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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Enhancing Collaborative Care in Retinal Diseases: A Focus on Injection Therapies

Dr. Sambhara:
Let's briefly go over the learning objectives for today. Today, we hope to integrate key features on imaging with pertinent patient-specific factors to inform referral decisions for retinal diseases. We're going to discuss strategies for effective patient education on the importance of timely intervention and sticking to treatment for retinal diseases, and we're going to focus on cultural competencies, which is sometimes really overlooked in our eye care practices, to help improve communication skills, to better address patient concerns and decision-makings in retinal disease care. And finally, we'll talk about how we can do it together in a collaborative manner.

So in order to understand what we're up against, it's really important to understand the epidemiology of retinal disease and also why early intervention is so important. So let's stack the deck of cards here. Just in the United States alone, almost a million and a half patients have advanced AMD, and that's defined as either geographic atrophy or neovascular disease. And nearly 2 million Americans suffer from vision-threatening complications from diabetic retinopathy, which include both DME, diabetic macular edema, as well as neovascular disease or proliferative diabetic retinopathy. And this isn't a monolith here by any stretch. We do have regional and geographic hot spots across the United States for both diseases, and in Wisconsin, where I'm located, we know that there's a higher preponderance of patients with both diabetes as well as AMD.

But the one thing that seems to be common, no matter where you are and no matter what background you come from, across race or ethnicity, is that diabetic retinopathy does seem to get worse based on age. And the older you are, the more likely you're going to have ocular manifestations of your underlying systemic condition of diabetes.

And so why is this important? It's because we know that these are both treatable diseases, meaning diabetic eye disease as well as macular degeneration, and when you reach the point to where intervention needs to happen, at the level of the retina specialist, many times it involves serial anti-VEGF injections; for some patients, as many as monthly shots annualized, which could be as much as 12 injections a year. And so it's no surprise as to why patients may fall off, there may be caregiver fatigue, and quite frankly, even provider fatigue. And there has been published literature that suggests that upwards of 40% of patients discontinue treatment with anti-VEGF therapy because of some of these factors.

And at the end of the day, vision remains king. We treat retinal disease in the current iteration with serial injections, which leads to bolus dosing and pulsatile anti-VEGF therapy, which can lead to fibrosis and atrophy over time. And so this sets up a vicious cycle here: frequent injections and the need for continual care can lead to patient and caregiver burden, but it also can lead to missed clinic visits and suboptimal long-term outcomes. In fact, upwards of 25% of patients may fail to follow up and be lost to follow-up because of what we're seeing on the left-hand side of the slide, and we have to understand that these statistics are amplified in minority communities.

And so what are the actual consequences of not being treated in a timely fashion? We don't have to look far or hypothesize; we can go back to pivotal clinical trial data and extension studies to really hammer the point home here. We know in the pivotal RISE and RIDE

studies that helped get ranibizumab its label for treating retinal disease is that in the open-label extension period where patients were then treated via a PRN dose schedule, as patients weaned off of the study into the OLE, the open-label extension, and back into real-world treatment, we see that vision actually suffers because of undertreatment, typically due to treatment delays.

And this was also seen in the pivotal CATT studies, the Comparative Avastin Treatment Trial, which compared bevacizumab head-to-head against ranibizumab monthly dosed, and showed that they were similar in visual outcomes, which was great because that was a 2-year study. But what happened at the end of CATT was the open-label extension, known as HORIZON, and then a follow-up study subsequently called SEVEN-UP.

And in HORIZON and SEVEN-UP, patients were treated via a relaxed PRN treatment regimen, treated based on physician discretion. And what happens when we take our foot off the gas pedal? There's no more damning slide than this one here. We see that at the end of CATT, patients gained vision, but through HORIZON and SEVEN-UP, typically due to undertreatment, as patients were treated via a relaxed PRN schedule, they lost vision. All the initial vision gains that happened through the 2-year period were all wiped out during HORIZON and actually during SEVEN-UP.

And what we found was patients ended up with even worse vision than where they began during the study period. So this just lets us know that undertreatment leads to vision loss.

We also know that retinal thickness variability is no good. The pulsatile saw-toothing anatomic variability that we see in diabetic eye disease as well as in macular degeneration is no bueno and no good for the retinal anatomy, which leads to poor visual outcomes. In fact, Veeral Sheth and colleagues published this recently, which showed that if you split retinal thickness variability and fluctuations into quartiles, the retinas that ended up with the poorest vision typically had the most amount of fluctuation.

And so the bottom line is that this leads to the idea of needing more durable care. If we look at data from the European Union, only about 60% of patients actually follow up with their subscribed treatment intervals for macular degeneration. And when we look at what US retina specialists want and desire, based on the ASRS practice and trend survey that's published annually, over 80% of US retina specialists say that they undertreat due to scheduling limitations, patient noncompliance, or provider preference. And that's just a terrible thing that we kind of regress to the mean or to the lowest common denominator, even though we know that undertreatment leads to vision loss.

And we can look at real-world data from the Vestrum Health database that really shows that and illustrates it well. Tom Ciulla published this recently, which shows that over a 3-year period, if you count up and quantify the number of injections that are given in macular degeneration patients, it correlates with vision outcomes. The patients who ended up with the higher number of injections over that 3-year period had better vision. And it's a linear association, as you can see in this slide. The more you're treated, the better off you are in the long run.

And so we really need to figure out why this isn't happening in the current state. And in order to better understand that we need to optimize how we refer patients, when we refer patients, and who are the patients that need to be seen urgently versus patients that need to be seen in a less urgent fashion.

And that also dovetails with how we communicate effectively with our patients. Because really the conversation about how acute a situation is, how important the need for follow-up is, happens at the time of referral, well before a patient has ever been seen in my clinic or in a retina specialist office, and so we have to understand the barriers for initiating care and adhering to care. We also need to be culturally sensitive, because, again, these diseases affect everybody, and not just 1 specific demographic. And so we want to be culturally sensitive and competent to socioeconomic disparities or determinants of care and provide support in order to try and minimize any of those blind spots we may have. And then we want to be able to pass the baton off to the retina specialist, where we're able to help simplify things, provide support, and embolden caregivers to make sure that we can create a culture of compliance. And by creating a community between the patient, the retina specialist, and the referring doctor's office, we can help maintain compliance, minimize loss to follow-up, and maximize patient vision outcomes.

So let's transition to talking about how we can optimize referral to the retina specialist's office. In order to better understand who to refer, we should really split it up based on common, ubiquitous diseases that exist and make up the vast majority of what we see in a retina specialist's office, and that includes diabetic retinopathy, DME, retinal vein occlusion, and AMD.

Now, we're going to talk about these conditions individually, but I think the take-home points here, broadly speaking, is that when we see high-risk proliferative diabetic retinopathy, that is a patient who needs to be seen urgently, because if treated promptly, that is still a medical patient that could potentially avoid surgery.

And when we look at center-involving diabetic macular edema, that should involve a prompt referral. As we talk about retinal vein occlusions, BRVO and CRVO are a little different than one another, and the retinal vein occlusion fundus photo that we see up here is more likely an ischemic vein occlusion. It's an ischemic central retinal vein occlusion, and that is probably something that involves more prompt referral. AMD, whether we're talking about geographic atrophy or neovascular AMD, again, it varies in terms of the urgency. GA, probably less urgent. Neovascular AMD, time is tissue, we want to see those patients urgently. So let's dive into the specifics of these disease states.

So when we talk about categorizing diabetic retinopathy, there are many different scales that we can use to talk about DR. In the modern era, we use DRSS, or Diabetic Retinopathy Severity Score, which is a numerical scale that's typically used in the clinical trial setting. But in day-to-day practice, a lot of us are still using diabetic retinopathy grading based on the original ETDRS studies from a few decades ago, and we can actually use that to make a quick and dirty estimation of somebody's diabetic retinopathy status, the presence of microaneurysms alone being mild NPDR, the presence of more than just microaneurysms, peripheral hemorrhages, causing moderate retinopathy. And we've all probably heard of the 4-2-1 rule from the ETDRS studies that help classify severe NPDR. Intraretinal hemorrhages in all 4 quadrants, venous beating in 2 quadrants, or the presence of an IRMA, intraretinal microvascular abnormality, in >1 quadrant, and that would be indicative of severe NPDR. And then we have proliferative diabetic retinopathy, which is either the presence of neovascularization by itself or with vitreous or preretinal hemorrhage. DME, which is a separate pathology, can happen at really any stage of diabetic retinopathy.

And so based on American Optometric Association, ADA, and ICO guidelines for follow-up for diabetic eye disease, it's important to understand that a type 2 diabetic really needs to be seen for a screening visit at the moment of diagnosis. With type 1 diabetes, the recommendation is to be seen within 5 years of diagnosis, because typically that happens earlier in life.

But when it comes to follow-up and referral, we really need to parse out the severity of disease in order to understand the follow-up regimen for both diabetic retinopathy as well as vision-threatening DME. And in somebody who does not have any apparent retinopathy, that is somebody who can likely be followed annually. But once you start seeing signs of DR, we should really keep a closer look on the situation and a pulse on that patient much quicker and sooner. So annually to biannually is fine for mild NPDR. When you get to moderate NPDR, we're talking about biannual visits to quarterly. And in severe NPDR, because there is this ischemic drive for possible neovascularization, we want to see those patients more often than every 3 months. By the time a patient converts to proliferative diabetic retinopathy, that is a patient that needs to be referred to a retina specialist. And if they have low-risk disease, probably within 2-4 weeks. And high-risk features, which we'll talk about in a minute, are consults that we want to see much more soon and urgently.

Now at any point in disease, as I said, whether it's moderate to severe, DME can occur, and it's important to understand whether somebody has center-involving DME or not. Typically, center-involving DME will cause drops in visual acuity, and you'll typically see at the foveal center point, edema on OCT and multimodal imaging. Those are patients that really need to be referred to a retina specialist, versus non–center-involving DME, doesn't necessarily need to be referred urgently; those patients still need to be seen, but I think that it's fair to monitor those patients. And I find that when you show a patient their imaging and you show them what a normal OCT looks like, and then you show them what their OCT looks like, it can work very well in enforcing a closer follow-up schedule and regimen.

Now, the one thing I want to add here is that there are biomarkers that really portend closer follow-up or earlier referral. The presence of lipid exudates or hard exudates on fundoscopic examination or hyperreflective foci, which would be the OCT correlate, really speaks to chronicity of disease. And when you see yellow, hard exudates that approach the parafovea or get closer to the fovea, those are patients that really need to be seen, because once foveal exudates occur and you have hard exudates at the fovea, that typically leads to photoreceptor atrophy, scotomas in vision, and permanent vision loss. We want to really avoid hard exudates in the parafoveal and foveal area. And the one thing we know is that intravitreal therapies typically do a good job at drying up hard exudates. And so when you see hard exudates, it speaks to chronicity of disease, but also potentially importance for referral.

So what is high-risk PDR that needs to be referred? Well, it's the presence of any of the 3 following, which is neovascularization at the

disc that's >1/4 to 1/3 the disc area size; neovascularization elsewhere, which is at least 1/2-disc area in size; or the presence of vitreous or preretinal hemorrhage.

So let's go and transition to central retinal vein occlusions. Again, CRVOs and BRVOs are not all created the same, but the important thing to understand about CRVOs and BRVOs is that there typically is a systemic driver leading to these conditions. The same way that diabetic retinopathy is caused by systemic diabetes mellitus, RVOs typically have systemic risk factors that need to be optimized. And when we're thinking about it, blood pressure is, by and large, the biggest to think about. Hyperlipidemia is another one. Ocular risk factors would be glaucoma, for both CRVOs as well as BRVOs. And we also know from the old CVOS studies is that diabetes is a risk factor for vein occlusions. So we need to really pay attention to systemic comorbidities and optimize cardiovascular risk factors when patients come in with these diagnoses. The bottom line is that all RVOs are referable pathology, and the urgency really depends on whether it's ischemic or not, which is more likely in a CRVO but not unheard of in the setting of BRVOs, as well as the presence of macular edema.

Now it's important, as the primary eye doctor, to try to get the ball rolling. Get a letter sent to the PCP. If a patient has a known history of hypertension or diabetes or hyperlipidemia, still send a follow-up for the primary care doctor to follow up on those metrics to make sure that they're being treated and adequately managed. And if a patient doesn't have a known history of said diseases, have them see a PCP to get a workup.

Are there any CRVOs or BRVOs that make me pause a little bit? Yeah, for sure. CRVOs and BRVOs that happen younger and earlier in life, right? So younger folks who walk in with vein occlusions are ones I worry a little bit more about. There's a saying in medicine, when you hear hooves, you think horse, not zebra, but if you have a young patient with a vein occlusion, start thinking zebras. And by zebras, I'm talking about hypercoagulability issues and potentially getting more exhaustive blood work, or at least in concert with a primary care doctor, to rule out the weird and wacky conditions that might predispose a patient to getting a vein occlusion earlier in life.

So what are imaging modalities that we typically use to manage RVOs and, really, AMD and diabetes? It's fundus photography. Fundus photos, and really our funduscopic exam, to be quite frank with you, are going to be the most sensitive way to look for neovascularization. OCTs are great to help confirm the diagnosis, and when we're talking as a referral source, certainly FAs are more accurate than funduscopic exam to look for neovascularization, but assuming that the primary eye doctor's office doesn't routinely do fluoresceins, then we're really talking about fundus photos and OCTs, as well as OCTAs. FAs are still very valuable in a retina specialist clinic, but I find myself using them more in the clinical trial setting and less often than I'd like to because of the time it takes, as well as the comfort for patients and the fact that we run high throughput clinics, and that's where OCTA becomes very handy. And now OCTA is in a renaissance. We're not just seeing them in retina specialists' offices; we're seeing them in the referring doctors' offices too. And OCTA can give us much of the same information as an FA in a point-of-care setting that still is able to withstand the rigors of a busy optometric or general comprehensive ophthalmologic practice. We can look at flow deficits, we can see neovascularization, and we can get important information about whether a vein occlusion is ischemic or not.

So let's transition and talk about age-related macular degeneration. Diagnosing AMD is very critical, particularly when somebody is at the intermediate stage, because when somebody has intermediate dry AMD, the risk of developing both geographic atrophy as well as choroidal neovascularization is higher. The fact is, patients with intermediate AMD need to be seen more often, like 2-3 times a year, and we really need to hammer home the points about smoking cessation, diet and lifestyle modification, as well as AREDS 2 vitamin supplementation, Amsler Grid utilization. These are all preventative measures that the patient can take to try to decrease the risk of progression. Because we all know the conversion from dry to wet is not pretty. That is a very important disease to identify, because patients can lose vision, and they lose vision from subretinal fluid, hemorrhage, exudation, and eventually fibrosis, if not treated and identified in a prompt fashion. And so when I look at wet AMD, I look at that in my practice as being a ticking time bomb. Time is tissue. I personally want to see a wet AMD patient in <7 days in my practice, and we're usually pretty good about getting them in quicker than that.

So how can we clinically classify AMD? The presence of drusen, which is pathognomonic for a diagnosis of AMD, isn't necessarily always AMD. And what do I mean by that? It's not just the presence of drusen, but it's also the other features. It's the size of the drusen, as well as pigmentary changes, that help us prognosticate or stage AMD. The presence of drupelets, so small drusen, really fine drusen, is just macular drusen, not necessarily AMD. But the moment you start seeing drusen that are slightly larger, so <125 µm but >63 µm in size, you might say, well, how do I know how big that is? Look at a venule coming off of the disc, and the width and the caliber of that venule is about 125 µm. And so when you see a druse that's about the size of a venule, or just smaller, you know you're in that

range of 63-125 µm, and that's early AMD. Again, importantly, no pigmentary changes. But the moment you start seeing pigment modeling or clumping or a single large druse, you are now in the realm of intermediate AMD, which is at higher risk of progressing to advanced AMD, which involves either the presence of geographic atrophy or neovascular AMD. Again, nAMD should be a prompt referral.

So this is where multimodal imaging has really changed the game for neovascular AMD. In the era of multimodal imaging with first time domain and now modern spectral domain, swept-source OCT, we are able to tell differences in retinal anatomy to the micron level, the 1,000th of a millimeter level. And we can see in AMD, we see the presence of fluid, either intraretinal, subretinal or sub-RPE, the presence of a choroidal neovascular complex, and now with OCTA we can see that arterialized vascular complex in all its great detail, which you see on the image on the right here.

The fundus exam can also be very useful, especially when you see blood, because when we go back to the early CATT studies, we know that there are some poor prognostic features for wet AMD, or neovascular AMD, and that's the presence of blood on the fundus exam, the presence of intraretinal fluid. So this is a bad sign in this OCT, intraretinal fluid, large leakage on FA. These are all bad signs in the presence of fibrosis because that leads to scotomatous areas in vision. And so when we see wet AMD, we really need to get those patients referred in, because what we see on the fundus photo, for example, what we see here on where my cursor is, versus what that actual CMV looks like can be very, very different. For example, this fundus photo has fluid likely but no overt blood. But look at the size and complexity of that CNV complex. That is what we're fighting against. And the earlier we get these patients into our practice, the better we can inactivate or attempt to inactivate those CNVs.

So I see a question in the group chat: Do you usually treat severe NPDR with anti-VEGF? Or do you wait until PDR or DME develops? Would you want to see those patients sooner? What imaging would you like to see from their history? I think those are all wonderful questions. I think it really depends is the answer. We have great clinical data now to suggest that anti-VEGF can be used to treat diabetic retinopathy and actually lead to 2-step improvements in DRSS. And we've seen that both in the PANORAMA dataset for 2-mg aflibercept, as well as in the PHOTON dataset for 8-mg aflibercept, and we've also seen it in the Pavilion study for ranibizumab, port delivery system. We know that anti-VEGF can regress diabetic retinopathy severity.

I think in my personal practice, anecdotally, what I'll tell you is that we would open up the flood gates if I started treating every diabetic that didn't have DME but had diabetic retinopathy. I think I make a special exception for severe NPDR, because some patients who are high risk for conversion to PDR may actually benefit from anti-VEGF to quiet down the disease. And for me, I think it's use my best judgment. If a patient is noncompliant or seemingly a flight risk and may have a little edema, or maybe not clinically significant edema but significant enough retinopathy, talking about severe retinopathy, that is somebody that I may have that discussion with about why it's important to see them for follow-up.

Now I want to make a transition to talk about how we can be better communicators and better educators for patients. One thing I find still in my own day-to-day practice is, how can I take all that complex information that I know and that you all know, and how can we boil it down into easily packaged information that can resonate well with the patient? And by resonating well and by playing well with the patient, it's information that will encourage them to follow up. It's information that will embolden them and their caregivers to get their systemic risk factors under control. That's what we're trying to achieve here by educating and being better communicators. And we can all be better communicators. And I'm still trying to find new analogies, idioms, expressions that I can use to better educate patients. Because the reality is, we still have a problem with compliance and attrition and loss to follow-up, and we need to improve the blind spots we all may have.

And why does it matter? It matters because prompt referral really leads to better vision. Time is tissue, right? And when we look at underserved groups, particularly those in minority populations, we do a really bad job with patient adherence. And the reality is, the better we are at educating, the more compliant a patient is with following through with the referral, and the more compliant they are with continuing treatments or even initiating treatments. The better we are at communicating, the better we are at protecting vision.

Then why does it matter? If we look at a study of almost 1,300 “normal” eyes, who had dilated fundus exams, 1/4 of those eyes actually had AMD, and 30% of those eyes had referable pathology, referable AMD. And so it's important to try to figure out who we're seeing, what pathology can be managed in house, what pathology needs to be sent, and even if it doesn't need to be referred, what pathology needs to be followed a little closer.

The Vestrum Health database did a similar exercise, looking at folks with DME, and a >5 years of follow-up with retina specialists. And the reality is, from the moment they walked in, the vast majority had DME at their first visit, and almost 60% had fellow-eye disease or bilateral disease, meaning these patients may have been better served if they were referred slightly earlier.

And so we can all do a better job of getting patients in sooner, but also, how can we make sure they stick with treatment? The reality is, in the diabetic setting, it may be hard, because these are patients who are typically younger, who are working age, and these are also patients who typically have multiple comorbidities; they're sicker. People don't get diabetic retinopathy because of well-controlled diabetes; they typically get it because of poor control. And poor control is correlated with increased rates of hospitalization.

And in fact, if you look at hospitalized patients, almost 44% of patients in this one study had diabetic retinopathy, and 25% actually had DR that was undiagnosed, unbeknownst to them. 20% had vision-threatening diabetic retinopathy, so either NV or DME. And DR was 4X greater in the setting of comorbid renal disease. And I can't highlight that point enough, patients who are prerenal or who are on hemodialysis, those patients are sicker, and they tend to have much, much worse diabetic retinopathy and diabetic macular edema that sometimes is recalcitrant to anti-VEGF therapy, where you're just hammering away.

What is a prerenal patient? A patient who has creatinine values that are high, or creatinine clearance values that are low, those patients who are stage 2, 3 chronic kidney disease, the ones who are teetering on the level of hemodialysis, those patients who have diabetic retinopathy, hold them close and refer quick, because they can go south quickly. And in a world of jackhammers, I feel like we're using chisels when we treat them many times, because their diseases are so difficult to manage.

But what are the barriers for treating folks with chronic disease? It's typically there's a systemic disease, right? They might be too sick or have too many doctors' appointments. Many of these patients may have transportation issues. And the fact is, folks who are sicker tend to be underinsured or uninsured, as terrible as it sounds, and that typically runs with poor socioeconomic status, right?

And that really involves identifying cultural-specific barriers. And when we look at patients in the Hispanic diaspora, we know that those patients with diabetic retinopathy are more likely to present with more advanced disease with PDR, live in neighborhoods of lower socioeconomic status, have lesser education, potentially be unemployed, rely on financial programs, or have to pay out of pocket and be referred with higher A1c's and poor systemic control. We know that Black patients are less likely to be referred to an ophthalmologist or a retina specialist, and there are all sorts of barriers to care that dovetail with these facts that we see. The language barriers that exist, language is a huge predictor of poor communication and poor compliance. The budding medical costs associated with underinsurance or uninsurance, the financial stress, having to be able to choose between putting food on your table or having a roof over your head or having your eyes treated. That's a decision that we never want anybody to have to battle with.

So when you look at a national survey of patients with DR, what we found is that Black and Hispanic patients do feel that there could be a lack of respect due to past biases, less courtesy happening in the clinic, poorer service. And Hispanic individuals particularly have a greater challenge at finding childcare.

So these are blind spots that, when we are in the churn-and-burn trenches of our clinics, seeing a multitude of pathology in patients, we never want to lose sight of who we are treating and who is in the exam chair. We are treating, ultimately, the patient and not the picture, not the OCT, nor the wide-field picture or the fundus photo; we are treating the patient. And I have to remind myself constantly of that, because when I see 50, 60, 70, 80 patients a day, it can be very easy to lose sight of who the patient is that we're treating, and to be sensitive to some of the blind spots that I may even still carry to make sure that I can really hammer home the points of what we're doing, why it's important, and doing so in a collaborative manner with the referring provider as well as the patient caregiver or family member that may be with them.

This is also where telemedicine may come in. Telemedicine is using and deploying fundus photography as well as maybe even OCTs outside the retina specialist or comprehensive ophthalmologist or optometrist clinic setting. So maybe putting a fundus photo or an OCT machine in a primary doctor's office.

And so systems like this are not unique, and they've been springing up over the past several years. And what we found is now with studies, we can compare time to referral versus standard of care, normal dilated exams versus telemedicine exams, and what we find is that telemedicine can actually be quite cost effective. We especially see this in underrepresented regions and underserved regions where the eye care provider-to-patient ratio or in that region or country may be very low. So in the developing world, for example,

telemedicine is critical. But what it does involve is high up-front costs, right? You need to have the hardware, and so in settings where the hardware can be deployed, it's actually a phenomenal type of device to use.

And so telemedicine comes in many forms, whether it's home monitoring or actually telehealth that takes place outside an eye doctor's office and in a primary care setting. But the fact is, it is a way to identify and deal with bottlenecks that currently exist in the eye care offices.

But we also really need to improve patient-provider relationships, meaning I need to do a better job. As a doctor that sees many patients, we really need to try and do a better job to emphasize what the diagnosis is, why we're treating the patient, and showing them progress to help create that culture of compliance and reinforce the tenants of disease treatment and response to therapy.

And so in patients with nAMD or DME who receive anti-VEGF, we've seen studies that show that the doctor-patient relationship is really the primary driver for adherence, and the reason for loss to follow-up, or maybe undertreatment, is actually due to the injections themselves, so irritation, pain, discomfort. And we can do a better job to identify those barriers and tackle them. Like, hey, I get that this isn't comfortable, but look at where your vision was and look at where it is. I get that there is a little discomfort associated with the procedure we do, but look at the picture of where you started, and now look where you're at. Hey, you may have been <20/40, which is a great cutoff I typically use for functional vision. And now look, you're better than 20/40, you can still hold on to that driver's license. I think that there are many ways that we can provide feedback as a retina specialist to help hit home the point of why maintaining therapy with anti-VEGF is so important.

And so we also know that patient navigators and health coaches with transportation vouchers is effective, and this may not work in every setting. But what is a patient navigator? It's having the same point of contact at your office. So if it's the same person that's helping put the referral in, if it's my practice at the Eye Clinic of Wisconsin, following up with that patient to say, hey, did you end up getting scheduled? When's that appointment? Okay. Just a simple phone call from that scheduling office perspective can really do a good job at making sure that the referral actually takes place and the patient follows through. And from my side, it's my schedulers from the specialist office that call the patient to let them know when their appointment is, but not just that—24 to 72 hours prior to the appointment, calling them and letting them know, hey, this is why you're coming in, there is a chance you may require an injection, so come with a driver, really setting the stage so that the patient doesn't have to have a delay in care and that we can get everything done on that initial consult itself. And we know that if we do that, we have a better job and a better likelihood of getting patients in and seeing patients for subsequent appointments. Patients are way more likely to attend follow-up if we just give them that little TLC when it comes to encouraging coming to that first visit and also reminding them for follow-up.

So we also need to manage fears, right? And this is where I think my referral source in North Central Wisconsin does a fantastic job. When I walk in the room, it's really easy because I have fantastic optometrist colleagues and ophthalmology colleagues who really already set the stage. Hey, you've got diagnosis X, it's going to require treatment Y; in many cases, that's intravitreal therapies with injections. And dispelling some of the concerns off the rip, before the patient's ever in my office and exam chair, is amazing, and I can't thank my referral sources enough for really planting the seed and doing that very difficult work on the front end, because when a patient walks into my office, it's the first time I'm seeing them. And when I'm seeing as many patients as I am, although I try and spend more time and provide more TLC with a consult, I'm always going to be playing from behind, because I don't yet have that longitudinal relationship. I don't yet have that trust that you, the referring doctor, have with that patient, having had seen them potentially for years. And so for that, I'm utterly thankful, because you guys do a great job about acquiescing a patient's anxiety and fear when it comes to getting an injection in the eye, letting them know this is a quick procedure. You feel pressure, not pain; it won't be sharp. You can play a video if you'd like that shows them what it's about and dispel any myths, like, listen, the exam light is only for a little bit, the retina specialist keeps it low. And then also providing personal follow-up. And I don't necessarily expect you to do that as a referring provider, but certainly as retina specialists, it's great when we're able to touch base, or our staff is able to call and follow up with the patient and let them know, we're here for you, but also solicit some feedback and ask them whether it was as bad as what they thought it would be. And I think when that typically happens, patients are more locked in, more likely to follow up, and we just have a better overall experience.

And so ultimately, we just need to understand that we all have blind spots. We need to pay attention to what those are in our specific regions and areas and understand that those patients may need a little more TLC. We want every patient to get to the same rung on the ladder, but not all patients start with the same resources, and some patients need to be pulled up 2 or 3 rungs to get to that same space and that same spot.

So what are specific cultural barriers that exist in North Central Wisconsin? Although we do have seasonal migrant Hispanic workers that are in our region, there is a particularly high preponderance of Hmong Asian people in North Central Wisconsin. It is the largest minority in our geography. I believe 10% of the population of Wausau is Hmong Asian people, and I can look no further than my clinic. Just a couple of hours ago, I saw a non-English speaking Hmong patient who had a new diagnosis of severe NPDR bilaterally with DME. And one thing that worked well, because that patient came alone, was using interpreter services. And we have a fantastic video iPad interpreter service we use that got me on the line with a native Hmong speaker who was able to help communicate effectively my sentiments.

And I want to be very clear about using interpreters. One thing that I found to be very helpful is don't talk about the patient when you're using an interpreter, right? The discussion is between me and the patient. It's not between me and the interpreter. So don't speak to the patient in third person or about the patient to the interpreter. For example, don't say, can you tell him he needs an injection in the eye? No, that's not how you want to do it. It's best if we talk directly to the patient and pause to let the interpreter do their job. We want this to be a back-and-forth conversation with the provider and the patient, not with the provider and the interpreter. And so and that's exactly what I did today.

The other thing I did today, and what I try and do in general, is encourage the patient to bring family for follow-up, because when a patient comes by themselves, if they don't speak English, we're bombarding them with a lot of information about a severe diagnosis that can cause vision loss, and that is causing vision loss significant enough to merit intervention. So we want to make sure we can help communicate effectively, not just to the patient, but family members if they can be present for subsequent appointments, if they're not there at the initial consult, because, again, it takes a village.

So with that, I want to transition to supporting treatment adherence and preventing loss to follow-up. How do we do that? What's the secret sauce? Well, we really want to understand what those risk factors for nonadherence are, and there is a plethora you can see listed here. There are tons of reasons, and there are probably reasons that we haven't thought of that are not listed here as to why patients may have barriers to care. And the reality is we need to understand and be mindful and cognizant of all of them.

Early in my career, I would almost shame patients for not coming in, and it didn't take too long for me to realize that sometimes the system isn't set up for the best outcomes for patients. And we really want to do our best not to parent patients, but to be encouraging and let them know that, hey, we can't change what happened, but we can control what happens in the future, right? No sense in playing Monday morning quarterback and to shame somebody for not coming in and having a poor visual outcome or a vision-threatening event because of lack of follow-up, but better understand why that happened, do a root cause analysis so then we can better equip that patient with the knowledge going forward of why it's important to follow up and let them know that we will still do the best we can for them.

And so how do you do that? Again, appointment reminders that we talked about really work well, and we've seen that published in data, especially with minorities like Black and Hispanic patients, as well as the underinsured populations and the poorly insured populations, that when you just add a text message in a day and age when everybody has a cell phone, a text message reminder can really do the trick. EHR messaging was also important in ensuring follow-up after that initial consult visit.

And culturally tailored patient education has also been shown to be important. This is not an eye-specific program, but the Latinos en Control program really show that when you try to come at disease state education at the level of the patient, using terminology and culturally appropriate tools, we can actually lead to better compliance, lower A1c's in this case, a diabetic population, and better overall care for the patient.

But caregivers are such a big part of the equation, and so we know that caregiver adherence, meaning having caregivers as a part of the conversation and discussion, help drive patient adherence and compliance with both treatment and follow-up.

So how do we optimize communication between all the different doctors that exist? I think we've got to invest in education on those initial visits, utilize handouts and videos, also really have the caregiver involved and patient family involved. If we can talk about financial assistance programs off the jump as the specialist, we can really acquiesce any fears about patients not being able to afford care. And when we can provide encouragement, don't gentle parent somebody, give them the real encouragement and be glass half full as to what their visual situation is and why it's important. And emphasize the wins, no matter how small they may be. And it's important to minimize treatment burden, especially with the advent of newer, more durable therapies.

So again, we talked about the importance of care coordinators, patient navigators, that same follow-up person who can help let the patient have a continuity or a point person who they go to that provides that continuity of care. And when we do that, we know that patients are more likely to follow up. And again, you guys are the first line of defense. As the general ophthalmologist or optometrist, you guys do such an incredible job at managing eye disease. And so it's just providing that continuity of care, reinforcing when somebody has referable pathology, don't just stop at the fax machine when you fax the referral over to the specialist. Also try and reach out to the patient, ensure that they have a follow-up scheduled. And make sure that when you see them for your routine follow-up, let them know that, yeah, we're in communication. If you don't see a follow-up note for me or the retina specialist, ask for it, and that way we can tag team patient care in a more effective manner.

Simplify treatment. Most retina specialists treat via a treat-and-extend paradigm, and that's much easier now, because we can reach hemispheres and stratospheres of extension that were previously never thought of as being achievable with last assigned dosing regimens from clinical trials as long as 20 or 24 weeks with these new second-generation agents faricimab and aflibercept 8 mg, as well as the promise of extended durability as long as ≥6 months with the implantable surgical port delivery system device. We are in a renaissance of retina, where we can get good vision outcomes with fewer treatments overall.

So let's talk about FARETINA, the DME study. What we see in FARETINA is that the number of injections that happen over the first 6 months in DME-treated patients through 2 years decreases over time. And the one slide that we don't have up right now from FARETINA is patient vision. Because you might say, “Well, didn’t you say, Doc, that there's provider fatigue and patient fatigue and caregiver fatigue? Maybe that's why these patients are not being treated as often.” And what I would tell you is, actually, if you look at FARETINA-DME, these patients are being treated less often because they have stable disease. They're being treated less often and maintaining vision gains, which is amazing. And we've seen that also in the FARETINA-AMD sister study for macular degeneration, similar vision with fewer injections over time with faricimab.

The real-world data from IRIS investor Nitish Mehta presented this recently, and it's looking at aflibercept 8 mg in the setting of neovascular AMD, especially in switch patients. So patients switching from a first-generation agent to aflibercept 8 mg.

And what we see here is that those patients in IRIS and Vestrum who were then transitioned to 8-mg aflibercept ended up with extension, on average, about 3-4 weeks longer. And when you look at the ones who are still treated with a high frequency but maybe not as often as 4-6 weeks, like the one 6-8 weeks or greater, they gain 2-3 weeks of an additional durability based on IRIS and Vestrum data.

What about the port delivery system? We know from clinical trials that this has the promise to unlock levels of durability never seen before in both DME, diabetic retinopathy, as well as in neovascular AMD. We've seen that in Archway, in Ladder, in Pagoda, and in Pavilion for diabetic retinopathy. We know that the port delivery system, the ranibizumab port, was FDA-approved several years ago, voluntarily pulled off market to optimize the actual implant and the refill injector, and now what we see is that it has double the overmold strength, so we don't see some of the issues you may have heard of initially on deployment and launch, and now the refills are also easier.

But why is it important, PDS? I think the graph that we see here really demonstrates why PDS is so critical. Because in patients in Pavilion who received PDS, they did not require supplemental treatments based on the criteria we see here on the left and in Pagoda for DME. And so this was the re-treatment criteria, actually, for Pagoda, and we didn't see heavily re-treated patients in the clinical trial, to the tune of like ≤5%, meaning these patients could go ≥6 months without their mandatory redosing. And the reality is, in the real world, some of these patients go far longer than 6 months. So similar vision, outcomes, fewer injections.

In Wisconsin, the way I help support follow-up is having a care team that really reaches out to patients to help map out their clinic appointments, and it starts at the check-in and check-out desk. When a patient checks in, not only are they checking in for their appointment, but they're being reminded of their following appointments. And if they don't have a follow-up, they're being reminded to stop at the check-out desk to make that follow-up appointment.

And when patients are making follow-up appointments, they're not just making 1 appointment with me, they're being asked if they have a follow-up appointment with their referring eye doctor. And if they're referring eye doctor’s internally, we can see if they're due, and we try and make that as well. So we really want to make sure we catch these patients and encourage them to show up for follow-up.

So I want to end with key take-home points from our talk today. Really lean into multimodal imaging, as well as patient-specific factors to help guide who to see and when to see them, meaning who to refer and when to refer them. We really need to do a better job at educating ourselves on our own blind spots to better help spend a little more time with those who need it most, understand socioeconomic determinants of care, understand the barriers to care that may exist, and try to smooth them over as much as possible. And we really want to leverage the team in its entirety, the patient, their family or caregivers, yourself, as well as the referral doctor, the retina specialist, and primary care doctor or endocrinologist, to better optimize patient outcomes.

With that, I want to end with any questions. And it looks like we have one final question. For patients who present for the first time with advanced disease, who may not understand how advanced their disease is, how do you get them up to speed and buy into aggressive treatment off the bat? I think that's a fantastic question. And in fact, that was literally my scenario today. A couple of hours ago, I had a patient who was non-English speaking, I was using an interpreter, and they were coming without any family. They actually had to go to work. They work in a factory; they had to go to work or wanted to after their appointment. I think for many patients who, quite frankly, have severe disease because they haven't had an eye exam recently, they come in and they just think it's a quick Band-Aid. “Just give me a refraction, give me a pair of glasses, and let's fix it.” When the reality is their disease is much more advanced than that. And the best thing for me, that I find that works well, no matter if you're English speaking or not, is showing a patient what a totally normal retina looks like, or a totally normal fundus photo looks like, and then showing them their OCT or their fundus photo. And I think that sometimes that can, at the very minimum, help encourage closer surveillance or follow-up, or at least quicker initiation of care.

So with that, I want to thank you for your time. Thank you for spending your evening with me. Good night.