Screening for Early Stage (pre-clinical) Type 1 Diabetes Mellitus

Goals of screening:

1. Prevent DKA and its associated short- and long-term morbidity and mortality
2. Minimize requirement for ER, hospitalization, ICU at time of stage 3 T1D
3. Advance preventative therapies through clinical trial recruitment
4. Offer interventions to delay progression to stage 3 T1D

What is the screening test:

Islet autoantibody (IAb) testing: minimal blood volume required (can be capillary or dried blood spot samples), minimally invasive, can be collected at home or in the outpatient setting

4 autoantibodies are typically measured: Insulin autoantibody (IAA), Glutamic acid decarboxylase-65 (GAD65), Insulinoma-associated protein 2 (IA-2), Zinc transporter (ZnT8) *–refer to attached Table 1: Individual IAb characteristics*

Who should you consider screening:

First degree relatives (parents, siblings) of someone with T1D

May also consider in younger (<20 years old) second degree relatives (half-sibling, grandchild, niece/nephew, aunt/uncle)

When to get the screening test:

Screening should be initially considered between 2-3 years of age and repeated between 5-7 years age.

Or at any point in an older aged child/adolescent/young adult with a family history who has not been screened before.

Where to get the screening test:

Health care providers may order the autoantibody panel (Quest Diagnostics Test "Diabetes Type 1 Autoantibody Panel", Test Code 13621) – cost of these tests is subject to the patient's insurance coverage

Eligible patients may also request testing directly and ***at no charge*** from the following two organizations:

TrialNet: www.trialnet.org

- Between the ages of 2 and 45 years and have a first-degree relative with T1D
- Between the ages of 2 and 20 years and have a second-degree relative with T1D
- Sample can be collected via any of the following options:
    - One of their clinical sites (closest is Boston)
    - Home kit: collect a finger-stick blood sample at home and then ship back via FedEx
    - Lab kit: mailed to patient's home, can be brought to Quest Diagnostics or LabCorp lab for a blood draw

Autoimmune screening for kids (ASK): www.askhealth.org

- Also screens for celiac (TTG antibodies) in addition to islet autoantibodies
- Available to ALL U.S. children (ages 1–17) and adults with or without a family history of these conditions
- Sample can be collected via any of the following options:
    - At their clinical sites (only in Colorado)
    - Home kit: collect a finger-stick blood sample at home and then ship back via FedEx
    - Lab kit: mailed to patient's home, can be brought to any LabCorp lab for a blood draw

What to do with a positive screening test:

Recommendations based on international consensus guidelines: Moshe et al.; Consensus Guidance for Monitoring Individuals with Islet Autoantibody–Positive Pre-Stage 3 Type 1 Diabetes. Diabetes Care 25 July 2024; 47 (8): 1276–1298.

If positive for only a ***single autoantibody("At Risk" classification)***:

1. Confirm autoantibody status with a repeat autoantibody panel, ideally obtained within 3 months of initial result
2. Educate patient and caregivers regarding symptoms of diabetes mellitus (polyuria, polydipsia, age-inappropriate enuresis, extreme fatigue, weight loss despite increased appetite, blurred vision) and diabetic ketoacidosis (vomiting, abdominal pain, Kussmaul breathing, altered mental status)
3. Clearly document in patient's medical record that patient is at risk for development of T1D
4. If patient is < 3 years old at initial seroconversion: repeat autoantibody panel with metabolic monitoring (random blood glucose and A1c) every 6 months for 3 years and then annually for another 3 years
5. If patient is ≥ 3 years old at initial seroconversion: repeat autoantibody panel and metabolic monitoring (random blood glucose and A1c) annually for 3 years
6. Review risk for progression to stage 3 diabetes with patient and their caregiver *-refer to attached table 5*
7. Periodic education regarding symptoms of diabetes mellitus and DKA

If positive for ***multiple autoantibodies ("Early Stage T1D" classification)***:

1. Confirm autoantibody status with repeat autoantibody panel, obtained within 3 months of initial result
2. Educate patient and caregivers regarding symptoms of diabetes mellitus (polyuria, polydipsia, age-inappropriate enuresis, extreme fatigue, weight loss despite increased appetite, blurred vision) and diabetic ketoacidosis (vomiting, abdominal pain, coo small breathing, altered mental status)
3. Clearly document in patient's medical record that patient is at risk for development of T1D
4. Obtain baseline glycemic testing (oral glucose tolerance test is the gold standard) as soon as possible after obtaining confirmation of positive autoantibody results - *refer to attached table 2 for all glycemic testing options and table 3 for interpretation of glycemic testing results*
5. Establish stage of T1D based on glycemic testing results *-refer to attached table 4*
6. Review risk for progression to stage 3 diabetes with patient and their caregiver *-refer to attached table 6*
7. Consider consultation with endocrinology for patients with stage 1 T1D if PCP does not feel comfortable coordinating recommended surveillance monitoring
8. Consult endocrinology for all patients with stage 2 T1D

How to follow up and monitor patients with multiple positive autoantibodies:

Recommendations for glycemic monitoring for ***stage 1 T1D*** are age-dependent:

- If patient is < 3 years old: HbA1c and random blood glucose every 3 months
- If patient is 3-9 years old: HbA1c and random blood glucose every 6 months
- If patient is > 9 years old: HbA1c and random blood glucose every 12 months

Recommendations for glycemic monitoring for ***stage 2 T1D***:

- HbA1c and random blood glucose every 3 months
- Review eligibility for disease modifying therapy (teplizumab)
- Consider 10 days of continuous glucose monitoring (CGM) every 3 months
- Monitor for signs and symptoms of T1D

Disease-modifying therapy (teplizumab)

- Indicated for patients with Stage 2 T1D that are ≥ 8 years old
- Consists of a single 14-day course of daily IV infusions
- Current data indicates that teplizumab therapy can delay the progression to Stage 3 T1D by 2-3 years

Table 1: Autoantibodies against islet cell antigens detected in stages 1-3 Type 1 diabetes mellitus

Autoantibody	Islet specificity	Typical characteristics
IAA	Insulin	• Common as a first detected autoantibody in young children (157,158) • Appearance is more common in younger children (159) • Frequency of appearance declines with age • Not informative for individuals treated with insulin, who often develop antibodies in response to injected insulin
GADA	GAD	• Common as a first detected autoantibody in childhood, up until age 15 years (157,158,160) • Adult-onset cases most often present with GADA (161) • Is associated with slower progression to T1D (162) and is often found as a single positive islet autoantibody, especially in adults
IA-2A (also known as ICA512)	Tyrosine phosphatase islet antigen-2	Presence is associated with more advanced islet autoimmunity and faster progression to stage 3 T1D (55,163)
ZnT8A	Zinc transporter type 8, a transmembrane protein in the β-cell granule	Presence can improve risk stratification in individuals with single $GADA^+$, IAA^+, or $IA\text{-}2A^+$ status (164)

IA-2A, insulinoma antigen-2 autoantibody; ICA, islet cell autoantibodies; ICA512, islet cell autoantigen 512; T1D, type 1 diabetes.

Moshe et al.; Consensus Guidance for Monitoring Individuals with IAb–Positive Pre-Stage 3 T1D. *Diabetes Care* 25 July 2024; 47 (8): 1276–1298.

Table 2: Glycemic testing options and their characteristics

Method	Pros	Cons	Metrics obtained
Standard OGTT†	• Similar to test for GDM: OGTT with 2 × blood draws (compared with 3 × draws in GDM test), performed routinely in clinical care	• Requires 2 blood draws: fasting and at 2 h	• 120-min OGTT-derived glucose • M120
Random glucose	• One-off sample • Low cost	• Requires a blood draw or fingerstick test • Less sensitive than 120-min OGTT	• Similar to 120-min OGTT-derived glucose (96) if obtained 2 h postprandially
Standard HbA_{1c} test	• Highly specific for clinical diagnosis of stage 3 T1D • Can use capillary sample • Longitudinal HbA_{1c} may be as informative as OGTT (66)	• Indicates 3-month mean glucose. Often normal in asymptomatic or recent-onset stage 3 T1D • May be affected by age, nondiabetes disease states (e.g., renal, hematological syndromes) • Not suitable in the home setting	• Risk of progression to "clinical disease": HbA_{1c} >39 mmol/mol (>5.7%) (170) • 10% rise from baseline (at first positive islet autoantibody) over 3–12 months (66,67) suggests dysglycemia and progression to stage 2 T1D • Consider use of CGM if 10% rise in HbA_{1c} is confirmed, or higher frequency of SMBG, to monitor risk for progression
CGM‡	• Can be used at home • Can be blinded for physician review only in some regions • Optimal duration of CGM wear is validated in adults and children >2 years of age with diagnosed T1D, at all glycemic levels (171)	• Risk of anxiety for unblinded user seeing CGM fluctuations and experiencing alarms • Requires appropriate education on use and interpretation • Many primary care HCPs are unfamiliar with interpretation • Cost and access issues • Duration of wear not validated in early-stage T1D	• Sensitive in detecting individuals with asymptomatic stage 3 T1D and dysglycemia in stage 2 T1D (73) • Risk of progression to "clinical disease," i.e., 10% of time with glucose >7.8 mmol/L (>140 mg/dL) has been associated with an 80% risk of progression to T1D within 12 months (72)

Moshe et al.; Consensus Guidance for Monitoring Individuals with IAb–Positive Pre-Stage 3 T1D. *Diabetes Care* 25 July 2024; 47 (8): 1276–1298.

Table 3: Glycemic testing result interpretation

Test	Normoglycemia	Dysglycemia	Diabetes
Fasting glucose	< 100 mg/dL	100-125 mg/dL	≥ 126 mg/dL
2 hour OGTT	< 140 mg/dL	140-199 mg/dL	≥ 200 mg/dL
Random glucose	< 140 mg/dL	140-199 mg/dL	≥ 200 mg/dL
HbA1c	<5.7%	5.7-6.4%	≥ 6.5%

Table 4: Stages of Type 1 diabetes mellitus

	At Risk	Stage 1	Stage 2	Stage 3
Beta cell autoimmunity	Single IAb+	≥2 IAb+	≥2 IAb+	≥1 IAb+
Blood glucose levels	normoglycemia	normoglycemia	dysglycemia	hyperglycemia in Diabetes range
Symptoms	no	no	no	yes

Table 5: Risk for progression of single IAb+ to Stage 3 T1D

	Risk for progression to Stage 3		
	5-year	15-year	Lifetime
Single IAb+ that reverts – within 2 years		12%	
Single IAb+ that persists after 2 years		30%	
Single IAb+ that goes on to multiple IAb+ within 2 years		82%	

Table 6: Risk for progression of multiple IAb+ to Stage 3 T1D

Risk for progression to Stage 3			
	5-year	15-year	Lifetime
Stage 1 ≥2 IAb+, normoglycemia	44%	80-90%	
Stage 2 ≥2 IAb+, dysglycemia	75%	>90%	100%