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The P4 Approach: Revolutionizing Diabetic Macular Edema

Announcer:
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Dr. Singh:
This is a program that's provided by Global Education Group and Avlis International, and here's my faculty for tonight's program. On my left is Arshad Khanani from Sierra Eye Associates; Dr. David Boyer from Retina Vitreous Associates Medical Group in Los Angeles, California, and Dr. Ur. Thank you for joining us from St. Paul's Hospital Diabetes Center. Dr. Ur is an endocrinologist and will talk to us today about the advances in diabetes that we have been able to achieve in the past couple of years. Here are financial disclosures related to this presentation. So, what we're going to talk about today is really how we integrate our care across this multidisciplinary team. We'll discuss some of the emerging treatment options, how we really predict patients may or may not do well with some certain therapies, if there's some kind of a baseline effect that we might be able to determine whether a patient might be responsive or not to an anti-VEGF therapy or other therapies we might have available. And we'll outline some of the communication strategies we have not only with each other as clinicians, but also with your patients and how you approach them in clinical practice. So I'm going to start off today's program just with defining this P4 approach. What does this mean for all of us in our clinical areas. We know there is a long-term trend in diabetes for diabetes growth over the next couple of years. Here's a heat map showing the increases in diabetes from 2015 to 2030, and these numbers are about showing that in the year 2030, approximately 20% of the U.S. population will be diabetic. This is actually a worldwide issue; not just the U.S., and, in fact, the places that are growing the fastest are places like the middle east, India, China; those areas are actually growing at a 30% rate of diabetes in their population, which is astronomically growing in the past couple of years with changes in diets and changes in lifestyle. What about visual impairment? Well, in 2015, we see that our population is about 320,000,000 in the U.S. with about 4.2 million actually considered visually impaired, and that might be due a lot in part and parcel to our diabetic eye diseases and, as you can see in 2020, 2025, and 2030 we are seeing an increase in that visual impairment as that population is aging. What I find most interesting in the past 10 years is that the way we treat patients has not changed very much, right? So anti-VEGF actually came out in the year 2005, and we had advancements in that different anti-VEGFs in 2007 and 2008. And then pre anti-VEGF era we were really monitoring diabetic retinopathy annually. We were doing diabetic macular edema management four times a year with focal laser, and our treatment goal was really visual stabilization. And that has really transformed significantly in the past couple of years with the advent of these anti-VEGF therapies we have. Today, we monitor DR annually, if not even more frequently, depending on their level of diabetic retinopathy. Our DME management has gone to almost 12 times a year in some patients, resulting in significant number of patients we see per day. On average, a retina specialist may see up to 70 patients a day with 30-35 anti-VEGF injections per day, as well as OCT-guided therapy. We use that for all of our clinical practices right now. And the real goal has improved. The bar which we decide on how patients do is really treatment improvement. Now we are not stabilizing the disease, we're trying to make a difference in how they will both work in their activities of daily living, as well as in their environment today. So we have these patient challenges we all face as clinicians, right? We have lots of different good patients in our

population. We have the not always well-behaved, sometimes-behaved that follow their diets every so often, generally sensible patients that do pretty well, patients that are in diabetes and are in total denial and don't want any treatments. I've had patients show me rocks that they're using and holding against their bodies to cure their diabetes, and the worse cases of denial. And we have patients that are transformed. I have many patients that have had proliferative disease and have had great panretinal laser and have done great in the last couple of years, just because they've had to go on to that level of losing vision or losing visual field before they realize they needed treatment on an annual or semi-annual basis. But the compliance is a challenge, and this is a really great study that was done by Mike Singer and a few other people, which looked at the compliance rate of diabetics in our population. So on the left side, you can see the cancellation rates in those patients with wet AMD and DME, which are pretty equal, but on the right side you see the no-show rates. These are patients getting anti-VEGF injections, and the no-show rates are almost triple that you see in the wet AMD population. Now the current challenge also in diabetes care is that we have multiple different healthcare providers, varied sites of care, and high resource utilization. These patients are very expensive to the population, very expensive to insurance companies, and we try to minimize their visual impairment by hopefully getting them in early, treating them early, and preventing these long-term complications. So what's the P4 approach? Well, we want to make this predictive. We want to be able to use some of our technologies now to be able to predict perfusion or changes in their retinopathy over time. We look at their response to treatment. We also look at it being personalized, determining when we can get our best possible maximal therapeutic response, and we do this in clinical practice today, right? We do treat-and-extend regimens for our patients, and they might be varied as far as their disease states. We might see very different levels of treat-and-extend in those populations over time. We also have patients who are participatory and we want to try to involve them in their own care and be able to be good stewards of their own body and their own retinopathy. And finally, we want them to be preventative; realize when they have early disease that needs to be treated early, and we're going to talk today a lot about preventing them from going on to developing vision or site-threatening retinopathy. When they're at the mild, moderate, and severe level, we can actually intervene and prevent these patients from developing severe complications from diabetic eye disease. Here's just one example of that you can see here. So, with the predominant peripheral lesions you see, just by that photograph you took in that office, you can see a 3.2-fold risk of increase in going on to developing proliferative disease within a three to four-year period. So for me, and when I look at those patients in practice and I see these patients with predominantly peripheral lesions, that's a patient I'm going to consider committing to anti-VEGF therapy earlier, knowing that their progression rate is there. That's what we're trying to talk about tonight, is really using a more personalized approach and how we identify these patients and developing strategies to manage these patients over time. So this is hopefully going to improve our diagnostic and therapeutic decision-making, and improve the communication between our specialists, including the endocrinologists and the retina specialists we see here tonight, and improve management and compliance and patient outcomes with this disease state. So we obviously don't just work in a vacuum as retina specialists. We have the optometrists who refers us the patient, who might do glasses screening evaluation, and might be the first line caregiver for these patients. We have the retina specialists who deliver anti-VEGF therapy and deliver treatment for that patient. We have the patient themselves, which have to be participatory in this process. And finally we have the endocrinologist really to help us better evaluate and better manage this patient. And one of the really big advances in endocrinology has been long-acting insulin. The levels of both proliferative retinopathy and diabetic retinopathy in general have gone down because of increased glycemic compliance and the development of these sorts of conditions. So we are hopefully tonight going to show you different levels of how you can empower and improve your patients, how you are going to enhance communication with specialists like Dr. Ur and others in endocrinology and optometry, how we're going to promote effective work-streams amongst each other to work better in coordination to help improve outcomes. So with that, I'm going to turn it over to Dr. David Boyer to start this part of the presentation.

Dr. Boyer:

Thank you very much, Rishi. At the 2015 FDA NAI workshop that was focused on diabetes, it highlighted the need for earlier intervention, and I think Rishi has pointed that out. But you can see here very quickly that control of the diabetes, control of the lipids, control of the blood pressure, and stopping smoking are things that we can encourage our patients to do and have a major effect on reducing progression of retinopathy. And I think sometimes the people when they look at the photographs on our camera, we show them the damage or they come in and they want to know what we can do, but we also have to tell them what they can do. We know that the longer the patients have diabetes, the greater chance they have of having both diabetic retinopathy in general, so greater than 20 years over 30% of patients will have some form of proliferative retinopathy. And about 20% will have diabetic macular edema. About three-quarters of the time, our patients who come in with diabetic disease have bilateral disease. So it's kind of unusual not to see it bilaterally. We do sometimes see it in one eye and sometimes we even question whether it's a vein occlusion or really part of the diabetic retinopathy that we're seeing. It's so common to have it in both eyes. So we're talking about something that can affect sometimes asymmetrically and, if you see a lot of asymmetry, you should start to look for other reasons; carotid artery disease, other reasons that may give you asymmetry or are you dealing with a vein occlusion. But it's important to check both eyes even though they may present with the one eye. Certainly, there have been a lot of articles written about the intervascular endothelial growth factors as the anti-VEGFs began to emerge as a treatment for proliferative diabetic retinopathy instead of PRP, and there are advantages and

disadvantages, and we should discuss this because this is a conversation that you have to have with your patients; they have to know the advantages and they have to know the disadvantages. The advantages of PRP are typically it is able to be completed one, two, or maybe three sessions. If often is long-lasting, requiring no additional treatment, though in the study about 45% of the time you needed additional PRP from completion of the initial to the median time for additional PRP was seven months. And it cost less than ranibizumab or other anti-VEGF therapies. No risk of endophthalmitis and no risk of systemic exposure to anti-VEGF therapy. What are the advantages? The advantages are anatomic and visual efficacy has been proven. There is less visual loss. The visual fields remain good. The vision seems to be a little better. There is decreased chance of needing a vitrectomy, decreased chance of bleeding, decreased chance of developing diabetic macular edema. PRP is rarely given, but it is given in some of these cases. But what about using it in combination? It's not an either/or. A lot of times I go to meetings and I hear people say, 'Well, do you do PRP or do you do anti-VEGF for this?' and I think it's really a question of combining that and discussing with the patient that they may need both to get to the best visual result. And is this really sustainable? There is recently an article from Wills Eye Hospital that pointed out in a group of patients that did not come in that were on anti-VEGF therapy, they had a very bleak response one year later without treatment; whereas the group that had been treated with laser had a much better prognosis. So which anti-VEGF do we use? I think the important thing here is that all thee of the anti-VEGFs; bevacizumab, ranibizumab, and aflibercept on average improve visual acuity, and certainly in the group of patients that were 20/32 to 20/40, there's really no significant difference. In the first year, if you were 20/15 to 20/320, aflibercept seemed to have better control, less edema, and better visual results, but at year two, aflibercept and ranibizumab were both fairly equal, though bevacizumab, as you'll see, had not really caught up. What about the treatment – the treatment burden that we have? This is a very interesting slide because this is a combination of Protocol I RISE/RIDE, VIVID/VISTA, and BOLT. BOLT was a study done for bevacizumab and then Protocol I, as you know, was doing deferred and prompt laser with ranibizumab. You can see the number of injections fairly considerably and, if you go down and look at the two-step improvement, you can certainly see that the patients who received the most injections, those in the clinical trial, had the best improvement in the diabetic retinopathy severity. When you began to reduce the number of injections, the diabetic retinopathy severity did not improve as much. Is there room for us to improve? We have great drugs. I think there is room for us to improve because if you look at Protocol I and Protocol T, ranibizumab there was still 40% of the patients still had fluid after the six monthly injections. There was a little bit less with aflibercept, and certainly 66% of the patients who had persistent fluid or diabetic macular edema using bevacizumab, indicating that we have a better dry agent with aflibercept, though very close behind would be ranibizumab. What about if the patient doesn't respond – what do you do? And there's a lot of debate about this, but this is just a post-talk analysis of VISTA and VIVID and this has been done also for ranibizumab, and it shows that with continued monthly injections, you continue to get improvement; perhaps not as fast and perhaps not as much as we would like to see, but certainly here in the limited early responder chart, you can see that they gained about 6.6 letters. The patients who responded early, gained 12 letters, so they limited early responders, gained about half as much, but they did gain vision over a period of time. So there are other options, which we'll go through the use of steroids and other things, or changing medications, and we'll talk about that in a little bit. We know the data, but how are we really doing? Everybody in this room knew that you should give monthly injections because we all read the trials; they were all monthly injections and then aflibercept went to every eight weeks; whereas, ranibizumab continued monthly, and the results were phenomenal. Are we really doing that in private practice? And the answer is no. The answer is, for some reason, there's a big disconnect here. If you look at this article, the vision outcomes following antivascular endothelial growth factor in clinical practice. Over 12 months, the mean number of ophthalmology visits was 9.2, which is pretty good, and that's a fair number of – you're talking about every six weeks. The mean number of intravitreal injections, however, was 3.1, ranging from 1 to 12. And almost 70% of patients received less than three injections, which means that we're severely undertreating most of our patients who have this condition. And at 12 months, the mean improvement, the best corrected visual is 4.7 letters. I just showed you pictures and it showed even in the poor early responders 6 letters of vision, and the good responders 12 letters. So we really are under-treating and we're getting less vision improvement and less improvement in diabetic retinopathy severity. The proportion of patients gaining 10 or more letters was 31%, or 15 letters about 24%. But we have people losing 10 letters about 11% of the time, and 15 letters 8.3%, which was never seen in our clinical trials, and this is from undertreatment. And the eyes receiving adjunctive laser surgery during the first six months showed similar changes in corrected vision, not very much difference 3.1 versus 5.3 letters. So cutting corners, you go from RISE and RIDE that had almost 11-12 injections in the first year to Protocol I, which had about 8-9, then you go down to what our EMR studies are showing where they're only getting approximately 2-3. The visual acuity improvement goes way, way down. Well, in 2014, the American Society of Retina Surgeons did a PAT survey and they said to the retinal surgeons, 'How are you guys doing? Are you treating more than six times per year?' and, overwhelmingly, the answer was, 'Yes, we treat more than six times a year.' That doesn't seem to hold up, however, when you look at claims data. In claims data, it's a little over 50% in the U.S., and internationally a little bit less that get greater than six injections per year. So I think our concept is we're really treating very well, but in actuality when you look at the actual numbers, it doesn't appear that way. So here's another way of looking at it, and I think the most astounding – because when I see patients that come in that did not receive adequate treatment, probably the biggest thing I think of, and I don't know about the panel, but I think they couldn't afford it, it wasn't available to them. But if you look at

your insurance claims, about 3.6 anti-VEGFs a year. Look at a Kaiser – Kaiser in my area does an excellent job of treating patients. Patients get treatment whenever they need it. They are less than 3 treatments per year. Patients don't have to pay for it, they just have to show up and the doctor has to see them. So you can see here in clinical trials, we're talking anywhere from 8 to almost 12 treatments a year, and in clinical practice we're talking anywhere from about 2.3 to about 4 treatments, so we're really grossly undertreating the patients. And I think we're leaving a lot of vision on the table and I think we're doing a disservice to a lot of our patients. What are the advantages of treating early? You know, I think that Rishi brought up the possibility that you can take these patients that have peripheral lesions, you pick them up early and use anti-VEGF therapy and perhaps make them go wait, change the diabetic retinopathy severity. So this was evaluating the impact of intravitreal aflibercept on diabetic retinopathy progression. You can see here that, with treatment, very few patients actually went on to developing proliferative disease and going on to requiring vitrectomy, so you can see the group that was not treated that, unfortunately at week 100, the group that was getting laser did unfortunately progress. PANORAMA is a newer study that showed that intravitreal aflibercept for the improvement of moderately-severe to severe nonproliferative retinopathy showed a definite improvement in 58% of patients at a two-step improvement. And this is in line with what we found with ranibizumab also when it became approved and had a label change when they went back and looked at Protocol I. Now Protocol T has also gone back and looked at the same thing and they're coming up with similar results. So at week 24, patients who received 4.4 injections, so about every 5-6 weeks, 58% received aflibercept and showed two-step improvement as I pointed out compared to 6% for the sham group, and secondary endpoints were assessed at week 100. So how do we communicate this to our patients? How do we go about giving our information, our knowledge about the disease to the patient so they can become more proactive? And I think, you know, conveying the study findings and discussing how the findings apply to each patient and managing expectations, I find probably one of the most important things for me to do is, when I have a patient that I can sit down and take in front of the camera and show them the hemorrhages or show them the non-perfusion and show them what's going on, and explain to them that this is like a window to your blood supply. This is a window to your blood supply and your kidneys, a window to blood supply and your heart. You're getting these changes throughout your body and this is what it's causing here, and we don't have to put you through an invasive procedure basically to try to see the circulation of your kidneys. So I find that talking to them about that and talking to them about, you know, the medical treatment and how important that is, is really important. How do you go about doing it?

Dr. Khanani:
Well, I think I do the same thing you do where you need to educate the patient, and I think a forced visit is really crucial. When they show up to your clinic, they're kind of nervous about, 'Why am I here? My vision is usually fine or pretty good sometimes with DME or DR.' And so I do the same thing – I do the wide-field imaging as Rishi said, and I educate them based on that I show a normal picture and then I put their picture and I show them the blood flow, the leakage, and I say it's the only thing we can see, but just like Dr. Boyer said, the kidneys and the heart and the feet, and I usually ask like if they have neuropathy, and most of them will have neuropathy by the time they have retinopathy. And then I talk about treatment options, and I say it's a team effort. If you don't do your part – if I do my part and you don't your part, we're not going to have a win. We have to work together in this situation and, if you do that based on our findings from clinical trials, you're not going to be on this treatment forever. And, you know, depending on whether they have DR or DME or not, so obviously if they have mild to moderate NPDR, education and not treatment at the first visit, then I say quit smoking, lose some weight, get your A1c controlled. So I think, you know, first visit to me is the most important, and I think if they're going to do it, they're going to do it right after their first visit. If they don't do it after that, then most of the time they're not compliant.

Dr. Boyer:
Rishi, let me ask you a question. I think that the people have to buy into that this is an ongoing process; this is not one and done, this is going to be going on for years. How do you approach that with the patients?

Dr. Singh:
So, that's a great question, David. You know, I think I try to give them, as most people do, examples in their own life that might be able to explain it, so I talk about the fact that they have a burning house right now. And the house is burning and we need to put out the fire. And they'll ask me, 'How do I put that out?' Well, the answer is anti-VEGF therapy in some cases and PRP in others. Using more practical examples like this, I find to be very useful. Unfortunately in Ohio, people look at those photographs and they look like Rorschach images to them sometimes. So you find out more about their personality than psychology maybe than you should about what they think about their disease state. But, you know, I think that's probably the most practical way I've been able to do it. I had talked to them about whether they know their hemoglobin A1c, and I tell them it's just as important as knowing your zip code. I talk about the fact that they need to work with either their diabetologist or endocrinologist to improve their diabetes care.

Dr. Boyer:
Dr. Ur, this is a question that always comes up in my mind and I don't know the answer. There are patients, as Rishi said, that know their A1c and they come in and apologize if it was 7.2 and they say it used to be 6.5. Then I have other patients that come in and say,

'Um, it's 9 and my doctor said that's okay.' I mean, you don't want to break that relationship up – how would you expect us to deal with somebody who really doesn't get adequate medical care and you don't want to stop this situation?

Dr. Ur:
Well, it's a huge factor. Obviously, access to good medical care is an important starting point. The level of education of the patient is another. And the simple answer is that there isn't one size that fits all. You need to adapt the therapy and strategy and approach for the social psychological circumstances, socioeconomic circumstances of the patient. Diabetes is a great equalizer in that sense. It really brings out these issues. Unfortunately, it's a stress test for society in general with increased incidence of diabetes. The only thing that I would say to you is that you have one fantastic advantage over the endocrinologists, and that is that we're dealing very often with very theoretical things. Yes, you need to know your A1c and it's important to get it down, but what does it really mean to them? It doesn't mean anything in their lives. But losing your vision or being able to show somebody a demonstrable change in their retina as a consequence of their disease is what I call a teachable moment. And there are very few teachable moments in diabetes, and you need to grab them and really impose that on the patient.

Dr. Singh:
Okay, so now we're going to spend some time with Dr. Ur, who is going to give us an endocrinologist's perspective on the diabetic patient.

Dr. Ur:
Thank you very much. I'm very happy to be here and to welcome you. I guess I'm the designated Canadian, as well, so welcome everyone to Canada. If you want to talk to me later about political asylum, I would be very happy to do so. We will talk about diabetic retinopathy, first of all. And then I'll talk about treating diabetes in general because I think this is an opportunity for you to hear about some of the newer drugs, some of the newer studies that pertain to diabetes in general. Of course, retinopathy is the most important complication of diabetes, and I don't say that because I'm talking to a room full of ophthalmologists, but because for historical reasons, diabetes is defined on the basis of retinopathy. The original clinical biochemical definitions of diabetes related to the blood sugars at which you start to get retinopathy; the famous Egyptian study that's always used epidemiologically for that purpose. Secondly, retinopathy was the first complication that we were able to demonstrate benefit in through improved glycemic control in the DCCT study, and then subsequently in other studies. And thirdly, ophthalmological outcomes are probably the first to demonstrate the most effective cost benefit in terms of reducing complications through screening programs and intervention programs, so I think retinopathy certainly is an area where we have a huge amount of data and, of course, we know that the highest rates of proliferative retinopathy are found in people with type 1 diabetes, simply because of the duration of exposure to the disease. Of course diabetes is the most common cause of blindness among working-age individuals and, as we're seeing this huge increase in type 2 diabetes and as people are living longer with type 2 diabetes and ending up on insulin, we're seeing more retinopathy in that category. Important opportunity perhaps to remind you that we talk about type 1 and type 2 now, and no longer name them adult-onset and childhood-onset and so on. Type 1 diabetes is the autoimmune condition, whereby antibodies usually in youth damage the pancreas, the islet cells specifically, and then very rapidly you lose the ability to produce insulin. Type 2 diabetes is a genetic disease, hereditary factors of about 50%, with 10% in type 1. And there are various phenotypes, but typically these patients are obese, they're insulin-resistant and, over time, they lose the ability to produce insulin, and ultimately end up with an insulin deficiency that looks very much like type 1, and that's why you see these older patients on combination therapies with different insulin products. And of course retinopathy in and of itself is also an additional risk for falls, hip fractures. There is a four-fold increase in mortality amongst people with retinopathy and, particularly in type 1 diabetes it's certainly a marker for early death. The risk factors for progression include longer duration of diabetes and, obviously there is a direct correlation with A1c. Hypertension and dyslipidemia, low hemoglobin levels, pregnancy, particularly obviously with type 1, and the presence of nephropathy in the form of proteinuria, and obviously retinopathy itself is a risk factor. Typically, in terms of communicating diabetic retinopathy to my patients, I make sure at every visit I have a checklist and there are five things on that checklist; A1c, blood pressure, LDL cholesterol – those are the biochemical parameters. And then there are three clinical parameters that I always check; the feet, have they had their feet examined recently, have they been immunized for the flu, and have they seen an ophthalmologist. And that is at every visit I ensure that they have that and it is discussed. Obviously the multiple risk factors that we spoke about and we talk about outcomes and how we can prevent these complications. One thing that I do throw in now to patients, which is helpful in managing particularly in type 1, is the fact that we are now on the cusp of an era of essentially curing diabetes. I'm sorry if it's going to put everyone out of business, but we are coming very close to an age of stem cell transplantation in diabetes. We are doing research here in Vancouver, looking at stem cell transplants. So I tell people with type 1 diabetes this is something we couldn't promise people 20, 30, 40 years ago when I was first practicing and looking after diabetes. I can pretty well guarantee you that within the next 10 or 15 years, there is going to be a cure for type 1 diabetes. And that is not any good news for you in 10 years' time, but it is an incentive now for you to make damn sure that you look after yourself so that you come out of this without complications. In terms of delaying the progression of the disease with the tools that we have right now, it is all about glycemic control, of course, but blood pressure and lipid-lowering

therapy have been shown to be important in retinopathy, as well. I mentioned the DCCT; this is really the granddaddy of diabetes studies and with intensive glycemic control and A1c reduction of 2% between the two groups, resulted in a primary prevention relative reduction of 76%, and the secondary intervention group that already had retinopathy, a 54% reduction. So this is absolutely huge, and really is the cornerstone of management, and this was published in the early 90s; 1992 it was published in *The New England Journal*, then since then really we've had the era of long-acting insulin pumps and much more aggressive management of type 1 diabetes in order to get better outcomes, and you've already alluded to that. Blood pressure, though, is also important, and this is the UK PDS study, which was a type 2 study done in the later part of the 1990s, where by a more aggressive strategy and tighter blood pressure control resulted in a reduction in progression of retinopathy. It's important to note that what was tight control in the UK PDS is not what we would really call type tight control now. And this is very, very bad blood pressure control, versus slightly better blood pressure control rather than really tight control. And you can see there is a dose effect. More recently, we've had the ACCORD study, which included an eye component. Of course it was a very complex study, and I was one of the investigators and I can tell you that it caused more problems than helped, but one thing that we have seen in the ACCORD eye study is that glycemic control and lipid control did result in improvements in retinopathy in these patients with type 2 diabetes. The lipid control was a study in which patients were randomized to receive either simvastatin and fenofibrate or simvastatin and placebo, so what resulted in the lipid benefit is the addition of fenofibrate, and that's also been seen in the field study, which actually was published before the ACCORD was even started. And the field study had essentially a question of looking at a diabetic group of individuals and looking at cardiovascular outcomes, but as a third-order outcome, they looked at retinopathy, and this was unexpected and they found really quite a significant benefit as you can see in those clear biological effects; over time, it's nothing spurious there. The outcome being retinopathy requiring laser, so then the real effect and then that was replicated in the ACCORD STUDY. Since these are not primary outcomes, it's difficult to translate that into an effective clinical intervention. I wouldn't say that I would ever put somebody on fenofibrate because I see they have bad retinopathy. It's more a question of an added benefit from putting somebody on a fibrate because they have elevated triglycerides. Very briefly, the last few minutes I'm just going to talk about some pharmacotherapies that we're now using, obviously mainly in type 2 diabetes. So, choosing initial therapy is fairly straightforward and really depends on the extent of the hyperglycemia, almost always start with metformin; that's really the cornerstone of therapy and we individualize the therapy based on the characteristics of the person with diabetes and the agent that we're going to use. We usually say that we need to reach the target within three to six months of diagnosis and then we want to keep them at the target. Certainly, people get very worked up about transient elevations in blood sugar with having intercurrent illness or whatever; there's not a lot of evidence that makes a huge amount of difference in aggressive management in those circumstances, and particularly important. Typically if the A1c is only 1.5 points over target, then we talk about initiating healthy behavior interventions, we start people on metformin, and that's the usual start. If it's more than 1.5% over the target, then we usually consider starting a second agent concurrently. The third category of patient is somebody who has symptomatic hyperglycemia and/or metabolic decompensation. This is a very important entity because these are people who have an aggressive decline in their condition, who may well actually have presented, not necessarily to the endocrinologist, but somewhere else. And this is one of the pearls that I want to give you, because sometimes the ophthalmologist is the one that diagnoses diabetes because you see advanced diabetic changes in somebody who has had essentially silent disease up until that point. But if they've got symptomatic hyperglycemia and metabolic decompensation, in other words their losing weight and they look quite sick, they really need to be seen urgently. It's not somebody you can just send off and they need to go to a diabetes center for some education; they need to be seen acutely and they almost invariably need to be started on insulin. So that's a special category. Generally, though, in most circumstances, we talk about getting to target within three to six months of diagnosis. In terms of those patients that are diagnosed by the eye care team, the things that I think really represent acuity are very, very high glucose levels, presence of significant comorbidities, and that metabolic decompensation that I described. And if you're sending a patient to us, obviously if you can get fasting glucose and A1c, if you can report on weight loss, and if they're really sick, then measuring ketones and other evidence of metabolic decompensation; I wouldn't expect more from an ophthalmologist. Obviously it's very, very important that we communicate. I have very good relations with the ophthalmologists; I have two or three that I work with specifically, and we regularly meet to discuss patient care issues and research and so on. Obviously this is a team approach and it ensures that people get adequately and timely care, and it means that we're able to cover for each other and improve detection of previously undiagnosed comorbidities and complications. In terms of strategies for improved co-management, clearly communication, standardized protocols, use of video education – I think we need to use more of these tools,. We do a lot more remote consultation now. Much of diabetes care doesn't actually necessitate the patient physically being present in the hospital in order to look at these kind of numbers, so I do a lot more telephone consultation, which allows me to keep on top of the patients and make sure they go see their ophthalmologist, and we use things like automated messaging to remind patients of their ophthalmology, vaccinations, and other clinical parameters they need to be compliant with. There are a couple of medications that I just wanted to mention that are newer; empagliflozin and canagliflozin are new agents that work in the kidney by opening the kidney up to sugar loss, so it's basically like a diuretic but for sugar and so you pee out your glucose. The extraordinary thing is that when these drugs were studied for cardiovascular outcome, they had a very dramatic impact on cardiovascular outcome, so not only did they cause

a blood sugar drop of about somewhere around 1-2% in A1c, but they also result in cardiovascular benefit and this is the first category of drug that has ever been shown to do that. The third drug that I want to highlight, liraglutide, is one of a group of drugs called GLP-1 analogs and these are injectable agents that work by stimulating insulin secretion from the pancreas and suppressing glucagon production. These drugs are also effective at lowering sugar from about 1-2% A1c, but have also been shown to result in cardiovascular benefit as well. You're going to see more and more patients on these agents, liraglutide, other newer GLP-1 analogs, and a number of other SGLT2 inhibitors coming down the line. None of them, as far as I know, have any evidence of any eye side effects or any eye issues, and the benefits that we would expect to see are generic A1c-lowering benefits that we would expect to see in terms of eye outcomes. That was my last slide. I was going to stop there.

Dr. Singh:
Now I'm going to turn it over to Dr. Arshad Khanani. He is going to talk about how we can become personalized and predictive with our anti-VEGF therapy in current practice.

Dr. Khanani:
Thank you, Rishi, and great talks by Dr. Boyer and Dr. Ur. So, my goal today is to talk about personalized and predictive treatment; how we can take the data from clinical trials and implement it in our practice so we can actually predict the treatment outcomes and personalize it based on patient's disease. Identifying early in the course of treatment which patients will respond and which patients will not is paramount to any personalized treatment regimen. The first trial I'm going to talk about is Protocol I and you can see that the long-term response of anti-VEGF therapy for DME, and this trial could be predicted after three injections. When you look at the different groups, sham plus prompt laser, ranibizumab plus prompt laser, ranibizumab plus deferred laser, as well as triamcinolone plus prompt laser. You look at two years in this trial, 52.8% of anti-VEGF eyes had less than two lines of visual acuity gain. There is really an unmet need in terms of DME that there is a sealing effect from anti-VEGF therapy and obviously there are new therapies that are going to come or be looked into to see if we can actually not leave vision on the table as Dr. Boyer said earlier. 45.7% of eyes treated with anti-VEGF had greater than 250 microns of fluid at two years. Basically, it's telling us that there is a subset of patients that anti-VEGF therapy really doesn't work, and if it works they still have pretty swollen retinas. So what they did was they looked at eyes with less than a 5-letter gain after three injections and what was shown was that if they had less than 5-letter gain after three injections, there was limited additional improvement for these patients throughout the duration of the study. If you look at that curve, especially the bottom one, you see that it kind of looks pretty consistent after the initial treatment. Obviously, this is a little bit different than the data you saw earlier from RISE and RIDE, and VIVID and VISTA where monthly treatment or every-other-month treatment showed slow improvement over time. There is a subset of patients where if they don't respond to early anti-VEGF treatment, they may not have too much improvement over long-term, and the discussion then starts about what is their baseline visual acuity, is it 20/50 or worse, or 20/50 or better in terms of what anti-VEGF we use, do we switch anti-VEGF, or do we go to steroids. Obviously, we have two FDA-approved steroids on the market which we can utilize early so we have better disease control and lead to better outcomes in terms of visual acuity. In this trial though, when you look at the baseline characteristics, one criticism is well the baseline characteristics were different in this trial, so is that the reason that the patients who had less than 20% improvement or more than 20% improvement had, because of the baseline characteristics. Even if you account for these changes, the early response to anti-VEGF remains a significant factor for long-term behavior in and after adjusting for baseline characteristics, so that's the criticism people have for this early analysis for Protocol I. The good news is that even if you account for that you still have a subset of patients that you can predict whether they are going to do good over long-term or not based on their first three injection response. Now we look at a lot of prognostic indicators in different studies. You have RISE and RIDE; it's a long list and I'm not going to go over it, but, basically, the general theme is that obviously people who have good visual outcomes, 20/40 or better, people who have subarachnoid fluid, patients with good baseline visual acuity as mentioned, and who have large improvement in their visual acuity and those are the patients that obviously had poor visual acuity to start with, younger age, shorter duration of diabetes; so, that is why it is really important to not only control diabetes early so we don't get into this situation but, if you do, try to do the lifestyle changes and medical interventions that Dr. Ur said to kind of control the disease early so we don't get to this stage. In terms of factors having no effect on outcomes in RISE and RIDE and macular cystoid spaces, hard exudates, renal disease, and the interesting part is A1c and I would like to get Dr. Ur's thought later during Q&A because a lot of these retina trials do not show the baseline A1c has any impact or long-term outcome. Obviously, you have to keep in mind that most trials will enroll 10 or less or 12 or less, so we're not dealing with super, super high A1c levels. In terms of prognostic indicators in READ-2 study, you can see worse outcome if they had less than 20/100, lower baseline visual acuity, focal atrophy which makes sense, focal pigmentation. There are better outcomes with patients who had greater than 20/100 and high baseline visual acuity. Factors having no effect were age, duration of DME, race, macular ischemia, extensive laser, baseline CRT, and restore, again. So, the idea is that there are a lot of prognostic indicators. How do we take this and implement it in our clinic? I think the bottom line here is that we need to intervene early, we need to diagnose early and I think we need to co-manage with our endocrinologists and primary care doctors so we can take care of these patients earlier and earlier. Protocol I, again, another set of prognostic factors that you can read. So,

predictive baseline factors - this is a great paper by one of our good friends, Dilsher. What they did was look at the baseline factors affecting changes in diabetic retinopathy severity, scale score after intervention with aflibercept, or laser for diabetic macular edema. What they found was that a strong association was present between baseline DRSS score and greater than 2 step DRSS score improvement at week 100 for DME patients and VIVID and VISTA. Obviously, Rishi, you're also an author on this – I failed to mention that. Personalizing the treatment plan to optimize outcomes, consider the key risk factors. Personalized risk profiling, early intervention and treatment, more frequent monitoring for those at high risk, early detection of the non-responder as we talk about Protocol I, identification of genotypic and phenotypic factors. Again, looking at the baseline visual acuity in terms of picking what anti-VGEF to use and whether we need to switch early or we need to switch to a different modality like a steroid and also knowing your patient's cross burden and compliance issues. Dr. Boyer did a great job explaining the fact that we all think that our patients actually show up for their appointments until we look at our own data. You look at the HR data, Kaiser data, and this happened to me, we said oh yeah my patients don't do that until I got a medical student to do a project to look at that over the summer and I was shocked how noncompliant our patients are, even in AMD and DME. I contributed our data to Michael Singer's paper and I was shocked to see -- because we get so busy in clinic sometimes, that we don't realize what patient didn't show up and we say come back in four to six weeks initially and we feel like we are doing that but, in the end, if you look at the data it's pretty bad, as Dr. Boyer mentioned earlier. As you know, many people with diabetes do not attend regular screening, they present with late stage retinopathy with results and a poor visual outcome, and I think it depends on where you practice. In Reno, I do see a pretty late-stage cases. I talk to my friends in the Bay Area and they usually don't see much diabetes because their population is very compliant and they intervene early, and it could be related to the level of education or awareness of disease. Some people have poor acceptance of the need for treatment and ongoing treatment, as Rishi said earlier, sometimes they will try to do everything else. I had several patients that were going blind and they would not do medicine, but they will do alternative medical therapy until they are blind pretty bad and then they are going to have that come-to-Jesus moment and then maybe it's too late to recover vision in those patients. Patient challenges, if you look at the national diabetes audit in the UK, what it looked at was whether the patients with diabetes age 12 or older had their required assessment annually, A1c, and blood work, and what-not, and it found out that 38.7 with type 1 diabetes and 58.7 with type 2 only completed their assessment. It is pretty shocking to look at this data. 75% of people newly diagnosed with diabetes were offered education, and only 5.3% attended. That again, brings us home the point that it has to be collaborative medicine, it has to be personalized. In terms of patient challenges and compliance, you talk about ABCs, awareness, belief that they do not require a retinal exam, and cost. Cost is a big issue; patients tend to be younger and there is the cost of missed work, cost of co-pays, and cost of drugs. I think the burden of treatment is pretty high. Distance; some of my patients travel three or four hours, sometimes they don't have rides, and if they are getting an intravitreal injection, it may be difficult to drive, and if they may need bilateral treatment they need to bring a driver with them. Effort to attend another clinic, we know based on the data from Nancy Olcam, most diabetics will have over 25 visits a year, and it is very difficult for them to maintain their monthly or bi-monthly visit with a retinal specialist, and the fear. I think that is something we don't really see, I think our staff sees the anxiety level more when they come in expecting an injection in their eye, especially young males, it is very difficult. They will not share with us and feel we don't need to see it. There was a paper done looking at the anxiety levels and they were pretty high in patients who were getting intravitreal treatment. There is guilt surrounding to control blood glucose level, their fear of eye exam, and really the idea that they need to have treatment whether it is laser or intravitreal injections. These are a lot of challenges we have to deal with in terms of compliance with our patients. Patients play a large part on their own outcomes as we talked about earlier; it depends on their education about diabetes, and their motivation, so they have to be informed and educated, medication compliance and as I said earlier it is a team effort. No matter what we do, if they are not controlling their A1c, and Dr. Ur made a great point about blood pressure and smoking, then we are going to still continue to have bad outcomes even with continued treatment. And then having a regular eye exam is also very important. What can we do? We can empower collaboration between health care professionals, that's why programs like this are very crucial, encourage roles within allied health, education programs for all new diabetics covering diabetes, potential blindness in the eye and all other systemic systems, strong patient communication, diabetes passport tool to increase patient to feel ownership of their disease, and facilitate communication between health professionals, show a patient their retinal images and highlight any changes, if they understand images as Rishi said, and improve deterioration to increase future attendance and good glycemic control. Sometimes actually just OCT helps too. A patient will come in and say, 'How does my OCT image look today after the last injection,' and they actually, over time, learn how to read OCTs, and I'm like, 'Wow, you don't need me anymore, only when you need treatment.' Other patients have no clue why they are there and what they are getting treatment for, so I think a lot of it depends on patient awareness of disease and I think we have to do a better job of that. The future of personalized medicine – patient's specific molecular diagnosis of diabetic retinopathy, proteomic analysis of which is fluid detection of neuroretinal degeneration and inflammation, as well as vascular proliferation. We have some new molecules in the retina that are come address not only VEGF, that tie to ANG2 pathway. Treat patients based on their individual characteristics similar to individualized diagnosis and treatment of cancer patients. So I will now give it back to Rishi for some real-world case examples.

Dr. Singh:

Thanks, Arshad. And I think my closing thought on this is that I think, for the most part, we realize in the past couple of years, both with the benefits of these medications that Dr. Ur spoke about tonight, as well as with our anti-VEGF therapy, there is really no reason for these patients to go really blind from these conditions. That idea that these patients will certainly develop diabetic retinopathy over time, lose vision, and have blindness in their lifetime can be staved off with both of these different advances we've had in the past couple of years.

Announcer:
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