ISPAD Clinical Practice Consensus Guidelines 2022: Stages of Type 1 Diabetes in Children and Adolescents

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.

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Introduction

This guideline serves as an update and replacement to 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 low-income countries may not be able to offer screening, where priorities may differ.

WHAT IS NEW

- 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

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 young people with multiple islet autoantibodies progress to stage 3 within 15 years, compared to ~15% who have a single islet autoantibody. **A**
- Progression rates are similar between individuals with a family history of T1D and those from the general population. **A**

- Targeted screening *and* follow up identifies individuals with stage 1, stage 2, and pre-symptomatic stage 3 diabetes**,** reduces the incidence of diabetic ketoacidosis (DKA), reduces rates of hospitalisation, and directs individuals towards 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 metabolic surveillance programs for those identified with autoantibodies. **B**
- As immunotherapies with the capacity to delay 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**
- OGTT is recommended to stage disease in individuals with 2 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 fingerstick blood glucose, 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**
- Fingerstick blood glucose testing or 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**

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 pr-esymptomatic

Stage 3 Blood glucose above ADA diagnostic thresholds

Stage 4 Long standing T1D

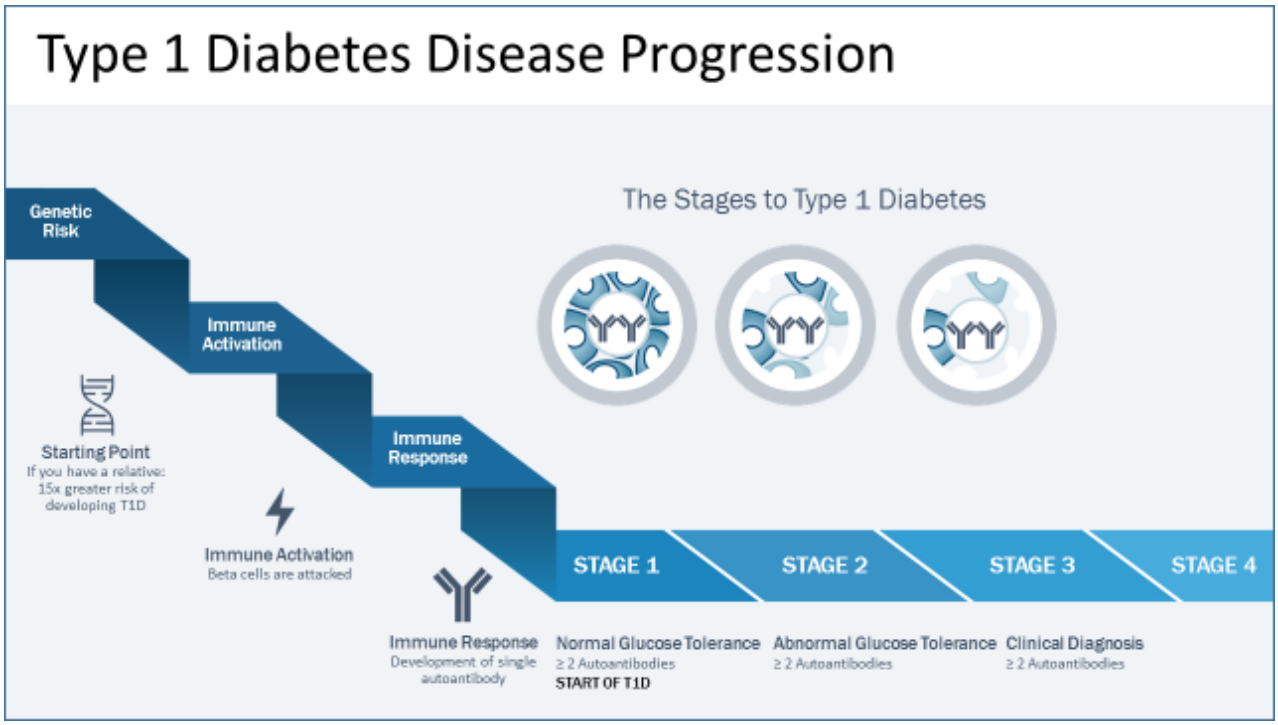

Figure 1: The stages of T1D (DiabetesTrialNet.org).

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), especially in children, is followed by 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.

Risk of T1D

Individuals with a first degree relative with T1D have an approximately 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 approximately 85% of children 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 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 stage 3 T1D.[6-9]

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 declines exponentially with age in young people as does

the influence of genetic factors, although there is a paucity of data in adults.[21-23] Furthermore, once a young person 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]

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]

Screening for Pre-symptomatic T1D

Screening for risk of T1D is gaining international momentum. While the focus is still largely on screening in the context of research trials including implementation science studies, it is possible that screening may become standard of care, embedded in local health systems.

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.

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 altogether. 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, and
3. Advance preventative therapies through clinical trial recruitment

Screening programs significantly reduce DKA rates, usually to less than 5%, and reduce hospitalisation when coupled with long-term follow up. [3,29-32] The rates of DKA at diagnosis range from 15-80% worldwide[33-38] with DKA prevention at diagnosis having potential lifelong benefits, including avoidance of acute morbidity (cerebral oedema, shock), neurocognitive impairment, and mortality.[39,40] There are also non-causal associations between DKA at onset and future risk of DKA,[37,41] severe hypoglycemia[41] and suboptimal long-term glycemic control,[42-44] which, in turn, increase the risk of serious future diabetes-related complications.[45] Furthermore, parental anxiety at diagnosis is approximately halved for children in screening programs compared to the general community.[3] The additional time provided for counselling, 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.[3,46]

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

Target Population for Screening

Given the current inability to intervene 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 statistically significantly different between individuals with a family member compared to the general population.[6,47] Routine screening for family members as part of clinical care has been proposed as an intermediary step towards general population screening.[48] However, as DKA rates are lower in individuals with a first degree relative of T1D compared to those without[41,49] 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.[1,2,50]

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 2 diabetes, or 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.[51,52] Several groups have tried to determine optimal ages for performing autoantibody screening; modelled 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] Notably, sampling from 2 years of age does not capture all children who will develop T1D and misses the small, but important, subset of children 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.[35,36,53,54]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 (DIPP/TEDDY ref?). This 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).[55]

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 enrolling children into prevention trials, while lower thresholds may be better suited to efforts prioritizing DKA prevention, given they capture a greater proportion of future cases.[35,37,53] 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.[56]

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.[55,57-59] More frequent monitoring may be beneficial in very young children, 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]

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, in children who are identified or monitored outside of a research setting, less intensive methods may be suitable. Here, the goal should be on counselling families about future risk of stage 3 T1D, the options for glycemic monitoring, how to identify

signs and symptoms of hyperglycemia, preparation for a smooth transition to insulin therapy and preventing DKA.

Oral glucose tolerance test (OGTT)

In the setting of multiple autoantibodies, the standard 2-hour 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 ≥11.1mmol/L (≥200mg/dL) obtained at 30, 60, and 90 minutes after glucose administration have been used in the research setting to inform the risk of progression.[60,61]

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

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

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

- 2-hour glucose <7.8mmol/L (<140mg/dL) = stage 1 (normal glucose tolerance)
- 2-hour glucose 7.8-11.1mmol/L (140-199mg/dL) = stage 2 (impaired glucose tolerance)
- 2-hour glucose ≥11.1mmol/L (≥200mg/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-

timepiont Diabetes Prevention Trial-Type 1 Risk Score (DPTRS),[62,63] the 2-timepoint DPTRS60[64] and Index60[65] and the single timepoint M120.[66] These scores have similar levels of performance and are superior to using impaired glucose tolerance (IGT) alone.[64] However, they have predominantly been developed using data from first-degree relatives being followed in longitudinal natural history studies.[62-68] The exception is the M120 which additionally uses data from general population children.[66]

Whilst the OGTT is recommended as the gold standard for staging children and young people, especially those seeking entry into intervention trials, it is not always feasible or acceptable.[69] Alternative approaches are discussed next (**Table 1**).

Table 1. Metabolic surveillance 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)[62-66]
Random venous glucose	One-off sample Low cost	Requires a blood draw	Similar to 2-hour OGTT-derived glucose[67]
HbA1c	Highly specific Can use capillary sample	Insensitive, often normal in asymptomatic or recent onset stage 3 diabetes, may be	Risk of progression to 'clinical disease': HbA1c >5.7%, or

		affected by disease states*	10% rise over 3-12 months[70]
CGM	Use at home	Optimal duration and frequency of CGM wear not yet determined. Cost, access, requirement to wear continuously	Risk of progression to 'clinical disease': 10% > 7.8mmol/L (>140mg/dL)[71] Realtime monitoring over 24 hours
Self-monitoring blood glucose	Simple Use at home	Optimal timing and frequency has not been determined, random result	Immediate result

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

Glycosylated hemoglobin (HbA1c)

HbA1c is a specific but insensitive indicator of early onset diabetes.[72] 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);[70] 2) two HbA1c values > 41mmol/mol (5.9%) (median time to "clinical diagnosis": 0.9 year, hazard ratio 11.9); and 3) HbA1c >39mmol/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 HbA1c can be observed or in the setting of an undiagnosed hemoglobinopathy or other conditions that affect hemoglobin turnover.[73]

Continuous glucose monitoring (CGM)

Normative data taken from children, young people and adults who are islet autoantibody-negative demonstrate a narrow variability in glucose using CGM.[74] CGM provides real time data and may be useful in identifying children with increased glucose variability in addition to elevated blood glucose levels.[75] In the largest pediatric study to date assessing CGM as a tool to predict progression, a cut-off of 10% time spent at >7.8mmol/L (>140mg/dL) had an 80% risk of progression to stage 3 T1D over one year (91% specificity, 97% NPV, 88% sensitivity, 67% PPV).[71] However, further validation is needed, especially in very young children, particularly to provide better evidence of when and how to begin insulin therapy.

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

In the Finnish DIPP study, the median time to diagnosis after a random plasma glucose ≥ 7.8 mmol/l (140mg/dl), was 1.0 year in children at stage 1.[67] Random plasma glucose is a simple and low-cost measurement with comparable predictive characteristics to that of OGTT-derived 2 h glucose, but with relatively poor sensitivity of 21% (95% CI 16%, 27%) and a specificity of 94% (95% CI 91%, 96%).[67]

Surprisingly little evidence exists for the accuracy of capillary SMBG in pre-symptomatic T1D in childhood, but it is a simple method that could be used in isolation or alongside other metrics. Adult data suggests that capillary glucose is a reliable comparator to venous glucose (85->90% accuracy for diabetes or IGT) during the OGTT.[76,77]

Recommendations for staging and follow up

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-hour postprandial or random glucose, dependent on risk stratification. More frequent surveillance may be offered to children at high risk of progression (e.g., those who seroconvert at a young age, with high IA-2A, or 3-4 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 approximately 12 months, providing an opportunity to counsel individuals/carers and to commence education as an outpatient. Home fingerstick glucose measurements can provide families with real time data to allow early detection of hyperglycemia and prevention of DKA.

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.[60] 'Positive' genetic and islet autoantibody screening results are associated with increased parental stress,[3,46,78,79] particularly in mothers;[3,79] however this declines rapidly within 3-12 months.[3,78] Furthermore, research programs that have followed children both at high genetic risk and those identified though 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 were only ~50% of those 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.[80] The psychological burden in children and parents who continue to undergo glycemic surveillance without developing stage 3 T1D for some years remains uncertain.

Cost-Effectiveness

A major consideration is the total cost and the incremental cost-effectiveness for screening, education and glycemic surveillance programs. Cost-effectiveness analyses in the US for islet autoantibody-only screening suggests that screening can be cost-effective with a 20% reduction in DKA at diagnosis and a 0.1% (1.1mmol/mol) reduction in HbA1c during a lifetime.[81,82] Further economic modelling is required, including assessment of different screening and surveillance 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,[83-85] but not all[86] 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 remain on access to and improvements in clinical care for stage 3 T1D, coupled with correct etiological diagnosis.

Efforts to Slow Disease Progression

Primary and Secondary Prevention Efforts

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 diabetes is referred to as secondary prevention (**Table 2**). 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, demonstrated efficacy in delaying progression from stage 2 to stage 3 T1D.[87,88] 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.[87-89] Subsequent analysis demonstrated that the median delay might actually have been as long as 3 years in subjects treated with teplizumab versus placebo.[88] 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.

Table 2: Primary[55,59,90-94] and Secondary[88,95-108] Prevention Trials in Pre-T1D and Intervention[89,109-128] 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	Relative, Genetically at-risk infants,	Stage 3	Unsuccessful
Pre-POInT	PO	Insulin	Relative, HLA risk, AAb-, 3-7y	AAb and T cell responses	**Successful**

Pre-POInT-early	PO	Insulin	Relative, HLA risk, AAb-, 6m-2y	AAb and T cell responses	Unsuccessful*
POInT	PO	Insulin	Relative, HLA risk, AAb-, 4-7m	Islet autoimmunity	Ongoing
SINT1A	PO	*B. Infantis* probiotic	Relative, genetic risk, 7d-6wk	Islet autoimmunity	Ongoing
Secondary Prevention					
ENDIT	PO	Nicotinamide	Relative, ICA+, normal OGTT	Stage 3	Unsuccessful
DPT-1	IV/ SC	Insulin	Relative, ICA+, IAA+, FPIR below threshold, 3-45y	Stage 3	Unsuccessful
DPT-1	PO	Insulin	Relative, ICA+, IAA+, FPIR above threshold, 3-45y	Stage 3	Unsuccessful*
DIPP	IN	Insulin	HLA risk, ≥2 AAb+ 1, 1-15y	Stage 3	Unsuccessful
INIT-I	IN	Insulin	Relative, ≥1 Ab, normal FPIR, 4-32y	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+, 5-40y	Stage 3	Unsuccessful
EPPSCIT	SC	Insulin	Relative, ≥2 AAb, 7-14y	Stage 3	Unsuccessful
TN-07	PO	Insulin	Relative, Stage 1 (IAA+ required), 3-45y	Stage 3	Unsuccessful*
Fr1da	PO	Insulin	Stage 1, 2-12y	Immune responders then Stage 2/3	Ongoing
DiAPREV-IT	SC	GAD	Stage 1 (GADA+ required), 4-17y	Stage 3	Unsuccessful
TN-10	IV	Teplizumab	Stage 2, 8-45y	Stage 3	**Successful**
TN-18	IV	Abatacept	Stage 1, 6-45y	Stage 2	Ongoing
TN-22	PO	Hydroxy-chloroquine	Stage 1, 3-45y	Stage 2 or 3	Ongoing
Intervention					
TN-05	IV	Rituximab	Stage 3, new onset, 8-40y	AUC C-peptide	**Successful**
AbATE	IV	Teplizumab	Stage 3, new onset, 8-30y	AUC C-peptide	**Successful**
Protégé	IV	Teplizumab	Stage 3, new onset, 8-35y	Insulin dose+HbA1c	Unsuccessful*

T1DAL	IM	Alefacept	Stage 3, new onset, 12-35y	AUC C-peptide	Unsuccessful*
EXTEND	IV	Tocilizumab	Stage 3, new onset, 6-17y	AUC C-peptide	Unsuccessful
T-Rex	IV	Autologous Tregs	Stage 3, new onset, 8-17y	AUC C-peptide	Unsuccessful
TN-09	IV	Abatacept	Stage 3, new onset, 6-45y	AUC C-peptide	**Successful**
START	IV	High-dose ATG	Stage 3, new onset, 12-35y	AUC C-peptide	Unsuccessful*
TN-19	IV	Low-dose ATG	Stage 3, new onset, 12-45y	AUC C-peptide	**Successful**
T1GER	SC	Golimumab	Stage 3, new onset, 6-21y	AUC C-peptide	**Successful**
TN-14	SC	Canakinumab	Stage 3, new onset, 6-36y	AUC C-peptide	Unsuccessful
PROTECT	IV	Teplizumab	Stage 3, new onset, 8-17y	AUC C-peptide	Ongoing
TN-08	SC	GAD	Stage 3, new onset, 3-45y	AUC C-peptide	Unsuccessful
Diamyd	SC	GAD	Stage 3, new onset, 10-20y	AUC C-peptide	Unsuccessful
DIAGNODE-3	IL	GAD	Stage 3, ≤6 months duration, 12-28y	AUC C-peptide	Ongoing
Anti-CD40	SC	Iscalimab	Stage 3, new onset, 6-21y	AUC C-peptide	Ongoing

*post-hoc subpopulation response
HLA, human leukocyte antigen; AAb, autoantibody; 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 normal glucose tolerance (via OGTT); Stage 2=multiple AAb-positive with abnormal glucose tolerance; Stage 3=clinical diagnosis of T1D

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.[129] Ultimately, a relatively short list of 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.[89,117,121,122,130,131] However, a growing number of studies continue to emerge and 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.[131]

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 heavily Caucasian, in part due to 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 Caucasian participants. Moreover, there is emerging evidence that GRS does not differ by ethnicity.

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 prevention of DKA at presentation, and accelerated discovery of preventative interventions, through improved 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 intervention trials, according to their regional location. 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 interventions at stages 1, 2, and 3 trial the effects of immune-modulators acting on T cells directly and indirectly, and antigen specific therapies, with recognition of the likely benefits of combined therapies. 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 and rheumatoid arthritis.

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