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Standards of Care in Diabetes 2025: Diabetes-Associated Autoantibodies

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Abstract

The American Diabetes Association recently released the "Standards of Care in Diabetes-2025". Recommendation 2.7 was added to recommend that antibody testing should be done in those with type 1 diabetes (T1D) risk factors such as a positive family history or elevated genetic risk. Despite T1D being associated with other autoimmune disorders, there is no ADA recommendation to test diabetes-associated autoantibodies in this population. Additionally, many have not undergone genetic risk testing and would be missed by this updated recommendation. There could be even further liberalization of type 1 diabetes T1D screening in the future to help alleviate these concerns.

Keywords: Type 1 diabetes (T1D); Diabetes-associated autoantibodies (DAA); Screening; Risk; Dysglycemia; American Diabetes Association (ADA); Standards of care (SoC)

Commentary Article

The incidence and prevalence of type 1 diabetes (T1D) have been increasing in industrialized nations in recent years [1]. Attempts to address this are being made such as a new American Diabetes Association (ADA) recommendation that may end up falling short. In 2024 it was recommended that antibody testing could be used to screen for presymptomatic type 1 diabetes [2]. Recommendation 2.7 was added to the ADA's "Standards of Care in Diabetes-2025" to expand screening applications and can be seen below [3].

"Autoantibody-based screening for presymptomatic type 1 diabetes should be offered to those with a family history of type 1 diabetes or otherwise known elevated genetic risk. B"

Awareness of the importance of screening for T1D has been increasing worldwide. Italy became the first country to mandate by law celiac disease and T1D screening in all individuals aged 1 to 17 years old [4]. Diabetic ketoacidosis (DKA) is the most common first presenting symptom of T1D for the majority of newly diagnosed patients. Rates of DKA as the first manifestation of T1D have increased drastically over time from 31% in 2008 to 58% in 2017 [5,6]. The rates increased markedly from 45.6% in 2019 to 68.2% in 2020 during the lockdown measures imposed in that region during that time according to an Alberta, Canada multi-hospital retroactive study [7]. Long-term outcomes and morality are worsened when T1D is diagnosed following a DKA event, necessitating efforts to improve this trend. To lower the risk of DKA as the presenting sign of T1D, it is important to educate parents and caretakers of the pediatric population of typical symptoms associated with T1D such as weight loss, polydipsia, polyuria, nocturia, enuresis, and malaise. Widespread screening for T1D in the pediatric population would help decrease rates of new T1D presenting with DKA as well. T1D was classified into 3 stages initially for research purposes [8]. T1D is characterized by the presence of 2 or more diabetes-associated autoantibodies (DAA). There are four major DAA that are commonly used in clinical practice and that the ADA recognizes as clinically significant: glutamic acid decarboxylase (GAD65), insulin, tyrosine phosphatases islet antigen 2 (IA-2) and IA-2b, and zinc transporter 8 (ZnT8) [9,10]. Stages 1 and 2 of T1D are presymptomatic. Dysglycemia is a characteristic of stage 2 T1D that distinguishes it from stage 1 T1D, for which euglycemia is a defining feature. Presymptomatic T1D includes both stage 1 and

stage 2 T1D. What this may mean for most scenarios is that anyone with a family history of T1D should get tested. However, Recommendation 2.7 effectively ignores that approximately 85% of the population has no family history [11]. Genetic risk is not assessed as widespread in the US. The ADA itself recommends genetic testing only if diabetes is already diagnosed and either neonatal diabetes is suspected or the patient has diabetes that does not neatly fit into T1D or type 2 diabetes (e.g., MODY) [3]. The other variable to consider when evaluating T1D autoantibody screening is genetic risk. However, currently, the ADA does not appear to recommend genetic testing unless working up confirmed diabetes in neonates. T1D genetic risk scores, calculated from autoimmune diabetes-associated genes, can identify more than 77% of the individuals that will progress to T1D within 10% of the population [11] (Table 1).

Table 1: *Stages of Type 1 diabetes.*

	Stage 1	Stage 2	Stage 3
Characteristics	• Euglycemia* • Presymptomatic	• Dysglycemia† • Presymptomatic	• Hyperglycemia †† • Symptomatic
Diagnostic Criteria	• ≥2 Autoantibodies	• ≥2 Autoantibodies • ↑A1c, IFG, IGT • ADA prediabetes criteria	• +/- autoantibodies • ADA diabetes criteria

* Euglycemia: A1c <5.7%, post-prandial blood glucose <140 mg-dL, and fasting blood glucose <100 mg/dL

† Dysglycemia: A1c 5.7-6.4%, post-prandial blood glucose 140-199 mg/dL, and/or fasting blood glucose 100-125 mg/dL

†† Hyperglycemia: A1c ≥6.5%, post-prandial blood glucose ≥200 mg/dL, and/or fasting blood glucose ≥126 mg/dL

IFG: impaired fasting glucose; IGT: impaired glucose tolerance

Widespread newborn T1D genetic risk score testing could effectively identify individuals at high risk of developing T1D. More firm recommendations to test T1D genetic risk could emerge in the future as data continue to accumulate. The likelihood that an individual is not diagnosed with T1D but has completed genetic testing is relatively low since genetic testing is not widespread in the US. The result is that for most people the new recommendation essentially calls only for a family history of T1D since prior genetic testing is unlikely. Given that approximately 85% of individuals with T1D have no family history of T1D, the new recommendation will likely benefit fewer people than expected. Many people who could benefit from T1D screening may not hear about it from their physicians. The ones who do hear from their physicians may not receive insurance reimbursement for T1D screening if the insurance companies are not sufficiently compelled to pay. Likewise, many individuals diagnosed with other autoimmune conditions that incur increased risk of T1D may wish to be screened for T1D but do not have any family history of T1D and subsequently do not fit into the recommendation.Individuals who do not meet Recommendation 2.7 criteria may pursue other options to screen for T1D. Commercial lab companies charge approximately $400 out of pocket to test for the four clinically relevant DAA mentioned above [12]. More affordable DAA testing is not currently available but may become more readily available in the US in the future. Researchers are currently in the process of validating a 3-titer assay that tests for autoantibodies to GAD65, IA-2, and ZnT8 [13]. The test appears to be more sensitive than individual testing DAA alone, likely a result of the collective titers versus the detection of multiple single titers. Patients who express interest in T1D screening may also desire to participate in clinical trials. Clinicians should be aware of such trials and be prepared to provide information to patients. Family history of T1D, among others, is a common criterion for participation in trials designed to medically slow the progression of T1D [14]. Progress is being made to help prevent severe complications such as DKA as a presenting symptom of T1D. Close follow-up is warranted as data emerge from this practice. Broadened recommendations could help ensure insurance coverage shortly. It would be beneficial from a population-wide perspective to increase avenues to T1D screening in the form of DAA, which are highly predictive of progression to symptomatic T1D.

Conflict of Interest

The authors declare no conflict of interest.

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