

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^{1@}, Kirstine J Bell², Rachel EJ Besser³, Kristina Casteels^{4,5}, Jenny J Couper^{6,7}, Maria E Craig⁸⁻¹⁰, Helena Elding Larsson^{11,12}, Laura Jacobsen¹, Karin Lange¹³, Tal Oron¹⁴, Emily K. Sims¹⁵, Cate Speake¹⁶, Mustafa Tosur^{17,18}, Francesca Ulivi¹⁹, Anette-G Ziegler²⁰, Diane K Wherrett²¹, M. Loredana Marcovecchio²²

[@]Corresponding author

¹ Department of Pediatrics, Division of Endocrinology, University of Florida, USA

² Charles Perkins Centre and Faculty Medicine and Health, University of Sydney, Australia

³ Centre for Human Genetics, NIHR Biomedical Research Centre, University of Oxford

⁴ Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium

⁵ Department of Development and Regeneration, KU Leuven, Leuven, Belgium

⁶ Women's and Children's Hospital, South Australia.

⁷ Robinson Research Institute, University of Adelaide, Australia

⁸ The Children's Hospital at Westmead, Sydney, Australia

⁹ Discipline of Pediatrics and Child Health, University of Sydney, Australia

¹⁰ School of Women's and Children's Health, University of New South Wales

¹¹Department of Clinical Sciences Malmö, Lund University, Lund, Sweden

¹²Department of Pediatrics, Skåne University Hospital, Malmö/Lund, Sweden

¹³Department Medical Psychology, Hannover Medical School, Hannover, Germany

¹⁴The Institute for Endocrinology and Diabetes, Schneider Children's Medical Center of Israel, Petah-Tikva, Israel

¹⁵Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN USA

¹⁶Center for Interventional Immunology, Benaroya Research Institute at Virginia Mason, USA

¹⁷Department of Pediatrics, The Division of Diabetes and Endocrinology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA

¹⁸Children's Nutrition Research Center, USDA/ARS, Houston, TX, USA

¹⁹ Fondazione Italiana Diabete ETS, Milan, Italy

²⁰Institute of Diabetes Research, Helmholtz Zentrum München, and Forschergruppe Diabetes,

Klinikum rechts der Isar, Technische Universität München, Germany

²¹Division of Endocrinology, Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, Canada

²² Department of Paediatrics, University of Cambridge and Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

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: Juvenile Diabetes Research Foundation

PLS: Progression Likelihood Score

SMBG: Self-Monitoring fingerstick Blood Glucose

TEDDY: The Environmental Determinants of Diabetes in the Young

T1D: Type 1 Diabetes

Introduction

This guideline serves as an update to the 2022 International Society for Pediatric and Adolescent Diabetes (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 is included. Lastly, opportunities and challenges associated with the recent United States Food and Drug Administration (FDA) approval of teplizumab as an immunotherapy to delay progression are discussed.

WHAT IS NEW

- Stages 1, 2a, 2b, 3a, 3b, and 4 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 U.S. 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.

Stages of T1D

T1D is characterized by four stages based on antibody status and clinical features (Figure 1):

Stage 1 Multiple islet autoantibodies confirmed on at least 2 samples (using validated assays). Individuals with Stage 1 have normal glycemia and are asymptomatic.

Stage 2 Multiple islet autoantibodies confirmed on at least 2 samples with elevated fasting glucose or

impaired glucose tolerance documented by oral glucose tolerance test (OGTT), HbA1c 5.7-6.5% (39–48 mmol/mol), or $\geq 10\%$ 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*).

Stage 3 Hyperglycemia meeting American Diabetes Association (ADA) glycemic and clinical diagnostic criteria. Individuals 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 Long standing T1D

The stages of T1D inform the progression of the condition. Children with a single islet autoantibody 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 autoantibodies have early-stage T1D. Amongst children living with Stage 1 (normoglycemia), 44% will progress to Stage 3 T1D in 5-years and 80->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].

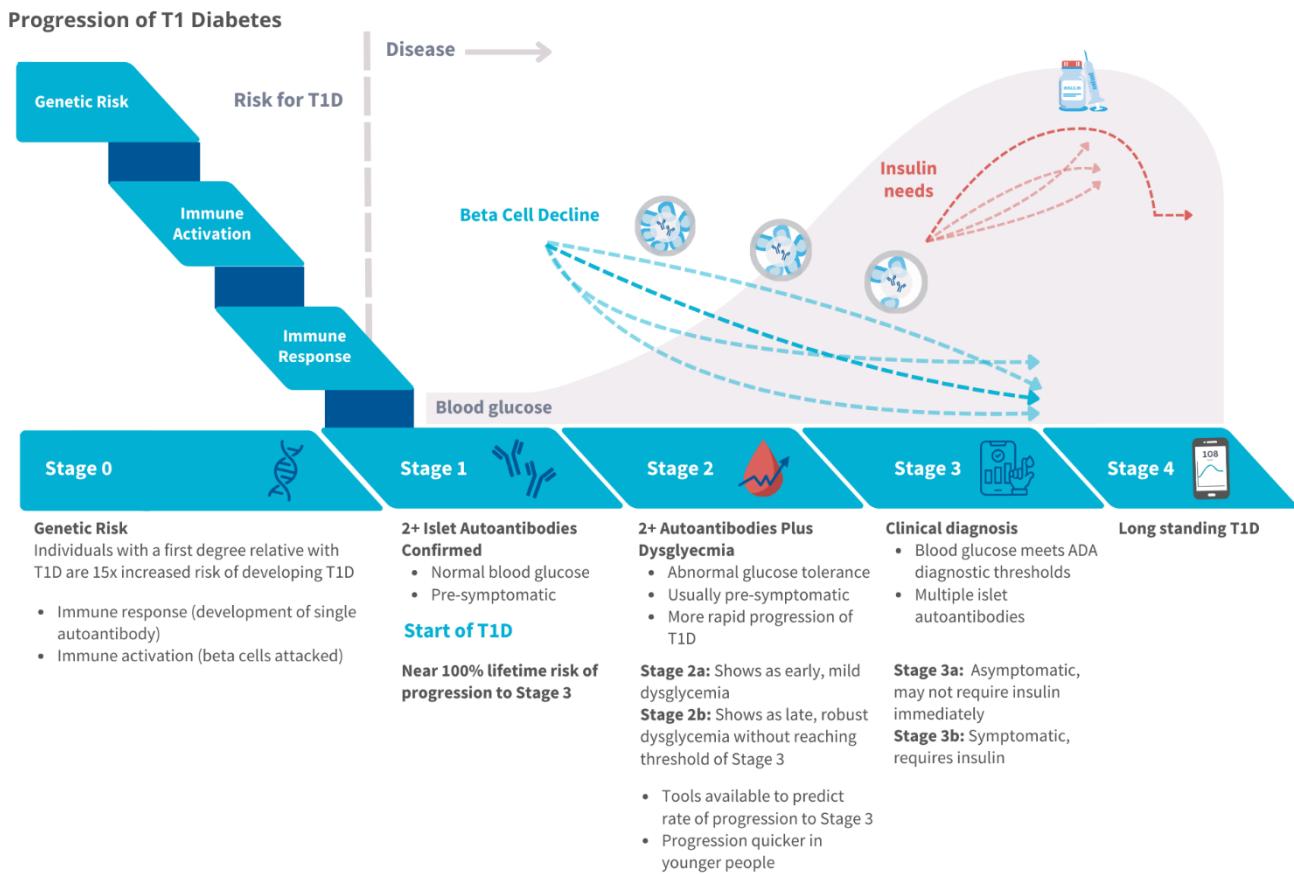


Figure 1: Stages of Type 1 Diabetes (T1D). A small proportion of people who have increased genetic risk of T1D progress at variable rates to immune activation and the development of islet autoimmunity. Clinically available islet autoantibodies include ICA, GADA, IAA, IA2A, and ZnT8A. Once 2 or more islet autoantibodies 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 individuals 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 individuals with T1D fluctuate between stages. Many of the glycemic thresholds are arbitrary but remain useful to describe individuals 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.

Development and progression of T1D

- Individuals with a first degree relative with T1D have 15-fold increased risk of developing T1D compared to persons without a known family history of T1D. [A]
- Individuals with two or more islet autoantibodies 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 autoantibodies progress to Stage 3 within 15 years, compared to only 15% who have a single islet autoantibody. [A]
- Progression rates to Stage 3 T1D amongst those with two or more islet autoantibodies are similar in individuals with a family history of T1D and those from the general population. [A]

Genetic Risk

Individuals with a first degree relative with T1D have a 15-fold increased relative lifetime risk of T1D compared to the general population. The prevalence of T1D amongst individuals with a first degree relative is 5% by age 20 compared to 0.3% amongst 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]. 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 individuals 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 autoantibodies, 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 in 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 individuals and interact with different gene–environment and environment–environment factors. In addition, environmental exposures may influence the development of an insulin (IAA) or glutamic decarboxylase (GADA) antibody as the first appearing autoantibody. Initiating autoantibody responses may reflect unique T1D endotypes, or subtypes defined by distinct pathophysiological mechanisms. [35]

Screening for Early-stage T1D

- General population screening programs using autoantibody testing alone or combinations of genetic and autoantibody testing can identify high-risk children and young people. [A]
- Screening and follow up should be completed to identify individuals with Stage 1, 2, and 3a T1D, reduce incidence of diabetic ketoacidosis (DKA) and hospitalization, and to direct individuals towards interventions or studies seeking to delay or prevent ongoing beta cell loss. [A]
- Screening for islet autoantibodies 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 autoantibodies. [E]
- As screening programs expand, individuals with Stage 1, 2a, 2b, and 3a T1D will be more commonly identified. Additional sub-classifications 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 individuals 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 health care systems. [E]

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 pre-symptomatic T1D have been developed in both the US (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 [38].

Goals of Screening

The long-term vision for T1D screening programs is to identify individuals at risk of or with early-stage T1D and offer them preventative approaches capable of delaying or preventing the condition entirely.

Currently achievable benefits driving recommendations for screening include:

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 [41-46], whereas screening programs combined with long-term follow up reduce DKA rates to less than 5% [7, 39-42]. DKA prevention at diagnosis has potential lifelong benefits, including avoidance of acute morbidity (cerebral oedema, shock), neurocognitive impairment, and mortality [47, 48]. There are also non-causal associations between DKA at onset and risk of future DKA episodes [44, 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)** [42-46].
3. **Improving quality of life and reducing psychological stress.** Parental anxiety at clinical diagnosis is halved for children participating in screening programs compared to those diagnosed from the general population [7]. Time afforded for counselling, preparation for insulin therapy and education may help reduce parental anxiety and smooth the transition to symptomatic T1D and insulin therapy [7, 47].
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

individuals and families screening leads to increased stress and anxiety and many diagnosed with Stage 1, 2a, or 2b T1D have a limited understanding of its progression [48].

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, and available resources.

The two strategies currently used for T1D screening are:

1. Genetic-risk/family history-based islet autoantibody screening
2. Population-wide islet autoantibody 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 individuals with islet autoantibodies, it fails to identify 90% of those who will ultimately develop T1D. As such, alternative approaches utilize either general population or genetic-risk stratified screening are being increasingly utilized. As use of GRS continue to scale, thresholds for at-risk populations can be altered to suit the screening purpose [49-51]. Furthermore, advancements in islet autoantibody assays permit ultra-low blood volume testing, including use of capillary samples and dried blood spots, which facilitate minimally-invasive collections at home or in community settings [52, 53]. 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 [54-56]. Additional studies and analyses are needed to balance sensitivity, specificity, public health priorities, and cost effectiveness when developing specific screening programs.

Autoantibody Screening Approaches in the General Population

Optimal ages for performing autoantibody screening in the general population continue to be refined

using growing data sets from international cohort studies. One analysis suggested that one-time autoantibody 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, 57]. Alternative models derived from a compilation of prospective cohorts studies suggested that optimal time to identify T1D onset in adolescence (10 to 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%) [58]. 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 [49, 51, 59, 60].

Autoantibody Screening in Children with Increased Genetic Risk

Optimal islet autoantibody testing frequency in genetically at-risk children remains unclear. Observational studies have used varying frequencies of autoantibody 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 autoantibody testing while still others have performed autoantibody testing just once between 1 and 5 years of age [61-64]. More frequent autoantibody 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.

Glycemic Surveillance in Children and Young Adults with Islet Autoimmunity

- ISPAD endorses the published 2024 Consensus Guidance for monitoring of children with single and multiple islet autoantibodies. [E]
- OGTT is recommended to stage T1D in people with 2 or more islet autoantibodies 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 high risk of progression [E]
- 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, 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 individuals with early-stages T1D. [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 [65].

OGTT is the gold standard for staging persons with two or more islet autoantibodies (Figure 2). However, when OGTT is not feasible, alternative approaches including HbA1c, capillary or venous glucose (2-hour 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 autoantibody (IA-2A), or 3-4 islet autoantibodies or other high progression risk metrics [1, 7, 66].

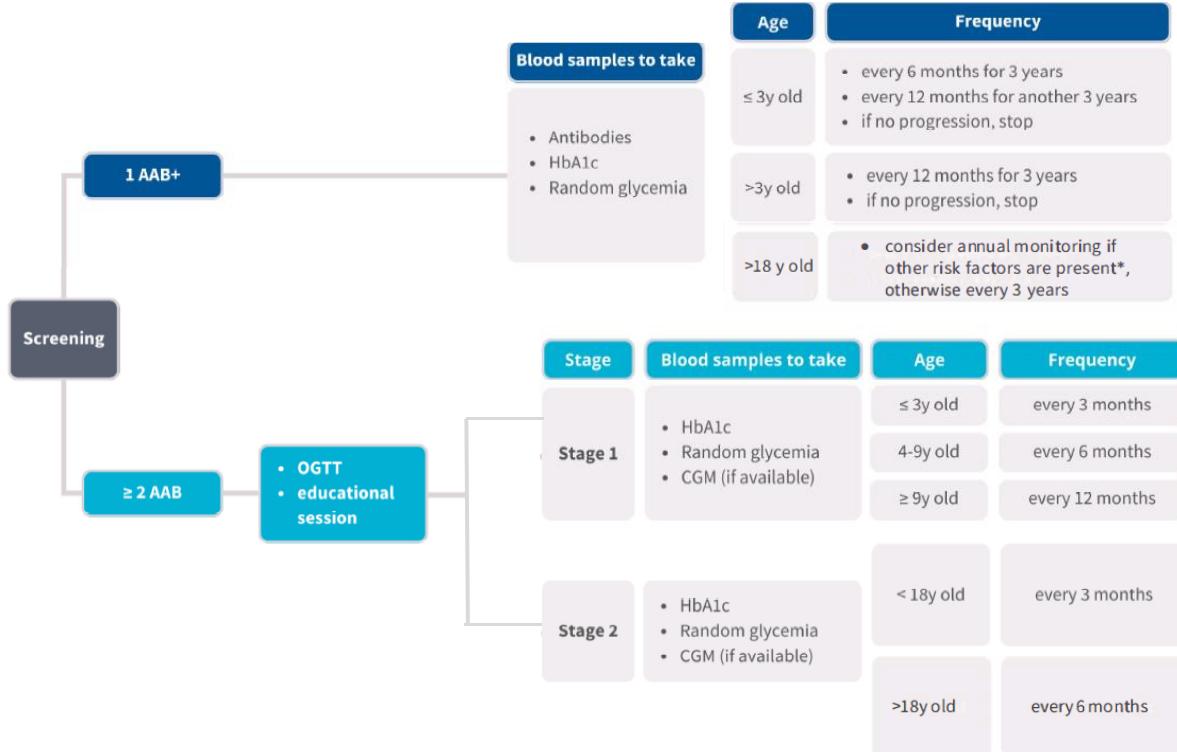


Figure 2. Screening and Monitoring in Children and Adolescents with Single or Multiple Autoantibodies. Age and number of islet autoantibodies dictate the frequency and intensity of recommended monitoring for those with single or multiple autoantibodies. Single or multiple autoantibodies status should be confirmed in a second sample, preferably using an independent reference laboratory. CGM: continuous glucose monitoring; OGTT: oral glucose tolerance test. * ‘other risk factors’: first-degree relative with T1D; elevated genetic risk for T1D if tested; dysglycemia; or history of stress hyperglycemia

Single Autoantibody

- Single autoantibody status should be confirmed in a second sample, preferably using an independent reference laboratory. [B]
- 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. [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 autoantibody who spread to multiple antibodies (Stage 1) do so most frequently within two years from seroconversion. This spreading is most frequently observed in children under 5 years of age [4, 67]. In single autoantibody positive children under 3 years of age, the JDRF guidance advises monitoring autoantibody status every 6 months for 3 years, then annually for another 3 years [65]. Metabolic monitoring in children positive for a single antibody by annual random venous or capillary BG and HbA1c testing should be considered [65, 68, 69]. As with all screening and monitoring programs, the economic and psychological impacts of repeated screening must always be considered [1, 7].

Multiple Autoantibodies

- Confirm multiple autoantibody 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-hour post-high carbohydrate meal 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 autoantibodies [65]. 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 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 counselled 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 [65, 70, 71].

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 autoantibodies, as

those who do not receive on-going monitoring and education have high rates of DKA [72].

Oral glucose tolerance test (OGTT)

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 [73-81]. Fasting, intermediate, and 2-hour glucose values defining Stage 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 include the 5-timepoint Diabetes Prevention Trial-Type 1 Risk Score (DPTRS) [74, 75], the 2-timepoint DPTRS60 [77], Index60 [78], the single timepoint M120 [79] and the progression likelihood score (PLS) [81]. ADA criteria should continue to be used to document the diagnosis of Stage 3 T1D. Asymptomatic and symptomatic Stage 3 T1D are categorized as Stage 3a and Stage 3b respectively.

While the OGTT remains a gold standard it is not always feasible or acceptable [82]. Alternative approaches are suggested and discussed below (Box 1).

BOX 1.

Fasting plasma glucose (FPG):

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

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

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

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

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

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 [74, 75]. Several studies have shown the utility of HbA1c in predicting progression to clinical T1D [83-85]. 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 $\geq 5.9\%$ predicted progression to stage 3 T1D in 1 year [83]. The TEDDY study supported these findings, showing that an increase of $\geq 10\%$ 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 autoantibodies [84, 85]. Notably, the 2024 ADA Standards of care include HbA1c of 5.7-6.4% (39-47 mmol/mol) or $\geq 10\%$ increase in HbA1c as diagnostic of Stage 2 T1D [86]. 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 [87]. 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 [57].

Continuous glucose monitoring (CGM)

CGM is increasingly being used as a tool to predict progression to Stage 3 T1D [88-90], and to detect people who are asymptomatic in Stage 2 and Stage 3a [91]. CGM can provide real time data and may be useful as it detects increased glucose variability, elevated glucose levels and reduced time in range [88]. Different cut-offs for glucose values have been posited to predict progression to Stage 3 T1D [89, 90]. In one study, a cut-off of 10% time spent above 140mg/dL (7.8mmol/L) indicated an 80% risk of progression to Stage 3

T1D over one year (88% sensitivity, 91% specificity, 67% positive predictive value, 97% negative predictive value) [89]. Whilst 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 [92].

Random venous glucose and self-monitoring fingerstick blood glucose (SMBG)

In the DIPP study, median time to diagnosis after a random plasma glucose ≥ 7.8 mmol/l (140mg/dl), was 1 year in children with Stage 1 T1D [80]. 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%]) [80]. 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 [93, 94]. 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 [65] 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 or capillary glucose monitoring are 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.

Table 1. Metabolic surveillance tools for children with multiple islet autoantibodies.

Metric	Pros	Cons	Utility/Predictive Value
OGTT	<ul style="list-style-type: none"> Gold standard Used to Stage disease and predict progression 	<ul style="list-style-type: none"> Requires glucose load and 1 to 5 blood draws over 2 h 	Glycemic staging Risk scores for progression (DPTRS, DPTRS60, Index60, M120, PLS) ⁶⁵⁻⁶⁹
Random venous glucose	<ul style="list-style-type: none"> One-off sample Low cost 	<ul style="list-style-type: none"> Requires a blood draw 	Similar to 2-hour OGTT-derived glucose ⁷¹
HbA1c	<ul style="list-style-type: none"> Highly specific Can use capillary sample 	<ul style="list-style-type: none"> Insensitive, often normal in Stage 3a T1D May be affected by other disease states* 	Risk of progression to 'clinical disease': HbA1c \geq 5.9% (41 mmol/mol), or 10% rise over 3-12 months ⁷⁵
CGM	<ul style="list-style-type: none"> Provides real-time continuous monitoring. May enable early detection of Stage 2 diabetes 	<ul style="list-style-type: none"> Optimal duration and frequency of CGM wear not yet determined Cost, access, evidence to wear continuously are needed Data may cause anxiety and undesirable behaviour change Not currently considered superior to OGTT in the context of research trials⁷⁶ 	<p>Risk of progression to 'clinical disease': Time above 7.8mmol/L (140mg/dL) is $>10\%$⁷⁷</p> <p>$>20\%$ above 7.8mmol/L ($>140\text{mg/dL}$) indicates need to test for Stage 3 T1D⁷⁸</p>
Self-monitoring blood glucose (SMBG)	<ul style="list-style-type: none"> Simple Use at home Lower cost vs other methods 	<ul style="list-style-type: none"> Optimal timing and frequency have not been determined Random result 	Immediate result
Urinary glucose testing	<ul style="list-style-type: none"> Simple Use at home Lower cost vs other methods 	<ul style="list-style-type: none"> Untested in this context Less reliable than SMBG due to the altered renal threshold for glucose 	Immediate result

* see glycemic control targets and glucose monitoring chapter for further details

Education

- Ongoing structured individualized education for those identified with islet autoantibodies 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 children and young people 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 identified with islet autoantibodies, ongoing structured individualized education is recommended to improve risk perception and prevent DKA at diagnosis [42-44]. 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 parents 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 [95]. Education not only imparts factual knowledge, but also supports parents psychologically in coping with the often unexpected, elevated risk or diagnosis. The ADA standards for diabetes self-management education and support (DSMES) and the ISPAD guidelines [96, 97] can be used to guide education for individuals with Stage 1 and 2 T1D. However, age, rate of progression and family dynamics should inform education topics and determine 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 [98]. 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 for each child and family.

Psychological Burden of Screening

- Positive genetic and islet autoantibody screening results in children may be associated with parental stress, depressive symptoms, anxiety and diabetes-specific sorrow. [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]

Screening for early stage T1D can engender anxiety in children and parents and imposes the burden of monitoring prior to insulin requirement. Positive genetic and islet autoantibody screening results are associated with parental stress, depressive symptoms, and anxiety [7, 47, 70, 71, 99, 100], particularly in mothers [7, 100], which improve rapidly within 3-12 months [7, 99]. In programs utilizing genetic screening, the majority of those at high-risk will never develop T1D [16, 20], and in those with early-stage T1D, the latency period before progression to clinically-evident condition may last for years [73]; all of these factors must be considered when considering the psychological burdens of screening.

Research programs that have followed children both at high genetic risk and those identified through islet autoantibody surveillance programs report reduced stress in children and their parents at the time of Stage 3 diagnosis compared to non-screened controls recently diagnosed with Stage 3 diabetes [7]. The Fr1da study showed that initial stress scores in those developing stage 3 T1D were halved in families of screened vs non-screened children [7]. These findings are likely explained by the high rates of depression and parenting stress when Stage 3 T1D is unexpected and diagnosis requires urgent

insulin initiation and rapid assimilation of unfamiliar information [101, 102].

The degree and duration of psychological burden in children and parents who continue to undergo glycemic surveillance without developing Stage 3 T1D for some years and in those who drop out of follow up remains uncertain. Nevertheless, it has been reported that parents' depressive and anxiety symptoms decline with time, whereas diabetes-specific anxiety and sorrow seem to persist longer and vary depending on the development of the autoimmune process [48, 70, 71]. Additionally, members of certain vulnerable groups-ethnic minorities with eventual linguistic and educational gaps or parents with a history of depression may respond with greater depressive and anxiety symptoms [48, 70, 71]. Outcomes in children with Stage 3 T1D are strongly influenced by their parents' mental health and coping with the condition [103, 104]. As such, there is a need for psychosocial support to be integrated into the clinical follow up of children with Stage 2 T1D. In addition, efforts should be made to identify and provide customized support for highly stressed parents and children at any stage.

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 for screening, education and glycemic surveillance programs. [20, 56] Cost-effectiveness analyses in the US for islet autoantibody-only screening suggest it can be cost-effective with a 20% reduction in DKA at diagnosis and a 0.1% (1.1mmol/mol) reduction in HbA1c over a lifetime [105, 106]. New autoantibody measurement techniques, such as multiplex electrochemiluminescence assays need less 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, 56]. 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.

In some, but not all lower-resource countries, islet autoimmunity 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, add 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 have 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 an 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 (Supplementary table 1). 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 β-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, imatinib, and baricitinib [117-122] (Supplementary 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 at 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 US, 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-day intravenous infusion course compared to the placebo group [115, 126, 128, 129].

Challenges with teplizumab use include its limited availability for Stage 2 T1D due to small number of individuals, 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 use of Teplizumab in clinical practice [130].

It is important to note that the clinical trial that led to the U.S. FDA approval for teplizumab enrolled only 44 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 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 individuals 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. 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 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 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.

Conflicts of interest:

Michael Haller – Scientific Advisory Board: SAB BIO, Consultant: Sanofi, Mannkind

Cate Speake – participation ton an immunology advisory board for Vertex Pharmaceuticals

Kristine Bell- no conflict of interest

Rachel Besser – independent consultant/advisor to PreventBio

Anette-Gabriele Ziegler consultancy for pharmaceutical company

Helena Elding Larsson, Mustafa Tosur, Laura Jacobsen, Francesca Ulivi, Karin Lange, Tal Oron, Loredana Marcovecchio Diane K Wherrett- none

References

1. Ziegler, A.G., et al., *Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children*. Jama, 2013. **309**(23): p. 2473-9.
2. Krischer, J.P., et al., *The 6 year incidence of diabetes-associated autoantibodies in genetically at-risk children: the TEDDY study*. Diabetologia, 2015. **58**(5): p. 980-7.
3. Bingley, P.J., D.C. Boulware, and J.P. Krischer, *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): p. 542-9.
4. Anand, V., 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): p. 2269-76.
5. Allen, C., M. Palta, and D.J. D'Alessio, *Risk of diabetes in siblings and other relatives of IDDM subjects*. Diabetes, 1991. **40**(7): p. 831-6.
6. Dahlquist, G., et al., *The epidemiology of diabetes in Swedish children 0-14 years--a six-year prospective study*. Diabetologia, 1985. **28**(11): p. 802-8.
7. Ziegler, A.G., et al., *Yield of a Public Health Screening of Children for Islet Autoantibodies in Bavaria, Germany*. Jama, 2020. **323**(4): p. 339-351.
8. Parkkola, A., et al., *Extended family history of type 1 diabetes and phenotype and genotype of newly*

- diagnosed children.* Diabetes Care, 2013. **36**(2): p. 348-54.
9. Ziegler, A.G., 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): p. 255-262.
 10. Robertson, C.C., 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): p. 962-971.
 11. Lambert, A.P., 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): p. 4037-43.
 12. Nguyen, C., et al., *Definition of high-risk type 1 diabetes HLA-DR and HLA-DQ types using only three single nucleotide polymorphisms.* Diabetes, 2013. **62**(6): p. 2135-40.
 13. Noble, J.A., et al., *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): p. 1134-48.
 14. Erlich, H., 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): p. 1084-92.
 15. Hippich, M., 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): p. 847-857.
 16. Bonifacio, E., 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): p. e1002548.
 17. Aly, T.A., et al., *Extreme genetic risk for type 1A diabetes.* Proc Natl Acad Sci U S A, 2006. **103**(38): p. 14074-9.
 18. Laine, A.P., et al., *Non-HLA Gene Polymorphisms in the Pathogenesis of Type 1 Diabetes: Phase and Endotype Specific Effects.* Front Immunol, 2022. **13**: p. 909020.
 19. Pociot, F., et al., *A nationwide population-based study of the familial aggregation of type 1 (insulin-independent) diabetes mellitus in Denmark. Danish Study Group of Diabetes in Childhood.* Diabetologia, 1993. **36**(9): p. 870-5.
 20. Sharp, S.A., 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): p. 200-207.
 21. Winkler, C., et al., *Feature ranking of type 1 diabetes susceptibility genes improves prediction of type 1 diabetes.* Diabetologia, 2014. **57**(12): p. 2521-9.
 22. Redondo, M.J., 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): p. 1887-1894.
 23. Onengut-Gumuscu, S., et al., *Type 1 Diabetes Risk in African-Ancestry Participants and Utility of an Ancestry-Specific Genetic Risk Score.* Diabetes Care, 2019. **42**(3): p. 406-415.
 24. Patel, K.A., et al., *Type 1 Diabetes Genetic Risk Score: A Novel Tool to Discriminate Monogenic and Type 1 Diabetes.* Diabetes, 2016. **65**(7): p. 2094-2099.
 25. Perry, D.J., 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): p. 4529.
 26. Bonifacio, E., et al., *An Age-Related Exponential Decline in the Risk of Multiple Islet Autoantibody Seroconversion During Childhood.* Diabetes Care, 2021.
 27. Hoffmann, V.S., 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): p. 125.
 28. Krischer, J.P., 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): p. 2247-2257.
 29. Beyerlein, A., 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): p. 602-605.
 30. Bonifacio, E., et al., *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): p. 403-11.
 31. Fourlanos, S., 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): p. 1546-9.
32. Penno, M.A., 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**: p. 124.
33. Kim, K.W., 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): p. 271-279.
34. Oakey, H., 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): p. 2198255.
35. Johnson, S.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): p. 591-602.
36. Bosi, E. and C. Catassi, *Screening type 1 diabetes and celiac disease by law.* Lancet Diabetes Endocrinol, 2024. **12**(1): p. 12-14.
37. Megan Herr, J.K. *New ICD-10 codes for severity of hypoglycemia.* 2024 April 10th, 2024 10.07.24]; Available from: <https://pbn.decisionhealth.com/Blogs/DetailPrint.aspx?id=201085>.
38. [cited 2024 22/05/2024]; Available from: <https://www.birmingham.ac.uk/news/2024/launch-of-new-international-medical-code-for-presymptomatic-type-1-diabetes>.
39. Barker, J.M., et al., *Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up.* Diabetes Care, 2004. **27**(6): p. 1399-404.
40. Hekkala, A.M., et al., *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): p. 314-319.
41. Winkler, C., et al., *Markedly reduced rate of diabetic ketoacidosis at onset of type 1 diabetes in relatives screened for islet autoantibodies.* Pediatr Diabetes, 2012. **13**(4): p. 308-13.
42. Hummel, S., et al., *Children diagnosed with presymptomatic type 1 diabetes through public health screening have milder diabetes at clinical manifestation.* Diabetologia, 2023. **66**(9): p. 1633-1642.
43. Hummel, S., et al., *Presymptomatic type 1 diabetes and disease severity at onset. Reply to Schneider J, Gemulla G, Kiess W et al [letter].* Diabetologia, 2023. **66**(12): p. 2389-2390.
44. Schneider, J., et al., *Presymptomatic type 1 diabetes and disease severity at onset.* Diabetologia, 2023. **66**(12): p. 2387-2388.
45. Fredheim, S., et al., *Diabetic ketoacidosis at the onset of type 1 diabetes is associated with future HbA1c levels.* Diabetologia, 2013. **56**(5): p. 995-1003.
46. Duca, L.M., et al., *Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes Predicts Poor Long-term Glycemic Control.* Diabetes Care, 2017. **40**(9): p. 1249-1255.
47. Smith, L.B., 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): p. 1025-1033.
48. O'Donnell, H.K., 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): p. 2155-2161.
49. Kao, K.T., et al., *Incidence Trends of Diabetic Ketoacidosis in Children and Adolescents with Type 1 Diabetes in British Columbia, Canada.* J Pediatr, 2020. **221**: p. 165-173 e2.
50. Ampt, A., et al., *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): p. 901-908.
51. Rabbone, I., 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): p. 363-366.
52. Cortez, F.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): p. e0242049.
53. Liberati, D., et al., *A novel LIPS assay for insulin autoantibodies.* Acta Diabetol, 2018. **55**(3): p. 263-270.
54. Naredi Scherman, M., 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**: p. 1386513.
55. Hendriks, A.E.J., et al., *Clinical care advice for monitoring of islet autoantibody positive individuals with presymptomatic type 1 diabetes*. Diabetes Metab Res Rev, 2024. **40**(2): p. e3777.
56. Sims, E.K., et al., *Screening for Type 1 Diabetes in the General Population: A Status Report and Perspective*. Diabetes, 2022. **71**(4): p. 610-623.
57. Ghalwash, M., et al., *Two-age islet-autoantibody screening for childhood type 1 diabetes: a prospective cohort study*. Lancet Diabetes Endocrinol, 2022. **10**(8): p. 589-596.
58. Ghalwash, M., 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): p. 261-268.
59. Alonso, G.T., et al., *Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes in Colorado Children, 2010-2017*. Diabetes Care, 2020. **43**(1): p. 117-121.
60. Dabelea, D., et al., *Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study*. Pediatrics, 2014. **133**(4): p. e938-45.
61. Ziegler, A.G., 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): p. e028578.
62. Ferrat, L.A., et al., *A combined risk score enhances prediction of type 1 diabetes among susceptible children*. Nat Med, 2020. **26**(8): p. 1247-1255.
63. Hommel, A., et al., *Screening for Type 1 Diabetes Risk in Newborns: The Freder1k Pilot Study in Saxony*. Horm Metab Res, 2018. **50**(1): p. 44-49.
64. Ziegler, A.G., 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): p. e052449.
65. Phillip, M., et al., *Consensus Guidance for Monitoring Individuals With Islet Autoantibody-Positive Pre-Stage 3 Type 1 Diabetes*. Diabetes Care, 2024.
66. Weiss, A., et al., *Progression likelihood score identifies substages of presymptomatic type 1 diabetes in childhood public health screening*. Diabetologia, 2022. **65**(12): p. 2121-2131.
67. Krischer, J.P., 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): p. 2271-2281.
68. So, M., et al., *Characterising the age-dependent effects of risk factors on type 1 diabetes progression*. Diabetologia, 2022. **65**(4): p. 684-694.
69. Chmiel, R., et al., *Progression from single to multiple islet autoantibodies often occurs soon after seroconversion: implications for early screening*. Diabetologia, 2015. **58**(2): p. 411-3.
70. Houben, J., 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): p. 1707-1716.
71. Johnson, S.B. and L.B. Smith, *General Population Screening for Islet Autoantibodies: Psychosocial Challenges*. Diabetes Care, 2023. **46**(12): p. 2123-2125.
72. Elding Larsson, H., 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): p. 2347-52.
73. Insel, R.A., 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): p. 1964-74.
74. Sosenko, J.M., et al., *Incident dysglycemia and progression to type 1 diabetes among participants in the Diabetes Prevention Trial-Type 1*. Diabetes Care, 2009. **32**(9): p. 1603-7.
75. Sosenko, J.M., 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): p. 979-84.
76. Sosenko, J.M., 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): p. 271-6.
77. Sosenko, J.M., et al., *The development, validation, and utility of the Diabetes Prevention Trial-Type 1*

- Risk Score (DPTRS).* Curr Diab Rep, 2015. **15**(8): p. 49.
78. Simmons, K.M., 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).
79. Bediaga, N.G., et al., *Simplifying prediction of disease progression in pre-symptomatic type 1 diabetes using a single blood sample.* Diabetologia, 2021. **64**(11): p. 2432-2444.
80. Helminen, O., et al., *OGTT and random plasma glucose in the prediction of type 1 diabetes and time to diagnosis.* Diabetologia, 2015. **58**(8): p. 1787-96.
81. Sosenko, J.M., 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): p. 940-2.
82. Driscoll, K.A., 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): p. 360-368.
83. Helminen, O., et al., *HbA1c Predicts Time to Diagnosis of Type 1 Diabetes in Children at Risk.* Diabetes, 2015. **64**(5): p. 1719-27.
84. Vehik, K., 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): p. 2342-2349.
85. Salami, F., 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): p. 1586-1593.
86. *2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes-2024.* Diabetes Care, 2024. **47**(Suppl 1): p. S20-s42.
87. Vehik, K., et al., *Performance of HbA1c as an early diagnostic indicator of type 1 diabetes in children and youth.* Diabetes Care, 2012. **35**(9): p. 1821-5.
88. Steck, A.K., et al., *Continuous Glucose Monitoring Predicts Progression to Diabetes in Autoantibody Positive Children.* J Clin Endocrinol Metab, 2019. **104**(8): p. 3337-3344.
89. Steck, A.K., et al., *CGM Metrics Predict Imminent Progression to Type 1 Diabetes: Autoimmunity Screening for Kids (ASK) Study.* Diabetes Care, 2022. **45**(2): p. 365-371.
90. Wilson, D.M., et al., *CGM Metrics Identify Dysglycemic States in Participants From the TrialNet Pathway to Prevention Study.* Diabetes Care, 2023. **46**(3): p. 526-534.
91. Kontola, H., et al., *Exploring Minimally Invasive Approach to Define Stages of Type 1 Diabetes Remotely.* Diabetes Technol Ther, 2022. **24**(9): p. 655-665.
92. Montaser, E., et al., *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): p. 631-642.
93. Priya, M., 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): p. 586-91.
94. Dunseath, G.J., et al., *Performance evaluation of a self-administered home oral glucose tolerance test kit in a controlled clinical research setting.* Diabet Med, 2019. **36**(7): p. 862-867.
95. Lange K, Z.A., . *Fr1da: Typ 1 Diabetes früh erkennen und gut behandeln.* 3. überarbeitete Auflage, Medtrix-Verlag Wiesbaden (Fr1da: Information brochure for parents and children – early diagnosis and care for children. GPPAD). 2023.
96. Davis, J., et al., *2022 National Standards for Diabetes Self-Management Education and Support.* Diabetes Care, 2022. **45**(2): p. 484-494.
97. Lindholm Olinder, A., et al., *ISPAD Clinical Practice Consensus Guidelines 2022: Diabetes education in children and adolescents.* Pediatr Diabetes, 2022. **23**(8): p. 1229-1242.
98. Kolb, L., *An Effective Model of Diabetes Care and Education: The ADCES7 Self-Care Behaviors™.* Sci Diabetes Self Manag Care, 2021. **47**(1): p. 30-53.
99. Johnson, S.B., et al., *My Child Is Islet Autoantibody Positive: Impact on Parental Anxiety.* Diabetes Care, 2017. **40**(9): p. 1167-1172.
100. Melin, J., et al., *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): p. 878-889.
101. Whittemore, R., et al., *Psychological experience of parents of children with type 1 diabetes: a systematic mixed-studies review.* Diabetes Educ, 2012. **38**(4): p. 562-79.
 102. de Wit, M., et al., *ISPAD Clinical Practice Consensus Guidelines 2022: Psychological care of children, adolescents and young adults with diabetes.* Pediatr Diabetes, 2022. **23**(8): p. 1373-1389.
 103. Silina, E., M. Taube, and M. Zolovs, *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).
 104. Trojanowski, P.J., et al., *Parenting and Psychological Health in Youth with Type 1 Diabetes: Systematic Review.* J Pediatr Psychol, 2021. **46**(10): p. 1213-1237.
 105. McQueen, R.B., et al., *Cost and Cost-effectiveness of Large-scale Screening for Type 1 Diabetes in Colorado.* Diabetes Care, 2020. **43**(7): p. 1496-1503.
 106. Karl, F.M., et al., *Costs of Public Health Screening of Children for Presymptomatic Type 1 Diabetes in Bavaria, Germany.* Diabetes Care, 2022. **45**(4): p. 837-844.
 107. Gu, Y., et al., *High-throughput multiplexed autoantibody detection to screen type 1 diabetes and multiple autoimmune diseases simultaneously.* EBioMedicine, 2019. **47**: p. 365-372.
 108. Fawwad, A., et al., *Clinical features, biochemistry and HLA-DRB1 status in youth-onset type 1 diabetes in Pakistan.* Diabetes Res Clin Pract, 2019. **149**: p. 9-17.
 109. Ibrahim, T.A.M., et al., *Clinical features, biochemistry, and HLA-DRB1 status in youth-onset type 1 diabetes in Sudan.* Pediatr Diabetes, 2021. **22**(5): p. 749-757.
 110. Zabeen, B., et al., *Clinical features, biochemistry and HLA-DRB1 status in children and adolescents with diabetes in Dhaka, Bangladesh.* Diabetes Res Clin Pract, 2019. **158**: p. 107894.
 111. Ahmadov, G.A., 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**: p. 252-259.
 112. Jacobsen, L.M., et al., *Comparing Beta Cell Preservation Across Clinical Trials in Recent-Onset Type 1 Diabetes.* Diabetes Technol Ther, 2020. **22**(12): p. 948-953.
 113. Nguyen, H.V., et al., *Cost-Effectiveness of Low-Dose Antithymocyte Globulin Versus Other Immunotherapies for Treatment of New-Onset Type 1 Diabetes.* Diabetes Technol Ther, 2022. **24**(4): p. 258-267.
 114. *An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes.* N Engl J Med, 2020. **382**(6): p. 586.
 115. Sims, E.K., et al., *Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals.* Sci Transl Med, 2021. **13**(583).
 116. Dayan, C.M., et al., *Changing the landscape for type 1 diabetes: the first step to prevention.* Lancet, 2019. **394**(10205): p. 1286-1296.
 117. Herold, K.C., 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): p. 3766-74.
 118. Orban, T., 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): p. 412-9.
 119. Haller, M.J., et al., *Low-Dose Anti-Thymocyte 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): p. 1267-1276.
 120. Quattrin, T., et al., *Golimumab and Beta-Cell Function in Youth with New-Onset Type 1 Diabetes.* N Engl J Med, 2020. **383**(21): p. 2007-2017.
 121. Rigby, M.R., et al., *Alefacept provides sustained clinical and immunological effects in new-onset type 1 diabetes patients.* J Clin Invest, 2015. **125**(8): p. 3285-96.
 122. Warshauer, J.T., J.A. Bluestone, and M.S. Anderson, *New Frontiers in the Treatment of Type 1 Diabetes.* Cell Metab, 2020. **31**(1): p. 46-61.

123. Taylor, P.N., 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): p. 915-925.
124. Ramos, E.L., et al., *Teplizumab and β -Cell Function in Newly Diagnosed Type 1 Diabetes*. N Engl J Med, 2023.
125. Oram, R.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): p. 1124-1131.
126. Herold, K.C., et al., *Teplizumab: A Disease-Modifying Therapy for Type 1 Diabetes That Preserves β -Cell Function*. Diabetes Care, 2023. **46**(10): p. 1848-1856.
127. Herold, K.C., et al., *An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes*. N Engl J Med, 2019. **381**(7): p. 603-613.
128. MEDICATION GUIDE TZIELD™ (TEE-zeeld) (teplizumab-mzwv) injection, for intravenous use. 2022 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761183s000lbl.pdf]. 2022 01/29/2024]; Available from:
129. Sclafani, J. *FDA APPROVES TEPLIZUMAB TO DELAY ONSET OF TYPE 1 DIABETES*. 2022 01/29/2024]; Available from: <https://beyondtype1.org/teplizumab-fda-approval-2/>.
130. Mehta, S., et al., *Pediatric Endocrine Society Statement on Considerations for Use of Teplizumab (Tzield™) in Clinical Practice*. Horm Res Paediatr, 2024: p. 1-12.
131. Foster, T.P., et al., *Low-Dose Antithymocyte Globulin: A Pragmatic Approach to Treating Stage 2 Type 1 Diabetes*. Diabetes Care, 2024. **47**(2): p. 285-289.
132. Knip, M., et al., *Hydrolyzed infant formula and early β -cell autoimmunity: a randomized clinical trial*. Jama, 2014. **311**(22): p. 2279-87.
133. Hummel, S., et al., *Primary dietary intervention study to reduce the risk of islet autoimmunity in children at increased risk for type 1 diabetes: the BABYDIET study*. Diabetes Care, 2011. **34**(6): p. 1301-5.
134. Vaarala, O., et al., *Removal of Bovine Insulin From Cow's Milk Formula and Early Initiation of Beta-Cell Autoimmunity in the FINDIA Pilot Study*. Arch Pediatr Adolesc Med, 2012. **166**(7): p. 608-14.
135. Bonifacio, E., et al., *Effects of high-dose oral insulin on immune responses in children at high risk for type 1 diabetes: the Pre-POINT randomized clinical trial*. Jama, 2015. **313**(15): p. 1541-9.
136. Assfalg, R., et al., *Oral insulin immunotherapy in children at risk for type 1 diabetes in a randomised controlled trial*. Diabetologia, 2021. **64**(5): p. 1079-1092.
137. *Effects of insulin in relatives of patients with type 1 diabetes mellitus*. N Engl J Med, 2002. **346**(22): p. 1685-91.
138. Skyler, J.S., et al., *Effects of oral insulin in relatives of patients with type 1 diabetes: The Diabetes Prevention Trial--Type 1*. Diabetes Care, 2005. **28**(5): p. 1068-76.
139. Näntö-Salonen, K., et al., *Nasal insulin to prevent type 1 diabetes in children with HLA genotypes and autoantibodies conferring increased risk of disease: a double-blind, randomised controlled trial*. Lancet, 2008. **372**(9651): p. 1746-55.
140. Krischer, J.P., et al., *Effect of Oral Insulin on Prevention of Diabetes in Relatives of Patients With Type 1 Diabetes: A Randomized Clinical Trial*. Jama, 2017. **318**(19): p. 1891-1902.
141. Gale, E.A., et al., *European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes*. Lancet, 2004. **363**(9413): p. 925-31.
142. Harrison, L.C., et al., *Pancreatic beta-cell function and immune responses to insulin after administration of intranasal insulin to humans at risk for type 1 diabetes*. Diabetes Care, 2004. **27**(10): p. 2348-55.
143. Jacobsen, L.M. and D.A. Schatz, *Insulin immunotherapy for pretype 1 diabetes*. Curr Opin Endocrinol Diabetes Obes, 2021. **28**(4): p. 390-396.
144. Vandemeulebroucke, E., et al., *Insulin treatment in IA-2A-positive relatives of type 1 diabetic patients*. Diabetes Metab, 2009. **35**(4): p. 319-27.

145. Carel, J.C., P. Landais, and P. Bougnères, *Therapy to prevent type 1 diabetes mellitus*. N Engl J Med, 2002. **347**(14): p. 1115-6.
146. Elding Larsson, H., et al., *Safety and efficacy of autoantigen-specific therapy with 2 doses of alum-formulated glutamate decarboxylase in children with multiple islet autoantibodies and risk for type 1 diabetes: A randomized clinical trial*. Pediatr Diabetes, 2018. **19**(3): p. 410-419.
147. *Hydroxychloroquine for Prevention of Abnormal Glucose Tolerance and Diabetes in Individuals At-risk for Type 1 Diabetes Mellitus (T1D)*. ClinicalTrials.gov Identifier: NCT03428945. Retrieved from <https://www.clinicaltrials.gov/ct2/show/record/NCT03428945>. 2018.
148. *CTLA4-Ig (Abatacept)for Prevention of Abnormal Glucose Tolerance and Diabetes in Relatives At -Risk for Type 1*. ClinicalTrials.gov Identifier: NCT01773707. Retrieved from <https://www.clinicaltrials.gov/ct2/show/NCT01773707>. 2013.
149. *Fr1da-/Fr1da-Plus-Study in Bavaria: Early Detection for Early Care of Type 1 Diabetes (Fr1da-Plus)*. ClinicalTrials.gov Identifier: NCT04039945. <https://clinicaltrials.gov/ct2/show/NCT04039945>.
150. Russell, W.E., et al., *Abatacept for Delay of Type 1 Diabetes Progression in Stage 1 Relatives at Risk: A Randomized, Double-Masked, Controlled Trial*. Diabetes Care, 2023. **46**(5): p. 1005-1013.
151. Pescovitz, M.D., et al., *B-lymphocyte depletion with rituximab and β-cell function: two-year results*. Diabetes Care, 2014. **37**(2): p. 453-9.
152. Pescovitz, M.D., et al., *Rituximab, B-lymphocyte depletion, and preservation of beta-cell function*. N Engl J Med, 2009. **361**(22): p. 2143-52.
153. Sherry, N., et al., *Teplizumab for treatment of type 1 diabetes (Protégé study): 1-year results from a randomised, placebo-controlled trial*. Lancet, 2011. **378**(9790): p. 487-97.
154. Hagopian, W., et al., *Teplizumab preserves C-peptide in recent-onset type 1 diabetes: two-year results from the randomized, placebo-controlled Protégé trial*. Diabetes, 2013. **62**(11): p. 3901-8.
155. Rigby, M.R., et al., *Targeting of memory T cells with alefacept in new-onset type 1 diabetes (T1DAL study): 12 month results of a randomised, double-blind, placebo-controlled phase 2 trial*. Lancet Diabetes Endocrinol, 2013. **1**(4): p. 284-94.
156. Greenbaum, C.J., et al., *IL-6 receptor blockade does not slow β cell loss in new-onset type 1 diabetes*. JCI Insight, 2021. **6**(21).
157. *Safety and Efficacy of CLBS03 in Adolescents With Recent Onset Type 1 Diabetes (The Sanford Project T-Rex Study)*. ClinicalTrials.gov Identifier: NCT02691247 Retrieved from <https://clinicaltrials.gov/ct2/show/results/NCT02691247>.
158. Orban, T., et al., *Reduction in CD4 central memory T-cell subset in costimulation modulator abatacept-treated patients with recent-onset type 1 diabetes is associated with slower C-peptide decline*. Diabetes, 2014. **63**(10): p. 3449-57.
159. Gitelman, S.E., et al., *Antithymocyte globulin therapy for patients with recent-onset type 1 diabetes: 2 year results of a randomised trial*. Diabetologia, 2016. **59**(6): p. 1153-61.
160. Haller, M.J., et al., *Low-Dose Anti-Thymocyte Globulin (ATG) Preserves β-Cell Function and Improves HbA(1c) in New-Onset Type 1 Diabetes*. Diabetes Care, 2018. **41**(9): p. 1917-1925.
161. Moran, A., et al., *Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicentre, randomised, double-blind, placebo-controlled trials*. Lancet, 2013. **381**(9881): p. 1905-15.
162. *Recent-Onset Type 1 Diabetes Trial Evaluating Efficacy and Safety of Teplizumab (PROTECT)*. ClinicalTrials.gov Identifier: NCT03875729 . Retrieved from <https://clinicaltrials.gov/ct2/show/NCT03875729>.
163. Wherrett, D.K., et al., *Antigen-based therapy with glutamic acid decarboxylase (GAD) vaccine in patients with recent-onset type 1 diabetes: a randomised double-blind trial*. Lancet, 2011. **378**(9788): p. 319-27.
164. Ludvigsson, J., et al., *GAD65 antigen therapy in recently diagnosed type 1 diabetes mellitus*. N Engl J Med, 2012. **366**(5): p. 433-42.
165. *Diamyd Administered Into Lymph Nodes in Individuals Recently Diagnosed With Type 1 Diabetes*,

- Carrying the HLA DR3-DQ2 Haplotype (DIAGNODE-3). ClinicalTrials.gov Identifier: NCT05018585. Retrieved from <https://clinicaltrials.gov/ct2/show/NCT05018585>.*
166. *Study of Safety and Efficacy of CFZ533 in Type 1 Diabetes Pediatric and Young Adult Subjects (CCFZ533X2207). ClinicalTrials.gov Identifier: NCT04129528. Retrieved from <https://clinicaltrials.gov/ct2/show/NCT04129528>.*
167. Gitelman, S.E., et al., *Antithymocyte globulin treatment for patients with recent-onset type 1 diabetes: 12-month results of a randomised, placebo-controlled, phase 2 trial.* Lancet Diabetes Endocrinol, 2013. **1**(4): p. 306-16.
168. Waibel, M., et al., *Baricitinib and β -Cell Function in Patients with New-Onset Type 1 Diabetes.* N Engl J Med, 2023. **389**(23): p. 2140-2150.
169. Krogvold, L., et al., *Pleconaril and ribavirin in new-onset type 1 diabetes: a phase 2 randomized trial.* Nat Med, 2023. **29**(11): p. 2902-2908.
170. Forlenza, G.P., et al., *Effect of Verapamil on Pancreatic Beta Cell Function in Newly Diagnosed Pediatric Type 1 Diabetes: A Randomized Clinical Trial.* Jama, 2023. **329**(12): p. 990-999.
171. Boughton, C.K., et al., *Closed-Loop Therapy and Preservation of C-Peptide Secretion in Type 1 Diabetes.* N Engl J Med, 2022. **387**(10): p. 882-893.
172. McVean, J., et al., *Effect of Tight Glycemic Control on Pancreatic Beta Cell Function in Newly Diagnosed Pediatric Type 1 Diabetes: A Randomized Clinical Trial.* Jama, 2023. **329**(12): p. 980-989.
173. Martin, A., et al., *A randomized trial of oral gamma aminobutyric acid (GABA) or the combination of GABA with glutamic acid decarboxylase (GAD) on pancreatic islet endocrine function in children with newly diagnosed type 1 diabetes.* Nat Commun, 2022. **13**(1): p. 7928.
174. Lagarde, W.H., et al., *Human plasma-derived alpha(1) -proteinase inhibitor in patients with new-onset type 1 diabetes mellitus: A randomized, placebo-controlled proof-of-concept study.* Pediatr Diabetes, 2021. **22**(2): p. 192-201.

Supplementary material

Supplementary table 1: Primary [61, 64, 132-136] and Secondary [115, 127, 137-150] Prevention Trials in Pre-T1D and Intervention [117-120, 124, 151-174] Trials in New Onset Stage 3 T1D

Trial	Route	Intervention	Population	Primary Outcome Assessment	Outcome Achieved
Primary Prevention					
FINDIA	PO	Bovine insulin-free formula	Genetically at-risk infants	Islet autoimmunity	Successful
Pre-POInT	PO	Insulin	Relative, HLA risk, AAb-, 3-7y	AAb and T cell responses	Successful
POInT	PO	Insulin	Relative, HLA risk, AAb-, 4-7m	Islet autoimmunity	Ongoing
SINT1A	PO	<i>B. Infantis</i> probiotic	Relative, genetic risk, 7d-6wk	Islet autoimmunity	Ongoing
TRIGR	PO	Hydrolyzed casein formula	Relative, genetically at-risk infants,	Stage 3	Unsuccessful
BABYDIET	PO	Late gluten exposure	Genetically at-risk infants	Islet autoimmunity	Unsuccessful
Pre-POInT-early	PO	Insulin	Relative, HLA risk, AAb-, 6m-2y	AAb and T cell responses	Unsuccessful*
Secondary Prevention					
TN-10	IV	Teplizumab	Stage 2, 8-45y	Stage 3	Successful
Fr1da	PO	Insulin	Stage 1, 2-12y	Immune responders then Stage 2/3	Ongoing
TN-28	IV	Low-dose ATG	Stage 2 + Presence of one high risk marker, 12-34y	Stage 3	Ongoing

<i>ENDIT</i>	PO	Nicotinamide	Relative, ICA+, optimal OGTT	Stage 3	Unsuccessful
<i>DPT-1</i>	IV/ SC	Insulin	Relative, ICA+, IAA+, FPIR below threshold, 3-45y	Stage 3	Unsuccessful
<i>DPT-1</i>	PO	Insulin	Relative, ICA+, IAA+, FPIR above threshold, 3-45y	Stage 3	Unsuccessful*
<i>DIPP</i>	IN	Insulin	HLA risk, ≥2 AAb+ 1, 1-15y	Stage 3	Unsuccessful
<i>INIT-I</i>	IN	Insulin	Relative, ≥1 Ab, optimal FPIR, 4-32y	FPIR change	Unsuccessful
<i>INIT-II</i>	IN	Insulin	Relative, Stage 1, FPIR above threshold, 4-30y	Stage 3	Unsuccessful
<i>Belgian Registry</i>	SC	Insulin	Relative, IA-2A+, 5-40y	Stage 3	Unsuccessful
<i>EPPSCIT</i>	SC	Insulin	Relative, ≥2 AAb, 7-14y	Stage 3	Unsuccessful
<i>TN-07</i>	PO	Insulin	Relative, Stage 1 (IAA+ required), 3-45y	Stage 3	Unsuccessful*
<i>DiAPREV-IT</i>	SC	GAD	Stage 1 (GADA+ required), 4-17y	Stage 3	Unsuccessful
<i>TN-18</i>	IV	Abatacept	Stage 1, 6-45y	Stage 2 or Stage 3	Unsuccessful
<i>TN-22</i>	PO	Hydroxy-chloroquine	Stage 1, 3-45y	Stage 2 or 3	Unsuccessful
<i>Intervention</i>					
<i>TN-05</i>	IV	Rituximab	Stage 3, new onset, 8-40y	AUC C-peptide	Successful
<i>AbATE</i>	IV	Teplizumab	Stage 3, new onset, 8-30y	AUC C-peptide	Successful
<i>PROTECT</i>	IV	Teplizumab	Stage 3, new onset, 8-	AUC C-	Successful

			17y	peptide	
<i>Anti-CD3</i>	IV	Otelixizumab	Stage 3, new onset, 16-27 y	AUC C-peptide	Successful
<i>Protégé</i>	IV	Teplizumab	Stage 3, new onset, 8-35y	Insulin dose+HbA1c	Unsuccessful*
<i>TN-09</i>	IV	Abatacept	Stage 3, new onset, 6-45y	AUC C-peptide	Successful
<i>TN-19</i>	IV	Low-dose ATG	Stage 3, new onset, 12-45y	AUC C-peptide	Successful
<i>T1GER</i>	SC	Golimumab	Stage 3, new onset, 6-21y	AUC C-peptide	Successful
<i>BANDIT</i>	PO	Baricitinib	Stage 3, new onset, 10-30 y	AUC C-peptide	Successful
<i>DiViD Intervention</i>	PO	Pleconaril and ribavirin	Stage 3, new onset, 6-15 y	AUC C-peptide	Successful
<i>CLVer</i>	PO	Verapamil	Stage 3, new onset, 7-17y	AUC C-peptide	Successful
<i>DIAGNODE -3</i>	IL	GAD	Stage 3, ≤6 months duration, 12-28y	AUC C-peptide	Ongoing
<i>JAKPOT T1D (TN31)</i>	PO	Ritlecitinib and Abrocitinib	Stage 3, new onset, 12-35 y	AUC C-peptide	Ongoing
<i>Abatacept and Insulin</i>	SC + inhalation	Abatacept and nasal insulin	Stage 3, new onset, 6-21 y	AUC C-peptide	Ongoing
<i>UST1D2</i>	IV	Ustekinumab	Stage 3, new onset, 18-35y	AUC C-peptide	Ongoing
<i>RELAY (TN25)</i>	IV	Rituximab + Abatacept vs. Rituximab alone	Stage 3, new onset, 8-45 y	AUC C-peptide	Ongoing
<i>Repeat BCG Vaccination</i>	IM	BCG vaccination	Stage 3, new onset, 8-18y	HbA1c	Ongoing
<i>GLADIATOR</i>	PO	Ladarixin	Stage 3, new onset, 14-45	AUC C-peptide	Ongoing
<i>TADPOL</i>	PO	DFMO	Stage 3, new onset,	AUC C-peptide	Ongoing

			6-40 y		
<i>FABULINUS</i>	IC/SC	Frexalimab Anti-CD40L	Stage 3, new onset, 12-35 y	AUC C-peptide	Ongoing
<i>T1DAL</i>	IM	Alefacept	Stage 3, new onset, 12-35y	AUC C-peptide	Unsuccessful*
<i>EXTEND</i>	IV	Tocilizumab	Stage 3, new onset, 6-17y	AUC C-peptide	Unsuccessful
<i>T-Rex</i>	IV	Autologous Tregs	Stage 3, new onset, 8-17y	AUC C-peptide	Unsuccessful
<i>START</i>	IV	High-dose ATG	Stage 3, new onset, 12-35y	AUC C-peptide	Unsuccessful*
<i>TN-14</i>	SC	Canakinumab	Stage 3, new onset, 6-36y	AUC C-peptide	Unsuccessful
<i>TN-08</i>	SC	GAD	Stage 3, new onset, 3-45y	AUC C-peptide	Unsuccessful
<i>Diamyd</i>	SC	GAD	Stage 3, new onset, 10-20y	AUC C-peptide	Unsuccessful
<i>CLOuD</i>	SC	Hybrid Closed Loop Therapy	Stage 3, new onset, 10-16 y	AUC C-peptide	Unsuccessful
<i>CLVer</i>	SC	Automated insulin delivery	Stage 3, new onset, 7-17 y	AUC C-peptide	Unsuccessful
<i>GABA with/without GAD immunization</i>	PO +/- IM	GABA with/without GAD-alum	Stage 3, new onset, 4-18 y	Fasting and AUC C-peptide	Unsuccessful
<i>Alpha₁-proteinase inhibitor</i>	IV	Alpha ₁ -proteinase inhibitor	Stage 3, new onset, 6-35 y	AUC C-peptide	Unsuccessful

*post-hoc subpopulation response

HLA, human leukocyte antigen; AAb, autoantibody; AUC: area under the curve; y, years; m, months; PO, per os (oral); IV, intravenous; SC, subcutaneous; IN, intranasal; IM, intramuscular; IL, intra-lymphatic; FPIR, first-phase insulin response

Stage 1=multiple AAb-positive with optimal glucose tolerance (via OGTT); Stage 2=multiple AAb-positive with impaired glucose tolerance; Stage 3=clinical diagnosis of T1D