

Patient Care[®]

PRESENTED BY

Medical Economics

TYPE 1 DIABETES

**Treatment options and
proactive intervention
to slow progression**

A magnified view of T cells with vibrant colors representing their function in identifying type 1 diabetes risk, highlighting cellular interactions and biological processes

Inside

Paving the Path to Prevention
**Managing Early Treatments
for T1D Progression**

Ahead of the Curve
**Early Interventions for
Delaying T1D**

PAVING THE PATH TO PREVENTION: **Managing Early Treatments for T1D Progression**

This Patient Care® Frontline Insights program, “Paving the Path to Prevention: Managing Early Treatments for T1D Progression,” features a panel of clinicians with extensive experience in diagnosing and managing type 1 diabetes in pediatric and adult populations. Led by Javier Morales, MD, associate clinical professor of medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell in Uniondale, New York, the 4-expert group discusses the expanding knowledge and essential role of screening for type 1 diabetes, the populations at greatest risk that warrant screening, and the need for regular monitoring of the staged progression of the autoimmune disease to avoid the development of diabetic ketoacidosis. Morales and colleagues also discuss the landmark FDA approval of teplizumab (Tzield), the first disease-modifying drug indicated to slow the progression of stage 2 type 1 diabetes to stage 3, or frank diabetes. The panelists review findings from the pivotal TrialNet 10 study (NCT01030861) that were the foundation for the FDA approval, as well as patient selection for the novel treatment. *The following transcript has been edited for clarity and length.*

MODERATOR

Javier Morales, MD

Associate Clinical Professor of Medicine
Donald and Barbara Zucker School
of Medicine at Hofstra/Northwell
Uniondale, NY
Vice President
Advanced Internal Medicine Group, PC
East Hills, NY

PANELISTS

David G. Robertson, MD

Partner, Atlanta Diabetes Associates
Atlanta, GA

Shira Eytan, MD

Park Avenue Endocrinology
and Nutrition PLLC
New York, NY

Bethany Kinsey, NP, CDCES

Wellstar Health System
Holly Springs, GA

Quentin Van Meter, MD

Van Meter Pediatric Endocrinology
Atlanta, GA

By **Grace Halsey** Senior Editor

Javier Morales, MD: David, do you believe there is a significant number of individuals with type 1 diabetes in the community who are undiagnosed?

David G. Robertson, MD: Absolutely, but it depends on the stage. By stage 3, with symptomatic hyperglycemia, many patients end up in the emergency room with diabetic ketoacidosis [DKA]. However, research suggests there could be 100,000 to 200,000 individuals with undiagnosed stage 1 or stage 2 type 1 diabetes, in addition to the more than 60,000 diagnosed annually.

Morales: Bethany, would you elaborate on the burden of type 1 diabetes?

Bethany Kinsey, NP, CDCES: Type 1 diabetes impacts not only patients but their entire support systems. And we need to reinforce that type 1 diabetes can occur at any age. [Although] 41% of diagnoses occur in individuals under age 20..., 59% of the diagnoses are made in adults. Thinking about who is at risk, family history is a major risk factor for type 1 diabetes. In fact, first-degree relatives have a 15-fold greater likelihood of developing the disorder. It's also important to know that up to 90% of new type 1 cases occur in people without a family history.

The emotional burden of this disease is immense — it literally impacts every aspect of life, including sleep, relationships, daily activities, everything. More than one-third of people with diabetes

report having diabetes distress, though my clinical experience tells me that number is higher. Almost two-thirds (63%) are afraid of complications of the disease, and 28% struggle to remain positive about the chronic condition.

Morales: Shira, how do you approach the emotional impact of diabetes in your practice?

Shira Eytan, MD: I make a point to ask about lifestyle concerns and make space for discussion. How are you sleeping? How is work? How's the stress level? If someone is really struggling, I'll refer [them] for a mental health evaluation or schedule more frequent visits to help them feel a little bit more in control and that they have adequate time to talk about all the ups and downs. It's about building support and giving patients the time they need.

Quentin Van Meter, MD: For school-aged children, I often ask about school performance, their grades, and their participation in extracurricular activities. Declining grades or disengagement from hobbies and sports can signal depression, and those are key signs for me to intervene.

Morales: Let's talk about screening for type 1 diabetes—not something we're used to hearing about. Shira?

Eytan: Screening for type 1 diabetes is a relatively new concept, but the American Diabetes Association [ADA] has issued guidelines to support it. Early screening, along with consistent monitoring and educating patients and caregivers about signs and symptoms, can prevent patients with early-stage type 1 from developing DKA—historically, the point when so many of our patients were diagnosed. So screening and monitoring can help reduce the potential for emergency [department] visits, hospitalizations, and even death.

Screening can also help us identify patients misdiagnosed as having type 2 diabetes—about 40%

“Screening can also help us identify patients misdiagnosed as having type 2 diabetes—about 40% of adults over the age of 30 with type 1 are initially misclassified.”

of adults over the age of 30 with type 1 are initially misclassified. And that is often a result of the lingering misconception that type 1 diabetes is a childhood disease. We're seeing that identifying the risk for type 1 diabetes early—and that's done through a simple blood test—can [give] our patients and their families time to learn about the disease, so the eventual diagnosis is less stressful and long-term outcomes are better.

Morales: We have been discussing screening, and we have mentioned staging of type 1 diabetes. Shira, would you please explain staging?

Eytan: As we've said, screening and staging are relatively new concepts. We know now that type 1 diabetes doesn't need to present as an emergency. We can track the development through stages.

Stage 1 type 1 diabetes is identified by the presence of 2 or more autoantibodies in the blood. There are 5 antibodies we can screen for, and having at least 2 confirms the presence of type 1 diabetes. At this stage, blood glucose levels are still [at a] normal [level], there are no symptoms, and insulin is not needed. But the immune system has started attacking pancreatic β cells.

In stage 2 type 1 diabetes, antibodies remain present, and the attack on β cells progresses. By this point, about 50% of β -cell function is lost. Blood glucose levels begin to fall slightly outside the normal range, [which is] what we'd call dysglycemia and similar to what we would see in prediabetes. This might show up in routine lab work, but the patient is still asymptomatic and not

requiring insulin.

Stage 3, or frank type 1 diabetes, is when the impact is clear. At this stage, most pancreatic β cells are destroyed, and the body can no longer produce enough insulin. Blood glucose levels are consistently high, and the person needs exogenous insulin. We also see the typical symptoms of type 1 diabetes now, such as frequent urination, extreme thirst, dry mouth, fatigue, weakness, unexplained weight loss, and increased appetite.

Morales: What if I screen a patient and only 1 antibody is positive, Shira?

Eytan: That's a great question. First, ensure you've screened for all 5 antibodies, as some panels only test for 3 or 4. If only 1 antibody is positive, recheck it and keep the patient on your radar. Antibody levels can fluctuate, so a second one may occur later. For younger patients, who tend to progress faster, I'd recheck sooner. In adults, I'd repeat testing within a year, and I'd also monitor blood glucose levels [at] 6 to 12 months, depending on their starting point and risk factors.

Morales: Shortly, we will discuss the option we have to delay the progression from stage 2 to stage 3 type 1 diabetes. But what are the consequences if we don't intervene to lengthen that period?

Van Meter: Stage 3 type 1 diabetes can occur very suddenly, especially in younger patients. If we don't intervene during stage 2, the risk for irreversible β -cell damage is high, and so is the risk of DKA. Rapid transition to stage 3 can lead to other

“Even though we don’t yet fully understand which patients progress rapidly, expanding screening efforts could help identify patterns and risk factors for faster progression from stage 1 or 2 to stage 3.”

serious complications, reduced treatment efficacy, and poor long-term glycemic control. That is especially true for people who are diagnosed while in DKA. We can’t prevent stage 3, but if we can delay the time between stages 2 and 3, we can avoid the most serious outcomes and use the interval to educate patients on the disease before it happens. Even though we don’t yet fully understand which patients progress rapidly, expanding screening efforts could help identify patterns and risk factors for faster progression from stage 1 or 2 to stage 3.

Morales: In the Northeast, we have many options for referring patients who are at risk for progression from stage 2 to stage 3, but access can be more challenging in rural areas. Bethany, would you speak to that?

Kinsey: We have patients [who] drive almost 2 hours to reach us, and we are the closest endocrine practice. In rural areas like North Georgia and the Blue Ridge Mountains, the services just aren’t available. When I worked in Savannah, Georgia, we saw patients who drove from 10 counties away. Access to care is a significant challenge in rural America.

Morales: Shira, in your practice, how do you screen for type 1 diabetes risk factors during routine appointments? Do you use the oral glucose tolerance test [OGTT]?

Eytan: The OGTT is not pleasant for the patient; it’s time-consuming and uncomfortable, so it’s not typically part of routine testing. However,

it was critical in the TrialNet study that led to the recent teplizumab approval and is required as part of the confirmatory tests for these patients. But we typically get an HbA_{1c} [hemoglobin A_{1c}] level [that] I think will give us more clues to potential issues in the general population.

Morales: Bethany, could you walk us through who in the general population we should screen for type 1 diabetes?

Kinsey: According to the ADA guidelines, screening should include individuals with other autoimmune diseases, such as celiac disease, Hashimoto thyroiditis, or Graves disease, and the first-degree relatives of individuals with autoimmune diseases. We know that certain ethnicities[/races] are at elevated risk, including non-Hispanic White, Black, and Hispanic populations.

As for timing for screening, data suggest that optimal windows for children are between the ages of 2 and 3, 5 and 6, and 9 and 11 years, so [we should start] to screen a child at high risk at 2 years of age. Plus, if a first-degree relative is newly diagnosed with type 1 diabetes, all other first-degree relatives should be screened immediately.

The guidelines also recommend that we...repeat screening every 2 years for people at high risk, even if initial results are negative. Incorporating autoantibody testing into routine well-child visits—for example, alongside a lipid panel at age 9 months—could make screening feasible on a larger scale. In my practice, where I see many patients

with Graves and Hashimoto disease, I discuss the risks with them, and they are often willing to be screened. I’ve occasionally identified autoantibodies in individuals who had no symptoms or even elevated glucose levels.

Morales: Bethany, would you provide more detail on the autoantibodies we should be screening for?

Kinsey: There are 5 autoantibodies commonly used to screen for type 1 diabetes (**Figure 1A**): insulin autoantibodies, GAD antibodies, IA-2 antibodies, zinc transporter 8 antibodies, and islet cell antibodies. Testing can be ordered through commercial labs like Quest or Labcorp (**Figure 1B**). For uninsured patients or those without access to these labs, the TrialNet program offers screening free of charge for those aged 8 to 45 years. They mail a test kit that can check for 3 of the antibodies. Some screening programs don’t test for all 5 autoantibodies initially, but if a test is positive for 1 or 2, the lab will run the remaining tests.

Morales: This is the perfect point to talk about how we can intervene in stage 2 to delay the onset of frank type 1 diabetes. David, could you explain the new drug teplizumab and its role in delaying type 1 diabetes progression?

Robertson: Teplizumab, or Tzield, is the first FDA-approved drug for delaying the onset of stage 3 type 1 diabetes. We have discussed [how] type 1 diabetes technically begins when 2 or more autoantibodies are detected. The mechanism of teplizumab works to delay the progression from stage 2, when dysglycemia is present but hyperglycemia hasn’t developed, to stage 3, which is characterized by significant β -cell loss and frank hyperglycemia.

Teplizumab is a monoclonal antibody that targets CD3 proteins on T lymphocytes (**Figure 2**). In type 1 diabetes, T lymphocytes attack pancreatic β cells, leading to progressive

Patient Care[®]

Elevate Your Patient-Centered Approach

Explore exclusive patient care insights in our e-newsletter. Subscribe for free to stay informed and inspired.



Scan the QR code
& Subscribe for Free!

*Follow us on
social media!*



@PatCareOnline



@PatCareOnline



@patientcareonline

β -cell destruction. Teplizumab suppresses this autoimmune response, helping to preserve β -cell function and prolonging the time before stage 3 develops.

The approval was based on [data from] the pivotal phase 2 TrialNet clinical trial, which enrolled 76 participants aged 8 to 45 years, all relatives of a person with type 1 diabetes and [who were] in stage 2 type 1 diabetes with dysglycemia and multiple positive autoantibodies. About two-thirds of the teplizumab group and 4...of 5 in the placebo group were younger than 18.

Participants received 14 daily infusions of teplizumab or placebo, with the dosage of the active drug gradually increased during the first 5 days. In the trial, the initial dose of teplizumab of 51 $\mu\text{g}/\text{m}^2$ body surface area was doubled daily until reaching the full dose of 826 $\mu\text{g}/\text{m}^2$ body surface area on day 5, which was administered through day 14.

The trial results were remarkable. The placebo group progressed from stage 2 to stage 3 in about 2 years [whereas] the teplizumab group experienced a delay in that progression of more than 4 years on average, so double the time before needing insulin and 2 additional years for patients and families to acclimate to the idea of

type 1 diabetes, learn about diabetes management, and even explore other interventions.

Morales: What about the safety profile of teplizumab, David?

Robertson: The most common adverse event in the trial was lymphopenia, which occurred in almost all participants. But severe or persistent lymphopenia, [in other words,] absolute lymphocyte count greater than 500/ μL for more than 5 days, was rare and generally led to therapy interruptions. Other [adverse] effects included mild rashes, which were manageable with antihistamines, and infrequent leukopenia, neutropenia, transaminase elevations, or headaches. We monitor patients closely, especially during the first week of treatment, with frequency decreasing if they tolerate therapy well.

Morales: While establishing infusion centers can be challenging, most areas have facilities where this therapy can be administered. In some cases, teplizumab infusions can be done at home (**Figure 3**). Shira, what's been your experience in New York City?

Eytan: In my practice, we use infusion centers for various non-diabetes-related needs. For teplizumab, though, I've exclusively used home infusions. It really depends

on availability in your area and the patient's comfort level. Most of my adult patients have preferred the convenience of home infusions when available.

Van Meter: It depends on resources and patient factors. Pediatric patients may require a higher level of care, such as a PICC [peripherally inserted central catheter] line, to manage repeated infusions. Infusion centers, hospital based or stand-alone, can handle the logistics of administering teplizumab, including monitoring and lab work. However, not all centers are set up for 7-day-a-week access, which can complicate scheduling.

Morales: Quentin, could you walk us through the FDA indications for prescribing teplizumab?

Van Meter: Per FDA labeling, teplizumab is indicated for patients aged 8 years or older who are in stage 2 type 1 diabetes. They must have at least 2 positive autoantibodies and evidence of dysglycemia without overt hyperglycemia. Specifically, fasting blood sugar [levels] should be between 100 and 125 mg/dL, and a 2-hour glucose tolerance test result should fall between 140 and 200 mg/dL.

I want to go back for just a moment and talk about a few more details of the infusion process. Premedications are recommended, including antihistamines, antipyretics, and antiemetics, to minimize [adverse] effects like fever, nausea, and skin reactions. Monitoring is also critical during the infusion process. Lab tests, such as lymphocyte counts, and vital signs should be checked regularly, especially as cytokine-related effects might occur with dose escalation, although the estimated incidence of cytokine storm is about 2% to 3%. For home infusions, providers must ensure mechanisms are in place for prompt intervention if adverse events arise. ■

MORE ONLINE Click to watch the entire discussion on video.

Watch Now

FIGURE 1A. Autoantibodies Preceding Type 1 Diabetes

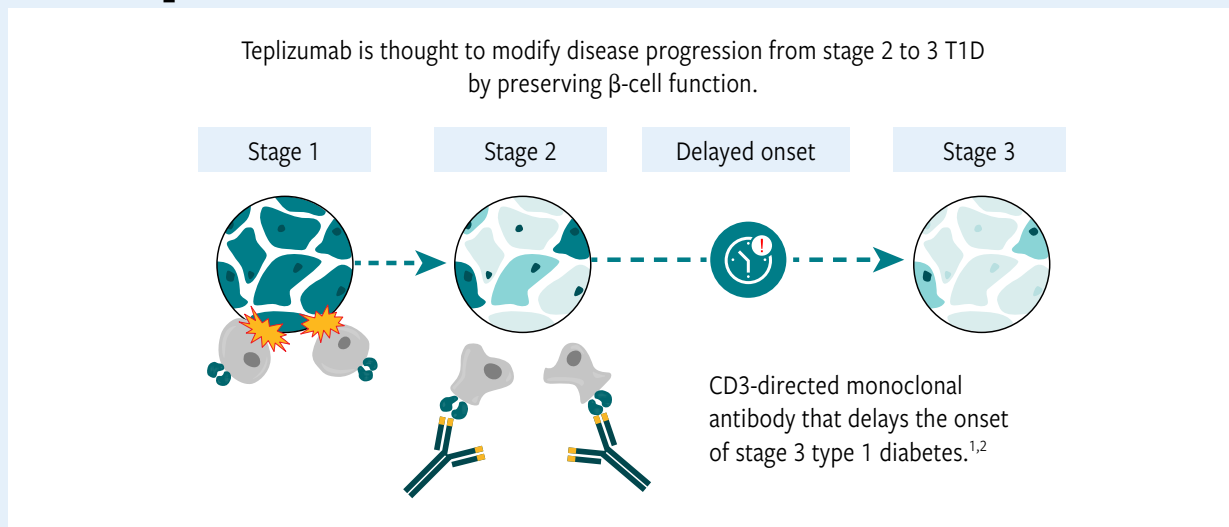
Insulin autoantibodies (IAA)
Glutamic acid decarboxylase autoantibodies (GADA)
Insulinoma-associated-2 autoantibodies (IA-2A)
Zinc transporter 8 autoantibodies (ZnT8A)
Islet cell autoantibodies (ICA)

FIGURE 1B. Types of Antibody Screening for Type 1 Diabetes*

	Tests	Screens for antibodies
Commercial labs	Blood draw	GADA, IA-2A, IAA, ICA, ZnT8A
TrialNet program	Blood draw or finger stick	GADA, IA-2A, IAA, ICA, ZnT8A*
Autoimmunity Screening for Kids	Blood draw or finger stick	GADA, IA-2A, IAA, ICA, ZnT8A
Online ordering	Finger stick	GADA, IA-2A, IAA

*Not an exhaustive list.

FIGURE 2. Teplizumab: Mechanism of Action



1. FDA approves first drug that can delay onset of type 1 diabetes. News release. FDA. January 1, 2023. Accessed February 12, 2024. <https://www.fda.gov/media/164864/download>

2. Thakkar S, Chopra A, Nagendra L, Kalra S, Bhattacharya S. Teplizumab in type 1 diabetes mellitus: an updated review. *touchREV Endocrinol.* 2023;19(2):22-30. doi:10.17925/EE.2023.19.2.7

FIGURE 3. Infusion Site Options

Setting	Pros	Cons
Doctor's office	Supervised by provider	Limited scheduling flexibility
Infusion centers	Specialized staff and equipment	Travel required
At home with nurse	Convenience	Scheduling and lack of immediate medical assistance

AHEAD OF THE CURVE:

Early Interventions for Delaying Type 1 Diabetes

In *Ahead of the Curve: Early Interventions for Delaying Type 1 Diabetes*, part of the *Patient Care Frontline Insights* video series, a panel of clinicians with expertise in treating type 1 diabetes discuss the essential role of screening for the autoimmune disorder, populations at greatest risk that warrant screening, and close monitoring of the disease's staged progression to avoid development of diabetic ketoacidosis. Led by Javier Morales, MD, the 3-expert panel also discuss the landmark FDA approval of teplizumab, the first disease-modifying drug indicated to slow the progression of stage 2 type 1 diabetes to stage 3, or frank diabetes. The panelists review findings from the pivotal TrialNet 10 study (NCT01030861) that were the foundation for the approval, as well as patient selection for the novel treatment. *The following transcript has been edited for clarity and length.*

MODERATOR

Javier Morales, MD

Associate Clinical Professor of Medicine
Donald and Barbara Zucker School of Medicine at Hofstra/Northwell
Uniondale, NY
Vice President
Advanced Internal Medicine Group, PC
East Hills, NY

PANELISTS

David G. Robertson, MD

Partner
Atlanta Diabetes Associates
Atlanta, GA

Andrea Stallings, MS, PA-C, CDCES, CDTG, BC-ADM

UC San Diego Health-La Jolla and Hillcrest Hospitals
La Jolla, CA

Shira Eytan, MD

Park Avenue Endocrinology and Nutrition PLLC
New York, NY

By **Grace Halsey** Senior Editor

Javier Morales, MD: Andrea, would you start off with some background on type 1 diabetes?

Andrea Stallings, MS, PA-C, CDCES, CDTG, BC-ADM: I work in adult endocrinology, and one of the trends that we've been seeing is a rising incidence of type 1 diabetes across all age groups. Annually, 64,000 people are diagnosed with type 1 diabetes in the US alone. While type 1 diabetes can develop at any age, having a first-degree family member with type 1 diabetes increases the risk significantly—from 1 in 300 in the general population to 1 in 20. That is a 15% increased risk of developing type 1 diabetes. Patients with diabetes face enormous burdens—not only physical but emotional and financial. This is particularly true for type 1 diabetes, which requires intensive daily management. Educating patients when they are well can empower them to live healthier lives and potentially delay disease onset. Early intervention and education are critical.

Morales: Your points about the burdens of diabetes are well taken. While much of the focus has traditionally been on type 2 diabetes, screening and early action in type 1 diabetes are vital because we now have effective strategies to delay progression.

Stallings: Absolutely. A patient-centered approach is key. By educating

patients about their condition and involving them in their care, we can improve adherence and outcomes. This requires a team effort involving nurses, advanced practice providers, and certified diabetes educators. Collaborative care is essential for achieving optimal outcomes.

Morales: Let's move on to type 1 diabetes screening. Dr Eytan, what are the current recommendations for screening for type 1 diabetes?

Shira Eytan, MD: The concept of screening for type 1 diabetes is relatively new. Even when we were training as endocrinologists, we didn't have a reliable method to predict whether someone would develop type 1 diabetes. However, with more research and data, we now know that screening for antibodies—through blood tests, which can be done in the office or in some cases even at home—can identify those at higher risk of developing type 1 diabetes.

Last year, the American Diabetes Association held a roundtable that recommended screening, along with consistent monitoring and education about the signs and symptoms of type 1 diabetes. This approach has been shown to prevent people with early-stage type 1 diabetes from progressing to diabetic ketoacidosis, which is often how type 1 diabetes is diagnosed and can lead to emergency room visits, hospitalizations, significant costs, and even death. Screening for antibodies before clinical symptoms appear is key.

Stallings: What's interesting is that in endocrinology, we focus on patients who already have type 1 diabetes. But it's important to remember that their first-degree relatives—like siblings—aren't our patients. That's why collaborating with primary care physicians is essential to ensure that first-degree family members of patients with type 1 diabetes are screened.

Eytan: Screening at the primary care level is critical for prevention.

“Educating patients when they are well can empower them to live healthier lives and potentially delay disease onset. Early intervention and education are critical.”

Screening can also provide the opportunity to reclassify patients who might have been misdiagnosed with type 2 diabetes. We often see patients who aren't responding to oral medications or who don't fit the classic type 2 diabetes profile. We can appropriately classify patients with the correct disease and get them better treatment once we screen for the right antibodies.

David G. Robertson, MD: I had a patient last week who reminded me that even we as endocrinologists can do better. I've been seeing this patient for almost 2 decades for his Graves disease. His primary care provider sent him for an early visit because his blood [glucose level] was high, and he wasn't responding to metformin. I was surprised because his HbA_{1c} [hemoglobin A_{1c}] was 5.8% just a year ago. We advised him to focus on diet and exercise. But did we screen for glutamic acid decarboxylase [GAD] or other antibodies? No, we didn't. Sure enough, his GAD test was strongly positive. I wish we had done that last year.

Eytan: It's easy to miss these patients, and they can progress rapidly if we don't think about it early enough. But this is still a relatively new concept, even for endocrinologists. Let's discuss the 3 stages of type 1 diabetes progression.

In stage 1, we detect at least 2 diabetes-related antibodies in the blood. We test for 4 main antibodies, and having 2 or more constitutes a diagnosis of type 1 diabetes. At stage 1, however, blood glucose levels and HbA_{1c} are normal, and the patient is

asymptomatic. The immune system is already attacking β cells, though, and destroying them, and only antibody testing will reveal this.

In **stage 2 type 1 diabetes**, the antibodies are still present, and β -cell function has further declined—about 50% are already lost. At this point, we start seeing dysglycemia. Blood glucose levels may fall outside the normal range, resembling prediabetes, with HbA_{1c} levels creeping up as high as 6%. Patients are still asymptomatic and don't yet require insulin, but these changes signal progression from stage 1 to stage 2.

Stage 3 is the classic presentation of type 1 diabetes. By this stage β -cell function is severely compromised, and the pancreas is no longer producing insulin or making very little. The patient is hyperglycemic, typically with an HbA_{1c} [level] above 6.5%. We also see the classic symptoms associated with type 1 diabetes now that include frequent urination, excessive thirst, fatigue, dry mouth, [and] hunger with unexplained weight loss, and, unfortunately, diabetic ketoacidosis [DKA] is often the first clinical presentation.

What we want to do is to shift the focus from diagnosing type 1 diabetes at stage 3 to identifying it earlier, preferably at stage 1. This gives us time to prepare patients and their families and potentially intervene before they develop DKA or other complications.

Javier: What if antibody testing reveals only a single positive antibody?

Eytan: Great question. If only 1 antibody is present, it doesn't guarantee the patient will progress to stage IV. However, the recommendation is to monitor regularly. In younger children, testing every 6 months is ideal. For adults, antibody testing is recommended annually along with monitoring glycemic status, particularly HbA_{1c}. You can extend the testing intervals if you're not seeing changes.

Morales: Shira, I think we should look more closely at stage 3.

Eytan: So stage 3 type 1 diabetes can occur very suddenly, especially in younger patients, who often progress more quickly from stage 2 to stage 3. This is why it's so important to identify stage 2 early on to allow time for preparation and intervention. Also, importantly, if we delay intervention at stage 2, the risk for irreversible β -cell damage is high and so is the risk of diabetic ketoacidosis. We also know that rapid transition to stage 3 is related to other severe complications, reduced treatment efficacy, and poor long-term glycemic control, especially for individuals whose first diagnosis of type 1 diabetes is DKA. If we can delay progression from stage 2 to stage 3, we have some time to educate patients, families, and caregivers, which can also help improve outcomes.

Morales: Andrea, who should we be screening for type 1 diabetes?

Stallings: Type 1 diabetes is an autoimmune disease, so people at risk for the disease include those with conditions such as thyroiditis, celiac disease, Hashimoto or Graves disease, rheumatoid arthritis, and vitiligo. We also know that some ethnic/racial groups are at a greater risk, including non-Hispanic White, Black, and Hispanic individuals. Genetic risk screening may not always be accessible in primary care, especially outside of academic centers, but it's worth considering.

We can start screening as early as

“Stage 3 type 1 diabetes can occur very suddenly ... This is why it's so important to identify stage 2 early on to allow time for preparation and intervention.”

age 2 or 3 years and then continue to recheck every other year. Frequency may need to be increased, though, for younger patients or those with higher risk. For example, if a relative is newly diagnosed, or if a patient has 1 antibody and falls into the pre-type 1 diabetes category, annual or biennial screening is recommended.

As for the antibodies themselves, the recommendations call for testing 5 (**Figure 1A**): insulin autoantibodies [IAAs], GAD antibodies, IA-2 antibodies, zinc transporter 8 [ZnT8] antibodies, and islet cell antibodies [ICAs].

Tests for the antibodies (**Figure 1B**) are often bundled into panels through commercial labs like Quest or Labcorp, though insurance coverage can vary. So patients should check with their insurance provider if their physician has assessed they are at risk and wants to test.

For people aged 2 to 45 years with a first-degree relative who has type 1 diabetes, the TrialNet program offers free screening, as does ASK [Autoimmunity Screening for Kids], which is now open to adults and is for the general population. Another option is Enable Biosciences Inc., which mails free screening kits. There is also a new website called Screen for Type 1 and that's a valuable resource for patients because it offers information on why screening is important and who should be screened, and they will mail test kits to your home.

If at least 1 antibody is positive, confirmatory testing is usually

covered by insurance. When 2 or more antibodies are positive, it's time to discuss prevention or delay strategies for diabetes progression. I'll add that I've used commercial labs like Quest and Labcorp without issues. I typically use ICD-10 [International Classification of Diseases, Tenth Revision] codes for family history of type 1 diabetes, prediabetes, or hyperglycemia. Coverage has generally been good in these cases, though experiences may vary.

Eytan: It's important to check all 4 primary antibodies [IAA, GAD, IA-2, ZnT8] at once. Some might skip ICA testing initially, but focusing on just 1, like GAD65, isn't enough. Patients can easily be positive for other antibodies, so missing these could delay the diagnosis. If unclear, you can repeat tests or add ICA later.

Morales: Once we know a patient is in stage 2 type 1 diabetes, we now have a novel treatment that can help delay the progression to stage 3. Dr Robertson, would you talk about teplizumab?

Robertson: Teplizumab is the first FDA-approved drug for delaying the onset of type 1 diabetes, so it is a disease-modifying therapy. It has shown significant benefits, including potentially reducing the risk of DKA as an initial presentation. To explain how it works, teplizumab is a monoclonal antibody that targets CD3, a surface protein on T lymphocytes. By reducing these T cells and their associated antibodies, it helps preserve β -cell function, delaying progression from

stage 2 to stage 3 type 1 diabetes (**Figure 2**).

In stage 1, β cells are functioning well, despite the presence of T-cell activity and antibodies targeting the β cells. As patients progress to stage 2, about 50% of their β -cell function has been lost. Some β cells are still functioning normally, while others are only partially functional. Dysglycemia becomes evident during this stage, which is why careful screening is critical.

Stage 2 is our window of opportunity to intervene, but it's important to note that the speed of progression from stage 1 to stage 2 can vary widely. Diagnosing stage 2 is not as simple as relying on an HbA_{1c} level. While many use an HbA_{1c} of 6.5% as a cutoff, the true definition of stage 2 is based on an oral glucose tolerance test [OGTT]. The OGTT identifies stage 2 patients by a 1-hour blood glucose level over 200 mg/dL and a 2-hour blood glucose between 140 and 200 mg/dL. For day-to-day use, though, continuous glucose monitoring is more practical.

Morales: Would you run through the details of the phase 3 trial that led to the approval of teplizumab, or Tzield?

Robertson: In this pivotal trial, participants were relatives of a person with type 1 diabetes and were in stage 2 type 1 diabetes themselves based on abnormal oral glucose tolerance tests and the presence of at least 2 autoantibodies. Participants were aged 8.5 to just under 50 years. The cohort was randomly assigned to receive a 14-day infusion of teplizumab (n=44) or placebo (n=32). The initial dose of teplizumab of 51 $\mu\text{g}/\text{m}^2$ body surface area was doubled daily until reaching the full dose of 826 $\mu\text{g}/\text{m}^2$ body surface area on day 5, which was administered through day 14. The results were remarkable. In patients treated with teplizumab, the average time to transition from stage 2 to stage 3

type 1 diabetes was just more than 4 years vs just over 2 years in the placebo group—a doubling of the time to new-onset diabetes. This is that critical window we've been talking about that allows patients and families to prepare for living with diabetes.

Morales: How did the treatment fare in terms of tolerability and adverse events?

Robertson: The treatment was generally well tolerated. Lymphopenia was almost universal, as teplizumab targets T lymphocytes, but severe lymphopenia was rare. Treatment could continue as long as the lymphocyte count stayed above 500 μL . We saw rash in about one-third, but that was transient. About one-[fourth] experienced leukopenia but [that] rarely necessitated stopping therapy. Other adverse events included headache, mild elevations in alkaline phosphatase [levels], nausea, diarrhea, and nasopharyngitis, none of which required interruption. Most patients were able to complete the full 14-day therapy with symptomatic management.

It's important to note that systemic immune reactions, including cytokine storm, can occur, but the estimated incidence [rate] is approximately 2% to 3%. There is

a premedication protocol recommended during the first 5 infusions that includes antipyretics, antiemetics, antihistamines, and normal saline boluses.

Morales: Shira, would you discuss patient selection for treatment with teplizumab and also options for administering the infusion?

Eytan: Teplizumab is approved for patients...8 years or older who have been diagnosed with stage 2 type 1 diabetes. In clinical practice, patients don't need to have a family history; they simply need to meet high-risk criteria. Diagnosis of stage 2 requires the 2 positive autoantibodies and evidence of dysglycemia [without overt hyperglycemia].

The infusion setting depends on the patient's circumstances and location (**Figure 3**). In major cities, home infusions are often a convenient option, especially for adult patients. A visiting nurse can administer the infusion at home. For pediatric patients or those in areas without home infusion options, the first 5 days may be completed in an infusion center before transitioning to home-based care. This hybrid approach also helps address the challenges of weekend infusions, as some centers don't operate on weekends. ■

MORE ONLINE Click to watch the entire discussion on video.

Watch Now

Patient Care[®]

Revolutionize Your Practice With Expert Advice

Discover must-reads and insights from industry experts. Subscribe to our e-newsletter and stay at the forefront of health care management.



**Scan the QR code
& Subscribe for Free!**

Follow us on social media!



@PatCareOnline



@PatCareOnline



@patientcareonline

