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YEAR IN REVIEW 2017: PRESENT AND FUTURE RETINA THERAPIES

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Year in Review 2017: Present and Future Retina Therapies

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a roundtable discussion with members of the Vit-Buckle Society executive committee.

ACTIVITY DESCRIPTION

It is clear that retina specialists will continue to see an increasing number of patients in the future, as both society ages and as more people develop sight-threatening retina diseases. The need to be fully educated on the various treatment options remains crucial to delivering the best patient care. This educational activity discusses and reviews medical retina presentations, papers, and posters from various meetings during 2017.

TARGET AUDIENCE

This certified CME activity is designed for ophthalmologists and retina specialists involved in the management of patients with retina disorders.

LEARNING OBJECTIVES

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

- Recognize the importance of early diagnosis and treatment of age-related macular degeneration (AMD) and diabetic macular edema (DME).
- Assess data from the latest clinical studies on AMD and DME.
- Explain to patients the various treatment regimens currently available and those under evaluation for retinal disorders.

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Year in Review 2017: Present and Future Retina Therapies

The retina field continues to evolve, regularly challenging ophthalmologists to stay informed and up to date. New data are regularly released that can inform current practice patterns and shape ongoing research, pushing the retina space forward. The following roundtable brings together thought leaders in the retina field to discuss some of these advances in the context of their management approaches and how recent and future data may impact the clinical practice of medical retina, imaging, and surgical retina.

— Charles C. Wykoff, MD, PhD, moderator

ADVANCES IN MEDICAL RETINA

Managing Diabetic Macular Edema

Q | CHARLES C. WYKOFF, MD, PHD: How do you manage a new, symptomatic patient with center-involved diabetic macular edema (DME) at baseline, and what do you use for imaging?

THOMAS ALBINI, MD: I prefer to use anti-VEGF agents, starting with either Avastin (bevacizumab; Genentech) or aflibercept (Regeneron Pharmaceuticals, Inc.) depending on the state of the patient's vision. If the vision is 20/50 or worse, I'll use aflibercept, otherwise my choice is bevacizumab. There are financial issues to consider as well.

After 3 to 6 months, if I'm not seeing the response I need, I'll add steroids with Ozurdex (dexamethasone; Allergan) or, occasionally, Iluvien (fluocinolone acetonide 0.19mg; Alimera). I tend to use steroids on those tough cases that have failed bevacizumab or aflibercept right off the bat.

I use optical coherence tomography (OCT) to image patients at baseline. If I'm concerned about ischemia, I'll get a fluorescein angiogram (FA) to look for it. But the imaging modality that's most important is OCT.

ROHIT ROSS LAKHANPAL, MD, FACS: I get an FA as a baseline along with an OCT. After that, I'll manage the patient with OCT for the next 3 to 4 months then follow-up with another FA at 1 year. However, I will do additional FAs during that 3- to 4-month period if there's some change in the vascular process, and if I'm not understanding why their DME isn't decreasing. I will generally employ a treat-and-extend methodology for treatment. I do not hesitate to change treatment if little to no response is noted after three treatment injections.

ANDREW MOSHFEGHI, MD, MBA: I also do an OCT to evaluate the macula at baseline. I also like to get a widefield fundus photograph to document the level of retinopathy for future comparison. I only get FAs if I'm trying to gauge the level of severity of the retinopathy in a patient with more severe disease. I don't generally get it at baseline for all diabetics.

DR. WYKOFF: In my practice, I typically obtain baseline widefield FAs on patients who are going to initiate treatment. I believe it's valuable to know what the retinal vasculature looks like before I start interventional treatment in order to measure their trajectory and establish endpoints. Visualizing the ischemic burden of an eye through widefield angiography helps me prognosticate and educate my patients.

GEETA LALWANI, MD: I also get a baseline FA on everyone. I've been surprised how much shows up on the FA that I didn't expect, particularly in peripheral ischemia. That information helps inform how closely I monitor the patient.

DR. WYKOFF: Protocol U was a phase 2 trial involving 129 patients with essentially three phases.[1] To be eligible, patients had to receive three anti-VEGF injections within 20 weeks and then have persistent DME with 20/32 or worse vision. Patients received three monthly ranibizumab injections (Genentech) at enrollment. If they still met enrollment criteria, they were then randomized to one of two arms: either ranibizumab alone or ranibizumab plus dexamethasone implant. Patients then underwent monthly visits with either continued monotherapy ranibizumab dosing or combination therapy with a minimum of 3 months between dexamethasone injections.

Data showed that the addition of the dexamethasone implant to eyes receiving ranibizumab for persistent DME didn't result in superior visual acuity gains, on average, compared to continuing ranibizumab monotherapy. However, there are important nuances to discuss. The combination group demonstrated a significantly greater reduction in central retinal thickness (CRT); this combination dosed population also had a significantly greater proportion of patients with DME resolution, 52% versus 31%; finally, there was a significantly greater proportion of patients who achieved 15 or more letters gained, 11% versus 2%, with combination dosing.

Do these data impact your clinical practice and the use of steroids for DME?

JORGE FORTUN, MD: These data actually support what I've been doing in practice and what's been evidenced by some of the recent retrospective analyses such as the EARLY analysis of Protocol I.[2,3] Presumably we have a patient population that's not an optimal

responder to anti-VEGF monotherapy. We know that the pathophysiology of the disease makes sense and that there's likely an inflammatory component. Therefore, adding a steroid helps. This study showed better OCTs at the 6-month mark. That's exactly the patient population you want to use steroids in because those patients, even despite continued anti-VEGF monotherapies, still have persistent edema on OCT.

DR. ALBINI: I think all of us use visual acuity as an important outcome, but we also use OCT on each visit. We all intuitively understand that it's better for the patient in the long run if we minimize the fluid in the macula. Protocol U is a study where the ultimate implementation in the clinic may be different from the conclusion of the study, which says there's no difference between the arms. However, the secondary outcome looking at CRT on the OCT is so strong that it actually supports the continued use of steroids.

DR. LALWANI: The study has led me to question if we should be using steroids earlier. We may be waiting too long. If we resolved edema faster, would the overall results change?

DR. FORTUN: I think there are analyses to suggest that. For example, the EARLY analysis tells you to stay in your lane.[2,3] Once you've achieved that and continue with anti-VEGF monotherapy, even with strict study guidelines of repeated injections, you're going to achieve your visual gain. Whatever that visual gain is, that's what you're going to get going forward. About a third of patients across all trials have persistent edema. There's a significant group of patients that we're not completely treating.

DR. WYKOFF: We saw that a greater proportion of patients in the combination arm had intraocular pressure (IOP) elevation and were started on IOP-lowering drops. Is that relevant or important in your practices?

DR. ALBINI: Absolutely. Ranibizumab plus dexamethasone implant is not a first-line therapy I would use. Instead, I would reserve it for difficult cases. Steroid complications are real, but they are manageable. The ultimate rate of glaucoma surgery was very low, just like in MEAD.[4,5] Therefore, I think this should be reserved for tougher cases.

DR. WYKOFF: Treatment burden was not evaluated in Protocol U.[1] Do you ever use steroids to decrease treatment burden rather than to achieve better visual outcomes?

DR. LAKHANPAL: You have to remember that these are patients who have chronic DME. Even if we reduce the central macular thickness, it may still not translate to improved visual acuity. I'm upfront with patients about that. However, the first step is reducing central swelling because otherwise they won't improve at all. We have to treat them fairly frequently, and all patients become fatigued with the monthly or every 6-week injections. It definitely helps to have something that you can say is a separate pathway that you're suppressing in order to decrease the DME. OCT generally demonstrates that. I do think it helps reduce treatment burden.

DR. ALBINI: Let's not forget about the BEVORDEX study, which showed impressive and very similar outcomes between bevacizumab and dexamethasone, head-to-head.[6,7] I now consider using dexamethasone as a primary therapy because of the lower number of injections for some patients that have a difficult time coming in monthly. There are data to support that approach.

Medical Management of Wet AMD

DR. WYKOFF: How do you image a new patient with symptomatic wet age-related macular degeneration (AMD) at baseline?

DR. LALWANI: I get an OCT and FA at baseline. I don't think that FA changes your management approach, but it does give you some classification for how large the lesion is. It also helps you assess how the patient will do. I do use OCT angiography (OCTA), but the learning curve for AMD is difficult.

DR. WYKOFF: All of us here today use some form of treat-and-extend to manage these patients. What are your intervals with current anti-VEGF treatment options, and what proportion of your patients are at a 12-week dosing interval currently?

DR. MOSHFEGHI: I do a limited treat-and-extend, in which I limit patients to 12 weeks at most for wet AMD. For DME, I don't place a limit. In my wet AMD practice, around 20% of patients are at 4 weeks, 20% are at 12 weeks, and everybody else is able to extend a little bit beyond 4 weeks. The average in my patient population is somewhere around 7 weeks.

DR. FORTUN: Like Dr. Moshfeghi, a minority of my AMD patients are on a monthly treatment regimen. I will consider a trial of observation, using a "defer-and-extend" protocol after reaching 12 weeks. OCTA has revealed a category of patients which could be termed "neovascular, nonexudative AMD." In this subgroup, often characterized by a low-lying pigment epithelial detachment without fluid, there are a choroidal neovascular membranes clearly visible on OCTA. These patients can maintain a stable visual acuity without injection but must be monitored periodically for new fluid which can lead to vision loss. In this subgroup, if the fellow eye has suffered significant vision loss, then I consider a 12-week injection maintenance regimen.

DR. LAKHANPAL: Initial imaging for a new AMD patient is FA and OCT to help determine how active the lesion is and the lesion architecture. Initially, I inform the patient that they'll undergo 4- to 6-week dosing until the lesion is less active and smaller. This may not translate in improved visual acuity, but it should stabilize the vision. Then, I generally employ a treat-and-extend methodology. The vast majority of my patients are in the 6- to 8-week category. They've

done a little bit better than when we first saw them, but they're not at a point where they're completely dry when I see them again, so I don't want to extend further. About 30% of my patients are at every 3-month dosing, and I inject those patients every time I see them. I have many patients who've gone blind centrally in the other eye from exudative in the past, making it even more important to keep the second eye controlled with precise dosing intervals.

DR. WYKOFF: How does fellow-eye status factor into your management decisions with wet AMD patients?

DR. LAKHANPAL: For me, it's important that I extend these patients extremely slowly. If they don't have preserved central vision in the fellow eye, and they are comfortable with 6 to 8 weeks of dosing in the active exudative eye, then that's what we'll do unless something changes. Protecting the better eye is the priority.

DR. FORTUN: I agree with Dr. Lakhanpal. Fellow-eye status informs how aggressively I'm going to extend. I will keep most of these monocular patients on a maintenance schedule once I get to 12 weeks.

DR. WYKOFF: For binocular patients with intermediate dry AMD and 20/20 visual acuity in one eye and active neovascular disease in the fellow eye with visual acuity of 20/200 or worse, when do you stop injecting those eyes if the patient doesn't notice a difference in their vision?

DR. ALBINI: That's a conversation you have to have with the patient, and it depends on how frequently they're getting injected in the other eye. Sometimes they need injections every 8 weeks in the better eye, and then you can alternate with the other eye. I always advise patients that the more injections they have, the better off they will be. The worse the fellow-eye is, the more aggressive I'm going to be with the better eye.

DR. MOSHFEGHI: Even if a patient doesn't notice a difference, I'm going to inject them anyway because it's keeping them from getting worse. I also tend have a conversation about deferring treatment with the patient when the vision starts dropping below 20/800. To me, 20/400 is still salvageable, reasonable, ambulatory vision.

Future Neovascular AMD Therapies

DR. WYKOFF: In the second year of the VIEW studies, all patients were switched from fixed dosing to a capped *pro re nata* (PRN) regimen.[8] And during that time, about 50% of aflibercept eyes and 43% of ranibizumab eyes received the minimum number of treatments, which was every 12-week dosing (Figures 1 and 2). Additionally, multiple prospective treat-and-extend trials have reported that approximately 20% and 40% of eyes can be maintained at 1 and/or 2 years with quarterly ranibizumab or aflibercept dosing. In this as context, what is your interpretation of the brolucizumab data for wet AMD from the phase 3 HAWK and HARRIER trials?[9] How do you anticipate this pharmaceutical being incorporated into your practice?

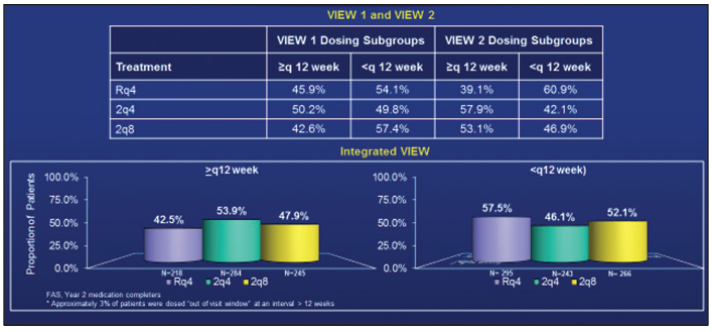

Figure 1. Proportion of patients who received Injections ≥ 12 weeks versus < 12 weeks in VIEW 1 and 2. In year 2, all patients were switched from fixed dosing to a PRN regimen.

Figure 2. Baseline disease characteristics by dosing interval in VIEW 1 and VIEW 2, showing a promising biological effect with Brolucizumab over the first 4 months.

DR. MOSHFEGHI: We've clearly seen a robust biological effect with brolucizumab in the first 4 months. However, we didn't see 12-week data or 8-week data parsed out. I'd like to see what that looks like. I'd also like to know what happened to the patients who needed more frequent injections than every 8 weeks. Were they removed from the study, or were they continued? The brolucizumab data aren't that much different from what we've seen with aflibercept. I think the researchers did a good job of designing the study in a way that made the drug look as good as possible. It was a rationally designed study, but not one that we can gain significant scientific or clinical data from.

DR. FORTUN: The dosing interval will play out in a real-world setting. To me, the interesting thing was the robust effect seen in drying and disease activity.

DR. WYKOFF: If a new pharmaceutical comes to market that is incrementally better at drying the retina, should we all switch?

DR. LALWANI: Yes. We've already done that with aflibercept.

DR. MOSHFEGHI: I agree. That's what I did with aflibercept as well. I took my suboptimal bevacizumab and ranibizumab responders and switched them to see how they did. If they did better, I kept them on the new drug. I'll probably do the same thing when brolucizumab comes out.

DR. LAKHANPAL: The other thing to consider is many of our patients are well informed and are aware of these new drugs that may be approved within the next year. I do caution patients that until the drug is approved, we can only discuss the results theoretically. Also, real-world results matter and experience with brolucizumab is limited as compared to our current treatments. Real-world data may be similar to what we currently have with aflibercept, or it may be different. More work is needed on brolucizumab, but it certainly looks promising.

DR. WYKOFF: What if a new pharmaceutical is only approved for 8-week dosing instead of monthly? Would you still switch to the new drug in patients who need monthly ranibizumab or aflibercept, with the possibility that you would not be reimbursed for any injection given more frequently than an 8-week interval?

DR. ALBINI: That's a difficult question. Physicians will have to decide how to tread those waters, and payers will have to decide whether they'll allow off-label, more frequent dosing when the physician has a strong argument that it's required.

New Data on Combination Dosing

DR. WYKOFF: Over the last year, we've seen two large trials that demonstrated no additional benefit of platelet-derived growth factor (PDGF) blockade with anti-VEGF monotherapy.[10] Most recently we saw a press release from Regeneron Pharmaceuticals, Inc., regarding two phase 2 studies of combination anti-VEGF and anti-angiopoietin 2 (Ang2) dosing.[11] According to the press release, combination dosing didn't provide "sufficient differentiation" to warrant phase 3 development. How do you interpret these data, and how do you define sufficient differentiation?

DR. ALBINI: We've been incredibly fortuitous in the degree to which wet AMD responds to anti-VEGF blockade. The bar has been set very high. I think what we're seeing is that these other strategies don't add much to what we're already doing with anti-VEGF. I would like to look very carefully at the secondary outcomes, however, to see if there's something there, although Regeneron says it's not sufficiently differentiated. Whether or not to move on with a phase 3 trial is a business decision to a great degree. But it would be interesting to know from a scientific point of view what the reason was for not moving forward.

DR. FORTUN: This is the law of diminishing returns. For the majority of our patients, anti-VEGF blockade is sufficient. The only thing that's limiting us is the degree to which we can keep anti-VEGF in the molecules of the eye. There may be a subset of patients that benefit from multifaceted blockade, but it's difficult to tease out those patients in a study.

DR. WYKOFF: There are three ongoing phase 2 trials from Roche and Genentech that are evaluating Ang-2 blockade using a different approach than Regeneron's. Instead of co-formulation, which Regeneron used, Roche/Genentech have a new drug called RG7716 (NCT03038880 [Stairway], NCT02699450 [Boulevard], and NCT02484690 [Avenue]).[12-14] RG7716 is a bispecific molecule that inhibits the activity of both Ang-2 and VEGF-A. These different approaches to blocking Ang-2 may allow different pathways to regulatory approval. Do you think we'll see a different outcome with these trials and a different decision to move ahead with RG7716?

DR. LAKHANPAL: I think these will be similar to the Regeneron trial where there's not enough of a difference to make phase 3 trials worth it. We already have great tools in our armamentarium. We really need to hit a home run to change the management of these patients at this point.

DR. WYKOFF: What if it showed equivalent visual acuity but better anatomic outcomes?

DR. LAKHANPAL: I would be on board with that. In AMD, you have to decrease fluid as quickly as possible. You have to be aggressive about it.

DR. LALWANI: I think it actually speaks to the brolucizumab data because it dried out the macula better, and you had longer intervals. It was a well-designed trial with a practical benefit.

Central Retinal Vein Occlusion

DR. WYKOFF: How do you manage a new patient with symptomatic central retinal vein occlusion (CRVO) at baseline?

DR. MOSHFEGHI: I get a widefield angiogram, fundus photography, and an OCT. If I'm at a location that has OCTA, I will use that as well for learning purposes; not for management.

DR. LAKHANPAL: I also get FA imaging to see how ischemic or nonischemic the CRVO appears. I usually begin with three or four injections of anti-VEGF therapy. I don't typically repeat FA unless I'm not seeing improvement. If a patient doesn't improve, I repeat the FA to reassess ischemia. I also use combination therapy with the dexamethasone implant in these eyes, because they tend to have a lot of fluid in the macula. Since CRVO is oftentimes linked with increased glaucoma and cataract risks, I do factor these considerations with the possible benefits when treating. If they are suitable candidates for combination therapy, then I employ that option frequently. I manage them a little bit more carefully with their primary ophthalmologist, who is checking their IOP during the therapeutic window.

DR. FORTUN: I think assessing macular profusion is key in CRVO. These patients tend to present in a more binary fashion whether you have marked ischemia or decent profusion. In patients where the potential is limited by macular profusion, then the strategy becomes a trial of aggressive therapy to see the maximum vision that can be achieved and decide if that level of improvement is beneficial. If it's

not, then the strategy switches to preventing neovascularization. The strategy for patients with CRVO and relatively good vision is like everything else — keep the macula dry with the least number of treatments necessary.

DR. WYKOFF: If the patient has 20/200 or 20/400 vision and doesn't notice any functional improvement with treatment, do you continue injection that eye?

DR. ALBINI: My threshold is 20/400, but you have to consider individual patient needs such as their overall injection experience. Injections aren't a big deal for some patients. For others, it's very traumatic. I try to encourage patients to continue therapy. Of course, I get more tolerant of deferring therapy the worse their vision gets. If a patient is 20/400 or 20/800, and they hate the injections, and I don't see any improvements, I'll consider stopping treatment.

DR. LALWANI: How do you follow patients after you stop injections?

DR. FORTUN: I see them monthly for about 3 months, and then I'll extend them for a little bit. The initial widefield angiography informs that decision for me because if there's marked global ischemia, then I'm anticipating a much higher rate of anterior segment neovascularization.

DR. LAKHANPAL: I tell my patients that if we stop doing injections, we still have to make sure that we decrease the risk of complications. If patients have areas that are ischemic, they need panretinal photocoagulation (PRP) to limit their neovascular glaucoma risk. I agree with Dr. Fortun that neovascular ischemia and neovascular glaucoma needs to be addressed approximately every 3 months in order to decrease future complications.

DR. MOSHFEGHI: I've had vein occlusions return in patients I've stopped injecting, especially in patients with CRVO.

DR. ALBINI: I think an effective approach to managing these patients in my clinic is the dexamethasone implant because you can do an injection every 6 months. That's a pretty low injection burden. It's a good way to reduce the complication rate but still keep the fluid under control.

DR. WYKOFF: In May 2017, data from the first 6 months of the randomized, non-inferiority SCORE2 trial was published. SCORE2 compared bevacizumab to aflibercept in the management of cystoid macular edema (CME) secondary to CRVO.[15-18] We saw equivalent visual acuity gains in the two arms with monthly dosing, but a significantly greater proportion of patients treated with aflibercept had resolution of CME compared to bevacizumab (54% vs 29%, respectively).[17] How do you interpret these data in the context of your CRVO management strategies?

DR. LALWANI: You want the macula to be as dry as possible. I've found this difficult because the visual acuity gains may be identical. If so, what are you gaining? It's hard to make that choice sometimes, especially considering the financial implications. Most of my patients respond well to bevacizumab, so I keep them on it.

DR. WYKOFF: Do your CRVO patients still have persistent fluid after six monthly doses? Is that common in your practice?

DR. LALWANI: No, it's not common for my practice.

DR. FORTUN: I don't see persistent fluid.

DR. ALBINI: No, I have very few patients like that.

DR. WYKOFF: Is it important to you that the bevacizumab used in SCORE2 was delivered to investigators in single-use glass vials instead of the plastic syringes that all of us use in clinical practice?

DR. ALBINI: I don't think we know the answer to that. There are certainly theoretical concerns with plastic syringes versus glass syringes, as well as oil droplet issues. My suspicion is that the ultimate clinical importance of that differentiation is minimal, but I could be wrong. It would be interesting to see a study of a head-to-head comparison over 2 years of using plastic syringes versus glass syringes. I'd like to get better formulations of bevacizumab, but that would impact the cost of the drug. There are multiple elements that have to be balanced.

DR. MOSHFEGHI: I don't think there's going to be much of an efficacy difference, but there may be some safety considerations.

DR. ALBINI: We use plastic syringes, but we do it in-house. We send each batch of bevacizumab to culture. We've been doing this since the start of bevacizumab use. The syringes are quarantined until the culture results come back negative. We have a lower rate of endophthalmitis with bevacizumab than we do with aflibercept or ranibizumab. I realize that's a unique situation that's not necessarily practical in a real-world setting. But I think the cost of doing so should be considered.

DR. WYKOFF: Do you regularly measure the potency, efficacy, or molecular stability of the repackaged bevacizumab in-house?

DR. ALBINI: No, the process is too expensive.

DR. MOSHFEGHI: We get our bevacizumab from a compounding pharmacy.

DR. FORTUN: We also get ours from a compounding pharmacy.

DR. WYKOFF: Have you changed your supplier of bevacizumab over the last year due to silicon oil or any other reason?

DR. LAKHANPAL: No; I'm pretty happy with what we're using.

DR. FORTUN: Do any of you discuss with your patients the differences between the branded drug and the compounded drug in terms of safety concerns regarding infection?

DR. ALBINI: I have an efficacy discussion, depending on the disease state, where there are data that one of the drugs may do better than the least expensive drug. On the other hand, if the data is fairly equivalent, I also tell the patient. Patients who have good insurance generally gravitate toward the more expensive drugs and seem to be happier there. Occasionally, patients will select the less expensive drug if they have the same efficacy.

DR. LAKHANPAL: I do bring up safety issues with bevacizumab. I also bring up efficacy differences with my patients and document that I've discussed it with them for medical-legal reasons.

DR. MOSHFEGHI: Do you have that conversation with the patients who have no other choice but to get bevacizumab?

DR. LAKHANPAL: Yes. I tell them that the choice is out of my hands, and that I prefer to use glass-delivered medications. However, there are certain insurances that require first-line bevacizumab.

DR. WYKOFF: This is a challenging situation. I think it is worthwhile to briefly discuss the risks of repackaging and then document that you've had that conversation with patients receiving repackaged bevacizumab.

GA Management

DR. WYKOFF: How do you image patients with geographic atrophy (GA)?

DR. MOSHFEGHI: I use color fundus photograph, OCT, and fundus autofluorescence.

DR. FORTUN: I actually don't find fundus autofluorescence that useful as a way of serially tracking these patients because it can only tell you a little bit about the status of the retinal pigment epithelium (RPE). I like to follow these patients with OCT because of eye-tracking technology, which allows you to precisely track the progression of the GA edge.

DR. MOSHFEGHI: That's an excellent point. So much is made of the En Face images on Spectral Domain OCT, but I agree that looking at raster scans is very helpful and gives you more information.

DR. FORTUN: I call it pseudo-microperimetry. It gives me functional information because I can see when that edge of GA starts to impact central fovea or perifoveal areas, where they may become more significant.

DR. WYKOFF: How do you discuss GA with your patients?

DR. LAKHANPAL: You have to empathize with these patients because they're the only patients for whom we have no solution. They'll get progressively worse over time. It's a difficult conversation to have. However, I do think providing hope for patients is important. Research is ongoing, and we may have a breakthrough at any point. This is an important message to leave them with at the end of the visit.

DR. MOSHFEGHI: I tell patients about the research being done. We're doing a stem cell study with colleagues at the University of Southern California. Even if the patient isn't eligible because their vision is too good, I tell them there may be a trial available if their vision worsens.

DR. ALBINI: That's a good point. We may forget to have these discussions with patients in a busy practice because these advances seem far away. But it's important to tell patients about the research being done. It's comforting to them. It's also important to note that there are many direct-to-consumer marketing campaigns selling unproven treatments, like stem cells, with little to no safety or efficacy data.[19] Those treatments can have extremely negative results. I try to warn patients about the risks of finding a provider who is willing to give them an unproven treatment because these marketing campaigns will find them (Figure 3).

DR. WYKOFF: What do you say to patients to steer them away from these self-funded stem cell groups?

DR. MOSHFEGHI: I tell them to talk to me before they go so I can fully evaluate what's being proposed. They might be going to a legitimate university-based or private practice doing a study, but those will not involve a patient paying to participate.

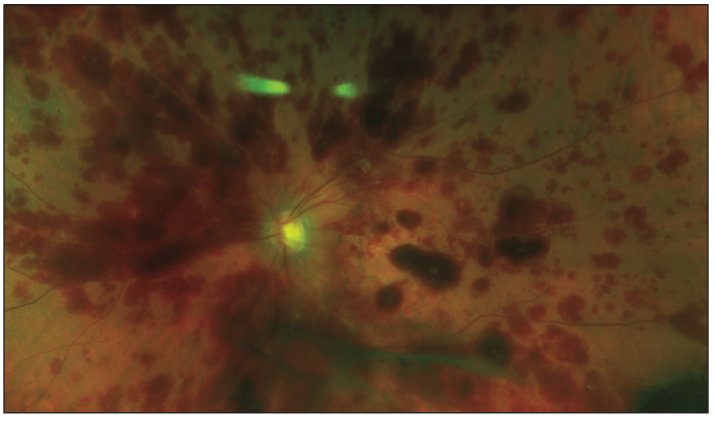

Figure 3. Diffuse preretinal and intraretinal hemorrhage is seen in this fundus photo of the left eye of a patient 13 days after intravitreal "stem cell" injection. Collections of cells can be seen in the vitreous cavity below the optic nerve and in the lower right corner. This retina detached 3 weeks later. Photo courtesy of Dr. Albini, originally published in the article, "Buyer Beware: Ignorance ≠ Bliss," in *Retina Today*, May/June 2017.

DR. FORTUN: I always inform them that any research that they're paying for is likely illegitimate. I also tell them there are a very limited number of ongoing stem cell trials.

DR. LALWANI: I tell them to be very wary of anyone asking you to pay for a trial.

DR. ALBINI: The payment part is very important. I don't know of any legitimate patient-funded research. I also tell them that people have had retinal detachments by participating in these types of so-called trials. Yes, their current vision at 20/200 is bad, but they can still navigate a room. Patients with retinal detachments can't. I hope that advice stays with them.

DR. FORTUN: I also tell patients that although I can't provide any medical assistance in regard to stem cells, I can provide them occupational help through low-vision optometric services or occupational therapy. That way they feel as though they are actively doing something to help their disease.

DR. WYKOFF: SPECTRI (NCT02247531) and CHROMA (NCT02247479) are large phase 3 trials that evaluated Lampalizumab treatment for GA. Both failed to meet their primary endpoint of slowing GA growth at 1 year. Although this was disappointing, the field heard positive efficacy results from the phase 2 FILLY trial (NCT02503332) in which blockade of complement C3 with APL-2 significantly slowed GA growth by 29% at 1 year with anticipation of progression to phase 3 initiation in 2018.[20,21] What do you make of these data? Do you think that the complement cascade is a viable pathway to target in GA?

DR. ALBINI: These studies illustrate the importance of duplicating clinical data. For example, the phase 2 MAHALO study on Lampalizumab looked pretty promising in a subset of patients. That's why Genentech moved it into phase 3 trials, which ended up not meeting the primary endpoint.[22] I don't get too excited over phase 2 study data. It's great Apellis is going forward with a phase 3 trial, but we need to see what happens in order to assess if complement blockade is the right way to go. There is no way to predict it.

DR. LALWANI: I'm hopeful about the FILLY trial data because it was a class of all-comers and is much stronger statistically than MAHALO. It was interesting that there was an increase in patients who developed choroidal neovascularization (CNV). It may give us some insight into understanding who develops CNV and why.

DR. WYKOFF: If you have a treatment for GA that slows progression, but it significantly increases your risk of conversion to wet, how do you factor that into your decision making?

DR. FORTUN: I think the data are too premature. It may not be causing neovascularization, but rather causing neovascularization that's already there to exude. This can easily be treated. These trials were conducted without OCTA. Some of these patients may have had unrecognized neovascularization that was there for a reason. It may be that this blockade caused that to exude. I think we're starting to realize in our understanding of the disease process, that neovascularization may not be a bad thing. Neovascularization is there to salvage RPE cells. Given that we have good current treatment options for exudative AMD if it develops, I would still be willing to use any agent that would prevent vision loss from atrophy. Interestingly, it may be that in retarding the natural progression to atrophy in some patients, we are giving the body time to salvage degenerating RPE and photoreceptors by creating CNV.

DR. WYKOFF: You all sound pretty comfortable with using a new pharmaceutical for the treatment of GA even if it increases the risk of development of neovascular AMD.

DR. ALBINI: I think that once we have something that works to slow GA, then we'll have to look at the sum of the clinical data with real-world use of anti-VEGF therapies once they develop neovascularization. I rather have treatment over no treatment.

DR. LAKHANPAL: My patients would be happy to know that we have something that can slow progression, even if it means that they may get a little exudation that needs treatment. At that point, an injection is an injection.

ADVANCES IN IMAGING
Integrating OCTA Into Clinical Practice

Q | **DR. WYKOFF:** When do you use OCTA in your practice? Is it reducing your dye-based angiography use?

DR. FORTUN: OCTA, as it exists now, may not quite be ready for prime time because the images are not easily reproducible or easily interpreted. As we move toward Swept Source technology, the images will get better. However, it's made a huge difference in how I manage patients with AMD and pachychoroid neovasculopathy. I think from a research standpoint, we're now starting to better understand the role of the CNV membrane beyond classifying it as fluid or not fluid.

DR. MOSHFEGHI: I think it's great for surveilling idiopathic, myopic, juxtafoveal, and telangiectasia causes of CNV. I've found it to be tremendously helpful in determining if CNV is present in central serous. I now use OCTA and not FA in these conditions.

DR. LAKHANPAL: Physicians in private practice have to determine if the current technology is worth the price tag. Is OCTA really going to change how you manage patients? At this point, I'm not certain it will.

DR. WYKOFF: Should retina specialists in general upgrade to OCTA or wait?

DR. LALWANI: Wait.

DR. LAKHANPAL: Wait.

DR. FORTUN: Wait. The technology is only going to get better.

Advances in Widefield Imaging

DR. WYKOFF: We've seen from Lloyd Aiello that the presence of predominantly peripheral lesions (PPLs) in diabetic retinopathy may be a significant prognostic indicator.[23] In his work, patients with PPLs had a nearly five-fold increased risk of developing proliferative diabetic retinopathy over 4 years of follow-up. A recent report of baseline data from the DRCR.net's Protocol AA[24] found that among the 766 eyes in the study, 40% had PPLs. Evaluation of data in the periphery conferred a worse diabetic retinopathy severity in about 13% of patients (1 in 12). Should all diabetics have widefield imaging, or is a dilated eye exam sufficient?

DR. FORTUN: I am a big believer in widefield imaging and widefield angiography. Widefield angiography is better at identifying peripheral lesions than I am. The quality of the cameras we have now is very high, as is the speed of image acquisition. We're at the point where the diagnostic capabilities of our diagnostic equipment are much better than us.

DR. ALBINI: This distinction wasn't as important a few years ago. You're going to use PRP anyway, so what's the difference? But now that we have the option, in my hands, adding anti-VEGF injections or steroids in high-risk cases may make sense.

DR. LAKHANPAL: When you're treating these patients for their DME, you're injecting anti-VEGF agents and changing the vasculature peripherally. When you start to treat-and-extend after that, you need to monitor the vasculature out in the periphery. I think it's a good way to do that and to follow these patients.

DR. FORTUN: If you have the capability to image the entire retina, why wouldn't you? Why wouldn't you inform yourself about the profusion status of the entire retina? It may change your management in how closely you follow patients. I call patients with PPLs feature-less diabetics. You look on funduscopy, and you don't see much, and then you get a widefield FA, and you realize that there is quite a bit of non-perfusion in the periphery. And although that patient may not have developed neovascularization, I'm still going to see that patient in 3 months rather than a year.

DR. ALBINI: I probably get more angiograms, and certainly more indocyanine green (ICG) angiographies, than the average retina specialist because I have a large amount of inflammatory cases in my clinic. My experience with widefield angiography on the Optos ultra-widefield system has been excellent. The eyelashes can be a problem, but a good photographer can deal with that. Otherwise, the images are so good that I see no benefit to other angiography systems.

DR. WYKOFF: Is anybody else using anything other than Optos or the Heidelberg Spectralis widefield lens?

DR. MOSHFEGHI: I have the Spectralis. It's good, but it's not as good for picking up PPLs.

DR. FORTUN: We will be evaluating Zeiss' Clarus 500. It's a little bit different in how it captures images. It captures two separate images and then stitches them together. Whatever technology you use, the ability to image the periphery is important.

DR. WYKOFF: Should retina specialists invest in widefield technology or wait?

DR. MOSHFEGHI: Yes, they should invest. It's too late actually.

DR. FORTUN: Agree — they need to invest.

DR. WYKOFF: It's a big price tag for not much reimbursement on these imaging modalities.

DR. MOSHFEGHI: Yes, but it'll really improve your practice.

DR. LAKHANPAL: I don't have it in all my offices, but I do have it in two. You have to be able to justify the cost.

ADVANCES IN SURGICAL RETINA

Surgical Management of Wet AMD

Q | **DR. WYKOFF:** The phase 2 LADDER trial, looking at a port-delivery system for sustained delivery of ranibizumab (NCT02510794), is fully enrolled.[25] What do you think the results of this ongoing trial will show? What are you looking for?

DR. ALBINI: I think it's going to greatly improve the quality of care these patients receive and the ease with which they get appropriate dosing of anti-VEGF medications. Patients won't need to be transported to the clinic by family members, which is a huge quality-of-life improvement for many people. I've been touting sustained release to my patients since I started practicing 10 years ago, saying it was 6 months away. It may actually be 6 months away now. In that regard, it will be very helpful.

I think we should expect the sustained release approach to have equivalent efficacy to monthly dosing. To me, the big question is safety. How common will endophthalmitis be in these patients? What other surgical side effects will we see?

DR. WYKOFF: What would the results of LADDER need to be for you to seriously consider incorporating a port-delivery system into your treatment paradigm?

DR. LALWANI: Minimum surgical complications and low rates of endophthalmitis.

DR. MOSHFEGHI: Less frequent rescue therapy.

DR. FORTUN: Reduced treatment burden.

DR. WYKOFF: I've placed two of these devices thus far and found surgical procedure to be efficient and minimally invasive. Following implantation, disease activity is monitored by examination, OCT, and visual acuity. In the presence of worsening exudative disease, the patient receives a refill of the device in the office.

Managing Macular Holes

DR. WYKOFF: How do you manage large recurrent or persistent macular holes?

DR. MOSHFEGHI: I've done some internal limiting membrane (ILM) flaps, but I haven't tried autologous transplantation. I may use it on a couple of patients.

DR. FORTUN: Large recurrent or persistent macular holes are found in an a very small population of patients. My primary intervention for macular holes is a complete ILM peel and good gas fill. In recurrent or persistent cases, you often find that the ILM peel or duration of tamponade was not sufficient. On re-operation it is common to find some amount of residual ILM.

DR. LAKHANPAL: I put ICG in. If the persistent open hole isn't large, I try to peel as much as I can temporally and then do an ILM flap. If it's a large chronic hole, larger than 500 µm, you have to temper the patient's expectations. You may not be able to close it, and their vision may not change. Piggybacking on what Dr. Fortun said, the Beaumont technique is easier to deal with than other techniques because you don't have as many issues with bleeding or transposing. My success rate with that technique justifies that it is reasonable for these large, oftentimes, chronic holes.

DR. LALWANI: If I cannot lift the ILM using a pinch-and-peel technique, then I create my ILM flap using the Finesse Flex loop (Alcon). With a persistent or large macular hole, the Finesse Flex Loop can be used to nudge the edges of the hole closer, almost lifting them from the surface of the RPE to allow movement.

DR. ALBINI: My macular hole practice is pretty small. I agree with the previous comments. It's important to make sure you've lifted the ILM off as much as possible and go back. My take-home on the different ILM flap techniques, be it a separation technique or a retinal transplant, is that we don't know which one to choose. It's not clear that there's real efficacy in terms of visual acuity outcomes for any of them. I'm not terribly excited about those techniques, and I stick to more traditional methods. But those techniques exist because when you try to peel additional membrane on some patients, you can't get anything. So, you have to try something else.

DR. WYKOFF: Is there a specific hole size that forces you to try something other than peel ILM?

DR. ALBINI: No, I don't think so. I don't know how you could justify a different approach given the high success rate of peeling ILM.

Surgical Technologies in the Pipeline

DR. WYKOFF: When is it time to incorporate intraoperative OCT (iOCT) in your practice? Who's using iOCT routinely?

DR. ALBINI: I don't use it routinely because I find it cumbersome and complicated. It also takes an extra person in the operating room to make it work. I use it sparingly — if I'm peeling something, and I want to make sure I've gotten all the membrane off, then I'll use it.

DR. WYKOFF: It sounds like in most of your surgical cases, you are using a microscope with the capability of doing iOCT. What portion of cases are you actually using the OCT capabilities?

DR. ALBINI: Under 10%. It's a very low percentage of cases.

DR. LALWANI: It's cumbersome and time consuming to set up.

DR. ALBINI: It also doesn't help me in routine cases. I'll use it for difficult cases where I'm not certain the entire membrane is gone. I've used it in the rare cases where I'm doing subretinal injection of anything just to watch the bleb rise. I've also used it to get a good sense of where the fluid I'm injecting is going while I'm injecting. But that's all — those are my main uses.

DR. LAKHANPAL: If it weren't so cumbersome, would you use it more?

DR. ALBINI: No. I don't believe it will be very helpful surgically.

DR. FORTUN: I just don't think it's ready for prime time. This technology will one day be integral, but it's not necessary as it exists now.

DR. WYKOFF: For those who don't have an iOCT, what would it take for you to obtain the technology?

DR. LALWANI: It would have to make a significant difference on my surgical outcomes. I can't see how it will do that.

DR. WYKOFF: How will heads-up vitreoretinal surgery impact clinical practice?

DR. LAKHANPAL: I've used this system for some time now and have been an early adopter. In my opinion, heads-up surgery will shift our practice, much like small-gauge vitrectomy did.

Private practices and institutions will use it differently. Teaching institutions should use heads-up surgery to teach fellows and residents the technique in real time. For a private practice, however, implementation will depend on how many surgeons will practically use it. I'm at a surgery center with five other retina specialists. I feel that we will be able to justify the cost based upon the improved visualization and possible benefits for patient outcomes. There's a learning curve, so many of my colleagues were hesitant at first. After they tried the system, though, they started using it and have been very pleased. Again, in private practice, justifying the cost of new technology is an important factor.

DR. ALBINI: If I were in private practice or further in my career, I would not see the utility of going through the learning curve for heads-up surgery. The learning curve is significant, and I don't think there is enough of a surgical benefit to justify it, let alone the expense.

DR. FORTUN: I've been performing heads-up surgery for some time now. It's invaluable for teaching; it really revolutionizes how you teach and is a must-have for training vitreoretinal surgeons. It doesn't make a great surgeon better, but it may help with posture. Implementing heads-up vitreoretinal surgery has to be an individual decision, and there's no real way of monetizing it.

DR. ALBINI: Teaching institutions will ultimately adopt this because it's a better way to teach people how to do surgery. As more and more surgeons are trained on it, I think it will become the norm.

DR. WYKOFF: What major surgical technique advances are on the horizon?

DR. FORTUN: Fluidics — a cutter design that allows us to keep higher flow. Right now, that's only available from DORC, Zuidland, The Netherlands, but this technology will make the transition to 27-gauge realistic. The problem with the 27-gauge is that the lumen size really limits our flow if we have standard guillotine cutters. However, the ability to maintain the port open for that length of time makes 27-gauge feasible. It also allows us to cut at a much higher rate, making things safer.

The other advancement on the horizon is Vitesse, a hypersonic, open-port vitrectomy system from Bausch + Lomb, Bridgewater, New Jersey. I've tried it in animal eyes, and it works, but we have yet to see how it will be incorporated in surgery. I think it theoretically provides a safe way of removing vitreous. That being said, we already have a safe way of removing vitreous.

My understanding is that the Vitesse has some limitations. There are many things, such as peeling, suction, and other manipulations, that we do with the cutter that Vitesse can't do alone. There are some unknowns, such as how it will remove membranes in diabetics. It could be combined with another technology, however, and then be able to do it all. We'll just have to see.

DR. ALBINI: Better illumination technologies are also on the horizon. I think we will have illuminated trocars and other sources of light that will significantly improve our view.

DR. WYKOFF: Thank you for your insights, everyone. This was a tremendous discussion. We covered a lot of ground. It is a privilege to practice retina, and I look forward to continued advances in the years ahead. ■

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YEAR IN REVIEW 2017: PRESENT AND FUTURE RETINA THERAPIES

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Name _____ ❑ MD participant ❑ non-MD participant

Phone (required) _____ ❑ Email (required) _____

Address _____

City _____ State _____ Zip _____

License Number _____

DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ 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
___ 1-5
___ 6-10
___ 11-15
___ 15-20
___ 20+

Region
___ Northeast
___ Northwest
___ Mid-West
___ 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

Training of Fellows ___ Yes ___ No

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Recognize the importance of early diagnosis and treatment of age-related macular degeneration (AMD) and diabetic macular edema (DME).	_____	_____	_____
Assess data from the latest clinical studies on AMD and DME.	_____	_____	_____
Explain to patients the various treatment regimens currently available and those under evaluation for retinal disorders.	_____	_____	_____

POST TEST QUESTIONS

1. **PLEASE RATE YOUR CONFIDENCE ON YOUR ABILITY TO APPLY UPDATES IN MEDICAL AND SURGICAL RETINA IN THE CLINIC BASED ON THIS ACTIVITY. (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 INTEND TO APPLY ADVANCES IN MEDICAL AND SURGICAL RETINA TO "REAL-WORLD" PATIENT ASSESSMENT, TREATMENT, AND MANAGEMENT. (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NEVER AND 5 BEING ALWAYS).**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

3. **WHAT IS THE PANEL'S PREFERRED FIRST-LINE ANTI-VEGF TREATMENT FOR PATIENTS WITH SEVERE VISION LOSS DUE TO DIABETIC MACULAR EDEMA (DME)?**
   a. Bevacizumab
   b. Ranibizumab
   c. Fluocinolone
   d. Aflibercept

4. **THE LONGEST TREAT-AND-EXTEND INTERVAL RECOMMENDED IN PATIENTS WITH WET AGE-RELATED MACULAR DEGENERATION (AMD) USING CURRENT ANTI-VEGF TREATMENT OPTIONS IS _____.**
   a. 4 weeks
   b. 8 weeks
   c. 12 weeks
   d. 14 weeks

5. **ANTICIPATED RESULTS OF THE PHASE 2 LADDER TRIAL FOR AMD WILL LIKELY IMPROVE PATIENT CARE IN WHICH OF THE FOLLOWING WAYS?**
   a. Improved quality of life
   b. Less endophthalmitis than conventional therapy
   c. Less frequent rescue therapy than conventional therapy
   d. More injections, but better anatomic outcomes

6. **THE DEXAMETHASONE IMPLANT IS USEFUL IN THE TREATMENT OF _____ (SELECT ALL THAT APPLY).**
   a. Dry AMD
   b. Central retinal vein occlusion (CRVO)
   c. DME
   d. Wet AMD

7. **THE PANEL RECOMMENDS WHAT PROCESS FOR DISCUSSING THE DIFFERENCE BETWEEN COMPOUNDED VERSUS BRANDED DRUGS WITH PATIENTS?**
   a. Discuss the efficacy of both options with patients, but not the potential safety issues of repackaging.
   b. Discuss the efficacy of both options, the potential safety issues of repackaging, and document the conversation with the patient.
   c. Discuss the potential safety issues of repacking drugs, but not the efficacy differences because insurance dictates the first-line drug of choice.
   d. Describe the compounding process to the patient and have the patient determine which regimen is preferable.

8. **SHOULD YOU DISCUSS EXPERIMENTAL THERAPIES LIKE STEM CELLS AND EARLY CLINICAL TRIALS WITH PATIENTS WITH GEOGRAPHIC ATROPHY (GA)?**
   a. No, the experimental therapies like stem cells are not ready for prime time and won't be for years. Discussing these trials gives patients a false sense of hope.
   b. Yes, but inform patients to be wary of any clinical trial where they are asked to pay for enrollment. These aren't legitimate and may ultimately harm their vision.

9. **THERE HAVE BEEN NUMEROUS TECHNOLOGICAL ADVANCES IN THE PAST YEAR. WHICH ONE DOES THE PANEL RECOMMEND BE INCORPORATED INTO PRACTICES NOW?**
   a. Optical coherence tomography angiography (OCTA)
   b. Heads-up vitreoretinal surgery
   c. Intraoperative OCT (iOCT)
   d. Widefield technology

10. **MRS. JONES PRESENTS WITH CLINICALLY SIGNIFICANT DME THAT IS AFFECTING HER VISION. AFTER THE INITIAL 3-MONTH DOSE-LOADING REGIMEN WITH AN ANTI-VEGF DRUG, SHE DOES NOT SHOW MUCH IMPROVEMENT IN EITHER VISION OR ANATOMY. WHICH RECENT CLINICAL TRIAL DATA WOULD SUPPORT A DECISION TO BEGIN THE USE OF INTRAVITREAL STEROIDS?**
    a. Protocol I
    b. Protocol AA
    c. Protocol U
    d. Protocol S

ACTIVITY EVALUATION/SATISFACTION MEASURES

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 as required by the Accreditation Council for Continuing Medical Education (ACCME).

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

I plan to make changes to my practice based on this activity? _____ Yes _____ No

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

____ Cost

____ Lack of administrative support

____ Lack of time to assess/counsel patients

____ Reimbursement/insurance issues

____ Patient compliance issues

____ Other. Please specify: _____

____ Lack of consensus or professional guidelines

____ Lack of experience

____ Lack of opportunity (patients)

____ Lack of resources (equipment)

____ No barriers

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 ACCME) 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 below.

_____