Addressing Unmet Needs in Retinal Disease: Pairing Therapeutic Advances with Personalized Care

CMEO Podcast Transcript

Darius M. Moshfeghi, MD:

Hello, I'm Darius Moshfeghi, and I'm pleased to welcome you to *Addressing Unmet Needs in Retinal Disease: Pairing Therapeutic Advances with Personalized Care*. This activity is supported through an independent educational grant from Merck and Company Incorporated. During our program today, we may include discussions of products or devices not currently labeled for use by the U.S. Food and Drug Administration (FDA). We will disclose to you whenever investigational or off-label uses of products or devices are mentioned. Again, I'm Darius Moshfeghi. I'm Chief of Retina at Stanford University, and I'm pleased to be joined today by Dr. Joseph Coney, who I'll ask to introduce himself. Joe?

Joseph M. Coney, MD, FACS, FASRS:

Well, Darius, thanks for having me today. My name is Joe Coney. I am a managing partner at Retina Associates in Cleveland, Ohio, and I'm glad to be here with you today.

Darius M. Moshfeghi, MD:

Thank you, Joe. Importantly, we have a few short pre-taped perspectives from a patient who lives with a retinal disease. And, as we all know, the patient is central to a successful care team.

Here are our learning objectives. After participating in this activity, clinicians should be able to better evaluate guideline-recommended strategies for the diagnosis and management of retinal disease, develop individualized management plans for retinal disease that address patient needs and access barriers, and identify the mechanistic link between blood–retinal barrier dysfunction and the rationale for emerging therapies for retinal diseases.

So, perhaps there's no better way to start our program than with a patient who has lived with visual impairment her entire life. And while she does not have the type of retinal disease under discussion today, she has achromatopsia. She offers universal perspectives on living with a retinal disease that impacts daily living. So, let's roll the first short video and meet Natasha.

Natasha Caudill:

Well, my name is Natasha, and I was born with achromatopsia, but my story's a little unique because I was actually adopted from Ukraine when I was two and a half. My parents adopted me and right away they were like, okay, something's up with her eyes, but they didn't actually know what was wrong. And of course, it's this rare eye disorder. In middle school, we moved to Tennessee. Luckily, we ended up moving pretty close to an ophthalmologist who actually specializes in achromatopsia, and we were able to get the formal diagnosis.

I think really my whole life I was kind of aware that my vision was different. I think the biggest issue for me was in school. It was really prevalent not being able to see the board and not being able to see colors in art class. And as I got older, moving into high school, I remember all my friends turned 16 and they got their license and they could drive, and I still can't drive. I can't see well enough to get a license.

And I think the biggest thing for me was when I moved away to college in 2016, moved to an entirely new state that I'd never been to before. And that was really the first time in my life that I really had to advocate for myself and my needs, which was definitely a big learning process of like, how do I get groceries and how do I talk to my professors about what I need in their classes? And so there were a lot of challenges in all aspects of my life.

Darius M. Moshfeghi, MD:

Well, that was great hearing from Natasha. Joe, this really resonates with me as a pediatric retina specialist. I'm sure you've seen a lot of this in your own practice.

Joseph M. Coney, MD, FACS, FASRS:

Yes, Darius, these are some of the more frustrating patients that I see in my office, because a lot of times there are not a ton of things that I can do. I know that when I deal with people who have come in for an evaluation for inherited diseases, such as this one, oftentimes these are difficult because their exams sometimes can look normal. And it may take them several times before they see the physician before you start to do a little deeper dive into their eyes. And as they get older you may see some clinical changes, but those things are very difficult.

But the things that she has gone through and her adaptation, I think, is a story that you and I are so familiar with, particularly when you look at diseases like macular degeneration and diabetes. As people get older, they really learn how to adapt to things. I am always surprised on how people have such visual disabilities and yet they are living by themselves, they're functioning. They may not be driving. Sometimes they color code things around their homes. And they've really gotten used to using technology. They've learned how to make the screens brighter with contrast or make things bigger. So, people have adapted, and it's really great to hear that at least she is still able to move on and go to college and still have a normal life.

Darius M. Moshfeghi, MD:

I absolutely agree. And that's a perfect transition, which leads us right into our first learning objective now showing on your screen. Could you kindly set the stage here?

Joseph M. Coney, MD, FACS, FASRS:

This learning objective is to evaluate the guideline-recommended strategies for diagnosis and management of retinal diseases. I think this is a big issue for not just what we see in the community but also things that we see in our office, particularly when it comes to macular degeneration as this is the leading cause of severe impairment in older individuals. Because people are getting older, these things are more common. And we're really in a pandemic right now, not just here in the United States but also worldwide, in that the number of individuals with diabetes continues to increase. And this is the leading cause of preventable blindness if it's called early. Inherent diseases are a little bit different. These are much more rare genetic retinal degenerations, which causes a progressive loss of vision over time.

When it comes to screening, for individuals who have macular degeneration, my most concern is for those individuals who have a first-degree relative or someone in their family has gone blind. I want to see these individuals around 55 or 65 years of age, depending on their symptoms. If they come in and they don't have any age-related macular degeneration (AMD), then I'm okay seeing them every 1 or 2 years. The majority of these

people are already seeing optometrists, so I can see them intermittently in between those appointments. If they have high-risk disease, I'd like to see them a little more often. I think a baseline exam is always critical. You should always do a dilated fundoscopic examination. But we see a lot of patients, and so photography for me is really helpful because it helps me to follow those patients long term.

I typically do get a fundus photograph, but lately I've really been getting optical coherence tomography (OCT), even if there's no pathology. But, if I think that someone may have a very subtle subretinal fluid or something that I'm really concerned about, OCT is something that can really pick that up really easy. But, OCT for me is also helpful in those individuals who have baseline geographic atrophy. It gives me a better evaluation of what's going on in the outer segments of the retina, the core capillaries and the retinal pigment epithelium, so I can monitor their progression as it gets toward the fovea. I don't do as many fluorescein angiograms anymore. I know that they still have a valued use. I do a fair amount of optical coherence tomography angiography. I can get a good idea of what's going on in the deeper segments of the retina, and this can be both diagnostic and therapeutic.

When it comes to diabetic retinopathy, this is the leading cause of blindness in these individuals. So for those who are type 1 you really want to see them in the first 5 years or around adolescence. Those who are type 2, because 25% to 30% of people will have retinopathy before they come in, you really want to see these people at diagnosis. The Johnson Clinic did a very nice trial, and those individuals who were known to be diabetic, 50% of them had sight-threatening problems and were not aware of it. So, oftentimes people will have a baseline disease before they come in for their first exam. And so, if someone has mild disease, I'm not that concerned. They don't progress as much. I may want to see them annually or every 2 years, but I'm really concerned about those who have more severe diabetic retinopathy, those individuals, because I know that if you have severe non-proliferative diabetic retinopathy (NPDR) or PDR the risk of vision loss can be as high as 50% within that first 3 to 5 years. And those individuals, I typically see a little more often.

Dilated fundoscopic examination is really important, and I think the most important thing you do is grade the level of retinopathy. I think that's the most important thing that we can do as a clinician, to make sure we get that right, and that will help you to know how to follow that particular person. Now, this is one case where I think widefield angiography is really helpful. No matter how good you are, it's really difficult to see featureless retina in the periphery. A fluorescein angiogram can clearly show those ischemic areas, those peripheral neurovascular membranes or neovascularizations that you may not see at the exam. And so this is where I do want to make sure I do a fluorescein angiogram to make sure I have the right grading.

Inherited retinal diseases, to me, are always the toughest, and I'm always more looking for their signs and symptoms of something, those who may have nyctalopia or visual field loss, or even central visual field loss, photophobia, nystagmus, any type of characteristic changes that I may notice on an exam. So, typically, these individuals have signs and symptoms out of proportion to what their exams are sometimes. These are individualized screenings. You really want to see them every 1 to 2 years once you have the diagnosis. And you also want to make sure you take a good family history. An exam is critical. I think the OCT is really helpful to look at the outer segments. Depending on what's going on in the patient, fundus autofluorescence can be helpful, particularly if you're looking for a light perfusion. And even electroretinogram is helpful if you think someone may have retinitis pigmentosa, or even electro-oculogram for those who may have Best disease.

I think the most that we can do as a clinician is make sure we do the genetic counseling and make sure we have molecular testing. And if you suspect that there may be a systemic issue associated with this disease, you want

to make sure that they get evaluated for that. The one thing that I offer in my clinic is that I try to get them early on to a low vision specialist, because I think it's easier for them to adapt to these types of devices if they're young and when they see very well.

Darius M. Moshfeghi, MD:

That's really a nice overview of what's going on here. Basically, we have two types of diseases. We have the retinal vascular diseases, macular degeneration, diabetic retinopathy, and macular edema, and then finally, retinal vein occlusions. Those are very responsive to treatments where we can use anti-VEGF intravitreal injections, and we're going to talk about a whole host of approaches to that. And then you have, on the other side, the inherited retinal diseases where management is mainly supportive and making sure that they know how to adjust to the circumstances that they're living with.

So, what we're going to speak about, moving ahead here, is how we manage these patients, because patients with these retinal vascular diseases can do very well, maintain good vision, but unfortunately the treatments require frequent observation. Much like Joe, I live off of the OCT, which is telling me whether or not my patient has fluid or they have macular edema, if it's encroaching on the center of the vision, if their vision loss is from that fluid or if it’s coming from atrophy.

I think it's very interesting to get a baseline of how our audience is doing. So, what is the approximate 5-year loss to follow-up rate for patients who are receiving the anti-VEGF intravitreal injections? The four choices are near 30%, almost 50%, nearly 60%, more than 80%, and then, my favorite, I don't know. So, the correct answer here is C, nearly 60% of patients stop taking anti-VEGF therapy and are lost to follow-up. This is very important because once these patients start to experience a visual decline, it's often not recoverable, particularly in neovascular macular degeneration disease, or what we call wet macular degeneration. Retinal vein occlusion (RVO) and diabetes are a little bit more forgiving on loss to follow-up, but really the onus here is to make sure that we can carry our patients long term. That involves either being on top of them all the time and making sure they're following up, or developing new therapies that last longer, or ideally a combination of both. And making sure our patients follow up is not just calling them up; it's getting them involved with resources that can maybe facilitate them if they have difficulty with transportation or there are financial issues and things like that. And we're going to get into some of that stuff in the next few slides.

So, these injections involve injecting right into the eye. What do I mean by injecting right into the eye? If you take a needle and you poke it into a grape, it's exactly like that except your eye's numb. You're awake; you're alert. We give you a little topical numbing medication. It sounds awful, but patients keep coming back for two reasons. One, it isn't as awful as it sounds. And two, they usually experience a fairly immediate improvement in visual acuity, whether that's qualitatively in the quality of their vision, they see fewer floaters, less distortion, greater contrast sensitivity, maybe even improved color vision. But oftentimes they get improved functional vision, particularly if they're a new patient who's showing up and they're at first-time diagnosis. They can gain anywhere between five letters and 10 letters of visual acuity, which is going from 20/30 all the way to 20/20 or from 20/50 to 20/30 for those of you who don't follow letters like Joe and I do here.

As you can see here, over time patients lose visual acuity when they're receiving injections, and oftentimes this is because they're getting fewer injections over time. More injections are associated with better visual acuity and better fluid control. As you can see here, starting visual acuity determines how well you're going to do. Patients with the least amount of vision end up gaining the most amount of visual acuity, which is really

encouraging for our patients because they now know that this medication is helping them. I don't have to tell them it's helping them. They get the injection and they come and tell me it's helping them, which is super satisfying for both of us.

Which brings us to our second learning objective here, to develop individualized management plans for retinal disease that address patient needs and access barriers. We're going to explore the patient-first approaches to retinal disease management, but first let's check in with Natasha again.

Natasha Caudill:

In terms of shared decision-making, I think sometimes we had it and sometimes we didn't have it. I do remember times where I'd be sitting in the ophthalmologist chair and my doctor would be there and he'd be talking, not just to my mom but to me as well. He'd be saying, "Here's what we can do. Here are options if we want to do this test or X, Y, and Z." And so in those times, even though, again, I didn't entirely understand what those tests were, it was a mutual conversation that we were all having.

I do think there were definitely times when it was more so like, "We're going to do this," and I didn't really have a choice. And of course I was just like, "Well, I'm a kid so I have to do what the adults tell me to do." But, again, it was kind of like, "Okay, I'd love to understand why we're doing these things." And I think my mom was pretty good at cluing me in, but there were definitely times where I had no idea what I was doing there. I was just doing the tests that I was being told to do.

We never had issues of transportation or costs or anything. It was always like, one of my parents was going to take off work to get me to the eye doctor. When I was really young when we lived in Alabama, and it was like a whole day because we had to drive almost 2 hours to get to my optometrist. So, again, I do feel very lucky to have had that access.

Darius M. Moshfeghi, MD:

So, Joe, Natasha brings up a couple of interesting points here. One is that it really takes a village, but in particular it's not just on her because she was a minor and had to be brought in. I see this a lot in my pediatric retina practice. You're going to be able to inform us more about barriers that face adult patients for different reasons, and this is an area of expertise that you've lectured on around the country, in particular with regards to diabetes. Can you tell us about that, Joe?

Joseph M. Coney, MD, FACS, FASRS:

Sure. This is something that's really near and dear to me. For one, it affects areas where I come from, south side of Chicago, for many years of redlining, where we live in an area which was kind of depressed, and this area is still depressed today. And it's really because of what we now know as social determinants of health. This can affect any population of people, any demographic area, but clearly it can really affect a lot of things in what you do in life, whether it's medicine, whether it's education, whether it's working.

There's a great definition that was put out by the World Health Organization. I want to read this thing for you because I think they sum it up nicely. It's the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life, including economic policies, system development agendas, social policies, and political systems. That's a really good summary because sometimes

how things are drawn up or policies are made, this governs how people live and where they live. And this has an impact on people's lives. These things long term can create disparities, and these disparities unfortunately affect certain people more than others, particularly Black and Hispanic patients.

When it comes to what we do, we know that when you come from these sorts of areas, there's also a downstream effect when it comes to vision. They typically don't know about their health condition very well. They don't know that diabetes really affects the eyes. They don't know that high blood pressure is really important in managing when they have diabetes. So, health literacy is of big, big importance. Also, where I come from, there's a lot of mistrust and distrust just with any type of institutional type of programs and so they may delay their therapy. We know that 50% of people who have diabetes are not coming in on a timely manner, and because these are set up, they're coming in with more advanced disease. I think for what we can do, we need to understand what the social vulnerability is for a particular area.

And there's actually an index with a number that is given to a particular geographic location, and it shows that if that number is high the number of disparities are greatest. If you look at this on a map, it will show you that diabetic macular edema is at the highest at those levels, as well as certain disparities. Access to care. Natasha had a problem with access to care. When you have to travel more than 20 miles away from an office, we know that your care goes down. When you present to an office that goes down, you're most likely not to get involved in clinical trials, or just have exposure to certain things. And when it comes to clinical trials, I think that it's really important for us as clinicians in these areas, you've been involved with clinical trials for a long time, that we are creating diverse populations. Ninety percent of the DNA therapy that we have and 90% of clinical trial data that we have are based on European ancestry. So, unfortunately, we have to do sometimes phase IV trials to really understand how it affects a certain population, and we really shouldn't have to do that. I think we have to feel comfortable. We have to address our own implicit biases and try to get people involved in trials that are ordinarily not included, to make sure that the medications that we're bringing forward are equally as effective as well as safe.

When I think about all this, I'm always coming back to diabetes because diabetes for me is the biggest thing that I see in my practice. And as you said earlier, it's one of those things that is preventable and yet we still have low rates of screenings in the Black and Hispanic populations. This can be for a variety of reasons, either lack of understanding or socioeconomic and financial barriers. We know that if you are of a certain means of both education and financially, they're less likely to present to an ophthalmologist. It's very time-consuming. Typically, when it comes to diabetics, this is the working-age population. It's very difficult to take off time to come to the doctor each time. And transportation is an issue because sometimes it may be only one vehicle in the office and they may not be on a transportation line that can take them from one place to another. We know that rural areas also have an issue. Also, in the rural areas there are health qualified centers, and only 70% of those centers will have an eye lane, so they may never see an ophthalmologist on time, at least not in a timely manner.

And, again, I think the most important thing for our patients who logistically don't speak English is that it's really good to give them literature in their own language so they can understand really what's going on. I think it's our job to help our patients prioritize their eyes so they know the importance of really what we do. Twenty-six percent to 28% of individuals who are Black or Hispanic are less likely to seek an ophthalmologist than non-white Hispanic patients. When we look at the prevalence of diabetes, Black and Hispanic patients present at a much higher rate of diabetes. Their rate of progression tends to be faster, and they typically present with a

higher incidence of vision-threatening diabetic eye disease. These are really, really important because we know that these, again, are preventable things. And typically when they come in they have already reached a level where the best thing we can do sometime is stabilize their vision versus what you said earlier, take them from 20/40 to 20/20.

And then lastly, I think social determinants of health can also affect individuals with macular degeneration. We know, again, that having come from a lower socioeconomic status has also been associated with a higher incidence of having AMD and also a poor visual prognosis. And that has to do with lower education, lower income, as well as just the neighborhood deprivation. There are higher odds of you having a decrease in vision from AMD if you're divorced or widowed or you live by yourself. I do find that for my patients who have a strong support system, particularly if they have children, that it's really helpful because sometimes there are older people and the only people they have for a long time was their spouse. And now their spouse is not there to help them take care of themselves.

The one thing that I always talk about with patients, and it's the one modifiable risk factor, is really smoking and alcohol. We know that these things can also increase your risk for more advancing forms of macular degeneration. So, health style modification can be very helpful in this population.

Darius M. Moshfeghi, MD:

Joe, thanks for highlighting all of that. When you come to this slide, you see it's a team-based approach for retinal disease management. Basically, everyone's involved. Here, we have a bunch of medical technicians, caregivers, ophthalmologists, optometrists, social workers, but your family, your transportation people. It moves even beyond that to social services. All of that plays into how you're going to do when you have one of these chronic diseases for which we have good treatments available.

That kind of leads us into getting our audience involved again with another scenario. A 72-year-old woman with wet macular degeneration has received three monthly anti-VEGF injections with anatomical improvement. The fluid went away. However, she tells you she's considering stopping treatment because she feels overwhelmed by the frequent visits and says, "I don't think this is sustainable for me." She lives alone, relies on her daughter for transportation, and expresses concern about being a burden. What is the most appropriate next step? Choice A is to reinforce that these visits and injections are important. Choice B is to transition to a fixed extended-interval regimen. Choice C is to explore her concerns in greater depth, including assessment of logistical and psychological barriers. D is to document her reluctance but firmly recommend staying the course. And E, of course, my favorite, is I don't know. The correct answer, of course, is to find out what her concerns are in greater depth, including the assessment of logistical and psychological barriers, which would be choice C. So, Joe, I'm going to turn this over to you to discuss focused action and physician competence.

Joseph M. Coney, MD, FACS, FASRS:

Darius, I think this is really important. We always want to leave people with things that they can immediately integrate into their practice. And I think that there's a lot for us to learn and a lot that I've learned really from my patients, and one thing that I've really learned is humility. Patients want to understand that you have a certain feeling for them. This is really just going back and just making a communication with your patient. A good way to do this here is really taking an enhanced history. In my electronic medical records we have a little area where I'm able to put down something about the patient, maybe where they're from, an activity they like, if they're a

golfer, so when they come in I can have a conversation with them about the things that we've talked about before. This kind of resonates because it helps them understand that that's a great communication between you and the patient.

One thing I've really learned from my patients is that communication is really, really critical. You can do everything right for a patient, you can make the right diagnosis, institute the right therapy, but if the patients don't feel like they're heard or understood, they feel like the care is just not as good as they had hoped and they feel like they want to go someplace else. This also increases adherence to the office, which sometimes drops off, particularly in populations which are much more difficult to treat. Understanding the culture of patients I think is critical. Just understanding that the different aspects of patients' lives helps us to be a better communicator. And the better you can communicate with a patient I think the more they can understand. And then this tends to lead into a part where you can educate them better about their disease process. "Mrs. Johnson, your A1C was 8.5 and this year is 7.5. We're very happy with how you're doing." I mean, having that discussion with them I think really, really means a lot.

And, again, pass out information about their condition. Every new patient in my office gets a brochure, and we have it in the Spanish language and we'd like to share with that or videos that we can direct them to, and I think that is really, really helpful. But the cultural humility piece is something that I think we all can do. You can practice this with your colleagues, your residents, and your fellows, and you can learn from how you project your ways and how you deal with your own implicit bias and microaggressions and things that you may not be aware of. I think we all need to do a better job with our patients. These are things that we can institute in our practice to be much more effective communicators.

Darius M. Moshfeghi, MD:

Joe, thank you very much for that. One of the things, the very first question, that I always get asked is, "How long am I going to be on this therapy?" And for diabetes and RVO I really don't know the answer to that question and I usually say, "Well, we're going to treat you for a few months and then we're going to see how you respond." But for wet macular degeneration, it's often the case that they're going to be on the intervention for as long as they live.

So, let's take a look at a short patient case. This is a 77-year-old man with wet macular degeneration and he presents with visual acuity that's really good, 20/25 in both eyes. He had received one injection in the right eye. While he was traveling and when he returned back to Stanford, he came in to establish care with us and he had bilateral neovascular macular degeneration. What I want you to focus on in this case series here is that over 16 years he receives a whole lot of injections in both eyes. And throughout that entire time, when we look at the OCT, which is basically how thick or how thin the retina is, and for our case that's representative of the amount of fluid. He has evidence of disease activity based on the thickness of the retina throughout the entire time that he's seeing me, despite all of these injections in his eyes. But the reward is he maintains visual acuity, but it shows that this patient is at risk for losing that vision if we were ever to stop those injections.

I'm just going to get into it. They started off with relatively good vision, 20/25 in both eyes. And the OCT on the right-hand side is showing us that there's fluid and thickening for different reasons in both eyes. And this is 16 years ago. Then the patient receives a whole bunch of injections, monthly injections for 2 years, and gets good vision. But as you can see at the bottom of the photograph here, there's still evidence of ongoing disease activity. Then as we move along 7 years in advance, the patient still has pretty good vision. You can drive in all

50 states if you're at least 20/40 in one eye or better. And this patient here is 20/40 and 20/30, but they've been still receiving a bunch of injections. They did have an inflammation about 6 years earlier and then recovered quite well from that.

And then here you see as we move into the 20/20s, the patient is still having pretty dramatic fluid in both eyes and yet still has good vision. As we get into February 2024 it looks basically the same from 2 years earlier. Again, we switched over to one of the newer second-generation molecules, faricimab, which we thought could get us a lot longer out. And he was able to move from 4-week injections to 8-week injections but continued to have fluid on 8-week injections. And then here we are in 2026 and the patient has received about 150 injections in both eyes, which is 300 injections total, and continues to have disease activity in both eyes but has spectacular vision, 20/40 and 20/30. This gentleman is now in his low 90s and is able to read without any extraneous aids. So, overall, this is a pretty good win case, but it highlights the problem: this patient has to come back or is going to lose vision. Joe, you've seen a bunch of cases like this. You want to briefly comment on that?

Joseph M. Coney, MD, FACS, FASRS:

Yes. Great case. This is not uncommon for us to have persistent swelling for patients. We do know that some patients can tolerate fluid better than others. Typically, they tolerate subretinal fluid better than intraretinal fluid. You look at all our data. Typically people with intraretinal fluid would have a progressive decrease in vision over time. It's interesting in this case here that, I do think, and particularly in the right eye, that everything is stable and the fluids tend to increase after the inflammatory event. And so there is some surface retinal disease, so as a clinician we have to determine if that epiretinal membrane (ERM) or any other traction may have, is that a part of the process? And it's really hard for us sometimes to know if this is an exudative component or just a cavitation from other lining diseases. Typically, what I do in these patients, and if we've already introduced the second generation, I will go ahead and push those patients out slowly and see if it fluctuates. I'm more concerned about fluctuating fluid, but I definitely agree that long-term maintenance at some interval is better than as-needed dosing.

Darius M. Moshfeghi, MD:

Thank you. Which brings us to our third learning objective: to identify the mechanistic link between blood–retinal barrier dysfunction and the rationale for emerging therapies in retinal disease. But before we go there, we're going to hear from Natasha one more time.

Natasha Caudill:

My visual acuity is pretty bad. Obviously I can wear glasses. That's only going to do so much, to be honest. Obviously it's going to correct my vision a little bit. It helps me read up close, but I can't see things far away. And that's something that really nothing is going to fix. I'm glad that my optometrists and my ophthalmologists have been able to help me as much as they can, but I think the extra step is like, okay, we've corrected everything we can on our side, what can we do to help you manage what you can't see? Growing up, it was like, here's a little monocle that you can use, or here are basically binoculars that you can take with you, and here are accessibility tools to help you, especially throughout school. Having those resources and even just having doctors to tell me about things that I didn't even know were resources I could use has been really helpful.

And to be honest, a lot of it now is just things I find on my own. I'm constantly trying new accessibility tools. I have an app on my phone that you can point at a crosswalk signal and it will actually tell me when I can cross the street safely. That was only something I found a couple of years ago after kind of risking my own life every time I crossed the street beforehand. So, I think if doctors can take that extra step of like, all right, here's what we're going to help you with, the things that you can't see, just really important, because again, it's all part of your treatment plan even if it's not explicitly medical.

Darius M. Moshfeghi, MD:

I think this is super useful information for us. Every year I find out if my patients have gotten their spectacles updated or replaced. And then the second thing is I find out if they're plugged in with a primary care ophthalmologist to manage something simple like dry eye, which is not simple to manage, but from a retina disease perspective it seems a lot easier sometimes. How do you go about trying to improve your patients' lives?

Joseph M. Coney, MD, FACS, FASRS:

We have brochures and nice communications with our low vision specialists. I am not a low vision expert by any means, and I let them know in the practice on why they're going there because they need something beyond the scope of what I can provide. And once they go through a complete evaluation, they have all sorts of things which may be helpful for patients. Some unfortunately may not be approved by insurance because I think that's the barrier. There are things out there, but how can they get access to it? But some of the federal-funded programs will help them get a closed caption monitor. I've had some patients even using glasses that would take a photograph of the photo and it reads to them. And that has been really helpful. So, there are all these things out there that I may not be aware of or don't really know how to train people on, but I think that we wait too long to get people involved with the low vision specialist.

Darius M. Moshfeghi, MD:

Thank you, Joe. Now we're going to move on to the “sciency” aspect of this and talk about the link between pathophysiology and emerging therapeutics, which sounds like a lot. So, the eye is made up of two blood-retinal barriers, and you can think of these as special doors beyond which you need a key card to get past if you're not inside the eye. The first one is called the inner blood-retinal barrier and it's located inside the retina. The second one is the outer blood-retinal barrier, which is between the retina and then another layer of blood vessels, which is called the choroid. Within the retina, it's actually at the tight junctions of these retinal capillary endothelial cells. And then the one between the retina and the choroid is, again, these tight junctions between the retinal pigment epithelial cells. And there are a whole bunch of cells that work to make this happen, but I'm not going to get into that.

There are two different blood sources. One is the central retinal artery, which eventually traces its way all the way back to the internal carotids and then back all the way to the heart. The other one is coming from the choriocapillaris, which is this multi-layered unit underneath the retina, which kind of acts like that little fan in your computer to cool off the retina. And the inner blood-retinal barrier is associated with a whole bunch of pathologies. Most often we think about it with diabetic and the retinal vein occlusions, whereas the outer blood-retinal barrier is associated with different kinds of pathologies such as wet macular degeneration and the pigment epitheliopathies and central serous chorioretinopathy.

That's a lot to kind of keep track of. As we're moving ahead, there are basically four main sustained delivery approaches. And this is how we move from 4 weeks to 8 weeks, 12 weeks, potentially 16 weeks, and even longer, maybe 6 months. There are four different things that we're going to be talking about in high level: second-generation anti-VEGF agents, kind of like a surgical refillable reservoir that you have in your eye; tyrosine kinase inhibitors (TKIs), which is kind of like an anti-VEGF; and then finally gene therapy, which is kind of like a genetic modification of anti-VEGF. So, Joe, can you take us through these second-generation molecules?

Joseph M. Coney, MD, FACS, FASRS:

Sure. I think these really have revolutionized at least what we do for patients. I mean, we've been using anti-VEGF medications, which is a medicine to decrease permeability in the eye or on abnormal blood vessels. And the problem with that is that people needed repeat injections, oftentimes every 4 to 8 weeks. And like you said earlier, people drop off over time, so these sub-therapeutic points in patients' lives where they fluctuate with the variability of the OCD going up and down, over time they lose vision, they have fibrosis, and you cannot get that vision back.

But with the second generation, I think these are more durable drugs. For example, with aflibercept HD, this dose is four times stronger than the dose that we had the second generation. And this higher molar dose is allowing patients, 80% are going out more than 12 weeks, and sometimes even 16 and 20 weeks. Faricimab was the first bispecific molecule that we had. So, up to this point everything worked on some of the exact same factors, which is really VEGF. And this also has an effect on Ang-2, which is also important for inflammation as well as permeability. And, again, we saw patients in the trial going out 16 weeks.

And it seems like these smaller molecules tend to be more associated with certain inflammatory events, and it was very difficult for us to get over that hump. But it seems like we've come to a point where at least the second-generation medications are well tolerated. They have very low risk of inflammation, very low risk for vasculitis, and it has really, really improved the quality of lives of my patients because they have decreased the burden of therapy for coming in more often needing more frequent treatments.

Darius M. Moshfeghi, MD:

Thank you, Joe. That's a nice introduction to get us into our ongoing problem, which is we have these patients with chronic disease and we know we can keep them on good visual acuity if we get them coming in and we continue to give them injections. So, this is a patient I inherited from one of my junior fellows who was on the East Coast. When this patient moved out here to the West Coast, she came in almost 70 with type 2 diabetes and had received 43 injections with the other physician of aflibercept in both eyes, relatively good vision, 20/50 and 20/40, relatively poorly controlled, with an elevated hemoglobin A1C, and then overall had some signs of non-proliferative diabetic retinopathy.

And it's very interesting, if you take the last picture of the patient that I showed you on the last case report in the right eye, and you look at the first picture of the OCT here, that was wet AMD, and this is diabetic macular edema; they look very much alike. It goes to show you that when you're looking at the OCT, unless you see atrophy or you see drusen that are giving away the game, there are a lot of findings that kind of overlap in this disease, but it shows you why the anti-VEGF works across multiple different classes here. So, here, the patient shows up, 20/30 in the right eye, 20/20 in the left eye, there's obvious distortion in the right eye, and had received in that timeframe 43 aflibercepts in each eye.

A couple of months later, still 20/30, still 20/20 in the right and left eye, respectively. And then we switch over to the second-generation faricimab anti-VEGF agent, the so-called bispecific molecule, which has both an anti-VEGF and an anti-Ang effect, which works to stabilize the capillaries. You see that stabilization didn't really help the OCT a lot, which is not shocking because sometimes when you get these chronic macular edemas, the cyst just becomes recalcitrant and we're really trying to maintain the photoreceptor health as opposed to really push out the fluid. But you see the left eye is very responsive, still receiving 12 injections of aflibercept. In 2024, she switched back in the right eye to aflibercept, but the higher dose one, and then in the left eye continued with 10 monthly aflibercept injections. And you can see monthly as kind of a ballpark approximation because patients can't make it every month or they're vacationing or it's just how it works out, maybe they're sick.

Then, finally 2026 rolls around and we're alternating with every other month where the patient has figured out a way to get the insurance payor to give them aflibercept every other month and faricimab on the off months. And it's the only patient who had this going on. I don't know how she got this going. But anatomically, maybe there's a little bit of improvement in the right eye. The left eye is fairly stable. In between, dehydrates. Visual acuity, great. 20/30 in the right eye, 20/20 in the left eye. Again, as you see, there's not a lot of push in the right eye. Over time, sure it has improved a little bit but continues to have that large cyst right near the center of the vision. As 2026 has rolled around, the patient has received close to 80 injections in the right eye and slightly more than 80 injections in the left eye to achieve good vision, 20/30 in both eyes, and a modest improvement in anatomy in the right eye and a stabilization of anatomy in the left eye. And at the end of the day, this is kind of par for the course with a lot of our patients, wouldn't you say, Joe?

Joseph M. Coney, MD, FACS, FASRS:

Yes, Darius. I think this is another great case, and congratulations to you for over the number of years have not lost any vision, and that's really great. But the burden for her has been great. One thing that I typically do with my diabetic patients who have persistent swelling, it's important for me to figure out what the driver is. Is it a VEGF-driven disease or is there anything else like an inflammatory event? So, sometimes what I do, I want to challenge them with the steroid and just see if the cyst collapses. We have two types of steroids which are approved for diabetic macular edema.

If the fluid resolves and I know that there's an inflammatory component, and I think they do very well with a longer-acting durable drug that can keep them stable, if things are stable, which means they don't change with the steroid or with the anti-VEGF injections, these people may just have chronic swelling. And so I typically will continue to extend them out, and what I'm looking for is fluctuating fluid. But again, here, this patient has actually done fairly well, a number of injections, and this is the burden that we typically see with our patients. I think your patients love you because it's really difficult for patients to come in this much without getting injection fatigue.

Darius M. Moshfeghi, MD:

Thank you, Joe. My technicians don't love me as much as you do, having called these patients up and bringing them back in, but it's very satisfying when they do well, which brings us to our next and final audience response question, and this is highlighting the role of blood-retinal barrier, which is a central pathophysiologic feature of diabetic macular edema, which is contributing to the vascular leakage and the retinal thickening. An investigational agent, MK-3000, in development for diabetic macular edema, is designed to address blood–

retinal barrier dysfunction through which of the following mechanisms? Choice A is activation of Wnt signaling in retinal vasculature. Choice B is long-term intraocular VEGF suppression via viral vector-mediated gene transfer. Choice C is complement inhibition to reduce inflammatory-mediated retinal damage. Choice D is dual inhibition of VEGF-A and Ang-2 to stabilize pathologic neovascularization. And again, my favorite, I don't know. In this case, the answer is choice A. MK-3000 is a novel agent that activates the Wnt signaling in retinal vasculature and is thought to help with the management of the blood retinal barrier.

So, Joe, as we're looking ahead and we've got a lot of emerging agents coming here, we've got the Wnt agents and we've got a whole bunch of named chemicals here, it's hard to really keep track of. Some of them are gene therapies, some of them are dual inhibition agents. What are you thinking about and how do you talk about these with your patients as we move ahead?

Joseph M. Coney, MD, FACS, FASRS:

Really, I'll just sum it right up in more simple terms. We have barriers to therapy, and we have different routes of administration to address certain barriers. Historically, we've had a very difficult time to have vectors in the eye and cross the internal limiting membrane. Our earlier studies were shown to develop gene therapies, and these are gene therapies where biofactories are created. They get incorporated into your retinal cells and they make the same anti-VEGF injections that we're giving on a monthly basis. So, the goal is to have sustained release. You don't have the fluctuations in vision to maintain that vision long term. So, the subretinal space and suprachoroidal space were two things that were very easy for us, where we can put medicine and we know we can get an effect. But the difficult part was trying to go past the internal limiting membrane, but now we have vectors that we can inject in the eye and these are all in clinical trials that can do the exact same thing. They can make the same type of molecules that inhibit VEGF suppression long term.

And then you have, you alluded to earlier, something called TKIs. These TKIs are little small molecules. They're also given in the intravitreal through various mechanisms or various delivery platforms. And this is the first time that we have something maybe a little more novel, right? Everything we had before really blocked VEGF. Well, this actually goes intracellular. They have an effect a little bit more downstream, so you can decrease permeability. The difference between these is that in gene therapy we're hoping that in some cases that it may be “one and done” and TKIs we're hoping to address durability, maybe extend them 6 months, maybe 9 months. I think no matter what we have, these are so early in clinical trials. There's still a lot to be learned. There's a lot to be gained. We do have people out 5 years on some of these trials, but safety I think is really going to drive the discussion along with efficacy. But I think safety is going to be the most important thing.

When it comes to gene therapy, there's still this “black box” which we don't know how people are going to do long term. And I think for all of us, we're very excited about it. One thing for sure is that in the phase I, II trial, so far the durability of these drugs has really decreased the number of injections that patients required. I would like to get your thoughts. Once these drugs are approved, if they ever get approved, what are you most concerned about with these newer medications that we're looking at in clinical trials?

Darius M. Moshfeghi, MD:

Thank you, Joe. Basically, when we're looking at gene therapy, you're giving what we in the retina community are referring to as a gain of function. So, you're adding something that we didn't have before, and what you're adding to the eye is this anti-VEGF long-term production asset inside the eye. And since you're genetically

modifying the cells, this can go on and on and on. But it's predicated on two things really. One is that it goes to where you want it to go and that's the vector, which in this case is an adeno-associated virus (AAV) viral vector. AAV serotype 2 (AAV2), I think, is often used. But when you talk to the scientists, and at Stanford recently we've had a string of people speaking on gene therapy, and you ask them about where else it goes and where else it binds, they have very limited knowledge of where it binds. So, what they call off-target events are unpredictable inside the eye. When you ask them about where it can go outside of the eye, they have no idea.

And these binding domains where the vector can bind to are not well-known, which cells throughout the body can actually have this. So, maybe you put it in the eye and it's very specific for a cell on the retinal pigment epithelium, but it's also possible that somewhere in the ovary it has that. And you may not want to have your cell expressing in the ovary, which is why the safety concerns that you're alluding to, even though we have 5-year data, it may be that at 10 years we have a different problem. I don't like that unknown aspect of it. I like the ability to shut off something, which is why I like the concept of a TKI or a refillable reservoir or a second-generation agent as opposed to a more permanent sort of thing that I might not be able to turn off when I need to. But as we move ahead here, I no longer do incisional surgery. I make a referral out for any of my patients who want the port delivery system, but can you tell us about that or if you've had any experience on that?

Joseph M. Coney, MD, FACS, FASRS:

Yes. I think the port delivery system is a really good bridge. It uses knowledge we already know. It uses high-dose ranibizumab, which is the first approved therapy to treat both neovascular AMD as well as diabetic macular edema. The goal is really to put this reservoir in the eye. It's sown into the sclera and the medicine's given right into the vitreous, and the goal is to have a longer projection of a continuous dose of therapy for about 6 months. And what was so interesting about the phase III and even the extension port trial is that about 95% of individuals did not require a supplement injection before the refill. This was compared to monthly ranibizumab. These were treated, experienced eyes. They had a mean of three to five injections before they could have the implant. So, these eyes already were treated previously, that showed that they had a response to anti-VEGF therapy. But it was really surprising to me that over that course of 5 years they were able to maintain vision with a stable OCT, and we typically see much more fluctuations in this population of people.

Now with that being said, it's surgery, and I think that's really what limits its use. I think that there has been a lot of modification when it comes to how to put the device in, but clearly if there's someone who has ocular surface disease or if they have a thin conjunctival or a Tenon's capsule or they are eye rubbers, these are people who may not be the best candidates for this particular device.

Darius M. Moshfeghi, MD:

Which kind of brings us back to the TKIs before we complete here. And this is a big year. We just had the first pivotal trial readout, which was a successful outcome for axitinib for the TKIs, and we're going to have probably two more readouts for the vorolanib later this year. These are small molecules that are taken up intracellularly, and then they kick in variably over 4, 8, 12 weeks. And then, theoretically, at least in the case of vorolanib, and it has been demonstrated now in a superiority trial that axitinib can give you this long-term suppression of VEGF. And it has two advantages, theoretically, over either the surgical implant or the gene therapy approach, and that one you don't have to have surgery, which is nice. And then the second advantage is you don't have to worry about the off-target effects and long-term theoretic problems affiliated with gene therapy. We're going to learn

more about this in the coming weeks as this data are presented at the Macular Society and we learn more about the totality of this data. It's an exciting time to be here in retina today in 2026. We're on the cusp of really dramatically transforming our patients' lives.

But that's all the time we have today. I want to thank my colleague Joe Coney for his astute insights and clinical expertise as well as his leadership on advocating for all of our patients, making sure that they're equally represented in our trials and that they have equal access to our pharmaceuticals as well as clinical care. And a special thanks and shout out to Natasha Caudill for helping in the planning of this activity and providing our patient perspectives.

By way of summary, I'd like to offer three SMART goals. SMART stands for specific, achievable, time-limited, measurable, and relevant. Within 3 months of completing this activity, implement at least one enhancement in screening or diagnostic workflow for AMD, diabetic retinopathy, or inherited retinal diseases, such as adjusting follow-up intervals or standardizing documentation of disease severity, in alignment with guidelines. Incorporate a structured discussion of at least one social determinant of health—for example, transportation, caregiver support, financial barriers, health literacy, language—into treatment planning for patients with retinal disease and also document it in the medical record. And then improve confidence in explaining to patients how blood–retinal barrier dysfunction contributes to disease progression and how emerging therapies are designed to address specific pathophysiologic mechanisms.

For additional resources, please visit the CME Outfitters website. You can also visit the CME Outfitters Virtual Education Hub. To receive credit for today's activity, please complete the post-test and evaluation, and thank you for participating. Both Joe and I and Natasha appreciate your patience and attention.