Advancements in Diabetes Seminar
Clinical Advancements in Diabetes Eye Care

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Dr. Mark Horton:

I am optometrist and subsequently trained as an ophthalmologist and came to the IHS in somewhat of a circuitous process in 1986 and then doing a lot of things out here, but really what has been -- so I spent most of my time here for the past decade or so has been this program. And it's been a very successful program. And the JVN Teleophthalmology Program is one of the largest and highest performance teleophthalmology programs in the country if not the world. So, this has led to an opportunity to have a presence in Indian Country regarding diabetes eye care in general and perhaps making the eligible tips, to chat a little bit to the group about that.

Let's see if I can make this work here. Now, of course everybody in this room knows the information on this chart that the Native Americans have one of the highest prevalence rates of diabetes in the country. The endemic nature of the diabetes in Indian country is paralleled by an endemic of diabetic eye disease, making this an entirely appropriate subject for this group.

Now, just as diabetes touches every cell in the body, it touches every cell in the eye. And there can be ocular complications from diabetes from every piece that you can see there from beginning with the lids all the way back to the brain. But when we're talking about -- usually, when people talk about diabetic eye disease, what they really mean is that the disease, the complications of the disease in the retina and even more specifically, they tend to be talking about retinopathy and maculopathy. So, if I can beg the indulgence of the group to kind of contain or corral the notion of diabetic eyes disease, means not all the many, many individual conditions that it could be, we're going to be talking about retinopathy and maculopathy for the most part. But please understand that diabetic eye disease is really a broad spectrum of disorders.

Now, diabetic retinopathy, it occurs in virtually all diabetics eventually. We've done a great job in allowing our patients to survive their diabetes and this has made them increasingly vulnerable to the complications of diabetes. And diabetic retinopathy is the leading cause of new blindness in working-aged adults. Now, that occurs despite the fact that blindness due to diabetes can essentially be eliminated by timely diagnosis and treatment. So, you got to say though, "Wait a minute, what the heck is going on here? It's the leading cause of new blindness, but it ain't got to be." And the reason for that is this graph down here, about half of Native Americans and Alaskan Natives with diabetes do not get timely diagnosis and treatment. And of course, there is more to it than that. But fundamentally, the single largest reason why diabetic retinopathy continues to be the leading cause of new, severe and moderate vision loss among working-aged adults in our population and outside Indian Country

is simply the cause that folks are failing standard of care for diagnosis and therefore, they can't get the timely treatment.

Diabetic retinopathy is merely preventable, by simply adhering to accept the standards of care and best practices. So, we'll begin -- first, we'll begin with identify all patients with diabetes. There is a significant fraction of the population that doesn't know they have diabetes. But first is to identify the folks with diabetes, control confounding factors and comorbidities, diagnose the level of diabetic retinopathy yearly and of course, that's what we're talking about, an annual diabetic retinopathy examination and apply timely treatment.

If we do that, if we do those best practices, then folks can find another reason, the current second reason for vision loss, but it does not have to be diabetic retinopathy. Here is the process, there has to be a well-working team including the primary care diabetes team and the eye care team lead to systemic control of the diabetes and timely/early diagnosis and treatment. We'll talk a little bit about why there is a distinction between those because we don't -- currently, we do not treat diabetic retinopathy until it's in its advanced stages but there's going to be some issues. I'll discuss later on in the discussion that suggests that maybe we should begin treating diabetic retinopathy early rather than late.

The minimum standard of care is an annual eye examination. So, if you're a diabetic and of course, we're dealing with type 2 diabetics almost exclusively but not exclusively. But with respect to type 2 diabetes, as soon as you have the diagnosis, it's an eye exam right now and one every year and more frequently based upon the severity of diabetic retinopathy.

Now, what we are trying to do is we're trying to diagnose the severity of diabetic retinopathy and hoping to find the severity level of zero. No diabetic retinopathy, but we look in the back of the eye, we look at the retina and we identify all of those things you see written up there. And we organize diabetic retinopathy into two buckets primarily. One called non-proliferative diabetic retinopathy and another one called proliferative diabetic retinopathy. Now, these exist on a seamless continuum. And one goes to the other, but proliferative diabetic retinopathy is the final tunnel pathway to blindness in patients with diabetes. Diabetic macular edema can occur in both categories, but the good news if there is any good news about this is that usually diabetic macular edema is a source of modern vision loss, not severe vision loss or blindness.

Now, the diabetic retinopathy has been very well studied and categorized in the multiple or very fine levels. But when we diagnose it clinically, we group it into these categories based upon the diabetic lesions that we see in the back of the eye, how many we see, what kind they are and where they are situated. Now, I'm not trying to make everybody into an eye doctor today, but I wanted you to have some basic understanding of how we talk about diabetic retinopathy and diabetic macular edema. Diabetic macular edema exists either in a mild or severe form and the mild form that we call not clinically significant, and the other one, cleverly, is clinically significant and the clinically significant is what we treat.

Now, the standard care as I mentioned is an annual diabetic retinopathy examination unless you have a severity level that's high enough to warrant something other than that. And so, it actually can be more frequent than that. So, you can see how we adjust the periodicity of the examinations based upon the severity level. And here are some severity levels for you to see. And once again, just for completeness, you cannot be an eye doctor and not have some eyeball drawings. So here you go and you could see how as you move from mild to moderate

to severe, you can see how you need -- you see more lesions. And that's basically how we do it. We look at the lesion, and add them up and categorize them and turn that into a diagnosis. And these lesions down here, the one I'm pointing to here and the next one, this is proliferative disease, all these little fuzzy things here are when new vessels grow in response to the ischemic effects from the diabetes and this is the final common pathway to blindness. And this is an example of diabetic macular edema, but of course, they all don't look like that. But I just want you to get a hint of what it is we're seeing when we look in the back of the eye. Now, please know that diabetic retinopathy has been very carefully studied, and we know a great deal about it, we know how to diagnose it, we know how to treat it, what to expect when we do treat it.
And what we can do other than an eye surgery to influence the progression of diabetic retinopathy, and we're going to talk a little bit about that a little bit.

And here is a key study that was done, the DCCT, the Diabetes Control and Complications Trial that looked at standard versus intensive control. And understand that in 1983, standard versus intensive control was defined a little differently. You can see that we don't call standard control 7.9 A1C anymore. But just to understand that this is what they were looking at in this study. And what was shown was that intensive control was good for diabetic retinopathy. With no baseline diabetic retinopathy, you can see these two tracings that with standard control, the onset, the prevalence was here or the incidence was here. And with intensive treatment, it was much, much slower. So, this is good news and there are things we can do to kind of slow down the onset of progression of diabetic retinopathy that doesn't have anything to do with laser beams in your eye. So, this shows a 36% reduction with intensive control as defined by DCCT. And even if you wait until the patient showed some mild to moderate diabetic retinopathy, there were still significant benefit to the patient by intensive control of their glucose. So, if there was intensive control, overall, there was about a 50% reduction in the progression of diabetic retinopathy and development of severe disease, proliferative disease that required treatment and at 59% or 60% or so, reduction in the need for laser surgery.

Now, this impact affected other end-organs as well. As you can see, the microvasculopathy that results in the retinopathy, nephropathy, or peripheral neuropathy was favorably impacted in DCCT by intensive control. Once again, let me remind you what they call intensive control back then is not what we do now. Now, this study was continued for another 10 years called the EDIC Study. But look at the long-term effects of intensive treatment and look at the complications. And what was shown is that they were long-term benefits that were proved here. And in fact, there was a metabolic memory that even after the study was discontinued and there were some slippage in the control of the glucose, that there was some sort of memory that protected the patient in the future. So, in this sense, knowing something about the patient and starting interventions early that's basically behavior changes in the patient to get better control of the glucose can have some long-term benefit even if a long-term control is always maintained. Once the processes is leading to microvasculopathy are initiated, they tend to be self-perpetuating. So, we need to be thinking about the benefits of early control versus waiting for a patient to reach threshold for laser surgery, and because that occurs late.

Now, the UKPDS, UK Prospective Diabetes Study was a very similar study that was done on type 2 diabetes. But they also looked at standard versus intensive control of blood pressure in addition to glucose and found familiar outcomes. There was a significant decrease in progression of diabetic retinopathy and need for surgery when we reduce the glucose and the blood pressure. In fact, blood pressure control was almost as important as glucose control for

doing this. Once again, there were legacy affects for the A1Cs, but not much of the legacy effects for intensive blood pressure control.

So basically, the focus of primary care department taking care of these diabetics every day are treating their diabetic retinopathy. So, the real treatment for diabetic retinopathy occurs early in the course of the disease by the primary care providers of diabetes care chain. So control the blood pressure, control the glucose, control the lipids and there will be decreased risk for diabetic retinopathy development progression and need for laser surgery or the other forms of treatment that have been developed more recently.

Now, the pathophysiology is the elevated glucose that leads to vision loss both in a moderate and severe category. Now, we'll just very quickly run through that. Let me just show you that with hyperglycemia, there is endothelial damage, there is also some changes in the way blood cells flow in the vessels, there's oxidative stress on the tissues and inflammation. And this results in vascular permeability, when vessels get leaking, not leaking blood but leaking fluid, causes retinal edema, macular edema and moderate vision loss. Now, moderate vision loss is a level of vision loss that you can seemingly function well, but you may not be able to drive because you can't keep your vision necessary for a driver's license, that sort of thing, but you're not blind.

However, the same process from the hyperglycemia can also cause the blood vessels, the capillaries to occlude. This generates a cascade of chemicals that are elaborated, that leads to new blood vessel formations. And these new blood vessels, new vascularization is incompetent, they break, they bleed, they cause vitreous hemorrhage and scarring. Ultimately, retinal detachment and that is severe vision loss, that's essentially blindness. So these are the two mechanisms for both moderate and sever vision loss, and these are the pathways.

What I'm trying to show here is vitreous hemorrhage, retinal detachment and macular edema. Here are the ways that we lose vision from diabetic retinopathy. And we know from the early treatment diabetic retinopathy study that we can treat with a laser beam and we strategically put in lasers, apply these laser burns to the retina, and that protects the patient from severe vision loss. In fact, if you compare untreated high-risk disease to a low risk disease there is a profound decrease, about a 95% decrease in the incidence of severe vision loss, essentially blindness with untreated high-risk disease versus treated high-risk disease. So, this is why we have to diagnose these patients in a timely fashion, treat the patients when the treatment is most effective.

Now, more recently, we have drugs that we can actually inject inside the eye to influence the pathological mechanisms to vision loss. And most -- what I'm showing here is injections that are used primarily for diabetic macular edema. And when these drugs are injected in the eye, they cause the blood -- the leaky blood vessels to be less leaky and protect the patients from moderate vision loss. But some of this treatment is very pricey, as you can see there. So, the treatment can be anywhere from a thousand to almost $2,000 or some that last --have a duration of up to three years, that's almost $10,000. And these other treatments, you need to know, it's not one and done. There are multiple doses that occur over a period of months. So, this is very costly but it is very effective in preventing moderate vision loss. And this is the primary area where we use these intravitreal injections. Although, they can be used in proliferative diabetic retinopathy as well.

Now, when all else fails or if we get to the disease too late, then we have to take the patient to the operating room and put instruments inside the eye and gobble up the disease. And that's what your screen is showing here. This is very costly. This is very costly for the health system. The outcome, it tends not to be quite as good as preventative treatments that occur with the laser treatment. And it can require multiple treatments that expose the patients to risk of multiple occasions and adds additional expense. But it has been known to be very effective in salvaging vision in patients who passed into the most dangerous, high risk areas of diabetic retinopathy. The purpose is to remove vitreous hemorrhage, allow laser treatment and repair the retinal detachment if that's there.

Now, I think what's important to recognize is that the best care, the most appropriate care that we can apply, is provided by the folks listening to this presentation. Primary care management of diabetic retinopathy is extremely useful. And in fact, we have shown that the efforts of the primary care team in Indian country over the past 20 years has resulted in about a 50% reduction in the prevalence of diabetic retinopathy. This is just remarkable. When I tell you that primary care providers are preventing -- there's no question about it. If they're preventing vision loss in much greater numbers than eye doctors. So, it's always better to prevent the disease than it is to be good at treating it. So, everybody in this room should feel gratified that what you're doing is working. And it's not just working in the eye, there's a same reduction in the prevalence of diabetes-related, end stage renal disease over the same period and almost assuredly for the very same reason. And as we continue to examine this more closely, I'm very confident that we'll find that there's been similar reductions in other end-organ diseases in diabetes. So, please understand what an important role you are all performing for our patients in that regard.

Now, in that context, there's been some studies done over the past decade or so that are pointing to other treatment modalities that could be provided by primary care folks. And I'm speaking now of fenofibrate. A fenofibrate randomized clinical control trial in 2005 and then followed up again in 2010, showed that fenofibrate, particularly when applied early in the course of diabetic retinopathy has a profound decrease in the progression of diabetic retinopathy and the need for treatment. Both of these studies, they're done in different populations, but they were both very large randomized clinical trials and provided some very important information suggesting that fenofibrate would be useful in this regard. Now, there were some evidence gaps left in these two studies and there needs to be additional research done to better understand how and when this can be done. But one thing we know for sure is that the mechanism of the fenofibrate has nothing to do with the lipid effects of the drug. This is a drug with which we're very familiar, it's been used for treating this dyslipidemia for quite a while. We know quite a bit about it. But with respect to diabetic retinopathy and maybe other forms of microvasculopathy due to diabetes, the effect is not due to lipids.

So why am I emphasizing this so? Because a lot of folks say they don't need another lipid drug, "if fenofibrate works, oh my God, all my patients are on statins anyway". Please understand that these studies look at the effects of fenofibrate with or without statins. And the results, the beneficial effect of fenofibrate has nothing to do with the lipid effect. There's probably at least five or six different mechanisms of fenofibrate and it's one or more of those and not the lipid effect. The other thing we know is to treat early in the course of the diabetic retinopathy, but as I mentioned, this is a gap in the evidence from these randomized clinical trials. We do not know the precise timing, but treating early in the course of diabetic retinopathy, but probably not when there's no clinically evident diabetic retinopathy,

somewhere in there is the right time. And quite likely, there are collateral benefits to other in-organs, specifically the kidney and peripheral nerves.

And the other thing we know from our several decades of experience with fenofibrate, is that it's very safe. Now, the flowing history of fenofibrate from dyslipidemia has shown it to be safe. However, the fenofibrate category throughout has gotten a little bit of a bad reputation, primarily caused of gemfibrozil, that it has -- it can interact with statins to cause some problems. Fenofibrate has a very low instance of that as oppose to gemfibrozil, it's about 5%. But this drug was well tolerated in both the FIELD and ACCORD Study, and I think we can feel comfortable that although it's not risk free, nothing is, it is a very safe drug. In fact, it's common only and well used for diabetic retinopathy in Australia and other countries. And in fact, in the our own neck of the woods, the Canadian Diabetes Association in 2016 and the ADA in 2017 says, "They need to look at this and consider it as a form of a primary care based intervention for diabetic retinopathy". And I won't deliver this now, but you can go look at the CDA and ADA recommendations in that regard.

But the basic plan is to treat early in the course of the disease. If we do that, it can be done by the PCP without special referral and it reduces the need for a difficult and costly travel to subspecialty care and other collateral cost to the patient and to society. And importantly, and the reason why I'm emphasizing this is as the director of the Telemedicine Program, it is nationally incorporated into a primary care based teleophthalmology program. Because if you have a primary care based program for surveilling for diabetic retinopathy, that could be coordinated with the primary care provider to simply begin or at least offer the patient the opportunity for fenofibrate treatment if an appropriate level of diabetic retinopathy is indicated.

Now, what now? This is not something that must be done, but I'm suggesting as to the CDA and the ADA that you consider that it be done. And this is what this process could do. Currently, what we do is we have a coordination of primary care and specialty care for management of diabetic retinopathy. And we refer 100% of our patients to the eye doctor, the specialty clinic, for a diabetic retinopathy examination. About half make it to the eye doctor and about half don't. This is very well documented. It is without question. It actually occurs both in and outside of Indian country. The half with diabetic retinopathy, about 5% are discovered to have high risk disease and need to be considered for treatment. And the rest get circulated back into the system.

However, what I offer for consideration is the panel on the right wherein the primary care clinic surveils 100% of patients with diabetic retinopathy,100%, and then sends the advanced cases to the eye doctor for consideration. So if a patient is seen to be at threshold disease and sent to the eye doctor, the eye doctor can evaluate that patient and their need for intervention. And then all folks within the category of severe level of diabetic retinopathy for whom fenofibrate may offer some advantage and that can be initiated, and just keep the patient in the system and keep the system going. And hopefully enjoy up to 78% reduction in an onset and progression of diabetic retinopathy, needs the treatment.

Keep in mind that 40% to 60% percent of our patients have failed to receive these treatments to prevent vision loss due to diabetic retinopathy. So, we have to follow all of our patients into a systematic program whereby best practices are adhered to. Patients have a chronic disease that is asymptomatic. They don't realize that they're in trouble until its progressed to a vision loss, and that's not the ultimate time for treatment. So, we need to be aware of that and look

for a, using a system that is better to achieving outcomes that favor the patient and favor the health care system. Now, what I'm showing here, that we have a system that's used everywhere in the country. And it is essentially designed to achieve the results that it gets. As I mentioned, about half of the patients don't make it, so we shouldn't be too surprised that we have the outcomes that we do. The kicker is to do something different to improve these clinical outcomes.

Now, before we all start hitting the Jim Beam or a handful of Prozac, let's recognize that it is not just Indian Country where this problem is occurring. And in fact, in Indian Country where we have a tougher job than the general U.S. population, we are actually doing better than a whole bunch of the country. Now, the folks of Medicare age, they tend to be performing better into the 60s, about the 60 or maybe even mid 60s' surveillance rate. Understand that everybody else is in the 50s or worse and we're about 60%. So we're doing significantly better than the rest of the population below the age of 65, but it's still not good enough. It is not a problem with eye doctors. Patients, are asymptomatic with a chronic condition requires an inconvenient examination. This is a primary care diabetes management problem. I'm not chastising anybody. We're doing everything the same way everybody else does it, and it just doesn't work for about half of the patients. So we must be smarter than the disease, we must understand the patient. Because no patient is going to say, well listen, what I really wanted to do is go blind, so I'm going to ignore what you're telling me. We just need to understand the circumstances that results in half of our patients not getting standard of care and be smart enough to fix it.

Now, others have been. In the VA, in the United Kingdom, telemedicine is used as the default method for diabetic retinopathy surveillance and enormous strives have been made. And in fact, in United Kingdom, for the first time in 50 years of doing measurements, diabetic retinopathy is no longer the leading cause of blindness among their working-age adults. Now, this is an important thing to recognize. The United Kingdom has found a way to alter the epidemiology here. And all they've done, they've used telemedicine in a primary care environment as the default method for surveilling for diabetic retinopathy, and it has been extremely effective. So, it's worth looking at what the UK did and what the Veterans Administration has done.

The VA now -- I mean, there's a totally different -- they have a totally different patient population and totally different healthcare system. And so, we can't -- it's not an apples-and-apples situation, but they are examining about 90%, maybe even into the mid 90s of their diabetic population. And remember, we're getting 60% and we're doing better than most. So, the recommendation that's coming from this data is that we need to be looking at changing the paradigm for surveilling for diabetic retinopathy and move it to the primary care area.

Now, we search pretty hard to identify the number of patients that we examine for diabetic retinopathy. In fact, that's a GPRA element. But there are only certain numerator components we can count. We obviously -- you can count a dilated examination by an optometrist or ophthalmologist. You can also use a scientific protocol. The scientific protocol is called the ETDRS, Early Treatment Diabetic Retinopathy Methodology, very complicated and requires a fair amount of time and considerable inconvenience to the system and to the patient, but it is the gold standard. The ETDRS is the gold standard, and it is used for research primarily.

However, we can also use any other photographic method that has been formally validated to ETDRS. So, you can't just use -- you just can't pick up a camera and start taking pictures and call it done. It has to be proven, using strict scientific protocol to be equivalent to the gold standard ETDRS. And these three can be used, but what I'm suggesting is that the photographic method that has been validated by ETDRS is a form that can be used in the primary care clinic, and therefore interleaved with the normal workflow of the diabetic patient. And then maybe you start taking a bite out of these -- out of the fraction of patients that don't make it to an eye doctor.

So, we do have a validated telemedicine program in Indian country, the IHS-JVN Teleophthalmology Program. It's designed to reduce vision loss with timely diagnosis and treatment using telemedicine in the primary care setting. It's been very carefully studied, essentially funded, it is not absolutely free to participate but it's darn near free and it's been in clinical operation since 2001 and we have a lot of data about it. And we know it to be quicker, painless, because it uses low level of illumination, no pupil dilation. And because it's not invasive, it can be used in the primary care environment and interleaves with other patient encounter events. So, a patient is in the primary care department, getting other things done. And since it's non-invasive, it can be incorporated into the normal workflow and the patient re-introduced into the same workflow they were in when it's done and it's validated. It's been very carefully studied and it's shown to be equivalent or better than a live eye exam for the purpose of establishing the presence or absence and level of severity of diabetic retinopathy and macular edema.

Now, we currently use two different cameras, based upon the setting, and in each instance, the retinal image acquisitions is achieved by a certified imager. Demographics are harvested from RPMS. The imager is trained to supplement the history, do some patient education. And the images are transmitted to the reading center, along with the patient's health summary, so that diagnosis can be made in the context of their general health status. So when the images get through the reading center, they read out on some monitors like you see here, where the image analysis is done. We use computers to assist in the standardization and quality of the diagnosis. Of course, the readers are all eye doctors and they validate those with their eye doctor brain, but the computer is assisting in the process and the computer also automates the documentation.

Now, we have two different cameras and our legacy camera takes pictures of the back of the eye to simulate the ETDRS protocol. But our newest camera also takes a much broader scope of imaging to look at about 80% of the retina. They're a little bit more than 80% of the retina. And we've got to some science that shows that this is an important improvement. Gathering more data to look at, allows us to make a more accurate diagnosis and maybe even provide additional risk stratification that you cannot get with examining just the back of the eye and you don't get with doing a live eye exam examination.

Now, we looked at our first year experience of these ultra-widefields of the eye exam and published that paper a year or so ago. We looked at about 25,000 patients, 8,000 of which were with the ultra-widefield. And what we saw with this new technology is there was about 80% reduction in the ungradable rate to about 3% to 4%. And there was a two times increase in the rate of diagnosed diabetic retinopathy. So that means compared to looking at just the back of the eye, we saw twice as much, we were able to detect twice as much pathology. And what we saw reduced in a more severe level of diabetic retinopathy in almost 10%. And

importantly, this whole process -- and this would be in a more accurate method for diagnosing diabetic retinopathy, it reduced unnecessary referral and possibly travel by about 4,000 patients per year and that was only having 8,000 studies done with the ultra-widefield.

So, additional science has been collected and this is not IHS science, the previous science came from Indian country. But this modification was -- looked at additional benefits, it comes from looking at widefield and we found that it is extremely useful for risk stratifying the patients. So, looking at these peripheral fields as an additional element of the examination, compared to the additional protocol looking at just the very back of the eye, show that this information can be used to better identify who is at risk for progressing to a higher level of diabetic retinopathy, a more severe level, and also for needing treatment. Very important information and this typically cannot be done by a live eye examination but can be done with using this technology that I've described to you.

Now, we've talked a lot about diabetic retinopathy being a leading cause of new blindness, primarily because patients are not getting timely treatment because half of the population is failing in that standard of care. This is a study also done in Indian country and published in Diabetes Care some time ago now, over a decade ago, where we showed a 50% increase in the diabetic retinopathy surveillance and laser treatment. So, not only did it was associated with a 50% increase in the fraction of patients that met standard of care for diabetic retinopathy examinations, but 50% more lasers were done in the same patients, and that translates immediately into improved clinical outcomes. So, surveilling for diabetic retinopathy in a primary care environment works, and it works great. So, it's something that we should really foster in Indian country and elsewhere. And in fact, if you read the best practices for diabetes eye care in the IHS, the telemedicine program is in there.

Now, just to prove that we're not frittering away the later taxpayer dollars, we did a cost analysis of this program and we showed that the IHS-JVN program is both less costly, this is a good thing, and more effective, that's even a better thing for detecting diabetic retinopathy, identifying not just patients that require laser treatment and preventing severe vision loss. So, what we basically have is something that's cheaper than a conventional approach to diabetic retinopathy surveillance and better. And it's great when you get that all on the same package.

Now, what I'm attempting to show here, this list is not absolutely up-to-date, but it gives you an idea of where we're positioned. Every state that's shaded in there as a state that has at least one IHS-JVN Program deployment and all those little dots are individual deployment sites. The red dots are our legacy technology and the green dots are the ultra-widefield technology. And currently, we are in the process of changing all these red dots or at least most of those red dots to green dots. So, in the next two or three years we expect all of our sites to have the ultra-widefield technology. The reason why they don't have all the technology now, is that the camera is obscenely expensive. We're working to get it at a lower price and gathering the funding that's necessary to allow us to offer this technology to all of our patients. Right now, it's being deployed at the larger sites for obvious public health reasons. And then as we get a funding, we move them to increasingly to the smaller sites as well.

Now, our experience as shown here, you can see where in 2016 we saw almost 23,000 patients. In 2017, when the smoke clears, it's going to be more like 26,000 patients. So you can see that we've ramped up considerably over the years, beginning with our first clinical program in 2000. The impact of this is shown here. Let me explain this to you just a little bit.

What I've tried to do is take that previous graph which showed our cumulative examinations if I can get this little arrow to work here. There we go. And you could see where this started to ramp up about 2008. It really started to ramp up to a pretty sizable number. And you can see that before 2008, the linear regression analysis shows that the annual diabetic retinopathy rate was slowly decreasing. It was slowly decreasing through about 2008 and there was an inflection that's coincident with the ramp up in annual examinations by the JVN and now the regression analysis shows a consistent increase.

So, we like to observe that since this ramped up, the annual diabetic retinopathy examination rate in Indian Country has gone up a little over more than 20%. And every percent increase in our annual examination rates equates to somewhere between 85 to a hundred American-Indian/Alaska Natives who did not lose vision due to diabetic -- I should say did not suffer serious or moderate vision loss due to diabetic retinopathy. So this is a very important graph to help us understand the human impact of innovative programs like this in Indian Country.

So, the best practices for continuing to protect our patients with vision loss due to diabetes, patient education, control of confounding factors and glucose, of course, glucose, lipids, blood pressure and folks who are using tobacco, it says smoking. Our slide is smoking, but I suspect that smokeless tobacco isn't particularly good either. Possibly fenofibrate, they're still some gaps in our evidence there, but I feel strongly that fenofibrate is an opportunity for making further in roads in this. And of course, annual examinations for timely diagnosis and treatment of this disease. So, I managed to get this done with about ten minutes left to go. If there's any questions, I would be glad to entertain them now. Oh my gracious, we got a question or two going on here.

Jan Frederick:

We did, we have them saved there for you Dr. Horton, some good questions.

Dr. Mark Horton:

Okay, well let me respond. There's a question about steroid use. Would it increase the blood sugar in a diabetic? We all know that a diabetic patient who is treated with systemic steroids will very commonly see a dangerous rise in their blood sugar. Good news is, that doesn't occur in when it's injected inside the eye, it can cause other problems. It can cause a cataract, it can cause glaucoma. But usually this -- of course, cataract can be treated and so can glaucoma, but it doesn't result in loss of control of the diabetic patient.

Steroids is not our first use and there's good uses for steroid injection inside the eye. But something called Anti-VEGF vascular endothelial growth factor, a drug that actually competes with that, is the first choice. So, that's not a choice we typically go for -- it doesn't have so much to do with the loss of control of diabetes, but more for the other complications of glaucoma, I mean the steroid use in the eye.

Another question. What is the recommended daily dosage fenofibrate to help reduce or prevent retinopathy? It's the manufacturer suggested dose and it's adjusted for renal function. I won't go into great length here, but most of the manufacturers provide at least two dosages of the fenofibrate and that's adjusted based upon their renal function. So I would say, look at the manufacturer's recommendation and use the drug accordingly. Although, that the drug and its

dosage, it was created for management of dyslipidemia, the ACCORD Eye Trial and the FIELD Trial used the same dosing regimen.

What I will mention to you though is to recognize that the formulation of fenofibrate occurs in three or four forms. The traditional form of fenofibrate is virtually insoluble in water and it has to be taken with meal. So, I would encourage you if you want to use fenofibrate, I would use either the choline version, use the choline version of the drug or the micronized version. And both of those do not have to be coordinated with a meal, and therefore you're likely to improve your patient compliance. So, I would say use the manufacturer's dosage based and that's suggested based upon renal function and look at either the choline form of the drug or the micronized or nano-ized form of the drug.

How can we improve our numbers as far as getting patients to come in for the eye exams? There are some things that we just have to accept. And the information is just compelling, that simply telling our patient to call me and once a year get their eye exam is only effective in getting the about half of demand. Now, we could continue to do that. We can have a robust case management program where we pester them at home, on their phones or text them. We can do special things like that. But the evidence shows that if you have a standard eye care program, you're going to reduce the number of folks that fails to have a care by about a half. So you're going to see about half the population.

If you do some high level of efforts, something special sort of thing, whatever that might be, you can reduce the next fraction down by about a half again. So if you just really do a high level effort, whatever it is to go and get it, you got to manage to get up somewhere in the high 60's or 70's. Recognize high level of effort. Now, Lord knows we're not adequately funded in Indian Country to do what we need to do. So anytime you raster up to a high level of effort to do anything, that means you're rastering down the available effort left to do something else. So you have to be very wise about how you allocate your medical resources.

So, the message I'm giving you is -- if you have an eye care program, of course you got to have an eye care program. But with or without an eye care program, if you have one eye doctor or ten eye doctors, you need to have a primary care based method for a photographic surveillance of diabetic retinopathy. That is what is working. And the folks that are in this business recognize that at this point of the game, there's not a whole lot of other options for surveillance. Because consistently, over decades, half the populations do not come in and get an examination and we could chat about why that is. But basically, that's the way it works.

Can you count JVN toward GPRA? Absolutely, positively, no question about it. Even if they're ungradable, and let me tell you why that is, why that's appropriate. If you come into the eye doctor and you come in for an eye examination and your pupils don't dilate, or you have cataracts and you don't get an adequate examination, you can count that. You get to count that. GPRA, you don't have to absolutely show that everything you do is totally effective but that you have implemented a standard of care and you were effective in the implementation of it. So, I've seen a fair amount of angst about if Indians come back as gradable, can I count those? Yeah, just like you can count my -- my eye exams are ungradable. If the patient comes in and they have cataracts, I can't see the back of the eye. I get to count that. And there's a legitimate reason for it. Now, understand that we've not perhaps maybe done the patient as much benefit as we would have like. But the GPRA is about reporting back up to OMB how well we have used the taxpayers' dollars in the administration of our healthcare. And

if you get the patients bottom in your chair and you do your best effort to do the examination, then that counts. Now, that's a Mark Horton vantage on that. I don't know if you agree completely with the logic, but that's -- but if you can count a live of eye exam that didn't produce data just because you did your absolute best to give the patient what they needed and I don't see any reason why using a validated program that's better than a lot of eye exam, they would enjoy the same sort of approach.

You start the fenofibrate -- this is a little bit tricky. I must give you what I think is -- the best plan to use fenofibrate is given on level of science that we have. So, I would say as soon as a patient shows any level of diabetic retinopathy, begin fenofibrate. It probably doesn't have its largest effect when the patient shows no level of diabetic retinopathy. So without additional findings, I can't give you any better information on that. But I would say that if somebody has one microaneurysm that's due to diabetes, it would be appropriate to try fenofibrate as long as the patient doesn't show any adverse effects of the fenofibrate, I would continue that. There is no -- as opposed to treating their dyslipidemia, there is no laboratory test to find out if it is working. You have to just continue it because that's how the ACCORD Trial and FIELD Trial was done. They looked at patients over a four to five-year period and noticed the difference in the onset in progressive diabetic retinopathy. So that would be the -- there is not laboratory method, you just have treat and wait and see what you get.

Detroit Urban uses the Welch Allyn RetinaVue, it's quick and easy. We get a report back from ophthalmologist in two business days. That's right. I'm very familiar with the Welch Allyn device. It produces a category one, what we called an ATA, American Telemedicine Associations category one outcome. It essentially tells you yes or no, you have diabetic retinopathy. It may -- some folks may have it or it gets slightly more than. But I can't tell you, I reviewed 20 years worth of literature on this telemedicine modality and I can promise you that there's no way that that single image is going to produce a sensitivity and specificity that you would accept as achieving standard of care. Now, that does not mean that it's of no value, it doesn't mean that at all. I'm very familiar with the Welch Allyn technology. I know the folks there at Welch Allyn. It's a good equipment but it's designed to do a specific thing and that specific thing is not to replace or substitute in any way for dilated retinal exam.
What it's designed to do is to triage the patient and find out the patients that are most in need of a live eye exam. So, that's going to be a pretty big fraction of the population with diabetes. Well, when I say pretty big fraction, as compared to if you had a sensitivity and specificity that was commensurate with a live eye exam. It would be a much smaller fraction that you have to refer. So, I agree with you about the RetinaVue. It's quick and it's easy and you get a report back from an ophthalmologist. But just understand that it doesn't have the sensitivity and specificity that's necessary to really substitute as a standalone substitute for a dilated retinal exam like any ATA category three study, like the JVN program.

Jan Frederick:

Well, Dr. Horton, I'm sorry to rush you. We're at the top of the hour, but you've just given us a great deal of wonderful and impressive information. And we really appreciate you taking time to do the presentation today. I'm going to invite Dr. Ann Bullock to say anything in closing if she would like to. Dr. Bullock is the Director of the Division of Diabetes. Dr. Bullock, are you there?

Dr. Ann Bullock:

I am, yes, and I know we're running out of time. But I just want to take this opportunity to thank Mark Horton, not only for his great presentation and all of this information today. As you can tell that no one is more knowledgeable than Dr. Horton about this topic, especially in our communities. But Dr. Horton is going to be – he keeps threatening to retire. I keep trying to send him subliminal thoughts that he doesn't want to. But he certainly deserves it, then we think -- we may be losing him to the great world of retirement here at the end of the calendar year. So I just want to thank him not only for his presentation today, but for his long and excellent career. He has literally help save the division of many of our people through all of these efforts. So, thank you Dr. Horton and honor you for that. And I also of course want to thank everyone for joining today. So, that's all for me. Thanks everybody.

Jan Frederick:

Thank you Dr. Bullock and thank you again Dr. Horton for your presentation and just your significant contribution to eye care in Indian Country.