Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting: https://reachmd.com/programs/cme/testing-and-screening-for-type-1-diabetes-t1d-genes-antigens-autoantibodies-methodology-and-clinical-utility/14285/

Released: 01/10/2023
Valid until: 01/10/2024
Time needed to complete: 30 minutes

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

Testing and Screening for Type 1 Diabetes (T1D): Genes, Antigens, Autoantibodies, Methodology and Clinical Utility

Announcer:
Welcome to CME on ReachMD. This activity, entitled *Testing and Screening for Type 1 Diabetes (T1D): Genes, Antigens, Autoantibodies, Methodology and Clinical Utility* is Jointly provided by Partners for Advancing Clinical Education (PACE) and HealthmattersCME and is supported by an independent educational grant from Provention Bio.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the Learning Objectives.

Dr. Atkinson:
Hello everyone. My name is Dr. Mark Atkinson. I'm the Director of the Diabetes Institute at the University of Florida, and a member of the Departments of Pathology and Pediatrics here. I'm here today to help lead discussion on what I think is one of the most important emerging topics in the field of type 1 diabetes. And that is that of autoantibody screening to identify the risk of individuals for this disease. The slide actually brings back a lot of memories. I started my career in type 1 diabetes some 40 years ago, and in 1983, I used to work a lot in this situation, like you see on the right side of the screen, drawing blood from individuals with a hope of identifying those at risk for the disease. Back then, that was a dream of mine that we would see this occur.

I never thought it would take almost 4 decades to occur, but right now, I believe we're at that point. And it's an honor today to bring three internationally recognized experts in the field of type 1 diabetes together in order to help bring you, the audience, together on a number of issues and matters related to autoantibody screening for type 1 diabetes risk. This will be a very positive presentation, I believe, for reasons that it is a very positive message. Our first speaker will be Dr. Emily Sims, who is a much-respected rising superstar in pediatric endocrinology. She is coming to us from Indiana University in Indianapolis, and she is going to introduce the topic to us. So, Emily, it's up to you. Thank you.

Dr. Sims:
Thanks for that really nice introduction, Mark. And thank you to everyone who's tuning in and paying attention today. I'm going talk to you about testing and screening for type 1 diabetes genes, antigens, autoantibodies, methodology, and clinical utility. So, I thought I would start this talk with a little bit of an introduction to type 1 diabetes and the pathophysiology underlying type 1 diabetes. We know that type 1 diabetes is an autoimmune disease that leads to destruction of the insulin-producing beta cells in your pancreas. And we also know that people who ultimately develop type 1 diabetes start with some sort of genetic predisposition to disease. If you have a first-degree relative with type 1 diabetes, your risk is about 15-fold compared to someone who doesn't have a relative. Although interestingly, most people who present with new type 1 diabetes do not have a family history. Then, people with genetic predisposition encounter some sort of environmental trigger that tips the scales towards islet autoimmunity. And if this process goes unchecked and progresses, you have eventual loss of beta cells and beta-cell function that initially leads to changes in your blood sugar and ultimately frank hyperglycemia, with symptoms of polyuria and polydipsia and ultimately the need for exogenous insulin.

So, you might say, why do I care about type 1 diabetes? Well, it's here and it's increasing. This is a graph of the incidence of type 1 diabetes over time in many different countries, including the United States shown in a darkish purple color towards the middle of the

graph. You can see that the incidence of type 1 diabetes is increasing over time. So, it's something that we should be paying attention to. Another thing people might say as well, type 1 diabetes is bad, but we've got a pretty good treatment for type 1 diabetes.

We have insulin, and indeed we're just coming upon the 100th anniversary of insulin being discovered by Banting and Best. And man, this is a really amazing drug. When you think about patients who had a diagnosis of type 1 diabetes before this discovery, and the impact that it had on their lives, it's really incredible to consider. These are pictures of two of Dr. Banting's most famous patients, Teddy Ryder and Elizabeth Hughes, before insulin was available to patients with type 1 diabetes and then after they were treated with insulin. As you can see, indeed insulin really has been transformative for patients with type 1 diabetes. And then, you know, since that time period, we've really had remarkable advancements in the care that we can provide to our patients with type 1 diabetes. And this has ranged from discoveries that have improved our ability to monitor glucose, most recently with CGMs or glucose monitors that allow for continuous glucose monitoring, as well as changes in the way that we deliver insulin, most recently with insulin pumps that talk to glucose sensors and have semi-automated delivery that can really improve the patient burden and the quality of life for our patients. But even so, I would argue that we really have a long way to go in the way that we provide care to our patients. The reasons I say this are multi-fold. First of all, we know that life expectancy is still reduced in people who have type 1 diabetes. So, these are data from the Scottish Diabetes Registry, which is a registry that follows everyone in the country with type 1 diabetes who's over age 20. And you can see life expectancy data in these graphs for men on the left and women on the right. As you can see compared to someone who doesn't have type 1 diabetes, the life expectancy for people with diabetes is reduced by 11 to 13 years depending on sex.

And so, you know, some people might say, well, we know that some of these complications that can reduce life expectancy and cause morbidity, mortality, and diabetes can be reduced if you can just maintain glycemia in the goal range, where our targets are. But this is really hard, too. So, these are data from the T1D Exchange Registry, which is a registry in the United States of endocrine clinics. And these are hemoglobin A1C data from people with type 1 diabetes from 2010 through 2012, which are shown in orange and 2016 to 2018, which are shown in blue. And the solid line in dark navy or black underneath is the goal A1c at the time. In fact, the goals for pediatrics have decreased since these data were published. But as you can see, unfortunately for all age groups, we're not meeting those goal metrics. And this is especially true for pediatric age groups and people in that adolescent age group.

So, another kind of really important complication to consider is even before we have a chance to intervene in people's diabetes, there's also the risk of diabetic ketoacidosis or DKA at the time of type 1 diabetes onset. In the United States, depending on where you're located, rates of DKA typically range from 25% to 50% at diagnosis, and they appear to be increasing over time. The graph on this slide shows DKA rates from the Barbara Davis Center in Colorado, and rates over time from the private and public insurance type 1 diabetes populations. And as you can see, over time they're increasing and most recently we're above 50%. As we all know who've taken care of patients with DKA, this can be associated with significant short-term morbidity and mortality, including cerebral edema, risk of DVTs, and hyperosmolarity, and additionally, just the kind of stress for a family and a patient of an ICU admission, which is potentially or definitely associated with additional significant cost. And then we also know that there are long-term impacts of this on neurologic function and children especially, and long-term glycemic control.

So, these are also data that came from the Barbara Davis Center, in which the investigators modeled the effect of DKA on long-term hemoglobin A1c values and people with type 1 diabetes and adjusted for potential other confounders that might impact long-term A1c. And as you can see, the people who presented with severe DKA who are shown on the red line, compared with people who didn't have DKA at diagnosis, who are shown on the black dashed line, had about an average of 1.4% increase in their A1c over time. So again, presenting with DKA at diagnosis can lead to long-term impacts on glycemic control, which we know are important for long-term health outcomes in type 1 diabetes.

So, what's the case for screening for type 1 diabetes? Well, the first thing is that we can do it; we can effectively screen for and identify asymptomatic or presymptomatic type 1 diabetes. How do we do this? Well, we do it via measurement of islet autoantibodies. And so, these are the 4 biochemical autoantibody assays that are currently most widely available that you will see a lot of people use. These include insulin (it's abbreviated IAA), islet antigen 2 or IA-2, zinc transporter 8 or ZnT8, and glutamic acid decarboxylase or GAD65. These are all beta-cell autoantigens that the immune system is picking up, and you can recognize as autoantibodies in blood.

And this idea that we can identify people in this very early asymptomatic or presymptomatic stage of type 1 diabetes first got a lot of traction from these data that were published in *JAMA* in 2013, and combined data from 3 different birth cohorts, from different locations, and importantly, that included populations of people both who had family history of type 1 diabetes, but also people who didn't have a family history. So, they were from the general population. And this was a group of >500 children that were followed over time for development of islet autoantibodies and type 1 diabetes. And what the investigators found was that once these children developed more >1 of these islet autoantibodies, by 15 years of follow up, about 84% of them had developed type 1 diabetes, such that over a lifetime, once you develop multiple islet autoantibodies, your risk of developing clinical disease really approaches 100%.

And based on this, the type 1 diabetes community has adopted this staging system where now we consider what we used to think of as the diagnosis or the start of type 1 diabetes, the clinical diagnosis, as Stage 3 disease. And if you develop multiple islet autoantibodies, because we know that your long-term risk of type 1 diabetes or clinical type 1 diabetes is almost 100%, now we call that Stage 1 diabetes. And then someone who has multiple islet autoantibodies plus changes in their glucose but hasn't met those ADA criteria to diagnose diabetes, that's Stage 2 type 1 diabetes. And then again, Stage 3 would be what we traditionally considered clinical diagnosis of disease, meaning those kinds of classic criteria for diabetes based on A1c and the two-hour, the fasting glucose.

So, I think there are a lot of natural questions that come from these data, the first being, when would you expect these islet autoantibodies to develop? And the great news is that we have some really good information from some of these natural history birth cohorts that can inform us in these questions. So, these are data from the BABYDIAB study that followed infants at genetic risk for the development of autoantibodies and diabetes. As you can see, there's actually this period between 9 months and two years of age when most islet autoantibodies develop in these genetically at-risk infants. And not all antibodies are created equal. There's a difference in kind of which antibodies most commonly occur first. As shown in these data, insulin autoantibodies actually are the ones that tend to appear first in these infants that ultimately develop islet autoantibodies.

Additionally, not all antibodies are created equal with what they mean in terms of subsequent risk of rates of progression of diabetes. So, I thought these data are really interesting. We are looking at children from the Fr1da cohort. So, these are individuals from the general population who were screened for autoantibodies, and then followed for diabetes development after they developed autoantibodies. And so, they were really interested in looking at risk factors for the rate of progression to diabetes once you got to Stage 1. So, you develop multiple islet autoantibodies, what risk factors mean that you're going to develop clinical diabetes sooner? One thing that the investigators found was that the presence of a positive IA-2 antibody titer or higher IA-2 antibody titer was associated with more rapid progression to clinical diabetes, so associated with increased risk versus some of the other islet antibodies.

And finally, there's been a growing recognition that there are probably different phenotypes within type 1 diabetes. So not everybody's type 1 diabetes acts exactly the same. Some people have a more severe phenotype and different progression of disease, maybe different clinical features. And some of this seems to also be connected to islet autoantibodies. So, in the TEDDY study, which stands for The Environmental Determinants of Diabetes in the Young (it's another birth cohort of people with family members and from the general population at increased genetic risk, followed over time for islet autoantibodies and diabetes), the investigators have determined that there seems to be a different phenotype depending on whether children develop insulin autoantibodies or GAD autoantibodies first. Children who develop insulin autoantibodies typically, again, develop the autoantibody early, in the first year of life, have a younger age of diabetes onset, tend to be boys (although both sexes can have this phenotype), and tend to have higher-risk HLA genotypes compared to people who develop GAD autoantibodies first, who actually can develop autoantibodies more commonly throughout early childhood, have an older age of diabetes onset, tended to be girls, and have lower-risk HLA genotypes.

Okay. So, when should we be doing this screening? Well, this is a complicated question and a lot of people have proposed different approaches to this. There are a few things to think about. We know that serum conversion typically happens very early. And so, we really want to capture really young individuals who are going to progress early to diabetes and we know are at high risk of presenting with DKA that can be really life threatening. But we also don't want to miss people who develop autoantibodies later. So, we have to balance sensitivity as well as participant burden with multiple checks. And so, people have had different approaches for what might be the best way to do this. People from the TEDDY study have a really smart analysis, which is shown on this slide.

Here you can see in the rainbow-colored graph a plot of the cumulative risk of getting any islet autoantibodies depending on what age you are. As your age increases for these genetically at-risk individuals, your risk of developing autoantibodies decreases over time. And then they looked at your five-year risk of getting multiple autoantibodies. So, Stage 1 classification, the risk is very high in those first 2 years and then really starts decreasing over time, such that by the time you get to 7 or 8 years of age, it's pretty small. And so, these investigators looked at combining 2 different age time points to see what was the best benefit or the best balance of sensitivity and positive predictive value. And, what they came up with is that maybe the best approach to screening would be doing autoantibody testing at 2 years, followed by another test in that 5 to 7-year period so that you're capturing those very early severe presentations, but then also getting people who develop autoantibodies a little bit later in childhood.

Other people have taken different approaches. Some natural history studies do testing every year in people who are at high genetic risk. But those are studies that are designed to understand natural history and not necessarily think so much about feasibility and cost. Then other programs have thought more about balancing sensitivity and costs. So, for example, Type 1 Diabetes TrialNet, which is an international program that provides free autoantibody screening to family members of people with type 1 diabetes, repeats testing yearly for people who test single autoantibody positive, but don't necessarily meet those early Stage 1 criteria. And additionally, they currently don't do re-screening for people who test autoantibody negative, although this policy is being revisited. But there are more

data that that suggests that we can reconsider this.

So, for example, people who have single autoantibody positivity, we know that at first, they're probably at higher risk compared to someone who screens autoantibody negative. But we can look back at natural history data to see that long term, their risk gradually decreases over time. So, the graph on the bottom right of the screen is, again, data from the BABYDIAB study that looked at children who seroconverted to single autoantibody positivity and when they converted to multiple autoantibody positivity, if they did. As you can see, most of these people who went on to develop multiple islet autoantibodies, it really happened in the first couple of years after they tested positive for single autoantibodies. So, it may be that looking back at some of these data, we can refine our policies for testing and, as an example, for single autoantibody-positive individuals after a couple of years, if they haven't progressed to Stage 1, we may be able to back off on screening. And then additionally, I think another caveat is that in my opinion, the optimal testing or timing of testing or screening for adult-onset type 1 diabetes has not been super-rigorously tested and needs to be better studied.

Okay, so we talked about autoantibodies. There are also some other measures that people are really interested in for identifying people at increased risk. This includes genetic and metabolic screening. The genetic screening typically tests for high-risk HLA genotypes, and also additional genes that might increase risk. A lot of people are incorporating these into a risk score that is easier to interpret and apply. This kind of testing is often applied as part of screening programs that test newborns, because it requires a pretty small amount of blood and can use a capillary stick or a blood spot. This would still require autoantibody testing. But the idea would be that you would carve out a population of people who are at high genetic risk so that you have to test less people for autoantibodies over time.

A lot of people are really interested in metabolic testing as well. This can include testing of C-peptide, insulin, and glucose, as well as markers of beta-cell stress and health. This kind of testing is often performed as part of an oral glucose tolerance test, which can be really useful for staging, whether you're in Stage 1 or Stage 2 type 1 diabetes, but also for monitoring of progression to Stage 3 or clinical diabetes. This testing is often used to really better understand, once people have developed early-stage type 1 diabetes, what their risk is for how quickly they're going to progress to Stage 3 disease. I will say that both of these tools are very useful, but right now are probably mostly utilized as part of research protocols. But I think people should stay tuned because I think they can both be really helpful in carving out people at higher and lower risk and making screening more feasible for widespread use. So, I think they're going to become more and more used.

So, back to the case for screening. I hope I've convinced you that we can effectively identify asymptomatic type 1 diabetes, but what can we do about it? I think there are a couple of important goals that this screening can achieve, especially if you also educate and monitor participants. The first one is that we can prevent DKA onset. These are data from multiple screening studies that show the expected rate of DKA without screening on the far right, and then the DKA rates that they actually observed in the studies with screening education and monitoring. And as you can see, the rates are reduced by about 3- to 10-fold—so really, really drastically reduced when you intervene in these populations and educate them about type 1 diabetes risk of DKA and then follow them for the development of diabetes.

Additionally, there are a couple of other really important things that we can accomplish with type 1 diabetes screening. The first is this idea that you provide these families the opportunity to have a smoother progression into the diagnosis of clinical type 1 diabetes. If you think of the way that this has traditionally happened, these families overnight get this diagnosis, and their world changes and they start on insulin, have to do this really fast education. It can be a really stressful experience, and probably not the best way to learn about type 1 diabetes and how to get this new type of care that really involves big lifestyle changes. But someone who's identified through screening, they have time to process, get education, and work with their pediatric endocrinologist to get a plan to slowly start insulin as they need it. So, it can potentially be a lot better. And then finally—I'm not going to talk about this very much because this is the focus of Dr. Gitelman's session—identifying people in early-stage type 1 diabetes also identifies people where there are opportunities for intervention with disease-modifying therapies that can potentially change the course of their disease.

Another really important point I just wanted to touch on is that screening can be performed in the United States and it's really very accessible. This is a really handy chart from asktheexperts.org, which is a program that's associated with the ASK research screening program in Colorado. And it provides information on different screening programs that are available to people in the United States. If it's possible, I would recommend getting involved in a research-based program, which will be free to participants and also automatically provide monitoring and follow up, usually depending on the program. Depending on where you're located, CASCADE and PLEDGE can be options for this, for people in the general population. And then for everyone in the United States, Type 1 Diabetes TrialNet is available to family members who are first- or second-degree relatives of people with type 1 diabetes. This can be obtained in person or families can actually order a kit online to do home testing through capillary sticks. So, it can be really, really convenient. There is also direct consumer testing available through Enable Biosciences, as well as testing that PCPs can order through clinical laboratories for their patients.

So, what are the current guidelines from our diabetes organizations? The American Diabetes Association and their most recent guidelines said that screening can be considered an option in first-degree family members. But otherwise, it's currently recommended in the setting of a research trial. One thing to think of about is that unfortunately most people that present with type 1 diabetes don't have a family member. So, what about people in the general population? ISPAD, or the International Society of Pediatric and Adolescent Diabetes, and their most recent guidelines actually addressed this a little more directly. They kind of acknowledge the benefits of screening that we already talked about, including identifying early diabetes, reducing DKA and hospitalization, and potential for intervention. They highlighted that screening should be associated with education and monitoring, but also that general population programs can be useful to identify high-risk children. Interestingly, they commented that when immunotherapy is capable of delaying progression or approved, and economic issues are optimized for screening, that they expect general pediatric population screening to be implemented in many regions. So, I think this is something we should all be paying attention to that's potentially coming.

All right. To summarize my session, I hope I've convinced you that we need to improve our current treatment strategies for type 1 diabetes, and that screening for islet autoantibodies can identify people who have pre-symptomatic disease and is widely accessible, particularly for people who are family members of people with type 1 diabetes who can get free screening through TrialNet. And then additionally that there's a lot of potential benefits for this early identification of type 1 diabetes in these early stages, including a smoother transition to insulin treatment, drastically reducing DKA and hospitalization at diagnosis, and allowing for the possibility of intervention with disease-modifying therapies. My opinion is that major needs in this area moving forward include clear guidelines for monitoring and follow up of people who have positive screens, as well as a clear pathway and plan for testing, monitoring, and intervention in people who don't have a family history who again, represent most of the people who present with type 1 diabetes.

Dr. Atkinson:
Emily, thank you so much for that amazing introduction to this topic. I think you covered it extremely well. One of the things I think we get used to in medical research is we hear about a study where 300 patients were subject to a research investigation and then an outcome comes. Can you just reemphasize the difference of the situation here in terms of the number of people that globally have been examined in terms of screening and the amount of time that it's taken to get to this point?

Dr. Sims:
Yeah, I mean, this is a great question. I think this is something that's been decades and decades in the making, right? So, Dr. Bottazzo in the 1970s was the first person who discovered that people who are at risk for type 1 diabetes have these islet autoantibodies in their blood. And since then, there's been tons of researchers working on optimizing these assays so that they're reproducible. And we have really great data that they work really well to identify and predict the onset of type 1 diabetes. The data I showed from the 2013 *JAMA* paper that combined birth cohorts had data from >500 kids who developed type 1 diabetes. But, you know, thousands and thousands of children with islet autoantibodies have been studied over a long, long, long, period of time.

We have some really rich natural history data that have given us this information with lots of people working together to provide it. The other study that I think has been really informative, at least for the United States, has been the Diabetes Prevention Trial-Type 1, which was a prevention trial to test the effect of giving insulin to delay or prevent the onset of type 1 diabetes. But as part of that study, which was implemented in the 1990s and reported in early 2000, it required identifying lots of people who were at high risk. And they showed that you were really able to effectively identify and follow these individuals, and then kind of built up this rich natural history cohort that we've used to accumulate a lot of important information about diabetes risk and progression, and has led to a lot of other really important studies.

Dr. Atkinson:
Great. Emily, thank you for that answer. So, I know from personal experience, this is what I would define as a low-risk procedure, but in case anybody has fears about this, can you just say why I'm right that this is a low-risk procedure in terms of a blood draw?

Dr. Sims:
Yeah, I totally agree with you. This is very low risk. The only physical risk associated with this testing would be the risk associated with the blood draw. It's a pretty small volume of blood so, it's not something that's going to give anybody any symptoms, but just the kind of discomfort that you'd associate with getting your blood drawn. Some of the testing is capillary sticks, which can be even more convenient and take less volume. The other kind of thing that you might think of is the risk that's associated with waiting for the result of the testing and the kind of anxiety associated with that. But we actually have pretty good data about that as well, from some of the natural history studies that have been performed, that suggest that people do have increased anxiety when they first get a result about being at risk for type 1 diabetes, but that subsides pretty quickly over time. And that when you look at the anxiety that those families have at the time of diagnosis, it's much, much, much reduced compared to families who haven't had the opportunity to get education and monitoring ahead of time, when the period of diagnosis is a super stressful life-changing time.

Dr. Atkinson:
And you would say that this test is amenable to people in either urban or rural populations? This is not a test that's just limited to people in major cities, meaning this could be, at least in the United States and globally, a test that could be used no matter where their geographic locale.

Dr. Sims:
Yeah, I totally agree with that. I mean, how you get the test depends on, you know, your path to testing; how you choose to get the testing. But the clinical lab testing is really widely available. I mean, I think probably at almost every hospital. And then the really nice thing about the Type 1 Diabetes TrialNet program is that they've worked really hard to make testing convenient for families so that they can order a test kit online even and have the kit shipped to their house for testing locally, which is great.

Dr. Atkinson:
All right. And my last question for this session is you showed the various risk factors based on the type of autoantibody, and BMI. Are these autoantibody markers thought to be specific for type 1 diabetes, or is this something that is present in individuals with type 2 diabetes?

Dr. Sims:
I would usually say that someone who has islet autoimmunity has type 1 diabetes, although this is an interesting question because I think especially in adults, a lot of times people get diagnosed with type 2 diabetes, and they're misdiagnosed. They actually have type 1 diabetes. And so, if people had thought to check for the islet autoantibodies, they might have realized that. So, I think that sometimes it is underdiagnosed in adults. And then the other thing I would say about that is that, you know, sometimes people can have a little bit of a mixed picture. We know type 2 diabetes results from people inheriting a predisposition of beta-cell function, and some insulin resistance. So, you can certainly also inherit those things as well as islet autoimmunity. That can give you kind of a mixed picture, but typically people who have islet autoimmunity are going to require insulin administration consistent with type 1 diabetes.

Dr. Atkinson:
So, to that answer, which was a great one actually, there's a potential benefit throughout an individual's lifetime, right? Meaning you gave a lot of data about early life screening, but in somebody that in later life may be not performing well or responding well, I should say, to traditional type 2 medications, if they have screening maybe that could identify them as being essentially misdiagnosed or ineffectively diagnosed, and as having type 1 diabetes.

Dr. Sims:
I totally agree with that statement. And in fact, I mean, I'm a pediatric endocrinologist, but I screen everybody with new diabetes with autoantibodies because I think it can be very informative for how I'm going to approach care for my patient.

Dr. Atkinson:
Thank you, Dr. Sims, for bringing this very informative presentation to us. I think you've told us a lot about the importance of type 1 diabetes autoantibody screening, laying an intellectual foundation, if you will, and setting a stage for why such an activity is really important for improving healthcare moving forward around type 1 diabetes. Thank you very much.

Announcer:
You have been listening to CME on ReachMD. This activity is Jointly provided by Partners for Advancing Clinical Education (PACE) and HealthmattersCME and is supported by an independent educational grant from Provention Bio.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.