Hormone Research in Paediatrics

Clinical Practice Committee Publication

Horm Res Paediatr 2024;97:529–545
DOI: 10.1159/000543035

Received: November 11, 2024
Accepted: November 23, 2024
Published online: December 11, 2024

ISPAD Clinical Practice Consensus Guidelines 2024: Screening, Staging, and Strategies to Preserve Beta-Cell Function in Children and Adolescents with Type 1 Diabetes

Michael J. Haller[a] Kirstine J. Bell[b] Rachel E.J. Besser[c] Kristina Casteels[d, e] Jenny J. Couper[f, g] Maria E. Craig[h, i, j] Helena Elding Larsson[k, l] Laura Jacobsen[a] Karin Lange[m] Tal Oron[n] Emily K. Sims[o] Cate Speake[p] Mustafa Tosur[q, r] Francesca Ulivi[s] Anette-G. Ziegler[t] Diane K. Wherrett[u] M. Loredana Marcovecchio[v]

[a]Division of Endocrinology, Department of Pediatrics, University of Florida, Gainesville, FL, USA; [b]Charles Perkins Centre and Faculty Medicine and Health, University of Sydney, Sydney, NSW, Australia; [c]Centre for Human Genetics, NIHR Biomedical Research Centre, University of Oxford, Oxford, UK; [d]Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium; [e]Department of Development and Regeneration, KU Leuven, Leuven, Belgium; [f]Women's and Children's Hospital, North Adelaide, SA, Australia; [g]Robinson Research Institute, University of Adelaide, Adelaide, SA, Australia; [h]The Children's Hospital at Westmead, Sydney, NSW, Australia; [i]Discipline of Pediatrics and Child Health, University of Sydney, Sydney, NSW, Australia; [j]School of Women's and Children's Health, University of New South Wales, Sydney, NSW, Australia; [k]Department of Clinical Sciences Malmö, Lund University, Lund, Sweden; [l]Department of Pediatrics, Skåne University Hospital, Malmö/Lund, Sweden; [m]Department of Medical Psychology, Hannover Medical School, Hannover, Germany; [n]The Institute for Endocrinology and Diabetes, Schneider Children's Medical Center of Israel, Petah-Tikva, Israel; [o]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, USA; [p]Center for Interventional Immunology, Benaroya Research Institute at Virginia Mason, Seattle, WA, USA; [q]The Division of Diabetes and Endocrinology, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA; [r]Children's Nutrition Research Center, USDA/ARS, Houston, TX, USA; [s]Fondazione Italiana Diabete ETS, Milan, Italy; [t]Institute of Diabetes Research, Helmholtz Zentrum München, and Forschergruppe Diabetes, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; [u]Division of Endocrinology, Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada; [v]Department of Paediatrics, University of Cambridge and Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

What Is New

- Stages 1, 2a, 2b, 3a, 3b, and 4 type 1 diabetes (T1D) are being used in clinical, research, and regulatory settings.
- General population screening programs for T1D are expanding in both research and clinical settings.
- Effective screening and monitoring programs include individualized education, psychological support, and metabolic surveillance for those identified with islet autoantibodies.
- The anti-CD3 monoclonal antibody (teplizumab) has been approved by the US Food and Drug Administration (FDA) to delay progression from Stage 2 to Stage 3 T1D
- These insights emphasize that trials and effective screening and treatments in early-stage T1D need to be inclusive for all children and young people irrespective of geographic location and health systems.

karger@karger.com
www.karger.com/hrp

Correspondence to:
Jenny J. Couper, jennifer.couper@adelaide.edu.au

Keywords
Screening · Stages · Preservation · Beta cell · Children · Type 1 diabetes

Abstract
The International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines represent a rich repository that serves as the only comprehensive set of clinical recommendations for children, adolescents, and young adults living with diabetes worldwide. This guideline serves as an update to the 2022 ISPAD consensus guideline on staging for type 1 diabetes (T1D). Key additions include an evidence-based summary of recommendations for screening for risk of T1D and monitoring those with early-stage T1D. In addition, a review of clinical trials designed to delay progression to Stage 3 T1D and efforts seeking to preserve beta-cell function in those with Stage 3 T1D are included. Lastly, opportunities and challenges associated with the recent US Food and Drug Administration (FDA) approval of teplizumab as an immunotherapy to delay progression are discussed.

List of Abbreviations

ADA:	American Diabetes Association
AAB:	autoantibodies
BMI:	body mass index
CGM:	continuous glucose monitoring
DIPP:	diabetes prediction and prevention
DKA:	diabetic ketoacidosis
DPTRS:	Diabetes Prevention Trial-Type 1 Risk Score
DSMES:	diabetes self-management education and support
FDA:	Food and Drug Administration
FPG:	fasting plasma glucose
GADA:	glutamic acid decarboxylase autoantibody
GPPAD:	Global Platform for the Prevention of Autoimmune Diabetes
GRS:	genetic risk scores
HbA1c:	glycosylated hemoglobin A1
HLA:	human leukocyte antigen
IAA:	insulin autoantibodies
IA-2A:	insulinoma associated-2 autoantibody
IFG:	impaired fasting glucose
IGT:	impaired glucose tolerance
ISPAD:	International Society for Pediatric and Adolescent Diabetes
JDRF:	Juvenile Diabetes Research Foundation
OGTT:	oral glucose tolerance test
PLS:	progression likelihood score
SMBG:	self-monitoring fingerstick blood glucose
TEDDY:	The Environmental Determinants of Diabetes in the Young
T1D:	Type 1 Diabetes

Stages of Type 1 Diabetes

Type 1 diabetes (T1D) is characterized by four stages based on antibody status and clinical features (Fig. 1):

Stage 1 includes multiple islet autoantibodies (AABs) confirmed in at least 2 samples (using validated assays). Individuals with Stage 1 have normoglycemia and are asymptomatic.

Stage 2 includes multiple islet AABs confirmed on at least 2 samples with elevated fasting glucose or impaired glucose tolerance (IGT) documented by oral glucose tolerance test (OGTT), glycosylated hemoglobin (HbA1c) 5.7–6.5% (39–48 mmol/mol), or ≥10% change in HbA1c. Additional sub-classifications or stages are likely to be adopted as clinicians and researchers seek to describe specific subpopulations. **Stage 2a** encompasses those with marginally elevated glucose levels. Stage 2b includes those with glucose levels nearing Stage 3 thresholds (see section on OGTT for glycemic thresholds defining stage). While Stages 2a and 2b are formally defined in prior literature, we propose this nomenclature to provide clinicians and researchers with additional descriptive terms for these people.

Stage 3 includes hyperglycemia, meeting American Diabetes Association (ADA) glycemic and clinical diagnostic criteria. People may be symptomatic or asymptomatic. Additional sub-classifications or stages are likely to be adopted as clinicians and researchers seek to describe specific subpopulations. **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 includes long-standing T1D. The stages of T1D inform the progression of the condition. Children with a single islet AAB do not have T1D but are considered "at risk" since they carry an approximately 15% risk of developing Stage 3 T1D within 15 years [1]. In contrast, children with 2 confirmed AABs have early-stage T1D. Among children living with Stage 1 (normoglycemia), 44% will progress to Stage 3 T1D in 5 years, and 80 to >90% will progress within 15 years. In children living with Stage 2 T1D (dysglycemia), 75% will progress to Stage 3 T1D in 5 years and nearly 100% during their lifetime [1–4].

Development and Progression of T1D

- 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 [**A**].
- People with two or more islet AABs have early-stage T1D and should no longer be referred to as being "at risk for T1D" [**A**].
- The vast majority (90%) of young people with multiple islet AABs progress to Stage 3 within 15 years, compared to only 15% who have a single islet AAB [**A**].
- Progression rates to Stage 3 T1D among those with two or more islet AABs are similar in people with a family history of T1D and those from the general population [**A**].

Genetic Risk

People with a first-degree relative with T1D have up to a 15-fold increased relative lifetime risk of T1D compared to the general population. The prevalence of T1D among people with a first-degree relative is 5% by age 20 compared to 0.3% among the general population [5–7]. Nevertheless, more than 90% of children diagnosed with T1D do not have a family history of this condition [8, 9]. Those from the general population who go on to develop T1D generally also have an increased genetic risk.

More than 70 genetic T1D variants have been identified through genome-wide association studies [10]. Human leukocyte antigen (HLA) DR and HLA DQ loci confer approximately half of the genetic risk for T1D [11–13]. The highest-risk HLA haplotypes are DRB1*03:01-DQA1*05:01-DQB1*02:01 (also expressed as DR3-DQ2) and DRB1*04:01-DQA1*03:01-DQB1*03:02 (also expressed as DR4-DQ8). In the general population, children with the HLA DR3-DQ2/DR4-DQ8 genotype have 5% risk for islet autoimmunity and T1D [14–16]. First-degree relatives of persons already known to have T1D who themselves carry HLA DR3-DQ2/DR4-DQ8 have a further increase in risk that reaches around 20% [15, 17]. Additional risk provided by non-HLA risk genes is roughly equivalent to that provided by HLA DR-DQ alone [16, 18].

The highest non-HLA genetic contribution arises from the *INS* and *PTPN22* genes [19]. These, and other risk regions, are included in (poly)genetic risk scores (GRS) that combine HLA and non-HLA genes to substantially improve risk estimates for islet autoimmunity and T1D, particularly in the general population [16, 20–22]. With ongoing refinement, GRS continue to see increasing sensitivities (70–80%) and specificities (85–90%) and can be used to identify people with increased risk for T1D [23–25]. Notably, the risk of developing islet autoimmunity declines exponentially with increasing age. Also, genetic factors are not as predictive of this risk in older children, and there is a paucity of data in adults [26–28]. Furthermore, once a young person develops multiple islet AABs, HLA, and GRS offer little additional predictive value for stratifying the rate of progression to diabetes [7, 22, 29, 30].

Environmental Exposures

The incidence of T1D continues to increase globally. However, 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 to the pathogenesis of T1D [31]. Environmental exposures are likely to interact with genes to drive islet autoimmunity and dysglycemia. The effects of nutrition, growth, and intercurrent infections, along with their interactions with biological "omic" systems (i.e., proteome, transcriptome, genome, metabolome, microbiome, virome, and lipidome) have been explored in at-risk birth cohorts [32–34]. Putative exposures likely vary between people and interact with different gene-environment and environment-environment factors. In addition, environmental exposures may influence the development of insulin autoantibody (IAA) or glutamic decarboxylase (GADA) antibody as the first appearing AAB. Initiating AAB responses may reflect unique T1D endotypes or subtypes defined by distinct pathophysiological mechanisms [35].

Screening for Early-Stage T1D

- General population screening programs using AAB testing alone or combinations of genetic and AAB testing can identify children and young adults with, or at risk of T1D [**A**].
- Screening and follow-up should be completed to identify people with Stages 1, 2, and 3a T1D, reduce the incidence of diabetic ketoacidosis (DKA) and hospitalization, and to direct individuals toward interventions or studies seeking to delay or prevent ongoing beta-cell loss [**A**].
- Screening for islet AABs repeated twice during childhood may provide the most cost-effective means of identifying those who will develop T1D. Optimal ages for screening may depend on background population risk [**B**].
- Screening should be coupled with education and metabolic surveillance programs for those identified with islet AABs [**E**].
- As screening programs expand, individuals with Stages 1, 2a, 2b, and 3a T1D will be more commonly identified. Additional subclassifications or stages are likely to be adopted as clinicians and researchers seek to describe specific subpopulations [**E**].
- Consider offering access to information regarding available prevention studies to people who screen positive for genetic or immunological markers of T1D [**E**].
- Optimal screening T1D risk programs will depend largely on resources available in individual countries and healthcare systems [**E**].

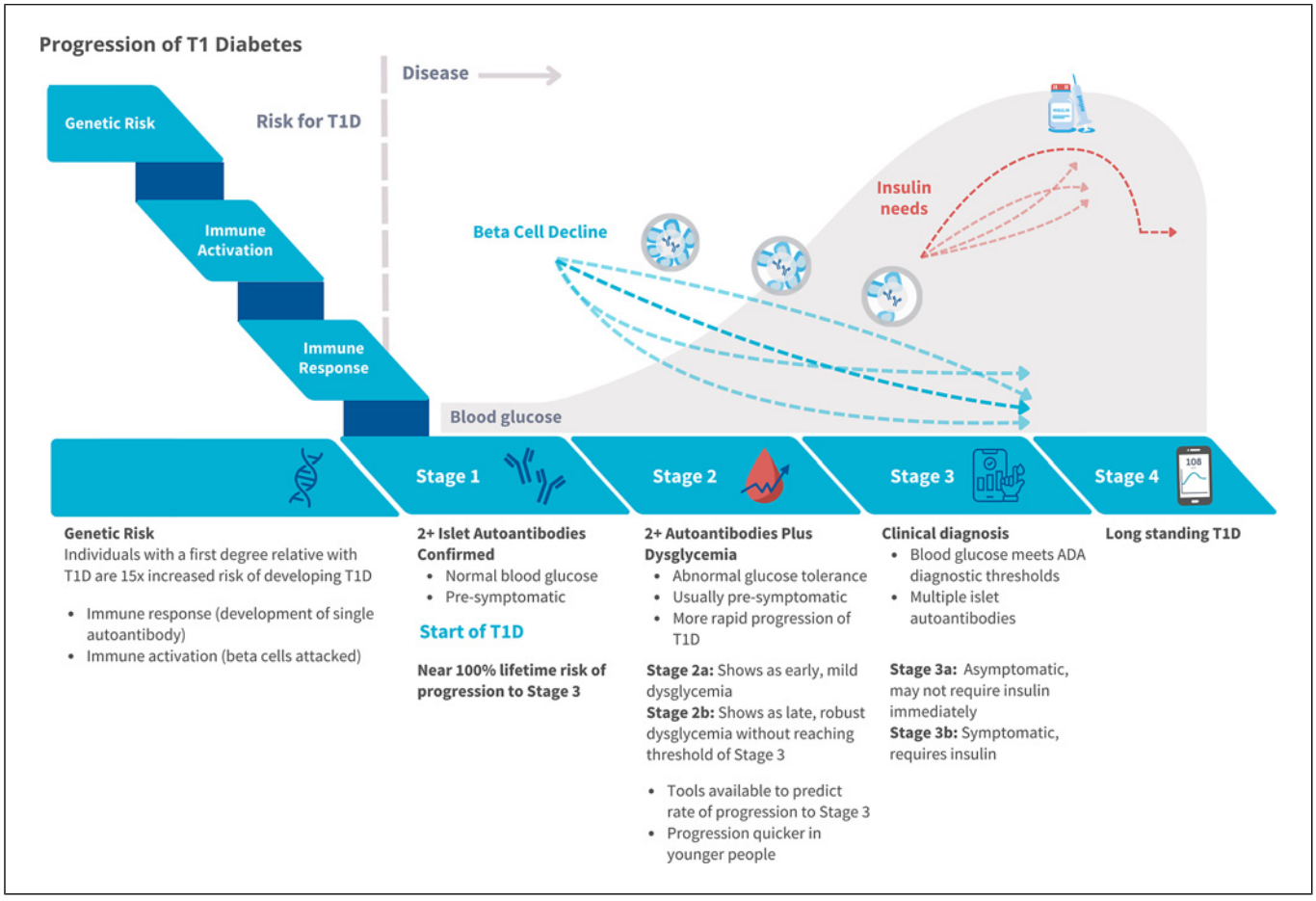

Fig. 1. Stages of type 1 diabetes (T1D). A small proportion of people who have increased genetic risk of T1D progress at variable rates to immune activation and the development of islet autoimmunity. Clinically available islet AABs include ICA, GADA, IAA, IA-2A, and ZnT8A. Once 2 or more islet AABs are confirmed (Stage 1) there is near certainty of progression to clinical diabetes during the person's lifetime. Stage 1 is typically followed by the development of dysglycemia (Stage 2), though this stage may not be detected when T1D progression is rapid. People who develop Stage 3 T1D may be asymptomatic (Stage 3a) or symptomatic (Stage 3b). Discussions regarding initiation of insulin in people with Stage 3a T1D must balance risk and benefit. Established T1D is described as Stage 4. All people with Stage 1 or greater have T1D and should not be referred to as having "risk" for the condition. Use of stages should not be overly dogmatic as many people with T1D fluctuate between stages. Many of the glycemic thresholds are arbitrary but remain useful to describe people with T1D for both clinical and research purposes. Rates of decline of beta-cell function vary as does the course of insulin requirements after diagnosis.

Screening for T1D is gaining international momentum. While most initiatives are being performed in the context of research and implementation of science studies, screening for T1D may become standard of care in many parts of the world. Indeed, in 2023 Italy became the first country worldwide to include, by law, a Public Health National Policy that supports screening for T1D and celiac disease in the general pediatric population [36]. Furthermore, in support of screening programs, billing and diagnosis codes for presymptomatic T1D have been developed in both the USA (Effective October 1st, 2024: 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) [37] and the UK (Presymptomatic diabetes mellitus type 1 – 1290118005) [38].

Goals of Screening

The long-term vision for T1D screening programs is to identify people at risk of or with early-stage T1D and offer them preventive approaches capable of delaying or preventing the condition entirely. Currently, achievable benefits driving recommendations for screening include the following:

1. **Prevention of DKA and its associated short- and long-term morbidity and mortality**. Rates of DKA at diagnosis of Stage 3 T1D are 15–80% worldwide in the general population [39–44], whereas screening programs combined with long-term follow-up reduce DKA rates to less than 5% [7, 39, 40, 45, 46]. DKA prevention at diagnosis has potential lifelong benefits, including avoidance of acute morbidity (cerebral edema, shock), neurocognitive impairment, and mortality [47, 48]. There are also non-causal associations between DKA at onset and risk of future DKA episodes [42, 49], severe hypoglycemia [49], and suboptimal long-term glycemic outcomes identified in some [50–53], but not all studies [54], which, may in turn, increase the risk of future diabetes-related complications [55].
2. **Improving short-term outcomes (symptoms, weight loss, DKA, prolonged hospitalization) [40–44].**
3. **Improving quality of life and reducing psychological burden at the time of T1D diagnosis**. Caregiver anxiety and depressive symptoms increase in response to their child's multiple islet AAB positive test results. Preparation for insulin therapy, education, and psychological support may help reduce caregiver anxiety and smooth the transition to Stage 3 T1D and insulin therapy [7, 47], but more research is needed in these areas.
4. **Providing opportunities for people to participate in research studies**. Despite the benefits associated with screening for T1D, potential harms must also be considered. For some people and families, screening leads to increased anxiety and depressive symptoms [48–50] and many diagnosed with Stages 1, 2a, or 2b T1D have a limited understanding of its progression [50].

Screening Modalities

Optimal approaches to screening depend on several factors, including local screening objectives, background population risk, the structure of the local healthcare system, and available resources.

The two strategies currently used for T1D screening are as follows:

1. Genetic risk/family history-based islet AAB screening
2. Population-wide islet AAB screening

Until recently, most screening programs focused on those with a family history of T1D. While family history-based screening markedly increases per-test probability of identifying people with islet AABs, it fails to identify 90% of those who will ultimately develop T1D. As such, alternative approaches increasingly utilize either general population or genetic risk stratified screening. As the use of GRS continues to scale, thresholds for at-risk populations can be altered to suit the screening purpose [51–53]. Furthermore, advancements in islet AAB assays permit ultra-low blood volume testing, including the use of capillary samples and dried blood spots, which facilitate minimally invasive collections at home or in community settings [54, 55]. Programs such as the Global Platform for the Prevention of Autoimmune Diabetes (GPPAD), Fr1da, Autoimmunity Screening for Kids (ASK), Population Level Estimate of T1D Risk Genes in Children (PLEDGE), Combined Antibody Screening for Celiac and Diabetes Evaluation (CASCADE), the Australian T1D National Screening Pilot, and the TRIAD study continue to demonstrate the feasibility of general population and genetic risk stratified screening and follow-up programs [56–58]. Additional studies and analyses are needed to balance sensitivity, specificity, public health priorities, and cost-effectiveness when developing specific screening programs.

AAB Screening Approaches in the General Population

Optimal ages for performing AAB screening in the general population continue to be refined using growing data sets from international cohort studies. One analysis suggested that one-time AAB 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 [26, 59]. Alternative models derived from a compilation of prospective cohort studies suggested that the optimal time to identify T1D onset in adolescence (10–18 years of age) is either a single screen at age 10 years (sensitivity 63%) or repeated screening at both ages 10 and 14 years (sensitivity 72%) [60]. 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 [51, 53, 61, 62].

AAB Screening in Children with Increased Genetic Risk

Optimal islet AAB testing frequency in genetically at-risk children remains unclear. Observational studies have used varying frequencies of AAB screening in children with increased genetic risk. In The Environmental Determinants of Diabetes in the Young (TEDDY) study, screening was performed every 3 months through 2 years of life. However, other studies have employed annual AAB testing while still others have performed AAB testing just once between 1 and 5 years of age [63–66]. More frequent AAB testing (e.g., 6 monthly) may be beneficial in children less than 3 years of age given their more rapid progression to Stage 3 T1D and increased risk of severe DKA.

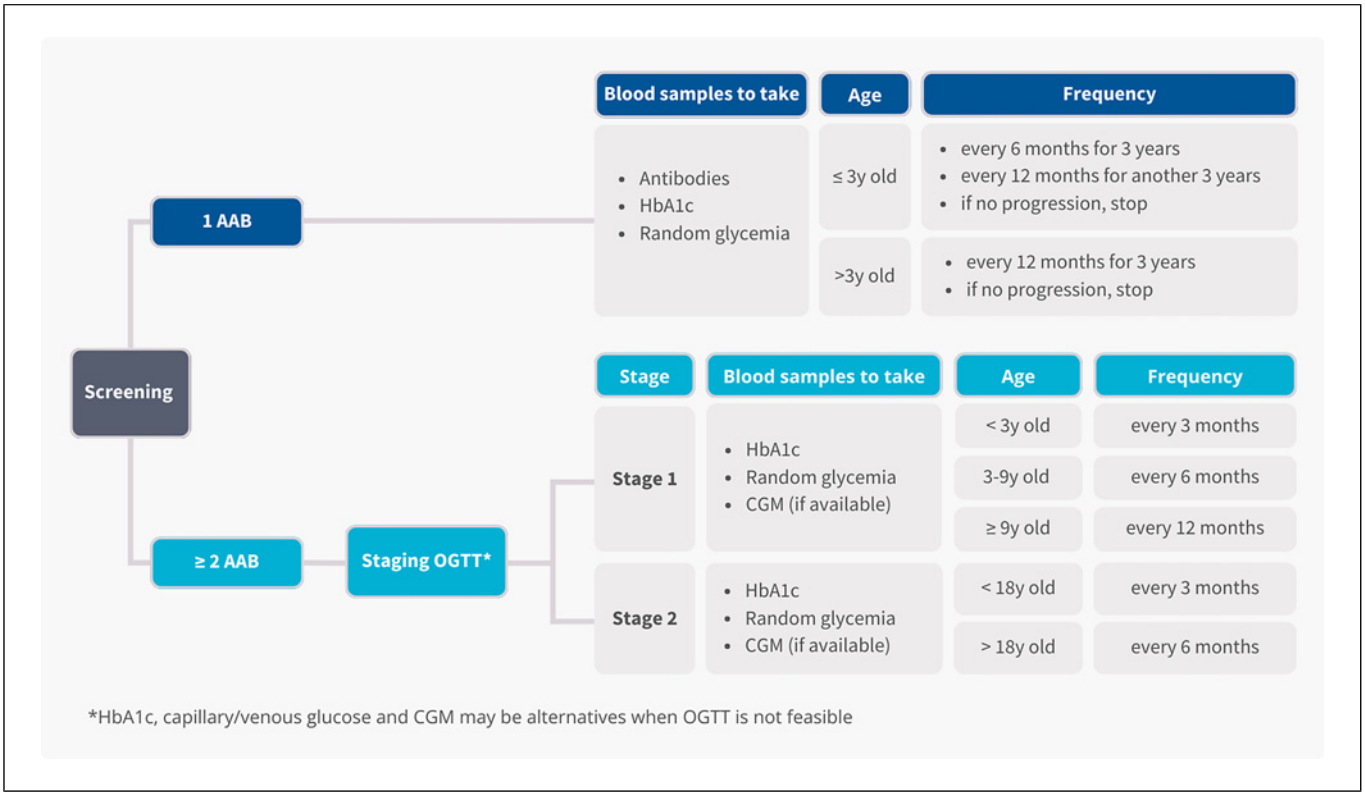

Fig. 2. Screening and monitoring in children and adolescents with single or multiple AABs. Age and number of islet AABs dictate the frequency and intensity of recommended monitoring for those with single or multiple AABs. Single or multiple AABs status should be confirmed in a second sample. AAB, autoantibodies; CGM, continuous glucose monitoring; OGTT, oral glucose tolerance test.

Glycemic Surveillance in Children and Young Adults with Islet Autoimmunity

- International Society for Pediatric and Adolescent Diabetes (ISPAD) endorses the published 2024 Consensus Guidance for monitoring of children, adolescents and young adults with single and multiple islet AABs [**E**].
- OGTT is recommended to stage T1D in people with 2 or more islet AABs and counsel them on T1D progression, and it is also recommended to be completed prior to recruitment into prevention trials [**E**].
- Self-monitoring of fingerstick blood glucose, urinary glucose, HbA1c, and continuous glucose monitoring (CGM) are simple measures that can inform T1D progression and may be considered where OGTT is impractical or not available [**E**].
- Surveillance frequency should depend on the risk of progression, with more frequent monitoring offered to children at higher risk of progression [**E**].
- All families need to be counseled about the expected progression to Stage 3 T1D, how to cope with the often-unexpected diagnosis of early-stage T1D, options for glycemic monitoring, and how to identify signs and symptoms of hyperglycemia, and have a team to contact [**E**].
- Partnerships between primary care providers and endocrinologists/diabetologists may be required to follow people with early-stage T1D [**E**].
- Evaluation of all people with Stage 2 T1D by a pediatric endocrinologist/diabetologist is recommended [**E**].

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 or receive T1D modifying therapies [67]. OGTT is the gold standard for staging persons with two or more islet AABs (Fig. 2). However, when OGTT is not feasible, alternative approaches including HbA1c, capillary or venous glucose (2-h postprandial, random or fasting), and CGM can provide important information for people with early-stage T1D, parents, and providers. Home fingerstick glucose measurements and urine test strips can provide real-time data for early detection of hyperglycemia and DKA prevention. Surveillance frequency should depend on the risk of

progression, with more frequent monitoring offered to children at high risk of progression e.g., those with dysglycemia in Stage 2, those who seroconvert at a young age, with high insulinoma-associated-2 AAB (IA-2A), or 3–4 islet AABs or other high progression risk metrics [1, 7, 68].

Single AAB

- Single AAB status should be confirmed in a second sample, preferably using an independent reference laboratory **[B]**.
- In single AAB-positive children <3 years of age, AABs should be monitored every 6 months given the rapid progression in this age group. After 3 years of age, AAB status should be checked annually for 3 years and then stop if there is no progression beyond single antibody status **[B]**.
- Metabolic monitoring via HbA1c or random capillary/venous glucose should be offered every 6 months in children <3 years of age and may be considered annually for at least 3 years, thereafter **[B]**.
- Ongoing education on signs/symptoms of DKA remains important even for those who become seronegative or do not progress **[C]**.

Children with a persistent single islet AAB who spread to multiple antibodies (Stage 1) do so most frequently within 2 years of seroconversion. This spreading is most frequently observed in children under 5 years of age [4, 69]. In single AAB-positive children under 3 years of age, the Juvenile Diabetes Research Foundation (JDRF) guidance advises monitoring AAB status every 6 months for 3 years, then annually for another 3 years [67]. Metabolic monitoring in children positive for a single antibody by annual random venous or capillary BG and HbA1c testing should be considered [67, 70, 71]. As with all screening and monitoring programs, the economic and psychological impacts of repeated screening must always be considered [1, 7].

Multiple AABs

- Confirm multiple AAB status in a second sample, preferably using an independent reference laboratory **[B]**.
- For children and young people in Stage 1, monitor HbA1c and random capillary/venous glucose every 3 months in children under 3 years, every 6 months in children 3–9 years, and annually in children over 9 years **[E]**.
- OGTT remains the gold standard for diagnosing Stage 2 T1D **[A]**.
- A 2-h post-high carbohydrate meal, venous glucose, can be used when an OGTT is not practicable **[E]**.
- Consider monitoring glucose metabolism (HbA1c and random glucose) every 3 months in children and adolescents with Stage 2 T1D and every 6 months in those older than 18 years **[E]**.
- Consider using home glucose monitoring via fingerstick or urine testing during illness or if symptoms develop **[E]**.
- CGM can be used to monitor in place of HbA1c where practicable, and based on an individual and family's circumstances, desires, and needs **[E]**.

Glycemic staging and ongoing monitoring should be offered to persons positive for multiple islet AABs [67]. Glycemic monitoring is important for identifying children suitable for early clinical interventions or those seeking to participate in prevention trials. The intensity of those efforts should depend not only on the risk of progression but also on the goals of the family and resource availability. Various monitoring tools are available (Table 1). Participation in prevention programs generally requires OGTT staging (see next section). In other children, less intensive methods may be suitable. All families should be counseled about the expected progression to Stage 3 T1D, how to cope with the diagnosis of early-stage T1D, options for glycemic monitoring, and how to identify signs and symptoms of hyperglycemia [48, 67, 72].

All families should have a team to contact and be given materials for home glucose monitoring. Additional efforts should be made to ensure follow-up of children with multiple AABs as those who do not receive ongoing monitoring and education have high rates of DKA [73].

Oral Glucose Tolerance Test

The standard 2-h OGTT following 1.75 g/kg (75 g maximum) oral glucose administration remains the gold standard test for informing on T1D progression and staging [74–82]. Consumption of at least 150 g of carbohydrates in the 3 days prior to OGTT is recommended. Fasting, intermediate, and 2-h glucose values defining Stages 1, 2a, 2b, and 3 T1D are provided below (Box 1). Suggested glycemic thresholds for Stage 2a and 2b should be used for descriptive purposes only. When combined with OGTT glucose data, metrics such as age, sex, C-peptide, presence of IA-2A, HbA1c, and BMI, allow for the calculation of scores providing additional information on the speed of progression to Stage 3 T1D. These tools, typically utilized in the research setting, include the 5-timepoint Diabetes Prevention Trial-Type 1 Risk Score (DPTRS) [75, 76], the 2-timepoint DPTRS60 [78], Index60 [79], the single timepoint M120 [80] and the progression likelihood score (PLS) [82]. ADA criteria should continue

Table 1. Currently available glycemic monitoring tools

OGTT	• Gold standard • Used to stage disease and predict progression	• Requires glucose load and 1 to 5 blood draws over 2 h	Glycemic staging risk scores for progression (DTPRS, DTPRS60, Index60, M120, PLS)
Random venous glucose	• One-off sample • Low cost	• Requires a blood draw	Similar to 2-h OGTT-derived glucose
HbA1c	• Highly specific • Can use capillary sample	• Insensitive, often normal in Stage 3a T1D • May be affected by other disease states[1]	Risk of progression to "clinical disease": HbA1c ≥5.9% (41 mmol/mol), or 10% rise over 3–12 months
CGM	• Provides real-time continuous monitoring • May enable early detection of Stage 2 diabetes	• Optimal duration and frequency of CGM wear not yet determined • Cost, access, evidence to wear continuously are needed • Data may cause anxiety and undesirable behavior change • Not currently considered superior to OGTT in the context of research trials	Risk of progression to "clinical disease": time above 7.8 mmol/L (140 mg/dL) is >10% >20% above 7.8 mmol/L (>140 mg/dL) indicates need to test for Stage 3 T1D
SMBG	• Simple • Use at home • Lower cost vs other methods	• Optimal timing and frequency have not been determined • Random result	Immediate result
Urinary glucose testing	• Simple • Use at home • Lower cost vs other methods	• Untested in this context • Less reliable than SMBG due to the altered renal threshold for glucose	Immediate result

OGTT, oral glucose tolerance test; CGM, continuous glucose monitoring. [1]See glycemic targets and glucose monitoring chapter for further details.

to be used to document the diagnosis of Stage 3 T1D. Asymptomatic and symptomatic Stage 3 T1Ds are categorized as Stage 3a and Stage 3b, respectively.

While the OGTT remains a gold standard, it is not always feasible or acceptable [83]. Alternative approaches are suggested and discussed below (Box 1).

Box 1

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

2-h 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 (IGT)
- 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.

Glycosylated Hemoglobin

HbA1c is widely used in clinical practice as an indicator of glycemic outcomes in people living with Stage 3/4 T1D and is generally not affected by short-term variations in food intake and physical activity. In some settings, HbA1c offers a more practical marker of glucose metabolism and T1D staging than the OGTT [75, 76]. Several studies have shown the utility of HbA1c in predicting progression to clinical T1D [84–86]. 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. Data from the T1D prediction and prevention (DIPP) study indicated that a 10% rise in HbA1c values taken 3–12 months apart, an additional rise during the subsequent 6 months, and two consecutive values of ≥5.9% predicted progression to Stage 3 T1D in 1 year [84]. 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 with genetic risk and islet AABs [85, 86]. Notably, the 2024 ADA Standards of care include HbA1c of 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in HbA1c as diagnostic of Stage 2 T1D [87]. Nonetheless, 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 [88]. 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 [59].

Continuous Glucose Monitoring

CGM is increasingly being used as a tool to predict progression to Stage 3 T1D [89–91], and to detect people who are asymptomatic in Stage 2 and Stage 3a [92]. CGM can provide real-time data and may be useful as it detects increased glucose variability, elevated glucose levels and reduced time in range [89]. Different cut-offs for glucose values have been posited to predict progression to Stage 3 T1D [90, 91]. In one study, a cut-off of 10% time spent above 140 mg/dL (7.8 mmol/L) indicated an 80% risk of progression to Stage 3 T1D over 1 year (88% sensitivity, 91% specificity, 67% positive predictive value, 97% negative predictive value) [90]. While CGM may be a practical alternative to OGTT, controversies still exist in the use of CGM in monitoring early-stage T1D and further evidence is needed to help understand its role, including the use in clinical trials, whether to be used masked or unmasked CGM, its acceptability in this setting, duration and frequency of sensor wear, and its use in guiding when and how to start insulin therapy. Machine learning technologies are a promising and evolving area that may also provide additional insights in the interpretation of CGM data [93].

Random Venous Glucose and Self-Monitoring Fingerstick Blood Glucose

In the DIPP study, the median time to diagnosis after random plasma glucose ≥7.8 mmol/L (140 mg/dL) was 1 year in children with Stage 1 T1D [81]. Random plasma glucose ≥7.8 mmol/L provided a relatively low sensitivity (21% [95% CI 16%, 27%]) but high specificity (94% [95% CI 91%, 96%]) [81]. Surprisingly, little evidence exists for the accuracy of capillary SMBG in predicting or monitoring Stage 1 or Stage 2 T1D in children. That said, adult data suggest that capillary glucose is a reliable comparator to venous glucose (85–>90% accuracy for diabetes or IGT) during the OGTT [94, 95]. Further evidence is needed to inform optimal frequency and appropriate glucose values for utilizing SMBG in those with early-stage T1D. However, it may be pragmatic to use levels for IFG, IGT, and frank hyperglycemia in this context. As recommended by the JDRF guidance [67] and endorsed by this ISPAD guideline, random venous, or capillary glucose should be measured at the same time as HbA1c in children and young people with early-stage T1D.

Urine Glucose Testing

When neither venous nor capillary glucose monitoring is available, home urine glucose testing offers a non-invasive and inexpensive way to detect hyperglycemia above the renal threshold. Urine ketone testing may also be available and can be useful in ruling out ketonuria.

Education

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

In children, adolescents, and young adults identified with islet AABs, ongoing structured individualized education is recommended to improve risk perception and prevent DKA at diagnosis [40–42]. Education plays a critical role in promoting recommended self-monitoring and in helping families to appreciate opportunities for both clinical and research-based interventions. These favorable outcomes may, in part, be due to the structured and person-centered training of caregivers/families immediately after the results of the screening are communicated. In several studies prospectively following children with Stage 1 and 2 T1D, families are assigned a contact person to answer questions at any time and are provided with guidebooks specifically designed for children [96]. Education not only imparts factual knowledge but also supports caregivers/families in

coping with the often-unexpected, elevated risk or diagnosis. The ADA standards for DSMES and the ISPAD guidelines [97, 98] can be used to guide education for people with Stage 1 and 2 T1D. However, age, rate of progression, and family dynamics should inform education topics and determine the intensity of educational interventions. Educational programs need to include strategies for healthy coping, symptoms awareness, plans for glycemic monitoring, consideration of research or treatment opportunities to delay progression, and introduction to insulin therapy [99]. Finally, diabetes education should be targeted, accessible in multiple settings, engaging and person-centered, and should consider the cultural, linguistic, emotional, developmental, and socio-economic framework of each child and family.

Psychological Burden of Screening

- Positive genetic and islet AAB screening results in children may be associated with parental stress, depressive symptoms, and diabetes-specific anxiety [**B**].
- There is a need to assess emotional, cognitive, and behavioral functioning in persons at risk and with early-stage T1D and their family members, followed by appropriate support and information [**E**].
- Consider integration of psychosocial support for children with early-stage T1D into routine clinical visits, to be delivered, whenever possible, by healthcare providers with diabetes-specific training [**E**].

Positive genetic and islet AAB screening results have been associated with parental symptoms of depression and diabetes-specific anxiety [7, 47–50, 72, 100], particularly in mothers [7, 49, 100]. In programs using genetic screening, the majority of those at high-risk will never develop T1D [16, 20] and anxiety declines among caregivers whose genetically at-risk children remain negative for islet AABs [16, 20, 49]. Among caregivers whose child develops early-stage T1D, diabetes-specific anxiety is common and may remain high, particularly among caregivers of children who are multiple AAB positive [16, 20, 49, 50]. Since the latency period before progression to clinically evident T1D may last for years [74], the unpredictable timing of the child's diagnosis with clinical T1D only adds to the psychological burden. However, the Fr1da study showed that 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 [7].

Since psychological distress is common among parents and children at the time of Stage 3 T1D diagnosis [101, 102], some have speculated that screening programs identifying children at Stage 1 or Stage 2 T1D, before clinical onset of T1D, might reduce the burden experienced by children and families at the time of clinical diagnosis. 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. However, the caregivers of children identified through the screening study did report lower parenting stress and better quality of life in their children compared to caregivers whose children were diagnosed with no prior screening study experience; the impact on the children themselves was not examined [47].

The nature, degree, and duration of psychological burden in children and caregivers who continue to undergo glycemic surveillance without developing Stage 3 T1D for some years, in those who discontinue follow-up, and in those who develop Stage 3 T1D remain an important understudied area of inquiry. The available literature to date has focused solely on parents of at-risk children; studies are needed to address any possible psychological burden on the children themselves. Additionally, members of certain vulnerable groups – ethnic minorities, those with limited education, or those with a history of depression may respond with greater depressive and anxiety symptoms [48, 50, 72]. Since mental health outcomes in children with Stage 3 T1D are associated with their caregivers' own mental health and coping with T1D [103, 104], psychosocial support needs to be available for both children diagnosed with Stage 1 or Stage 2 T1D and their caregivers. Since the need for psychological support can change over time and with the child's developmental level, psychological support needs to be available on an ongoing basis.

Cost-Effectiveness

- Screening for T1D risk may be cost-effective if the long-term glycemic benefits of early diagnosis and intervention are realized [**B**].
- The potential cost-effectiveness of immune interventions is unknown at this time [**E**].

A major consideration for wider expansion of screening is the total cost and the incremental cost-effectiveness of screening, education and glycemic surveillance programs [20, 58]. Cost-effectiveness analyses in the USA for islet AAB-only screening suggest it can be cost-effective with a 20% reduction in DKA at diagnosis and a 0.1% (1.1 mmol/mol) reduction in HbA1c over a lifetime [105, 106]. New

AAB measurement techniques, such as multiplex electrochemiluminescence assays, needless sample volume and labor time (as compared to radio-binding assays) and thus are more cost-efficient [107].

GRS stratified screening protocols could also improve cost-effectiveness as this approach may identify the small subset of the general population from which the majority of future T1D diagnoses will come [20, 58]. Further economic modeling 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.

In some, but not all lower-resource countries, islet autoimmunity 4 and genetic risk may be more heterogeneous, adding further complexity to screening [108–111]. Lower-resource countries often have higher rates of DKA and associated mortality; however, the lower T1D incidences may make screening efforts less cost-effective. Priorities in such countries remain on access to and improvements in clinical care for Stage 3 T1D, coupled with correct etiological diagnosis.

The approval of preventive therapies, such as teplizumab, adds significant treatment costs to delaying T1D progression. However, such efforts may result in substantial health benefits that justify their cost-effectiveness [112]. Nevertheless, additional lower-cost options are clearly needed [113].

Efforts to Slow T1D Progression: Primary and Secondary Prevention Efforts

- A growing list of therapies has demonstrated the capacity to slow beta-cell loss in Stage 3 T1D [**A**].
- Providers are advised to encourage people at all stages of T1D to participate in research studies [**E**].
- Teplizumab is a Food and Drug Administration (FDA)-approved option to delay progression of Stage 2 T1D to be considered in individuals with Stage 2 T1D [**C**].
- Intervention trials in early-stage T1D need to be inclusive for all children and young people irrespective of geographic location and health systems [**E**].
- There is a need for registries to document long-term outcomes in people who utilize approved and off-label therapeutics [**E**].

Efforts to prevent the development of autoimmunity have historically been referred to as primary prevention, while efforts to delay progression from Stage 1 or Stage 2 to Stage 3 T1D are referred to as secondary prevention (online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000543035). While a number of immune and metabolic-based therapies have been studied, teplizumab, a monoclonal antibody targeting the T-cell surface marker CD3, is the only therapy that has, to date, been approved by a regulatory agency for use in delaying progression from Stage 2 to Stage 3 T1D [114, 115]. Trials with other drugs targeting (1) autoimmune responses; (2) antigen presentation; (3) glycemic dysregulation; and (4) beta-cell stress/dysfunction, are underway.

Stage 3 T1D Interventions

Stage 3 interventions or "new onset" studies seek to halt the condition, preserve residual beta-cell function, and potentially delay or prevent complications of T1D in children and adults with newly diagnosed (6–12 weeks) Stage 3 T1D. Numerous efforts have been made to intervene at this relatively late stage due to the ease in identifying people who might still receive benefit [116]. 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 [117–122] (online suppl. Table 1).

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 [123]. 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. Based on the existing US approval of teplizumab for intervention in Stage 2 T1D, and the recently published PROTECT study demonstrating efficacy in Stage 3 T1D [124], teplizumab could become the first agent to receive regulatory approval for use in Stage 3 T1D. Moving forward, use of "induction and maintenance" combination therapies, driven by an individual's stage, genetic risk, and response biomarkers is likely to provide more effective means of preserving beta-cell function in T1D [122].

Notably, clinical trials for Stage 3 T1D have not historically been conducted in low-resource countries. These trials have also enrolled mostly white participants in study sites primarily located in the USA, UK, Europe, and Australia. So far, neither efficacy nor risks have been shown to differ by racial/ethnic background in published Stage 3 trials; however, it is possible such differences could be missed due to the preponderance of white participants [125].

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 [124, 126], and delays the onset of Stage 3 T1D in those with Stage 2 T1D [127]. In a phase 2, randomized, placebo-controlled trial of 76 people who 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 2.7 years in the teplizumab group with a single 14-days intravenous infusion course compared to the placebo group [115, 126, 128, 129].

Challenges with teplizumab use include its limited indication for Stage 2 T1D (i.e., few people are currently being identified), high cost ($194,000 USD), and logistical difficulties with its 14-day infusion course. A recent Pediatric Endocrine Statement provides an overview of considerations for the use of Teplizumab in clinical practice [130].

It is important to note that the clinical trial that led to the US FDA approval of teplizumab enrolled only 76 relatives of people with T1D who had Stage 2 T1D, nearly all of whom were white, non-Hispanic. Although its effectiveness in delaying T1D clinical diagnosis in those without a family history of T1D and other racial/ethnic groups was not formally studied, the FDA-approved indication encompasses all people (8 years and older) with Stage 2 T1D. While FDA-approved, it is not widely accessible globally, restricting its standard of care status. Nonetheless, where approved, it can be offered to people with Stage 2 T1D [129]. In centers lacking access to infusion dedicated areas on weekends, leveraging home health services to provide infusion over weekends or on days 6–14 could be a potential solution. Additional studies are needed to determine clinical efficacy in a wider population and if subsequent courses of teplizumab or other therapeutics will further delay progression of T1D.

Access to Intervention Therapies and Off-Label Therapeutics

Intervention trials in early-stage T1D should ideally be inclusive for all children and young people across the globe. In addition, with numerous agents showing promise across T1D stages, requests for off-label prescribing are rising. Off-label use of disease-modifying therapy may be considered where systematic monitoring of C-peptide levels, efficacy, and adverse reactions is feasible and can be guided by experienced clinicians [131]. Data on off-label prevention and intervention therapy should ideally be recorded in registries for future analysis.

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, and 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. As detailed throughout this guideline, children and young people with early-stage T1D should receive personalized diabetes education, scheduled metabolic assessments, and appropriate psychological support. Finally, with the approval of teplizumab in Stage 2 T1D in the USA, 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.

Methodology

A literature search was conducted to gather updated evidence, using a combination of relevant medical subject headings (MeSH, Emtree) and free-text terms specific to each chapter's focus. Studies published from 2021–2022 onward, related to children and young adults, were retrieved from MEDLINE. The Project Officer, in collaboration with chapter leads and co-authors, performed the literature searches. The resulting articles were then uploaded to COVIDENCE for screening and review. Two authors/experts involved in drafting this guideline version, independently screened the articles. Any disagreements were resolved by a third reviewer. Where relevant, further literature was included.

The draft chapter was posted on the ISPAD forum to allow feedback from the greater ISPAD membership. Modifications were made with authorship consensus, with the chapter receiving endorsement from the ISPAD editorial team.

Recommendations were graded as per the ADA evidence grading system for "Standards of Medical Care in Diabetes" [132]. This hierarchical A-E grading system sets A as having the highest level of evidence, and E having the lowest. Literature search terms are summarized in online supplementary material 1.

Conflict of Interest Statement

M.J.H. – Scientific Advisory Board: SAB BIO; consultant: Sanofi and Mannkind. C.S. – participation on an Immunology Advisory Board for Vertex Pharmaceuticals. R.E.J.B. – independent consultant/advisor to Prevention Bio. A.-G.Z. – Advisory Board: Provention Bio/Sanofi; DMC for Provention Bio/Sanofi, Sanofi,

and ITB-MED. K.J.B., K.C., J.C., M.E.C., H.E.L., M.T., L.J., F.U., K.L., T.O., M.L.M., D.K.W., and M.L.M.: no conflicts of interest to declare.

Funding Sources

The 2024 Consensus guidelines were supported by unrestricted grants from Abbott Diabetes Care, Dexcom, Medtronic, and Sanofi. These companies did not take part in any aspect of the development of these guidelines.

Author Contributions

M.J.H. and M.L.M. co-directed the guideline development process. M.J.H., K.J.B., R.E.J.B., K.C., J.J.C., M.E.C., H.E.L., L.J., K.L., T.O., E.K.S., C.S., M.T., F.U., A.-G.Z., D.K.W., and M.L.M. contributed equally to the content of individual chapters. M.J.H. synthesized these contributions to develop the original full draft of the guideline. Subsequently, K.J.B., R.E.J.B., K.C., J.J.C., M.E.C., H.E.L., L.J., K.L., T.O., E.K.S., C.S., M.T., F.U., A.-G.Z., D.K.W., and M.L.M. participated in revising both the original manuscript and subsequent versions. M.L.M., as the editor of the guideline, supervised the overall development and revision process.

References

1 Ziegler AG, Rewers M, Simell O, Simell T, Lempainen J, Steck A, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. JAMA. 2013;309(23):2473–9. https://doi.org/10.1001/jama.2013.6285
2 Krischer JP, Lynch KF, Schatz DA, Ilonen J, Lernmark Å, Hagopian WA, et al. The 6 year incidence of diabetes-associated autoantibodies in genetically at-risk children: the TEDDY study. Diabetologia. 2015;58(5):980–7. https://doi.org/10.1007/s00125-015-3514-y
3 Bingley PJ, Boulware DC, Krischer JP; Type 1 Diabetes TrialNet Study Group. The implications of autoantibodies to a single islet antigen in relatives with normal glucose tolerance: development of other autoantibodies and progression to type 1 diabetes. Diabetologia. 2016;59(3):542–9. https://doi.org/10.1007/s00125-015-3830-2
4 Anand V, Li Y, Liu B, Ghalwash M, Koski E, Ng K, et al. Islet autoimmunity and HLA markers of presymptomatic and clinical type 1 diabetes: joint analyses of prospective cohort studies in Finland, Germany, Sweden, and the U.S. Diabetes Care. 2021;44(10):2269–76. https://doi.org/10.2337/dc20-1836
5 Allen C, Palta M, D'Alessio DJ. Risk of diabetes in siblings and other relatives of IDDM subjects. Diabetes. 1991;40(7):831–6. https://doi.org/10.2337/diab.40.7.831
6 Dahlquist G, Blom L, Holmgren G, Hägglöf B, Larsson Y, Sterky G, et al. The epidemiology of diabetes in Swedish children 0-14 years: a six-year prospective study. Diabetologia. 1985;28(11):802–8. https://doi.org/10.1007/BF00291068
7 Ziegler AG, Kick K, Bonifacio E, Haupt F, Hippich M, Dunstheimer D, et al. Yield of a public health screening of children for islet autoantibodies in Bavaria, Germany. JAMA. 2020;323(4):339–51. https://doi.org/10.1001/jama.2019.21565
8 Parkkola A, Härkönen T, Ryhänen SJ, Ilonen J, Knip M; Finnish Pediatric Diabetes Register. Extended family history of type 1 diabetes and phenotype and genotype of newly diagnosed children. Diabetes Care. 2013;36(2):348–54. https://doi.org/10.2337/dc12-0445
9 Ziegler AG, Danne T, Dunger DB, Berner R, Puff R, Kiess W, et al. Primary prevention of beta-cell autoimmunity and type 1 diabetes: the Global Platform for the Prevention of Autoimmune Diabetes (GPPAD) perspectives. Mol Metab. 2016;5(4):255–62. https://doi.org/10.1016/j.molmet.2016.02.003
10 Robertson CC, Inshaw JRJ, Onengut-Gumuscu S, Chen WM, Santa Cruz DF, Yang H, et al. Fine-mapping, trans-ancestral and genomic analyses identify causal variants, cells, genes and drug targets for type 1 diabetes. Nat Genet. 2021;53(7):962–71. https://doi.org/10.1038/s41588-021-00880-5
11 Lambert AP, Gillespie KM, Thomson G, Cordell HJ, Todd JA, Gale EAM, et al. Absolute risk of childhood-onset type 1 diabetes defined by human leukocyte antigen class II genotype: a population-based study in the United Kingdom. J Clin Endocrinol Metab. 2004;89(8):4037–43. https://doi.org/10.1210/jc.2003-032084
12 Nguyen C, Varney MD, Harrison LC, Morahan G. Definition of high-risk type 1 diabetes HLA-DR and HLA-DQ types using only three single nucleotide polymorphisms. Diabetes. 2013;62(6):2135–40. https://doi.org/10.2337/db12-1398
13 Noble JA, Valdes AM, Cook M, Klitz W, Thomson G, Erlich HA. The role of HLA class II genes in insulin-dependent diabetes mellitus: molecular analysis of 180 Caucasian, multiplex families. Am J Hum Genet. 1996;59(5):1134–48.
14 Erlich H, Valdes AM, Noble J, Carlson JA, Varney M, Concannon P, et al. HLA DR-DQ haplotypes and genotypes and type 1 diabetes risk: analysis of the type 1 diabetes genetics consortium families. Diabetes. 2008;57(4):1084–92. https://doi.org/10.2337/db07-1331
15 Hippich M, Beyerlein A, Hagopian WA, Krischer JP, Vehik K, Knoop J, et al. Genetic contribution to the divergence in type 1 diabetes risk between children from the general population and children from affected families. Diabetes. 2019;68(4):847–57. https://doi.org/10.2337/db18-0882
16 Bonifacio E, Beyerlein A, Hippich M, Winkler C, Vehik K, Weedon MN, et al. Genetic scores to stratify risk of developing multiple islet autoantibodies and type 1 diabetes: a prospective study in children. PLoS Med. 2018;15(4):e1002548. https://doi.org/10.1371/journal.pmed.1002548
17 Aly TA, Ide A, Jahromi MM, Barker JM, Fernando MS, Babu SR, et al. Extreme genetic risk for type 1A diabetes. Proc Natl Acad Sci U S A. 2006;103(38):14074–9. https://doi.org/10.1073/pnas.0606349103
18 Laine AP, Valta M, Toppari J, Knip M, Veijola R, Ilonen J, et al. Non-HLA gene polymorphisms in the pathogenesis of type 1 diabetes: phase and endotype specific effects. Front Immunol. 2022;13:909020. https://doi.org/10.3389/fimmu.2022.909020
19 Pociot F, Nørgaard K, Hobolth N, Andersen O, Nerup J. A nationwide population-based study of the familial aggregation of type 1 (insulin-dependent) diabetes mellitus in Denmark. Danish Study Group of Diabetes in Childhood. Diabetologia. 1993;36(9):870–5. https://doi.org/10.1007/BF00400364
20 Sharp SA, Rich SS, Wood AR, Jones SE, Beaumont RN, Harrison JW, et al. Development and standardization of an improved type 1 diabetes genetic risk score for use in newborn screening and incident diagnosis. Diabetes Care. 2019;42(2):200–7. https://doi.org/10.2337/dc18-1785
21 Winkler C, Krumsiek J, Buettner F, Angermüller C, Giannopoulou EZ, Theis FJ, et al. Feature ranking of type 1 diabetes susceptibility genes improves prediction of type 1 diabetes. Diabetologia. 2014;57(12):2521–9. https://doi.org/10.1007/s00125-014-3362-1
22 Redondo MJ, Geyer S, Steck AK, Sharp S, Wentworth JM, Weedon MN, et al. A type 1 diabetes genetic risk score predicts progression of islet autoimmunity and development of type 1 diabetes in individuals at risk. Diabetes Care. 2018;41(9):1887–94. https://doi.org/10.2337/dc18-0087

23 Onengut-Gumuscu S, Chen WM, Robertson CC, Bonnie JK, Farber E, Zhu Z, et al. Type 1 diabetes risk in African-Ancestry participants and utility of an ancestry-specific genetic risk score. Diabetes Care. 2019;42(3):406–15. https://doi.org/10.2337/dc18-1727
24 Patel KA, Oram RA, Flanagan SE, De Franco E, Colclough K, Shepherd M, et al. Type 1 diabetes genetic risk score: a novel tool to discriminate monogenic and type 1 diabetes. Diabetes. 2016;65(7):2094–9. https://doi.org/10.2337/db15-1690
25 Perry DJ, Wasserfall CH, Oram RA, Williams MD, Posgai A, Muir AB, et al. Application of a genetic risk score to racially diverse type 1 diabetes populations demonstrates the need for diversity in risk-modeling. Sci Rep. 2018;8(1):4529. https://doi.org/10.1038/s41598-018-22574-5
26 Bonifacio E, Weiß A, Winkler C, Hippich M, Rewers MJ, Toppari J, et al. An age-related exponential decline in the risk of multiple islet autoantibody seroconversion during childhood. Diabetes Care. 2021;44(10):2260–8. https://doi.org/10.2337/dc20-2122
27 Hoffmann VS, Weiß A, Winkler C, Knopff A, Jolink M, Bonifacio E, et al. Landmark models to define the age-adjusted risk of developing stage 1 type 1 diabetes across childhood and adolescence. BMC Med. 2019;17(1):125. https://doi.org/10.1186/s12916-019-1360-3
28 Krischer JP, Liu X, Lernmark Å, Hagopian WA, Rewers MJ, She JX, et al. Characteristics of children diagnosed with type 1 diabetes before vs after 6 years of age in the TEDDY cohort study. Diabetologia. 2021;64(10):2247–57. https://doi.org/10.1007/s00125-021-05514-3
29 Beyerlein A, Bonifacio E, Vehik K, Hippich M, Winkler C, Frohnert BI, et al. Progression from islet autoimmunity to clinical type 1 diabetes is influenced by genetic factors: results from the prospective TEDDY study. J Med Genet. 2019;56(9):602–5. https://doi.org/10.1136/jmedgenet-2018-105532
30 Bonifacio E, Krumsiek J, Winkler C, Theis FJ, Ziegler AG. A strategy to find gene combinations that identify children who progress rapidly to type 1 diabetes after islet autoantibody seroconversion. Acta Diabetol. 2014;51(3):403–11. https://doi.org/10.1007/s00592-013-0526-2
31 Fourlanos S, Varney MD, Tait BD, Morahan G, Honeyman MC, Colman PG, et al. The rising incidence of type 1 diabetes is accounted for by cases with lower-risk human leukocyte antigen genotypes. Diabetes Care. 2008;31(8):1546–9. https://doi.org/10.2337/dc08-0239
32 Penno MA, Couper JJ, Craig ME, Colman PG, Rawlinson WD, Cotterill AM, et al. Environmental determinants of islet autoimmunity (ENDIA): a pregnancy to early life cohort study in children at-risk of type 1 diabetes. BMC Pediatr. 2013;13:124. https://doi.org/10.1186/1471-2431-13-124
33 Kim KW, Allen DW, Briese T, Couper JJ, Barry SC, Colman PG, et al. Higher frequency of vertebrate-infecting viruses in the gut of infants born to mothers with type 1 diabetes. Pediatr Diabetes. 2020;21(2):271–9. https://doi.org/10.1111/pedi.12952
34 Oakey H, Giles LC, Thomson RL, Lê Cao KA, Ashwood P, Brown JD, et al. Protocol for a nested case-control study design for omics investigations in the environmental determinants of islet autoimmunity cohort. Ann Med. 2023;55(1):2198255. https://doi.org/10.1080/07853890.2023.2198255
35 Johnson SB, Lynch KF, Roth R, Lundgren M, Parikh HM, Akolkar B, et al. First-appearing islet autoantibodies for type 1 diabetes in young children: maternal life events during pregnancy and the child's genetic risk. Diabetologia. 2021;64(3):591–602. https://doi.org/10.1007/s00125-020-05344-9
36 Bosi E, Catassi C. Screening type 1 diabetes and celiac disease by law. Lancet Diabetes Endocrinol. 2024;12(1):12–4. https://doi.org/10.1016/S2213-8587(23)00354-6
37 Megan Herr JK. New ICD-10 codes for severity of hypoglycemia. 2024. [cited April 10th, 2024 10.07.24]. Available from: https://pbn.decisionhealth.com/Blogs/DetailPrint.aspx?id=201085
38 New international medical code for pre-symptomatic type 1 diabetes. [cited 2024 May 22]; Available from: https://www.birmingham.ac.uk/news/2024/launch-of-new-international-medical-code-for-presymptomatic-type-1-diabetes
39 Winkler C, Schober E, Ziegler AG, Holl RW. Markedly reduced rate of diabetic ketoacidosis at onset of type 1 diabetes in relatives screened for islet autoantibodies. Pediatr Diabetes. 2012;13(4):308–13. https://doi.org/10.1111/j.1399-5448.2011.00829.x
40 Hummel S, Carl J, Friedl N, Winkler C, Kick K, Stock J, et al. Children diagnosed with presymptomatic type 1 diabetes through public health screening have milder diabetes at clinical manifestation. Diabetologia. 2023;66(9):1633–42. https://doi.org/10.1007/s00125-023-05953-0
41 Hummel S, Gemulla G, Kiess W. Presymptomatic type 1 diabetes and disease severity at onset. Reply to Schneider J [letter]. Diabetologia. 2023;66(12):2389–90.
42 Schneider J, Gemulla G, Kiess W, Berner R, Hommel A. Presymptomatic type 1 diabetes and disease severity at onset. Diabetologia. 2023;66(12):2387–8. https://doi.org/10.1007/s00125-023-05999-0
43 Fredheim S, Johannesen J, Johansen A, Lyngsøe L, Rida H, Andersen MLM, et al. Diabetic ketoacidosis at the onset of type 1 diabetes is associated with future HbA1c levels. Diabetologia. 2013;56(5):995–1003. https://doi.org/10.1007/s00125-013-2850-z
44 Duca LM, Wang B, Rewers M, Rewers A. Diabetic ketoacidosis at diagnosis of type 1 diabetes predicts poor long-term glycemic control. Diabetes Care. 2017;40(9):1249–55. https://doi.org/10.2337/dc17-0558
45 Barker JM, Goehrig SH, Barriga K, Hoffman M, Slover R, Eisenbarth GS, et al. Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up. Diabetes Care. 2004;27(6):1399–404. https://doi.org/10.2337/diacare.27.6.1399
46 Hekkala AM, Ilonen J, Toppari J, Knip M, Veijola R. Ketoacidosis at diagnosis of type 1 diabetes: effect of prospective studies with newborn genetic screening and follow up of risk children. Pediatr Diabetes. 2018;19(2):314–9. https://doi.org/10.1111/pedi.12541
47 Smith LB, Liu X, Johnson SB, Tamura R, Elding Larsson H, Ahmed S, et al. Family adjustment to diabetes diagnosis in children: can participation in a study on type 1 diabetes genetic risk be helpful? Pediatr Diabetes. 2018;19(5):1025–33. https://doi.org/10.1111/pedi.12674
48 Houben J, Janssens M, Winkler C, Besser REJ, Dzygalo K, Fehn A, et al. The emotional well-being of parents with children at genetic risk for type 1 diabetes before and during participation in the POInT-study. Pediatr Diabetes. 2022;23(8):1707–16. https://doi.org/10.1111/pedi.13448
49 Johnson SB, Lynch KF, Roth R, Schatz D; TEDDY Study Group. My child is islet autoantibody positive: impact on parental anxiety. Diabetes Care. 2017;40(9):1167–72. https://doi.org/10.2337/dc17-0166
50 O'Donnell HK, Rasmussen CG, Dong F, Simmons KM, Steck AK, Frohnert BI, et al. Anxiety and risk perception in parents of children identified by population screening as high risk for type 1 diabetes. Diabetes Care. 2023;46(12):2155–61. https://doi.org/10.2337/dc23-0350
51 Kao KT, Islam N, Fox DA, Amed S. Incidence trends of diabetic ketoacidosis in children and adolescents with type 1 diabetes in British Columbia, Canada. J Pediatr. 2020;221:165–73 e2. https://doi.org/10.1016/j.jpeds.2020.02.069
52 Ampt A, van Gemert T, Craig ME, Donaghue KC, Lain SB, Nassar N. Using population data to understand the epidemiology and risk factors for diabetic ketoacidosis in Australian children with type 1 diabetes. Pediatr Diabetes. 2019;20(7):901–8. https://doi.org/10.1111/pedi.12891
53 Rabbone I, Maltoni G, Tinti D, Zucchini S, Cherubini V, Bonfanti R, et al. Diabetic ketoacidosis at the onset of disease during a national awareness campaign: a 2-year observational study in children aged 0-18 years. Arch Dis Child. 2020;105(4):363–6. https://doi.org/10.1136/archdischild-2019-316903

54 Cortez FJ, Gebhart D, Robinson PV, Seftel D, Pourmandi N, Owyoung J, et al. Sensitive detection of multiple islet autoantibodies in type 1 diabetes using small sample volumes by agglutination-PCR. PLoS One. 2020; 15(11):e0242049. https://doi.org/10.1371/journal.pone.0242049
55 Liberati D, Wyatt RC, Brigatti C, Marzinotto I, Ferrari M, Bazzigaluppi E, et al. A novel LIPS assay for insulin autoantibodies. Acta Diabetol. 2018;55(3):263–70. https://doi.org/10.1007/s00592-017-1082-y
56 Naredi Scherman M, Lind A, Hamdan S, Lundgren M, Svensson J, Pociot F, et al. Home capillary sampling and screening for type 1 diabetes, celiac disease, and autoimmune thyroid disease in a Swedish general pediatric population: the TRIAD study. Front Pediatr. 2024;12:1386513. https://doi.org/10.3389/fped.2024.1386513
57 Hendriks AEJ, Marcovecchio ML, Besser REJ, Bonifacio E, Casteels K, Elding Larsson H, et al. Clinical care advice for monitoring of islet autoantibody positive individuals with presymptomatic type 1 diabetes. Diabetes Metab Res Rev. 2024;40(2):e3777. https://doi.org/10.1002/dmrr.3777
58 Sims EK, Besser REJ, Dayan C, Geno Rasmussen C, Greenbaum C, Griffin KJ, et al. Screening for type 1 diabetes in the general population: a status report and perspective. Diabetes. 2022;71(4):610–23. https://doi.org/10.2337/dbi20-0054
59 Ghalwash M, Dunne JL, Lundgren M, Rewers M, Ziegler AG, Anand V, et al. Two-age islet-autoantibody screening for childhood type 1 diabetes: a prospective cohort study. Lancet Diabetes Endocrinol. 2022; 10(8):589–96. https://doi.org/10.1016/S2213-8587(22)00141-3
60 Ghalwash M, Anand V, Lou O, Martin F, Rewers M, Ziegler AG, et al. Islet autoantibody screening in at-risk adolescents to predict type 1 diabetes until young adulthood: a prospective cohort study. Lancet Child Adolesc Health. 2023;7(4):261–8. https://doi.org/10.1016/S2352-4642(22)00350-9
61 Alonso GT, Coakley A, Pyle L, Manseau K, Thomas S, Rewers A. Diabetic ketoacidosis at diagnosis of type 1 diabetes in Colorado children, 2010-2017. Diabetes Care. 2020;43(1): 117–21. https://doi.org/10.2337/dc19-0428
62 Dabelea D, Rewers A, Stafford JM, Standiford DA, Lawrence JM, Saydah S, et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. Pediatrics. 2014;133(4): e938–45. https://doi.org/10.1542/peds.2013-2795
63 Ziegler AG, Achenbach P, Berner R, Casteels K, Danne T, Gündert M, et al. Oral insulin therapy for primary prevention of type 1 diabetes in infants with high genetic risk: the GPPAD-POInT (global platform for the prevention of autoimmune diabetes primary oral insulin trial) study protocol. BMJ Open. 2019;9(6):e028578. https://doi.org/10.1136/bmjopen-2018-028578
64 Ferrat LA, Vehik K, Sharp SA, Lernmark Å, Rewers MJ, She JX, et al. A combined risk score enhances prediction of type 1 diabetes among susceptible children. Nat Med. 2020; 26(8):1247–55. https://doi.org/10.1038/s41591-020-0930-4
65 Hommel A, Haupt F, Delivani P, Winkler C, Stopsack M, Wimberger P, et al. Screening for type 1 diabetes risk in newborns: the Freder1k pilot study in saxony. Horm Metab Res. 2018;50(1):44–9. https://doi.org/10.1055/s-0043-120921
66 Ziegler AG, Arnolds S, Kölln A, Achenbach P, Berner R, Bonifacio E, et al. Supplementation with Bifidobacterium longum subspecies infantis EVC001 for mitigation of type 1 diabetes autoimmunity: the GPPAD-SINT1A randomised controlled trial protocol. BMJ Open. 2021;11(11):e052449. https://doi.org/10.1136/bmjopen-2021-052449
67 Phillip M, Achenbach P, Addala A, Albanese-O'Neill A, Battelino T, Bell KJ, et al. Consensus guidance for monitoring individuals with islet autoantibody-positive prestage 3 type 1 diabetes. Diabetes Care. 2024; 47(8):1276–98. https://doi.org/10.2337/dci24-0042
68 Weiss A, Zapardiel-Gonzalo J, Voss F, Jolink M, Stock J, Haupt F, et al. Progression likelihood score identifies substages of presymptomatic type 1 diabetes in childhood public health screening. Diabetologia. 2022;65(12):2121–31. https://doi.org/10.1007/s00125-022-05780-9
69 Krischer JP, Liu X, Lernmark Å, Hagopian WA, Rewers MJ, She JX, et al. Predictors of the initiation of islet autoimmunity and progression to multiple autoantibodies and clinical diabetes: the TEDDY study. Diabetes Care. 2022;45(10):2271–81. https://doi.org/10.2337/dc21-2612
70 So M, O'Rourke C, Ylescupidez A, Bahnson HT, Steck AK, Wentworth JM, et al. Characterising the age-dependent effects of risk factors on type 1 diabetes progression. Diabetologia. 2022;65(4):684–94. https://doi.org/10.1007/s00125-021-05647-5
71 Chmiel R, Giannopoulou EZ, Winkler C, Achenbach P, Ziegler AG, Bonifacio E. Progression from single to multiple islet autoantibodies often occurs soon after seroconversion: implications for early screening. Diabetologia. 2015;58(2):411–3. https://doi.org/10.1007/s00125-014-3443-1
72 Johnson SB, Smith LB. General population screening for islet autoantibodies: psychosocial challenges. Diabetes Care. 2023;46(12): 2123–5. https://doi.org/10.2337/dci23-0061
73 Elding Larsson H, Vehik K, Bell R, Dabelea D, Dolan L, Pihoker C, et al. Reduced prevalence of diabetic ketoacidosis at diagnosis of type 1 diabetes in young children participating in longitudinal follow-up. Diabetes Care. 2011;34(11):2347–52. https://doi.org/10.2337/dc11-1026
74 Insel RA, Dunne JL, Atkinson MA, Chiang JL, Dabelea D, Gottlieb PA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care. 2015;38(10):1964–74. https://doi.org/10.2337/dc15-1419
75 Sosenko JM, Palmer JP, Rafkin-Mervis L, Krischer JP, Cuthbertson D, Mahon J, et al. Incident dysglycemia and progression to type 1 diabetes among participants in the Diabetes Prevention Trial-Type 1. Diabetes Care. 2009; 32(9):1603–7. https://doi.org/10.2337/dc08-2140
76 Sosenko JM, Skyler JS, Mahon J, Krischer JP, Greenbaum CJ, Rafkin LE, et al. Use of the Diabetes Prevention Trial-Type 1 Risk Score (DPTRS) for improving the accuracy of the risk classification of type 1 diabetes. Diabetes Care. 2014;37(4):979–84. https://doi.org/10.2337/dc13-2359
77 Sosenko JM, Skyler JS, DiMeglio LA, Beam CA, Krischer JP, Greenbaum CJ, et al. A new approach for diagnosing type 1 diabetes in autoantibody-positive individuals based on prediction and natural history. Diabetes Care. 2015;38(2):271–6. https://doi.org/10.2337/dc14-1813
78 Sosenko JM, Skyler JS, Palmer JP; Diabetes Type 1 TrialNet and Diabetes Prevention Trial-Type 1 Study Groups. The development, validation, and utility of the diabetes prevention trial-type 1 risk score (DPTRS). Curr Diab Rep. 2015;15(8):49. https://doi.org/10.1007/s11892-015-0626-1
79 Simmons KM, Sosenko JM, Warnock M, Geyer S, Ismail HM, Elding Larsson H, et al. One-hour oral glucose tolerance tests for the prediction and diagnostic surveillance of type 1 diabetes. J Clin Endocrinol Metab. 2020;105(11):e4094–101. https://doi.org/10.1210/clinem/dgaa592
80 Bediaga NG, Li-Wai-Suen CSN, Haller MJ, Gitelman SE, Evans-Molina C, Gottlieb PA, et al. Simplifying prediction of disease progression in pre-symptomatic type 1 diabetes using a single blood sample. Diabetologia. 2021;64(11):2432–44. https://doi.org/10.1007/s00125-021-05523-2
81 Helminen O, Aspholm S, Pokka T, Ilonen J, Simell O, Veijola R, et al. OGTT and random plasma glucose in the prediction of type 1 diabetes and time to diagnosis. Diabetologia. 2015;58(8):1787–96. https://doi.org/10.1007/s00125-015-3621-9
82 Sosenko JM, Skyler JS, Beam CA, Boulware D, Mahon JL, Krischer JP, et al. The development and utility of a novel scale that quantifies the glycemic progression toward type 1 diabetes over 6 months. Diabetes Care. 2015;38(5):940–2. https://doi.org/10.2337/dc14-2787
83 Driscoll KA, Tamura R, Johnson SB, Gesualdo P, Clasen J, Smith L, et al. Adherence to oral glucose tolerance testing in children in stage 1 of type 1 diabetes: the TEDDY study. Pediatr Diabetes. 2021;22(2):360–8. https://doi.org/10.1111/pedi.13149

84 Helminen O, Aspholm S, Pokka T, Hautakangas MR, Haatanen N, Lempainen J, et al. HbA1c predicts time to diagnosis of type 1 diabetes in children at risk. Diabetes. 2015;64(5):1719–27. https://doi.org/10.2337/db14-0497
85 Vehik K, Boulware D, Killian M, Rewers M, McIndoe R, Toppari J, et al. Rising hemoglobin A1c in the nondiabetic range predicts progression of type 1 diabetes as well as oral glucose tolerance tests. Diabetes Care. 2022;45(10):2342–9. https://doi.org/10.2337/dc22-0828
86 Salami F, Tamura R, You L, Lernmark Å, Larsson HE, Lundgren M, et al. HbA1c as a time predictive biomarker for an additional islet autoantibody and type 1 diabetes in seroconverted TEDDY children. Pediatr Diabetes. 2022;23(8):1586–93. https://doi.org/10.1111/pedi.13413
87 American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: standards of care in diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S20–42. https://doi.org/10.2337/dc24-S002
88 Vehik K, Cuthbertson D, Boulware D, Beam CA, Rodriguez H, Legault L, et al. Performance of HbA1c as an early diagnostic indicator of type 1 diabetes in children and youth. Diabetes Care. 2012;35(9):1821–5. https://doi.org/10.2337/dc12-0111
89 Steck AK, Dong F, Taki I, Hoffman M, Simmons K, Frohnert BI, et al. Continuous glucose monitoring predicts progression to diabetes in autoantibody positive children. J Clin Endocrinol Metab. 2019;104(8):3337–44. https://doi.org/10.1210/jc.2018-02196
90 Steck AK, Dong F, Geno Rasmussen C, Bautista K, Sepulveda F, Baxter J, et al. CGM metrics predict imminent progression to type 1 diabetes: autoimmunity screening for Kids (ASK) study. Diabetes Care. 2022;45(2):365–71. https://doi.org/10.2337/dc21-0602
91 Wilson DM, Pietropaolo SL, Acevedo-Calado M, Huang S, Anyaiwe D, Scheinker D, et al. CGM metrics identify dysglycemic states in participants from the TrialNet pathway to prevention study. Diabetes Care. 2023;46(3):526–34. https://doi.org/10.2337/dc22-1297
92 Kontola H, Alanko I, Koskenniemi JJ, Löyttyniemi E, Itoshima S, Knip M, et al. Exploring minimally invasive approach to define stages of type 1 diabetes remotely. Diabetes Technol Ther. 2022;24(9):655–65. https://doi.org/10.1089/dia.2021.0554
93 Montaser E, Breton MD, Brown SA, DeBoer MD, Kovatchev B, Farhy LS. Predicting immunological risk for stage 1 and stage 2 diabetes using a 1-week CGM home test, nocturnal glucose increments, and standardized liquid mixed meal breakfasts, with classification enhanced by machine learning. Diabetes Technol Ther. 2023;25(9):631–42. https://doi.org/10.1089/dia.2023.0064
94 Priya M, Mohan Anjana R, Pradeepa R, Jayashri R, Deepa M, Bhansali A, et al. Comparison of capillary whole blood versus venous plasma glucose estimations in screening for diabetes mellitus in epidemiological studies in developing countries. Diabetes Technol Ther. 2011;13(5):586–91. https://doi.org/10.1089/dia.2010.0218
95 Dunseath GJ, Bright D, Jones C, Dowrick S, Cheung WY, Luzio SD. Performance evaluation of a self-administered home oral glucose tolerance test kit in a controlled clinical research setting. Diabet Med. 2019;36(7):862–7. https://doi.org/10.1111/dme.13961
96 Lange KZA. Fr1da: Typ 1 Diabetes früh erkennen und gut behandeln. 3. überarbeitete Auflage, Medtrix-Verlag Wiesbaden (Fr1da: Information broschure for parents and children – early diagnosis and care for children. GPPAD). 2023.
97 Davis J, Fischl AH, Beck J, Browning L, Carter A, Condon JE, et al. 2022 national standards for diabetes self-management education and support. Diabetes Care. 2022;45(2):484–94. https://doi.org/10.2337/dc21-2396
98 Lindholm Olinder A, DeAbreu M, Greene S, Haugstvedt A, Lange K, Majaliwa ES, et al. ISPAD clinical practice consensus guidelines 2022: diabetes education in children and adolescents. Pediatr Diabetes. 2022;23(8):1229–42. https://doi.org/10.1111/pedi.13418
99 Association of Diabetes Care and Education Specialists, Kolb L. An effective model of diabetes care and education: the ADCES7 self-care Behaviors™. Sci Diabetes Self Manag Care. 2021;47(1):30–53. https://doi.org/10.1177/0145721720978154
100 Melin J, Maziarz M, Andrén Aronsson C, Lundgren M, Elding Larsson H. Parental anxiety after 5 years of participation in a longitudinal study of children at high risk of type 1 diabetes. Pediatr Diabetes. 2020;21(5):878–89. https://doi.org/10.1111/pedi.13024
101 de Wit M, Gajewska KA, Goethals ER, McDarby V, Zhao X, Hapunda G, et al. ISPAD Clinical Practice Consensus Guidelines 2022: psychological care of children, adolescents and young adults with diabetes. Pediatr Diabetes. 2022;23(8):1373–89. https://doi.org/10.1111/pedi.13428
102 Whittemore R, Jaser S, Chao A, Jang M, Grey M. Psychological experience of parents of children with type 1 diabetes: a systematic mixed-studies review. Diabetes Educ. 2012;38(4):562–79. https://doi.org/10.1177/0145721712445216
103 Silina E, Taube M, Zolovs M. Exploring the mediating role of parental anxiety in the link between children's mental health and glycemic control in type 1 diabetes. Int J Environ Res Public Health. 2023;20(19):6849. https://doi.org/10.3390/ijerph20196849
104 Trojanowski PJ, Niehaus CE, Fischer S, Mehlenbeck R. Parenting and psychological health in youth with type 1 diabetes: systematic review. J Pediatr Psychol. 2021;46(10):1213–37. https://doi.org/10.1093/jpepsy/jsab064
105 McQueen RB, Geno Rasmussen C, Waugh K, Frohnert BI, Steck AK, Yu L, et al. Cost and cost-effectiveness of large-scale screening for type 1 diabetes in Colorado. Diabetes Care. 2020;43(7):1496–503. https://doi.org/10.2337/dc19-2003
106 Karl FM, Winkler C, Ziegler AG, Laxy M, Achenbach P. Costs of public health screening of children for presymptomatic type 1 diabetes in bavaria, Germany. Diabetes Care. 2022;45(4):837–44. https://doi.org/10.2337/dc21-1648
107 Gu Y, Zhao Z, Waugh K, Miao D, Jia X, Cheng J, et al. High-throughput multiplexed autoantibody detection to screen type 1 diabetes and multiple autoimmune diseases simultaneously. EBioMedicine. 2019;47:365–72. https://doi.org/10.1016/j.ebiom.2019.08.036
108 Fawwad A, Govender D, Ahmedani MY, Basit A, Lane JA, Mack SJ, et al. Clinical features, biochemistry and HLA-DRB1 status in youth-onset type 1 diabetes in Pakistan. Diabetes Res Clin Pract. 2019;149:9–17. https://doi.org/10.1016/j.diabres.2019.01.023
109 Ibrahim TAM, Govender D, Abdullah MA, Noble JA, Hussien MO, Lane JA, et al. Clinical features, biochemistry, and HLA-DRB1 status in youth-onset type 1 diabetes in Sudan. Pediatr Diabetes. 2021;22(5):749–57. https://doi.org/10.1111/pedi.13209
110 Zabeen B, Govender D, Hassan Z, Noble JA, Lane JA, Mack SJ, et al. Clinical features, biochemistry and HLA-DRB1 status in children and adolescents with diabetes in Dhaka, Bangladesh. Diabetes Res Clin Pract. 2019;158:107894. https://doi.org/10.1016/j.diabres.2019.107894
111 Ahmadov GA, Govender D, Atkinson MA, Sultanova RA, Eubova AA, Wasserfall CH, et al. Epidemiology of childhood-onset type 1 diabetes in Azerbaijan: incidence, clinical features, biochemistry, and HLA-DRB1 status. Diabetes Res Clin Pract. 2018;144:252–9. https://doi.org/10.1016/j.diabres.2018.09.009
112 Jacobsen LM, Bundy BN, Greco MN, Schatz DA, Atkinson MA, Brusko TM, et al. Comparing beta cell preservation across clinical trials in recent-onset type 1 diabetes. Diabetes Technol Ther. 2020;22(12):948–53. https://doi.org/10.1089/dia.2020.0305
113 Nguyen HV, Schatz DA, Mital S, Jacobsen LM, Haller MJ. Cost-effectiveness of low-dose antithymocyte globulin versus other immunotherapies for treatment of new-onset type 1 diabetes. Diabetes Technol Ther. 2022;24(4):258–67. https://doi.org/10.1089/dia.2021.0329

114 An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. N Engl J Med. 2020;382(6):586.
115 Sims EK, Bundy BN, Stier K, Serti E, Lim N, Long SA, et al. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. Sci Transl Med. 2021;13(583):eabc8980. https://doi.org/10.1126/scitranslmed.abc8980
116 Dayan CM, Korah M, Tatovic D, Bundy BN, Herold KC. Changing the landscape for type 1 diabetes: the first step to prevention. Lancet. 2019;394(10205):1286–96. https://doi.org/10.1016/S0140-6736(19)32127-0
117 Herold KC, Gitelman SE, Ehlers MR, Gottlieb PA, Greenbaum CJ, Hagopian W, et al. Teplizumab (anti-CD3 mAb) treatment preserves C-peptide responses in patients with new-onset type 1 diabetes in a randomized controlled trial: metabolic and immunologic features at baseline identify a subgroup of responders. Diabetes. 2013;62(11):3766–74. https://doi.org/10.2337/db13-0345
118 Orban T, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R, et al. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. Lancet. 2011;378(9789):412–9. https://doi.org/10.1016/S0140-6736(11)60886-6
119 Haller MJ, Long SA, Blanchfield JL, Schatz DA, Skyler JS, Krischer JP, et al. Low-dose antithymocyte globulin preserves C-peptide, reduces HbA1c, and increases regulatory to conventional T-cell ratios in new-onset type 1 diabetes: two-year clinical trial data. Diabetes. 2019;68(6):1267–76. https://doi.org/10.2337/db19-0057
120 Quattrin T, Haller MJ, Steck AK, Felner EI, Li Y, Xia Y, et al. Golimumab and beta-cell function in youth with new-onset type 1 diabetes. N Engl J Med. 2020;383(21):2007–17. https://doi.org/10.1056/NEJMoa2006136
121 Rigby MR, Harris KM, Pinckney A, DiMeglio LA, Rendell MS, Felner EI, et al. Alefacept provides sustained clinical and immunological effects in new-onset type 1 diabetes patients. J Clin Invest. 2015;125(8):3285–96. https://doi.org/10.1172/JCI81722
122 Warshauer JT, Bluestone JA, Anderson MS. New frontiers in the treatment of type 1 diabetes. Cell Metab. 2020;31(1):46–61. https://doi.org/10.1016/j.cmet.2019.11.017
123 Taylor PN, Collins KS, Lam A, Karpen SR, Greeno B, Walker F, et al. C-peptide and metabolic outcomes in trials of disease modifying therapy in new-onset type 1 diabetes: an individual participant meta-analysis. Lancet Diabetes Endocrinol. 2023;11(12):915–25. https://doi.org/10.1016/S2213-8587(23)00267-X
124 Ramos EL, Dayan CM, Chatenoud L, Sumnik Z, Simmons KM, Szypowska A, et al. Teplizumab and β-cell function in newly diagnosed type 1 diabetes. N Engl J Med. 2023;389(23):2151–61. https://doi.org/10.1056/NEJMoa2308743
125 Oram RA, Sharp SA, Pihoker C, Ferrat L, Imperatore G, Williams A, et al. Utility of diabetes type-specific genetic risk scores for the classification of diabetes type among multiethnic youth. Diabetes Care. 2022;45(5):1124–31. https://doi.org/10.2337/dc20-2872
126 Herold KC, Gitelman SE, Gottlieb PA, Knecht LA, Raymond R, Ramos EL. Teplizumab: a disease-modifying therapy for type 1 diabetes that preserves β-cell function. Diabetes Care. 2023;46(10):1848–56. https://doi.org/10.2337/dc23-0675
127 Herold KC, Bundy BN, Long SA, Bluestone JA, DiMeglio LA, Dufort MJ, et al. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. N Engl J Med. 2019;381(7):603–13. https://doi.org/10.1056/NEJMoa1902226
128 MEDICATION GUIDE TZIELD™ (TEE-zeeld). (Teplizumab-mzwv) injection, for intravenous use. 2022. [01/29/2024]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761183s000lbl.pdf
129 Sclafani J FDA approves teplizumab to delay onset of type 1 diabetes. 2022. Available from: https://beyondtype1.org/teplizumab-fda-approval-2/
130 Mehta S, Ryabets-Lienhard A, Patel N, Breidbart E, Libman I, Haller MJ, et al. Pediatric endocrine society statement on considerations for use of teplizumab (Tzield™) in clinical practice. Horm Res Paediatr. 2024:1–12. https://doi.org/10.1159/000538775
131 Foster TP, Jacobsen LM, Bruggeman B, Salmon C, Hosford J, Chen A, et al. Low-dose antithymocyte globulin: a pragmatic approach to treating stage 2 type 1 diabetes. Diabetes Care. 2024;47(2):285–9. https://doi.org/10.2337/dc23-1750
132 Knip M, Åkerblom HK, Becker D, Dosch HM, Dupre J, Fraser W, et al. Hydrolyzed infant formula and early β-cell autoimmunity: a randomized clinical trial. JAMA. 2014;311(22):2279–87. https://doi.org/10.1001/jama.2014.5610