



Talking to Patients and Families About T1D Risk and Screening Tests

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THE IMPORTANCE OF EARLY IDENTIFICATION

Type 1 diabetes (T1D) is a chronic autoimmune disease; it most commonly presents in childhood and adolescence but can also present in adulthood.¹ Characterized by insulin deficiency and hyperglycemia, unrecognized T1D can rapidly develop into diabetic ketoacidosis (DKA), which is a potentially life-threatening complication that can be a traumatic first presentation of a T1D diagnosis.² This traumatic potential introduction to the disease can be avoided, however, when T1D is identified early, at presymptomatic stages. Early identification can also offer better opportunities to enroll in clinical trials focused on delaying or preventing T1D.²

RISK FACTORS FOR T1D

T1D is caused by the complex interplay of genetic and environmental factors. In the general population, the risk of developing T1D by age 20 is about 0.3%; having a first-degree relative with T1D increases the risk approximately 15-fold, resulting in an approximately 5% risk.² Similarly, the lifetime risk of developing T1D among the general population is estimated at 1%, whereas the risk among individuals with a first-degree relative with T1D is 10% to 20%.³ Genome-wide association studies have identified more than 60 genetic variants that contribute to T1D risk, including genes that encode human leukocyte antigen (HLA) type and immune system components (eg, CTLA4, IL2RA).^{2,4,5}

Although family history contributes to an individual's risk of T1D, approximately 93% of patients with T1D do not have an affected relative.⁶ Over the past 30 years, the global incidence of T1D has increased, but the prevalence of high-risk HLA variants has decreased, underscoring the role of environmental factors in T1D pathogenesis.² Complex interactions between environment and physiology can influence immune tolerance and T1D risk.² Other possible risk factors include enterovirus infection during pregnancy or childhood and the timing and type of exposure to dietary antigens in infancy.^{7,8}

T1D STAGES AND DIAGNOSIS

Stages of Physiologic Change

Despite its heterogeneous etiology, T1D follows a predictable pathophysiologic pattern that involves the development of autoimmunity and glucose intolerance.² Autoantibodies to insulin, GAD65, IA-2, and/or ZnT8 can develop, leading to T-cell-mediated β -cell reactivity. As functional β -cell mass decreases, glucose tolerance becomes impaired, eventually leading to symptomatic T1D. The progression of T1D through this process can be classified into 3 stages according to these physiologic changes^{2,9}:

- **Stage 1:** 2 or more autoantibodies, presymptomatic, normoglycemic
- **Stage 2:** 2 or more autoantibodies, presymptomatic, dysglycemic
- **Stage 3:** Islet autoimmunity, symptomatic, clinical diagnosis

Presenting Symptoms

The classic presentation of new-onset T1D in adolescents involves polyuria, polydipsia, and recent weight loss. Notably, in approximately one-third of children, atypical presentation, rapid onset of symptoms, or delayed diagnosis can lead to an increased risk of DKA at diagnosis.^{2,10}

The development of DKA is associated with both short- and long-term consequences. DKA requires immediate hospitalization, as it can be fatal. Furthermore, patients with DKA at diagnosis have been shown to have significantly worse glycemic control over time.¹¹ These potential consequences underscore the need for increased awareness of T1D risk factors, signs, and symptoms among parents and clinicians.^{10,12} Notably, younger age, lower body mass index, and ethnic minority status have been associated with an increased risk of DKA at diagnosis.^{10,12}

Until recently, what is currently termed “stage 3 T1D” was the only recognized clinical diagnosis, but T1D can now be identified at earlier stages. In 2015, the new staging system was developed by JDRF in collaboration with The Endocrine Society and the American Diabetes Association, leading to standardized classification of earlier stages of T1D.⁹

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Diagnostic Criteria

When T1D is suspected, laboratory testing for autoantibodies and glucose tolerance is recommended. Proposed diagnostic criteria for each stage of T1D are outlined in Table 1.¹ Additionally, C-peptide levels can be measured as a marker of severe endogenous insulin deficiency to support T1D diagnosis in adults and may help differentiate between T1D and type 2 diabetes.^{1,13,14}

TABLE 1. Diagnostic Criteria by Stage of T1D

Stage	Diagnostic Criteria
1	<ul style="list-style-type: none">• ≥ 2 autoantibodies• Absence of impaired glucose tolerance or impaired fasting glucose
2	<ul style="list-style-type: none">• ≥ 2 autoantibodies• Dysglycemia (impaired glucose tolerance and/or impaired fasting glucose):<ul style="list-style-type: none">◦ Fasting plasma glucose of 100-125 mg/dL (5.6-6.9 mmol/L)◦ 2-hour plasma glucose of 140-199 mg/dL (7.8-11.0 mmol/L)◦ HbA1c of 5.7%-6.4% (39-47 mmol/mol) or $\geq 10\%$ increase
3	<ul style="list-style-type: none">• Clinical symptoms• Diabetes by standard criteria

Adapted with permission from American Diabetes Association. 2. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes-2021*. *Diabetes Care*. 2021;44(suppl 1):S15-S33.

T1D AUTOANTIBODY SCREENING

Why Screen for Autoantibodies?

Several studies have shown that the number of islet autoantibodies correlates with a risk of developing T1D. In a combined analysis of BABYDIAB, BABYDIET, DAISY, and DIPP data, 69.7% of children with multiple autoantibodies developed T1D within 10 years (annualized rate, 11.0%).¹⁵ Progression to T1D occurred more quickly in children with multiple autoantibodies than in those with single autoantibodies; it also occurred more quickly in children younger than 3 years with autoantibody seroconversion.¹⁵ More recently, in a population-based study in Bavaria, Germany, the 3-year risk of developing T1D among individuals who screened positive for 2 autoantibodies was 24.9% (annualized rate, 9.0%).¹⁶

The Value of T1D Autoantibody Screening

Given that the pathophysiologic processes contributing to T1D progression can begin years before symptom onset, early autoantibody testing in asymptomatic individuals can identify those who may later develop T1D.¹⁷ This is valuable information to have, as it can not only offer an opportunity to educate parents about early symptoms, but also help them mentally prepare and reduce the risk of a traumatic diagnosis (eg, hospitalization due to DKA).¹⁷

Educational opportunities. If results from a screening test suggest that an individual has a higher risk of developing T1D, the patient/caregivers should be made aware of symptoms of T1D, such as polydipsia, polyuria, unexplained weight loss, fatigue, dry mouth, increased appetite, weakness, blurred vision, fruity-smelling breath, nausea, vomiting, yeast infections, and bedwetting.¹⁸⁻²⁰ Families and individuals may also be encouraged to begin mentally preparing for the lifestyle changes that are necessary when a patient is insulin dependent.^{2,17,21} Furthermore, patients and caregivers can be introduced to the benefits of enrolling in clinical trials for T1D prevention, which are an option with early testing.^{2,17,21}

Reduced risk of DKA and severe clinical disease course. Large longitudinal trials have shown that children who are screened for T1D and receive long-term follow-up have a less severe clinical disease course, including a lower incidence of DKA and hospitalization at diagnosis.²²⁻²⁴ In the DAISY trial, for example, only 3.3% of children who were identified as genetically high risk and who were followed closely were hospitalized at diagnosis compared with 44% of the general T1D population.²² Similarly, participants in the TEDDY trial (who were known to have an increased risk of developing T1D and were followed closely from 3 months of age) had a significantly lower rate of DKA compared with individuals in large national registries.^{23,24}

Participation in clinical trials. An additional benefit of diagnosing early stage T1D is the identification of individuals who may be eligible to participate in prevention-focused clinical trials. Research is ongoing to identify therapies that may slow or prevent T1D progression, including agents that have been shown to inhibit the immune response.²⁵ Results from previous trials suggest that a window of opportunity may exist in T1D, and the early administration of disease-modifying therapies may be critical to delaying the progression of autoimmunity.²⁶

The Limitations of T1D Autoantibody Screening

Despite the potential benefits of T1D autoantibody screening, the following limitations also need to be considered:

- Autoantibody test results cannot tell patients whether or when they will develop T1D^{17,21}
- Although higher levels of autoantibodies at younger ages have been linked with T1D risk, absolute risk varies by individual, and some individuals who test positive for autoantibodies might test negative at later time points^{17,21,27}
- Autoantibody testing may cause increased anxiety and psychological distress in patients and caregivers, which can be addressed with education and counseling^{16,28}

AVAILABLE T1D AUTOANTIBODY SCREENING PROGRAMS

T1D autoantibody screening is now available through national programs for the general population (T1Detect) and for individuals with an affected relative (TrialNet). TrialNet is a research-based screening and clinical trial program intended for individuals who have a higher risk of developing T1D based on family history or previous autoantibody testing.²¹

In contrast, T1Detect is an education and awareness program intended to expand T1D screening among the general population; individuals are not required to have a family member with T1D to order a test and undergo screening through T1Detect using the T1D autoantibody detection panel.¹⁷ Because the majority of individuals with T1D do not have a family history of T1D, T1Detect will help increase the number of people who can be screened and receive early indications of their T1D risk. A physician referral is not needed to order a test through T1Detect, but it is strongly recommended that individuals follow up with their healthcare providers upon receiving their results to review and interpret them.¹⁷ Both programs provide in-home testing, and their key differences are outlined in Table 2.

In addition to the national programs discussed above, local T1D autoantibody screening programs are available in some parts of the United States, including:

- **ASK** (Autoimmunity Screening for Kids), which provides screening for T1D and celiac disease for Colorado children and their parents: www.askhealth.org
- **PrIMeD** (Precision Individualized Medicine for Diabetes), which provides screening of children living in Virginia to identify those at risk of developing T1D: <https://sif.virginia.edu/primed>
- **PLEDGE** (Population Level Estimate of Type 1 Diabetes Risk Genes in Children), which provides screening of children younger than age 6 who are patients at Sanford Health (health system headquartered in South Dakota): <https://research.sanfordhealth.org/fields-of-research/diabetes/pledge>
- **CASCADE** (Combined Antibody Screening for Celiac and Diabetes Evaluation), which provides newborn screening of all children born in Washington: <https://cascadekids.org>

FOR MORE INFORMATION, VISIT:

- ▶ **TrialNet:** www.trialnet.org/our-research/risk-screening
- ▶ **T1Detect:** www.jdrf.org/t1d-resources/t1detect

TABLE 2. Available Options for In-Home T1D Screening

	T1Detect	TrialNet
Type of program	Education and awareness program	Research-based screening and clinical trial program
Autoantibodies detected	<ul style="list-style-type: none"> • IAA • GAD • IA-2A • More autoantibodies to be included in the future 	<ul style="list-style-type: none"> • GAD • mIAA <p>For those positive for mIAA or GAD:</p> <ul style="list-style-type: none"> • ICA • IA-2A • ZnT8A
Who can get a test?	Individuals who are interested in and can afford the test	Individuals who have not been diagnosed with diabetes and who are: <ul style="list-style-type: none"> • Between the ages of 2.5 and 45 years and have a first-degree relative with T1D • Between the ages of 2.5 and 20 years and have a second-degree relative with T1D <p>OR</p> <p>Individuals who have tested positive for at least 1 T1D autoantibody outside of TrialNet</p>
Testing process for patients	<ol style="list-style-type: none"> 1. Go to JDRF website at www.jdrf.org/t1d-resources/t1detect and navigate to the order form 2. Order and pay for an in-home test kit 3. When the test kit arrives, collect blood samples with the finger prick 4. Return the samples with the prepaid materials 	<ol style="list-style-type: none"> 1. Complete an online consent form at www.trialnet.org/participate 2. Order an in-home test kit (if in the United States) 3. When the test kit arrives, collect ~10 drops of blood with a finger prick 4. Return the samples with the prepaid materials
Cost	\$55 plus sales tax; can be subsidized to an out-of-pocket cost of \$10 for those with financial hardship	Free
Can patients with negative results retest?	Yes	No

IAA = insulin autoantibodies; IA-2A = insulinoma-associated antigen-2 autoantibodies; ICA = islet cell antibodies; mIAA = micro-insulin autoantibodies.

Data derived from JDRF. T1Detect. www.jdrf.org/t1d-resources/t1detect. Accessed May 20, 2021; TrialNet. Pathway to Prevention. Study details. www.trialnet.org/our-research/risk-screening. Accessed May 20, 2021; and TrialNet. Pathway to Prevention of T1D. ClinicalTrials.gov. Identifier: NCT00097292. <https://clinicaltrials.gov/ct2/show/NCT00097292>. Updated February 6, 2020. Accessed May 20, 2021.

ADDITIONAL RESOURCES

For clinicians:

- JDRF HCP resources page: www.jdrf.org/t1d-resources/hcp

For patients and families:

- For T1D resources and support from JDRF, go to: www.jdrf.org/t1d-resources
- To receive support through JDRF's T1D Connections Program or Online Diabetes Support Team, go to: www.jdrf.org/t1d-resources/personal-support
- To find mental health providers who specialize in diabetes-related support and can help patients cope with their test results and diagnosis at an early stage of T1D, go to: https://professional.diabetes.org/mhp_listing

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