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MANAGING THE DIABETIC EYE:

REAL-WORLD STRATEGIES FOR IMPROVING ADHERENCE AND VISUAL OUTCOMES

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Managing the Diabetic Eye:
Real-World Strategies for Improving Adherence and Visual Outcomes

CONTENT SOURCE
This continuing medical education (CME) activity captures content from a virtual roundtable discussion.

ACTIVITY DESCRIPTION
An expert panel of retina specialists from across the country discuss the benefits of consistent treatment for diabetic eye disease and how to improve patient adherence to follow up visits, as well as expand communication with the patient's care team in order to improve visual outcomes with currently available therapies.

TARGET AUDIENCE
This certified CME activity is designed for retina specialists.

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

- **Discuss** the benefits of consistent anti-VEGF treatment.
- **Explain** why patients with diabetic retinopathy (DR) and diabetic macular edema (DME) are so often lost to follow-up.
- **Execute** patient education plans on the importance of frequent DME treatment to improve treatment and exam compliance.
- **Apply** best practices and strategies in a cross-disciplinary approach to diabetes management to better manage patients.

GRANTOR STATEMENT
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PRETEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation/Satisfaction Measures for CME Credit.

1. Please rate your confidence in your ability to explain why patients with diabetic retinopathy (DR) and diabetic macular edema (DME) are so often lost to follow-up (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

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

2. Please rate how often you execute patient education plans designed to improve treatment and exam compliance (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. Out of the following options, which of the following is not a current strategy to help increase patient adherence to diabetic eye exams?

a. Calls and text messages to patients reminding them it's time for screening.
b. Written communication from an ophthalmologist to a primary care provider.
c. Free rides to medical appointments or free community diabetic eye screening.
d. Anti-VEGF pills taken by mouth daily.

4. Why are patients with DR often lost to follow-up?

a. Patients don't understand the severity of their ocular condition and may also have many other medical appointments, therefore often neglecting eye care.
b. Because DR is a mild condition without visual issues, they are not told further appointments will be needed to monitor the condition.
c. They receive one laser treatment and do not require further follow-up.
d. They don't have a retinal specialist in their area.

5. What do the panelists recommend clinicians do during the first visit with a diabetic patient to improve adherence to yearly eye exams?

a. Defer all counseling to the primary care physician.
b. Order a multifocal electroretinogram.
c. Educate the patient on HbA1c with their primary care physician, on the need for smoking cessation, and thoroughly explain the condition to help the patient better understand their ocular condition.
d. Educate the patient about the need for consistent primary care provider appointments and prescribe insulin.

6. A 56-year-old black male with type 2 diabetes has had good HbA1c control but has frequent setbacks. He has, however, kept up with yearly diabetic eye exams. He works as an editor for a living and needs good vision to remain employed. His HbA1c is currently 10.7%. His visual acuity (VA) OU is 20/30, and he has some signs of macular edema including cysts and exudate just outside the center fovea. What are your next treatment steps for this patient?

a. Anti-VEGF treatment every 4 weeks
b. Laser treatment followed by anti-VEGF
c. Observation
d. Discuss all options with the patient and develop a personalized treatment plan dependent upon his comfort level

7. A 42-year-old white female with type 1 diabetes presents to your office for the first time complaining of hazy vision. She uses a CGM and pump and her HbA1c is well controlled at 8%. Her VA is 20/40 OU. She admits that she hasn't had a diabetic eye exam for several years because her provider retired, she switched jobs, and she hasn't had time to find a new clinician. She presumed that because her systemic disease is well controlled that her risk for DR was low. She has preretinal subhyaloid hemorrhage with widespread midperipheral leakage neovascularization elsewhere. You determine she is at high risk for progression to proliferative DR (PDR). How would you recommend treating this patient?

a. Panretinal photocoagulation (PRP)
b. Combination of anti-VEGF injections and PRP
c. Vitrectomy with endolaser
d. Discuss all options and develop a personalized treatment plan depending upon her comfort level

8. What was a key takeaway from Protocol W?

a. Proactive anti-VEGF treatment does not reduce the chance of developing center-involved DME (CI-DME), but has significant visual benefit in patients who progress to CI-DME.
b. Proactive anti-VEGF treatment can reduce the chance of developing CI-DME with vision loss by 16%.
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.

9. Based on PANORAMA data, which is the better treatment strategy for patients with moderate to severe NPDR?

a. Fixed-interval anti-VEGF, up to every 16 weeks
b. Anti-VEGF as needed
c. Observation
d. PRP

10. How is mild NPDR classified on retinal imaging?

a. One retinal hemorrhage and microaneurysms
b. More than one retinal hemorrhage
c. Microaneurysms only
d. Cotton wool spots and more than one retinal hemorrhage

Managing the Diabetic Eye:

Real-World Strategies for Improving Adherence and Visual Outcomes

The world may still be recovering from the COVID-19 pandemic, but there is another ongoing pandemic that is also global and agnostic to race, region, or gender: diabetic eye disease. About 10% of the global adult population has diabetes, and its incidence is growing.[1,2] *About 100 million adults worldwide have diabetic retinopathy (DR), 10% of which is vision threatening.*[3] *In the United States and other industrialized nations, DR and diabetic eye disease is the primary cause of blindness.*[2] *The following roundtable discussion brings together thought-leaders in diabetic eye care to discuss how to move the needle on patient adherence to screening and improve visual outcomes with currently available therapies.*

— Allen C. Ho, MD, FACS – Moderator

IMPROVING SCREENING ADHERENCE AND MINIMIZING LOST TO FOLLOW-UP

Q | Allen C. Ho, MD, FACS: More and more, we're seeing patients present with advanced DR because patients with diabetes are not getting their recommended annual diabetic eye exams or are lost to follow-up (LTFU).[4] What are some strategies to resolve these problems in the United States?

Priya Sharma Vakharia, MD: These are very challenging issues that boil down to outreach to primary care physicians (PCP). Diabetic patients are more likely to have a diabetic eye exam if their PCP suggests it.[5] Other studies have shown that written communication from an ophthalmologist to a PCP increases adherence to follow-up exams in patients with diabetes.[6] We also have to make our retina clinics as accessible as possible. Many clinics do telehealth screening with Optos retinal imaging or another type of photography to encourage screening because the biggest barrier is often just getting patients to an eye care specialist.[4,7,8] Teleophthalmology has been shown to increase access to care, particularly for patients in rural areas, save patients time and money on travel, and better identify patients who need an immediate retinal exam.[7,9-12]

Ehsan Rahimy, MD: We need to make ourselves as readily available as possible. Retinal specialists are a somewhat limited community and we rely on our optometry colleagues to help. Many of us have been involved in outreach and education programs during the last couple of years to improve screening and get patients identified at an earlier stage. The good news is there's a lot of health-tech disruption going on right now that is geared toward diabetic eye screening. We've deployed cameras for teleretinal screening to the endocrinologist's office, the internal medicine doctor's office, and to Walgreens. Home fundus photography monitoring is just around the corner.

However, the larger problem is, at the end of the day, diabetic patients have too many office visits and medical obligations.[13] They're forced to pick and choose what are they going to prioritize, which is why so many patients are LTFU. Unfortunately, they don't necessarily notice that something is wrong with their vision until it's too late. We must remove as many of these barriers as possible to at least allow these patients to get screened.

Avni P. Finn, MD, MBA: One of the biggest barriers to screening and, subsequently, reasons for LTFU is access. This is a working population; they don't have time for frequent doctor visits. Despite gains made after the Affordable Care Act was passed, many diabetics remain uninsured.[14]

Q | Dr. Ho: One of the ways to minimize diabetic eye disease and diabetic vision loss is to optimize foundational systemic health parameters. Yet many patients don't know their HbA1c. How do you encourage patients to consider systemic factors and controllable factors in their hands to optimize their vision health?

Eric Nudleman, MD, PhD: I work at an academic center that is not limited by insurance; all patients are accepted. And, like in the rest of the country, only 50% of our patients with known diabetes actually have an annual diabetic eye exam. There are many factors at play here, including the fact that this is a working-age population and the travel time it takes to see a physician. There are also discrepancies in education and ethnicity. Much has been written about this in the literature, but numerous studies have shown that racial and ethnic minority patients are more likely to have worse glycemic control and less likely to be screened for DR than their white counterparts.[15-17] Socioeconomic factors are also an issue, with low socioeconomic status an independent risk factor for nonadherence to screening guidelines.[18]

Regarding motivation, I think there is an educational opportunity in the first visit. Show them a photo of their eye during that first appointment. Teach them about the anatomy. Show them the blood vessels. A widefield angiogram is a particularly useful tool in terms of teaching patients and showing them where they have disease. Take the extra couple of minutes to emphasize that this disease can happen and they won't notice it until it affects the center of their retina or they have another complication. We don't want it to get to that point, so we have to keep monitoring

it to ensure it doesn't worsen and then treat when appropriate. Having that conversation, informing patients that this is a potentially blinding disease, and really looking at them in the eye and making that connection at the first visit is critical.

Dr. Ho: If you have a 50-year-old working male who smokes, is hypertensive, and has an HbA1c of 11%. He comes in with 20/30 visual acuity (VA) OU. How do you motivate this patient to take better care of his systemic disease?

Robert Avery, MD: I agree that showing patients photos of any pathology is very helpful. Many people are asymptomatic, but they quite frequently have something visible on Optos widefield retinal imaging or fluorescein angiography (FA). A patient such as the one you describe with an 11% HbA1c is at risk for disease progression that will affect his vision as well as other organs. I explain to patients like this that this is a vascular disease, and they have this problem everywhere; they can help themselves immensely by controlling their sugar, by lowering their blood pressure, and by giving up smoking. Many people do not even know their HbA1c, so I ask them during every visit. Encouraging better systemic care is something overlooked by many retinal specialists, yet it can have the most impactful effect on the patient overall.

Q | Dr. Ho: How do you evaluate new patients or existing patients in terms of imaging, aside from examination?

Dr. Nudleman: I like the widefield angiogram and Optos imaging. I also obtain optical coherence tomography (OCT). I walk each patient through what the imaging modalities show us, what we're looking for and what we plan to follow. I find that really helpful, especially if they have some edema, which they often do. You can show patients where there's swelling in the retina and explain there's a breakdown in the blood-retinal barrier. You can show them the cysts in the retina and explain there is dysfunction in the retinal vasculature. The most important thing we can do at that initial visit is educate them about the disease. We must ensure patients understand that what we're seeing in their eye is a reflection of what's happening systemically.

Dr. Finn: I also obtain all three imaging modalities with OCT, widefield fundus photography, and FA.

I find FA useful both clinically and as an educational modality because you can show the patient areas of nonperfusion. If this damage is happening to their eye, it's happening all over their body—their fingers, toes, kidneys, etc. It's also important for me to look at the presence and extent of the nonperfusion because that instructs me on the level of risk for this patient and their progression to a different stage of retinopathy. The OCT informs me if there is diabetic macular edema (DME) and helps me look for other signs like macular ischemia or extensive retinal thinning that could indicate a poor visual prognosis.

Dr. Vakharia: I nearly always obtain an angiogram. While the clinical exam is good, it's very easy to miss subtle findings. The widefield fluorescein allows us to pick up on small changes that can have some significance. I have found that patients are more compliant when their family members are on top of them about their sugar control. Because of the COVID-19 pandemic, we didn't allow family members to accompany patients for almost a year and a half. If a patient has severe disease, I'll print a picture of their FA and circle the areas that are concerning so they can show their family members. That helps bring everyone on board to encourage the patient to gain better control of their HbA1c.

Dr. Rahimy: Education applies both ways. We now live in a totally different era of diabetes management; so many strides have been made in the past several decades. It's not just about HbA1c anymore, and I've been alarmed at how little colleagues know about all these advances going on in the field. We live in the era of DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 agonists.[19] Studies show these new medications impact the eye.[20-22] We live in the era of continuous glucose monitoring (CGM) devices, which are becoming more prevalent. It's not just HbA1c, it's time-in-range.[23,24] Many of our endocrinology colleagues think time-in-range is a more important surrogate of disease control than HbA1c. I think it's very important for us in the retina subspecialty to be on top of this and educate ourselves about what else is going on in diabetes.

CLASSIFYING DIABETIC RETINOPATHY

Dr. Ho: I want to discuss the way we characterize diabetic eye disease, which is kind of phenotypic and based on fundus observations (Table).[25] Mild nonproliferative diabetic retinopathy (NPDR) is defined as microaneurysms only. That's it. If the patient has one hemorrhage, they have moderate NPDR. For severe NPDR, follow the 4:2:1 rule, which is four quadrants of at least 20 hemorrhages,

TABLE. CLASSIFYING DIABETIC RETINOPATHY

Diabetic Retinopathy Level	Retina Findings
Mild NPDR	MAs only
Moderate NPDR	At least 1 hemorrhage or MA and/or at least 1 of the following: • Retina hemmorhages • Hard exudates • Cotton wool spots • Venous beading
Severe NPDR	Any of the following but no signs of PDR (4-2-1 rule): • 20 intraretinal hemorrhages in each of 4 quadrants • Definite venous beading in≥2 quadrants • Prominent IRMA in≥1 quadrants
PDR	One of either: • Neovascularization • Vitreous/preretinal hemorrhage

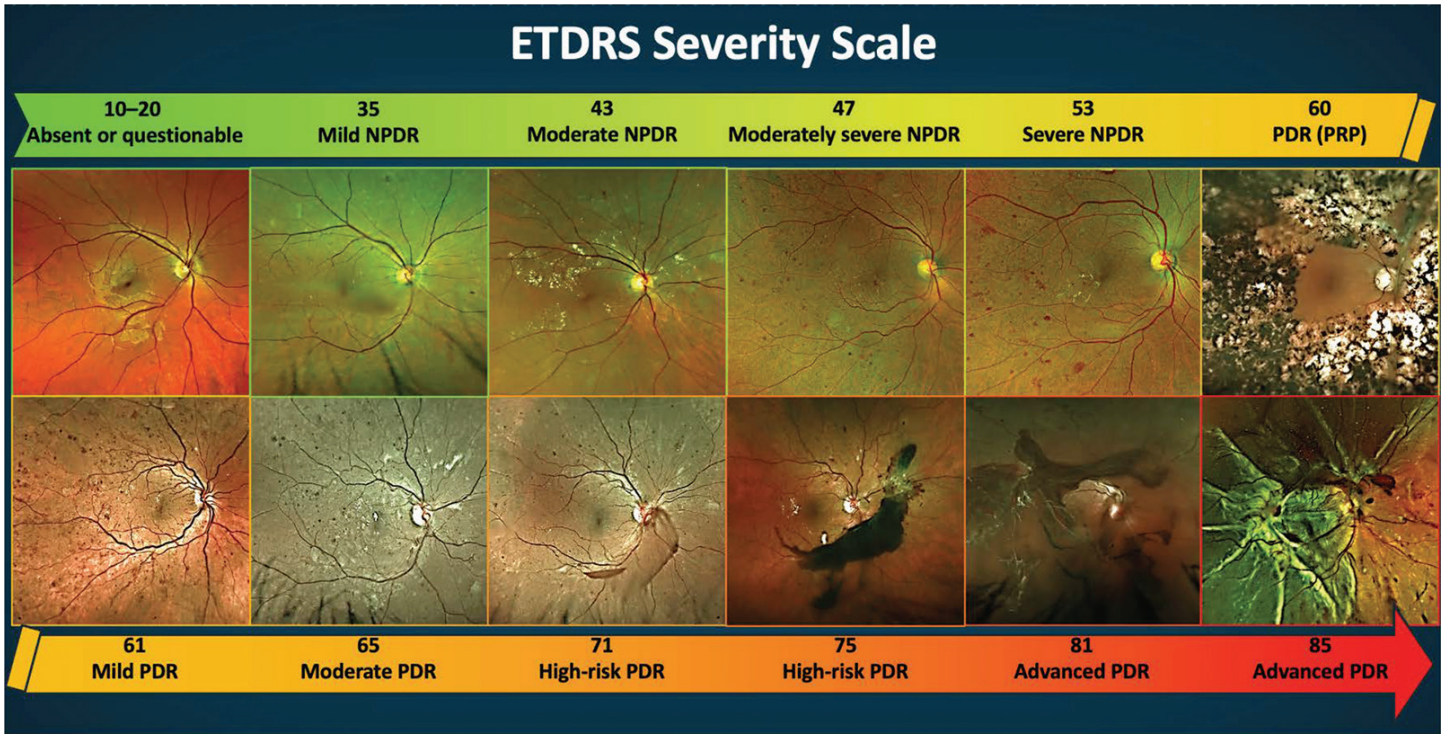

Figure 1. Early Treatment Diabetic Retinopathy Study severity scale.

at least two quadrants of venous beading, and at least one quadrant of intraretinal microvascular abnormalities.[26] This is difficult to diagnose in the era of COVID eye exams, and the angiogram definitely helps categorize disease in that sense. Proliferative diabetic retinopathy (PDR) is any presence of neovascularization or vitreous/panretinal hemorrhage.

We're often asked to consider the Early Treatment Diabetic Retinopathy Study (ETDRS) scores, but I don't think anyone uses them clinically to categorize patients. These scores are good to know because many of our clinical trials use these scores (Figure 1). This is a good reference for what these eyes look like, because we tend to characterize DR based on phenotypic appearance on fundus exam.

PDR SHOCK IN A PATIENT WITH WELL-CONTROLLED DIABETES

Dr. Nudleman: This case is of a 35-year-old woman who works as an emergency room physician. She is very involved in the diabetes education community and very aware of her disease. She has a CGM and a pump. She was diagnosed with type 1 diabetes at age 10. Her HbA1c is 6.6%. Six months before coming to see me she had no sign of DR on her imaging and was told everything was fine.

Figure 2 shows her imaging when she came to see me complaining of floaters. She has a subhyaloid hemorrhage OD, which was causing her symptoms. Her angiogram also shows neovascularization. There's a large frond of neovascularization elsewhere (NVE) superonasally and another frond inferonasally. There are little buds of neovascularization in the midperiphery and large areas of capillary dropout OS. This raises an important question: How often do patients come in with disease that is outside the ETDRS 7-fields? This question was examined in Protocol AA.[27] The histogram (Figure 3) clearly illustrates the disease is predominately outside the ETDRS-7 fields. What likely happened in this case is someone looked at her posterior pole and did not see any serious disease, and she was told everything was fine. But clearly this patient had disease outside of the 7-fields that was progressing, which eventually caused her hemorrhage. This case illustrates the importance of widefield imaging.

Figure 2. Case 1: Baseline imaging for 35-year-old patient with type 1 diabetes who complains of floaters.

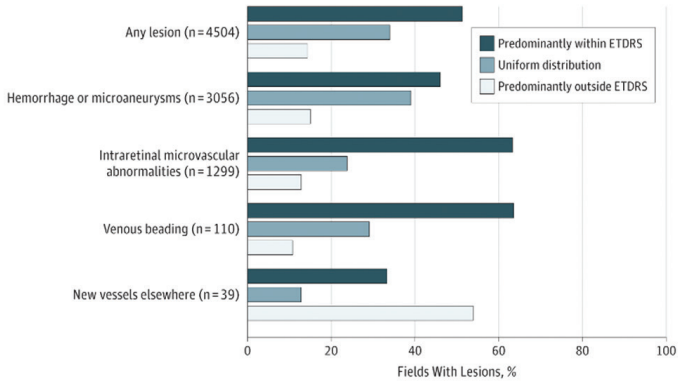

Figure 3. Case 1: Histogram showing disease location.

Dr. Ho: I don't typically do an FA nor do I have access to wide-field angiography in all my locations, but this certainly makes an argument for it. How did you treat her?

Dr. Nudleman: I treated her with aflibercept. She's had two injections so far, and the hemorrhage is clearing. The need for treatment was a surprise to the patient. Obviously, she had some years of poor control in her early 20s. But she's been doing very well for years. This brings us to another important point—patients aren't always aware that damage from poor control may not manifest for years. Getting things under control is absolutely helpful and must be stressed, but it doesn't eliminate the risk of having complications down the road.

MANAGEMENT ALGORITHMS FOR PATIENTS WITH DME OR RECALCITRANT DME

Q | Dr. Ho: Referring to the patient example I mentioned earlier—the 50-year-old smoker with an HbA1c of 11%. Let's say this patient now has center-involved DME (CI-DME) OD. His VA is 20/50. How would you manage this?

Dr. Finn: My initial treatment of choice in a patient with CI-DME is anti-VEGF. I use Protocol T to guide my decision-making on what agent I choose to initiate treatment. Protocol T was the first trial to compare the efficacy and safety of ranibizumab, bevacizumab, and aflibercept.[27] VA improvement was seen with all three agents, but improvement was greatest with aflibercept, particularly in patients with VA 20/50 or worse.

In this case, because the patient's VA is 20/50, I'd start with aflibercept. I'd give the patient a series of injections and then look at anatomic improvement rather than visual improvement. I find the visual improvement depends on many factors including the level of macular ischemia, extent of lipid deposits, and the chronicity of the fluid. After a series of injections, if I'm not seeing significant improvement, then I will consider switching the patient to an alternate treatment regimen such as steroids.[28]

Dr. Vakharia: I would also start with anti-VEGF therapy. I find that many of these patients are very steroid-responsive, although the visual outcomes between anti-VEGF and intravitreal steroids may be the same, as Protocol U showed.[29] The addition of intravitreous dexamethasone to continued ranibizumab therapy did not improve VA after 24 weeks compared to continued ranibizumab alone in patients with persistent DME after anti-VEGF treatment. However, I do find that you get a great anatomical response with intravitreal steroids, so it's something that I may offer earlier on in these patients. These patients have so many doctors' appointments and often need anti-VEGF every 4 weeks. Even giving them a little bit of an extension of that effect with an intravitreal steroid and having them come in once every 8 to 12 weeks can be helpful for their overall adherence.

Dr. Avery: I agree. I don't jump to steroids as rapidly because I used them before we had anti-VEGF therapy and it caused a lot of glaucoma. I'm not opposed to steroids, especially in recalcitrant cases when the edema doesn't respond well enough with anti-VEGF. Our improved delivery systems allow for a much more controlled release and seem to minimize the risk of glaucoma compared to what we used in the past.

CHOOSING BETWEEN OBSERVATION, LASER, OR ANTI-VEGF: A PATIENT WITH DME AND GOOD VISION

Dr. Nudleman: Our next case is a 67-year-old Japanese professor at the University of California, San Diego. He's had diabetes for 11 years, and he stopped taking his medications because he wanted to work on controlling his HbA1c off all medications. His HbA1c when I saw him was 10.2%. He's had poor vision OS since childhood due to amblyopia.

Figure 4 shows his imaging. He is 20/32 OD and 20/80 OS. You can see some intraretinal hemorrhages and exudate OD. If you look at the OCT that's cutting through the center of the fovea, it looks good. There are some exudates, but there's preservation of the foveal contour and no cysts. However, just outside the center, superiorly, you do see some cysts and exudate. It's the same thing OS. His vision is worse OS, but that's because of the amblyopia, not the edema.

This patient has very good vision, poorly controlled diabetes, and some macular edema. What does the literature tell us about management? Protocol V was a multicenter trial across 91 sites in the United States and Canada that enrolled 702 patients with CI-DME.[30] To be included on the trial, patients were required to have a VA of 20/25 or better. They were randomly assigned to one of three management strategies: initial treatment with aflibercept every 4 weeks (n = 226), laser photocoagulation, (n = 240), or observation (n = 236). Patients in the laser and observations arms were followed at 8 and 16 weeks and were switched to aflibercept if they experienced a decrease in 2 or more lines of vision at any visit or 1 line of vision in two consecutive visits.

Interestingly, 20 and 30% of patients on observation and on laser, respectively, did receive injections by the end of the 2-year study period. Yet, the number of patients who lost 5 or more

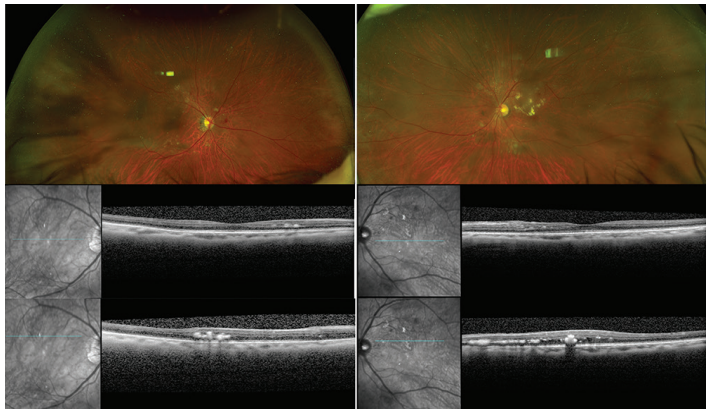

Figure 4. Case 2: Baseline imaging of 67-year-old with poorly controlled type 2 diabetes.

letters did not significantly differ between groups. The average VA was 20/20, just as it was at baseline. You see the same pattern in central subfield thickness. In the beginning, they all had good vision. They became a little less thick if they were injected early, but at the end of the study, everyone was about the same.

What does this tell us? One key thing is that you don't seem to be losing visual potential if you briefly delay treatment. If you wait for them to lose vision or to become a little bit thicker on OCT, you still can recover that vision.

Extrapolating these data to this case, I discussed the options with the patient and explained that I'd need to follow him closely and he would likely need treatment in the next 2 years. I don't have long-term follow-up, but Figure 5 shows his imaging after 4 months compared with baseline. It's about the same. I've continued with observation.

Dr. Rahimy: I'd consider early treatment with focal laser for this patient. It's fallen by the wayside but still has great utility. It's clear to me based on these images that the exudates are increasing over time, potentially encroaching into the fovea. I think focal laser treatment is a worthwhile discussion to have. You're mitigating the spread of that edema to become center-involving and may not end up needing future anti-VEGF therapy, rather than waiting for it to get there.

Regarding Protocol V, whenever I'm asked about these different treatment strategies and if it's okay to wait, I respond that it's better to treat. There's a lot of confirmation bias in clinical trials. At the end of the day, we need to discuss with the patient what they want and how aggressive they want to be in managing their disease. A patient may want to wait, and we can justify that from the literature. Another patient may want to treat their disease aggressively. We can justify that strategy as well. Different studies support whatever shared decision we arrive at with the patient.

Dr. Nudleman: You raise an excellent point about focal laser treatment. Very few focal lasers are being done nowadays. It was included as a treatment in the study arm, and although each cohort was about the same vision-wise, there were fewer patients

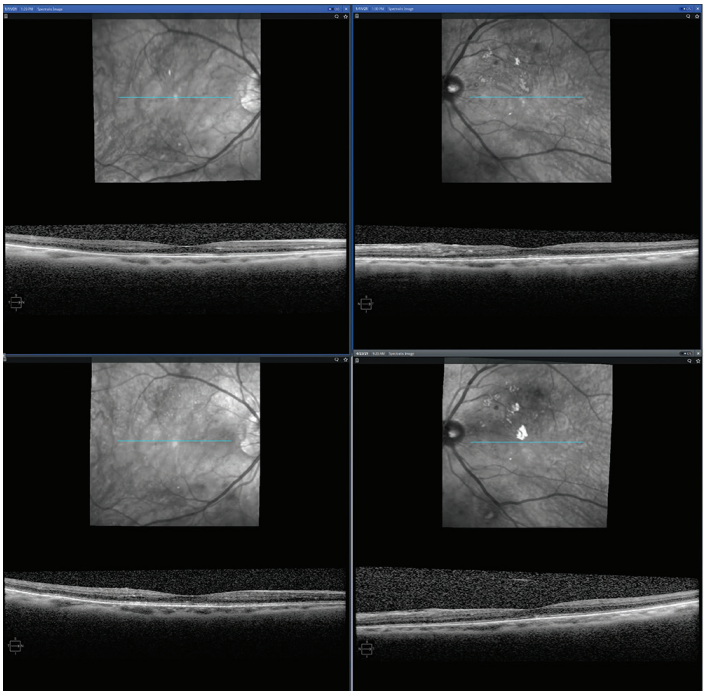

Figure 5. Case 2: After 4 months of observation.

in the laser arm that required injections. The ones who did get injections received them later.

Dr. Ho: I used focal laser for decades and it's shocking to me when my fellows don't know how to do it. Dr. Avery, do you agree that focal laser still has utility?

Dr. Avery: Yes, I agree there is still a role for it, but I have used it much less during the past 15 years. But if you have a patient without much disease in the foveal center, for instance, a circinate lipid ring threatening the fovea, then I agree it can lower the need for future anti-VEGF therapy. I don't, however, use it in patients with extensive, cystic, center-involved edema. I don't think it's time to abandon focal laser, but I certainly am using it less.

CHOOSING A MANAGEMENT STRATEGY FOR A HIGH-RISK PDR PATIENT WITH NO HISTORY OF EYE CARE

Dr. Finn: Our next case is a 37-year-old patient with type 1 diabetes who noted floaters OS for 1 month. She's had diabetes for more than 20 years. Her diabetes has been well-controlled with an insulin pump. Her last HbA1c was 7%. However, she has no prior ophthalmic exams, and only went to an optometrist when she noticed the floaters. This is someone who is plugged into the medical system and has an endocrinologist. She's been seen for her diabetes for a long time, yet hasn't been followed for eye care at all.

She has no hypertension and good kidney function. Her VA is 20/20 OD and 20/40 OS. Her anterior exam is unremarkable. Figure 6a shows her fundus photos. There are minimal observable

Figure 6. Case 3: Baseline imaging for patient with type 1 diabetes with no history of eye care.

changes OD, but OS you see a preretinal subhyaloid hemorrhage. There is also an area of fibrovascular proliferation superotemporally and maybe some traction. Her FA (Figure 6b) is quite remarkable. She has widespread midperipheral leakage throughout with NVE OD. There are obvious areas of NVE and the vitreous hemorrhage seen on color fundus photography OS.

This patient has high-risk PDR. Management options include anti-VEGF, panretinal photocoagulation (PRP), a combination of anti-VEGF and PRP, or a vitrectomy if there's vitreous hemorrhage. Her right eye looked good enough that we started anti-VEGF monotherapy, but we did combination treatment of anti-VEGF and PRP OS because of the vitreous hemorrhage. A month after her PRP, she developed a significant vitreous hemorrhage OS (Figure 7). She went from 20/40 VA to counting fingers. This is a young, anxious patient who is very afraid of surgical intervention. I observed her for a short period, but ultimately, she needed a vitrectomy. Figure 8 shows her postoperative image. There are some PRP laser scars around that area of traction. She's done very well.

Dr. Ho: What was your surgical strategy OS in the placement of the laser?

Dr. Finn: I like to do a complete anterior laser. I shy away from doing heavy posterior laser and try to leave some space between the macula and the periphery. I think with the advent of anti-VEGF, we really don't have to leave patients with this postage stamp and heavy PRP. I also try to spare the nasociliary nerves. I don't complete that laser 360°; I spare that nasal and temporal area so I'm not affecting their ability to dilate later. It also decreases pain.

Dr. Rahimy: That's a valid strategy. I'd want to make sure I trust this patient for follow-up and to receive ongoing anti-VEGF, if that's the goal. Some of the LTFU studies show that these patients

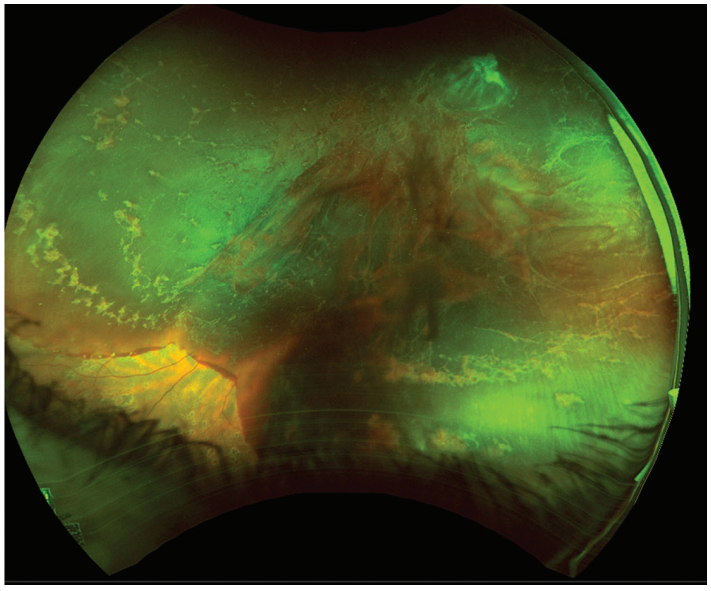

Figure 7. Case 2: Nonclearing vitreous hemorrhage post-combination anti-VEGF and PRP OS.

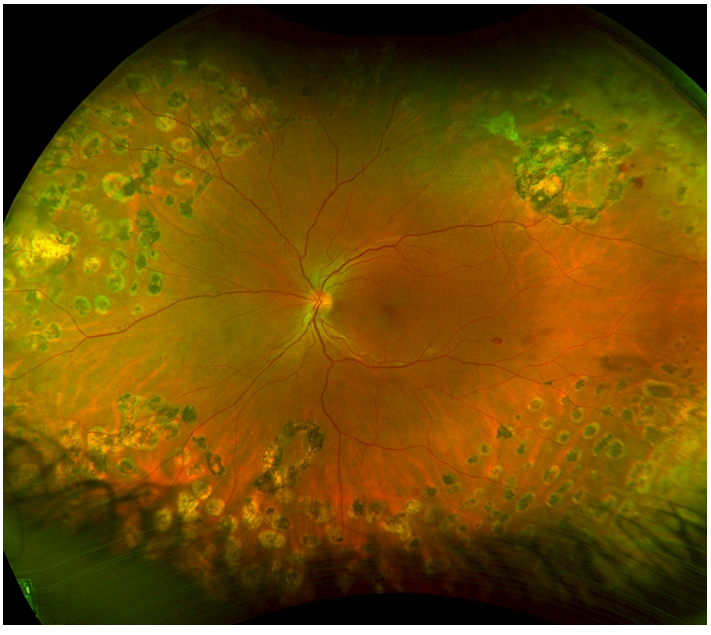

Figure 8. Case 2: OS imaging post-vitrectomy.

are potentially prone to reactivation of disease. It's important to continue to stress long-term follow-up in these patients.

Dr. Finn: Continuing her case, I was a little more aggressive with her right eye because of the history with her left. I did do PRP in that eye and then started doing regular anti-VEGF injections, initially starting with a short monthly series and moving to every 12 to 16 weeks. Despite this, she developed a vitreous hemorrhage in that eye. The vitreous hemorrhage OD was not quite as bad as the vitreous hemorrhage that developed OS. However, because of the history we intervened much sooner with a vitrectomy. She's done well in both eyes so far.

This was a challenging case. We don't have extensive clinical trial evidence for the best approach to manage a high-risk PDR. Protocol S randomized eyes to receive one to three sessions of PRP (n = 203) or ranibizumab 0.5 mg at baseline and then every 4 weeks (n = 191). At 2 years, VA improved by 2.8 letters in the ranibizumab group and only 0.2 letters in the PRP group (P = .001); ranibizumab resulted in VA that was noninferior to PRP.[31,32] Patients who received anti-VEGF injections were less likely to have worsening macular edema or peripheral vision loss as measured by automated visual field testing compared with the PRP-alone group. But only a small percentage of the patients in that study, 1%, had high-risk PDR. However, we also know that when patients get a PDR and then anti-VEGF injections, compliance is critical because their visual and anatomic outcomes are inferior to those who received PRP if they are LTFU.[33] That's why the American Academy of Ophthalmology Preferred Practice Pattern recommends PRP alone in any patient you suspect of being LTFU.[25]

In retrospect, would this have been a patient who benefitted from early vitrectomy because she had widespread NVE OS with vitreous hemorrhage and an area of localized traction? There are some advantages to performing an early vitrectomy in these patients, particularly when there is fibrovascular proliferation, vitreous hemorrhage, and attached hyaloid. I was reluctant to jump to vitrectomy early on because I wanted to balance the potential risks of surgery with a more conservative approach.

Dr. Ho: Dr. Nudleman, what's your thinking on the idea of earlier vitrectomy for a high-risk second eye?

Dr. Nudleman: Protocol AB compared aflibercept to vitrectomy with PRP in eyes with a vitreous hemorrhage from PDR.[34] The study compared the VA over 24 weeks after initial treatment with aflibercept versus surgery, followed by a follow-up period of 80 weeks during which treatment could include injections or surgery (based on protocol) for either group. A total of 32% of patients in the initial aflibercept group and 4% of patients in the vitrectomy/PRP cohort needed vitrectomy for nonclearing vitreous hemorrhage during the follow-up period. At 24 weeks, the vitrectomy group had a 5-letter advantage over the aflibercept cohort. But at the end of 24 months of follow-up, the groups were essentially the same; there was almost no difference in mean VA between them.[35]

The eyes with the worst vision, 20/800 or worse, tended to get better faster with initial surgery versus injections (compared to eyes with better vision, where there was no significant difference).[35] That's certainly a consideration, particularly in a patient who is monocular or a vitreous hemorrhage in both eyes. In those cases, it's reasonable to prioritize recovering vision as quickly as possible. But this trial gives us evidence to have a conversation with a patient. You can tell them it may take a year of anti-VEGF treatments to restore their vision, but surgery will get them there faster, in 12 to 16 weeks.

Q | **Dr. Ho:** Dr. Avery, you've studied diabetes for a long time, both translationally and in vivo. Based on your vast clinical experience, should we be thinking about earlier intervention to remove the hyaloid and the scaffold?

Dr. Avery: Yes, I believe we should, especially in type 1 diabetics with severe fibrovascular proliferation. When you take out the hyaloid and put in peripheral PRP out to the ora, in a way, you can often basically "cure" the disease in that eye. In the absence of the hyaloid, you're not going to get preretinal vascular proliferations and you reduce the risk of neovascular glaucoma when combined with PRP. I have started shifting toward earlier intervention because our techniques and equipment are better. The viewing with our wide-angle systems make it easier to treat the ora. By doing a very far peripheral PRP the loss of peripheral vision will hopefully will be less. In many cases, it makes sense now to go in earlier because you're going to have a better long-term result, even if the patient has poor compliance.

Compliance is one thing clinical trials don't realistically measure because frequently noncompliant patients either drop out of the trial or aren't included in the first place. But patients in the clinic are often quite different from a typical study patient. The very severe PDR with bad bleeding we see is often patients with poorly controlled diabetes. You must factor in compliance in your decision as to whether to go with injections and laser versus early vitrectomy and sort of "curing the disease." Patient compliance has a huge impact on my decision-making in this regard.

AFLIBERCEPT IN A PATIENT WITH NPDR WITHOUT DME

Dr. Ho: We have some algorithms for PDR, particularly high-risk PDR. You can find evidence on any argument you want to make. It's not confusion, it's that the data are subject to interpretation. For our next case, we'll discuss this topic through a patient with severe NPDR with a bad DRSS score and an angry looking fundus.

Dr. Rahimy: This case is a 64-year-old Filipino female. She has good vision: 20/20 OD, 20/40 OS. Her HbA1c is 8.5%. She was diagnosed with type 2 diabetes 15 years ago. She has hypertension and hyperlipidemia. Figure 9 shows her images pretreatment. She has scattered hemorrhages throughout the posterior pole and periphery. There is not much going on in the way in the macula.

I encountered this patient around the time PANORAMA data came out.[36] In my practice, I discuss studies and results with patients so they can make their own decision regarding their treatment. Clinicians obviously have strong opinions about the utility of anti-VEGF at this stage or potentially earlier stages. I think it's a mistake not to share the information with the patient and have a discussion that allows them to partake in that decision-making process. I've been pleasantly surprised with how many patients elect to proceed with therapy at early stages.

The patient opted to start treatment OS and observe OD for disease progression, together with improved diabetic control. She

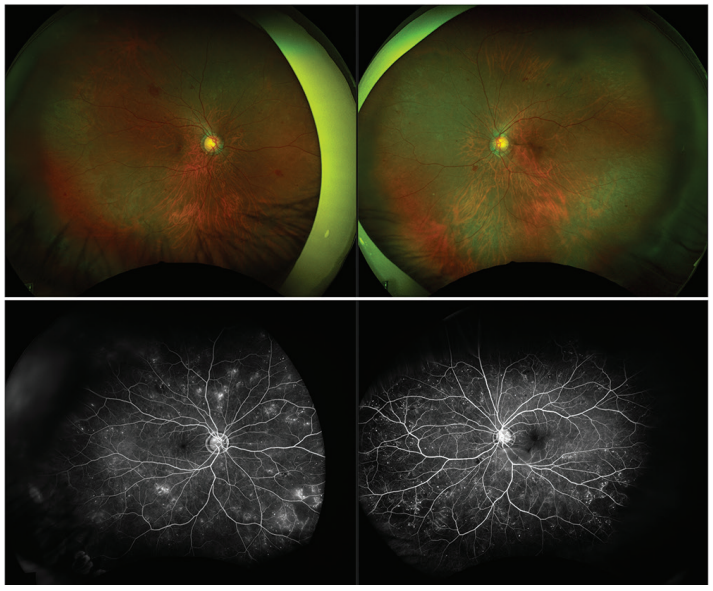

Figure 9. Case 3: Baseline imaging for 64-year-old patient with type 2 diabetes and good vision OU.

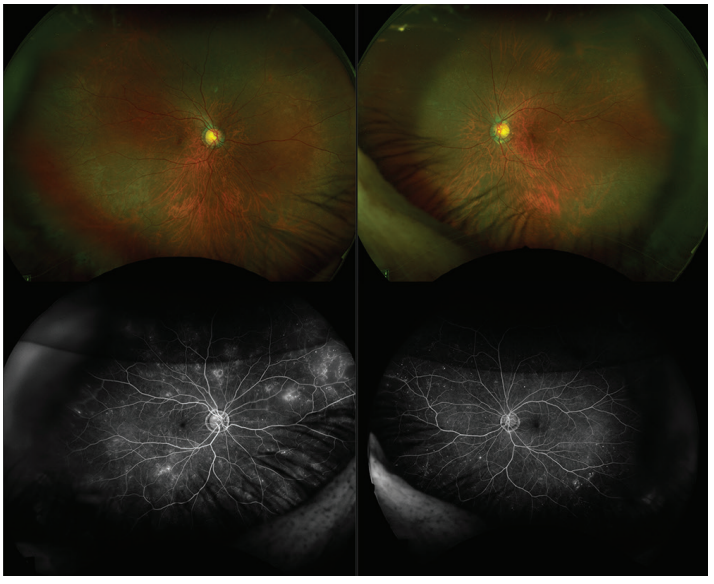

Figure 10. Case 3: Imaging posttreatment with anti-VEGF.

received five injections of aflibercept OS over the next 6 months. Her HbA1c improved from 8.5 to 7.8. OD VA slightly deteriorated from 20/20 to 20/25, but OS gradually improved from 20/40 to 20/25. Her follow-up FA looked a lot quieter (Figure 10). She's continued with therapy.

Dr. Ho: We have some evidence recently from Protocol W on treatment versus observation with rescue aflibercept in eyes with severe NPDR.37 Preventative aflibercept reduced the incidence of center-involved DME by 3-fold (16%) and reduced the incidence of PDR by 2-fold in patients with moderate to severe NPDR. However, there was no difference in VA between the aflibercept-treated and sham groups at 2 years.

We also have 2-year PANORAMA data on a similar population looking at different aflibercept regimens for patients with severe NPDR.[36] PANORAMA was a phase 3, double-blind trial that randomly assigned 402 patients to intravitreal aflibercept 2 mg every 16 weeks after 3 monthly loading doses (n = 135), intravitreal aflibercept 2 mg every 8 weeks after five monthly loading doses (n = 134), or sham (n = 133). During year 2, patients in the 8-week intravitreal aflibercept injection group could be shifted PRN. At week 100, there was a greater benefit for aflibercept-treated patients at the 16-week interval compared with less frequent treatment. The proportion of PRN-treated patients with a 2-step improvement from baseline in DRSS scores decreased from 79.9% at 52 weeks to 50% at 100 weeks. Patients on the 16-week treatment schedule had consistent 2-step or greater improvement in DRSS scores. Patients in the sham group also had more vision-threatening complications. PDR and/or anterior segment neovascularization developed in 3.7% of the PRN group, 3.0% in 16-week fixed-schedule group, and 20.3% of the sham patients. Central-involved DME occurred in 6.7% of the PRN patients, 8.2% of the fixed-schedule aflibercept patients, and 25.6% of the sham patients. If you reduce vision-threatening complications, won't you be better for vision over time? This is one conundrum we're in right now when deciding to treat or observe in patients with severe NPDR.

Dr. Vakharia: I think the biggest factor is compliance, which can be very difficult to judge. Anti-VEGF therapy requires a compliant patient. What is their occupation, and what are they using their vision for? How sensitive are they to their vision loss? Without good guidelines, it boils down to the individual patient and how aggressive they want to be with their treatment.

Dr. Ho: Dr. Finn, how do you manage these patients?

Dr. Finn: I consider treating patients who are likely to convert from severe NPDR to PDR. The more severe their NPDR, the more significant their nonperfusion on FA. I'm also more inclined to treat patients if they have multiple systemic comorbidities such as advanced nephropathy, repeated hospitalizations, or an amputation, even if their disease hasn't progressed to PDR or high-risk PDR, as this is an indication of more advanced systemic disease.

Dr. Ho: Dr. Nudleman, let's say we have a patient with severe NPDR who has been treated with anti-VEGF and has regressed as a result of treatment. Do you think we should view that patient the same as a patient who reached the same stage naturally?

Dr. Nudleman: I don't have an evidence-based answer for that question. What I would say is that the patient with pharmacologically induced regression was not always that way. They likely have ischemia. There's vascular damage, and you're treating it, but you haven't erased those existing disease drivers. So, no, I don't think these patients are the same. However, I am happy when I see disease regress with therapy. I'm in favor of treating them earlier, and I think the PANORAMA data[36] showing a 40% reduction in

edema and vision-threatening complications within 2 years is very powerful. When you start to see bad disease, intervening with the existing drugs we have is reasonable.

FINAL PEARLS ON MANAGING DIABETIC EYE DISEASE

Q | Dr. Ho: What are your final thoughts on managing diabetic eye disease?

Dr. Finn: Patient education is an important driving factor to empower the patient to have a role in decision-making. Involving the patient in their disease from the outset with education and showing them what their disease looks like is a powerful tool to change the course of their systemic disease. That's the bottom line. We want to make an impact, not only on their eye disease, but on the systemic disease overall.

Dr. Avery: Despite all these recent studies, learning how to treat DR is still an art. Many studies show relatively similar outcomes between fairly different techniques. Hence, there is no right or wrong treatment in many cases, so we can pay attention to many nuances in a patient's presentation, such as their compliance, when selecting a treatment. It's a great opportunity for us to play doctor again instead of following some routine flow chart.

Dr. Vakharia: Our field is evolving and much of that evolution centers on our imaging modalities. We're catching more peripheral retinopathy than we ever did with widefield angiography. Our diabetic patients are also on better therapies like CGM and insulin pumps. I'm excited to see how the field will change.

Dr. Rahimy: PANORAMA and Protocol W corroborate each other nicely in terms of the risk of going on to vision-threatening complications, which is alarmingly high. A substantial number of patients progress. We need to follow patients closely and consider treatment at earlier stages. Anti-VEGF is just one tool in our armamentarium to take care of these patients. Sometimes they need steroids, sometimes they need laser, and sometimes they need surgery.

Finally, I still can't get over how some specialists in our field treat PDR so differently from severe NPDR, as if they're different disease processes. They're not really that different. Both patient groups are prone to LTFU, to being hospitalized, and to all the different issues that come with diabetes. I treat these patients instead of observe because it's an opportunity to buy the patient some time and reduce their risk of progressing to PDR. I think longer term follow-up data from these key trials and real-world studies will potential elucidate that for the community.

Dr. Nudleman: We're fortunate to be practicing in this era. We have good imaging modalities, therapies, and surgical tools when needed. I think with appropriate screening, we can essentially eliminate the risk of blindness from DR, today. Now. We need to ensure patients have access to health care and are screened appropriately because 50% of patients who have diabetes don't get an annual diabetic eye exam. That needs to be improved.

Dr. Ho: We need a call to action to improve diabetic eye screenings in a public health campaign. There are a variety of initiatives from societies, industry, and diabetes associations working on this. I appreciate everyone participating in this conversation. Thank you for providing insights into the management of diabetic eye disease. ■

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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/2124-supp. If you experience problems with the online test, please email us at info@evolvemeded.com. Certificates are issued electronically, therefore, please provide your email address below.

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

Full Name_____

Phone (required) _____ Email (required) _____

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City _____ State/Country____ Zip/Postal Code_____

License Number _____ OE Tracker Number _____

DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ 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 consistent anti-VEGF treatment.	_____	_____	_____
Explain why patients with diabetic retinopathy (DR) and diabetic macular edema (DME) are so often lost to follow-up.	_____	_____	_____
Execute patient education plans on the importance of frequent DME treatment to improve treatment and exam compliance.	_____	_____	_____
Apply best practices and strategies in a cross-disciplinary approach to diabetes management to better manage patients.	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to explain why patients with diabetic retinopathy (DR) and diabetic macular edema (DME) are so often lost to follow-up (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

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

2. Based on this activity, please rate how often you intend to execute patient education plans designed to improve treatment and exam compliance (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. Out of the following options, which of the following is not a current strategy to help increase patient adherence to diabetic eye exams?

a. Calls and text messages to patients reminding them it's time for screening.
b. Written communication from an ophthalmologist to a primary care provider.
c. Free rides to medical appointments or free community diabetic eye screening.
d. Anti-VEGF pills taken by mouth daily.

4. Why are patients with DR often lost to follow-up?

a. The patients don't understand the severity of their ocular condition and may also have many other medical appointments, therefore often neglecting eye care.
b. Because DR is a mild condition without visual issues, they are not told further appointments will be needed to monitor the condition.
c. They receive one laser treatment and do not require further follow-up.
d. They don't have a retinal specialist in their area.

5. What do the panelists recommend clinicians do during the first visit with a diabetic patient to improve adherence to yearly eye exams?

a. Defer all counseling to the primary care physician.
b. Order a multifocal electroretinogram.
c. Educate the patient on HbA1c with their primary care physician, on the need for smoking cessation, and thoroughly explain the condition to help the patient better understand their ocular condition.
d. Educate the patient about the need for consistent primary care provider appointments and prescribe insulin.

6. A 56-year-old black male with type 2 diabetes has had good HbA1c control but has frequent setbacks. He has, however, kept up with yearly diabetic eye exams. He works as an editor for a living and needs good vision to remain employed. His HbA1c is currently 10.7%. His visual acuity (VA) OU is 20/30, and he has some signs of macular edema including cysts and exudate just outside the center fovea. What are your next treatment steps for this patient?

a. Anti-VEGF treatment every 4 weeks
b. Laser treatment followed by anti-VEGF
c. Observation
d. Discuss all options with the patient and develop a personalized treatment plan dependent upon his comfort level

7. A 42-year-old white female with type 1 diabetes presents to your office for the first time complaining of hazy vision. She uses a CGM and pump and her HbA1c is well controlled at 8%. Her VA is 20/40 OU. She admits that she hasn't had a diabetic eye exam for several years because her provider retired, she switched jobs, and she hasn't had time to find a new clinician. She presumed that because her systemic disease is well controlled that her risk for DR was low. She has preretinal subhyaloid hemorrhage with widespread midperipheral leakage neovascularization elsewhere. You determine she is at high risk for progression to PDR. How would you recommend treating this patient?

a. Panretinal photocoagulation (PRP)
b. Combination of anti-VEGF injections and PRP
c. Vitrectomy with endolaser
d. Discuss all options and develop a personalized treatment plan depending upon her comfort level

8. What was a key takeaway from Protocol W?

a. Proactive anti-VEGF treatment does not reduce the chance of developing center-involved DME (CI-DME), but has significant visual benefit in patients who progress to CI-DME.
b. Proactive anti-VEGF treatment can reduce the chance of developing CI-DME with vision loss by 16%.
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.

9. Based on PANORAMA data, which is the better treatment strategy for patients with moderate to severe NPDR?

a. Fixed-interval anti-VEGF, up to every 16 weeks
b. Anti-VEGF PRN
c. Observation
d. PRP

10. How is mild NPDR classified on retinal imaging?

a. One retinal hemorrhage and microaneurysms
b. More than one retinal hemorrhage
c. Microaneurysms only
d. Cotton wool spots and more than one retinal hemorrhage

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this CME 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: _____ High _____ Low _____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 nonpharmaceutical therapy _____

Change in diagnostic testing _____

Choice of treatment/management approach _____

Change in current practice for referral _____

Change in differential diagnosis _____

My practice has been reinforced _____

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 CME 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: _____

_____