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PREPARING FOR THE FUTURE:

Updates in Retinal Diseases and Novel Therapies

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Preparing for the Future:
Updates in Retinal Diseases and Novel Therapies

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CONTENT SOURCE

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

ACTIVITY DESCRIPTION

Based on a roundtable discussion in August, this supplement summarizes the challenges facing clinicians when managing diabetic eye disease and wet age-related macular degeneration (AMD) and the current and pipeline therapy options for these diseases.

TARGET AUDIENCE

This certified CE activity is designed for optometrists who care for patients with diabetes.

LEARNING OBJECTIVES

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

- **Describe** current therapy options for diabetic eye disease and wet AMD
- **Articulate** the challenges facing clinicians tasked with managing diabetic retinopathy, diabetic macular edema, and wet AMD
- **Summarize** pipeline candidates that are being developed for these patient populations

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PRETEST QUESTIONS

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

1. Please rate your confidence in your ability to describe the challenges facing clinicians when managing diabetic eye disease and wet age-related macular degeneration (AMD) and the current and pipeline therapy options for these diseases (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. According to 2020 estimates by the US Centers for Disease Control and Prevention, what percentage of the American population has diabetes?

a. 13%
b. 21%
c. 32%
d. 44%

3. Which of the following risk factors are important to consider in patients with wet AMD?

a. Tobacco use
b. Family history of AMD
c. Systemic hypertension
d. All of the above

4. According to the PANORAMA study:

a. Patients with proliferative diabetic retinopathy (PDR) who received aflibercept therapy every 4 weeks were reported to have at least a 2-step improvement in diabetic retinopathy severity scale (DRSS) compared to baseline
b. Patients with nonproliferative diabetic retinopathy (NPDR) who received aflibercept therapy every 4 weeks were reported to have at least a 2-step improvement in DRSS compared to baseline
c. Patients with PDR that received aflibercept therapy every 8 weeks were reported to have at least a 2-step improvement in DRSS compared to baseline
d. Patients with severe NPDR that received aflibercept therapy every 8 weeks were reported to have at least a 2-step improvement in DRSS compared to baseline

5. A 45-year-old woman with persistent diabetic macular edema (DME) presents to clinic. She asks specifically about intravitreal fluocinolone acetonide implant (IFAI) as an option for treatment. Which of the following are true regarding the IFAI?

a. IFAI is designed to last 3 to 4 months
b. There is no increased risk of cataract formation with IFAI
c. In randomized clinical trials, IFAI treated eyes were more likely to experience a 15-letter gain at 3 years compared to sham
d. No steroid challenge is required prior to considering IFAI

6. Compared to anti-vascular endothelial growth factor (VEGF) therapy, patients that undergo panretinal laser photocoagulation laser therapy are NOT at higher risk for which of the following?

a. Visual field defects
b. Worsening DME
c. Night vision defects
d. Endophthalmitis

7. According to DRCR Protocol T:

a. In DME patients with baseline VA 20/50, aflibercept was inferior to ranibizumab and bevacizumab at 1 year
b. Bevacizumab, ranibizumab, and aflibercept showed improved vision at 2 years compared to baseline
c. At 2 years, aflibercept showed superiority in visual acuity compared to ranibizumab
d. All of the above

8. Which of the following is true about the approved in-home monitoring device?

a. It is a home-based testing device to help detect changes in eyes with diabetic retinopathy
b. It is a home-based testing device to help detect changes in eyes wet AMD
c. Eye care providers receive alerts regarding any abnormalities detected by the artificial intelligence platform
d. B and C
e. A and C

9. According to phase 3 data on faricimab:

a. 80% of wet AMD patients were able to achieve 3-month treatment intervals in the first year and 45% extended to 4-month intervals
b. 45% of wet AMD patients were able to achieve 3-month treatment intervals in the first year and 80% extended to 4-month intervals
c. 80% of DME patients were able to achieve 3-month treatment intervals in the first year and 45% extended to 4-month intervals
d. 80% of DME patients were able to achieve 3-month treatment intervals in the first year and 45% extended to 4-month intervals

10. A patient presents with new onset vision changes including distortion. Imaging on optical coherence tomography shows a pigment epithelial detachment and subretinal fluid. What are important diagnoses to consider?

a. Exudative AMD
b. Vitelliform dystrophy
c. Central serous retinopathy
d. All of the above

11. Which of the following are true regarding port delivery system (PDS)?

a. After surgical implantation of the PDS device, the refill-implant must be performed in the operating room every 24 weeks
b. In the ARCHWAY study, the majority of patients in the PDS arm required supplemental intravitreal injections
c. PDS is being investigated for the treatment of DME
d. All of the above

12. What are some of the limitations to current anti-VEGF therapy for AMD?

a. Burden of frequent visits for patients
b. Inability to extend treatment intervals
c. Undertreatment
d. All of the above

13. Which of the following is true regarding the KITE and KESTREL studies?

a. Brolucizumab every 6 weeks followed by 12-week dosing intervals was found to be inferior to aflibercept for the treatment of DME in terms of visual acuity
b. Majority of patients were able to maintain 3-month dosing intervals with brolucizumab at 1 year for treatment of DME
c. Brolucizumab every 6 weeks followed by 12-week dosing intervals was found to be inferior to aflibercept for the treatment of wet AMD in terms of visual acuity
d. Majority of patients were able to maintain 3-month dosing intervals with brolucizumab at 1 year for treatment of wet AMD

Preparing for the Future:
Updates in Retinal Diseases and Novel Therapies

The treatment landscape in retina may soon undergo significant changes due to the number of drug candidates in the pipeline to treat wet age-related macular degeneration, diabetic macular edema, and diabetic retinopathy. Given that optometrists are often the first point of contact for patients with retinal disease, it follows that they familiarize themselves with the various treatment options to optimize patient care and education. As new technologies come to market, they will need to keep abreast of changes to continue offering top-flight care and collaborating with retina specialists.

To this end, I chaired a discussion with a panel comprised of two optometrists and two retina specialists. By joining together in conversation, we were able to review the best practices for modern retinal care, discuss the latest data on real-world treatment patterns and outcomes, and preview the pipeline technologies that may be approved for use in the coming months or years. Two sidebars in this discussion highlight cases, both of which illustrate the burden of care associated with current therapeutic options.

—Michael A. Singer, MD, Program Chair

RETINAL DISEASE IN THE OPTOMETRIC SETTING: THE FIRST ENCOUNTER WITH A CLINICIAN

Michael A. Singer, MD: Patients with retinal conditions such as wet age-related macular degeneration (AMD), diabetic retinopathy (DR), and diabetic macular edema (DME) often present to an optometric clinic, where patients encounter routine care from their primary eye care provider.

Q | Dr. Koetting, I'm curious to learn about your clinical experience with these patients. Are they presenting with visual complaints related to retinal disease, or is their disease detected during examination for other pathologies?

Cecelia C. Koetting, OD: In my experience, patients with retinal disease present for various reasons. In some cases, new patients who schedule an appointment for a comprehensive examination but have no complaints of visual disturbance show early signs of wet AMD or geographic atrophy (GA). We are on the lookout for age-related macular changes during comprehensive exams in patients who are older. Among our diabetic patient population, we make sure to look closely for evidence of DR and DME.

The practice where I work, Virginia Eye Consultants, has several retina specialists on staff. In some cases, I collaborate with them in treating patients with wet AMD or GA. For example, I might observe a patient with early-stage GA—for which there is no therapy approved by the US Food and Drug Administration (FDA)—to track lesion growth patterns. Alternatively, patients who are undergoing treat-and-extend (TAE) regimens of anti-VEGF therapy for wet AMD may present to my clinic between treatments. In those patients, I aim to detect disease activity and will report any unusual findings to the retina specialist with whom I'm working.

Mark T. Dunbar, OD: According to a 2013 review commissioned by the American Optometric Association, 85% of all comprehensive eye exams are performed by optometrists, so it shouldn't be surprising that many patients with retinal disease present to optometry clinics when we consider the epidemiology of retinal disease and the wide range of practices that offer optometric services.[1]

First, consider the range of touch points patients have with optometry. They might find an optometric clinic in a big box retailer or a warehouse club store, and may also access services in more traditional private practices, academic settings, and comprehensive eye care centers in which optometrists and ophthalmologists work alongside each other.

Further, consider the disease statistics in the United States. The US Centers for Disease Control and Prevention (CDC) 2020 estimates found that 13% of the American population has diabetes.[2] Estimates place the prevalence of DR in the United States at 7.7 million,[3] and the prevalence of DME at 746,000.[4] It is estimated that more than 1 million Americans have wet AMD,[5] a number that can be expected to grow as the population ages.[6]

In my estimation, a majority of optometrists in a number of clinical settings have access to optical coherence tomography (OCT) imaging platforms, which are foundational to accurate diagnosis and referral of retinal disease. As optometry increases its access to technology, such as OCT imaging and fundus photography, it will improve patient care at the first point of clinical contact.

Dr. Singer: Both of the optometrists on this panel work at referral centers alongside ophthalmologists, and therefore see patients who have shown some suspicion for disease.

Q | How often do patients with retinal disease present with imaging reports from a referring eye care provider?

Dr. Dunbar: Rarely, if ever.

Dr. Koetting: I agree. If I'm estimating generously, I would say it's 25% of patients—but that is only because our clinic stresses to our referral network that sending imaging reports leads to improved patient care.

Dr. Singer: Let's suppose a returning patient who has been identified as having early or intermediate AMD presents to the optometric clinic. During your exam, you detect fluid on OCT.

Q | What are the next steps you take to increase the likelihood that this patient follows up with a provider who can administer therapy?

Dr. Koetting: In this scenario, the patient is already aware they have early or intermediate AMD, and we have prepared them for the possibility that it will progress to the point that they need treatment. I explain to the patient that we have reached that point, which means it is time to refer them to a retina specialist within the next week. After providing details on who that retina specialist will be—oftentimes, it is a retina specialist who practices at Virginia Eye Consultants—I describe the treatment options, explaining that it is very likely they will receive an injection in their eye and, in rare cases, a laser-based therapy. In some instances, I decline to go into specifics about therapy. It depends on the patient's personality.

Dr. Dunbar: Going patient-by-patient on the question of detailing therapy is key. As clinicians who are sometimes tasked with mentally preparing patients for what could be a stress-inducing therapy, we must balance educating the patient and encouraging them to seek therapy. Some patients are unfazed by the idea of an intravitreal injection, but others are so frightened by the concept that they will not make an appointment with a retina specialist. If I sense a patient's fear regarding an injection, I emphasize that treatments for their condition exist, and a retina specialist can review those options after reviewing the benefits of each route.

Dr. Koetting: I mentioned earlier that I tailor a comprehensive eye exam to detect AMD in patients who are older. This is also valuable in patients with risk factors from AMD aside from age. Patients with a family history of AMD, a personal history of smoking, or who are presently obese or living with hypertension are at increased risk for developing AMD.[7] An eye exam focused on detecting wet AMD in particular is appropriate for patients with any of these risk factors: pigmentary abnormalities,[8] history of cataract surgery,[9] white race,[10] systemic hypertension,[10] and current smoking.[10]

Q | **DR. SINGER:** What is the nature of an optometric clinical exam for a patient with DME?

Dr. Dunbar: I immediately look for the presence of fluid accumulation and center-involving disease in a patient with DME. Even in a patient without center-involving DME, I am likely to refer them to a retina specialist if I think there is an eminent threat of their disease affecting visual function, as I would prefer they monitor it and administer prompt treatment if needed.

That is not to say, however, that all patients with center-involving DME require therapy. Data from the DRCR Retina Network's Protocol V study indicate that some patients with good vision (ie, >20/25 VA) demonstrated no significant vision loss after 2 years of observation, as long as they were given anti-VEGF therapy when disease worsened.[11]

For patients with DR, my algorithm varies depending on the status of proliferation and the severity of disease. I refer patients to a retina specialist if I detect evidence of proliferative DR (PDR). Regarding nonproliferative DR (NPDR), I monitor patients with mild and moderate NPDR myself, and refer them to a retina specialist after they reach a level of retinopathy that is more than moderate NPDR (ie, moderately severe to severe NPDR).

Some eye care providers may turn to data from the PANORAMA study to guide their interaction with patients with NPDR. In PANORAMA, researchers compared aflibercept to sham for the treatment of NPDR.[12] It was observed that 80% of patients who received therapy every 8 weeks experienced a 2-step improvement in DR severity scale (DRSS) scoring from baseline to month 52, whereas only 15% of patients who received sham therapy showed such improvement. Most importantly, 12% of sham patients demonstrated progression to PDR compared with 0% of patients in the 8-week treatment arm. For this reason, I generally refer any patient with at least moderate DR to a retina specialist, who can determine the best course of therapy for that patient.

Q | **DR. SINGER:** I would like the retina specialists on the panel to respond to what our optometric colleagues just described. How your practices interact with optometry in general?

Carl D. Regillo, MD: I practice at Mid Atlantic Retina, which is a large private practice with offices at Wills Eye Hospital in Philadelphia and at various locations throughout Southeastern Pennsylvania, Delaware, and New Jersey. We see patients from urban, suburban, and rural areas, and many of them are referred to our practice from optometrists.

I appreciate that Drs. Koetting and Dunbar are sensitive to patients' uncertainty regarding intravitreal injections. I would advise erring on the side of general commentary about treatment rather than the specifics of the route of administration, as I agree that the fear of an injection may be enough to prevent patients from scheduling their needed follow-up appointments. I have found that patients who don't know anyone who receives

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PATIENT WITH WET AMD WHO REQUIRES FREQUENT DOSING

Arshad M. Khanani, MD, MA

A 70-year-old woman presented to my clinic in January 2013. Upon examination, I diagnosed her with wet age-related macular degeneration (AMD). She has received 8 doses of ranibizumab, 15 doses of bevacizumab, and 37 doses of aflibercept during the course of her treatment. In 2019, she received 8 injections of aflibercept.

Given her high burden of treatment, the patient and I attempted to increase her treatment intervals via a treat-and-extend strategy. Figure 1 shows optical coherence tomography (OCT) imaging of the patient when she returned to the clinic 6 weeks after her most recent aflibercept injection. Subretinal fluid was observed, aflibercept was administered, and the patient was moved to a 5-week dosing interval.

Upon her return 5 weeks later, subretinal fluid had improved but was still present (Figure 2). A pigment epithelium detachment (PED) was also observed. Aflibercept was again injected, and the patient returned in 4 weeks. At her next visit, the patient showed evidence of slight subfoveal fluid, but it had mostly resolved (Figure 3). However, a persistent PED of 145 µm was present.

In this case, the patient was unable to go longer than 4 weeks without recurrent disease activity. She is a candidate who is well-suited for a treatment option for wet AMD that has a greater duration than, but a safety profile similar to, the drugs she has already been administered.

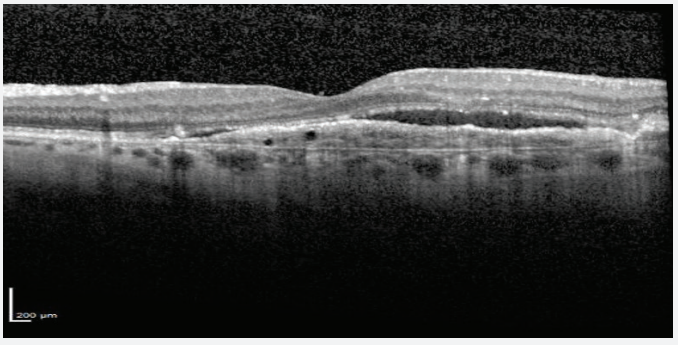

Figure 1. Six weeks after administration of aflibercept, the patient returned to the clinic with evidence of subretinal fluid.

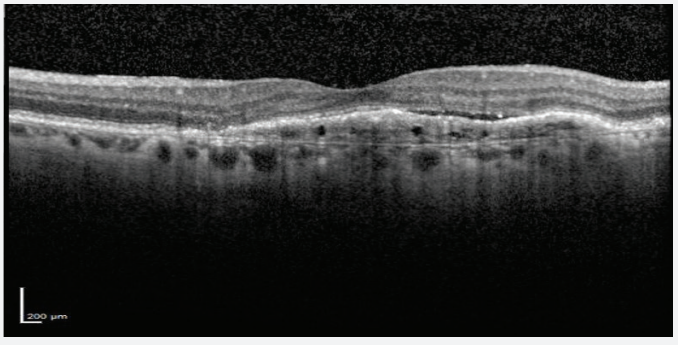

Figure 2. Five weeks after an aflibercept injection, the patient returned to the clinic for evaluation. Partial fluid resolution was observed, as was a PED.

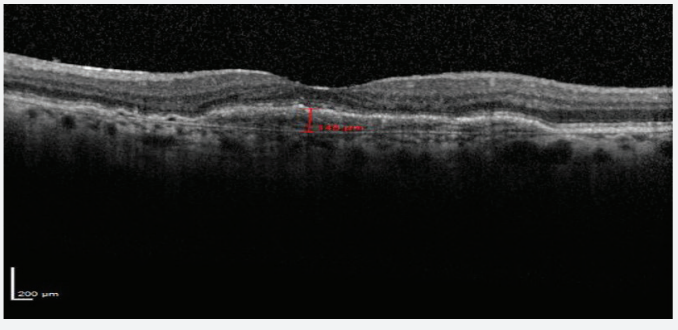

Figure 3. The patient's OCT image at 4 weeks showed nearly resolved subfoveal fluid and a persistent PED.

(Continued from page 6)

intravitreal injections may not understand that the procedure is well tolerated and carries very low risk of complication. Establishing a diagnosis and a need for further examination is, in my estimation, the wisest route to ensuring that patients make an appointment with the office to which they were referred by their optometrist.

Arshad M. Khanani, MD, MA: My clinic sees patients who are referred to us from optometrists and general ophthalmologists. I have found many of the patients who are referred to my clinic are prepared in general for the concept of specialty care, and might have some idea that laser and injections are within the spectrum of possible therapies. Some of these patients have obvious diagnoses, but many of them arrive to the clinic with evidence of suspicious anatomy that warrants further investigation before a diagnosis can be made. During that investigation, I make sure to rule out masquerading pathology—for example, ensuring that what appears to be wet AMD is not, in fact, vitelliform macular dystrophy or central serous chorioretinopathy.

TREATMENT OPTIONS FOR WET AMD, DR, AND DME

Q | DR. SINGER: Wet AMD and diabetic eye disease respond to similar therapeutic approaches. What therapies are used to address these pathologies?

Dr. Regillo: Although the pathophysiology of wet AMD, DR, and DME are different, they share a common underpinning: VEGF-regulated disease. In patients without advanced disease and among those who receive relatively frequent dosing with anti-VEGF agents, visual acuity often improves or is maintained and good disease control is established. In the United States, the anti-VEGF agents approved by the FDA for some of these indications include ranibizumab, aflibercept, and brolucizumab. Pegaptanib sodium was an early anti-angiogenic agent approved for the treatment of wet AMD, but is almost never used in modern practice. However, off-label use of the compounded anti-VEGF agent bevacizumab is often utilized by retina specialists for these conditions.

In tightly controlled clinical trials, patients who fit enrollment criteria were dosed with anti-VEGF agents on strict, frequent, and typically fixed schedules, resulting in significant mean visual gains. Reproducing those clinical trial settings in the real world has proven challenging. Heterogenous patient needs and responses to therapy have further complicated matters. Thus, rather than dosing all patients at a fixed interval, we seek to individualize therapy based on patient needs and the disease's response to therapy.

Some clinicians use an as-needed, or *pro re nata* (prn), dosing regimen for patients with wet AMD, DR, or DME who are undergoing anti-VEGF therapy. Others employ a TAE dosing pattern, in which a patient's treatment interval is increased each visit until disease recurrence is noted, thereby creating an individualized dosing schedule.

Consider real-world wet AMD treatment patterns in this context. Only 1% of US retina specialists use a monthly regimen for patients with wet AMD on a routine basis.[13] When comparing monthly injection regimens with TAE regimens for wet AMD in a clinical trial setting, it has been shown that TAE dosing patterns significantly reduce treatment burden without sacrificing visual function.[14,15]

TAE regimens have been found to be similarly effective for anti-VEGF treatment for DME.[16] Ranibizumab, aflibercept, and off-label bevacizumab are used to treat DME; ranibizumab is indicated for administration every 4 weeks,[17] and aflibercept is indicated for dosing every 8 weeks after 5 monthly doses.[18]

Both the intravitreal dexamethasone implant 0.7 mg (IDI) and the intravitreal fluocinolone acetonide implant 0.19 mg (IFAI) were approved for DME therapy by the FDA in 2014.[19,20] In randomized, sham-controlled trials, patients who underwent IDI or IFAI therapy were significantly more likely to experience a 15-letter gain from baseline at 3 years compared with sham.[21,22]

Sustained-release steroids reduce the need for frequent office visits among DME patients, although cataract formation and IOP elevation remain a concern. The IDI generally achieves a therapeutic effect for 3 to 4 months, and the IFAI is designed to last 36 months. Patients who receive an IFAI must, per the drug's label, have been previously treated with steroids and must not have demonstrated a clinically significant rise in IOP.

Clinicians treating PDR often use a combination of panretinal laser photocoagulation (PRP) and anti-VEGF therapy. PRP was established as a safe and effective therapy for PDR in the early 1980s,[23] and the anti-VEGF agents ranibizumab and aflibercept were approved by the FDA for the treatment of DR (with or without DME) in 2017 and 2019, respectively.[24,25] As of 2019, the percentage of retina specialists who would use PRP monotherapy to treat PDR without DME was roughly equal the percentage of those who would use PRP in combination with anti-VEGF therapy.[13] Patients with PDR who receive PRP therapy are at risk of complications that include visual field deficits, night vision defects, and exacerbation of DME.[23,26]

Q | DR. SINGER: How would you describe the relative safety and efficacy of the drugs you described?

Dr. Regillo: For wet AMD, aflibercept, ranibizumab, and bevacizumab are similarly safe, effective, and durable. There may be a superior drying effect with brolucizumab. However, cases of significant intraocular inflammation with vision loss from retinal vascular occlusions among wet AMD patients who received brolucizumab have been reported,[27] leading most clinicians to limit its use in practice and, if used, carefully monitor patients who are undergoing treatment.[28]

To understand the differences in DME therapy, we should turn to the DRCR Retina Network Protocol T study.[29] At 1 year, aflibercept was determined to be superior to ranibizumab and bevacizumab in DME patients with baseline VA of 20/50 or worse.[30] By 2 years, however, the superiority of aflibercept versus ranibizumab was no longer noted.[29] All three anti-VEGF agents improved vision compared with baseline at 2 years.[29]

Q | DR. SINGER: Real-world underdosing of patients with any of these diseases is a frustrating reality. What factors lead to underdosing of patients with wet AMD, DR, and DME?

Dr. Khanani: It appears the dosing regimens used in clinical trials are too high for real-world patients. Among working-age patients, for example, getting time off from work to visit the clinic poses a significant challenge.[31] Dr. Regillo mentioned that alternative dosing regimens (ie, prn, TAE) are effective for some patients, as they alleviate treatment burden. A handful of studies have found that treatment burden is too high for patients with diabetic eye disease,[11,32] which leads to these patients being lost to follow-up[33] and experiencing undertreatment.[34,35]

TAE regimens embody a contradiction in retinal care: although 62% of US-based retina specialists would employ a TAE protocol after at least 3 monthly loading doses for a treatment-naïve patient with wet AMD, 65% of them believe patients with wet AMD are undertreated in the real world.[13]

Real-world evidence illustrates treatment burden in wet AMD is similar to that of diabetic eye disease. My colleagues and I recently published the findings of the SIERRA-AMD study, which was a retrospective trial examining real-world wet AMD treatment patterns and outcomes in the United States.[36] In that study, we found that patients lost vision after 2, 3, and 4 years of treatment and received mean 7.5, 6.7, 6.6, and 6.4 injections in years 1, 2, 3, and 4, respectively. Creating more durable therapies could be key to reducing treatment burden without sacrificing visual outcomes.

Dr. Singer: We will discuss pipeline candidates that might extend treatment durations shortly. In terms of wet AMD treatment, although optometrists are not authorized to administer therapy for wet AMD, they remain an important entry point to care for thousands of patients per year.

Q | What is optometry's role in the treatment continuum?

Dr. Dunbar: Optometrists play an important role in the management of AMD via detection of disease activity. Recommending nutritional supplements in patients with intermediate AMD is important in reducing the risk of conversion from dry to wet AMD, as is prescribing an in-home AMD monitoring device. There is an approved device on the market that in addition to standard of care may play a key role in detecting early conversion to wet AMD—which, in turn, is likely to keep patients with good vision at or above 20/40 VA.

Patients who use this device undergo routine home-based testing. If the artificial intelligence platform detects aberrations from baseline that warrant review, a notification is sent to the monitoring center where in-house ophthalmologists review the results and, if appropriate, send an alert to the prescribing eye care provider that the patient needs to be seen for an in-person follow-up examination and possible treatment or referral.

A 2021 study determined that use of this device in addition to the standard of care was effective at detecting conversion from intermediate dry AMD to wet AMD.[37] This is important in light of findings by Ho et al, who determined that real-world patients with wet AMD whose VA was at least 20/40 at presentation remained at 20/40 or better after 2 years of anti-VEGF therapy, whereas patients whose VA was worse than 20/40 at baseline never achieved 20/40 VA.[38]

In short, the earlier wet AMD is detected, the better vision is after 2 years in real-world wet AMD patients. If optometrists want to provide a framework of success for their wet AMD patients, they should consider prescribing the AMD in-home monitoring device to patients with intermediate AMD.

Dr. Koetting: We used to ask patients to refer to an Amsler grid to determine if wet AMD activity was present. These grids were as low-tech as it comes, and they were not nearly as sensitive as home-based monitoring, which, in some cases, detects disease conversion in asymptomatic patients. Further, with Amsler grids, we relied on patients to inform us of changes to their vision. With the home-based monitoring device, our clinic is prompted from a centralized reading center to contact the patient if an in-person examination is needed, which keeps the line of communication between the patient and the clinician and also takes the onus of initiating communication off of the patient.

Dr. Regillo: Early detection is important for each of the disease states we're reviewing, but particularly so for wet AMD. As Dr. Dunbar stated, early detection in patients with good visual acuity means that, if they adhere to therapy, good visual acuity can be maintained for several years. I have observed that although prompt follow-up for DME is wise, retinal edema is better tolerated than choroidal neovascularization.

RECENT DEVELOPMENTS AND THE PIPELINE

Dr. Singer: Research into the safety and efficacy of drug candidates for retinal disease continues to provide hope that patients may soon have access to durable, safe, and effective therapy options.

Q | What are some of the drugs that are closest to regulatory approval?

Dr. Regillo: I expect decisions from regulatory bodies in the near future regarding faricimab for the treatment of wet AMD and DME, brolucizumab for the treatment of DME, and the port delivery system (PDS) with ranibizumab for the treatment of wet AMD.

Phase 3 data examining the safety and efficacy of faricimab for wet AMD found that about 80% of wet AMD patients were able to have at least a 3-month treatment interval in their first year of treatment, with approximately 45% of patients going at least 4 months between injections.[39] Similar results were observed in patients with DME, with 70% of patients achieving at least 3 months between injections, and approximately 52% requiring injections at least every

(Continued on page 11)

LIMITS TO EXTENDED INTERVALS IN WET AMD

Carl D. Regillo, MD

A 77-year-old woman presented to the clinic with distorted vision in her left eye for 3 weeks. Upon examination and imaging, we determined she had 20/60 VA and new-onset wet age-related macular degeneration (AMD) with choroidal neovascularization and subretinal fluid on optical coherence tomography (OCT; Figure 1). Aflibercept was administered. The patient returned in 4 weeks with improved macular anatomy and visual acuity, and she received a second intravitreal injection of aflibercept. On her third visit which was 4 weeks later, the subretinal fluid had resolved and VA was 20/30 (Figure 2).

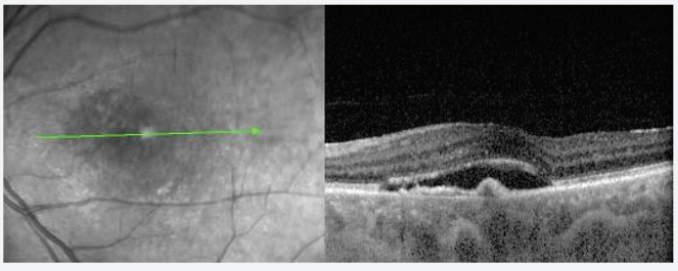

Figure 1. The patient presented with 20/60 VA and evidence of subretinal fluid on OCT.

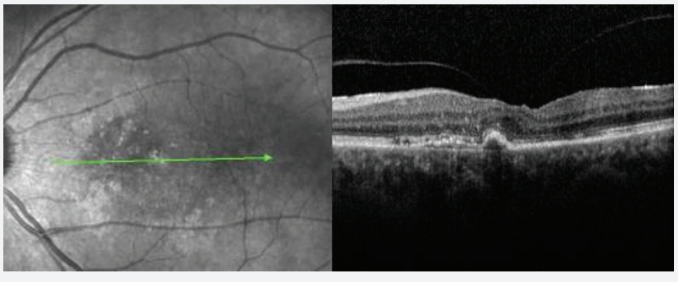

Figure 2. Four weeks after the patient's third injection of aflibercept, subretinal fluid had resolved and VA was 20/30.

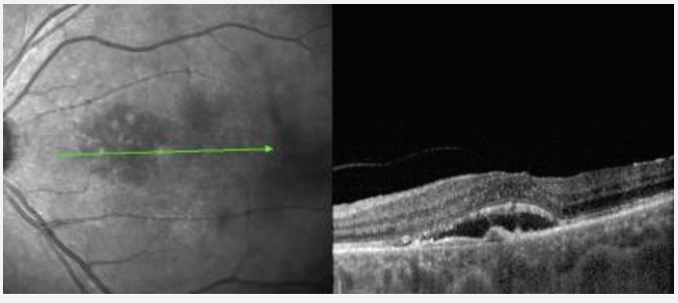

Figure 3. The patient returned after an 8-week interval, at which point VA dipped to 20/50 and subretinal fluid recurred.

This was a success story so far. I administered aflibercept and asked the patient to return in 6 weeks, at which point the affected eye was still dry and VA holding well at 20/30. After another injection, I asked her to return in 8 weeks. At that appointment, OCT imaging showed that subretinal fluid had recurred, and the patient's VA declined to 20/50 (Figure 3). I determined that, given the amount of fluid on OCT and the reduction in visual acuity, this degree of subretinal fluid in this patient should not be tolerated. Therefore, I reduced the treatment interval in this patient to 6 weeks, which, although more preferable than a 4-week interval, still places a large burden on the patient.

If forthcoming therapies are more durable, this patient may be a good candidate for a therapy switch. Until then, the patient will need to continue to return to the office every 6 weeks for the time being for ongoing anti-VEGF injections.

(Continued from page 9)

4 months.[40] The company submitted regulatory filings for the treatment of wet AMD and DME with the FDA in July 2021.[41]

Faricimab is a bispecific monoclonal antibody that neutralizes both VEGF-A and angiopoietin-2 (Ang-2), and this unique design may contribute to its durability. In a healthy eye, a balance of Ang-1 and Ang-2 helps maintain vascular stability.[42] Under pathologic conditions such as wet AMD and DR, Ang-2 is upregulated.[43] When Ang-2 binds to the TIE2 receptor on the cellular surface, leakage and upregulation of inflammatory cytokines and VEGF-A occurs.[44] This in turn leads to vascular instability and neovascularization.[44,45] If the FDA approves the drug, it will be the first drug that addresses retinal disease that targets two distinct pathways.[41]

Educating eye care providers about the mechanisms of this new approach to therapy will be key to adoption. Just as the field mobilized to educate physicians about the role of VEGF at the beginning of the anti-VEGF era, so too will we need to deepen our understanding of Ang-2's role in mediating the pathologic processes in these conditions.

Q | DR. SINGER: Brolucizumab is already approved for the treatment of wet AMD. What have the phase 3 DME studies found?

Dr. Khanani: The phase 3 KITE and KESTREL studies are comparing the safety and efficacy of brolucizumab and aflibercept for the treatment of DME.[46] These are randomized, global, phase 3 trials. Patients in the brolucizumab groups were treated every 6 weeks for five loading doses, after which they moved to 12-week dosing intervals (or 8-week intervals, if disease activity recurred), and patients in the aflibercept groups received five monthly loading doses followed by fixed 8-week dosing.

A data readout from the 52-week period of the 2-year trials found that, in KITE, brolucizumab 6 mg therapy was noninferior to aflibercept 2 mg for the treatment of DME in terms of BCVA change from baseline, which meant the study reached its primary endpoint.[46] More than half of patients in the brolucizumab 6 mg arm maintained 12-week dosing intervals at 1 year. No significant safety differences were noted among the two arms. In KESTREL, which evaluated brolucizumab 6 mg, brolucizumab 3 mg, and aflibercept 2 mg, the brolucizumab 6 mg arm met the primary endpoint.[47]

Brolucizumab is also under investigation for the treatment of PDR. In a study that will compare PRP and brolucizumab, patients in the brolucizumab arm will have the drug administered every 12 weeks after three loading doses.[48] The estimated completion date is Q1 2025.

Q | DR. SINGER: Dr. Regillo, I know you've performed plenty of research on the PDS for the treatment of wet AMD. Can you please describe the latest clinical data for PDS?

Dr. Regillo: The PDS is a refillable, scleral-based reservoir implant that continually dispenses a specific, high-concentration formulation of ranibizumab. It is surgically implanted, and refills of the implant are performed in the office. That process, termed a refill-exchange, removes any remaining drug in the reservoir and replaces it with a fresh batch.

In the phase 3 ARCHWAY study, patients with previously treated wet AMD were randomly assigned to receive PDS implantation with 100 mg/mL concentration of ranibizumab and refilled every 24 weeks or monthly ranibizumab injections at the standard FDA-approved dose.[49] The primary endpoint of the ARCHWAY study was mean change in BCVA averaged between weeks 36 and 40. In the PDS arm, 98% of patients went 6 months without needing supplemental therapy.[50] Patients in the ranibizumab injection arm gained mean 0.5 letters from baseline, and those who were implanted with the PDS demonstrated a gain of 0.2 letters from baseline.[50] These data led researchers to conclude the PDS was statistically both noninferior and equivalent to monthly ranibizumab therapy.[50] I speculate that the PDS will be a useful tool to alleviate the burden of treatment for patients with wet AMD who require frequent anti-VEGF injections. Genentech submitted a Biologics License Application to the FDA, which accepted the filing under priority review [*Editor's note: This roundtable discussion occurred prior to the Oct. 21, 2021, FDA approval of PDS.*].[51]

Q | DR. SINGER: For which other indications is the PDS under investigation?

Dr. Regillo: The safety and efficacy of the PDS is being evaluated for DME in the phase 3 PAGODA study[52] and for DR in the phase 3 PAVILION study.[53] The structure of PAGODA is similar to that of ARCHWAY. However, in PAGODA, the primary endpoint will be average change in BCVA from baseline averaged over weeks 60 and 64. It is estimated to be completed near the end of 2022.

PAVILION is also similar to ARCHWAY in trial design, with two important differences: PDS refill-exchanges will occur every 36 weeks, and the primary endpoint is the percentage of patients with at least a 2-step improvement from baseline on ETDRS-DRSS at 1 year. That study will be completed by early 2023.

Q | DR. SINGER: Two other medications appear to be intriguing future treatment candidates: KSI-301 and OPT-302. What can you tell me about those, Dr. Khanani?

Dr. Khanani: KSI-301 is an antibody biopolymer conjugate, which means the drug is comprised of a larger biopolymer to which an VEGF antibody is attached. This structure may lead to increased durability.

KSI-301 is under investigation to treat DME in the phase 3 GLEAM and GLIMMER studies,[54,55] and to treat wet AMD in the phase 2b/3 DAZZLE study.[56]

In GLEAM and GLIMMER, patients will be dosed with KSI-301 at a personalized regimen of 8 to 24 weeks or aflibercept monotherapy every 8 weeks for 100 weeks, with the primary endpoint occurring at 1 year.

In DAZZLE, patients with wet AMD who are randomized to KSI-301 will be dosed at one of three schedules (12, 16, or 20 weeks),

or will be dosed with aflibercept every 8 weeks. At 1 year, patients who receive aflibercept will be randomly assigned to continued aflibercept therapy or KSI-301.

The pipeline drugs we have talked about so far are to be administered in lieu of current therapeutic agents. OPT-302, however, is designed to be administered to patients alongside an anti-VEGF agent. The anti-VEGF agents used by clinicians today block VEGF-A. OPT-302 is designed to block the isoforms VEGF-C and VEGF-D.

The drug's safety and efficacy are being evaluated for wet AMD therapy in the phase 3 ShORe and COAST trials.[57] Patients in ShORe will be randomly assigned to receive OPT-302 in combination with ranibizumab every 4 weeks, every 8 weeks (after three monthly loading doses), or to receive ranibizumab plus sham. COAST is identical in design, but will employ aflibercept as the anti–VEGF agent with every 8 week dosing after the three monthly loading doses. The drug is also under investigation for the treatment of DME.[58]

It should be noted that use of OPT-302 would not decrease treatment burden, but rather may enhance the efficacy of the drugs already in use for treating wet AMD and DME.

Q | DR. SINGER: Some approaches are moving beyond the anti-VEGF paradigm. Dr. Regillo, what are the latest updates and data in the world of gene therapy?

Dr. Regillo: Two gene therapies of interest are under investigation in retina: RGX-314 and ADVM-022.

In phase 1/2, RGX-314 was administered to patients with wet AMD in the OR via a vitrectomy with subretinal injection. In phase 2, researchers will use an office-based suprachoroidal injection method. In the phase 1/2a AMD trial, patients with previously treated wet AMD were assigned to one of five dose-escalating cohorts. RGX-314 was administered 1 week after a single intravitreal anti-VEGF injection. Among the patients in cohorts 4 and 5 (ie, the two highest-dosed groups) at 1.5 years after administration, BCVA change was +1 and -1 letters from baseline, respectively, and decreases in central retinal thickness were -46 µm and -93 µm, respectively.[58] Patients in cohort 4 required mean 4.4 anti-VEGF injections during the 1.5 year follow-up, and those in cohort 5 needed 1.7 injections. Those reductions in treatment burden were 58% and 81%, respectively.

The drug will soon be evaluated for wet AMD in the ATMOSPHERE study, a pivotal trial.[59] It is also under investigation with the suprachoroidal injection delivery approach for wet AMD and DR without center-involved DME in the AAVIATE and ALTITUDE studies, respectively.[60,61]

The phase 1 OPTIC study is exploring the safety and efficacy of ADVM-022 in previously treated wet AMD patients who have demonstrated a response to anti-VEGF therapy. Among those assigned to the low- and high-dose groups of the drug, respectively, nine of 15 patients and 13 of 15 patients did not require supplemental anti-VEGF injections after 1 year.[62,63] These resulted in a reduction of annualized anti-VEGF injection frequency of 85% among the low-dose group and 96% among the high-dose group.[62,63]

The phase 2 INFINITY trial, which was assessing ADVM-022 for the treatment of DME, was unmasked in April 2021 following severe adverse events with inflammation and hypotony.[64]

Q | DR. SINGER: How do the optometrists on the panel discuss the future of eye care with patients who may not be well-versed in the science but are understandably excited about the possibility of improved efficacy and durability?

Dr. Koetting: I only discuss new technologies with patients if they are recently approved or near FDA approval. Keeping abreast of the latest treatment methods and potential innovations is particularly useful to optometrists who need to explain to patients that outdated treatment approaches they may have heard from a friend or family member who was treated several years ago may no longer be the standard of care.

Dr. Dunbar: Speaking in broad strokes about innovations is probably the best approach for optometrists who encounter patients with retinal disease. Encouraging data points that show that treatments may be less frequent as more data are collected might make the forthcoming care they face less intimidating. Optometrists can increase patient access to care by empowering them to follow-up with a retina specialist.

Dr. Singer: Increasing access to care and decreasing the care-related burdens falls on all clinicians who encounter patients with retinal disease. Optometrists, retina specialists, and researchers all have roles to play in the future of eye care, and interdisciplinary communication sessions such as this will be key in improving the lives of our patients. ■

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64. Adverum Provides Update on ADVM-022 and the INFINITY Trial in Patients with Diabetic Macular Edema [press release]. July 22, 2021; Adverum Biotechnologies; Redwood City, CA.

PREPARING FOR THE FUTURE:
Updates in Retinal Diseases and Novel Therapies

COPE Release Date: November 8, 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, go to http://evolvemeded.com/course/2144-supp. If you experience problems with the online test, email us at info@evolvemeded.com. *NOTE: Certificates are issued electronically.*

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 _____

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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

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	**Agree**	**Neutral**	**Disagree**
Describe current therapy options for diabetic eye disease and wet age-related macular edema (AMD)	_____	_____	_____
Articulate the challenges facing clinicians tasked with managing diabetic retinopathy, diabetic macular edema, and wet AMD	_____	_____	_____
Summarize pipeline candidates that are being developed for these patient populations	_____	_____	_____

PLEASE COMPLETE AT THE CONCLUSION OF THE PROGRAM.

1. **Based on this activity, please rate your confidence in your ability to describe the challenges facing clinicians when managing diabetic eye disease and wet age-related macular degeneration (AMD) and the current and pipeline therapy options for these diseases (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. **According to 2020 estimates by the US Centers for Disease Control and Prevention, what percentage of the American population has diabetes?**
   a. 13%
   b. 21%
   c. 32%
   d. 44%

3. **Which of the following risk factors are important to consider in patients with wet AMD?**
   a. Tobacco use
   b. Family history of AMD
   c. Systemic hypertension
   d. All of the above

4. **According to the PANORAMA study:**
   a. Patients with proliferative diabetic retinopathy (PDR) who received aflibercept therapy every 4 weeks were reported to have at least a 2-step improvement in diabetic retinopathy severity scale (DRSS) compared to baseline
   b. Patients with nonproliferative diabetic retinopathy (NPDR) who received aflibercept therapy every 4 weeks were reported to have at least a 2-step improvement in DRSS compared to baseline
   c. Patients with PDR that received aflibercept therapy every 8 weeks were reported to have at least a 2-step improvement in DRSS compared to baseline
   d. Patients with severe NPDR that received aflibercept therapy every 8 weeks were reported to have at least a 2-step improvement in DRSS compared to baseline

5. **A 45-year-old woman with persistent diabetic macular edema (DME) presents to clinic. She asks specifically about intravitreal fluocinolone acetonide implant (IFAI) as an option for treatment. Which of the following are true regarding the IFAI?**
   a. IFAI is designed to last 3 to 4 months
   b. There is no increased risk of cataract formation with IFAI
   c. In randomized clinical trials, IFAI treated eyes were more likely to experience a 15-letter gain at 3 years compared to sham
   d. No steroid challenge is required prior to considering IFAI

6. **Compared to anti-vascular endothelial growth factor (VEGF) therapy, patients that undergo panretinal laser photocoagulation laser therapy are NOT at higher risk for which of the following?**
   a. Visual field defects
   b. Worsening DME
   c. Night vision defects
   d. Endophthalmitis

7. **According to DRCR Protocol T:**
   a. In DME patients with baseline VA 20/50, aflibercept was inferior to ranibizumab and bevacizumab at 1 year
   b. Bevacizumab, ranibizumab, and aflibercept showed improved vision at 2 years compared to baseline
   c. At 2 years, aflibercept showed superiority in visual acuity compared to ranibizumab
   d. All of the above

8. **Which of the following is true about the approved in-home monitoring device?**
   a. It is a home-based testing device to help detect changes in eyes with diabetic retinopathy
   b. It is a home-based testing device to help detect changes in eyes wet AMD
   c. Eye care providers receive alerts regarding any abnormalities detected by the artificial intelligence platform
   d. B and C
   e. A and C

9. **According to phase 3 data on faricimab:**
   a. 80% of wet AMD patients were able to achieve 3-month treatment intervals in the first year and 45% extended to 4-month intervals
   b. 45% of wet AMD patients were able to achieve 3-month treatment intervals in the first year and 80% extended to 4-month intervals
   c. 80% of DME patients were able to achieve 3-month treatment intervals in the first year and 45% extended to 4-month intervals
   d. 80% of DME patients were able to achieve 3-month treatment intervals in the first year and 45% extended to 4-month intervals

10. **A patient presents with new onset vision changes including distortion. Imaging on optical coherence tomography shows a pigment epithelial detachment and subretinal fluid. What are important diagnoses to consider?**
    a. Exudative AMD
    b. Vitelliform dystrophy
    c. Central serous retinopathy
    d. All of the above

11. **Which of the following are true regarding port delivery system (PDS)?**
    a. After surgical implantation of the PDS device, the refill-implant must be performed in the operating room every 24 weeks
    b. In the ARCHWAY study, the majority of patients in the PDS arm required supplemental intravitreal injections
    c. PDS is being investigated for the treatment of DME
    d. All of the above

12. **What are some of the limitations to current anti-VEGF therapy for AMD?**
    a. Burden of frequent visits for patients
    b. Inability to extend treatment intervals
    c. Undertreatment
    d. All of the above

13. **Which of the following is true regarding the KITE and KESTREL studies?**
    a. Brolucizumab every 6 weeks followed by 12-week dosing intervals was found to be inferior to aflibercept for the treatment of DME in terms of visual acuity
    b. Majority of patients were able to maintain 3-month dosing intervals with brolucizumab at 1 year for treatment of DME
    c. Brolucizumab every 6 weeks followed by 12-week dosing intervals was found to be inferior to aflibercept for the treatment of wet AMD in terms of visual acuity
    d. Majority of patients were able to maintain 3-month dosing intervals with brolucizumab at 1 year for treatment of wet AMD

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 activity; may we contact you by email in 3 months to ask if you have made changes to your practice based on this activity? If so, please provide your email address below.

_____