The T1D Early Detection Toolkit

A Practical Guide to Establishing Islet Autoantibody Screening Programs

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INNODIA is an international non-profit organization providing specialized services to medicine developers focused on curative therapies for people living with type 1 diabetes (T1D). These services are delivered through its network of members and INPACT associates (the trained community of people living with T1D).

Introduction

Type 1 diabetes (T1D) is a chronic disease requiring lifelong dependence on exogenous insulin.[1,2] The global prevalence of T1D is rising, with cases projected to reach approximately 11.5–19.3 million by 2040, a 27–92% increase compared to 2025.[3,4] The rising prevalence is concerning due to the concurrent increase in diabetic ketoacidosis (DKA) at diagnosis, a potentially life-threatening complication associated with significant morbidity, mortality, and high healthcare costs.[5–8] In addition, the emotional and psychological burden on individuals and families at clinical T1D onset can be substantial.[9]

T1D is characterized by an autoimmune process where autoreactive T cells are activated to destroy the body's own insulin-producing beta cells in the pancreas.[10]
Islet autoantibodies (IAbs) are detectable markers of this ongoing beta-cell destruction, often appearing months to years before clinical symptoms emerge.[11,12] The detection of two or more IAbs indicates early-stage T1D, for which the lifetime likelihood of developing clinical T1D approaches 100% in children.[11,13] T1D progresses through several stages:[1,14,15]

STAGE 1
involves the presence of two or more IAbs with normal glucose levels

STAGE 2
is characterized by two or more IAbs and dysglycemia
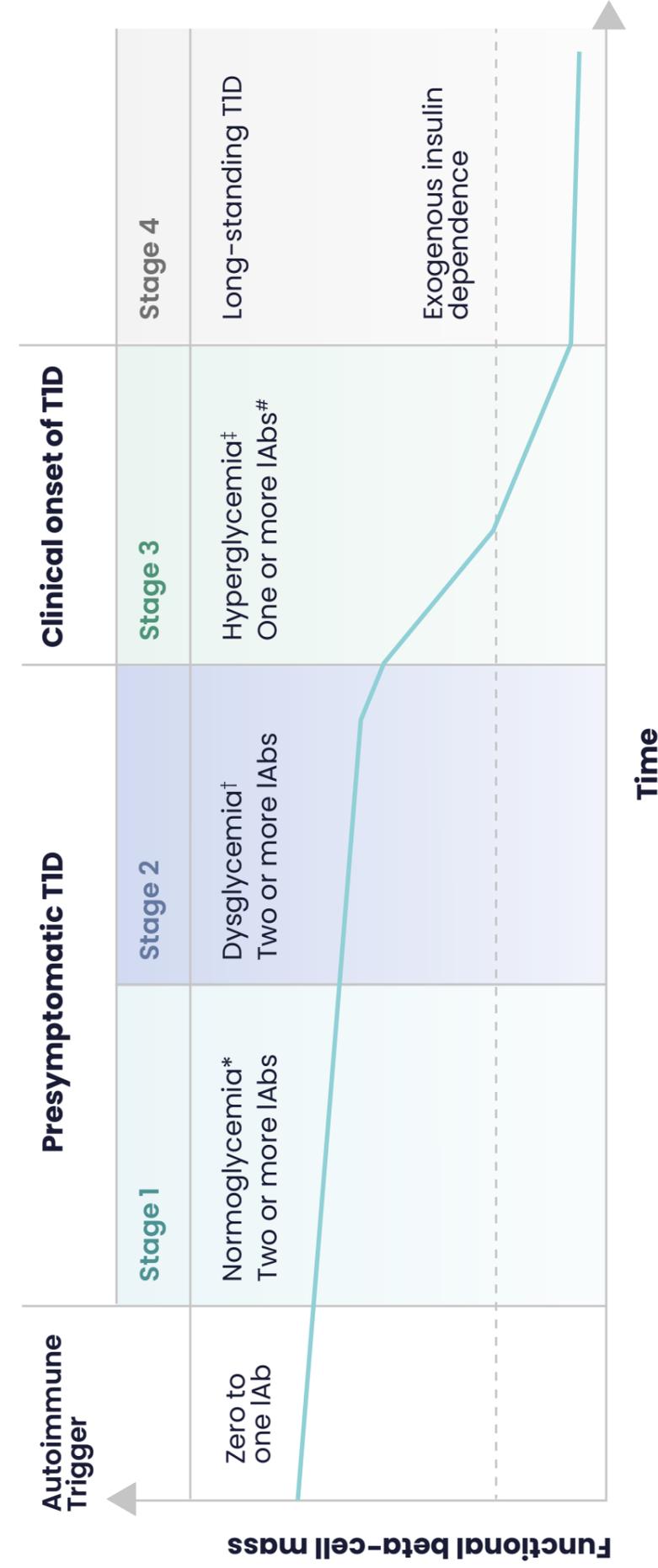
STAGE 3
marks the onset of hyperglycemia

STAGE 4
describes long-standing T1D

T1D Progresses in Four Distinct Stages, Linked to Functional Beta-cell Mass[1,13–18]

Autoimmune Trigger	Presymptomatic T1D		Clinical onset of T1D	
	Stage 1	Stage 2	Stage 3	Stage 4
Zero to one IAb	Normoglycemia* Two or more IAbs	Dysglycemia† Two or more IAbs	Hyperglycemia‡ One or more IAbs#	Long-standing T1D / Exogenous insulin dependence

Functional beta-cell mass (y-axis) vs Time (x-axis)

*Normoglycemia: Fasting plasma glucose (FPG) <5.6 mmol/L (<100 mg/dL), 120 min oral glucose tolerance test (OGTT) <7.8 mmol/L (<140 mg/dL), glycated hemoglobin (HbA1c) <39 mmol/mol (<5.7%).[18]
†Dysglycemia or glucose intolerance or not meeting diagnostic criteria for stage 3 T1D, with at least two of the following, or meeting the same single criteria at two time points within 12 months: FPG 5.6–6.9 mmol/L (100–125 mg/dL), 120 min OGTT 7.8–11.0 mmol/L (140–199 mg/dL), OGTT values ≥11.1 mmol/L (≥200 mg/dL) at 30, 60 and 90 min, HbA1c 39–47 mmol/mol (5.7–6.4%) or longitudinal ≥10% increase in HbA1c from the first measurement with stage 2 T1D, continuous glucose monitor (CGM) values >7.8 mmol/l (>140 mg/dl) for 10% of time over 10 days' continuous wear, and confirmed by at least one other non–CGM glucose measurement test listed.[18]
‡Hyperglycemia: Persistent hyperglycaemia with or without symptoms, as measured and confirmed by one or more of the following: one random venous glucose ≥11.1 mmol/L (≥200 mg/dL) with overt symptoms, 120 min OGTT ≥11.1 mmol/l (≥200 mg/dL), and/or two random venous glucose ≥11.1 mmol/L (≥200 mg/dL) and/or, FPG ≥7.0 mmol/l (≥126 mg/dl) and/or, laboratory-tested HbA1c ≥48 mmol/mol (≥6.5%), CGM values >7.8 mmol/L (>140 mg/dL) for 20% of time over 10 days' continuous wear and confirmed by at least one other non–CGM glucose measurement test listed.[18]
#Islet autoantibodies may become absent.[18]

Islet Autoantibody Testing

Screening for IAbs has emerged as a promising approach for early T1D detection. IAb screening offers the opportunity to identify individuals with early-stage T1D years before the onset of clinical symptoms, allowing for timely education, monitoring, and a reduction in the chance of potentially life-threatening DKA at presentation of clinical (Stage 3) T1D and subsequent morbidities.[19-22] It also allows for potential interventions to delay or prevent disease progression.[1,19,23]

The four primary IAbs are insulin autoantibody (IAA), insulinoma-associated antigen 2 autoantibody (IA-2A), glutamic acid decarboxylase autoantibody (GADA), zinc-transporter 8 autoantibody (ZnT8A); screening for all four is recommended.[1,2,24]

Who to Screen?

The decision of who to screen depends on multiple factors including your healthcare system and local priorities.

Certain factors increase the risk of developing T1D, including having a first-degree relative (FDR) with T1D, specific genetic variants (e.g., human leukocyte antigen haplotypes, HLA DR3-DQ2 and DR4-DQ8), and a personal or family history of other autoimmune diseases.[1,25] Screening programs that initially target people with FDRs may yield a higher rate of IAb positivity, and in practice can screen all ages, including adults, provided they have the requisite risk factors;[1,24] however, as only ~10% of individuals with T1D have a FDR with the condition,[1,26-32] general-population screening is required to identify the majority of people with early-stage T1D.[14] Genetic risk scores (GRS) may be useful for enriching a segment of the general population to receive IAb testing.[24,33]

General-population screening is likely to be most practical in children, who have existing regular contact with the healthcare system for early-years health programs.[23,34] Although the optimal age for screening is still under investigation, emerging data suggest that screening at multiple times during childhood may be most effective, given the variance in the timing of IAb seroconversion.[23]

Several studies have demonstrated the potential for general-population pediatric screening programs. The Fr1da study in Bavaria, Germany is a landmark population-based screening study that leverages existing pediatric care visits that occur after the peak islet autoantibody seroconversion incidence for screening.[27,34] In the United States, the ASK (Autoimmunity Screening for Kids) program in Colorado has established a model for general-population screening of children for type 1 diabetes and celiac disease.[35] In the UK, the ELSA study offers screening alongside routine childhood immunization visits.[36] This underlines the importance of understanding your local healthcare system when deciding who and when to screen.

Getting Started

This toolkit provides a practical, step-by-step guide for healthcare professionals (HCPs), including endocrinologists and primary care physicians, interested in establishing IAb screening programs in their own countries and centers. By implementing these strategies, HCPs can play a vital role in improving the lives of individuals at risk for or with early-stage T1D.

- Begin your journey by familiarizing yourself with the core requirements for a successful IAb screening program.

- Engage with local stakeholders and regional networks who can support you in setting up your program within your existing protocols, and help connect you with relevant expertise.

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Key Requirement For Initiating An IAb Screening Program

Establishing a successful IAb screening program requires careful planning and preparation to ensure people are appropriately screened, diagnosed, monitored and have access to adequate care, including psychosocial support. The following details the minimum requirements that should be met:

I. Use the Optimal Available Methodologies:
Select an initial testing method with strong sensitivity to reduce the number of false negatives, and a confirmatory test with strong specificity to reduce false positives. The assays selected should be diagnostically validated and amenable to large-scale implementation considering cost and availability.[1,2]

II. Establish Protocols for Confirmatory Testing:
Implement clear protocols for IAb screening and confirmation of positive results to minimize false positives and confirm the number and type of IAbs.[1-5]

III. Develop Clear Messaging:
Craft clear and concise messaging to effectively communicate to individuals and families both positive and negative results and their implications, including the need for monitoring.[1,2,4]

IV. Prepare for Monitoring:
Ensure a system is in place for monitoring glycemic levels in individuals who test positive for IAbs, including regular follow-up and re-screening as needed. Establish clear criteria and pathways for referral to specialists for monitoring where relevant.[3,5,6]

V. Understand Your Healthcare System:
Leverage existing care pathways or develop new ones to ensure appropriate referral and care for individuals with early-stage T1D.[6]

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Monitoring

Healthcare System

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I. Use the Optimal Available Methodologies

○ Sampling Methodologies

Islet autoantibody (IAb) testing can be performed on venous or capillary blood.[1] Capillary sampling has been validated against venous samples and may offer greater convenience and acceptability.[1-4] Self-collected capillary samples are usually whole blood in capillary tubes, which can be mailed at ambient temperatures.[1] While dried whole blood spots (DBS) are used in some settings,[2,5] not all IAb assays are validated for DBS and, unlike for serum-based measurements, there is no quality control standardization program for DBS. When selecting a sampling method for a T1D screening program, consider:

- Local regulatory considerations for self-collection.

- Cost: Expenses related to personnel, equipment, and reagents.[6-9]

- Assay Performance: Sensitivity and specificity of tests by method.[3,13,14]

- Local Availability: Infrastructure for collection, transport, and storage.

- Sample Collection: Suitability of capillary sampling for the population;[10] if capillary sampling is done initially, venous sampling is preferred for confirmatory testing.[11,12]

⚕ IAb Testing Methodologies

Several methodologies have been developed for IAb detection, each with its own advantages and limitations. Before beginning testing, evaluate available methodologies in your location. Positive results should be confirmed using a second validated assay.[4,9,12,15]

The assays listed on the next page are commonly in use and suitable for capillary sampling. With screening tests, trade-offs are made between certainty (positive predictive value) and sensitivity (proportion of true cases detected).[9] In diagnosing early-stage T1D, the ideal approach is high sensitivity within the first screening test to reduce false negatives, followed by confirmatory testing to confirm true positives.[9] General-population screening for polygenic risk scores can also be applied to enrich the population receiving IAb lab testing.[9,16] As this is an area of active research, genetic risk scores are not considered as part of this toolkit. However, regional and local networks may be available to support you with setting up genetic testing if appropriate for your screening program.

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☀ Please note this is not an exhaustive list and other methodologies may be available to you.

☀ Contact your local laboratory provider to determine which methodologies are available to you and consider those most practical to implement based on cost and lab capacity.

Available Assays

- **Enzyme-Linked Immunosorbent Assay (ELISA):**
ELISA is a commercially available assay that has the most data to support its use in clinical practice and is the most validated for general-population screening.[3,9,11] It is a low-cost and accessible method that provides an initial broad-spectrum screen of multiple IAbs.[8] It can exclude over 98% of samples from further testing.[9] Further testing is then required on positive samples to determine the specific number of IAbs present.[9,11]

- **Radiobinding Assay (RBA):**
Is considered the gold standard but has drawbacks including the use of radioactivity, expensive reagents, and is labor intensive compared with other available methods.[14-17]

- **Electrochemiluminescence (ECL):**
Multiplexed assay enabling simultaneous detection of four IAbs that uses smaller sample volumes than ELISA, although consumables are more expensive. Commercialization of this assay is in progress.[9,13,18]

- **Antibody Detection by Agglutination-PCR (ADAP):**
Commercially available in the US in a CLIA-certified lab and as a research use test across multiple studies.[19] A method with the potential for high throughput, it can detect the four key IAbs simultaneously and requires low serum volumes; however, it still requires further validation in at-risk populations.[6,9,14,19,20]

- **Luciferase Immunoprecipitation Systems (LIPS):**
Requires small serum volumes, minimal equipment, and is both rapid and sensitive; however, it is not readily amenable to multiplexing and no commercial assay exists. Assay sensitivity can also be variable based on placement of the luciferase tag and there is limited evidence in studies of early-stage T1D.[17,20-22]

- **Dissociation-enhanced Lanthanide Fluorescent Immunoassay (DELFIA):**
A novel multiplex method based on an adaptation of the ELISA 3 Screen test. It is commercially available in the US in a CLIA-certified lab to detect four antibodies and as a research use test to detect three antibodies (GADA, ZnT8, and IA-2A) with planned expansion to four antibodies.[5,23-25] It is currently primarily available for research use and is pending further validation in larger study cohorts.[5,24]

Checklist: How To Choose An Appropriate IAb Testing Methodology

When selecting an IAb testing methodology for your T1D screening program, consider the following factors:

Local Availability:
Determine the availability of different IAb testing methodologies and associated equipment in your region.[26,27]

Cost and Coverage:
Evaluate the cost of each IAb testing methodology, including reagents, equipment maintenance, and personnel training, and consider criteria required for payer coverage where relevant.[7–9]

Throughput:
Consider the number of samples that need to be processed and select a methodology that can accommodate the required throughput.[3,13,19]

Lab Expertise:
Ensure that the chosen laboratory has experience and expertise in performing the selected IAb testing methodology.[12]

Assay Performance:
Consider the sensitivity and specificity of different IAb assays for detecting relevant autoantibodies.[20]

Turnaround Time:
Evaluate the turnaround time for obtaining results and ensure that it meets the needs of your screening program.

By carefully considering these factors, you can select the most appropriate IAb testing methodology to ensure the success of your T1D screening program.

I. Use the Optimal Available Methodologies

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II. Establish Protocols for Confirmatory Testing

📋 Checklist: How to Choose an Appropriate IAb Testing Methodology

Confirmatory testing following an initial positive test result is crucial to ensure accurate diagnosis of early-stage T1D.[1-4] A checklist is presented in this chapter that can support the development of these protocols in your country:

☑ **Define Confirmatory Assay Procedures**

- Ensure confirmatory testing is conducted on a second, independently collected sample, as soon as possible, or at the very least within 6 months of initial testing.[3]

  - Depending on local practicalities, it may be appropriate to re-test the original sample with a second type of assay to reduce false-positive results, before collecting a second blood sample.[4]

- Ideally, it is recommended to use a different assay platform for confirmation (e.g., if ELISA is used for screening, confirm with ECL or RBA).[3,4]

- Define time window for second sample collection; this should be as soon as possible after the initial result and within 6 months.[2,3]

- Determine logistical process for re-contacting participants and arranging follow-up collection.[2]

☑ **Select Appropriate Testing Laboratories**

- Consult with laboratories that have experience in IAb measurements to guide establishment of testing protocols.[3,5]

☑ **Validate Local Capacity**

- Estimate the number of samples to be tested and ensure the laboratory has the capacity to screen these in a timely manner.

- Ensure capacity for timely collection, shipping, and processing of repeat samples.

☑ **Ensure Sample Integrity**

- A venous sample is recommended for the confirmation sample.[3,6]

- Ensure proper labeling and chain of custody for both samples.

- Store and transport samples appropriately to minimize hemolysis.[7,8]

☑ Define Next Steps

- Establish protocols for communicating results to patients and caregivers.[1-4]

- Plan follow-up steps for individuals with confirmed autoantibody positivity (e.g., staging, counseling, monitoring, referral).[2,3]

☑ Documentation & Quality Control

- Maintain records of both initial and confirmatory test results.[2,3]

- Document assay types, labs used, and time between collections.

- Implement regular audits to ensure protocol adherence and performance.

☑ Validate Local Capacity

- Ensure informed consent, where applicable, includes information about repeat testing and its purpose.

- Provide clear communication about the significance of initial and confirmatory results.[1,2,4]

☑ Align with Consensus Guidelines

- Review and integrate recommendations from relevant national and/or international guidelines.[3,9-11]

- Update protocols regularly based on emerging evidence and national standards.

💡 Establishing protocols for confirmatory testing requires input from multiple stakeholders, including clinical coordinators, laboratory staff and those responsible for reimbursement. Proactively start conversations with your colleagues for support with implementing screening protocols.

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III. Develop Clear Messaging: The Early Detection Communication Toolkit

This communication toolkit provides healthcare professionals (HCPs) with practical and developmentally appropriate language for:

1 Discussing the rationale for IAb screening (all ages)

2 Explaining IAb results (all ages)

3 Communicating risk and next steps (all ages)

4 Tailoring messaging by age, disease stage, and audience (e.g., caregiver vs. individual)

Example language is provided in this chapter in italics to support HCPs during conversations with people who are considering or undergoing IAb screening, and their caregivers.

1. Discussing The Rationale For Screening (All Ages)

When to screen?

Type 1 diabetes is an autoimmune disease where the body's immune system mistakenly destroys insulin-producing cells in the pancreas.[1,2] This can happen months to years before symptoms arise.[3-5]

- **What does autoimmunity mean?**
  Autoimmunity means the body's immune system, which normally protects us from things like bacteria, viruses, fungi and parasites, mistakenly targets healthy cells.[6] In T1D, the immune system damages the cells in the pancreas that produce insulin, affecting the body's ability to control blood sugar levels.[1,2]

Why Screen?

Screening for type 1 diabetes autoantibodies allows us to detect this autoimmune process early, potentially before any symptoms appear.[3] This provides us with an important opportunity to reduce the chance of potentially life-threatening diabetic ketoacidosis (DKA) and subsequent morbidities,[7–11] implement monitoring, prepare proactively, and potentially benefit from available treatments and research opportunities.[3]

Who to Screen?

*Approximately 90% of individuals diagnosed with T1D have no family history, meaning **screening can be beneficial** for everyone.[1,12–18]*

- *While the risk of developing T1D in the general population is approximately 1 in 300, individuals with a close family member (parent or sibling) with T1D have a higher risk (1 in 20). Those with certain genetic markers are also at increased risk of developing T1D during their lifetime.[3]*

When to Screen?

Although the optimal age for screening is still under investigation, emerging data suggest that screening at multiple times during childhood may be most effective to maximize the chance of catching the condition in its early stages.[3,19,20]

How Screening Is Done

Screening involves taking a small blood sample. This can be done either with a finger prick, or a suitable needle. We will then test your blood for T1D autoantibodies, which can be a sign of early-stage T1D.[19,21–25]

What Happens If the Test Is Positive

- **Explaining the next steps simply:**
  If the test is positive, we may ask you to provide another blood sample to confirm the result. If the presence of two or more T1D autoantibodies is confirmed, even if you have no symptoms, then this indicates you have an early stage of type 1 diabetes and might eventually require insulin therapy, although the timing of this progression remains uncertain. Those identified as having early-stage T1D will need to see their healthcare provider to develop a plan for blood sugar monitoring.[20,26]

How Screening Is Done

- **Anxiety or nervousness about screening:**
  It's completely normal to feel anxious or uncertain about screening results.[3,26] Knowing early allows us to proactively manage health risks and helps prevent sudden complications.[3] You will be supported at every step in your journey.

- **Highlighting the options available for people who have early-stage T1D:**
  People in the early stages of T1D may be eligible to participate in clinical trials investigating disease-modifying therapies that aim to delay or prevent the onset of symptoms. Individuals with early-stage T1D should also be regularly monitored for signs of progression, and both they and their caregivers educated and supported with access to a range of resources to support their health and wellbeing.

Confirmed Result	Meaning	Key Message	Expected Progression Timeline
Negative	No IAbs detected	There are no current signs of the autoimmune process associated with T1D.	Re-screening might be recommended in the future, depending on age and risk factors (such as genetic risk e.g., a family member with T1D, or family or personal history of other autoimmune diseases.[3,26,27]
Single IAb Positive	Slightly increased likelihood of T1D	Increased likelihood of developing T1D vs. the general public. Many people with just one antibody never develop type 1 diabetes, but re-screening and regular follow-up may be recommended to monitor any potential changes, particularly if they have risk factors for T1D such as a family history of the disease.[26] Single islet autoantibody positivity is not a diagnosis of early stage T1D.	~ 50% of children go back to being diabetes autoantibody negative. For those with persistent single autoantibody positivity, the 10-year risk of progression to clinical Stage 3 T1D is 14.5%.[26]
≥2 IAbs, normal glucose	Stage 1 T1D	In Stage 1, blood glucose remains normal, and the person does not have symptoms or require insulin; however, progression to clinical type 1 diabetes over time is very likely. Regular monitoring for progression and education on diabetes symptoms is recommended.[26]	While it is not possible to predict exactly when an individual will progress, it is very likely that children who develop Stage 1 T1D will progress to clinical Stage 3 T1D over the course of their lifetime, with 44% progressing to Stage 3 T1D within 5 years, and 70% within 10 years.[4,25] Adults are typically much slower to develop symptomatic T1D, with approximately 15% of adults with ≥2 IAbs developing Stage 3 T1D within 5 years, and approximately 40% within 10 years.[28] Once a person has tested positive for ≥2 IAbs, the likelihood of progressing to clinical Stage 3 T1D is the same with or without a family history of T1D.[5]
≥2 IAbs,* dysglycemia	Stage 2 T1D	In Stage 2, blood glucose is only slightly elevated (dysglycemia), and the person does not have symptoms or require insulin. It is uncertain whether adults with Stage 2 T1D will progress to symptomatic Stage 3 T1D;[28] however, progression to clinical type 1 diabetes over time is near certain for those diagnosed in childhood.[25,26]	Approximately 32% of children with Stage 2 T1D will progress to clinical Stage 3 T1D within 2 years, and it is very likely that they will meet the criteria for clinical Stage 3 T1D during their lifetime.[5, 26] In adults approximately 5-10% will become symptomatic within 2 years.[28]
≥1 IAbs, hyperglycemia	Stage 3 T1D	In Stage 3, blood glucose is elevated enough to meet the criteria for clinical type 1 diabetes. People may be asymptomatic or symptomatic and may need to start taking insulin depending on their glycemic status.[25,26]	
Variable*	Stage 4 T1D	People with Stage 4 T1D have long-standing insulin dependence, and may no longer be positive for T1D IAbs.[1,3,26,29]	

*Please note, some people with confirmed persistent prior multiple autoantibodies may lose IAb-positivity over time (thought to be due to lack of antigen exposure).[26,29]

Additional Factors to Consider when Interpreting IAb Test Results:

- **Age at detection:**
  Younger children with multiple IAbs tend to progress to clinical Stage 3 T1D more quickly than older children and adults.[30]

- **Family history of T1D and/or other autoimmune diseases:**
  Individuals with a first-degree relative with T1D have a higher risk of developing the disease.[3] A personal or family history of other autoimmune diseases, such as celiac disease or autoimmune thyroid disease, also increases the risk.[27] These risk factors can inform the decision to re-screen.

- **Insulinoma-associated antigen 2 autoantibody (IA-2A):**
  The presence of IA-2A, either alone or in combination with other IAbs, increases the likelihood of progression to clinical Stage 3 T1D.[31,32]

3. General Principles For Communicating About Risk And Progression

Communicating speed of progression effectively is crucial for ensuring that individuals and families understand the implications of IAb test results and can make informed decisions about monitoring and potential interventions.

- **Use clear and simple language:**
  Avoid medical jargon and technical terms. Explain concepts in a way that is easy to understand and ask people to repeat back key information.[20,26]

- **Provide context:**
  Explain the difference between having an increased likelihood/chance of developing T1D and having a diagnosis of early-stage T1D. Emphasize that autoantibody positivity does not mean that the individual will definitely develop clinical Stage 3 T1D.[26]

- **Use numbers carefully:**
  When discussing the speed of progression, use specific numbers and avoid mixing numerical concepts. For example, instead of saying "the 2-year risk of symptomatic, clinical disease is approximately 32%," say "*your child has an approximately 1 in 3 chance of progressing to clinical Stage 3, type 1 diabetes in the next 2 years*".[20]

- **Link information to actionable steps:**
  Connect the information on speed of progression to specific actions that the individual and family can take, such as monitoring blood glucose levels, and how to respond if they are outside the normal range.[26]

4. Tailoring Your
Message To Your Audience

Include children who are old enough in conversations about their case; however, be mindful that children and young people require communication tailored to their age, needs, and ability to understand.[33,34] Distinct age groups have different cognitive abilities that impact the type of information they can receive and process, as well as distinct emotional and communication needs.[34]

Consider how to adapt your communications from speaking entirely to caregivers in early childhood, to fostering autonomy and shared decision-making in adolescence, and empowering adults to take control of their health and wellbeing.

Use these guiding principles to develop clear messaging that can be communicated consistently to all people who undergo screening.

Remember to tailor your language to the person's age and individual needs.

COMING SOON
The next edition of this toolkit will introduce age-tailored communication tools and resources to support you during conversations with people undergoing screening.

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☼ Collaborate with
your local team
to establish
standardized
protocols for
regular follow-up,
glucose testing,
and coordination
between clinicians
and care staff.

Individuals with an increased likelihood of early-stage T1D (single IAb positive) or who have presymptomatic early-stage T1D (≥2 IAb positive) should be monitored regularly to prevent DKA, emergency care, or hospital admission, and enable timely intervention.

Monitoring in this context includes regular assessments of glucose levels (metabolic monitoring), regular education about symptoms of diabetes, and psychosocial support.[1–3]

Consensus guidance is available that highlights the scope, purpose, and frequency of monitoring for children, adolescents and adults depending on their IAb status and stage of their disease and is summarized in this chapter.[3]

Multiple Metabolic Monitoring Tools Are Available to Monitor Disease Progression[3]

- **Oral glucose tolerance test (OGTT)**

  Gold standard in research settings; used to stage disease and predict progression. This test requires glucose load and 2–5 blood draws over 2 hours.

- **Random plasma glucose**

  Low-cost test that requires a single blood sample, acquired by blood draw or finger prick. Offers lower sensitivity than 120-min OGTT.

- **HbA1c**

  Highly specific for clinical diagnosis of Stage 3 T1D, and can be performed using capillary samples. Low sensitivity and may lag actual glycemia by several weeks. Values can also be affected by age and non-diabetes disease states. Not suitable in the home setting.

- **Continuous glucose monitoring (CGM)**

  Monitoring with wearable CGMs is validated in adults and children >2 years of age with diagnosed T1D, at all glycemic levels. It can be used at home and blinded for physician review in some regions. Requires appropriate education on use and interpretation. Use may be limited by cost and access issues.

- **Self-monitoring of blood glucose (SMBG)**

  Comparatively low-cost test suited to home use. Can cause discomfort for users, which in turn affects accuracy and use. Optimal timing and frequency have not been determined.

- **C-peptide**

  A validated measure of beta-cell function; stimulated C-peptide in research settings is used to assess insulin production, for T1D staging, and to distinguish T1D from T2D.

Evaluate the pros and cons of each methodology as published in the Consensus Guidance when establishing your monitoring protocols and consider which healthcare provider will have the primary responsibility for monitoring within your IAb screening program.

The Frequency of Monitoring Depends on IAb Status, Glycemic Status, and Age[3]

	Single IAb-positive Normoglycemic	Stage 1 T1D Normoglycemic	Stage 2 T1D Dysglycemic
	IAb and metabolic monitoring*	Metabolic monitoring*	
Children and adolescents*	<3 years old: every 6 months for 3 years, then yearly for 3 years 3–17 years old: every year for 3 years	<3 years old: every 3 months 3–9 years old: at least every 6 months 9–17 years old: at least every 12 months	Every 3 months
Adults†	Every 3 years	Every 12 months†	Every 6 months‡§
Signs of progression	NA	A ≥10% longitudinal rise in HbA1c from the date of confirmed IAb positivity¶ may indicate disease progression necessitating an OGTT to assess T1D stage	
Signs of progression	If no progression, stop monitoring and counsel on symptom awareness	NA	Note that Stage 2 T1D warrants referral to specialists in T1D progression for discussion of risks and options for monitoring

*In children and adolescents, metabolic monitoring should include HbA1c and random blood glucose measurements (venous or capillary).

†Adjust frequency based on individual risk assessment, based on age number and type of IAbs, and glycemic status.

‡In adults with Stage 2 T1D, metabolic monitoring should include HbA1c with one other modality: blinded CGM, higher frequency SMBG, or 2-hour plasma glucose following 75g OGTT.

§Before commencing more intense monitoring for Stage 2 T1D, abnormal glucose results should be verified by at least two of the following methods: fasting plasma glucose, OGTT, HbA1c or CGM.

¶In children with Stage 1 T1D, this can be a sign of disease progression even if the 10% HbA1c increase is within the normal range (e.g., from 31 mmol/mol [5.0%] to 37 mmol/mol 5.5%]).

Establishing Systems and Alerts for Monitoring and Re-screening

- Ensure systems are in place for automatic scheduling and reminders for IAb re-screening, if appropriate, and regular monitoring of individuals with early-stage T1D in line with your monitoring protocol.[4]

- Clearly document results and recommended follow-up actions in patient records to facilitate coordination between healthcare providers.[3]

Psychosocial Support

- Regularly assess emotional and psychological responses to positive IAb status.[3,5]

- Provide accessible psychological support, integrated into regular medical visits by professionals trained in diabetes-specific mental healthcare.[3,5]

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V. Understand Your Healthcare System

Successfully implementing an IAb screening program requires a thorough understanding of your local healthcare system. This section provides guidance on how to leverage existing resources and establish appropriate referral pathways to ensure optimal follow-up and care for individuals with early-stage T1D.

💡 Connect with local clinicians, researchers, and regional networks who can support you with technical expertise and help you to navigate introducing new protocols for your center.

💡 Evaluate the most appropriate points-of-contact to implement a T1D early-detection program within existing treatment pathways.

1. Establishing Collaborative Networks

- **Engage major country screening centers, if they exist:** Identify these centers by consulting national diabetes associations, T1D organizations, or healthcare ministry resources. Work collaboratively with these centers to establish standardized screening protocols and referral pathways.[1-3]

- **Promote collaboration:** Encourage collaboration between different healthcare providers and organizations to avoid siloed screening efforts and ensure seamless care transitions.[1,4,5]

2. Leveraging Existing Referral and Care Pathways

- **Identify existing pathways:** Determine if there are existing referral pathways for individuals with diabetes or other autoimmune conditions that can be leveraged for IAb screening.[4]

- **Adapt existing pathways:** Modify existing pathways to accommodate the specific needs of individuals with early-stage T1D, including eaducation, monitoring, and access to clinical trials.[1,4]

- **Develop new care pathways:** If existing pathways are insufficient, collaborate with local healthcare teams/clinicians or institutions to identify achievable steps for appropriate follow-up and care for individuals with early-stage T1D.

3. Essential Components of Referral and Care Pathways

- **Clear referral criteria:**
  Establish clear criteria for referring individuals with positive IAb test results to specialized care.[4]

- **Standardized monitoring protocols:**
  Develop standardized protocols for monitoring individuals with early-stage T1D, including frequency of testing and specific tests to be performed.[4]

- **Access to education and support:**
  Ensure that individuals with early-stage T1D and their families have access to comprehensive education and support services, including diabetes educators, psychologists, and support groups.[4]

4. Disclaimer

- **Referral pathways depend on local healthcare infrastructure:** The availability of referral pathways and resources may vary depending on the local healthcare infrastructure. This toolkit provides general guidance, but it is essential to adapt the recommendations to your specific context.

5. Resources

- The **INNODIA EARLY T1D NAVIGATOR** tool is intended as a resource for members of the public interested in screening and monitoring in Europe, to be linked to clinical sites in their countries that are currently carrying out screening programs (in Europe).

www.innodia.org/innodia-early-t1d-navigation-tool

References – Chapter V
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Appendix

The following resources **provide essential guidance for** healthcare professionals involved in the early detection and management of T1D:

- **ISPAD Clinical Practice Consensus Guidelines**
  Comprehensive recommendations for screening, staging, and preserving beta-cell function in children and adolescents at risk for T1D

  - Besser REJ, et al. Pediatr Diabetes. 2022;23(8):1175-87.

- **Consensus Guidance on Monitoring from Breakthrough T1D**
  Practical strategies for monitoring individuals positive for IAbs to detect progression towards clinical T1D and prevent DKA

  - Phillip M, et al. Diabetologia. 2024;67(9):1731-59.

- **EDENT1FI Master protocol**
  A European initiative harmonizing screening protocols for early-stage T1D in children and adolescents, including procedures for IAb testing and follow-up care

  - Hoffmann L, et al. BMJ Open. 2025;15(1):e088522.

- **INNODIA Early Detection Protocol for Screening and Monitoring in EUROPE**
  The largest European network dedicated to preventing and curing type 1 diabetes, **INNODIA** is a valuable point of contact for HCPs based in Europe looking to establish T1D early-detection programs. In compliance with the international guidelines, **INNODIA** developed a program that enables **INNODIA** clinical sites in Europe to implement early T1D detection with confidence and consistency. **The INNODIA Family & Friends** early T1D detection program (**INNODIA DETECT**) includes: (i) master protocols for islet auto-antibody (IAb) detection and monitoring of IAb+ individuals, (ii) access to a centralized data repository (**INNODIA eCRF**) for streamlined data collection, and (iii) matchmaking support to connect clinical trials' Sponsors with the clinical sites monitoring presymptomatic T1D individuals.

  - INNODIA Family & Friends Early-Stage T1D Detection Protocol. Available at: https://www.innodia.org/innodias-clinical-trials/innodia-early-t1d-detection (Accessed September 2025).

- **BR1DGE**
  A global medical education program by Sanofi, offering resources and training modules to enhance understanding of presymptomatic T1D among HCPs

  - www.bridgeT1D.com/ (Accessed September 2025).

The landscape of T1D autoantibody screening is continuing to evolve. Publications for key screening methods that have informed the creation of this document are listed below; please note this is not an exhaustive list and new data may emerge.

3 Screen ELISA; the Fr1da experience, Germany

- Ziegler AG, Haupt F, Scholz M, et al. 3 Screen ELISA for high throughput detection of Beta cell autoantibodies in capillary blood. Diabetes Technol Ther. 2016;18(11):687-93.

ECL; approach used by the ASK study, USA

- He L, Jia X, Rasmussen CG, et al. High-throughput multiplex Electrochemiluminescence assay applicable to general population screening for type 1 diabetes and celiac disease. Diabetes Technol Ther. 2022;24(7):502-9.

Type 1 diabetes risk factors, risk prediction and presymptomatic detection: Evidence and guidance for screening

- Bonifacio E, Ziegler A-G. Diabetes Obes Metab. 2025;27 (Suppl 6):28-39.

ADAP; DiaUnion method, Denmark and Sweden

- Lind A, Freyhult E, de Jesus Cortez F, et al. Childhood screening for type 1 diabetes comparing automated multiplex Antibody Detection by Agglutination-PCR (ADAP) with single plex islet autoantibody radiobinding assays. EBioMedicine. 2024;104:105144.

LIPS; currently available in a research setting only

- Burbelo PD, Lebovitz EE, Notkins AL. Luciferase immunoprecipitation systems for measuring antibodies in autoimmune and infectious diseases. Transl Res. 2015;165(2):325-35.

DELFIA; primarily available for research use

- Dufrusine B, Natale L, Sallese M, et al. Development and validation of a novel method for evaluation of multiple islet autoantibodies in dried blood spot using dissociation-enhanced lanthanide fluorescent immunoassays technology, specific and suitable for paediatric screening programmes. Diabetes Obes Metab. 2025;27(1):414-8.

Notes