Received: 26 August 2022 | Accepted: 29 August 2022

DOI: 10.1111/pedi.13410

ISPAD GUIDELINES

ISPAD WILEY

ISPAD clinical practice consensus guidelines 2022: Stages of type 1 diabetes in children and adolescents

Rachel E. J. Besser[1] | Kirstine J. Bell[2] | Jenny J. Couper[3,4] | Anette-G. Ziegler[5] | Diane K. Wherrett[6] | Mikael Knip[7] | Cate Speake[8] | Kristina Casteels[9,10] | Kimberly A. Driscoll[11] | Laura Jacobsen[12] | Maria E. Craig[13] | Michael J. Haller[12]

[1]Wellcome Centre for Human Genetics, NIHR Biomedical Research Centre, University of Oxford, Oxford, UK

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

[3]Department of Pediatrics, University of Adelaide, South Australia, Australia

[4]Robinson Research Institute, University of Adelaide, Adelaide, Australia

[5]Institute of Diabetes Research, Helmholtz Zentrum München, and Forschergruppe Diabetes, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

[6]Division of Endocrinology, Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, Canada

[7]Children's Hospital, University of Helsinki, Helsinki, Finland

[8]Center for Interventional Immunology, Benaroya Research Institute at Virginia Mason, Seattle, Washington, USA

[9]Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium

[10]Department of Development and Regeneration, KU Leuven, Leuven, Belgium

[11]Department of Clinical and Health Psychology, University of Florida, Gainesville, Florida, USA

[12]Division of Endocrinology, Department of Pediatrics, University of Florida, Gainesville, Florida, USA

[13]Department of Pediatrics, The Children's Hospital at Westmead, University of Sydney, Sydney, Australia

Correspondence
Michael J. Haller, Pediatric Endocrinology, Department of Pediatrics, University of Florida Diabetes Institute, PO Box 100296, Gainesville, FL 32610, USA.
Email: hallemj@peds.ufl.edu

1 | INTRODUCTION

This guideline serves as an update to and replacement of the 2018 ISPAD consensus guideline on stages of type 1 diabetes (T1D). Herein, we provide an evidence-based summary of recommendations for screening children for T1D risk and discuss potential opportunities for clinical trials designed to delay progression to Stage 3 T1D and preserve beta cell function in those with Stage 3 disease. We again use the American Diabetes Association's metrics for grading evidence from A through E. We acknowledge that priorities may differ in low-income countries that may not be able to offer screening.

2 | WHAT IS NEW OR DIFFERENT

- Stages 1, 2, 3, and 4 T1D are being used in clinical, research, and regulatory settings.
- General population screening programs to determine T1D risk are expanding.
- Collaborative T1D networks testing interventions seeking to delay the disease process at all stages of disease are growing.
- Tools to predict T1D and response to interventions are improving.
- Anti-CD3 monoclonal antibody (teplizumab) is being evaluated by the U.S. Food and Drug Administration (FDA) for use to delay progression from Stage 2 to Stage 3 T1D.

The stages of type 1 diabetes (T1D) provide common ground for global efforts to prevent DKA and delay progression to disease in children and adolescents: An ISPAD consensus guideline.

Rachel E. J. Besser and Kirstine J. Bell contributed equally to these guidelines as co-first authors.

3 | EXECUTIVE SUMMARY: RECOMMENDATIONS AND PRINCIPLES

- Individuals with a first-degree relative with T1D have ~15-fold increased relative risk of developing T1D (A).
- Individuals with two or more islet autoantibodies and normoglycemia have stage 1 T1D (A).
- The vast majority (80 - 90%) of children with multiple islet autoantibodies progress to Stage 3 within 15 years, compared with ~15% who have a single islet autoantibody. Nearly 100% of children with multiple autoantibodies will ultimately progress to Stage 3 T1D (A).
- Progression rates are similar between individuals with a family history of T1D and those from the general population (A).
- Targeted screening and monitoring identifies individuals with Stage 1, Stage 2, and pre-symptomatic Stage 3 diabetes, reduces the incidence of diabetic ketoacidosis (DKA), reduces rates of hospitalization, and directs individuals toward studies seeking to delay or prevent ongoing beta cell loss (A).
- General population screening programs using combinations of genetic and autoantibody testing can identify high-risk children (A).
- Both general population and targeted screening should be coupled with education and monitoring programs for those identified with autoantibodies (B).
- Autoantibody screening at ages 2 and 6 years may provide for optimal sensitivity and positive predictive value in public health settings (B).
- When immunotherapies capable of delaying progression are approved by regulatory bodies and economic issues related to screening are optimized, general pediatric population screening for islet autoantibodies is expected to be implemented in many regions (E).
- Individuals who screen positive for genetic or immunological markers of T1D, whether identified through research or community-based screening programs, should have access to information regarding available prevention studies (E).
- An oral glucose tolerance test (OGTT) is recommended to stage disease in individuals with two or more islet autoantibodies prior to recruitment into prevention trials, and can be used to counsel individuals on risk of progression (E).
- Self-monitoring of blood glucose (SMBG), HbA1c, and continuous glucose monitoring (CGM) can be utilized to inform disease progression and may be considered where OGTT is impractical or not available (E).
- SMBG and CGM are simple measures that can be taught and provided to families allowing real-time information to prevent DKA (E).
- As screening programs expand, individuals with early and late Stage 2 and asymptomatic or symptomatic Stage 3 diabetes will be more commonly identified and additional sub-classifications or stages are likely to be adopted (e.g., Stage 3a [asymptomatic] or Stage 3b [symptomatic]) (E).

3.1 | Stages of T1D

T1D is characterized by four stages as shown in Figure 1.

Stage 1 Multiple islet autoantibodies, normal blood glucose, pre-symptomatic.

Stage 2 Multiple islet autoantibodies, abnormal glucose tolerance, usually pre-symptomatic.

Stage 3 Blood glucose above ADA diagnostic thresholds.

Stage 4 Established T1D.

A proportion of individuals who have increased genetic risk of T1D progress at variable rates to immune activation and the development of islet autoimmunity. The development of 2 or more islet autoantibodies (Stage 1), is typically followed by a period of pre-clinical dysglycemia (Stage 2), though this stage may not be detected in all individuals if progression is rapid. Individuals who develop Stage 3 T1D may be asymptomatic or symptomatic. Established T1D is described as Stage 4 T1D.

3.2 | Risk of T1D

Individuals with a first degree relative with T1D have an ~15-fold increased relative lifetime risk of T1D compared to the general population and the prevalence of T1D by age 20 years is ~5% compared to ~0.3%, respectively.[1–3] However ~85% of individuals with a new diagnosis do not have a family history of T1D.[4,5]

The various stages inform the risk of progression; children with a single islet autoantibody have a ~ 15% risk of reaching Stage 3 T1D within 10 years.[6] In contrast, children at Stage 1 have a 44% 5-year risk and 80≥90% 15-year risk of developing Stage 3 T1D, and children at Stage 2 have a 75% 5-year risk and a 100% lifetime risk of developing Stage 3 T1D.[6–9]

3.2.1 | 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-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 carrying HLA DR3-DQ2/DR4-DQ8 have a further increase in risk that reaches ~20%.[15,17] Additional risk provided by non-HLA risk genes is roughly equivalent to that provided by HLA DR-DQ alone.[16] The highest non-HLA genetic contribution arises from the *INS* and *PTPN22* genes.[18] These, and other risk regions, are included in polygenic risk scores that combine HLA and non-HLA genes to substantially improve risk estimates for islet autoimmunity and T1D, particularly in the general population.[16,19,20] Notably, the risk of developing islet autoimmunity

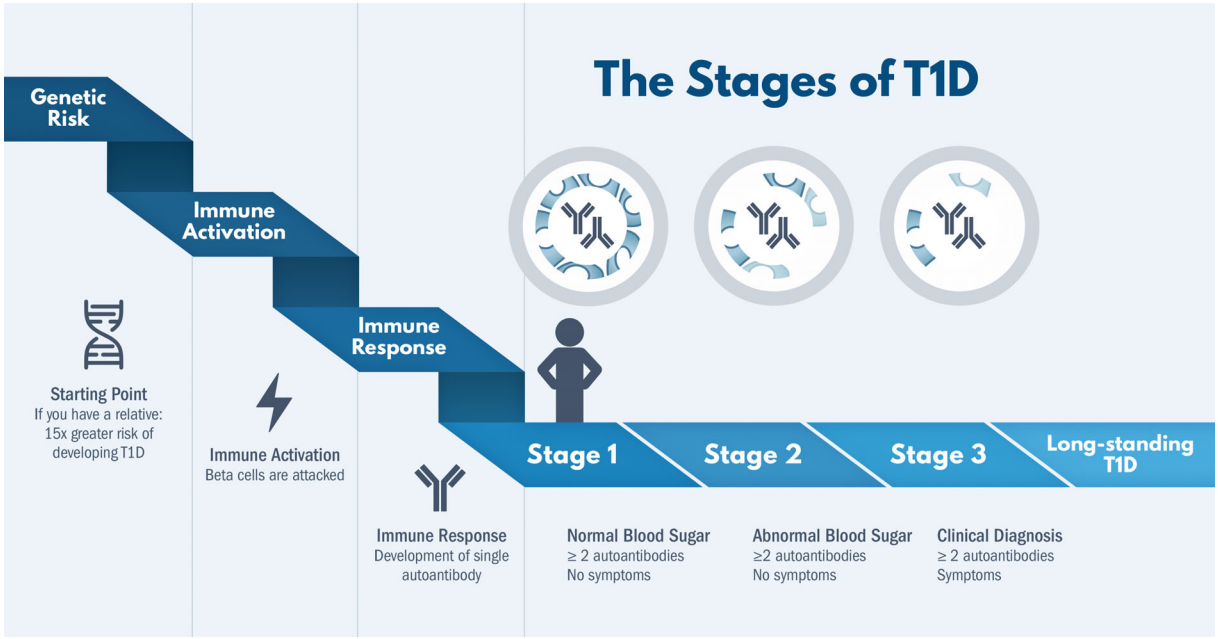

FIGURE 1 The stages of T1D (DiabetesTrialNet.org)

declines exponentially with age as does the influence of genetic factors, although there is a paucity of data in adults.[21–23] Furthermore, once a child develops multiple islet autoantibodies, HLA and polygenic risk scores have only limited further predictive value for stratifying the rate of progression to diabetes.[3,24–26]

3.2.2 | Environmental exposures

The increasing incidence of T1D globally coupled with a reduction in the proportion of individuals with the highest risk HLA haplotypes developing T1D, highlights the significant contribution environmental exposures play in the pathogenesis of T1D.[27] Different environmental exposures likely interact with multiple risk genes to drive the development of islet autoimmunity and the progression to Stage 3 T1D. Putative exposures are likely to vary across individuals and in combination with different gene—environment and environment—environment interactions. The impact of nutrition, growth, and infections and their interactions with the "omic" biological systems have been investigated in epidemiological studies and in at-risk cohorts, from birth, and more recently, from pregnancy.[28] The onset of islet autoimmunity from infancy implicates very early life exposures in some children.[28]

3.3 | Screening for pre-symptomatic T1D

Screening for risk of T1D is gaining international momentum. While the majority of screening programs remain within the context of research trials, implementation science programs in Europe, the United States, and Australia are actively demonstrating feasibility and acceptability.[29] In time, screening is likely to be embedded in local, regional, and national health systems as the standard of care. That said, optimal models for screening and staging for T1D remain unclear and will ultimately depend on several factors, including the screening objective, the structure of the local health care system, and available resources.

3.3.1 | Goals of screening

The long-term vision for T1D screening programs is to identify individuals at risk of, or with early-stage, T1D to offer them interventions to delay and, ultimately, prevent the condition. However, there are other important and currently achievable clinical benefits that drive current recommendations for screening, including to:

1. Prevent DKA and its associated short- and long-term morbidity and mortality.
2. Prepare children and families for a smoother transition to insulin therapy.
3. Advance preventative therapies through clinical trial recruitment.

Screening programs significantly reduce DKA rates, usually to less than 5%, and reduce hospitalization when coupled with long-term monitoring.[3,30–33] The rates of DKA at diagnosis range from 15% to 70% in Europe and North America and as high as 80% in under-resourced countries.[34–39] DKA prevention at diagnosis has potential lifelong benefits, including avoidance of acute morbidity (cerebral oedema, shock), neurocognitive impairment, and mortality.[40,41] There are also non-causal associations between DKA at onset and future risk of DKA,[38,42] severe hypoglycemia[42] and long-

term hyperglycemia[43–45] which increases the risk of serious future diabetes-related complications.[46] Furthermore, parental anxiety at diagnosis is approximately halved for children in screening programs compared to the general community.[3] The additional time provided for counseling, preparation for insulin therapy and education, delivered across time in the community or outpatient setting, may help reduce parental anxiety and smooth the transition to symptomatic T1D and insulin requirement.[3,47]

Screening also identifies children suitable for recruitment into clinical prevention trials, which include screening platforms such as T1D TrialNet, Type1Screen, Autoimmunity Screening for Kids (ASK), INNODIA and GPPAD (Global Platform for the Prevention of Diabetes).

3.3.2 | Target population for screening

Given the current inability to intervene effectively in the T1D disease process, international debate continues about whether screening should be population-wide or limited to first-degree family members. Notably, current evidence suggests that the rate of disease progression, once Stage 1 diabetes is confirmed, is not significantly different between individuals with a family member compared to the general population.[6,48] Routine screening for family members as part of clinical care has been proposed as an intermediate step toward general population screening.[49] However, as DKA rates are lower in individuals with a first-degree relative of T1D compared with those without[42,50] and the vast majority of individuals (at least 85%) who develop T1D do not have a family history of the disease, meaningful DKA prevention will ultimately require population-wide screening.[1,2,51]

3.3.3 | Screening modalities

There are currently two primary strategies used for T1D screening.

1. Population-wide islet autoantibody screening.
2. Genetic risk-stratified islet autoantibody screening.

Islet autoantibody screening aims to identify individuals in the target population with pre-symptomatic, Stage 1 or Stage 2 T1D. Advancements in islet autoantibody assays are enabling ultra-low blood volumes, including testing using capillary samples and dried bloodspots, which facilitate minimally invasive collection at home or in community settings.[52,53] Several groups have tried to determine optimal ages for performing autoantibody screening; modeled data from international cohort studies suggest the sensitivity of one-off autoantibody screening between the ages of 3–5 years is ~35% and can be improved to ~50% with repeated population screening at both 2–3 years and 5–7 years.[21,54] Notably, sampling from 2 years of age does not capture all children who will develop T1D and misses the small, but important, subset of infants and toddlers who rapidly develop T1D in the first 2 years of life and who have the highest rates of DKA with the greatest risk for associated morbidities.[36,37,55,56] Additional studies and analyses are needed to balance sensitivity, specificity, public health priorities, cost, and local resources when developing specific screening programs.

Genetic risk factors can be used to identify the subset of children with an increased risk of T1D who would benefit most from islet autoantibody screening. Such an approach[57,58] has also been used in GPPAD to efficiently identify children with the highest risk of developing T1D for prevention trials (e.g., in the Primary Oral Insulin Trial).[59]

Genetic risk can be broadly inferred through family history of T1D, as in T1D TrialNet, or assessed using a polygenic risk score in the general population. Some international programs, including GPPAD, evaluate polygenic risk scores from dried bloodspots collected as part of the existing Newborn Screening Program, thereby leveraging existing infrastructure and reducing the need for an additional screening intervention. As polygenic risk scores are a continuous scale, the threshold defining "at-risk" can be altered to suit the screening purpose. For example, lowering the threshold from the top 1% to the top 10% of infants by risk, reduces their risk of T1D from 10% to 2.4% but increases the number of future cases captured from ~30% to ~80%.[16,19] A high threshold may be considered more effective if the primary goal is to enroll children into prevention trials, while lower thresholds may be better suited to efforts prioritizing DKA prevention, because they capture a greater proportion of future cases.[36,38,55] Currently all polygenic risk scores for T1D have been developed using largely Caucasian datasets. While the incidence of T1D is higher in Caucasian individuals, a polygenic risk score that is either validated in or developed specifically for diverse ethnicities will be required for population-wide routine screening.[60]

3.3.4 | Follow-up in high genetic risk children

The optimal frequency of islet autoantibody testing in genetically high-risk individuals remains unclear. Clinical trials have utilized varying frequencies of antibody screening in high genetic risk children. Some efforts have screened every 3 months through 2 years of life (TEDDY), while some obtain annual antibodies, and others have proposed at least once between 1 and 5 years of age.[59,61–63] More frequent monitoring may be beneficial in infants and toddlers, given their rapid progression to Stage 3 T1D and increased risk of severe DKA. Nevertheless, the economic and psychological impacts of repeated screening must always be considered.[3,6]

3.3.5 | Glycemic surveillance in individuals with islet autoimmunity

Once a young person has multiple islet autoantibodies, they should be offered glycemic staging and ongoing monitoring to identify disease

progression. The intensity of those efforts should depend on the goals of the family or any related research study and will be influenced by resource availability. Those seeking staging for potential inclusion in a prevention trial generally require an OGTT (see next section), whereas, less intensive methods may be suitable in children who are identified or monitored outside of a research setting. Here, the goal should be to counsel families about future risk of Stage 3 T1D and the options for glycemic monitoring, how to identify signs and symptoms of hyperglycemia, preparation for a smooth transition to insulin therapy and preventing DKA.

3.3.6 | Oral glucose tolerance test

In the setting of multiple autoantibodies, the standard 2-h oral glucose tolerance test (OGTT) following 1.75 g/kg (75 g maximum) oral glucose administration remains the gold standard test for disease staging[58] (see "Stages of diabetes" section above). In addition, glucose values of ≥11.1 mmol/L (≥200 mg/dl) obtained at 30, 60, and 90 min after glucose administration have been used in the research setting to inform the risk of progression. Furthermore, mid OGTT glucose values ≥11.1 mmol/L (≥200 mg/dl) can be used to formally diagnose Stage 3 T1D in the setting of an elevated HbA1c or fasting glucose.[64,65]

Categories for fasting plasma glucose (FPG) are defined as follows:

- FPG <5.6 mmol/L (<100 mg/dl) = Stage 1 (normal fasting glucose)
- FPG 5.6–6.9 mmol/L (100–125 mg/dl) = Stage 2 (impaired fasting glucose)
- FPG ≥7.0 mmol/L (≥126 mg/dl) = Stage 3 T1D

Categories for 2-h plasma glucose following OGTT are defined as follows:

- Two-hour glucose <7.8 mmol/L (<140 mg/dl) = Stage 1 (normal glucose tolerance).
- Two-hour glucose 7.8–11.1 mmol/L (140–199 mg/dl) = Stage 2 (impaired glucose tolerance).
- Two-hour glucose ≥11.1 mmol/L (≥200 mg/dl) = Stage 3 T1D.

In the presence of multiple islet autoantibodies, the addition of other metrics such as age, sex, C-peptide, insulinoma-associated-2 autoantibody (IA–2A), HbA1c, and BMI allows calculation of scores which provide information on the risk of progression to stage 3 T1D. These include the 5-timepoint Diabetes Prevention Trial-Type 1 Risk Score (DPTRS),[66,67] the two-timepoint DPTRS60[68] and Index60[69] and the single timepoint M120.[70] These scores have similar levels of performance and are superior to using impaired glucose tolerance (IGT) alone.[68] While the majority of these scores have been developed using data from first-degree relatives being monitored in longitudinal natural history studies,[66–72] the recently published progression likelihood score from the Fr1Da program showed a 48% 2 year progression rate from stage 2 T1D to stage 3 T1D in children identified from the the general population.[73]

While the OGTT is recommended as the gold standard for staging children, especially those seeking entry into intervention trials, it is not always feasible or acceptable.[74] Alternative approaches are discussed next (Table 1).

3.3.7 | Glycosylated hemoglobin (HbA1c)

HbA1c is a specific but insensitive indicator of early onset diabetes.[77] The risk of progression is increased in the context of: (1) 10% rise in HbA1c in the non-diabetic range on two consecutive occasions collected 3–12 months apart (median time to "clinical diagnosis": 1.1 years, hazard ratio 5.7)[75]; (2) two HbA1c values >41 mmol/mol (5.9%) (median time to "clinical diagnosis": 0.9 year, hazard ratio 11.9); and (3) HbA1c >39 mmol/mol (5.7%), which is an independent predictor for progression.[3] Caution is needed in relying on HbA1c in young children who may progress rapidly, and may be missed before a rise in

TABLE 1 Monitoring tools in children with multiple islet autoantibodies

Metric	Pros	Cons	Information gained
OGTT	Gold standard Used to stage disease and predict progression	Requires glucose load and 2 to 5 blood draws over 2 h	Glycemic staging Risk scores for progression (DPTRS, DPTRS60, Index60, M120)[66–70]
Random venous glucose	One-off sample Low cost	Requires a blood draw	Similar to 2-h OGTT-derived glucose[71]
HbA1c	Highly specific Can use capillary sample	Insensitive, often normal in asymptomatic or recent onset Stage 3 diabetes, may be affected by disease states*	Risk of progression to "clinical disease": HbA1c >5.7%, or 10% rise over 3–12 months[75]
CGM	Use at home	Optimal duration and frequency of CGM wear not yet determined. Cost and access issues.	Risk of progression to "clinical disease": 10% > 7.8 mmol/L (>140 mg/dl)[76] Realtime monitoring over 24 h
Self-monitoring blood glucose	Simple use at home	Optimal timing and frequency have not been determined, unconfirmed glucose values	Immediate result

[a]See glycemic control targets and glucose monitoring chapter for further details.

HbA1c can be observed or in the setting of an undiagnosed hemoglobinopathy or other conditions that affect erythrocyte turnover.[78]

3.3.8 | Continuous glucose monitoring

Normative data taken from children, adolescents, and adults who are islet autoantibody-negative demonstrate a narrow variability in glucose using continuous glucose monitoring (CGM).[79] CGM provides real-time data and may be useful in identifying children with increased glucose variability in addition to elevated blood glucose levels.[80] In the largest pediatric study to date assessing CGM as a tool to predict progression, a cut-off of 10% time spent at >7.8 mmol/L (>140 mg/dl) had an 80% risk of progression to Stage 3 T1D over 1 year (91% specificity, 97% NPV, 88% sensitivity, 67% PPV).[76] However, further validation is needed, especially in very young children, to provide better evidence of when and how to begin insulin therapy.

3.3.9 | Random venous glucose and self-monitoring fingerstick blood glucose

In the Finnish DIPP study, the median time to diagnosis after a random plasma glucose ≥7.8 mmoL/L (140 mg/dl), was 1.0 year in children at Stage 1.[71] Random plasma glucose is a simple and low-cost measurement with comparable predictive characteristics to that of OGTT-derived 2-h glucose value, but with relatively poor sensitivity of 21% (95% CI 16%, 27%) and a specificity of 94% (95% CI 91%, 96%).[71]

Surprisingly little evidence exists for the accuracy of capillary self-monitoring fingerstick blood glucose (SMBG) in pre-symptomatic T1D in childhood, but it is a simple method that could be used in isolation or with other metrics. Adult data suggests that capillary glucose is a reliable comparator to venous glucose concentrations (85≥90% accuracy for diabetes or IGT) during the OGTT.[81,82]

3.3.10 | Recommendations for staging and monitoring

An OGTT is recommended as the gold standard for staging children for recruitment into clinical trials. When OGTT is not feasible, alternative approaches might include a 6–12 monthly HbA1c and 2-h postprandial or random glucose, dependent on risk stratification. More frequent monitoring may be offered to children at high risk of progression (e.g., those who seroconvert before age 2, with high IA–2A, or ≥3 islet autoantibodies).[3,6] If available, CGM could be added if dysglycemia is identified. HbA1c and CGM data can provide information on those progressing to insulin requirement within ~12 months, providing an opportunity to counsel individuals/carers and to commence education as an outpatient. SMBG measurements can provide families with real-time data to allow early detection of hyperglycemia and prevention of DKA.

3.4 | Psychological burden

A major concern with screening is engendering anxiety and imposing disease monitoring burden prior to insulin requirement, especially given there is currently no approved preventive therapy. The majority of children screened as being at increased genetic risk will never develop T1D[16,19] and for those with early-stage T1D, the latency period may last years.[64] "Positive" genetic and islet autoantibody screening results are associated with increased parental stress,[3,47,83,84] particularly in mothers[3,84]; however this declines rapidly within 3–12 months.[3,83] Furthermore, research programs that have monitored children both at high genetic risk and those identified through islet autoantibody surveillance programs[3] report reduced stress overall in children and their parents at the time when insulin therapy is needed compared to community controls. The Fr1da study showed that initial stress associated with multiple autoantibodies was only ~50% of that seen in families where children were diagnosed outside of the screening program.[3] These findings are likely explained by the high rates of depression and parenting stress when T1D is diagnosed and requires emergency insulin therapy.[85] The psychological burden in children and parents who continue to undergo glycemic monitoring without developing Stage 3 T1D for some years remains uncertain.

3.5 | Cost-effectiveness

A major consideration is the total cost and the incremental cost-effectiveness for screening, education, and monitoring programs. Cost-effectiveness analyses in the United States for islet autoantibody-only screening suggests that screening can be cost-effective with a 20% reduction in DKA at diagnosis and a 0.1% (1.1 mmol/mol) reduction in HbA1c during a lifetime.[86,87] Further economic modeling is required, including assessment of different screening and monitoring models of care as well as in individual countries due to differing health systems, burden of T1D, and costs of treatment locally. In the future, approval of preventive therapies will incur additional treatment costs but also likely result in substantial healthcare cost-savings and improved health benefits, further improving the incremental cost-effectiveness ratio.

In some,[88–90] but not all[91] lower resource countries, islet autoimmunity and genetic risk may be more heterogeneous, adding further complexity to screening. Lower-resourced countries often have higher rates of DKA and DKA associated-mortality, however, the lower T1D incidences in most of these countries may make screening efforts less cost-effective. Priorities in such countries continue to be correct etiological diagnosis as well as access to and improvements in clinical care for Stage 3 T1D.

3.6 | Efforts to slow disease progression

3.6.1 | Primary and secondary prevention efforts

Efforts to prevent the development of autoimmunity have historically been referred to as primary prevention, while efforts to delay

TABLE 2 Primary[59,63,95–99] and secondary[93,100–113] prevention trials in pre-T1D and intervention[94,114–133] trials in new onset T1D

Trial	Route	Intervention	Population	Primary outcome	Outcome achieved
Primary prevention					
BABYDIET	PO	Late gluten exposure	Genetically at-risk infants	Islet autoimmunity	Unsuccessful
FINDIA	PO	Bovine insulin-free formula	Genetically at-risk infants	Islet autoimmunity	**Successful**
TRIGR	PO	Hydrolyzed casein formula	Relatives, genetically at-risk infants	Stage 3	Unsuccessful
Pre-POInT	PO	Insulin	Relative, HLA risk, AAb neg, 3–7 y	AAb and T cell responses	**Successful**
Pre-POInT-early	PO	Insulin	Relative, HLA risk, AAb neg, 6 m–2 y	AAb and T cell responses	Unsuccessful[a]
POInT	PO	Insulin	Relative, HLA risk, AAb neg, 4–7 m	Islet autoimmunity	Ongoing
SINT1A	PO	*B. Infantis* probiotic	Relative, genetic risk, 7 days–6 weeks	Islet autoimmunity	Ongoing
Secondary prevention					
CORD	IV	Autologous Cord Blood	Relative or Gen Pop, Age < 15, ≥2 Ab	Stage 3	Ongoing
ENDIT	PO	Nicotinamide	Relative, ICA+, normal OGTT	Stage 3	Unsuccessful
DPT-1	IV/SC	Insulin	Relative, ICA+, IAA+, FPIR below threshold, 3–45 y	Stage 3	Unsuccessful
DPT-1	PO	Insulin	Relative, ICA+, IAA+, FPIR above threshold, 3–45 y	Stage 3	Unsuccessful[a]
DIPP	IN	Insulin	HLA risk, ≥2 AAb + 1, 1–15 y	Stage 3	Unsuccessful
INIT-I	IN	Insulin	Relative, ≥1 Ab, normal FPIR, 4–32 y	FPIR change	Unsuccessful
INIT-II	IN	Insulin	Relative, Stage 1, FPIR above threshold, 4-30y	Stage 3	Unsuccessful
Belgian registry	SC	Insulin	Relative, IA–2A+, 5–40 y	Stage 3	Unsuccessful
EPPSCIT	SC	Insulin	Relative, ≥2 AAb, 7–14 y	Stage 3	Unsuccessful
TN-07	PO	Insulin	Relative, Stage 1 (IAA+ required), 3–45 y	Stage 3	Unsuccessful[a]
Fr1da	PO	Insulin	Stage 1, 2–12 y	Immune responders then Stage 2/3	Ongoing
DiAPREV-IT	SC	GAD	Stage 1 (GADA+ required), 4–17 y	Stage 3	Unsuccessful
TN-10	IV	Teplizumab	Stage 2, 8–45 y	Stage 3	**Successful**
TN-18	IV	Abatacept	Stage 1, 6–45 y	Stage 2	Ongoing
TN-22	PO	Hydroxy-chloroquine	Stage 1, 3–45 y	Stage 2 or 3	Ongoing
Intervention					
TN-05	IV	Rituximab	Stage 3, new onset, 8–40 y	AUC C-peptide	**Successful**
AbATE	IV	Teplizumab	Stage 3, new onset, 8–30 y	AUC C-peptide	**Successful**
Protégé	IV	Teplizumab	Stage 3, new onset, 8–35 y	Insulin dose+HbA1c	Unsuccessful[a]
T1DAL	IM	Alefacept	Stage 3, new onset, 12–35 y	AUC C-peptide	Unsuccessful[a]
EXTEND	IV	Tocilizumab	Stage 3, new onset, 6–17 y	AUC C-peptide	Unsuccessful
T-Rex	IV	Autologous Tregs	Stage 3, new onset, 8–17 y	AUC C-peptide	Unsuccessful
TN-09	IV	Abatacept	Stage 3, new onset, 6–45 y	AUC C-peptide	**Successful**
START	IV	High-dose ATG	Stage 3, new onset, 12–35 y	AUC C-peptide	Unsuccessful[a]
TN-19	IV	Low-dose ATG	Stage 3, new onset, 12–45 y	AUC C-peptide	**Successful**
T1GER	SC	Golimumab	Stage 3, new onset, 6–21 y	AUC C-peptide	**Successful**
TN-14	SC	Canakinumab	Stage 3, new onset, 6–36 y	AUC C-peptide	Unsuccessful
PROTECT	IV	Teplizumab	Stage 3, new onset, 8–17 y	AUC C-peptide	Ongoing

(Continues)

TABLE 2 (Continued)

Trial	Route	Intervention	Population	Primary outcome	Outcome achieved
TN-08	SC	GAD	Stage 3, new onset, 3–45 y	AUC C-peptide	Unsuccessful
Diamyd	SC	GAD	Stage 3, new onset, 10–20 y	AUC C-peptide	Unsuccessful
DIAGNODE-3	IL	GAD	Stage 3, ≤6 m duration, 12–28 y	AUC C-peptide	Ongoing
Anti-CD40	SC	Iscalimab	Stage 3, new onset, 6–21 y	AUC C-peptide	Ongoing
BANDIT	PO	Baricitinib	Stage 3, new onset, 10–30 y	AUC C-peptide	Ongoing

Note: Stage 1 = multiple AAb-positive with normal glucose tolerance (via OGTT); Stage 2 = multiple AAb-positive with abnormal glucose tolerance; Stage 3 = clinical diagnosis of T1D. Bolded indicates emphasize those studies that have demonstrated capacity to prevent autoimmunity, delay progression of T1D or preserve beta cell function.

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

[a]Post hoc subpopulation response.

progression from Stage 1 or Stage 2 to Stage 3 diabetes are referred to as secondary prevention (Table 2). While a number of proposed therapies have been studied, teplizumab, a monoclonal antibody targeting the T cell surface marker CD3, is the only therapy that has, to date, demonstrated efficacy in delaying progression from Stage 2 to Stage 3 T1D.[92,93] This randomized, double-blind, placebo-controlled trial demonstrated Stage 3 T1D onset was delayed by a median of 2 years in first- or second-degree relatives of individuals with T1D, aged 8–50 years old, with stage 2 T1D at the time of enrolment.[92–94] Subsequent analysis demonstrated that the median delay might actually have been as long as 3 years in subjects treated with teplizumab versus placebo.[93] Teplizumab is currently being reviewed by the U.S. FDA. If granted approval, teplizumab will become the first immunotherapeutic with such a designation for individuals at risk for T1D. Trials with other drugs targeting (1) autoimmune responses; (2) antigen presentation; (3) glycemic dysregulation; and (4) beta cell stress/dysfunction are also underway.

3.6.2 | Stage 3 T1D Interventions

Stage 3 interventions or "new onset" studies seek to halt the disease, 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 of the disease due to the ease in identifying individuals who might still receive benefit.[134] Ultimately, relatively few agents are considered to have demonstrated capacity to delay C-peptide decline in Stage 3 disease; namely, cyclosporine, teplizumab, abatacept, alefacept, rituximab, golimumab, and low dose anti-thymocyte globulin.[94,122,126,127,135,136] However, a growing number of studies continue to focus on Stage 3. These studies not only have the prospect of providing direct benefit to newly diagnosed patients 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 disease. Ultimately a personalized medicine approach using targeted combination therapies and timing of treatment, driven by the individual patient genetic risk and response biomarkers is likely to be the most effective means of intervening in the disease process.[136]

Clinical trials at Stage 3 of disease have historically not been available in low-income countries. These trials have also enrolled study populations that were predominantly Caucasian, in part due to study sites primarily located in the United States, Canada, United Kingdom, 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 Caucasian participants. Moreover, there is emerging evidence that GRS does not differ by ethnicity.

4 | CONCLUSIONS AND RECOMMENDATIONS

Rapid expansion of screening and intervention networks, with the overall aim to prevent progression to Stage 3 diabetes and preserve beta cell function, has occurred in the last 5 years. General population screening for T1D has been propelled by technological advances in the prediction of genetic risk, low volume autoantibody assays, and advancements in trials of interventions to slow the progression of beta cell dysfunction. Screening to detect at-risk children offers the prospect of preventing DKA at presentation, and accelerated discovery of preventative interventions, through enhanced recruitment pools for clinical trials. Screening should therefore be accompanied by clinical care pathways to first reduce risk of DKA, and second, provide the young person or adult with age and stage-appropriate options to receive proven interventions or enter available intervention trials. If effective immunotherapies to delay progression and preserve beta cell function are approved by regulatory bodies, and the cost/benefit ratio related to screening is optimized, it is expected that screening will increasingly become standard practice within the general population. Primary prevention trials in infants and pre-schoolers are planned or

underway to develop immune tolerance, supplement with probiotics, or vaccinate against putative enterovirus (Coxsackie B) genotypes. Ongoing trials at Stages 1, 2, and 3 are evaluating the effects of immune-modulators acting directly and indirectly on T cells and antigen-specific therapies. It is thought that combined therapies will likely be most beneficial. The first therapeutic agent (the anti-CD3 monoclonal antibody, teplizumab) is under consideration by regulatory bodies to delay progression from Stage 2 to 3 T1D. Increasingly therapies will become more individualized to target different mechanisms in the disease pathway, analogous to treatments for other autoimmune diseases such as lupus erythematosus and rheumatoid arthritis.

AUTHOR CONTRIBUTIONS

REJB and KJB were co-first authors and reviewed the literature, drafted sections of the guidelines, oversaw completion of the first draft of the guidelines, and edited the manuscript. JJC, AGZ, DKW, MK, CS, KC, KAD, and JL reviewed the literature, provided drafts of sections and edited the manuscript. MEC was the lead of the ISPAD guidelines editorial committee, edited the manuscript, and served as co-senior author. MJH outlined the guidelines, reviewed the literature, drafted sections of the guidelines, edited the manusript, and served as the corresponding senior author. The authors gratefully acknowledge the editorial assistance of Dr. Leena Priyambada.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pedi.13410.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Jenny J. Couper https://orcid.org/0000-0003-4448-8629
Mikael Knip https://orcid.org/0000-0003-0474-0033
Kristina Casteels https://orcid.org/0000-0001-9690-3551
Kimberly A. Driscoll https://orcid.org/0000-0002-3006-4633
Laura Jacobsen https://orcid.org/0000-0002-5144-7836
Maria E. Craig https://orcid.org/0000-0001-6004-576X
Michael J. Haller https://orcid.org/0000-0002-2803-1824

REFERENCES

1. Allen C, Palta M, D'Alessio DJ. Risk of diabetes in siblings and other relatives of IDDM subjects. *Diabetes*. 1991;40(7):831-836.
2. Dahlquist G, Blom L, Holmgren G, et al. The epidemiology of diabetes in Swedish children 0–14 years--a six-year prospective study. *Diabetologia*. 1985;28(11):802-808.
3. Ziegler AG, Kick K, Bonifacio E, et al. Yield of a public health screening of children for islet autoantibodies in Bavaria, Germany. *JAMA*. 2020;323(4):339-351.
4. Parkkola A, Harkonen T, Ryhanen SJ, Ilonen J, Knip M. Finnish pediatric diabetes R. extended family history of type 1 diabetes and phenotype and genotype of newly diagnosed children. *Diabetes Care*. 2013;36(2):348-354.
5. Ziegler AG, Danne T, Dunger DB, 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):255-262.
6. Ziegler AG, Rewers M, Simell O, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *JAMA*. 2013;309(23):2473-2479.
7. Krischer JP, Lynch KF, Schatz DA, et al. The 6 year incidence of diabetes-associated autoantibodies in genetically at-risk children: the TEDDY study. *Diabetologia*. 2015;58(5):980-987.
8. Bingley PJ, Boulware DC, Krischer JP. 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):542-549.
9. Anand V, Li Y, Liu B, 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):2269-2276.
10. Robertson CC, Inshaw JRJ, Onengut-Gumuscu S, 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):962-971.
11. Lambert AP, Gillespie KM, Thomson G, 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):4037-4043.
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):2135-2140.
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):1134-1148.
14. Erlich H, Valdes AM, Noble J, 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):1084-1092.
15. Hippich M, Beyerlein A, Hagopian WA, 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):847-857.
16. Bonifacio E, Beyerlein A, Hippich M, 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.
17. Aly TA, Ide A, Jahromi MM, et al. Extreme genetic risk for type 1A diabetes. *Proc. Natl. Acad. Sci. U. S. A.* 2006;103(38):14074-14079.
18. 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):870-875.
19. Sharp SA, Rich SS, Wood AR, 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):200-207.
20. Winkler C, Krumsiek J, Buettner F, et al. Feature ranking of type 1 diabetes susceptibility genes improves prediction of type 1 diabetes. *Diabetologia*. 2014;57(12):2521-2529.
21. Bonifacio E, Weiss A, Winkler C, et al. An age-related exponential decline in the risk of multiple islet autoantibody seroconversion during childhood. *Diabetes Care*. 2021;44:2260-2268.

22. Hoffmann VS, Weiss A, Winkler C, 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.
23. Krischer JP, Liu X, Lernmark A, 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):2247-2257.
24. Beyerlein A, Bonifacio E, Vehik K, 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):602-605.
25. 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):403-411.
26. Redondo MJ, Geyer S, Steck AK, 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):1887-1894.
27. Fourlanos S, Varney MD, Tait BD, 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):1546-1549.
28. Penno MA, Couper JJ, Craig ME, 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.
29. Sims EK, Besser REJ, Dayan C, et al. Screening for type 1 diabetes in the general population: a status report and perspective. *Diabetes*. 2022;71(4):610-623.
30. Barker JM, Goehrig SH, Barriga K, et al. Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up. *Diabetes Care*. 2004;27(6):1399-1404.
31. 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):314-319.
32. 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):308-313.
33. Elding Larsson H, Vehik K, Bell R, 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):2347-2352.
34. Grosse J, Hornstein H, Manuwald U, Kugler J, Glauche I, Rothe U. Incidence of diabetic ketoacidosis of new-onset type 1 diabetes in children and adolescents in different countries correlates with human development index (HDI): an updated systematic review, meta-analysis, and meta-regression. *Horm. Metab. Res*. 2018;50(3):209-222.
35. Jensen ET, Stafford JM, Saydah S, et al. Increase in prevalence of diabetic ketoacidosis at diagnosis among youth with type 1 diabetes: the search for diabetes in youth study. *Diabetes Care*. 2021;44(7):1573-1578.
36. 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(165–173):e162.
37. 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):117-121.
38. 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):901-908.
39. Peng W, Yuan J, Chiavaroli V, et al. 10-year incidence of diabetic ketoacidosis at type 1 diabetes diagnosis in children aged less than 16 years from a large regional center (Hangzhou, China). *Front Endocrinol (Lausanne)*. 2021;12:653519.
40. Cameron FJ, Scratch SE, Nadebaum C, et al. Neurological consequences of diabetic ketoacidosis at initial presentation of type 1 diabetes in a prospective cohort study of children. *Diabetes Care*. 2014;37(6):1554-1562.
41. Ghetti S, Kuppermann N, Rewers A, et al. Cognitive function following diabetic ketoacidosis in children with new-onset or previously diagnosed type 1 diabetes. *Diabetes Care*. 2020;43(11):2768-2775.
42. Karges B, Prinz N, Placzek K, et al. A comparison of familial and sporadic type 1 diabetes among young patients. *Diabetes Care*. 2021;44(5):1116-1124.
43. Duca LM, Reboussin BA, Pihoker C, et al. Diabetic ketoacidosis at diagnosis of type 1 diabetes and glycemic control over time: the search for diabetes in youth study. *Pediatr. Diabetes*. 2019;20(2):172-179.
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):1249-1255.
45. Mazarello Paes V, Barrett JK, Taylor-Robinson DC, et al. Effect of early glycemic control on HbA1c tracking and development of vascular complications after 5 years of childhood onset type 1 diabetes: systematic review and meta-analysis. *Pediatr. Diabetes*. 2019;20(5):494-509.
46. Samuelsson J, Samuelsson U, Hanberger L, Bladh M, Akesson K. Poor metabolic control in childhood strongly correlates to diabetes-related premature death in persons <30 years of age-a population-based cohort study. *Pediatr. Diabetes*. 2020;21(3):479-485.
47. Smith LB, Liu X, Johnson SB, 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):1025-1033.
48. Krischer JP, Liu X, Lernmark A, et al. The influence of type 1 diabetes genetic susceptibility regions, age, sex, and family history on the progression from multiple autoantibodies to type 1 diabetes: a TEDDY study report. *Diabetes*. 2017;66(12):3122-3129.
49. Greenbaum CJ. A key to T1D prevention: screening and monitoring relatives as part of clinical care. *Diabetes*. 2021;70(5):1029-1037.
50. Jacobsen LM, Vehik K, Veijola R, et al. Heterogeneity of DKA incidence and age-specific clinical characteristics in children diagnosed with type 1 diabetes in the TEDDY study. *Diabetes Care*. 2022;45(3):624-633.
51. Familial risk of type I diabetes in European children. The Eurodiab ace study group and the Eurodiab Ace substudy 2 study group. *Diabetologia*. 1998;41(10):1151-1156.
52. Cortez FJ, Gebhart D, Robinson PV, 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.
53. Liberati D, Wyatt RC, Brigatti C, et al. A novel LIPS assay for insulin autoantibodies. *Acta Diabetol*. 2018;55(3):263-270.
54. Ghalwash M, Dunne JL, Lundgren M, et al. Two-age islet-autoantibody screening for childhood type 1 diabetes: a prospective cohort study. *Lancet Diabetes Endocrinol*. 2022;10(8):589-596.
55. Rabbone I, Maltoni G, Tinti D, 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):363-366.
56. Dabelea D, Rewers A, Stafford JM, et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. *Pediatrics*. 2014;133(4):e938-e945.
57. Nejentsev S, Sjoroos M, Soukka T, et al. Population-based genetic screening for the estimation of type 1 diabetes mellitus risk

in Finland: selective genotyping of markers in the HLA-DQB1, HLA-DQA1 and HLA-DRB1 loci. *Diabet Med*. 1999;16(12):985-992.
58. Teddy Study Group. The environmental determinants of diabetes in the young (TEDDY) study. *Ann. N. Y. Acad. Sci.* 2008;1150:1-13.
59. Ziegler AG, Achenbach P, Berner R, 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.
60. Perry DJ, Wasserfall CH, Oram RA, 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.
61. Ferrat LA, Vehik K, Sharp SA, et al. A combined risk score enhances prediction of type 1 diabetes among susceptible children. *Nat. Med.* 2020;26(8):1247-1255.
62. Hommel A, Haupt F, Delivani P, et al. Screening for type 1 diabetes risk in newborns: the Freder1k pilot study in Saxony. *Horm. Metab. Res.* 2018;50(1):44-49.
63. Ziegler AG, Arnolds S, Kolln A, 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.
64. Insel RA, Dunne JL, Atkinson MA, 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):1964-1974.
65. Sosenko JM, Palmer JP, Rafkin-Mervis L, et al. Incident dysglycemia and progression to type 1 diabetes among participants in the diabetes prevention trial-type 1. *Diabetes Care*. 2009;32(9):1603-1607.
66. Sosenko JM, Skyler JS, Mahon J, 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):979-984.
67. Sosenko JM, Skyler JS, Palmer JP. Diabetes type T, diabetes prevention trial-type 1 study G. the development, validation, and utility of the diabetes prevention trial-type 1 risk score (DPTRS). *Curr. Diab. Rep*. 2015;15(8):49.
68. Simmons KM, Sosenko JM, Warnock 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):e4094-e4101.
69. Sosenko JM, Skyler JS, DiMeglio LA, 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):271-276.
70. Bediaga NG, Li-Wai-Suen CSN, Haller MJ, et al. Simplifying prediction of disease progression in pre-symptomatic type 1 diabetes using a single blood sample. *Diabetologia*. 2021;64(11):2432-2444.
71. Helminen O, Aspholm S, Pokka T, et al. OGTT and random plasma glucose in the prediction of type 1 diabetes and time to diagnosis. *Diabetologia*. 2015;58(8):1787-1796.
72. Sosenko JM, Skyler JS, Beam CA, 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):940-942.
73. Weiss, A, Zapardiel-Gonzalo, J, Voss, F et al. Progression Likelihood score identifies substages of presymptomatic tpe 1 diabetes in childhood public health screening. *Diabetologia*. 2022. https://doi.org/10.1007/s00125-022-05780-9
74. Driscoll KA, Tamura R, Johnson SB, 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):360-368.
75. Helminen O, Aspholm S, Pokka T, et al. HbA1c predicts time to diagnosis of type 1 diabetes in children at risk. *Diabetes*. 2015;64(5):1719-1727.
76. Steck AK, Dong F, Geno Rasmussen C, et al. CGM metrics predict imminent progression to type 1 diabetes: autoimmunity screening for kids (ASK) study. *Diabetes Care*. 2022;45(2):365-371.
77. Vehik K, Cuthbertson D, Boulware D, et al. Performance of HbA1c as an early diagnostic indicator of type 1 diabetes in children and youth. *Diabetes Care*. 2012;35(9):1821-1825.
78. Stene LC, Hyoty H. A novel approach to the investigation of potential precipitating factors in type 1 diabetes. *Pediatr. Diabetes*. 2006;7(3):143-145.
79. Shah VN, DuBose SN, Li Z, et al. Continuous glucose monitoring profiles in healthy nondiabetic participants: a multicenter prospective study. *J. Clin. Endocrinol. Metab*. 2019;104(10):4356-4364.
80. Steck AK, Dong F, Taki I, et al. Continuous glucose monitoring predicts progression to diabetes in autoantibody positive children. *J. Clin. Endocrinol. Metab*. 2019;104(8):3337-3344.
81. Priya M, Mohan Anjana R, Pradeepa R, 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):586-591.
82. 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):862-867.
83. Johnson SB, Lynch KF, Roth R, Schatz D, Group TS. My child is islet autoantibody positive: impact on parental anxiety. *Diabetes Care*. 2017;40(9):1167-1172.
84. Melin J, Maziarz M, Andren Aronsson C, Lundgren M, Elding LH. 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):878-889.
85. 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):562-579.
86. McQueen RB, Geno Rasmussen C, Waugh K, et al. Cost and cost-effectiveness of large-scale screening for type 1 diabetes in Colorado. *Diabetes Care*. 2020;43(7):1496-1503.
87. 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):837-844.
88. Fawwad A, Govender D, Ahmedani MY, 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.
89. Ibrahim TAM, Govender D, Abdullah MA, et al. Clinical features, biochemistry, and HLA-DRB1 status in youth-onset type 1 diabetes in Sudan. *Pediatr. Diabetes*. 2021;22(5):749-757.
90. Zabeen B, Govender D, Hassan Z, 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.
91. Ahmadov GA, Govender D, Atkinson MA, et al. Epidemiology of childhood-onset type 1 diabetes in Azerbaijan: incidence, clinical features, biochemistry, and HLA-DRB1 status. *Diabetes Res. Clin. Pract*. 2018;144:252-259.
92. An anti-CD3 antibody, Teplizumab, in relatives at risk for type 1 diabetes. *N. Engl. J. Med*. 2020;382(6):586.
93. Sims EK, Bundy BN, Stier K, et al. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. *Sci. Transl. Med*. 2021;13(583):eabc8980.
94. Herold KC, Gitelman SE, Ehlers MR, 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):3766-3774.

95. Knip M, Åkerblom HK, Becker D, et al. Hydrolyzed infant formula and early β-cell autoimmunity: a randomized clinical trial. *JAMA*. 2014;311(22):2279-2287.
96. Hummel S, Pflüger M, Hummel M, Bonifacio E, Ziegler AG. 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):1301-1305.
97. Vaarala O, Ilonen J, Ruohtula T, 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):608-614.
98. Bonifacio E, Ziegler AG, Klingensmith G, 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):1541-1549.
99. Assfalg R, Knoop J, Hoffman KL, et al. Oral insulin immunotherapy in children at risk for type 1 diabetes in a randomised controlled trial. *Diabetologia*. 2021;64(5):1079-1092.
100. Herold KC, Bundy BN, Long SA, et al. An anti-CD3 antibody, Teplizumab, in relatives at risk for type 1 diabetes. *N. Engl. J. Med.* 2019;381(7):603-613.
101. Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N. Engl. J. Med.* 2002;346(22):1685-1691.
102. Skyler JS, Krischer JP, Wolfsdorf J, 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):1068-1076.
103. Näntö-Salonen K, Kupila A, Simell S, 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):1746-1755.
104. Krischer JP, Schatz DA, Bundy B, Skyler JS, Greenbaum CJ. Effect of Oral insulin on prevention of diabetes in relatives of patients with type 1 diabetes: a randomized clinical trial. *JAMA*. 2017;318(19):1891-1902.
105. Gale EA, Bingley PJ, Emmett CL, Collier T. European nicotinamide diabetes intervention trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes. *Lancet*. 2004;363(9413):925-931.
106. Harrison LC, Honeyman MC, Steele CE, 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):2348-2355.
107. Jacobsen LM, Schatz DA. Insulin immunotherapy for pretype 1 diabetes. *Curr. Opin. Endocrinol. Diabetes Obes.* 2021;28(4):390-396.
108. Vandemeulebroucke E, Gorus FK, Decochez K, et al. Insulin treatment in IA-2A-positive relatives of type 1 diabetic patients. *Diabetes Metab.* 2009;35(4):319-327.
109. Carel JC, Landais P, Bougnères P. Therapy to prevent type 1 diabetes mellitus. *N. Engl. J. Med.* 2002;347(14):1115-1116.
110. Elding Larsson H, Lundgren M, Jonsdottir B, Cuthbertson D, Krischer J. 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):410-419.
111. Hydroxychloroquine for Prevention of Abnormal Glucose Tolerance and Diabetes in Individuals At-risk for Type 1 Diabetes Mellitus (T1D).ClinicalTrialsgov Identifier: NCT03428945 Retrieved from https://www.clinicaltrials.gov/ct2/show/record/NCT03428945. 2018.
112. CTLA4-Ig (Abatacept)for Prevention of Abnormal Glucose Tolerance and Diabetes in Relatives At -Risk for Type 1. ClinicalTrialsgov Identifier: NCT01773707 Retrieved from https://www.clinicaltrials.gov/ct2/show/NCT01773707. 2013.
113. Fr1da-/Fr1da-Plus-Study in Bavaria: Early detection for early Care of Type 1 diabetes (Fr1da-plus). ClinicalTrialsgov Identifier: NCT04039945. https://clinicaltrials.gov/ct2/show/NCT04039945.
114. Pescovitz MD, Greenbaum CJ, Bundy B, et al. B-lymphocyte depletion with rituximab and β-cell function: two-year results. *Diabetes Care*. 2014;37(2):453-459.
115. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, et al. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. *N. Engl. J. Med.* 2009;361(22):2143-2152.
116. Sherry N, Hagopian W, Ludvigsson J, et al. Teplizumab for treatment of type 1 diabetes (Protégé study): 1-year results from a randomised, placebo-controlled trial. *Lancet*. 2011;378(9790):487-497.
117. Hagopian W, Ferry RJ Jr, Sherry N, 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):3901-3908.
118. Rigby MR, DiMeglio LA, Rendell MS, 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):284-294.
119. Greenbaum CJ, Serti E, Lambert K, et al. IL-6 receptor blockade does not slow β cell loss in new-onset type 1 diabetes. *JCI Insight*. 2021;6(21):150074.
120. 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.
121. Orban T, Beam CA, Xu P, 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):3449-3457.
122. Orban T, Bundy B, Becker DJ, 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):412-419.
123. Gitelman SE, Gottlieb PA, Rigby MR, 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):306-316.
124. Gitelman SE, Gottlieb PA, Felner EI, et al. Antithymocyte globulin therapy for patients with recent-onset type 1 diabetes: 2 year results of a randomised trial. *Diabetologia*. 2016;59(6):1153-1161.
125. Haller MJ, Schatz DA, Skyler JS, 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):1917-1925.
126. Haller MJ, Long SA, Blanchfield JL, 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):1267-1276.
127. Quattrin T, Haller MJ, Steck AK, et al. Golimumab and Beta-cell function in youth with new-onset type 1 diabetes. *N. Engl. J. Med.* 2020;383(21):2007-2017.
128. Moran A, Bundy B, Becker DJ, et al. Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicentre, randomised, double-blind, placebo-controlled trials. *Lancet*. 2013;381(9881):1905-1915.
129. 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.
130. Wherrett DK, Bundy B, Becker DJ, 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):319-327.
131. Ludvigsson J, Krisky D, Casas R, et al. GAD65 antigen therapy in recently diagnosed type 1 diabetes mellitus. *N. Engl. J. Med.* 2012;366(5):433-442.
132. 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.

133. 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.
134. 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):1286-1296.
135. Rigby MR, Harris KM, Pinckney A, et al. Alefacept provides sustained clinical and immunological effects in new-onset type 1 diabetes patients. *J. Clin. Invest.* 2015;125(8):3285-3296.
136. Warshauer JT, Bluestone JA, Anderson MS. New Frontiers in the treatment of type 1 diabetes. *Cell Metab.* 2020;31(1):46-61.

How to cite this article: Besser REJ, Bell KJ, Couper JJ, et al. ISPAD clinical practice consensus guidelines 2022: Stages of type 1 diabetes in children and adolescents. *Pediatr Diabetes*. 2022;1-13. doi:10.1111/pedi.13410