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CME Activity

From Trials to Treatment: Real-World Applications in Medical and Surgical Retina

Part 3 of 3

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From Trials to Treatment: Real-World Applications in Medical and Surgical Retina

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a roundtable held in November 2017.

ACTIVITY DESCRIPTION

Age-related macular degeneration (AMD) is a well-known leading cause of vision impairment in developed countries and can result in irreversible vision loss if left untreated. In the United States alone it is estimated the number of people with advanced stages of AMD will hover around 3 million by 2020. With all the current and ongoing interest in treatments for retina disorders, it is imperative retina specialists remain educated on the latest developments.

TARGET AUDIENCE

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

LEARNING OBJECTIVES

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

- Discuss the outcomes of pivotal studies in AMD and how study results may differ from "real-world" dosing methods.
- Identify patient subtypes (eg. RAP lesion, pigment epithelial detachments, occult lesions) that will require long-term treatment and imaging evaluation.
- Develop a long-term treatment plan for patients with AMD based on results from clinical trials and extension studies.
- Compare the extended safety outcomes of anti-VEGF therapies as published in long-term studies.

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From Trials to Treatment: Real-World Applications in Medical and Surgical Retina

PART 3 OF 3

Innovative treatments for age-related macular degeneration (AMD) and geographic atrophy (GA), including gene therapy, gene editing, cell-based therapies, and stem cell therapy, are currently in various stages of development. Although many of these novel therapies are not ready for commercialization, they provide a preview of what retina specialists can expect on the horizon in the next 3 to 5 years. The following roundtable gathered retina specialist experts to discuss current and ongoing clinical trials in AMD and GA and how these data may one day translate into novel treatments in the clinic. — Charles C. Wykoff, MD, PhD, moderator

Editor's note: Since the time of this roundtable, the U.S. Food and Drug Administration approved Spark Therapeutics' gene therapy Luxturna. The company has set pricing at $850,000. Discussions in this roundtable were not altered to reflect the US approval.

NON-EXUDATIVE AMD INCLUDING GA

AMD classifications

Charles C. Wykoff, MD, PhD: There is an ongoing move to update the nomenclature for dry AMD. What is the need to redefine advanced GA?

Karl Csaky, MD, PhD: I do think it is important to differentiate various aspects of the anatomical changes in stages of GA but mostly from a research perspective. There is more complexity than just what we traditionally think about in terms of GA. The nomenclature we have developed is primarily based on optical coherence tomography (OCT). It will be critical to try to differentiate some of these subtleties as we go into clinical trials and try to understand where drugs could have a potential effect, and as we transition into an OCT-based outcome variable.

Elias Reichel, MD: I'm not so sure we need to redefine advanced GA. What we really need to know is who is at the greatest risk for developing GA that results in significant vision loss (Figure 1). That will help in defining inclusion criteria for future studies and ultimately who best to treat with new therapies. Also, OCT angiography (OCTA) imaging of GA lesions may serve as a predictor of who develops choroidal neovascularization (CNV), and that may be useful for determining study inclusion criteria and who benefits from new drugs.

Dr. Wykoff: What does the practicing retina specialist need to know about the new nomenclature? What are the key differentiating features of the new nomenclature that may lead us to a better understanding of outcomes from different therapeutics?

Dr. Csaky: It is all about understanding what happens at the photoreceptor level. Where is the degeneration occurring, and at

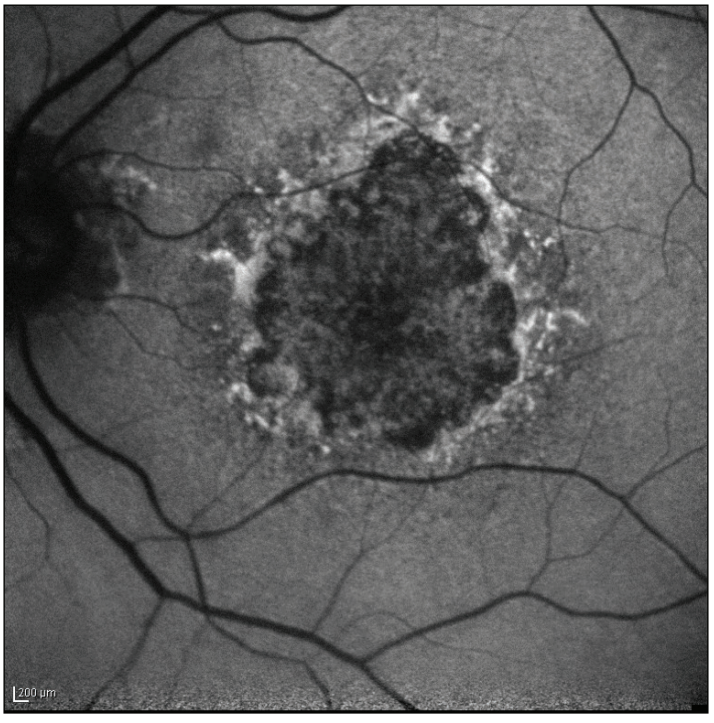

Figure 1. GA can cause the development of irreversible scotomas and areas of complete depigmentation of the RPE with sharp margins.

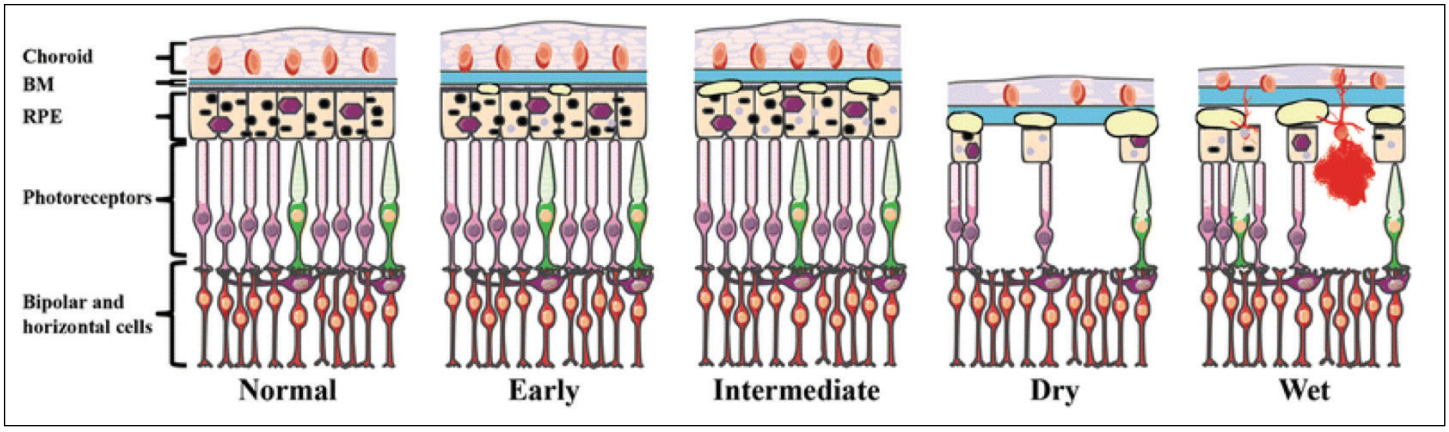

Figure 2. Illustration of the anatomical retinal pathology associated with the various AMD subtypes. Illustration courtesy of: Tan PL et al. *Human Genomics*. 2016;10:23. Available at: https://humgenomics.biomedcentral.com/articles/10.1186/s40246-016-0079-x Reproduced with permission under Creative Commons license (http://creativecommons.org/licenses/by/4.0/).

what layers in the OCT? How far along is the degeneration at various stages of GA development and expansion? Is it in the outer retina or in the outer retina plus inner retina? Understanding those subtleties, both in terms of future clinical trials inclusion criteria, as well as treatment outcomes, will be potentially essential as we go forward in developing novel treatments for GA.

Dr. Wykoff: Is it important to differentiate between the atrophic phenotypes observed in different diseases such as Stargardt disease, versus dry AMD, versus other atrophic diseases of the macula?

Byron Lam, MD: In Stargardt disease, one main outcome measure for clinical trials is well-demarcated GA. There are many studies under way looking at new treatments for Stargardt disease, including TEASE.[1] All of them are looking at some objective measures, like well-demarcated GA, so that is one objective endpoint. The disadvantage is that you exclude many patients who do not necessarily have a well-demarcated GA. You may also have areas of atrophy that don't quite coalesce, and that makes it very difficult to quantitate.

Dr. Wykoff: The pattern observed using fundus autofluorescence (FAF) has been a central part of the inclusion criteria for many clinical trials studying new therapeutics for GA. Is FAF also relevant to monogenetic inherited retinal diseases?

Dr. Lam: It is definitely true for Stargardt disease. It is very important to be able to measure the amount of GA area. Autofluorescence also comes into play in choroideremia. But there, you're actually using the autofluorescence to look at specific areas of viable retinal pigment epithelium (RPE). That viable area of RPE is where you will use gene therapy, because that is where you have some retained choroid and overlying photoreceptors.

Dr. Wykoff: How important is the identification of reticular pseudodrusen in your clinical practice?

Szilárd Kiss, MD: In every day clinical practice, reticular drusen or pseudodrusen come into play to explain that patient who may be 20/20 but still suffers from visual abnormalities. Contrast sensitivity, dim-light vision, and even reading speed may be significantly impaired even in a patient who is able to see well on a high-contrast chart in your office. It validates the patient's symptoms. Reticular pseudodrusen will also be important as soon as we have clinical trials examining treatments. We are beginning to recognize that dry AMD consists of several different phenotypes that may all require slightly differing treatment strategies and outcome measures (Figure 2).

POTENTIAL THERAPIES IN AMD

Monoclonal antibodies

Dr. Wykoff: Two large, exceptionally well powered phase 3 trials, SPECTRI and CHROMA,[2-4] evaluated lampalizumab for the treatment of GA. Both failed to meet their primary endpoint at 1 year. Specifically, lampalizumab dosing did not slow GA growth compared to sham injections in either trial. Why did blocking complement factor D in these trials not yield a clinical benefit?

Jonathan L. Prenner, MD: These results weren't terribly surprising given the phase 2 MAHALO data, where secondary analyses demonstrated that a particular subgroup (complement factor I biomarker) may have driven some of the efficacy seen.[5] The concept was that by enriching the study population with complement factor I-positive subjects in phase 3, the primary endpoint would be achieved. I think this was a classic error in terms of thinking about post hoc analysis and convincing yourself a signal exists that may not be there. Unfortunately for our patients, it translated into two large phase 3 trials not hitting their primary endpoints.

Dr. Csaky: One reason these studies failed to meet their primary endpoint is that altering complement factor D level and, by extension, downregulating the alternative complement pathway, may not be the primary driver for GA expansion. Factor D was a wonderful target; it's available as a downregulated factor because it's not in large quantities. The outcomes suggest that at least targeting factor D and manipulating the alternative pathway does not

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— Szilárd Kiss, MD

influence GA expansion.

Dr. Prenner: We have now seen many negative attempts at modifying the complement pathway in AMD. Some biomarkers suggest that the complement pathways are involved from a genetic perspective. We see complement in histologic specimens from patients with AMD. The implications and hypotheses start to make sense. But three big questions remain: Is the relationship of the complement system coincidental or causal; should we keep thinking about this pathway; and could AMD be an inflammatory disease rather than a complement-driven one?

Dr. Kiss: The shots on goal (so to speak) have been with off-the-shelf compounds. No one has developed a pathway inhibition to hit these targets specifically for AMD. What has happened is that the companies developed paroxysmal nocturnal hematuria complement inhibitors, then took those complement inhibitors and tried to explain to us why that particular pathway inhibition may be useful in a broad patient population of dry AMD patients.

Even when you have a well-thought out scientific plan to come up with a pathway inhibition, you may miss. I think we should still consider the complement pathway as a potential target for the treatment of dry AMD. However, a more targeted approach to patients who may have certain polymorphisms in specific complement components may be what is needed. A more personalized genetically tailored approach, targeting patients earlier in the course of their disease, may increase the chances of treatment success.

Dr. Prenner: It's not that the target is necessarily wrong — it may be that the assets that we have employed so far may not have been specific enough.

Dr. Reichel: Since the focus of the discussion is targeting the complement cascade, the issues are manifold. First, the cascade is exceedingly complicated — there are many bypasses and roundabouts that potentially could result in turning on one part of the cascade in an attempt to shut off other part(s) of the cascade. This could potentially result in untoward effects. Second, achieving the appropriate dosage of the drug necessary to turn off components of the cascade may be very difficult given the stoichiometry of some of the factors. In plain English, the concentrations of some of these factors, such as C3 and C5, are very high and can be reproduced very rapidly, therefore inhibition may be impossible. Finally, GA is slowly progressive so the effects of any drug are going to have to be monitored for a long time in order to see a significant treatment effect.

Dr. Wykoff: The phase 2 FILLY trial recently reported a statistically significant slowing of GA growth at the 12-month primary endpoint with APL-2 (pegcetacoplan) treatment.[6,7] Specifically, APL-2 administered monthly showed a 28.6% (P = 0.008) reduction in GA lesion growth compared to sham. When administered every other month, APL-2 showed a 20% reduction (P = 0.067). What is your interpretation of these data?

Dr. Csaky: The first thing to always recognize is that phase 2 data may be misleading. The data from the FILLY trial were similar to MAHALO data with the complement factor I subgroup.[5] Of course, a major difference from the MAHALO trial was the FILLY trial results were obtained from all comers not a subgroup. However, given the relatively small number of patients in the FILLY trial (n = 246), there is still uncertainty about what this means in terms of a larger phase 3 study.

Dr. Wykoff: Before the FILLY data were available, a theoretical argument for why this complement inhibitor may not work is that the levels of C3 are very high, and more of the protein can be produced efficiently by the liver. Because of simple stoichiometry, one might hypothesize that one can't possibly block enough C3 with

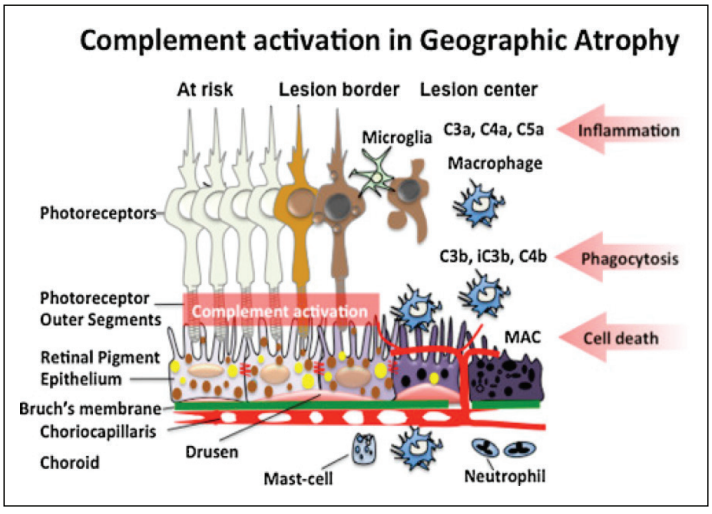

Figure 3. Generation of complement anaphylatoxins C3a, C4a, and C5a at the choriocapillaris-Bruch's-RPE interface, C3 and C4 opsonization and formation of the membrane attack complex (MAC), together with increased presence of phagocytic cells, promotes further loss of photoreceptors and RPE. Illustration courtesy of: van Lookeren Campagne et al. *Immunobiology*.

"I think what we are learning with GA is that there are variable outcomes between patients, just like there are with CNV. In small trials, you can see a signal, but that does not necessarily mean biological activity."

— Karl Csaky, MD, PhD

monthly intravitreal injections to generate a meaningful clinical response (Figure 3, page 6). Why are we seeing such a strong signal in FILLY?

Dr. Csaky: Just like with the MAHALO, we saw a signal.[5] You can see a positive outcome signal in many phase 2 trials. I think what we are learning with GA is that there are variable outcomes between patients, just like there are with CNV. In small trials, you can see a signal, but that does not necessarily mean biological activity. In the case of the true efficacy of APL-2, we are waiting for the results of larger phase 3 trials.

Dr. Wykoff: Is it important to you that there appeared to be no impact of APL-2 on visual acuity, and that visual acuity decreased in all three arms of FILLY through 1 year?

Dr. Prenner: I am not so concerned about that at this point. I am concerned a bit about the rate of neovascularization and conversion to wet AMD in the study cohort however.

Dr. Kiss: It does concern me. The every other month group did not show significant difference in the growth at 1 year. The every month group did.[6,7] In that particular group, 18% of those patients developed new-onset CNV and wet AMD. And even if you parse it out with those that have had wet AMD in the other eye, we know from natural history studies that they have a slightly higher incidence up to 29%. That means a third of your patients may develop wet AMD, and 10% of those who did not have wet AMD in the other eye will still develop it. Furthermore, three patients in FILLY developed endophthalmitis. That is fairly concerning, given the small number of patients in the trial.

Gene therapy

Dr. Wykoff: Where are we with gene therapy for wet AMD, and where is the field headed?

Dr. Kiss: There have thus far been three failed phase 1/2a clinical trials involving gene therapy for wet AMD.[8-10] From these clinical trials, we have learned that gene therapy is safe regardless of whether it is through an intravitreal injection or subretinal delivery in the operating room. Unfortunately, these trials have been disappointing with respect to the efficacy. This may be due either to the choice of vector or the gene delivery product.

RegenXBio has just announced that they have completed enrollment of the second dose-escalation cohort for a subretinal gene therapy that uses a product similar to ranibizumab.[11] The vector, RGX-314, is injected into the subretinal space following a pars plana vitrectomy and produces what is essentially ranibizumab.

Adverum Biotechnologies has also announced that they will begin a gene therapy trial using their proprietary gene vector technology to delivery aflibercept.[12] ADVM-022 is delivered via an intravitreal injection, and a phase 1 clinical trial is expected to start in early 2019. Thus, gene therapy for wet AMD is following closely behind gene therapy for inherited retinal diseases (IRD) in becoming a clinical reality.

Dr. Wykoff: What data are available regarding gene therapy for dry AMD?

Dr. Reichel: Gene therapy is a viable treatment modality for wet AMD. Hemera Biosciences is developing gene therapies that block the last step of the complement cascade allowing for long-term transgene production in the hopes they are reducing the progression of GA. Hemera is using CD59 (protectin) to block MAC from forming. MAC has been implicated in both the pathogenesis of dry and wet AMD. Gene therapy allows for the continuous and chronic therapy with the expression of the CD59 transgene.

Dr. Csaky: There are attempts to deliver proteins that might protect the retina and RPE from the effects of complement activation. For example, an adeno-associated virus (AAV) vector injected intravitreally expressing soluble CD59 (sCD59) is being tested. sCD59 appears to inhibit the membrane attack complex (MAC) that results from complement activation, and that can damage cells. A phase 1 trial is underway in patients with GA.[13]

Dr. Kiss: There is some preclinical, phase 1 evidence that indicates the AAV2 vector may be a useful pathway in terms of preventing progression or development of GA.[8] As we have seen from our wet AMD gene therapy trials, choice of vector and gene therapy product is important to optimize clinical outcomes.

Stem Cells

Dr. Wykoff: For good reason, there has recently been a lot of negative press regarding for-profit, patient-funded "stem cell" research that is largely unregulated.[14] Unregulated human research in this domain needs to stop. Where are we with high-quality research evaluating stem cells for the treatment of dry AMD?

Dr. Kiss: We are in the laboratory. People tend to talk about stems cells as this one thing when in fact they are three or four

different concepts. One concept that has been used by several companies is that milieu that is produced by the cells that you put in there. It is not necessarily that the cells take up an RPE differentiation, but it is that they produce a milieu where you either decrease the death of a certain number of cells or you wake up some cells. On the other hand, you can also think of stem cells as replacement stem cell therapy. The stem cells that are delivered actually take up residence, and they may become a photoreceptor or an RPE cell. Even within replacement stem cell therapy, you have two big questions: What kind of stem cells are you using, and what are the sources?

Dr. Wykoff: There was a *Lancet* article in 2012 that discussed stem cells being surgically placed into human eyes.[15] What has since happened to that line of research?

Dr. Csaky: We have been involved with several stem cell trials,[16] if you want to call them "stem cells." The term "stem cell" is a bit of a misnomer for what we are injecting at this point. In many cases we are injecting cells that appear to secrete neuroprotective factors rather than cells that will replace injured or dead cells. We're injecting cells, but of various origins. We're hoping to answer basic questions. Can the cells be placed without side effects? Can they be maintained? Are they rejected? There is some basic biology that we're learning from these clinical trials that we have done.

We have examined the effects of subretinal transplantation of both purified human neural stem cells (StemCells, Inc.) and human umbilical tissue derived cells (CNTO cells, Janssen Research & Development, LLC). We are also uncovering new challenges. The concept that we could follow these cells in situ once we inject them has turned out to be more challenging than what we thought, because a lot of things happen in the subretinal space when these cells are placed. It is not straightforward. Are the possible therapeutics we might see in these trials a result of the transplanted cells staying in place and doing good things or are the changes simply a reaction by the recipient tissues? The current stem cell trials are not meant to prove efficacy; they are meant to teach us what we need to continue to learn before we are ready to take them to the next phase.

"The current stem cell trials are not meant to prove efficacy; they are meant to teach us what we need to continue to learn before we are ready to take them to the next phase."

— Karl Csaky, MD, PhD

Dr. Prenner: I think we have to be more refined about what the asset is and be more thoughtful than we have been. Early failures do not mean that a stem cell approach is not a viable therapeutic option, but it means we have to be more disciplined about what to test next.

Dr. Csaky: There are efforts being made on redefining the composition of what we are placing in patients. Do viable RPE cells need to be transplanted on an artificial matrix? Additionally, there are efforts on co-culturing photoreceptors on RPEs on an artificial matrix that have been shown in animals to create synapsis with intact inner retinas. Those are going into nonhuman primates. That could be a viable tissue-replacement approach that could be on the horizon within the next 3 to 5 years for a phase 1 study.

I do think that there are efforts that are moving along quite quickly, such as the understanding of how we define the cell type. I think there will be other efforts soon, such as what is the minimal required cells and for what disease state? How do you measure efficacy beyond the anatomic aspects? I think these efforts will converge relatively quickly and allow us to design and execute clinical trials that might improve visual function in patients with degenerative retinal diseases.

GENE THERAPY FOR MONOGENETIC MACULAR DISEASES

Dr. Wykoff: Where is the field in developing gene therapies for inherited retinal dystrophies (IRD)?

Dr. Reichel: We are about 3 months away from seeing approval of a gene therapy for an IRD — that is Spark Therapeutics' AAV2 subretinal delivery for *RPE65* in Leber congenital amaurosis (LCA) and retinitis pigmentosa. This will be the first gene therapy to be approved for a genetic disease in the United States. This is an exciting time for gene therapy and retina specialists and pediatric ophthalmologists who are very soon going to be actively involved in identifying these patients and treating them.

Dr. Lam: We are all very excited about the *RPE65* gene therapy treatment from Spark Therapeutics[17-19] and hopeful that FDA approval will come in 2018. The questions are in the details. What patient is the therapy recommended for? Could we use it off-label for patients with a more advanced disease? How much will the therapy cost? There are several hurdles that will have to be worked out after approval. The targeted population is low, between 600 and 1,200 patients. But this is an incredibly important breakthrough for anyone with an IRD.

Dr. Csaky: The preclinical data was, at times, impressive. What do you think about the primary outcome and the totality of the efficacy that we can expect in patients who are getting the correct gene replacement? In other words, what can patients expect?

Dr. Lam: It is going to come down to the stage of disease the patient has at time of intervention. For example, if you have a child under the age of 6 with fairly intact retinal anatomy, but who has an *RPE65* genetic defect, that patient has a better chance of

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— Byron Lam, MD

obtaining a good result than a 35-year-old who already has some disorganization of the retina. That said, we should expect some variability in the response regardless of age or disease stage. This is important, because we don't want ophthalmologists thinking every patient will have a dramatic improvement in mobility. There will be a range of efficacy.

Dr. Prenner: What about the durability of the effect?

Dr. Lam: We know we can't treat the entire retina, and the areas left untreated will continue to degenerate. Some papers have shown that you could have some retinal degeneration in the areas that you do treat.[20] Durability is a very important question that we don't have a good sense of yet. We should have some additional, informative data in about 5 years.

Dr. Prenner: What are the benefits and challenges of gene editing versus gene therapy for IRD?

Dr. Reichel: Gene editing can be highly nonspecific, and there can be significant off-target effects. With conventional, monogenic gene therapy, however, that is highly unlikely.

Dr. Kiss: Gene therapy involves placing a piece of DNA into the cytosol of your target cell. This therapeutic DNA then results in the expression of a gene product, which either replaces an abnormal gene product (as in *RPE65*), or produces a molecule which is not normally produced in that cell, such as anti-VEGF therapy with wet AMD. The native cellular DNA is not modified in gene therapy.

Gene editing, one the other hand, involves the alteration of the genetic material of your target cell. Here, two viral vectors are required — the first vector carries with it your target protein (e.g., *RPE65*); the second has the CRISPR/Cas9 machinery that edits the target cell's DNA. When both vectors transfect the target cell, the native DNA is "edited" and changed to the desired sequence.

Dr. Wykoff: Should retina practitioners across the country be routinely genotyping patients with suspected IRD?

Dr. Lam: Gene testing is very practical in that it provides an inheritance pattern for these genetic diseases that can be difficult to diagnose. For example, gene testing can be helpful in a patient whose retinal findings are nonspecific. For the retina researcher, gene testing is more targeted toward the gene therapy than we were thinking about. We talk a lot about *RPE65* as a target for LCA,[21-24] but other targets include choroideremia, X-linked retinoschisis, X-linked RP, achromatopsia, Stargardt, and Usher type 1 B. There are a number of clinical trials examining these, but they are still in phase 1/2. The choroideremia target is a little further ahead than the rest with an upcoming phase 3 trial by Nightstar Therapeutics expected in 2018. If that trial has positive results, maybe it can be considered for FDA approval in 3 or 4 years or so. Time will tell. Genetic testing is great if the patient is willing to pay for it, and if there is a good reason for providing them with prognosis information or diagnosis with a specific inheritance pattern.

Dr. Wykoff: What laboratories do you recommend physicians consider using if they would like to perform genetic testing for their patients?

Dr. Lam: There are many: the Carver Lab, GeneDx, and PreventionGenetics come to mind. It comes down to the panel, the cost of the test, and the turnaround time. Patients want results in 6 to 8 weeks at most. They don't want to wait 3 to 6 months.

Dr. Prenner: The Carver Lab has the benefit of being a bit more cost sensitive as they are funded by a foundation. Massachusetts Eye and Ear Infirmary also has a superb panel. There are options, but you have to make sure patients are able to manage the finances associated with it because it is quite expensive.

Dr. Csaky: The patient also has to understand that genetic testing should be accompanied by genetic counseling. They have to understand the implications of a positive result, as well as the potential issues for their children and family.

Dr. Lam: You can also do a next-generation sequencing panel testing for greater than 280 genes. Or you can do whole-exome sequencing. The rate of finding something positive is probably somewhere between 65% and 75%. But the problem is you have to deal with the variance of unknown significance, of which there can be many. The wider the net for your genetic testing, the more difficult the data will be to interpret.

Dr. Reichel: Physicians should be pushing for reducing the price of genetic testing for all pathologic genetic conditions. The cost right now is somewhat prohibitive, but the value that is achieved by improving someone's visual function with LCA or preventing cancer is exceedingly high. Our health care system has to figure this out — there are big cost savings here for what could be a small investment in genetic testing.

Dr. Kiss: We tend to think of a test as giving you a "yes" or "no" result. But with genetic testing, oftentimes the answer is "we're not

sure." The "we're not sure" comes in two forms for IRDs. The most obvious one is the variant of unknown significance. There are polymorphisms that we are not completely sure if they are pathogenic or not. We also don't know all the genes that cause these diseases; we may know perhaps 80% of genetic causes of IRDs; the remaining 20% is not yet understood. Counseling patients about how the genetic testing can be valuable, especially in an age where we have targeted therapies where patients can enroll in clinical trials, is important. But you need to have the caveats.

Dr. Wykoff: What should a retina practitioner do if a patient is requesting genetic testing, and the practitioner is not accustomed to performing such testing and has no experience with genetic counseling?

Dr. Lam: It comes down to the practitioner's level of interest and what services are available in the area. If you are in an area that doesn't have an IRD expert, refer your patient to a clinical trial if they have a genetic condition undergoing a gene therapy trial. You can also order a genetic test through a CLIA laboratory.

Dr. Csaky: Gene therapy is incredibly complex. The concept may be straightforward, but the reality is we are early in our clinical research and are still unlocking several new challenges. Gene therapy is very exciting and holds great promise, but it is still a challenging area, and the translation is not as straightforward and simple as we thought it would be. Therefore, I think it is important that we don't give patients unrealistic expectations about where we are heading. The field is moving, but it is slow and cautious.

Dr. Kiss: When you think about gene therapy, you think about it within different aspects. First, you think about the vector that is being used, AAV being the most common. Within the vector, you have different types of AAVs. Some of them are designer, others are available in nature. You also have the payload within the vector and the way to manufacture both. The manufacturing process becomes critical to not only delivering therapy, but to make sure it doesn't cause any harm. And of course, the most obvious question is do we go subretinal or intravitreal? For something like an *RPE65* mutation, your target is the RPE cells. For other IRDs, you may want to replace proteins in the photoreceptors. We may use "gene therapy" as one term, but there are many variables that go into it.

Dr. Lam: The variables in gene therapy are clearly there, but the variables are unique to the specific disease. The immune response will be different. Your cellular target's going to be different. Your viral vector could have a different role in terms of producing an immune response. Each of these diseases are unique.

Dr. Prenner: Part of the problem in the world that we live is that patients now see press releases about these incremental breakthroughs and suddenly they want stem cell treatment for their dry AMD. It's difficult to tell patients and their hopeful families that we are trying very hard but the technology isn't there yet. It's going to be a long road.

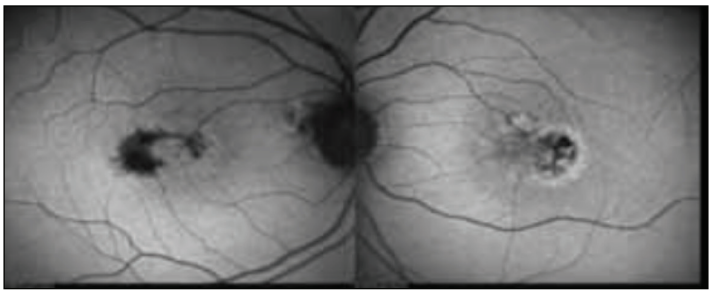

Figure 4. An autofluorescence image of a patient with MacTel, courtesy of Mark C. Gillies, MB BS, PhD, FRANZCO.

CELL-BASED THERAPIES FOR RETINAL DISEASES

Dr. Wykoff: Emily Chew, MD, presented compelling data from a phase 2 trial of ciliary neurotrophic factor (CNTF) for macular telangiectasia type 2 (MacTel type 2) at the Retina Subspecialty Day meeting before the American Academy of Ophthalmology annual meeting.[25] What is your interpretation of this data (Figure 4)?

Dr. Csaky: CNTF has been studied before in GA and RPE.[26-28] The consensus was that there wasn't overwhelming enthusiasm. But there now appears to be some efficacy in a phase 2 study of MacTel type 2 in terms of visual function and microperimetry.

The study evaluated the effect of CNTF delivered in a device (NT-501) on the change in the area of ellipsoid zone loss at 24 months compared to baseline. The study enrolled 69 patients (99 eyes) with MacTel type 2 from 11 clinical sites in the United States and Australia, randomized to treatment or sham. The mean BCVA at baseline was 20/30. The CNTF implant reduced the risk of progression at 24 months ($P = 0.039$), but there was no change in visual acuity between groups. There was, however, a stabilization of the reading speed in the treated eyes. The sham eyes experienced reduced reading speed at 24 months compared with baseline ($P = 0.016$). The treated eyes also demonstrated retinal thickening in the macular area, while the sham eyes did not. The device was well-tolerated. Miosis was found in 18% of the study eyes, but none of the patients on trial had the implant removed.

This is the first time that this cell-based secretory factory approach appears to have some promise for a disease that has a large degree of heterogeneity.

Dr. Wykoff: Do we understand the mechanism of action of CNTF on retinal degenerative diseases such as MacTel?

Dr. Csaky: That is still not clear. The action of CNTF on prevention of photoreceptor degeneration is still not well understood. In animal degenerative retinal models, for example, anatomic but not functional improvement has been seen following CNTF exposure. There also appears to be some cross-talk necessary between Muller cells and the photoreceptors, and this complexity has translated into human clinical trials. CNTF exposure in humans causes an overall thickening of the retina with an expansion of the retinal cell volume, which is not always associated with improved

visual function. Therefore, CNTF is thought to be some type of neuroprotective agent, but the true mechanism of how it is working is still unknown.

Dr. Lam: CNTF provides broad neuroprotection, and the neuroprotection has been shown for ganglion cells and for cone photoreceptors, to a certain extent. Growth factors are naturally occurring and are beneficial. But when you put in an amount that is not physiologic, you are going to have other cells respond to it in different ways and in different proportions. Time will tell if it works for MacTel.

Dr. Wykoff: What are the latest clinical trial data in nonarteritic anterior ischemic optic neuropathy (NAION)?

Dr. Lam: A phase 3 trial is currently underway examining the effect, safety, and tolerability of QPI-1007 on visual function in patients with recent-onset NAION.[29] The study has a good concept. You introduce a small-interference RNA into the vitreous, and that blocks the caspase apoptosis pathway. It is certainly a logical target. Visual acuity is one of the primary endpoints. We don't know the results, however, so we just have to wait and hope that it works.

Dr. Kiss: There is currently no treatment for NAION; you watch the optic nerve die in front of you. It is exciting to have any treatment for this disease in a phase 3 trial. But like Dr. Lam said, we don't know what the results will be.

FUTURE THERAPIES FOR EXUDATIVE RETINAL DISEASES

Dr. Wykoff: One-year data from the phase 3 HAWK and HARRIER trials comparing brolucizumab (6 mg) and aflibercept (2 mg) were presented for the first time at the American Academy of Ophthalmology annual meeting.[30] Combined, the trials included more than 1,800 wet AMD patients. Patients received three monthly loading doses of the assigned treatment, followed by 12-week dosing intervals for patients receiving brolucizumab, with an 8-week dosing option depending on disease activity. Aflibercept was given every 8 weeks after loading. How do you interpret these data in the context of the limited top-line data released to date?

"There is currently no treatment for NAION; you watch the optic nerve die in front of you. It is exciting to have any treatment for this disease in a phase 3 trial. But like Dr. Lam said, we don't know what the results will be."

— Szilárd Kiss, MD

Dr. Csaky: At this point, the efficacy shown isn't superior to what is already available. But all of us think that brolucizumab is clearly noninferior to aflibercept. The big question is whether brolucizumab will have improved durability compared to the other anti-VEGF agents.

Dr. Prenner: The topline data look good. Brolucizumab had consistent visual gain at 48 weeks, and more than half of patients maintained those gains on a 12-week dosing interval. There was also less disease activity at week 16 with brolucizumab compared with aflibercept, and fewer patients had intraretinal or subretinal fluid on brolucizumab. The safety profile of brolucizumab was comparable to aflibercept. That being said, we need to explore in more detail what the study design implications are and how we are going to adopt the drug into our clinical practice. I think that at the very least we are going to have another good way of treating wet AMD. With some experience and time, we may be able to parse out which patients would benefit from brolucizumab treatment.

Dr. Kiss: It is exciting. It is nice to see something actually hit the primary endpoint. In terms of the way we parse it, I agree that we are going to have to start using it and figure it out as we go. Is there durability? Are there certain patients that respond? Those questions have yet to be answered, but it is nice to have something new in our armamentarium.

Dr. Reichel: The results look pretty similar to aflibercept. Further, there appear to be more ocular serious adverse events at the 6 mg dose relative to aflibercept. I would also like to see more of the subgroup visual acuity data. What was the final visual acuity gain in those who were treated every 12 weeks?

Dr. Wykoff: In the studies, 57% of patients in HAWK and 52% of patients in HARRIER were maintained on quarterly dosing after the loading phase through the 1-year endpoint.[30] But the criteria used to determine when more frequent brolucizumab dosing was employed need to be considered carefully. I am concerned that some patients may have been driven to lose vision before they were able to receive more frequent dosing. How do you interpret this? What would the proportion of patients been at quarterly dosing if the dosing interval was based solely on fluid state?

Dr. Prenner: I suspect the percentage would be lower in that case. The study design will have to be considered when you are thinking about how to apply it to patients. The trial has preselected a patient population who are anti-VEGF responders at week 16 before they are allowed to enter the 3-month dosing group. We know it is not going to be 3 months for all patients. On the flip side, it will be 3-month dosing for some patients, and we need to make sure that we are allowing that patient population to benefit from reduced drug exposure. It is going to be a fun challenge to figure this out in the clinic.

In comparison, I typically treat patients every other month with aflibercept now. Looking at my entire AMD population regardless of drug, about 25% of my patients are on monthly dosing, 50% are every 2 months, and 25% are every 3 months.

Dr. Wykoff: The entire field is sensitive to reimbursement issues, which are many times tied to on-label pharmaceuticals. Usually this is in relation to using medications more frequently than the FDA-approved package insert, but what about longer intervals? For example, ranibizumab currently has an on-label use of quarterly dosing. Do you think that aflibercept needs quarterly dosing specifically listed in their FDA-approved package insert?

Dr. Prenner: Yes, and I think it is coming. The flip side is that in order to be a functional drug in our office, brolucizumab has to have 4-week dosing. It is going to get way too complex for us, and for patients, to have people who require more than 8-week dosing with brolucizumab to be changed to a different asset. It will be very difficult to then switch their drug on the fly when they are in the office. I think both of those labels will be important going forward.

Dr. Csaky: The insurance issues we face in the clinic are not trivial. There are various timeframes that certain insurance companies require between injections. There are many complexities in how the label needs to be written, how the reimbursements then need to be scheduled, and how the insurance companies are going to pick this up.

Dr. Wykoff: What about systemic safety issues with brolucizumab? Topline data do not suggest that there are any safety concerns, but the granular data haven't been released. Are you worried about a systemic signal, such as hypertension, with brolucizumab given the higher molar concentration of VEGF binding capability compared to aflibercept or ranibizumab?

Dr. Csaky: I keep thinking about that. This is pushing the envelope based on size, the amount given, and the plasma levels. So far, that theoretical and data-driven concept of VEGF blockade in the systemic circulation hasn't translated into significant Anti-Platelet Trialists' Collaboration-defined events. But we'll have to wait and see.

Dr. Kiss: Should we worry about GA? There was an indication from the topline results that this is a better drying agent. Will we be drying too much?

Dr. Csaky: We know that VEGF coming from RPE cells serves as a normal important protective protein for underlying choroidal endothelial cells. Brolucizumab is the smallest anti-VEGF we will be using. Is it going to penetrate the retina and block the VEGF that is normally secreted by the RPE cells? We all produce VEGF that has a therapeutic benefit on the choriocapillaris. Are we going to then risk generating GA or damage to the choroid in choriocapillaris?

Dr. Prenner: That brings up another consideration. Inhibiting VEGF in an intermittent pulsatile fashion for 2 days and then having the next 30, 60, or 90 days without inhibition seems to work well for many patients with AMD. What is it going to look like when we have an implant or sustained-release approach? Will we overcook the goose?

"To me, the big unmet need is mechanism of action. We haven't targeted or explored different mechanisms of actions of drugs that may have a bigger impact on the disease than what we have now with our anti-VEGF agents."

— Karl Csaky, MD, PhD

Dr. Kiss: I think it's a real concern that should not be ignored. There are two things on the horizon: a sustained-delivery device that releases anti-VEGF therapy through 6 months and gene therapy with longer anti-VEGF activity. I think the effect of pan-VEGF blockade over the long term may do some harm. We tend to think of pulsatile VEGF blockade as a limitation, but maybe that is the right way to go. Our current treatment program seems to work pretty well.

Dr. Wykoff: If brolucizumab is FDA approved, we will have three agents that are FDA approved and one that is used for retina pathologies off-label. Other companies are continuing to develop additional anti-VEGF agents such as abicipar. Is there space for more anti-VEGF agents in clinical practice? What is the unmet need?

Dr. Kiss: You are going to have to show value, which is improved visual acuity, over what is out there, along with durability. I don't think anyone will be able to show either.

Dr. Csaky: To me, the big unmet need is mechanism of action. We haven't targeted or explored different mechanisms of actions of drugs that may have a bigger impact on the disease than what we have now with our anti-VEGF agents.

Dr. Wykoff: What are your thoughts about the angiopoietin-2 (Ang2) pathway?

Dr. Reichel: It is a complicated pathway, and its relationship with VEGF inhibition and VEGF receptors makes it even more difficult to comprehend. In general, I am pessimistic about these additive therapies to anti-VEGFs in that the bar has been set so high that it is going to be near-impossible to show superiority.

Dr. Csaky: Downregulation or the blocking of Ang2 is a reasonable target. I think it will be the next big phase of therapeutics coming down the pipe especially for diabetic macular edema. Hopefully, there will be more value with this class of drugs because we will actually disease modify for the first time.

Dr. Prenner: I think, unfortunately, we are going to have to temper our expectations for any of these secondary targets. I think Ang2 will show an incremental improvement at best, and one that may not be clinically relevant.

Dr. Wykoff: The phase 2 LADDER trial is currently under way, which is examining the efficacy and safety of the ranibizumab port delivery system for the management of neovascular AMD.[31] What is the potential role for port delivery systems in your clinical practice?

Dr. Reichel: It may be useful for a small percentage of my patients. I believe in PRN therapy, and generally patients in the first year of therapy require such a varied number of treatments that it will be impossible to predict who will benefit from this delivery system. By year 2 there are a few patients who do require frequent therapy (every 2 months or less) who may prefer the port delivery system. Finally, I am always concerned about externalized hardware (even when covered by the conjunctiva) and the risk of endophthalmitis. Also, a surgical procedure is needed for placing the port delivery system, and at this point, the bias for most retina specialists is to keep the procedures in the office.

Dr. Prenner: If it works and it is safe, I think it is going to play an important role for a small percentage of patients. Most of my patients receive medication every 8 weeks. Most of those people, at 85-years-old, are not going to choose to have surgery. I think it will be important for certain patients, particularly people who are not responding as well as we would like them to. But the vast majority of patients will prefer a non-surgical approach.

Dr. Kiss: We have to remember that the LADDER trial was halted a couple of times because of the complication rate; there was hemorrhage that was non-clearing that required another surgical intervention. Some of the study modifications, which included patients not being able to be on anticoagulation agents, made recruitment difficult. The cost is another issue. Port delivery will not be cheap, and that has to be taken into account.

Dr. Prenner: I think if there is a better outcome, then we are going to all switch.

Dr. Csaky: There has to be a value add. The value will be minimal if it's simply another "me too" product or only benefits a small percentage of patients. For all new agents, we have to ask what the added value is, how is it benefitting patients visually, and what is the durability?

Dr. Wykoff: Thank you all for your insights. It's a privilege to practice retina; I look forward to continuing to advance our field together.

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FROM TRIALS TO TREATMENT: REAL-WORLD APPLICATIONS IN MEDICAL AND SURGICAL RETINA

Instructions for CME Credit

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

Name _____ ❑ MD participant ❑ non-MD participant

Phone (required) _____ ❑ Email (required) _____

Address _____

City _____ State _____ Zip _____

License Number: _____

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 educational 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
Discuss the outcomes of pivotal studies in age-related macular degeneration (AMD) AMD and how study results may differ from "real-world" dosing methods.	_____	_____	_____
Identify patient subtypes (eg. RAP lesion, pigment epithelial detachments, occult lesions) that will require long-term treatment and imaging evaluation.	_____	_____	_____
Develop a long-term treatment plan for patients with AMD based on results from clinical trials and extension studies.	_____	_____	_____
Compare the extended safety outcomes of anti-VEGF therapies as published in long-term studies.	_____	_____	_____

1 *AMA PRA Category 1 Credit*™

POST TEST QUESTIONS

Expiration Date: January 1, 2019

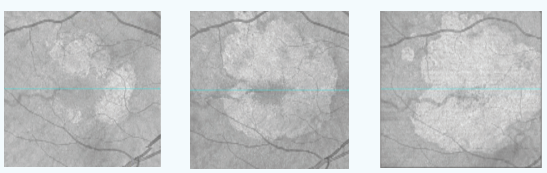
1. Please rate your confidence on your ability to apply updates in medical and surgical retina in the clinic based on this activity. (Based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

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. A patient presents in 2010 with 20/25 visual acuity (OU). Intraocular pressure is 15 mmHg. Based on the images below from 2010 (presentation, left), 2015 (middle), and 2017 (right), what is your diagnosis?



a. Wet AMD
b. *RPE565* genetic defect; Stargardt disease
c. Geographic atrophy
d. Macular telangiectasia

4. A mother presents in your office with her 2-year-old child. Upon examination, the child has strabismus and nystagmus, as well as photophobia, but has a fairly intact retinal anatomy. What might you recommend as treatment?

a. Evaluate the retina under slit lamp and recommend anti-VEGF therapy.
b. Observe the child and recommend follow-up visits every 3 months.
c. Offer genetic testing to determine if there is an *RPE65* defect that would lead to a diagnosis of Leber's Congenital Amaurosis.
d. Offer genetic testing to determine if there is an *RPE65* defect that would lead to a diagnosis of Stargardt.

5. Which is not a reason for why complement factor D has failed to show efficacy in clinical trials?

a. Complement factor D is an ineffective target.
b. The targets have been with off-the-shelf compounds, and targets need to be specific for AMD.
c. Complement factor D may be too far downstream to have an effect.
d. Targeting factor D and manipulating the alternative pathway does not influence GA expansion.

6. In the FILLY trial, what percentage of patients in the every month dosing group developed new-onset choroidal neovascularization (CNV) and wet AMD?

a. 10%
b. 20%
c. 16%
d. 18%

7. Where does the field currently stand with stem cell research in dry AMD?

a. We are in the laboratory still uncovering new challenges.
b. We have established safety but noted severe side effects.
c. We have established efficacy but not safety.
d. We have established safety but not efficacy.

8. If approved, Spark Therapeutics' AAV2 subretinal delivery for *RPE65* will be the first gene therapy for the treatment of _____ in the United States. Select all that apply.

a. Stargardt disease
b. Wet AMD
c. Leber congenital amaurosis
d. Retinitis pigmentosa

9. Genetic testing may be practical in patients who _____.

a. Are relying on insurance to cover the costs.
b. Need a concrete yes or no answer to a genetic condition.
c. Are refractory to pharmacologic interventions.
d. Are looking for an inheritance pattern of a genetic condition.

10. What percentage of patients in HAWK were maintained on quarterly dosing after the loading phase through the 1-year endpoint?

a. 52%
b. 57%
c. 50%
d. 60%

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 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 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.

_____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