
بسم الله النور

screening or not screening T1D ISPAD 2024 Recommendations

An Overview of Updated Guidelines and Clinical Implications

- The presence of IAb+ for a presymptomatic period of variable duration in first-degree relatives of individuals with T1D has been known for more than 40 years

- Decades of subsequent research and monitoring of individuals with islet autoantibody positivity has led that T1D is a continuum of stages, from **genetic risk** through to **autoimmunity** and then **metabolic disease**

- Treatment options have moved on from monitoring and managing metabolic disease to include options for modulating the autoimmune response

Why should you SCREEN?

screening or not screening T1D

"Not knowing" can have major financial, emotional and social burdens

50% of adults with T1D

spent at least $5,000 on emergency care for their T1D symptoms before or during their diagnosis, with nearly **1 in 4** (24%) spending at least $10,000.

64% of adults with T1D

say their emotional health declined when they first received their diagnosis; **61%** said knowing about their risk sooner would have helped with these feelings.

71% of adults with T1D

made changes to some of their interests or plans after receiving their diagnosis. 37% of this group say they would not have done so if they had known sooner about their risk of developing T1D.

screening or not screening T1D

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Nearly all adults with T1D and caregivers recommend early screening for type 1 diabetes

92% of adults with T1D

say they would recommend friends and family members get an early autoantibody test for T1D to understand their risk of developing the disease.

This jumps to
96% for caregivers

Purpose of monitoring in IAb in children, adolescents

Why Screen for T1D?

- Prevention of diabetic ketoacidosis (70%).
- Better planning for disease management.
- Improved long-term health outcomes.
- Screening identifies individuals with islet autoantibodies before clinical symptoms appear.

Why Screen for T1D?

- With the availability of new therapies that can **delay or prevent type 1 diabetes**
- The opportunity for dramatically changing the future of this disease is enormous.

Global Burden of Type 1 Diabetes

- **Over 1.5 million** children and adolescents globally affected by T1D.
- Increasing incidence rates worldwide.
- Significant healthcare **costs** and long-term **complications**.
- ISPAD 2024 guidelines address screening as a potential tool for **early detection and prevention.**

Screening Programs

- **ISPAD 2024** recommends expanding screening for T1D in research and clinical settings.
- **Key focus on:**
- **Identifying** islet autoantibodies.
- **Early intervention** strategies.
- **Improved outcomes** and quality of life for individuals at risk.
- **Collaboration between** research and clinical teams.

Screening Programs

- who should be monitored
- which endpoints to monitor
- The frequency and duration of monitoring
- initiation of insulin during stage 3 type 1 diabetes
- How to provide psychosocial and educational support for affected individuals and families

Autoantibodies against islet autoantigens detected in stage 1–3 type 1 diabetes

The Requirement for Monitoring

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)
ICA	Multiple antigens, undefined	Detected by indirect immunofluorescence on islet cell tissue. While not frequently measured other than in research studies, it does add to risk determination in the presence of other biochemical autoantibodies

The first positive test should be confirmed with a second test within 3 months

Screening Methods for T1D

- 1- Genetic Risk Assessment:
- Identifies high-risk individuals based on HLA genotyping.
- 2- Autoantibody Testing:
- Measures islet autoantibodies (ICA, GAD, IA-2A, ZnT8,IAA).
- 3- Glucose Monitoring:
- Oral glucose tolerance test (OGTT)
- Continuous glucose monitoring for dysglycemia.

increased risk of relatives

- People with a **first degree relative** with T1D have up to a 15-fold increased risk of developing T1D compared to persons without a known family history of T1D.

- Siblings of patients 6–7% lifetime risk
- offspring of mothers and fathers with T1D have a 1.3–4% and **6–9%** risk
- .

Screening in Relatives of Individuals With T1D

- Screened more than 4,400 first-degree relatives.
- The most frequently found AAs are GADA and IAA
- ~5% of relatives to have at least one AA
- About half of these had multiple AAs

Because of the enriched risk in relatives, screening programs and clinical trials have often **targeted** this group

Staging criteria for autoantibody-positive individuals in pre-stage 1 and stage 1–3 type 1 diabetes

TABLE 1 ADA criteria for normoglycaemia, dysglycaemia and hyperglycaemia.[9]

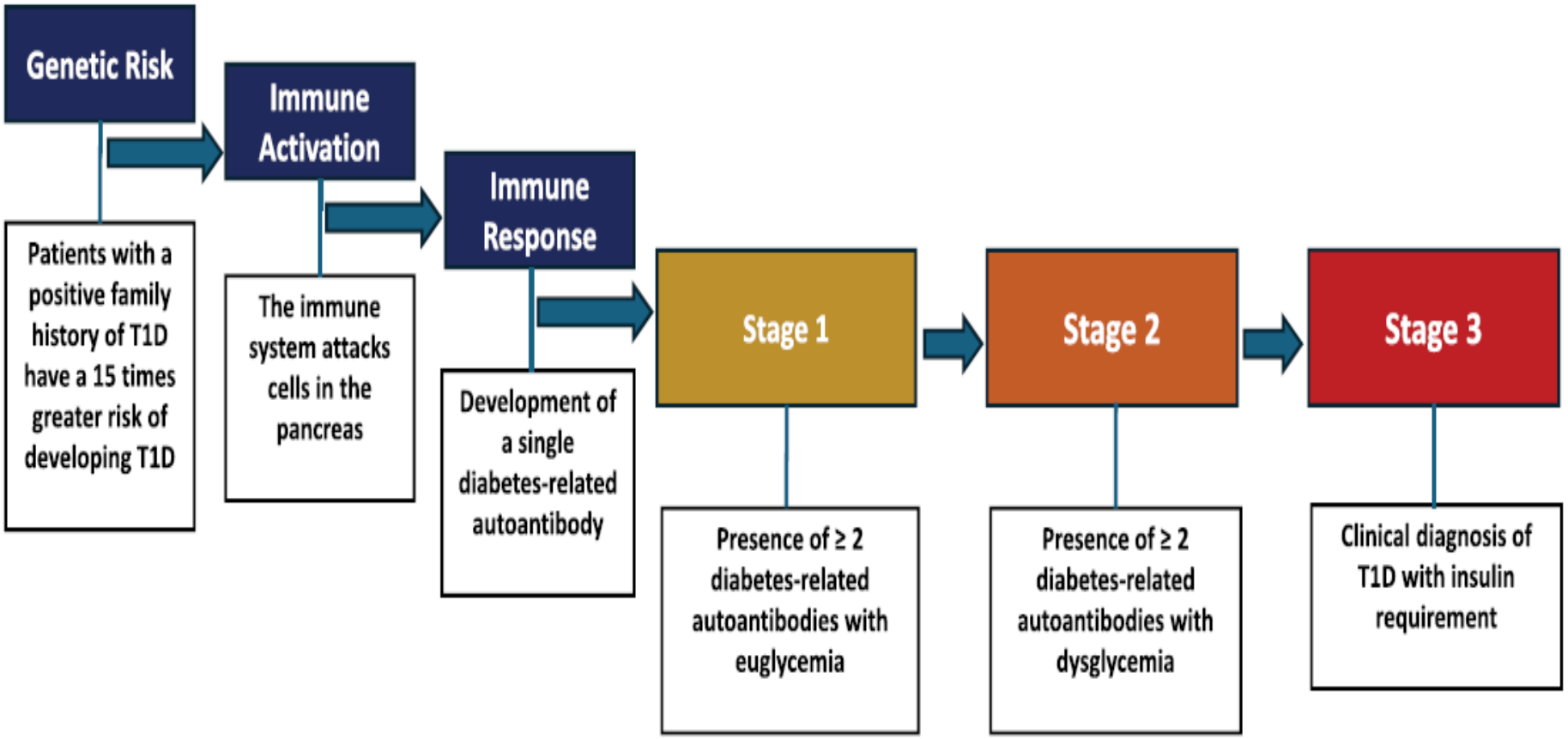
	Normoglycaemia (stage 1)	Dysglycaemia (stage 2)	Hyperglycaemia (stage 3)
Fasting plasma glucose	FPG <100 mg/dL (<5.6 mmol/L) OR	FPG 100–125 mg/dL (5.6–6.9 mmol/L) OR	FPG ≥126 mg/dL (≥7.0 mmol/L) OR
Haemoglobin A1c	HbA1c <5.7% (<39 mmol/mol) OR	HbA1c 5.7%–6.4% (39–47 mmol/mol) OR HbA1c ≥10% increase from previous visit OR	HbA1c ≥6.5% (≥48 mmol/mol) OR
Oral glucose tolerance test	2 h PG <140 mg/dL (<7.8 mmol/L)	2 h PG 140–199 mg/dL (7.8–11.0 mmol/L)	2 h PG ≥200 mg/dL (≥11.1 mmol/L) OR
Additional criteria used in research studies [10]		30-, 60- or 90-min PG ≥200 mg/dL (≥11.1 mmol/L)	
Random plasma glucose			Symptoms + PG ≥200 mg/dL (≥11.1 mmol/L)

At risk

Genetic screening and/or family history or with only single IAb status have pre-stage 1 type 1 diabetes

New staging

- . **Stage 3a** describes those who are asymptomatic but who meet glycemic diagnostic criteria.
- **Stage 3b** describes those with classic onset with overt hyperglycemia and symptoms (e.g., polyuria, polydipsia, and unexplained weight loss) and an immediate need for insulin initiation.
- **Stage 4** Long standing T1D



ICD-10 Codes[a]	
E10.A0	Type 1 diabetes mellitus, presymptomatic, unspecified
E10.A1	Type 1 diabetes mellitus, presymptomatic, Stage 1
E10.A2	Type 1 diabetes mellitus, presymptomatic, Stage 2

Prediction of T1D based on antibody

Prediction of T1D based on antibody

- Those with IA-2A had **higher risk**
- Those with GADA had **less risk**

- Those with IAA and GADA had only a **17%** **5 year** risk T1D
- Those <12.0 years of age with multiple Ab had an estimated 5 year T1D rate of 35% vs those who were ≥12.0 years of age 22%

Prediction of T1D based on antibody

- progression rate is higher for young children who have single IA-2A positivity **(40.5%)** compared with GADA positivity **(12.9%)** or IAA positivity **(13.1%)**
- However, it must be noted that **fewer than 10%** of children with single IAb status are **IA-2A.**
- IA-2A positivity conferred a higher risk relative to the presence of other autoantibodies

HR 1.97

Prediction of T1D based on antibody

- incidence of diabetes at 5 years of follow-up in those with 2 vs >2 autoantibodies at baseline was 29% and 31%
- up to 50% of children with single IAb status revert to being islet autoantibody negative

Prediction of T1D based on antibody

- The vast majority **(90%)** of young people with **multiple islet autoantibodies** progress **to Stage 3 within 15 years**
- **C**ompared to only **15%** who have a **single islet autoantibody**.

Prediction of T1D based on antibody

- Children with single positive islet autoantibodies who revert back to islet autoantibody negative within 2 years of seroconversion have a risk of only **12%** to develop stage 3 type 1 diabetes over the next 15 years,
- while this risk is **30%** in those children that remain single islet autoantibody positive after 2 years

Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children

- Progression to **T1D** at 10-year follow-up after islet autoantibody seroconversion in
- **585** children with multiple islet autoantibodies was **69.7%**
- **474** children with a single islet autoantibody was **14.5%** with most of that progression (10%) happening in the first 2 years after becoming IAb^{+}
- Risk of diabetes in children who had no islet autoantibodies was **0.4%**

Who should be monitored?

Any child, **adolescent**, or adult who has tested positive for islet autoantibodies in early-stage type 1 diabetes (T1D)

Nearly 100% of individuals in early-stage T1D with two or more persistent islet autoantibodies will progress to a stage 3 (clinical) diagnosis

Prediction T1D based on staging

Prediction T1D based on staging

- . Amongst children living with Stage 1
- 44% will progress to Stage 3 T1D in 5-years
- 80-90% will progress within 15 years.

Prediction T1D based on staging

In children living with Stage 2 T1D

- 75% will progress to Stage 3 T1D in 5-years

Nearly 100% during their lifetime

Prediction T1D based on family history

Prediction T1D based on family history

- The prevalence of T1D amongst people with a first degree relative is 5% by age 20 compared to 0.3% amongst the general population.
- Nevertheless, more than 90% of children diagnosed with T1D do not have a family history of this condition .

Genetic Risk

Role of Genetics in Screening

- **HLA genotypes** associated with higher risk of T1D:
- DR3-DQ2 and DR4-DQ8 haplotypes.
- Those from the general population who go on to develop T1D generally also have **an increased genetic risk**

Genetic Risk

- More than 70 genetic T1D variants have been identified
- Children with the HLA DR3-DQ2/DR4-DQ8 genotype have 5% risk for islet autoimmunity and T1D

Genetic Risk

- For children with HLA genotype DR3/DR4-DQ8 10-year risk, 76.6%
- The majority of children at risk of T1D who had **multiple islet autoantibody** seroconversion progressed to diabetes over the next 15 years.
- Future prevention studies should focus on this high-risk population.

Genetic Risk

- .HLA, *INS*, *PTPN22* and *CTLA4* are considered to be confirmed type 1 diabetes **susceptibility genes**
- Also, genetic factors are not as predictive of this risk in older children, and there is a paucity of data in adults
- The risk of developing **islet autoimmunity** declines exponentially with increasing age
- Furthermore, once a young person develops multiple islet autoantibodies
- HLA and Non-HLA risk genes offer little additional predictive value for stratifying the rate of progression to diabetes

Environmental Exposures

- The incidence of T1D continues to increase globally.
- There has been a significant reduction in the proportion of people with the highest risk HLA haplotypes developing T1D.
- This observation likely highlights the significant contribution environmental exposures play in the pathogenesis of T1D

Environmental Exposures

- Environmental exposures are likely to interact with genes to drive islet autoimmunity and dysglycemia.
- Environmental exposures may influence the development of IAA or GADA antibody as the first appearing autoantibody.
- Initiating autoantibody responses may reflect unique T1D endotypes

Screening for Early-stage T1D

Screening for Early-stage T1D

Screening and follow up should be completed to identify people with

- Stage 1, 2, and 3 T1D
- **Reduce** incidence of DKA and hospitalization
- To direct individuals towards **interventions**
- **or studies seeking to delay or prevent ongoing beta cell loss**.

Screening for Early-stage T1D

- Screening **should be coupled** with **education and metabolic surveillance programs for those identified with islet autoantibodies**
- Optimal screening T1D risk **programs** will depend largely on resources available in individual countries and health care systems

Optimal ages for screening

- Screening for islet autoantibodies **repeated twice during childhood**

- **screening** performed at 3-5 years of age provided only 35% sensitivity for diagnosing T1D by age 15 years
- while **sensitivity could be improved to ~82% with testing at both 2 and 6 years**
- **Occasionally suggested performed** autoantibody testing just once between 1 and 5 years of age

Optimal ages for screening

- Optimal time to identify **T1D onset in adolescence** at age 10 years (sensitivity 63%)
- **or both ages 10 and 14 years (sensitivity 72%)**
- Notably, sampling after 2 years of age **misses the** small but important subset of children who rapidly develop T1D **in the first 2 years of life** and have the highest rates of DKA

Optimal ages for screening

- in TEDDY study screening was performed every 3 months through 2 years of life.
- Other studies have employed annual autoantibody testing.

Goals of Screening

- Prevention of DKA , prolonged hospitalization
- Rates of DKA at diagnosis of Stage 3 T1D are 15-80%
- whereas with screening programs rates to less than 5%

Goals of Screening

- Improving quality of life and reducing psychological burden
- Caregiver **anxiety and depressive symptoms** increases in response to their child's multiple islet autoantibody positive test results.

Goals of Screening

- Preparation for insulin therapy, education, and psychological support may help reduce caregiver anxiety but **more research is needed in these areas**
- Providing opportunities for people to participate **in research studies**.

Screening Modalities

Optimal approaches to screening depend on several factors, including

- local screening objectives
- Background population risk
- The structure of the local health care system
- Available resources.

Screening Modalities

The two strategies currently used for T1D screening are

- **Genetic-risk/family history-based** islet autoantibody screening
- **Population-wide** islet autoantibody screening

Clinical Advice for Monitoring of Single IAb (At-Risk) Children

Follow up children with Single Autoantibody

- Single autoantibody status should be confirmed **in a second sample**
- **In single autoantibody positive children <3 years of age**, autoantibodies should be monitored **every 6 months** given the rapid progression in this age group.
- **After 3 years of age**, autoantibody status should be checked **annually for 3 years** and then stop if there is no progression beyond single antibody status

Follow up children with Single Autoantibody

- **Metabolic monitoring** via HbA1c or **random capillary/venous glucose** should be offered every 6 months in children <3years of age
- **May be considered annually for at least 3 years, thereafter**
- Ongoing education on signs/symptoms of DKA remains important even for those who become seronegative or do not progress

Follow up children with Single Autoantibody

- Children with a persistent single islet autoantibody who spread to multiple antibodies (Stage 1) do so most frequently **within two years from seroconversion**.
- **This spreading is most frequently observed in ch**ildren under 5 years of age

Monitoring for Multiple Autoantibody-Positive Children

Early-Stage Type 1 Diabetes

Follow up children with multiple Autoantibodies& Stage 1

- Confirm multiple autoantibody status in a **second sample**
- Monitor HbA1c and random capillary/venous glucose every 3 months in children under 3 years
- Every 6 months in children 3-9 years
- Annually in children over 9 years.

Glycemic Surveillance

Glycemic Surveillance in Children and Young Adults with Islet Autoimmunity

- Once early-stage T1D has been identified, regular glycemic surveillance is recommended to
- Allow T1D staging
- inform education and provide opportunities to participate in research
- Receive T1D modifying therapies

Glycemic Surveillance in Children and Young Adults with Islet Autoimmunity

- **OGTT i**s recommended to stage T1D in people with 2 or more islet autoantibodies
- Recommended to be completed prior to recruitment into prevention trials.

Glycemic Surveillance in Children and Young Adults with Islet Autoimmunity

- Self-monitoring of fingerstick blood glucose, urinary glucose, HbA1c, and CGM,SMBG are simple measures that can inform T1D progression and may be considered where **OGTT is impractical or not available.**

Glycemic Surveillance in Children and Young Adults with Islet Autoimmunity

- **CGM can be** used to monitor in place of HbA1c
- SMBG test can be performed on two different days over a 2-week period (on each day, test either fasting or postprandial) and again thereafter once every 1–3 months.

Continuous glucose monitoring

CGM is increasingly being used as a tool to

- predict progression to Stage 3 T1D
- Detect people who are asymptomatic in Stage 2 and Stage 3a
- provide real time data and may be useful as it detects increased glucose variability, elevated glucose levels

Continuous glucose monitoring

- In one study, a cut-off of 10% of each day (10-14days) spent above 140mg/
- indicated an **80% risk** of progression to Stage 3 **T1D over one year**

  88% sensitivity, 91% specificity
- CGM may be a practical alternative to OGTT

Glycemic Surveillance in Children and Young Adults with Islet Autoimmunity

All families need be counselled about

- The expected progression to Stage 3 T1D
- How to cope with the often-unexpected diagnosis of early Stage T1D
- options for glycemic monitoring
- How to identify signs and symptoms of hyperglycemia
- Have a team to contact.

Glycemic Surveillance in Children and Young Adults with Islet Autoimmunity

- Partnerships between primary care providers and endocrinologists/diabetologists may be required to follow people with early stages T1D.
- Evaluation of all people with Stage 2 T1D by a pediatric endocrinologist/diabetologist is recommended

Surveillance frequency

Depends on the risk of progression

More frequent monitoring offered to children at high risk of progression

- Those with Dysglycemia in Stage 2
- Those who seroconvert at a young age, with IA-2A, or 3-4 islet autoantibodies

Glycemic Surveillance in Children with multiple Autoantibodies& Stage 2 T1D

- . Consider monitoring HbA1c and random glucose every 3 months
- Every 6 months in those older than 18 years.
- OGTT remains the gold standard for diagnosing Stage 2 T1D.

Oral glucose tolerance test

- The standard 2-hour OGTT following 1.75 g/kg (75 g maximum) oral glucose administration remains the gold standard test for informing T1D progression and staging
- Consumption of at least 150g of carbohydrates on the three days prior to OGTT is recommended.
- Fasting, intermediate, and 2-hour glucose values defining Stage 1, 2a, 2b, and 3 T1D

Fasting plasma glucose (FPG):

- FPG <5.6 mmol/L (<100 mg/dL) = Stage 1 T1D (normal fasting glucose)
- FPG 5.6-6.9 mmol/L (100-125 mg/dL) = Stage 2 T1D (impaired fasting glucose)
- FPG 5.6-6.4 mmol/L (100-115 mg/dL) = Stage 2a
- FPG 6.5-6.9 mmol/L (116-125 mg/dL) = Stage 2b
- FPG ≥7.0 mmol/L (≥126 mg/dL) = Stage 3 T1D*

Intermediate OGTT time points (30, 60, 90 minutes):

- Glucose ≥11.1 mmol/L (≥200 mg/dL = Stage 2 T1D)

2-hour plasma glucose (2-h PG) following oral glucose load:

- 2-h PG <7.8 mmol/L (<140 mg/dL) = Stage 1 T1D (normal glucose tolerance)
- 2-h PG 7.8-11.1 mmol/L (140-199 mg/dL) = Stage 2 T1D (impaired glucose tolerance
- 2-h PG ≥11.1 mmol/L (≥200 mg/dL) = Stage 3 T1D*

*Diagnosis of Stage 3 T1D in the absence of symptoms (Stage 3a) requires confirmatory testing

Prediction stage 3 T1D based on HbA1c

Glycosylated hemoglobin

- In some settings, HbA1c offers a more practical **marker of glucose metabolism** and T1D staging than the OGTT
- HbA1c starts to increase approximately 2 years **before a Stage 3 diagnosis**, reflecting the gradual deterioration in endogenous insulin secretion and increasing fluctuation in plasma glucose levels

Prediction stage 3 T1D based on HbA1c

- . Data indicated that a 10% rise in HbA1c values taken 3–12 months apart
- An additional rise during the subsequent **6 months**

Prediction stage 3 T1D based on HbA1c

- And two consecutive values of **≥5.9%** predicted progression to **stage 3 T1D in 1 year**

- increase in HbA1c of ≥10%, even in the normal range 5.0% to 5.5% indicates increased risk of disease progression to stage 3 type 1 diabetes within a **median of 1 year**

Comparison between OGTT& HbA1c for progression to Stage 3

- The TEDDY study supported these findings, showing that an increase of ≥10% in HbA1c from baseline is as informative as OGTT in predicting the likelihood of **developing Stage 3** in young people

Glycosylated hemoglobin

2024 ADA Standards of care include

- HbA1c of 5.7-6.4% or ≥10% increase in HbA1c as diagnostic of **Stage 2 T1D**
- Caution is needed in relying on HbA1c in young children who may progress rapidly, and may be missed before a rise in HbA1c can be observed,
- or in the setting of an **undiagnosed hemoglobinopathy**
- or other conditions that affect hemoglobin turnover

Surveillance frequency of glycosylated hemoglobin

- We concur with the JDRF **consensus** that states that children living with Stage 1 T1D should have HbA1c measured
- Once every 3 months when less than 3 years of age
- At least every 6 months when 3-9 years old
- and at least every 12 months in children over 9 years old

EDUCATION

Education

- Ongoing structured individualized education for those identified with islet autoantibodies and their caregivers/families is needed
- Education needs to be culturally, linguistically and socioeconomically congruent and tailored to personal needs.
- Education is the responsibility of all health professionals involved in the monitoring and care of persons with T1D.

- For those with Stage 2 T1D a review by an endocrinologist/diabetologist or diabetes educator every 6 months is recommended to reinforce understanding of the condition and expectations for progression.

Education

Ongoing structured individualized education for those identified with islet autoantibodies and their caregivers/families is needed

- strategies for healthy coping
- symptoms awareness
- plans for glycemic monitoring
- Consideration of research
- Treatment opportunities to delay progression
  introduction to insulin therapy

PSYCHOSOCIAL SUPPORT

Psychological Burden of Screening

- Positive screening results in children may be associated with parental stress, depressive symptoms, and anxiety.

- The severity of depressive symptoms in parents of children diagnosed with Stage 1 or Stage 2 T1D was significantly lower than depressive symptoms reported by parents of children diagnosed with Stage 3 T1D without prior screening participation

Psychological Burden of Screening

- One published study addressing this found no differences in anxiety between caregivers of children diagnosed with T1D as part of a screening/monitoring study compared to caregivers of children diagnosed with no prior screening/monitoring experience

Cost-Effectiveness

Cost effectiveness analyses indicated

- 20% reduction in DKA at diagnosis
- 0.1% reduction in HbA1c
- Further economic modelling is required, including assessment of different screening and surveillance models of care in individual countries due to differing health systems, burden of T1D, and local costs of treatment.

Cost-Effectiveness

- The approval of preventive therapies, such as teplizumab, add significant treatment costs to delaying T1D progression.
- Nevertheless, additional lower-cost options are clearly needed

Efforts to Slow T1D Progression.

Primary and Secondary Prevention Efforts

- A growing list of therapies have demonstrated the capacity to **slow beta cell loss in Stage 3 T1D**.

- Teplizumab is an FDA approved option to delay progression of Stage 2 T1D to be considered in individuals with Stage 2 T1D.
-

Efforts to Slow T1D Progression

- Intervention trials in early-stage T1D need to be inclusive for all children and young people irrespective of geographic location and health systems.

Stage 3 T1D Interventions

Stage 3 interventions or "new onset" studies seek to

- Halt the condition
- preserve residual β-cell function
- potentially delay or prevent complications of T1D in children and adults with newly diagnosed (6-12 weeks) Stage 3 T1D.

Stage 3 T1D Interventions

Multiple agents have demonstrated capacity to delay C-peptide decline in Stage 3 T1D, namely

- cyclosporine, teplizumab, abatacept, alefacept, rituximab, golimumab, low dose anti-thymocyte globulin, verapamil, imantinib, and baricitinib

Stage 3 T1D Interventions

- A growing number of studies continue to focus on Stage 3, where a recent meta-analysis demonstrated a link between maintenance of residual C-peptide and clinical outcomes such as reductions in HbA1c and insulin doses

Stage 3 T1D Interventions

- These studies not only have the prospect of providing direct benefit to people with newly diagnosed T1D but also provide required safety data, particularly in children, where C-peptide decline is faster than in adults,
- To support moving therapies into Stage 1 or Stage 2 T1D

Stage 3 T1D Interventions

- Based on the existing US approval of teplizumab for intervention in Stage 2 T1D efficacy in Stage 3 T1D
- To slow beta cell loss in Stage 3 T1D.
- Providers are advised to encourage people at all stages of T1D to participate in research studies.

Stage 3 T1D Interventions

- First agent to receive regulatory approval for use in Stage 3 T1D.
- **To preserving beta-cell function in T1D**

Teplizumab: Opportunities and Challenges

- Teplizumab- infusion to delay the onset of symptomatic type 1 diabetes (stage 3) should be discussed with selected individuals aged >8 years with stage 2 type 1 diabetes

Teplizumab: Opportunities and Challenges

- **The November 2022 US approval of Teplizumab to delay the development of Stage 3 T1D marked a major milestone in the T1D field**.
- Teplizumab is a CD3 directed monoclonal antibody that preserves beta-cell function in people with Stage 3 T1D
- **Delays the onset of Stage 3 T1D** in those with Stage 2 T1D

Teplizumab: Opportunities and Challenges

- In one study randomized, placebo-controlled trial of 76 people w ho were relatives of people with established T1D and had Stage 2 T1D, the median time to onset of clinical T1D was ultimately delayed by about 48 month in the teplizumab group with a single 14-day intravenous infusion course compared to the placebo group 24 month

Challenges with teplizumab use include

- High cost 194,000 USD
- logistical difficulties with its 14-day infusion course

screening for early T1D unanswered questions

- How to organize a screening in a specific country region with a specific Healthcare system
- How to organize screening in the setting of a specific belief backgrounds(religion, emotion Trust in system)
- How to communicate to the general population about T1D and importance of early detection

screening for early T1D unanswered questions

- How to define benefit of early detection
- How to organize monitoring
- How to integrate early detection in HC system
- How to communicate to HCP ,HC system and regulators on importance of early detection
- How to measure impact beneficial and harmful of early detection
- How do people with T1D see this early detection

Future Directions

- Research on new biomarkers for early detection.
- Development of cost-effective and accessible screening tools.
- Integration of screening into national health programs.
- Advances in immunotherapy to prevent progression to symptomatic T1D.

Role of Artificial Intelligence in Screening

- AI tools for predicting T1D risk based on genetic and environmental data.
- Improved accuracy in interpreting autoantibody profiles.
- Potential for personalized screening recommendations.

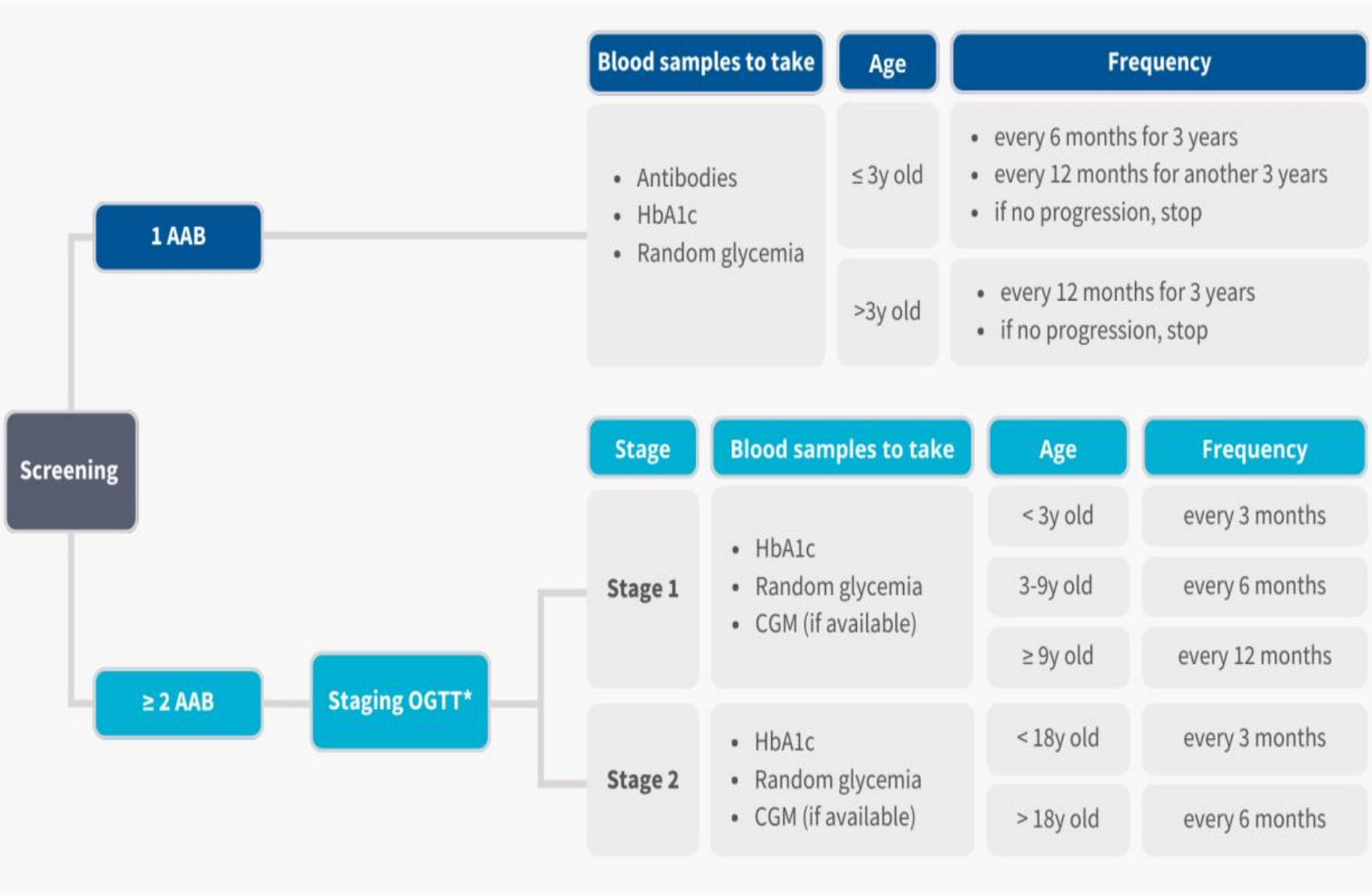
Conclusions

- Screening for early-stage T1D is an important tool for both researchers and clinicians.
- As evidenced by the success of both family-history targeted and general population programs, screening and staging provide important opportunities to
- Reduce DKA
- Begin education before insulin is required
- Offer condition modifying immunotherapies
- Encourage participation in studies seeking to delay progression to stage 3 T1D.
- In the coming years, general population screening programs will expand and a growing cohort of people with Stage 1 and Stage 2 T1D will be identified

Conclusions

- with the approval of teplizumab in Stage 2 T1D in the United States, a growing list of agents capable of slowing beta-cell decline, and improving tools to screen and stage T1D, clinical and research programs will continue to rapidly evolve

The ADA and ISPAD recommend screening for islet autoantibodies to establish the presence of presymptomatic T1D



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با تشکر از اساتید و همکاران محترم

Stage of T1D	Islet autoantibody status	Glycemic status	Symptoms	Insulin required
At-risk (pre-stage 1 T1D)	Single autoantibody or transient single autoantibody	• Normoglycemia • FPG <5.6 mmol/L (<100 mg/dL) • 120-min OGTT <7.8 mmol/L (<140 mg/dL) • HbA_{1c} <39 mmol/mol (<5.7%)	No symptoms	Not required
Stage 1 T1D (also referred to as early-stage T1D or presymptomatic T1D)	≥2 autoantibodies	• Normoglycemia • FPG <5.6 mmol/L (<100 mg/dL) • 120-min OGTT <7.8 mmol/L (<140 mg/dL)[114] • HbA_{1c} <39 mmol/mol (<5.7%)	No symptoms	Not required

Stage 2 T1D (also referred to as early-stage T1D or presymptomatic T1D)	≥2 autoantibodies*	Glucose intolerance or dysglycemia 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 • HbA_{1c} 39–47 mmol/mol (5.7–6.4%) or longitudinal ≥10% increase in HbA_{1c} (66,67) from the first measurement with stage 2 T1D • CGM values >7.8 mmol/L (>140 mg/dL) for 10% of time over 10 days' continuous wear (73)† and confirmed by at least one other non-CGM glucose measurement test listed	No symptoms	Not required

Stage 3 T1D	≥1 autoantibody	Persistent hyperglycemia 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 HbA_{1c} ≥48 mmol/mol (≥6.5%) • CGM values >7.8 mmol/L (>140 mg/dL) for 20% of time over 10 days' continuous wear (73)† and confirmed by at least one other non-CGM glucose measurement test listed	May include‡: • Polyuria • Polydipsia • Weight loss • Fatigue • DKA	+/− Insulin, based on glycemic status