do you feel like it's time to refer the patient to a retina specialist?

Dr. Pizzimenti: It's appropriate to refer most patients with center-involved DME for treatment. If the visual function is still very good in an eye with CI-DME and the patient is diligent about their follow-up appointment and self-care, I will monitor them every 3 to 4 months for stability versus progression.

Patients with severe NPDR or worse should be referred to the retina specialist for consideration of treatment. Rather than wait to refer when something bad happens, I'm providing proactive care. Of course, patients with any degree of PDR warrant prompt referral.

Dr. Ferrucci: Obviously, if the patient has PDR, that's going to warrant referral to the retina specialist. The American Optometric Association guidelines note we can wait 2 to 4 weeks,[56] but I don't see the advantage in waiting that long. If you have PDR, the earlier we can refer to a specialist, the better. Once a patient starts to move into the severe category, following the 4-2-1 rule (hemorrhages in all four quadrants, venous beading in two quadrants or the marked IRMA in one quadrant),[57] that's when it becomes advisable to send onto a retina specialist.

With DME, if it's center-involved that we can see on OCT, we send them over. When it's noncenter-involved DME, that's a little more of a gray area. At that point, I think it depends on the comfort level of the optometrist. If they're comfortable following the patient, then seeing the patient every 3 or 4 months is acceptable but referring to the specialist once the disease progresses. In general, sooner is sometimes better than later because it provides the retina specialist with more options to treat before there is extensive disease.

Dr. Fein: I would echo what Dr. Ferrucci said. I prefer to have noncenter-involved DME referred to a retina specialist as well, because I like to meet the patient, have a conversation, and hopefully not have to give them an injection or laser the first time I see them. Dr. Kumar also brought up a good point about the difficulty in distinguishing moderate/severe NPDR to PDR without additional advanced diagnostic testing. Our optometry and general ophthalmology colleagues do an excellent job of monitoring, but when patients start to move toward more severe NPDR, I think that's when it's appropriate to refer to a retina specialist.

COMANAGING THE REFERRED PATIENT

Q | **Dr. Singh:** Let's talk about the communication pieces. What types of information do you share with the referring physician about the patient? And what do you share with the retina specialist when you're referring?

Dr. Kumar: Once we're done with our clinical exam, we send a note to the referring physician. I want the referring doctor to know what stage the patient is in, whether there's any macular edema, and our treatment strategy. For example, if the patient has some degree of DME but VA is 20/25 and the specialist prefers to observe, I'll spell that out for the referring doctor, so they know we've talked about the importance of blood sugar and blood pressure control, etc. We have a feature on our electronic medical record that allows us to pull the OCT image into the note when we fax it to the referring clinic.

If we need to intervene with either an anti-VEGF or panretinal photocoagulation, I try to send a note every second or third visit as well.

Dr. Singh: Great. Dr. Ferrucci? You're referring the patients to the specialist. What information do you share in the referral notes?

Dr. Ferrucci: I applaud Dr. Kumar because that sounds like the perfect scenario. As an optometrist, that would be exactly what

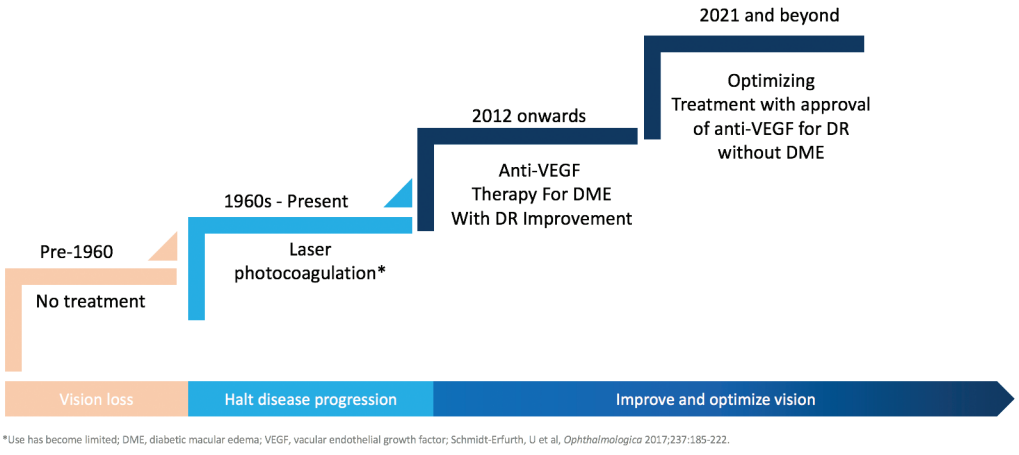


Figure 2. DR treatment evolution over time.[58]

We all have examples of noncompliant patients—the ones with PDR who show up every now and then for appointments. In this noncompliant population, I am much more likely to perform laser because I don't want them coming back months later with a tractional retinal detachment. One such patient of mine who fits those criteria didn't return to clinic for nearly 18 months, which made me happy I performed laser treatment. When I do PRP or combination therapy, though, it's a little bit lighter than what's been traditionally taught.

I would want from my retinal specialist. When I refer to a retina specialist, I include the medical basics (level of retinopathy, duration of diabetes, etc.). For me, the most important thing is to convey my specific concerns and how things have changed over time. These are likely patients I've been treating for years, whereas the retina specialist may be coming into it cold. I think it's helpful to have a snapshot of the patient over time to give some insight into how quickly the DR is progressing.

Dr. Fein: There are some good points here, including the issues that are most concerning to the optometrist. If it's clear (referred for DME, or worsening retinopathy, vitreous hemorrhage, etc.), it's still helpful to have a letter with some of the patient's background (diabetes duration, any concerns from the referring doctor or patient).

Dr. Pizzimenti: Excellent comments by Drs. Fein and Ferrucci. The referral note should be concise, with a clearly specified reason for the referral. I try to include a statement about the patient's glycemic status and how they've been trending during the past couple of years. Finally, I provide the retina office with an indication of the patient's ability to keep their follow-up appointments, as this may influence the type of treatment that is most appropriate.

TREATMENT EVOLUTION

Q | Dr. Singh: Let's discuss the DR treatment evolution (Figure 2). Let's talk about where we stand with this right now. How do you approach patients with PDR? Is it a combination approach? Is it a single approach with laser or anti-VEGF? Is it nuanced based upon the patient?

Dr. Kumar: It's certainly a topical point among retina specialists because everyone has their own kind of treatment strategy. I typically do a combination for most patients. If a patient presents with PDR in both eyes, with or without DME, I tend to start with a series of three anti-VEGF injections followed by PRP in both eyes.

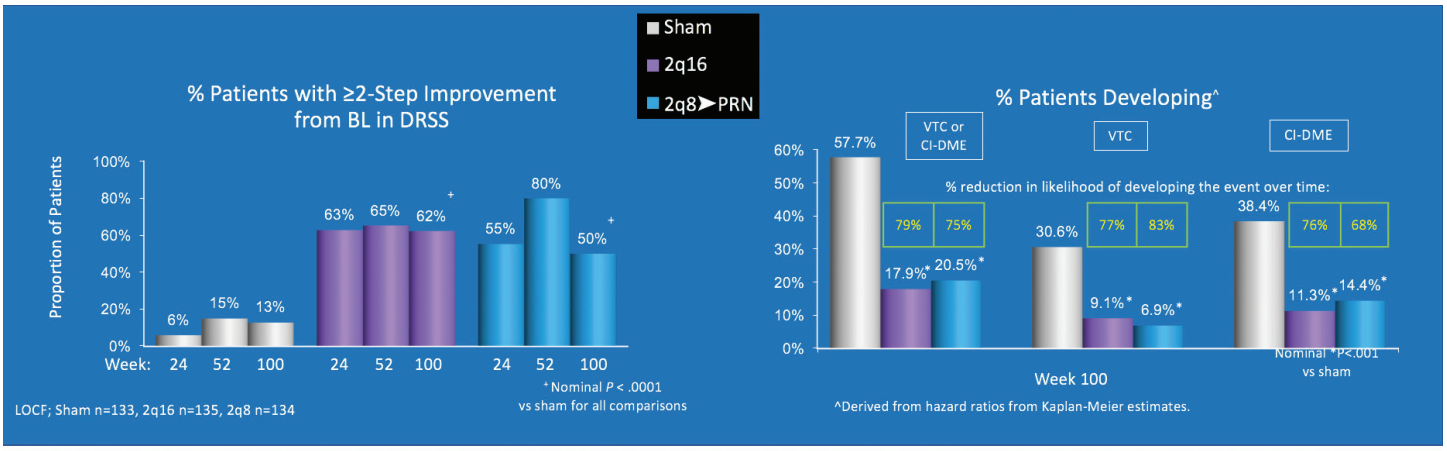
Dr. Fein: I also tend to use a combination therapy. Certainly, if the patient has DME, I treat with anti-VEGF first. If a patient has proliferative disease without DME, I tend to use a combination and give an anti-VEGF first and then follow with laser therapy. I like to have some anti-VEGF on board, while waiting for the full effect of the laser to occur, which may be 3 to 4 months following treatment.

Dr. Kumar's point about noncompliance can't be overstressed. We staff a fellow clinic at Washington Hospital Center, which tends to have a patient population who have trouble with compliance and follow-up. For those patients, when we see them for the first time and there's PDR without edema, I recommend laser. We know patients who are lost-to-follow-up (LTFU) with PDR and have not had PRP have significantly worse outcomes. Gao et al found that 25% of patients with NPDR and DME were LTFU.[59] At least with PRP, there's a reduced risk these same patients will have permanent vision loss.

Q | Dr. Singh: Dr. Kumar, would you share with us the differences you've seen in the anti-VEGF agents for both DR and DME?

Dr. Kumar: The decision of which agent we use is highly dependent on patient's medical insurance, particularly with step therapy. For DR, I think all of the agents work well with decreasing the DR severity. When a patient has chronic DME or DME that is not responding to ranibizumab or bevacizumab, I do see better results with aflibercept. We saw this also with the DRCR Protocol T in patients whose VA was worse than 20/50.[13,16] We are awaiting additional results on brolucizumab, but our center has enrolled patients.

Dr. Fein: I also look at Protocol T.[13,16] For me, this was a helpful study because patients were treatment-naive or hadn't been treated in the previous 12 months. From baseline to 1 year, the mean VA letter score improved by 10 to 13 letters with all three agents. But it was also a modified as-needed approach with monthly injections



ASNV = anterior segment neovascularization; CI-DME = center-involving diabetic macular edema; DRSS = Diabetic Retinopathy Severity Scale; PDR = proliferative diabetic retinopathy; VTC= vision-threatening complication.
Wykoff CC. Presented at: Angiogenesis, Exudation, and Degeneration 2020; February 8, 2020; Miami

Figure 3. PANORAMA 100-week conclusions.[9,53,62]

for 6 months unless their VA was 20/20 or better, or if the OCT met a specified endpoint. But in the subgroup of patients who had VA worse than 20/50, those treated with aflibercept had improved vision gains with fewer injections or need for laser. In my clinic, patients with VA of 20/50 or worse who also have chronic DME, I would prefer to use aflibercept as first-line therapy. Unfortunately, we don't always have the option to use our first-choice agent. We don't have as much step therapy in the Washington, DC, area as in other areas of the country, but it does seem to be coming.

For patients with VA better than 20/50, Protocol T showed relative similarities among all three agents, so I tend to use bevacizumab for the cost savings and ease-of-use from the insurance standpoint.

EMERGING THERAPIES

Dr. Singh: Dr. Kumar mentioned some of the emerging therapies, including brolucizumab. In both the KITE and KESTREL pivotal phase 3 studies on brolucizumab for DME, brolucizumab 6 mg was noninferior to aflibercept at week 52.[60] In KESTREL, patients were randomly assigned to brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg, while in KITE, randomization was between brolucizumab 6 mg and aflibercept 2 mg. The 6-mg arms showed noninferiority to aflibercept, with a comparable gain of 9 to 10 letters at week 52 achieved with a lower number of injections at longer intervals.

And there was a well-tolerated safety profile with no cases of retinal artery occlusion associated with inflammation or vasculitis.

But we also have data from faricimab. In YOSEMITE and RHINE, patients were randomized 1:1:1 to faricimab 6.0 mg every 8 weeks (q8w) after six initial every-4-week doses; faricimab 6.0 mg per personalized treatment interval (PTI) after four initial every-4-week doses; or aflibercept 2.0 mg every 8 weeks after five initial every-4-week doses.[61] Both studies met their primary endpoint and showed that faricimab dosed q8w or per PTI demonstrated noninferior visual acuity gains compared to aflibercept dosed every 8 weeks.

Q | Dr. Kumar, what's your level of interest in these emerging therapies?

Dr. Kumar: I, like most retina specialists, look forward to agents with increased durability and longer lasting therapy. Our goal should be to decrease the burden of treatment on the patient, clinic volume, and health care system. There are promising emerging therapies including faricimab, brolucizumab, and high dose aflibercept to name a few. My group is involved in several clinical trials that are specifically looking at DR. When we enroll patients for these studies, we discuss the risks and benefits of enrollment versus routine treatment in our clinic. The recent safety issues with brolucizumab made me a bit more hesitant about enrolling patients in those studies compared to the higher dose aflibercept study (NCT04429503). Patients were also more comfortable with the idea of potentially receiving the "routine" anti-VEGF medication versus a higher dose of the same medication.

Dr. Fein: I'm the principal investigator for the two high-dose aflibercept studies (both in DME and age-related macular degeneration). The goal of these studies is to look for improved outcomes and/or longer duration with the higher dose aflibercept. These studies are currently enrolling and there has not been any data released at this time. The faricimab data show almost 50% of patients were able to be dosed every 16 weeks by year 1. That's the longest durability of any phase 3 study to date. What both these future treatments suggest is that we need the same safety and efficacy we're used to with our current treatment landscape but with better durability. My patients are eagerly looking forward to not having to be dosed every month or every 6 weeks.

Dr. Singh: Figure 3 is PANORAMA, which showed a 2-step improvement in patients who had aflibercept every 8 weeks (80%); the 16-week interval was slightly less effective (65%) by the first year.[9,53,62] But in the 16-week group, you're still able to obtain some level of 2-step improvement. Has this had an effect on your treatment patterns?

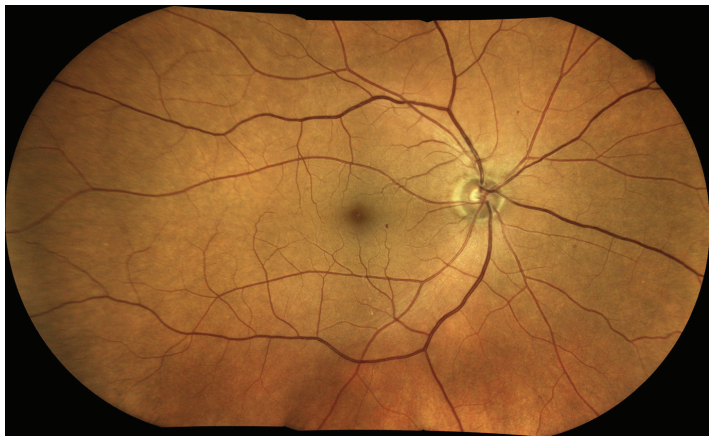


Figure 4. Mild NPDR on widefield.

Dr. Kumar: The PANORAMA data definitely helped my clinical decision making, for example, in patients who have one eye with PDR and the other eye with severe NPDR. I am more likely to treat these patients who have severe NPDR with anti-VEGF because of this data. First, they are already receiving treatment for the PDR in the other eye. Now I can show patients this data, which demonstrates the lower risk of developing vision-threatening complications and the fewer injections required per year.

Dr. Fein: The PANORAMA data is a very helpful tool for the reasons mentioned by Dr. Kumar. For patients with moderate to moderately severe NPDR, we may still monitor. I tell them there's a 60% chance of developing a vision-threatening complication by 100 weeks, but if we treat you, we may be able to modulate the retinopathy and reduce that risk. Anecdotally, despite the PANORAMA results, I think most retina specialists are not treating prior to vision-threatening complications. But the numbers and percentages of complications that occur without treatment is sobering and daunting. In the real world, though, the question is what is the endpoint? If you do start treating a patient with severe NPDR, how long do you treat them? And what happens 5 years later, after you've treated them? I don't know if we yet know the answer to that question.

Dr. Kumar: I completely agree. In my clinical practice most of the patients with NPDR that I'm treating have proliferative changes in the other eye. If both eyes are moderate or severe NPDR, I'll often encourage these patients to continue working to lower their sugar levels and blood pressure, and that we'll need to monitor them closely to ensure we catch progression quickly. We need to remember that there are risks associated with intravitreal injections.

Dr. Singh: These are all great points. Let's move onto seeing how we can apply them in real-world settings.

CASE 1: MILD NPDR—TO REFER OR NOT TO REFER

Dr. Ferrucci: In my practice, this is a typical kind of case. We have a 58-year-old male who has had type 2 diabetes for about 6 years; his last HbA1c was 8.3%. His VA is 20/20 in both eyes. Figure 4 shows the widefield image of his right eye, with small dot-blot hemorrhages, a few small microaneurysms. This is a patient I'd feel comfortable monitoring without referring. I would counsel the patient about the importance of yearly exams, and all the other risk factors we've previously discussed. What are your thoughts?

Dr. Singh: This is a very mild case, but it would be important to look in the retinal far periphery to look for predominantly peripheral lesions. Numerous papers have reported on progression rates in patients with those conditions,[63-66] and the DRCR.net's ongoing Protocol AA may give us more insight into whether ultra-widefield imaging improves our ability to assess DR and predict worsening disease.

Dr. Fein: We don't have an OCT for this patient, and while the retinopathy looks very mild, we know DME can exist at any level of DR.

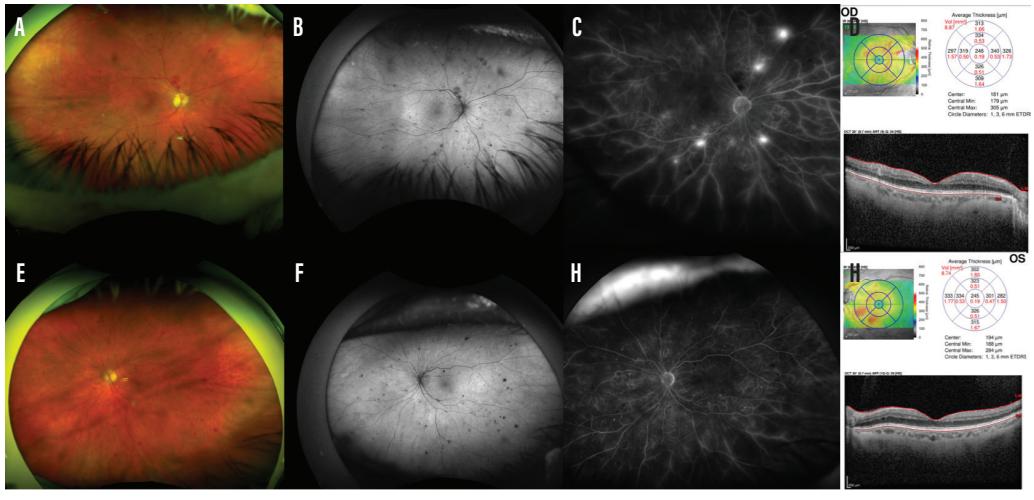


Figure 5. Severe NPDR in a noncompliant patient.

Dr. Ferrucci: Great point, and we did get an OCT for this patient. One additional point—widefield images are great, but they don't take the place of a good dilated retinal exam.

Dr. Pizzimenti: I agree. The combination of meticulous peripheral retinal examination and wide-field imaging is a powerful strategy. OCT-A may be valuable in this case as well, as it will noninvasively assess the central retinal perfusion and likely detect more microaneurysms.

CASE 2: SEVERE NPDR AND NONCOMPLIANCE

Dr. Kumar: This is a 70-year-old woman with insulin-dependent diabetes for more than 20 years. This was the patient I mentioned earlier who had a history of noncompliance. Her VA is 20/30 in both eyes. You can see intraretinal hemorrhages in all quadrants in both eyes. The FA shows there are small fronds of NVE of the right eye, and leakage in the left eye without neovascularization. The OCT didn't show any macular edema in either eye. See Figure 5.

Would you use an anti-VEGF or treat with laser? I opted for PRP in both eyes because of her history of noncompliance. As we discussed earlier, she was LTFU for almost 18 months.

Dr. Singh: You mentioned this was proliferative disease, but were there high-risk characteristics? Does that fall into your discussion or evaluation?

Dr. Kumar: That's a good point. This patient does not meet any of the high-risk criteria. In most cases, because I'm treating patients initially with anti-VEGF, I tend to use the "high-risk" and "not high-risk" with lower thresholds than I did previously.

Dr. Singh: It's a reasonable discussion, but now that we're doing more pattern laser or indirect laser, it's a far different treatment than we used to have.

Dr. Fein: Dr. Kumar, your point is well taken. On the fellow eye, you're not seeing any NVE. But because this patient has long-term diabetes and a history of noncompliance, I would lean toward treating the fellow eye. It's an easier conversation to have when you can show the patient what's happening in one eye and explain that the second one will likely follow.

Dr. Singh: Thank you everyone for this interesting discussion and intriguing cases. ■

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DR & DME: ADDRESSING BARRIERS TO EARLY TREATMENT

Release Date: Aug. 13, 2021
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INSTRUCTIONS FOR CME 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/2129-supplement. 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.

Please type or print clearly, or we will be unable to issue your certificate.

Full Name_____ ❑ MD/DO participant ❑ OD ❑ non-MD participant

Phone (required) _____ ❑ Email (required) _____

Address/P.O. Box _____

City _____ State/Country____ Zip/Postal Code_____

License Number _____ OE Tracker Number _____

DEMOGRAPHIC INFORMATION

Profession
___ OD
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
___ >50

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

Setting
___ Solo Practice
___ Community Hospital
___ Government or VA
___ Group Practice
___ Other
___ I do not actively practice

Models of Care
___ Fee for Service
___ ACO
___ Patient-Centered Medical Home
___ Capitation
___ Bundled Payments
___ Other

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Discuss the benefits of telemedicine for continued screening of diabetic patients for diabetic retinopathy (DR) and diabetic macular edema (DME) in order to provide timely treatment.	_____	_____	_____
Execute appropriate referrals of patients with DR and DME by working with your network to understand the need for timely referrals to a retina specialist based on the latest clinical data.	_____	_____	_____
Interpret clinical data supporting the treatment of patients with moderate nonproliferative diabetic retinopathy (NPDR) without macular edema with anti-VEGF therapy.	_____	_____	_____
Discuss longer duration therapies for DME and NPDR that are currently under investigation.	_____	_____	_____

POSTTEST QUESTIONS

PLEASE COMPLETE AT THE CONCLUSION OF THE ACTIVITY.

1. Based on this activity, 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 c. 3 e. 5
b. 2 d. 4

2. Based on this activity, rate how often you execute appropriate referrals of patients with diabetic retinopathy (DR) and diabetic macular edema (DME) by working with your network to understand the need for timely referrals to a retina specialist (based on a scale of 1 to 5, with 1 being never and 5 being always).

a. 1 c. 3 e. 5
b. 2 d. 4

3. A 65-year-old patient with type 2 diabetes for the past 10 years 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 the 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 DME in both eyes.

Action	Consistent	Nonconsistent
Early cataract extraction		
Optical coherence tomography angiography		
Intravenous fluoresceing angiography		
Referral to endocrinology for better glucose control		
Relaxed control of blood pressure		
Anti-VEGF treatment for severe nonproliferative disease		
Repeated exam in 3-6 months		
Indocyanine green angiography		
ERG/EOG measurements		
Control of lipids		
Widefield fundus photography		

4. What are the color photograph/ophthalmoscopy features of severe NPDR?

a. Severe hemorrhages in four quadrants, arteriovenous (AV) nicking in two quadrants, prominent intraretinal microvascular abnormalities (IRMA) in one quadrant
b. Severe hemorrhages in four quadrants, venous beading in two quadrants, prominent IRMA in one quadrant
c. Mild hemorrhages in four quadrants, AV nicking in two quadrants, prominent IRMA in one quadrant
d. Moderate hemorrhages in two quadrants, venous beading in two quadrants, prominent IRMA in one quadrant

5. Which one of these sets of features describe DRSS-defined high-risk PDR?

a. Neovascularization of the disc (NVD) greater than1/3 disc area with vitreous hemorrhage
b. Neovascularization elsewhere (NVE) less than 1/2 disc area with vitreous hemorrhage
c. Isolated vitreous hemorrhage
d. NVE greater than 1/2 disc area without vitreous hemorrhage

6. All of the following are considered risks for the development of PDR EXCEPT:

a. Duration of diabetes
b. Level of baseline retinopathy
c. Severe obesity
d. Level of glycemic control or HbA1c level

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

a. 20% c. 0% e. 60%
b. 30% d. 50%

8. You have a 37-year-old patient with type 1 diabetes for 20 years. She has well-controlled diabetes (insulin pump) and her last HbA1c was 7.0%. She has newly diagnosed PDR in both eyes with vitreous hemorrhage and an area of superotemporal traction and has been non-adherent with follow-up exams by her primary care physician. All of the following options would be reasonable next steps in the management of this patient EXCEPT:

a. Observation without treatment
b. Anti-VEGF
c. Panretinal photocoagulation (PRP)
d. Pars plana vitrectomy (PPV)

9. How much greater relative risk is there for a 36-year-old to develop DR having been diagnosed with diabetes 12 years ago versus 7 years ago?

a. 0.5x c. 1.5x e. 2.5x
b. 1x d. 2x

10. Longer duration of diabetes _____ the risk of retinopathy.

a. Decreases c. Has no affect on
b. Increases d. Risk is unknown

11. A 35-year-old woman with a history of type 2 diabetes presents for her annual evaluation. She has marked hemorrhages in four quadrants, exudates and thickening with the macula, plus evidence of neovascularization elsewhere present in the left eye as well as neovascularization of the disc with mild inferior vitreous hemorrhage. All of the following are evidenced-based approaches to the patient EXCEPT?

a. The patient may benefit from an ultra widefield angiogram to evaluate in more detail her PDR
b. The patient likely has severe NPDR. Close observation is warranted
c. The patient has proliferative diabetic retinopathy and therefore anti-VEGF or PRP is indicated
d. The patient should be investigated for signs of neuropathy and nephropathy

12. A 58-year-old male with type 2 diabetes (HbA1c 7.7%) has been coming to you for annual eye examinations for the past 5 years. Previously, he had demonstrated no signs of retinopathy on examination, but this year you notice several microaneurysms, and multiple dot and blot hemorrhages in both eyes. You perform optical coherence tomography angiography. This imaging modality is limited by its inability to show _____.

a. Microvasculature c. Collateral vessels
b. Leakage d. Neovascularization

ACTIVITY EVALUATION/SATISFACTION MEASURES

Your responses to the questions below will help us evaluate this CE activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low _____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low _____

This activity improved my competence in managing patients with this disease/condition/symptom _____ Yes _____ No

Probability of changing practice behavior based on this activity: _____ Yes _____ No _____No change needed

If 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 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

Please identify any barriers to change (check all that apply):

_____ Cost
_____ Lack of consensus or professional guidelines
_____ Lack of administrative support
_____ Lack of experience
_____ Lack of time to assess/counsel patients
_____ Lack of opportunity (patients)
_____ Reimbursement/insurance issues
_____ Lack of resources (equipment)
_____ Patient compliance issues
_____ No barriers
_____ Other. Please specify: _____
_____

The design of the program was effective for the content conveyed. ___ Yes ___ No

The content supported the identified learning objectives. ___ Yes ___ No

The content was free of commercial bias. ___ Yes ___ No

The content was relative to your practice. ___ Yes ___ No

The faculty was effective. ___ Yes ___ No

You were satisfied overall with the activity. ___ Yes ___ No

Would you recommend this program to your colleagues? ___ Yes ___ No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

_____ Patient Care
_____ Practice-Based Learning and Improvement
_____ Professionalism
_____ Medical Knowledge
_____ Interpersonal and Communication Skills
_____ System-Based Practice

Additional comments:

_____

_____ I certify that I have participated in this entire activity.

This information will help evaluate this CE activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address below.

_____

MODERN**OPTOMETRY**