RICHARD BERGENSTAL: Welcome back to our discussion of sensor-based glucose monitoring in the diabetes intelligence zone. This is module 2. And I'm Dr. Richard Bergenstal, the executive director of the International Diabetes Center in Minneapolis, Minnesota.

You remember in module 1 we talked about how to analyze an ambulatory glucose profile and what the key CGM metrics were. Now we're going to spend some time personalizing diabetes management getting it right down to the level of the individual making the best decision for that individual.

When I talk about personalizing diabetes management, it's a broad topic. And I'm going to talk about three different ways we personalize diabetes management. I call them the ABCs, the CKGs, and the GMIs. I know it sounds like a lot of spaghetti. But let's walk through this approach to personalizing management.

The first is the ABCs. When you're working in a clinical system, often the clinic system says, let's take the big picture. Let's be sure we're optimizing the D3, the D4, and the D5.

And you might say, well, wait what is that. Well, the D3 is the ABCs-- the A1C, the blood pressure, the cholesterol. Add not smoking, you get a D4. And add taking aspirin if you have heart disease, and you get a D5.

These are all quality measures. How are we doing on those? How can we personalize management to not make it just about glucose but the whole bigger picture? Well, in this journal article in the *Journal of General Internal Medicine,* which is an important one in primary care, you can see that the blood pressure and the cholesterol over the last decade or two are steadily improving.

But look at the A1C. While there was some improvement, it then was slipping. From 2010 up to the current, the A1C levels are actually deteriorating slightly. So we've got some work to do.

When we look across another large system-- this is our system in Minneapolis, over 60,000 patients-- we actually collect the D5, which is the ABC, and tobacco, and the aspirin. And you say, which of those 5 is the hardest to really get right. What do we have to spend personalized time trying to get correct? And you can see at a glance on the right hand side aspirin, using statins to control the LDL, tobacco cessation.

We're doing a pretty good job. Even the blood pressure we've got fairly well controlled, although recent articles saying that could be slipping a little bit on a nationwide and international basis. But look at that A1C. It's an outlier. That is by far our biggest gap in getting in control.

So while our clinic system may say, take a broad picture. We do have to focus to get that A1C controlled so we can get all of our metrics in range. It's going to take some innovation to get off this plateau. For several years, we've been at 70% in range. And we'd really like to get that to 85 or 90 like we have the other metrics.

So that's the ABCs. How about the CKG personalization of your treatment? Well, most everyone's aware of the new American Diabetes Association EASD algorithm for the treatment of type 2 diabetes. I call this the CKG algorithm.

You may say, well, why do you call it that. It's because when you look at this new algorithm, there's a built in set of first questions. I put in the red box there. That's the C and the K. And then we go to the G.

By that I mean the first question that the new algorithm says to ask is does this individual, like our patient on the left hand side, the 64-year-old with type 2 diabetes, do they have cardiovascular disease. The next question you asked, do they have chronic kidney disease. If so, those need to be addressed upfront regardless of the A1C. Then you ask, how about the glucose, the A1C. Is that optimized as well?

So this is personalizing the therapy based on their comorbidities that they have. And it's really important if we're going to optimize care.

You may not be able to read that first box. But if you look at it when I blow it up for you here-- and it basically just says, heart disease-- think about a GLP-1 or maybe an SGLT2. Chronic kidney disease, heart failure-- think about an SGLT2, maybe a GLP-1. But even so, you still have to think about glucose because that's important for all those microvascular complications.

So that's two ways to personalize care. Think about the ABCs. Think about the new management algorithms. The third I'd like to spend a little time on. That's called the GMI. And I call this the bridge from the A1C to our time and range that we talked about in module 1.

And I'll base this discussion off of an article that my colleague and I, Dr. Battelino, just published in *Diabetes Care.* It'll be out in October. This is the online version that's just out about how valuable continuous glucose monitoring is as a management tool.

What we say in that article-- and I show to you in the cartoon form here, but it makes the point. We're currently living in the A1C management era. I think no one would disagree with that. And I want to see if we can cross this bridge over into the CGM management era and tell you why it's important, and how we can personalize care to get there.

So we have the A1C. We want to move over to time and range and AGP that are part of the CGM we talked about in module 1. But your first question to me might be why. Why do we have to move off the A1C for management? What's wrong with the A1C?

I remember these papers and the DCCT, often quoted as the most important diabetes study ever done, showed as the A1C goes up, the rate of complications-- retinopathy, nephropathy, neuropaty-- go up. Since the end of the DCCT, which was in '93, and I marked it here on this slide at the bottom, that started the A1C era. And we've done pretty well. Look at the strokes and MI and amputations, renal disease, maybe a little flatter. We've made some progress in the A1C era.

It's a good-- A1C is a good population accountability measure. So what are the advantages and disadvantages again? Why are you talking about maybe moving beyond the A1C for management at least?

It's fairly standard. It's relatively cheap. It is related to vascular complications. And many algorithms have built in A1C for management.

So what are the limitations if those are the advantages? Well, the first limitation is just that A1C molecule again. Trying to explain that to patients and trying to motivate them to change based on glucose attaching to a red blood cell is a pretty hard concept to get across. Also the A1C is not a good indicator of hypoglycemia or glucose variability.

And there are many confounding conditions we've learned over the years of using A1C that make it less reliable. And I'm going to come back to that middle panel in the next slide. Also it's just an average measure. No patient likes to think, oh, you're just average. This is your average level of glucose. Well, I want to know m ore details about my glucose not just my average.

But let's focus on that middle panel for a second-- things that can affect the A1C to make it less reliable. And you'll notice at the bottom of the slide there's a reference of an article that Dr. Beck and I wrote called "The Fallacy of the Average-- Using the A1C to Assess Control Can Be Misleading."

And here's a main reason that I think it can be because there are many factors that impact our interpretation of the A1C. Race and ethnicity even makes a difference. African-Americans have slightly higher A1Cs. I'm not sure that's biologic as much as it probably is access to care and use of technology. But we have to take that into account.

Then the lifespan of the red cell-- if your red cell has a different lifespan that can change your laboratory A1C. And I'm going to talk to you more about that in just a moment. Hemoglobinopathies, loss of blood, hemolysis, pregnancy all affect the A1C measured in the laboratory, as do different variants of hemoglobin, as do variability in the short term. If you have very high sugars for a few weeks, it's going to affect the A1C. And the same with very low sugars.

So all of those factors together make us question if this is the most reliable measure for a given person. It may be great for a long term study. But how about for an individual?

Let me come back to that red cell lifespan. This is a bit complicated concept but one that really I think is important and starting to emerge. So I show you this graphic from Dr. Robert Cohen's work.

Let's say you're measuring the glucose in the blood. And the average red cell lives about 100 days. And the average of any red cell in the blood stream is about 49 days old, a given red cell. If you measure your blood sugar and it's 200. And you've measured it for several weeks. And that's the average-- is 200. That is usually an A1C of 8.6.

And if you look right in the middle of this graph, that square, it says, if you have an A1C, if you have a glucose of 200, and you have an average red cell lifespan like many people, you will have an A1C in the lab of 8.6. But if you happen to have a shorter red cell mean age, if your age of your red cells is 38 days on average, your lab will measure 7.5, whereas your blood says it's 8.6. If your red cells are older, you have a longer lifespan of your red cells, that lab will measure 9.9, whereas the bloodstream says no, it's only 8.6.

So you're going to get very different lab values back for the same glucose in your bloodstream depending on your age of your red cells. And different people have different lifespans of their red cells, probably shown even better in this graphic.

I always like to come back to patients and glucose profiles. Here's three glucose profiles on the left. I know these patients well. I've followed them for almost 35 years in that DCCT study we talked about at the beginning of this presentation.

All three of these patients had an A1C of 6.7. Congratulations for them, maybe for us, I don't know. They usually do the work. But they're under 7.

But now we look to the left at their profile, and we're not quite so happy. There really is quite a bit of variability so that the bottom profile patient had 9 times the rate of hypoglycemia as the top one, but they had the same A1C. The person on the bottom profile had twice the glucose variability-- I think you can see that just at a glance-- than the patient on the top. And the timing ranges were very different.

Which is better to guide your management, the A1C or the glucose profile? I think it's rather obvious, in these three patients at least.

So let's say you have the glucose. And you're just wondering from that glucose you have in front of you, whether it's a finger stick glucose or a really nice set of glucose from the continuous glucose monitoring, and you say, I wonder what my A1C would be based on these glucose.

Well, that was the basis of this study by Dr. David Nathan, where they looked at glucose measured across the world at many sites and many patients. And they took that mean glucose, and they compared it to a laboratory A1C. And then they came up with a formula and said from the glucose measurements you did, we can estimate what your A1C would be. It's called the estimated A1C.

So your patient sitting in front of you and has an estimated A1C-- or has a glucose of all their measurements of 185 milligrams per deciliter. What do you think their A1C would be? If I go back to the last line here, there's a little table that tells you, oh, well, that glucose will give you this A1C. Well, yes that's for the average of the whole population.

Now, when we take these and we look at this table, it turns out-- Dr. Nathan's study is on the right hand side. It's called the ADAG study. And it says, well, yes, a given A1C correlates to a given glucose. But there is a confidence interval around that glucose.

And the middle panel is the study that we did of several hundreds of patients using continuous glucose monitoring throughout their whole life of their red cell. And you see there is a variation around that. So your A1C of 185-- I'm sorry, your glucose of 185, what's your A1C.

Well, look at the table. 185-- where does it fit in that table? Well, it's seven, or it's eight. It fits into that confidence interval also. Or it's nine. A glucose in the bloodstream of 185 for one patient will give him an A1C of seven, another of eight, and another of nine. That doesn't give me a lot of confidence that the A1C is telling me the story of the glucose I'm actually exposed to.

And here's another way to look at it because many of you have seen us plot it this way. You plot the A1C against the mean glucose. And here's hundreds of patients all plotted on the glucose. And all those tables that you look up on all the websites are the black line. It's the average line. It's not the spread.

Each one of those dots is an individual. And they are unique. We have to personalize this.

Here's an A1C of eight. Well, one individual on the left hand side of this had an average glucose-- what is that-- 110, 115. Another person with an A1C of eight had a 220. There's just differences in how that glucose attaches onto the red cell-- the life span of the red cell. The factors that I talked about, and some we don't even know, that make that less reliable.

OK, let me bring it back to this GMI and this estimated A1C. You remember there's a term on the ambulatory glucose profile that we talked about in module 1 that's called the Glucose Management Indicator. Here it is at 7.6%.

This used to be called the estimated A1C. It was right there on the chart. We took the mean glucose. We plugged it into a formula, and we got it. Now it's called the GMI.

And here's a patient, just to bring this home-- 65-year-old, type 2 diabetes, metformin, insulin, short and long acting insulin, glucose profile. So congratulations, you did a glucose profile to try to understand this patient's glucoses. And you look up on the left hand corner here. And you say, estimated A1C 7% based on these thousands of glucose values.

OK, good. I'm waiting for my lab to come back as my doctor also drew the lab test. Can't wait for it to come back. OK, here it comes. Wait, 7.8%. I thought it was going to be seven. That's what all my glucoses showed.

So then this sets up a fury of phone calls. What's wrong with the sensor? It must be wrong. Well, no, what's wrong with the lab? It must be wrong. Wait, one of them is wrong. They're not matching up.

Well, the FDA heard these phone calls over and over again and said, well, if they don't agree, that's going to be confusing to patients. And that's going to be hard to explain. And the estimated A1C is really not an A1C. You're deriving it from glucose. So you shouldn't really use that term, A1C, because that's a laboratory measure. There's too much frustration here.

So the FDA said, can somebody-- can some group get together. And Dr. Beck and I led a group that sat down and thought about the terminology and said, we can come up with a term that captures this mean glucose and turning it into your glucose exposure. But we won't call it an A1C.

We'll estimate the A1C, but we won't use that term estimated A1C. We won't use a glucose index because dietitians and nutrition use that as glycemic index. So we have to have some other term that explains it. And so the term we came up with was called Glucose Management Indicator, the GMI.

And it's basically taking your mean glucose, putting it into a formula, and turning it into what we used to call the estimated A1C, but now we're using this term GMI. It replaces estimated A1C on the CGM reports. It shows you that you don't always expect the A1C and the GMI to be the same because the A1C, you remember, can be affected by so many factors. So we look at that. And we make up a chart of the CGM mean glucose, how it turns into the GMI, and you see that table here.

Now if I was to ask you, how often, when we took several patients and we got a really good measure of their average glucose at their GMI, how often did the GMI give you the same value as the lab A1C. You've got the formulas. Don't worry if you need the formulas.

Here's the table that people were surprised about. 19% of the time the laboratory A1C and the GMI, which is derived from the mean glucose in the blood from thousands of glucose values, were a good complete match within 0.1-- 19% of the time. 50% of the time they were 0.3 difference, which is starting to get clinically significant. And 28% of the time they were 0.5 or more difference.

So you really would start to make different clinical decisions based on that. So that's important to know what your GMI is and to put some clinical sense to it.

Now people said, well, you use the Dexcom sensor. And that's one type of sensor. I'm not so sure that would hold up if you used the Navigator sensor, which is made by Abbott-- and their current Libre system uses similar sensor technology-- or you use the Medtronic sensor.

So one of our colleagues in England did a very nice study with those other two sensors. And look at the table. It's almost identical to the one that we did-- 19%, and some 50% 0.3, and some 28% to 35% over 0.5. So it's a pretty consistent finding.

So the press and the blogs start to say, OK, the GMI is replacing the estimated A1C for CGM sensors. You better catch on to this wave because it's happening. And that's important. And I like that when we get the word out.

But I even liked it better when the response came back from the FDA because that's important. And they said, well, I think the authors did a service. They put some new terminology in that makes sense that won't lead to as much confusion and that may actually help with diabetes management because that's what this is all about really.

So you've got the GMI, which is sort of the estimated A1C new terminology, that's based on glucose sensing. And you've got a lab test. Now you won't expect them to be the same if there was an acute change in hyperglycemia.

If you just took steroids and your sugars went to 400, or you just had an episode of ketoacidosis because your infusions came on unhooked, you're going to have very high glucoses for a short time. But your A1C goes back three months. So that's OK. They shouldn't agree there.

Sometimes you're going to have a very low GMI because you started a ketogenic diet. And you're really not eating carbs. And your glucose just fell through the bottom. Or you started a brand new therapy that knocked your sugar down. Those are ones we would say, OK, they don't agree. Don't expect them to agree.

But if you're a fairly stable in your management. You're going along, and you're being checked from visit to visit. Now the difference between the lab and the GMI, this mismatch between the two, actually is important.

Here's a table we put in the paper just to explain it for patients, for physicians and clinicians, and educators to explain back to their patients. If they match pretty closely, fine. You happen to have the characteristics that your A1C gets glycosylated and your life span of the A1C is such that your CGM and your A1C match up.

But what if you're in category number two there in the middle-- an A1C of 8 from the laboratory but 7.8-- 7.2 based on your thousands of glucose values from your CGM. That's important. Your real exposure in your system is-- glucose is around a 7.2 A1C. So be careful how much you intensify. If you think you're 8 and you're trying to get down to 6.5, you're going to be in trouble because you're really about 7.2.

And then the bottom one is the opposite. Your blood shows that your about 8. But your lab is saying 7.2. And you really start to push. Or you see the 7.2 from the lab, and you let up and say, oh 7.2 A1C. I don't really need to do much. But yes, your CGM is really quite high.

So pay attention to the GMI. I think it's really a good measure to personalize your therapy based on-- it's your personalized A1C I like to call it.

And we don't have time today, but there's a whole literature about this mismatch between lab A1C and blood glucose. There's something called a hemoglobin glycation index.

Where we didn't have CGM before, we used to just have a fasting glucose. But you could predict your A1C from the fasting glucose. And there was often a mismatch there. And that became a term called the hemoglobin glycation index.

You can do a fructosamine which a lot of people do. And that measures glucose attaching to other proteins in the red cell. And that can help you sort out whether you have a red cell specific problem, and getting that why the A1C doesn't match.

Then you can use the GMI, which I just talked about. That's the one I would prefer at this moment. Look at that comparison. Use the GMI as your personalized A1C.

You can even do it off of finger sticks. But be careful. Be sure you have a lot of glucose data. Don't just do an occasional blood sugar. But if you have enough data you can estimate what the A1C would have been or equivalent to like a GMI.

And then finally, just watch for a few months and years coming. There's lots of fancy technology that's going to tell you the lifespan of the red cell, going to tell you your glycosylation rate, and really get this even more accurate than the GMI at the moment.

I'll just mention, a couple weeks ago at a European diabetes meetings, there was a paper that said this hemoglobin glycation index was a better predictor of kidney disease than the A1C was because it's more personalized. And those people who had a high HGI index were at more risk for kidney disease. But the A1C might have missed it. This is early, just been discussed, but keep your eye out on the value of personalizing that A1C.

So today we've discussed we've been in the A1C management era for a long time. It's held us in good stead. It's an important measure.

But once we've introduced the AGP and continuous monitoring, one of the metrics on that AGP is this glucose management indicator. I kind of call that GMI the bridge. It makes us more comfortable to move over to the time and range.

If you like A1C, at least use your personalized A1C in the middle for management. And then eventually you'll get comfortable using the time and range as your management guide for CGM management era.

So I hope that adds some clarity to personalizing therapy. So now as we complete module 2, we've talked about analyzing CGM and the AGP in number one. We've talked about personalizing the therapy to get it just right for that individual in module 2. And I hope you'll join us coming up in module 3 where we'll learn how to use all this data to actually make therapy adjustments and optimize the care. Thank you very much.