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Predicting Type 1 Diabetes Using Genetic Testing or Islet Antibody Screening: Are WE There Yet?

Announcer:
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Dr. Atkinson:
So, we're going to continue on with our notion of autoantibody screening in terms of identifying risk for type 1 diabetes and its importance. And here we're going to talk about some of the more pragmatic elements that are involved in this procedure, and really emphasize the notion of why. And I'm so pleased that we're going to have Dr. Linda DiMeglio, who is from Indiana University School of Medicine and Riley Children's Hospital, and also Deputy Director at NIH TrialNet. So many qualifications and why she's able to speak to us today with an expert perspective. And again, I look forward to hearing from her on how the combination of genetics, islet autoantibody screening, and other elements are taking us to a whole new level, if you will, in terms of type 1 diabetes research, care, and the future. Linda.

Dr. DiMeglio:
Thanks Mark for that kind introduction and for the invitation to speak about a topic I like to think a lot about. We're here today talking about the topic in part because population-based type 1 diabetes screening initiatives are expanding. And there are a series of reasons why this is the case. First and foremost, screening is associated with improved clinical outcomes, including preventing diabetic ketoacidosis at diagnosis. Secondly, screening can ease the transition to life with type 1 diabetes rather than an abrupt, new-onset situation. And thirdly, therapies to delay progression to insulin dependence are on the horizon. There are emerging data, using two different screening approaches, which is what I'll be focusing on today. The first is using genetic risk assessments, and the second is islet autoantibody screening. So, if we think about future directions for screening from today, stepping forward, one approach can be genetic risk assessments, which will be incorporated into universal newborn screening programs. And a second would be islet autoantibody testing in primary care offices, or through home-based testing as part of preventative care. So, when we think about the genesis of diabetes, we can understand the reasons why these two approaches are valid.

So firstly, in order to develop type 1 diabetes, you have to have a genetic predisposition. This is then coupled with an infection or other environmental trigger or something else that triggers the start of diabetes. This trigger leads to autoimmunity against beta-cell antigens that leads to loss of beta-cell function that leads to dysglycemia, followed by symptoms of hyperglycemia—so, polyuria, polydipsia—and eventually one becomes dependent on exogenous insulin. So, when we think about screening, we can screen at these two key points, to look for those at genetic risk or look for those who already have autoimmunity.

We'll start with the genetic risk assessments. So how does genetic screening work? Well, DNA testing for high-risk HLA genotypes, as I'll show you, and other genetic changes that are associated with higher risk for islet autoimmunity and ultimately type 1 diabetes can be performed. And, this is in general not something that can be a one-off effort, because of the issues with interpretation and the need for

follow-up. So, it is important that genetic screening is done as part of an organized screening program, and we'll talk about some of those options. Those who have a positive genetic screen are then followed up with autoantibody testing if at high risk. One such screening program that was run in several countries throughout the world was the TEDDY study. And I just want to take you through a little bit of what was done in TEDDY, so you can see the magnitude and the overall scale of what is necessary to do genetic screening for diabetes. So, in the TEDDY study, approximately 420,000 infants were screened in order to identify people at risk.

The TEDDY study was a unique cohort in that it over-selected for persons who are relatives of people with type 1 diabetes. About 90% of the people that came into TEDDY were from the general population without a known relative with type 1. And about 10% were relatives. Of those 424,000 people, approximately 5% were eligible based upon HLA. And of those, about 40% were enrolled in a 15-year follow-up study. So, this study illustrates one of the issues with genetic screening, which is that even when you do genetic screening and you have permission to get genetic screening, there is still an attrition in the follow-up of those people who are found to be at risk. I show you this table, because the haplotype genotypes that were used for HLA in this study were complex and also differed between those who were first-degree relatives, shown as FDR in that table, and those in the general population. So not only were there a number of HLA haplotypes that had to be determined, but they were tailored based upon estimated risk. And then, the study ultimately followed children at risk for 15 years and approximately 4% of those at risk developed type 1 diabetes. The study was initially powered to find 400 people at risk. So, the study powering was done very well, but you can see only about 1 in a 1000 people that were screened ultimately developed type 1 diabetes over 15 years. It doesn't mean that more of those people will not go on to develop diabetes going forward, but it just means you had to screen a huge number of people to find a case of somebody with diabetes.

I'm going to use that as a lead in to talk about some of the overall pros and cons of genetic screening for diabetes. One of the big pros is that we know that about 90% of those who develop type 1 diabetes do not have a relative with type 1 diabetes. So, using genetic screening will capture more of the people who will ultimately go on to diabetes than targeted testing of relatives, which is the way many screening programs are designed right now. And also, there are on the horizon and being used in research settings, genetic risk scores, which combine not only HLA but other genes and other factors related to risk for diabetes to further delineate the risk to figure out who's at highest risk of diabetes. Some of the cons of genetic screening as a first approach for screening for diabetes is, as I showed you, the major logistic effort and cost of doing this type of screening.

It's secondly important to recognize, and this is subtle point, but I wanted to mention it here, that HLA is really more predictive of who develops autoantibodies and who ultimately develops clinical type 1 diabetes. So, although it helps you get to that first step at figuring out who's going to get autoantibodies, it doesn't get you to kind of the finish line around who's going to develop clinical disease. These types of risk discussions to explain this to people, especially people who are unfamiliar with type 1 diabetes at baseline, it's very time consuming and requires a lot of effort. And as I showed you in that prior slide, most children who are positive genetic screen do not go on to develop type 1 diabetes, yet these children may need follow-up to see who develops autoantibodies over time. So, there's a burden, so to speak, to doing the follow-up in these settings.

And once you've done genetic screening, you need to embark upon next steps. So, once you've done it, risk is ascertained. The next step is generally islet autoantibody screening, which is where I'm going to focus the rest of this talk. It's important to note that newly released ISPAD guidelines suggest that this autoantibody testing might be best performed at ages 2 and 6 years. Now, those guidelines do not specify whether this in is in a population with higher genetic risks, but certainly you could use genetic screening to winnow down to a group that's at higher genetic risk and then target autoantibody testing at those ages.

So, a second approach that has been used for screening is to do islet autoantibody testing. So how does this work? Well, it's a blood test for autoimmunity that's associated with the development of type 1 diabetes. The results, as I'll show you, provide for type 1 diabetes risk assessment and staging. This can be performed as part of a research study or ordered through clinical or consumer lab. So, it is possible to get these autoantibodies done outside of a research setting. It's traditionally done with autoantibody panels and I'll spend a few minutes explaining why a panel is important. These panels can measure any one of 5 commercially available antibodies, including glutamic acid decarboxylase, islet antigen-2, zinc transporter 8, insulin antibody, and/or islet cell autoantibodies.

So why is it important that this be done using a panel? Well, the predictive value of a single autoantibody is insufficient to inform risk meaningfully in all clinical populations. If you only have 1 autoantibody, your lifetime risk of developing diabetes is nowhere near as high. Certainly not 100%. And detecting a single autoantibody does not tell you enough about how to move forward. You'd say, well, why not just measure and look for one and then move on to others? Well, sequential analysis is generally not practical in clinical settings. So, we do sequential analyses as part of the TrialNet protocol. But in general, in clinical settings, samples are often, I would say almost usually, discarded within specified timelines and/or there's often not enough specimen to add on an additional assay, even if you retain the specimen. If you do it all as a panel, it minimizes the distress or cost over repeat phlebotomy. It also decreases time away from work or school for the person getting screened and any caregivers. And it also decreases the number of medical visits for

counseling and ordering follow-up testing if you just do islet autoantibody screening through a panel.

So, what happens if you do islet autoantibody screening? Well, if you screen relatives of people with type 1 diabetes, you will find in general about a 3% risk of multiple islet autoantibodies. When you look at published research studies about islet autoantibody rates in relatives of people with type 1 diabetes, you often find numbers that are higher than that, but that's often because people are more likely to get screened when there's more than one family member that is affected. And that's going to be a pool that's enriched for people at risk. If you go to the general population, similar to the TEDDY experience, which actually was lower in those TEDDY numbers I showed you, the number that's quoted is a 0.3% risk of multiple islet autoantibodies.

It is important to note that once a person has 2 or more islet autoantibodies, the progression to Stage 3 or clinical type 1 diabetes is similar regardless of whether they have a family member with type 1 diabetes. So, in this important graph from a *JAMA* paper from 2013, what you see on the left-hand line, a general population screening approach for islet autoantibodies. In the middle is a mixed approach between general population and relatives. And the right-hand line is a familial screening program. And you can see that the rates of progression to type 1 diabetes out to 15 to 20 years are similar regardless of the population that's screened. So, once you have the islet autoantibodies, your risk is very similar.

So, what are the pros of islet autoantibody screening? Well, one is that if you know you have autoantibodies, you can participate in research to prevent or delay type 1 diabetes. You can contribute in that way to the greater good and the advancement of knowledge around type 1 diabetes. It also prompts closer monitoring in management. People who are known to be autoantibody positive will in general engage in follow-up visits. And I'll show you a rubric for doing some of that. And there's also more awareness of classic symptoms of polydipsia, polyuria, weight loss, and less ultimately DKA and severe presentations at diagnosis. It also allows for staged preparation for insulin therapy and lifestyle modification around an incipient diagnosis of diabetes versus urgent management.

So, this is just to show how islet autoantibody screening will permit staging of diabetes. In this graph, which comes from the Type 1 Diabetes Trial Network, you can see on the far-left-hand side, genetic risk that would lead to genetic screening, followed by immune activation, immune response. And in the middle of the slide, Stage 1 diabetes. Stage 1 diabetes is defined by people who still have normal blood sugars as defined by hemoglobin A1c and metabolic testing and have 2 or more autoantibodies. This is now recognized to be the start of type 1 diabetes. And then people, once they have those autoantibodies, they're followed, they will ultimately have a nearly a 100% lifetime risk of developing diabetes and we'll move through to Stage 2 diabetes, which is abnormal blood sugar with 2 or more autoantibodies, and then Stage 3 and then to longstanding type 1 diabetes.

So, there are some cons for islet autoantibody screening. One is that screening results alone cannot tell people precisely when they'll develop diabetes, just that they're at risk. It only says how many autoantibodies are present the day of the test. It's important to note that the numbers and the presence of these can change with time. The results have to be confirmed and staging corroborated by metabolic testing. So, you know where you fit on that slide I showed you. And the results may cause increased anxiety and psychological distress in people who are screened and their families, although the data suggested this attenuates very rapidly. There are no approved monitoring guidelines at the moment, although I'll take you through a rubric on how to do this. Depending on the cost of the autoantibodies and monitoring, it may not be cost effective to prevent DKA to do islet autoantibody screening on everybody. This is currently controversial because it depends on the costs and the populations that are screened. I think that there are not great cost-effectiveness data out there yet around this.

There are some populations where people are at increased risk. Certainly, the scales are, so to speak, weighted in favor of screening at this point. One is if people have other autoimmune conditions associated with increased risk of development of clinical type 1 diabetes. And it's interesting to note that the guidelines suggest screening those with primary autoimmune adrenal insufficiency annually for type 1 diabetes using autoantibody screening. And this is because while only 1% of individuals with type 1 diabetes have Addison's disease, the co-prevalence is much greater than the general population. So, the likelihood of finding diabetes in this population is much higher. Screening for type 1 diabetes could also be considered in patients with celiac disease, and data from SEARCH have found a co-prevalence of celiac disease and diabetes of about 7%. There are some screening protocols where there is proactive screening for celiac disease and type 1 diabetes in combination in the general population. And these include the Autoimmune Screening for Kids (or ASK study) and the Combined Antibody Screening for Celiac and Diabetes Evaluation (or CASCADE study).

So, what happens if you have type 1 diabetes autoantibodies that you find in screening? I'm just going to start at the bottom of the slide, which is that evidence-based guidelines for follow-up and monitoring after the screening are not yet available. They're currently in development. And the suggestions that I give you here are based on expert opinion and there's not exact consensus among experts, although what I'm going to show you here would be acceptable, I would say, to most as an approach. And I just want to give credit to Dr. Frank Martin, who was at JDF and helped develop these recommendations that I'll be talking you through now. So, if you're autoantibody negative when you're screened, it's still important to re-screen if you've got diabetes-like symptoms because certainly,

although it's rare, people can still have type 1 diabetes even if they screen negatively at first.

This is in part because the autoantibody screens do vary a little bit by labs. So, the accuracy of the testing and the exact kind of flavor of autoantibody that's being detected may vary a little bit by lab. But if you are autoantibody negative, you could consider re-screening at age 6 if you're age <5 years at the first screen, or age 11 if age 5 to 10 years at the first screen. I'll say that there are no guidelines right now that suggest that age 11 is a clear optimal next stage, but it's a reasonable approach. If your screening results are that you are confirmed to have a single autoantibody, that's positive. So, it's key that if you find a single autoantibody, the next step is to confirm it.

Then your blood sugars are normal, so you have a hemoglobin A1c that is normal. You would want, in the recommendation here, to follow up every 6 months with repeat metabolic testing. So, you could do hemoglobin A1c, OGTT, fasting, and 2-hour post-prandial glucose. You could potentially use CGM in this setting, although it may be difficult to get that covered by insurance. And then after you are single autoantibody positive for 2 years, you can move to yearly follow-up. It's important to note that if you have a single or multiple autoantibodies that are found to be positive regardless of the setting, [you] can be referred to an existing screening program, for example, TrialNet for confirmatory screening and also metabolic testing. If you are confirmed multiple autoantibody positive, there's a wider table here because you have more to do.

Firstly, these people can again be referred to an existing screening program, but if you're in Stage 1 type 1 diabetes (multiple autoantibody positive, normal blood sugars, normal hemoglobin A1c), the recommendation in general is to follow up in 6 months to exclude diagnosis and repeat metabolic testing. But those people, because they have multiple autoantibodies, it's also advised that they would call immediately if they have any diabetes-like symptoms. If you're in Stage 2 diabetes, meaning you have multiple autoantibodies, impaired glucose tolerance, and you can see the thresholds there, after OGTT, an intermediate hemoglobin A1c, a pre-diabetes A1c, at that point, the recommendation is to start some early type 1 diabetes education. So, you could do meter teaching, some dietary teaching to start checking some blood sugars at home, whether you use a continuous glucose monitor, a strip, check if kids are sick.

And so, if blood sugar is over 200 twice or you have symptoms, you're potentially at Stage 3. It's important that those kids and adults get followed by an endocrinologist. And here the follow-up accelerates to every 3 months to exclude diagnosis, repeat autoantibody metabolic testing. If you're Stage 3 type 1 diabetes, multiple autoantibody positive, hemoglobin A1c > 6.5%, repeat OGTT in the diabetes range or diabetes symptoms, you have early diagnosed Stage 3 diabetes. You need to assess metabolically how people are doing with polyuria, polydipsia, weight loss. Most people at this point will need to start insulin that day. Now, the caveat around this is that if you've been identified through a screening protocol, you may still be very early in Stage 3 diabetes and you may be able to wait a little bit on insulin, but these people definitely need meter teaching or CGM and need to be referred to an endocrinologist.

So, with that, hopefully you are ready for some recommendations. Population-based type 1 diabetes screening initiatives are expanding. Secondly, there are 2 basic approaches to screening. One is to start with a genetic risk assessment usually done in the context of newborn screening. And the second is to do islet autoantibody screening. Both approaches, as I've taken you through, have pros and cons. The optimal approaches are yet to be determined, but things are being implemented (especially the cost effectiveness of different approaches needs to be determined). And once that initial screening is performed, whether it's genetic risk assessment or islet autoantibody screening, then you need follow-up. So, if you've had a genetic risk screen or if you've had islet autoantibody screening, you need a metabolic screening to stage your diabetes, determine timing of interventions, whether that's immunomodulatory therapy potentially in the future or start of insulin or CGM. Our next speaker in this series will talk more about that. There's a lot more work to do in this space, and I know our discussion will focus on some next directions. And with that, I will turn things back over to our moderator. Thank you.

Dr. Atkinson:
Thank you, Linda, for an amazingly informative and updated presentation. I'm totally taken aback by it. So, I am the grandfather of 3 grandchildren, one, three, and five. And I have no family history of diabetes, but I encouraged my daughter and son-in-law to have screening. I really had to talk to them a lot about general population versus having a family history. I know you touched on this in your talk, but can you reemphasize the notion of why we don't need to just be in a situation of screening people who have a family history of the disease?

Dr. DiMeglio:
Well, I think one of the big benefits of screening the general population is that most people who develop diabetes do not have a family member who has type 1. So, you're not going to capture everybody at the highest risk if you focus on family members. And although family member screening has been really critical to a lot of our research in this area, if we only focus on family members, we are not going to capture 90% of the people before they develop diabetes. I would say with therapies for people in Stage 2 diabetes potentially on the horizon, that also changes the calculus around this a little bit. I spent part of the early part of my career talking about newborn

screening for congenital hypothyroidism and spending a lot of time thinking about the overall framework for when you screen. In general, you don't screen for disease unless you have a therapy for it, although that's changed a little bit with the availability of some of the metabolic screening that is done as part of the newborn screen where it's just really important to get the people that information. But, in this particular case, I think it's a very personal decision for the general population about whether or not people should be screened. It sounds like you've opted to do that in your family. On the flip side, there are sometimes people who have type 1 diabetes in their family that also do not want to be screened, but are just very vigilant for symptoms. But I think right now, given that the cost of screening is going down and that the availability of it is greater, I think it's a really good option for those people that want to pursue that.

Dr. Atkinson:
So, another thing is if you listen to either podcasts, or driving in your car or train and listening to any kind of broadcast, they talk about privacy. You need VPN on the internet or you need this other thing to maintain privacy. And in terms of medical tests, we've seen that too, whether it be oncology testing or infectious disease testing. Should people who have this screening performed, do they have reason to fear privacy issues or are these really set between the healthcare provider and the patient and the agency doing the test? Can you discuss that?

Dr. DiMeglio:
I would say it depends upon where you screen and how you get screened. I think that's certainly something that you would want to ask the person that you are engaging with to do the screening. As you mentioned, I'm Vice Chair for TrialNet and I'm very aware of the TrialNet protocol, which is that we have a certificate of confidentiality from the NIH that says that those results are kept confidential and we can't release them to anybody. We're also very cautious to make sure that they don't get into the medical records so that they can be found by an insurer. In general, in the United States, we have very strong privacy laws, but it may depend upon the laws around the world potentially. So, it may depend on laws of where you are and also who's offering the screening. I would say that I think it's something that the people doing work in this space think about very carefully and it would be hard to envision an issue with privacy around those results. But as far as the confidentiality or the discovery of those results, depending upon who runs them for you and where they're run, I think that that is an important thing for a person to think about as they're getting screened.

Dr. Atkinson:
Great. So, in the United States, we talk of ourselves as being a melting pot. And I think with globalization starting in the 20th century, now in the 21st century, we're seeing a lot of migration and mixtures of cultures and races and age groups. Another question that often comes up is, is there the same accuracy for these autoantibody tests in males versus females? We tend to think that autoimmune diseases occur more in females than males in general. But also, in terms of race: are these autoantibody tests just as accurate in African American populations, African populations globally, Hispanic populations, Asian populations, or is this something that's restricted to Caucasian populations?

Dr. DiMeglio:
There's two things to the question you asked. I'm going to answer them both. So, I'm going to answer first the question that you asked most directly, which is are these accurate regardless of age, regardless of sex, regardless of racial or ethnic background? And the answer to that would be yes. The second thing to note, and it's been well thought about particularly around the genetic risk scores and genetic risk screening, but also a little bit within autoantibody screening, is what the meaning is of the autoantibodies if they're detected or what the best strategy is for screening, And even which autoantibodies to test for first if you are doing staged autoantibody screening may vary a little bit by race or gender or a little bit by age. With that said, there is nothing in the literature to date that suggests this is not going to work for a given population or you shouldn't use it in a given age range or people of a certain race or ethnic background. But I think the interpretation and the strategy may vary a little bit based upon some of the factors that you mentioned.

Dr. Atkinson:
Great. One of the encouraging things to me is that these questions that you've been talking about, this is not just a United States issue, meaning there are many populations around the world, many countries, that are taking on this notion of general population screening above and beyond that of relatives. Do you want to comment about that in terms of what evidence do you think led these multiple countries to push forward here? Is it the data about the benefits or is it that it seems accurate across populations, or all of the above?

Dr. DiMeglio:
I would say yes and yes to some of that. I wish we had more data, and I think it's going to be important to get more health economics people into this space around the cost effectiveness of screening. Because ultimately what will move governmental policies is showing that you can make a difference that will impact cost and quality-adjusted life years and things like that for people living with diabetes. I think it will depend a little bit upon resources in a given area. Some of it does come down to questions about privacy and confidentiality in different areas. But I think as we're getting closer to more ability to have actionable steps and in particular right now, I think the data around prevention of DKA given the rise in DKA, particularly during the pandemic, and the fact that we're not doing well with some of

the other approaches to DKA (we now know that there are many adverse long-term effects of DKA, on glycemia over time, on insulin production, even some neurocognitive effects of DKA) that I think that definitely the costs are coming down and the benefit is going up.

Dr. DiMeglio:
So, I can't imagine this won't continue to expand.

Dr. Atkinson:
Great. Thank you very much.

Announcer:
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