Diabetes and Metabolism 51 (2025) 101603

Contents lists available at ScienceDirect

Diabetes & Metabolism

journal homepage: www.elsevier.com/locate/diabet

Position Statement

# Screening and care for preclinical stage 1–2 type 1 diabetes in first-degree relatives: French expert position statement☆

Roberto Mallone[a,b,c,*], Elise Bismuth[d], Charles Thivolet[e], Pierre-Yves Benhamou[f], Nadine Hoffmeister[g], François Collet[h], Marc Nicolino[i], Rachel Reynaud[j], Jacques Beltrand[a,k], on behalf of SFD, SFEDP and AJD[1]

[a] Université Paris Cité, Institut Cochin, CNRS, INSERM, Paris, France
[b] Assistance Publique Hôpitaux de Paris, Université Paris Cité, Service de Diabétologie et Immunologie Clinique, Hôpital Cochin, Paris, France
[c] Indiana Biosciences Research Institute, Indianapolis, IN, USA
[d] Assistance Publique Hôpitaux de Paris, Université Paris Cité, Service d'Endocrinologie et Diabétologie Pédiatrique, Hôpital Robert Debré, Paris, France
[e] Hospices Civils de Lyon, Université de Lyon, Centre du diabète DIAB-eCARE, Lyon, France
[f] Université Grenoble Alpes, INSERM U1055, LBFA, Endocrinologie, CHU Grenoble Alpes, France
[g] Aide aux Jeunes Diabétiques (AJD), Paris, France
[h] CHU Lille, Psychiatrie de Liaison et psycho-oncologie, Lille, France
[i] Hospices Civils de Lyon, Université de Lyon, Service d'Endocrinologie et Diabétologie Pédiatrique, Lyon, France
[j] Assistance Publique Hôpitaux de Marseille, Université Aix-Marseille, Service de Pédiatrie Multidisciplinaire, Hôpital de la Timone, Marseille, France
[k] Assistance Publique Hôpitaux de Paris, Université Paris Cité, Service d'Endocrinologie, Gynécologie et Diabétologie Pédiatrique, Necker Hospital, Paris, France

ARTICLE INFO

*Keywords:*
Autoantibodies
Insulin secretion
Ketoacidosis
OGTT
Screening
Stages

ABSTRACT

The natural history of type 1 diabetes (T1D) evolves from stage 1 (islet autoimmunity with normoglycemia; ICD-10 diagnostic code E10.A1) to stage 2 (autoimmunity with dysglycemia; E10.A2) and subsequent clinical stage 3 (overt hyperglycemia), which is commonly the first time of referral. Autoantibody testing can diagnose T1D at its preclinical stages 1–2 and lead to earlier initiation of care, particularly for first-degree relatives of people living with T1D, who are at higher genetic risk. Preclinical T1D screening and monitoring aims to avoid inaugural ketoacidosis and prolong preservation of endogenous insulin secretion, thereby improving glycemic control and reducing long-term morbidity. Moreover, early management can help coping with T1D and correct modifiable risk factors (obesity, sedentary lifestyle). New treatments currently under clinical deployment or trials also offer the possibility of delaying clinical progression. All these arguments lead to the proposition of a national screening and care pathway open to interested first-degree relatives. This pathway represents a new expertise to acquire for healthcare professionals. By adapting international consensus guidance to the French specificities, the proposed screening strategy involves testing for ≥ 2 autoantibodies (among IAA, anti-GAD, anti-IA-2) in relatives aged 2–45 years. Negative screening (~95 % of cases) should be repeated every 4 years until the age of 12. A management workflow is proposed for relatives screening positive (~5 % of cases), with immuno-metabolic monitoring by autoantibody testing, OGTT, glycemia and/or HbA1c of variable frequency, depending on T1D

*Abbreviations:* aAb, autoantibodies; ADAP, antibody detection by agglutination-PCR; BMI, body mass index; CGM, continuous glucose monitoring; CI, confidence interval; DKA, diabetic ketoacidosis; ECL, electrochemiluminescence; ELISA, enzyme-linked immunosorbent assay; GAD, glutamate decarboxylase; GRS, genetic risk score; HLA, human leukocyte antigen; HR, hazard ratio; IAA, insulin auto-antibodies; IA-2, tyrosine phosphatase; IASP, Islet Autoantibody Standardization Program; ICA, islet cell antibodies; ICD-10, International Classification of Diseases 10; OGTT, oral glucose tolerance test; LIPS, luciferaseimmuno precipitation system; PwT1D, person living with type 1 diabetes; SMBG, self-monitoring blood glucose; T1D, type 1 diabetes; TATR, time above tight range; TITR, time in tight range; ZnT8, zinc transporter 8.

☆ This Expert Position Statement has also been endorsed by the SFD Paramedical, the French Federation of Diabetic People (FFD), the French Society of Endocrinology (SFE), the French Federation of Endocrinologists/Diabetologists (FENAREDIAM), the National Professional Council of Endocrinology, Diabetology and Nutrition (CNP-EDN), the College of Diabetologists and Endocrinologists of General Hospitals (CODEHG), the French Society of Immunology (SFI) and the French Society of Clinical Biology (SFBC).

* Corresponding author at: INSERM U1016 Cochin Institute, GH. Cochin-Port Royal – 123 boulevard de Port Royal, F-75014, Paris, France.
*E-mail address:* roberto.mallone@inserm.fr (R. Mallone).

[1] SFD: Société Francophone du Diabète (Francophone Diabetes Society); SFEDP: Société Française d'Endocrinologie et Diabétologie Pédiatrique (French Society of Pediatric Endocrinology and Diabetology); AJD: Aide aux Jeunes Diabétiques (Association for French Diabetic Youth)

https://doi.org/10.1016/j.diabet.2024.101603
Received 30 August 2024; Received in revised form 29 November 2024; Accepted 11 December 2024
Available online 13 December 2024

stage, age, patient preference and available resources, as well as the definition of expert centers for preclinical T1D.

## Rationale for screening and care for preclinical type 1 diabetes

Type 1 diabetes (T1D) is an autoimmune disease that can be diagnosed before its clinical stage of permanent hyperglycemia and insulin deficiency by screening for islet autoantibodies (aAbs). Clinical T1D is associated with an excess mortality, and there are two major arguments in favor of early screening and management:

1). Prevention of diabetic ketoacidosis (DKA) [1]. In France, almost half of newly-diagnosed children present with DKA, and 58 % of death cases in children with T1D are linked to DKA [2]. Moreover, DKA at clinical onset has a short- and medium-term neurocognitive impact [3] and is associated with worse glycemic control over time [4–6], and hence with T1D morbidity. The initial metabolic control is indeed a major stake, as it predicts later control, particularly during adulthood [4–6]. Awareness campaigns on the warning signs of hyperglycemia are not sufficient to anticipate diagnosis. In France, a national campaign has led to only a modest and only transient reduction of DKA at clinical onset (from 44 to 41 %) [7]. Moreover, although the risk of inaugural DKA is generally lower in first-degree relatives (FDRs) of a person living with T1D (PwT1D), the difference with the general population is not statistically significant in most studies [8]. Hence, the simple knowledge of the disease does not afford early diagnosis.

2). The preservation of a residual endogenous insulin secretion (C-peptide), which also affords better glycemic control over time [9]. Besides avoiding DKA, screening facilitates such preservation in almost all cases (91–97 %) [10,11] by leading to a more favorable clinical presentation: no weight loss, lower HbA1c and glycemia levels [10–12]. This also translates, in ~28 % of cases, into an absence of immediate insulin needs [11], which alleviates early management and the experience of diagnosis by patients. The DCCT study clearly illustrated the association between glycemic control achieved by intensive T1D treatment, preservation of endogenous insulin secretion [reflected by an orally stimulated C-peptide level $\geq$ 0.2 nmol/l (0.60 ng/ml)] and a reduced risk of retinopathy progression, onset of microalbuminuria and severe hypoglycemic episodes [13]. The latter seem influenced by even lower C-peptide levels (0.03- 0.2 nmol/l; 0.09–0.45 ng/ml) [14]. In addition, the prospective EDIC study documented the benefits on long-term complications of optimal glycemic control during the first 6.5 years of the DCCT follow-up. As for type 2 diabetes, a "metabolic memory" effect (also known as the "legacy effect") has thus been described, with such benefits persisting over time despite an equivalent glycemic control thereafter [15]. The presence of a stimulated C-peptide even modestly higher (e.g. 0.15 vs. 0.10 nmol/l; 0.45 vs. 0.30 ng/ml) during the first 5 years of clinical disease translates into a risk reduction of 11 % for severe hypoglycemic episodes and of 27 % for retinopathy progression [16,17]. Similar benefits have been described for renal and cardiovascular complications: 10 % lower early HbA1c values (e.g. 7.2 % vs. 8 %) are associated with a hazard ratio (HR) of cardiovascular events of 0.72 30 years later [18,19], and with a risk of microalbuminuria and albuminuria at 4 years that is 53 % and 86 % lower, respectively [15,20]. A recent modeling [14] on $>$ 6000 PwT1D followed up for a median of 5 years and adjusted for age at diagnosis and T1D duration has shown that a C-peptide $\geq$ 0.2 nmol/l (0.6 ng/ml) has an impact on: *a)* insulin doses (27 % lower); *b)* HbA1c levels (2.6 % lower); *c)* hospitalizations for DKA (HR 0.44); *d)* incident retinopathy (odds ratio 0.51). Even the preservation of a minimal insulin secretion has therefore significant clinical and metabolic implications.

T1D meets several of the French *Haute Autorité de Santé* recommendation criteria for screening [21]. It can be diagnosed early according to defined preclinical stages [22]. Screening tests with suitable diagnostic performances are available. This screening affords a progressive transition toward clinical disease, thus affording DKA avoidance and some C-peptide preservation that has a major impact on long-term morbidity. Teplizumab, currently accessible as compassionate treatment in France, offers a first therapeutic option to delay clinical progression [23]; several other treatments are currently under trial. General population screening is already on the agenda of European and national health policymakers [24], as it would provide the most comprehensive coverage (since ~90 % and ~10 % of new T1D cases arise in families without and with affected FDRs, respectively). While acknowledging this limitation, FDR screening can yield a ~4-fold higher capture rate of preclinical stage 1–2 T1D cases (1.07 % vs. 0.29 % in the general population) [25] and is not only already possible, but indisputably useful to curb the natural history of T1D in this high-risk group. In France, the framework of diabetes prevention policies in the *Plan National Priorité Prévention* does not mention T1D screening [26]. These arguments invite to translate early T1D diagnosis from the clinical research setting into routine care by developing an appropriate screening and management pathway offered to families with an affected FDR. Healthcare professionals need to acquire novel skills to propose a sensible, informed and facilitating process, discuss its benefits and limitations, and organize the patient journey. This position statement aims to provide guidelines to the French diabetology community on how to screen for and manage preclinical T1D as part of routine care. To this end, this statement adapts international consensus guidance [27] to the French specificities and available resources, it addresses some limitations [28], and it extends this guidance to the initial screening steps, here focused on FDRs.

## The natural history of T1D: stage 1, 2, 3

T1D develops in stages [22] (Fig. 1), with the preclinical stages 1 and 2 starting months or years before clinical stage 3.

Stage 1 is marked by the presence of isolated, asymptomatic islet autoimmunity, defined by the detection of $\geq$ 2 of the 4 aAbs routinely tested that target the β-cell antigens insulin (also called IAA for insulin aAbs), GAD, IA-2 and ZnT8. These aAbs indicate an active β-cell destruction process, which does not yet translate into any glycemic abnormality at this stage. Stage 1 T1D can be preceded by a pre-stage 1, marked by the presence of a single aAb. At pre-stage 1, the risk of progression is overall low, but highly variable depending on the subsequent seroconversion or not for additional aAbs [29,30].

Stage 2 is defined by the association of aAbs with biomarkers of an initial, presymptomatic β-cell impairment, with loss of first-phase insulin secretion that translates into transient hyperglycemia, detectable at the early time points (30–90 min) of an oral glucose tolerance test (OGTT).

Stage 3 is marked by a more profound insulin deficiency with fasting and/or post-prandial hyperglycemia. While this stage is typically symptomatic (stage 3b), it can be preceded by a presymptomatic stage 3a [11].

The biomarkers used to diagnose these different stages are therefore (Fig. 1):

- At stage 1: immune biomarkers (aAbs);
- At stage 2 and 3: metabolic biomarkers (OGTT, glycemia and HbA1c).

Given the very high likelihood of clinical progression (Table 1), the

detection of ≥ 2 aAbs marks the onset of the disease, even if still preclinical. It is hence more appropriate to speak about T1D early diagnosis rather than risk screening. Only individuals at genetic risk (based on family history) without aAbs, or those with only a single aAb (pre-stage 1), can be classified as "at risk", whereas those with multiple aAbs already have preclinical T1D. This classification into stages calls for a revision of healthcare policies, as it no longer considers people at stages 1 and 2 as healthy, at-risk subjects, but rather as individuals already affected by an active, chronic and progressive autoimmune disease [31]. The International Classification of Diseases (ICD)−10 has recently integrated this novel classification by introducing the diagnostic codes E10.A0 (preclinical T1D, unspecified), E10.A1 and E10.A2 (preclinical T1D, stage 1 and 2, respectively). These changes position T1D screening as an essential first step toward early diagnosis, justifying a healthcare coverage.

## Limitations and benefits of screening

Screening should bring more benefits than drawbacks to the person screened. However, the individual perception of their relative weight varies widely. It is therefore important to present both sides in a balanced way.

### *Limitations*

The main limitation of screening is that it diagnoses a preclinical disease whose rate of progression varies greatly between individuals. While aAbs provide precise probability estimates, this probability spreads over several months or years, which requires longitudinal follow-up. This uncertainty can lead to chronic anxiety in the FDR/family screened, and may have an impact on family dynamics and the psychological development of children.

### *Benefits*

Firstly, a negative screening result is the most frequent outcome (~95 % of cases). Even if it does not completely eliminate the possibility of a positive result later in childhood, screening will therefore most often reassure the FDR/family screened. Secondly, a positive screening result yields several expected benefits, as it can lead to preventive measures and simplify the care pathway by:

- Preventing DKA: early T1D diagnosis through screening is associated with a marginal (~4 %) incidence of DKA at clinical onset [10–12];
- Correcting modifiable metabolic risk factors, such as obesity and sedentary lifestyles, which accelerate progression to stage 3 [25] and/or shorten remission periods [32];
- Allowing for early stage 3 management in an outpatient rather than emergency setting;
- Preserving some endogenous insulin secretion;
- Allowing to propose disease-modifying treatments that may delay clinical progression.

**Table 1**
Risk of clinical progression according to stage.

| | Risk of stage 3 T1DM | | | |
|---|---|---|---|---|
| | At 5 yrs | At 15 yrs | Lifelong | References |
| Pre-stage 1 | 7 % | ~15–40 %* | NA | [29,30] |
| Stage 1 | 44 % | 85–92 %** | >99 % | [36,37] |
| Stage 2 | 75 % | 100 % | >99 % | [36] |

For pre-stage 1 and stage 1, data is available only for children. *Estimated risk, highly variable depending on the subsequent seroconversion for other aAbs or lack thereof. **85 % or 92 % in the presence of 2 or 3 aAbs, respectively. NA, not available.

### *Ethical aspects*

Although the situation of preclinical T1D is different, the six principles of good practice for genetic testing for medical purposes (French decree of May 27, 2013) provide a useful framework:

*1) Right not to know; 2) Respect of independent decision-making; and 3) Informed consent*

A factual rather than incentive information on screening options and implications should be provided. A proposal for screening could indeed imply that it would be preferable to know, thus making it difficult to guarantee the right not to know. On the other hand, the sole fact of informing about screening can generate anxiety, as a decision needs to be taken. Healthcare professionals should therefore not shy away from

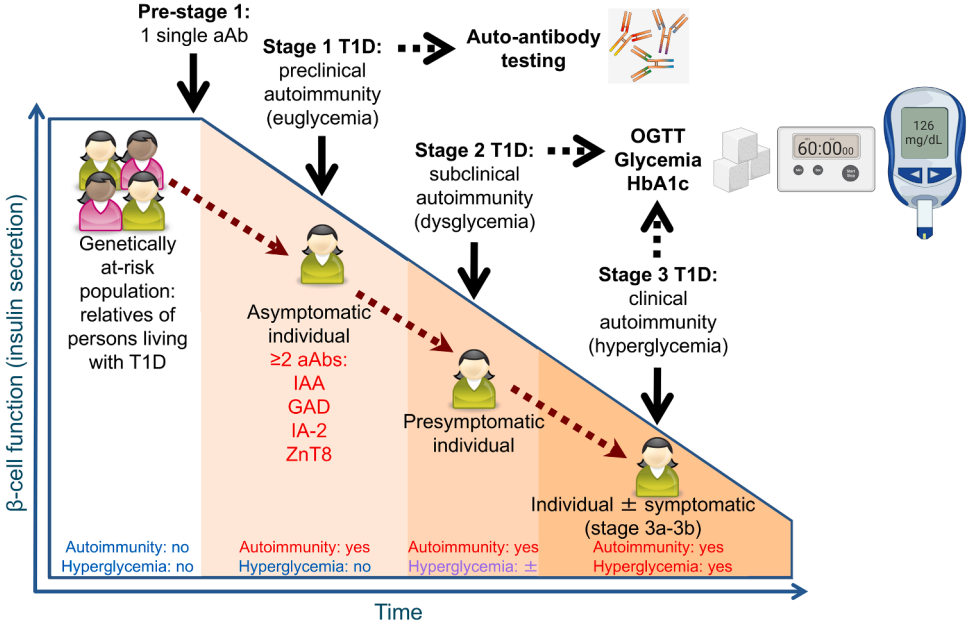


**Fig. 1.** T1D natural history and laboratory tests used to diagnose stage 1, 2 and 3. Note that the decline in insulin secretion is not always linear in time. It can progress at different rates and through more or less active phases of β-cell destruction, likely accelerating at the transition between stages.

supporting this decision-making process, by helping the FDR/family to prioritize what is most important to them in this decision [33], while respecting their eventual choice and the possibility of later withdrawal. This will enable each person to choose screening if desired, and to not feel influenced if they do not. The right not to know and respect of independent decision-making can be problematic when the parents decide for the child. This aspect should therefore be integrated in the information delivered.

*Benefits of the test*

What is feasible is not necessarily always desirable. Since screening can be a source of uncertainty, the beneficence-relevance and non-harmfulness of screening should be considered. Beneficence depends on the relevance of the screening indication, the support provided and the quality of follow-up. Preventing harmfulness requires ensuring that the information given is properly understood and that healthcare professionals are accessible and flexible in order to limit the constraints of follow-up, which can also influence long-term compliance. This personalized approach should take into account not only the T1D stage, but also the psychology, lifestyle and history of the FDR/family.

*Confidentiality*

As with all medical data, screening and follow-up results must remain confidential. This includes the right of the person to not declare a positive screening result, e.g. when subscribing an insurance or a loan (law 2002–303 of March 4, 2002 on patients' rights and the quality of the healthcare system).

*Equal access to care*

Screening should be accessible to all interested persons, regardless of their socio-educational status.

*Psychological impact of screening: literature data*

A positive screening result can be a source of anxiety for the FDR/family screened. On one hand, the screened individual will begin a medical follow-up of variable duration, potentially leading to insulin dependence. On the other, the diagnosis may lead to lifestyle changes, notably dietary restrictions, that may have an impact on the child's development or behavior.

The stress induced by screening has been analyzed in several prospective cohorts. In the German Fr1da general population study, the maternal stress upon announcement of a child's positive screening was equivalent to that experienced at T1D clinical onset [25]. However, this stress rapidly normalized over the following 12 months. Parents in another cohort reported better psychological adjustment (parental stress, child's quality of life) in the first year after clinical onset compared to controls without prior screening [34]. These results bring two key messages. On one hand, the stress of announcement is unavoidable when anticipating T1D management. On the other, its rapid normalization may suggest that the uncertainty of the situation is at least partly compensated by a feeling of security associated with this early management. This feeling may also derive from the better conditions of announcement of a positive screening compared with the urgent situation of clinical onset.

*Psychological aspects to integrate in the screening pathway*

Screening for preclinical T1D often equals to an early diagnosis, because it announces an event that will definitely occur in the future, although with a time uncertainty. On the other hand, it is not properly a preventative approach, because it is not yet possible to avoid clinical progression, but it is already possible to prevent the complications of a late diagnosis, subject to regular follow-up. FDRs/families are informed that they have a chronic, incurable disease, even if they can remain asymptomatic for a variable period. Therefore, several psychological aspects involving the whole family should be considered.

*Disruption of the parent-child relationship*

Parents may change their view of their child, considering him/her to be already ill without knowing when symptoms will appear. This uncertainty ("sword of Damocles" effect) can lead to stress, feeling of helplessness, difficulties with family planning, and overprotective behaviors, e.g. excessive capillary blood glucose testing, drastic changes in diet or physical activity. The screening result can also disrupt relationships among siblings, or the parents' relationship with each child. The configuration of the family is also relevant, as screening a sibling has different implications than screening a child of a PwT1D. The child's representation and understanding of the disease should also be considered. Conflicts with a parent/brother/sister and the psychological mechanism of "magical thinking" can lead, in the event of a positive screening, to feelings of responsibility, guilt or punishment.

*Preclinical biomarkers and bodily experience*

Preclinical biomarkers anticipate bodily experience, which can hinder the process of appropriating the disease. This can lead not only to distrust of one's own body, but also to a sense of intrusion due to monitoring by parents and/or medical teams. Monitoring glucose levels requires adapting to intrusive devices, which can be more difficult than at clinical stage 3 due to the absence of symptoms. The predictive knowledge introduced by screening can also lead to mistrust or insecurity about the future, and influence the relationship with the existential uncertainty necessary for psychological construction. Indeed, one of the main psychological consequences of screening and predictive medicine is that they can engender a "psychopathology of temporality" [35]. As several years can elapse before symptomatic T1D, the FDR/family will have to live with the anticipated knowledge of a disease that is not yet clinically declared, without knowing when it will. Hence, this prediction somehow inverts the relationship with temporality, because it makes a future event already present and can provoke a stunning of thought. A multidisciplinary approach to screening is therefore essential to anticipate and support any psychopathological risk and enable each individual to feel and behave as the actor of his/her own life.

## Stage 1 T1D: prognostic stratification

Table 1 shows the risk of progression to stage 3 at the preclinical stages 1 and 2.

At stage 1, different parameters can further stratify this risk of progression.

*Affected FDR*

T1D risk in FDRs of a PwT1D is 10–20-fold higher than in the general population [38]. However, once positive for $\geq 2$ aAbs, the risk of stage 3 T1D in children with or without an affected FDR is similar, with a cumulative risk of $> 99$ % (Table 1) [25]. In the French population, the a priori risk of T1D before the age of 20 is ~0.4 % in the absence of affected FDRs, whereas it is 4 % when the PwT1D is a sibling or the mother, and 8 % if it is the father [39]. In the case of a monozygotic twin of an index case, the risk is 18 % at age 20 and 65 % at age 60 [40].

*Age of screened FDR*

The risk of progression is strongly modulated by the age at seroconversion, and is particularly high before 3 years of age. While a

repeated screening is still recommended in the absence of aAbs after the age of 4, <20 % of those who seroconvert by age 10 will progress to stage 3, often at a slower pace (> 10 years later) [41].

*BMI*

The relative risk of preclinical (stage 1 or 2) T1D is 1.77 higher in obese children [95 %CI 1.08;2.71], as is the risk of clinical progression (1.48 [0.63;3.47]), even in overweight children (1.48 [0.73;3.03]) [25].

*Number of positive aAbs*

This is the major determinant of the risk of clinical progression. While the presence of a single aAb is not diagnostic of stage 1 (with a 15 % risk of progression at 10 years) [29], additional aAbs can appear over time. However, the majority of these pre-stage 1 individuals do not develop a second aAb; for those who do, seroconversion for a second aAb occurs shortly thereafter, with a median delay of 6.8 [3.2;17.0] months [42]. The presence of 2 aAbs marks the entry into preclinical T1D, with an 85 % risk at 15 years that increases further with 3 aAbs (92 % at 15 years) [36,37].

*aAb specificity*

A first seroconversion for IAA marks a higher risk of progression than for anti-GAD in children [43], while the descending risk hierarchy for the second aAb is: anti-IA-2 > anti-ZnT8 > IAA > anti-GAD [44].

*IAA*

IAA are found more commonly in children and mark a higher risk of progression at a very young age [45], often associated with the predisposing HLA haplotype DR4/DQ8 [39]. Specifically, a first seroconversion for IAA before the age of 4 confers a 73 % risk of multiple positive aAbs in the following 5 years, while this risk is only 11 % after the age of 4 [46–48], underlining the importance of the age factor. A single IAA positivity in children can therefore justify a closer surveillance in the short term. IAA are not informative in persons previously treated with insulin (e.g. for gestational diabetes).

*Anti-GAD*

Anti-GAD are often the first aAbs to appear in children > 3-year-old and in adults [49]. This later seroconversion is often associated with the predisposing HLA haplotype DR3/DQ2 [39] and marks a slower progression [42]. Anti-GAD titers can decrease or even become negative over time; seroreversion decreases the risk of progression in the case of a single anti-GAD aAb status [42]. A first seroconversion for a single anti-GAD rather than IAA aAb can therefore justify a less frequent surveillance. The risk of progression subsequently changes with age [48], with a stronger effect for anti-GAD and a weaker effect for IAA [50].

*Anti-IA-2 and anti-ZnT8*

They more commonly follow seroconversion for other aAbs [51]. Anti-IA-2 rarely revert [52] and are strongly associated with rapid progression independent of age [53,54]. Anti-ZnT8 are also predictive of faster progression, notably in adolescents and adults [55].

*aAb titers*

Even if prognostic stratification is mainly modulated by the number of aAbs, high/increasing anti-IA-2 titers mark an even higher risk of progression [56]. Conversely, high-titer anti-GAD are associated with a lower risk [57]. Caution should be taken with low aAb titers (e.g. < 3-fold above the positive cutoff), especially in the presence of a single aAb, as those results reflect false or transiently positive results in approximately two-thirds of cases [58].

*Sub-stages 1a-1b*

It is possible to distinguish two subgroups of individuals at stage 1a (low risk) and 1b (high risk) using a progression likelihood score based on values of HbA1c, glycemia at 90 min of OGTT and the presence and titers of anti-IA-2 aAbs [56]. While the risk of progression to stage 3 at 30 months is 8 % for stage 1 as a whole, it is 4 % for stage 1a and 46 % for stage 1b, which is similar to the risk at stage 2 (48 %).

*HLA genotype*

In the presence of aAbs, risk can be further stratified with an HLA Class II genotyping (HLA-DRB1, -DQB1 genes). The wide polymorphism of these loci, the linkage disequilibrium driving combined transmission of some alleles (DR4/DQ8, DR3/DQ2, DR15/DQ6) and the HLA nomenclature may make these results difficult to interpret for clinicians. While multiple nuances exist [59,60], the presence of a single predisposing allele (DQ2, mainly DQB1*02:01; DQ8, mainly DQB1*03:02) marks a moderate genetic risk, while the presence of two alleles (DQ2 and DQ8) marks a high risk. Conversely, the presence of the protective allele DQ6 (DQB1*06:02) marks a low risk, even in the presence of positive aAbs and/or of the predisposing alleles DQ2 or DQ8. First-line screening of at-risk individuals by HLA genotyping is not suitable in routine care, given its higher cost and the high prevalence of predisposing alleles in the general population. HLA genotyping (4 digits) can be used as a second-line strategy for further prognostic stratification in aAb+ individuals. Genetic risk scores combining other non-HLA predisposing alleles are promising [61] but not yet applicable to clinical practice.

The overall criteria of prognostic stratification at stage 1 T1D are summarized in Table 2.

## Stage 2 T1D: diagnostic criteria

When the screening returns ≥ 2 positive aAbs, the next step is to define whether this autoimmunity translates into an impairment of insulin secretion (stage 2, or even stage 3). The recommended diagnostic test is OGTT, because the presence of a glycemia ≥ 200 mg/dl at its intermediate time points is the most sensitive diagnostic criterion [27,31]. These early and transient hyperglycemias witness the loss of first-phase (rapid) insulin secretion [62], with a prolonged second phase that can sometimes lead to repeated episodes of postprandial hypoglycemia. OGTT is measured after an oral glucose load of 1.75 g/kg for a maximal load of 75 g, with blood draws every 30 min for 2 h.

Stage 2 diagnosis can also rely on less sensitive criteria: a glycemia at 2 h of the OGTT between 140 and 199 mg/dl (7.7–11.0 mmol/l); a moderate fasting hyperglycemia (100–125 mg/dl; 5.6–6.9 mmol/l), or a random glycemia between 140 and 199 mg/dl (7.7–11.0 mmol/l); HbA1c values that are either intermediate (5.7–6.4 %; 39–46 mmol/mol) or increase ≥ 10 % versus the previous value (i.e. even in the normal range < 5.7 %), as this increase predicts progression to stage 3 within a median of 12 months [63,64]. As in the recent Breakthrough T1D (formerly JDRF) consensus [27], we retain an additional criterion based on continuous glucose monitoring (CGM). *A* > 10 % time above tight range (TATR; > 140 mg/dl or 7.7 mmol/l) is associated with an 80 % risk of progression to stage 3 within 12 months (88 % sensitivity, 91 % specificity) [65]. For stage 2 diagnosis, the threshold is a TATR ≥ 10 % and < 20 % (as values ≥ 20 % are rather associated with stage 3 T1D) on at least 10 days of CGM [27]; this diagnosis must however be confirmed by at least one other criterion. The Breakthrough T1D consensus also acknowledges the possibility of reversion from stage 2 to stage 1 (and sometimes even from stage 3 to 2) and recommends a diagnosis based on the simultaneous presence of at least 2 criteria, or of only one criterion

**Table 2**
Criteria for prognostic stratification at stage 1 T1DM.

| Criterion | Prognostic stratification | Comments |
|---|---|---|
| T1DM FDR | None: 0.4 % Mother or sibling: 4 % Father: 8 % Monozygotic twin: 18 % | A priori T1DM risk (prior to screening) till 20 years of age. Risk further increases in multiplex families, with a younger age at clinical diagnosis of the index case, or if the unaffected FDR has autoimmune comorbidities. |
| Age | Higher risk of progression with younger age at seroconversion. | Notably for children ≤ 3-year-old. |
| BMI | Higher risk with associated obesity. | Risk of stage 1–2 and of progression to stage 3. |
| Number of aAbs | 3 aAbs > 2 aAbs | Little difference between the presence of 3 or 4 aAbs. |
| aAb specificity | 1st aAb: IAA > GAD (children), 2nd aAb: IA-2 > ZnT8 > IAA > GAD | No difference between a sequential seroconversion (e.g. IAA then GAD) and a simultaneous seroconversion (e.g. IAA and GAD at once). |
| aAb titers | High-titer IA-2: higher risk, High-titer GAD: lower risk | No difference for the titers of other aAbs. |
| Progression likelihood score | Based on HbA1c, 90 min glycemia at OGTT, anti-IA-2 titers | $Exp[(HbA1c-5.233) \times 1.125 + (OGTT_{90}-107.6) \times 0.0195 + (IA\text{-}2_{cat}-1.27) \times 0.662]$, *HbA1c in %;* $OGTT_{90}$ *in mg/dl;* $IA\text{-}2_{cat}$ *in tertiles (0, 1, 2, 3). Stage 1a (score ≤4, ≤90th percentile): 4 % risk at 30 months. Stage 1b (score >4, >90th percentile): 46 % risk at 30 months.* |
| HLA Class II (genetic risk) | DQ2 and DQ8: high risk DQ2 or DQ8: moderate risk DQ6: low risk Other alleles: neutral risk | DQ2=DQB1*02:01; DQ8=DQB1*03:02; DQ6=DQB1*06:02. A 4-digit genotyping is needed to correctly interpret results. |

documented at two different occasions within 12 months. This more restrictive criterion is here retained.

Insulin secretion becomes significantly compromised only in the 6–12 months before progression to clinical stage 3 [66], more often with glycemia > 200 mg/dl (11 mmol/l) at the 2 h of the OGTT [67]. The diagnostic criteria for stage 1, 2 and 3 are summarized in Table 3.

**Table 3**
Diagnostic criteria for stage 1, 2 and 3 T1DM in the presence of ≥ 2 aAbs
Stage 2 diagnosis is made with the simultaneous presence of 2 of the 6 criteria listed (OGTT at intermediate time points or at 120 min, fasting or random glycemia, HbA1c, CGM), or with the presence of a single criterion on 2 occasions within 12 months. *Values found at 2 separate occasions, or on a single occasion in the presence of hyperglycemia symptoms; **this diagnostic criterion must be confirmed by at least one other criterion.

| | Stage 1 T1DM | Stage 2 T1DM | Stage 3 T1DM |
|---|---|---|---|
| OGTT | *a)* 120 min <140 mg/dl; and, *b)* 30, 60 and 90 min < 200 mg/dl | *a)* 120 min 140–199 mg/dl; or *b)* 30, 60 or 90 min ≥ 200 mg/dl | 120 min, ≥ 200 mg/dl |
| Fasting glycemia | < 100 mg/dl | 100–125 mg/dl | ≥ 126 mg/dl |
| Random glycemia | – | 140–199 mg/dl | ≥ 200 mg/dl* |
| HbA1c | < 5.7 % | 5.7–6.4 % or increase ≥ 10 % | ≥ 6.5 % |
| MCG | – | TATR 10–20 %** | TATR ≥20 %** |

## Guidelines for T1D screening in FDRs of PwT1D

### *How to accompany the screening decision*

An informative stance should be adopted, announcing a *possibility* rather than a *proposal* for screening. This information can be given at any time but should avoid, unless explicitly requested, stress situations (e.g. clinical T1D onset of the index case, pregnancy in an affected family). Screening should neither be refused when requested nor imposed in case of reluctance after delivering information. It is useful to provide eligible FDRs and healthcare professionals with information supports, under preparation by scientific/medical societies and patient associations, in the form of a short practical guide and a suitable information campaign (posters, websites, social media) outlining the limitations and benefits of screening, the proposed follow-up and the attention to ethical principles. These information supports should also remind the warning signs of hyperglycemia and DKA; the threshold values of glycemia requiring specialist advice; and the contact information of expert regional hospital centers that can reply to the questions of FDRs/families and of their referring physicians.

### *FDRs eligible for screening*

Eligible persons are FDRs of PwT1D: children, parents, siblings and half-siblings.

### *Screening in children and in adults*

Our knowledge on the natural history of T1D is largely derived from prospective studies in children and is far less precise in adults, as we know their aAb prevalence but not incidence, i.e. the age of seroconversion. The ASK general population study has reported a similar aAb prevalence in children (3.2 %; 0.4 % with ≥ 2 aAbs) and adults (3.9 %; 0.6 % with ≥ 2 aAbs) [68]. While seroconversion can probably occur at any age, the clinical progression following a late seroconversion is unknown. It is possible that a large proportion of these aAbs may have been present for a long time and hence would indicate less aggressive autoimmunity. This exemplifies the age-related heterogeneity of preclinical T1D [69], mirrored by the residual insulin secretion after clinical onset, which shows a faster decline at younger age [70]; and by histopathological studies documenting more extensive insulitis and β-cell loss in children [71]. Based on this knowledge, screening is justified in both children – as some residual insulin secretion can only be preserved by careful management after early diagnosis – and adults, because they represent the larger proportion of new T1D cases (62 % vs. 38 % in children), with a median age of 39 years [72]. Even if DKA at clinical onset is overall less frequent in adults [73], mis-diagnosis as type 2 diabetes (~40 % of cases) [74] significantly contributes to its incidence.

### *Age of first screening*

#### *Evidence*

In children who progress to stage 3 T1D, seroconversion occurs more frequently before 3 years and very rarely before 6 months of age [47,75]. Moreover, aAb testing before 12 months of age can detect antibodies transferred by the mother [76], especially in the case of breastfeeding. Those can be either aAbs (if the mother has T1D or asymptomatic islet autoimmunity) or antibodies against exogenous insulin (if the mother has T1D or had insulin-treated gestational diabetes). Incidentally, maternal aAb transmission does not predispose to T1D and could even be partially protective [77].

#### *Guidelines*

A first screening can take place between 2 and 4 years of age. There is however no consensus on the upper age limit. We align with the pragmatic strategy of several cohorts (e.g. INNODIA) that propose a first

screening up to an age of 45 years.

*Repeated screening in case of prior negative result*

*Evidence*

A meta-analysis of 4 prospective cohorts (total 24,662 children) reported that screening with IAA, anti-GAD and anti-IA-2 aAb testing at the age of 2 then of 6 years can reach 82 % sensitivity (i.e., probability to find ≥ 1 aAb) and 79 % positive predictive value (PPV; i.e., probability of stage 3 progression before the age of 15) [78]. Complementary analysis on the same cohorts [79] documented that screening at 10 years of age would reach 90 % sensitivity and 66 % PPV before the age of 18.

*Guidelines*

In children screening negative between 2 and 4 years of age, repeated screening may be offered between 6 and 8 years and then between 10 and 12 years of age. More generally, repeated screening may be proposed 4 years after a first negative screening till 12 years of age. Thereafter, a single screening is probably sufficient to detect the majority of those with ≥ 1 aAb. Therefore, a negative screening at ≥12 years of age may not need to be repeated.

*Prescription and blood collection*

To be cost-effective and widely accessible, screening pathways should be advertised with information campaigns and organized across different settings, including hospital centers, private practice diabetologists/endocrinologists, and general practitioners in close collaboration with specialists. The support of an expert regional hospital organized ahead of any prescription is essential to answer questions of FDRs/families and physicians and for subsequent follow-up. Screening must not be started if the practitioner is not prepared to answer such questions or to refer to an expert center to deliver appropriate information.

Sampling can be performed by caregivers, medical laboratories or at home (using capillary self-collection kits).

*Available aAb assays*

The quality of available assays is highly heterogeneous and different techniques can be used: radio-binding or non-radioactive assays [80], using LIPS (luciferase immunoprecipitation system), or "bridging" techniques such as electrochemiluminescence (ECL) or ELISA. Islet cell antibodies (ICA) assayed by indirect immunofluorescence on human pancreas sections are seldom used today and have no place for first-line screening.

Simplified assays have also been developed specifically for screening purposes. Those validated and used in screening studies are:

1). RSR 2Screen or 3Screen assays [25]: they respectively provide a combined GAD/IA-2 or GAD/IA-2/ZnT8 aAb readout, i.e. without specifying which aAb is positive or negative. These assays, which do not include IAA, are nevertheless acceptable for the initial identification of stage 1 individuals (≥ 2 aAbs) to limit costs. They require small serum volumes and can be performed on capillary blood.
2). ADAP (antibody detection by agglutination-PCR) assays from Enable Biosciences [81,82]: they exploit the multivalency of aAbs to aggregate antigen-DNA conjugates in close proximity. DNA is amplified by PCR only when aAbs bind their antigens. This sensitive technique can measure all 4 aAbs simultaneously (including IAA), as well as anti-transglutaminase aAbs for celiac disease screening, and provides individual readouts for each aAb, but at higher cost. It can be performed on capillary blood spots collected on blotting paper [82].

*aAb assay options for screening*

*Evidence*

IAA and anti-GAD aAbs are the most frequently found at seroconversion [39]. Although missing single-IAA positivity, which is prognostically relevant in young children [45], initial testing for anti-GAD and anti-IA-2 aAbs proved satisfactory for general pediatric population screening [25]. Anti-ZnT8 rarely appears first. In the Fr1da study, ~6 % of cases were not confirmed as ≥ 2 aAb+ on a second venous blood sample [83]. This confirmation is critical also because approximately one-third of single-aAb+ results are false positives (particularly in the case of low titers), one-third represents a transient positivity, and only another third is indicative of persistent aAbs [58].

*Guidelines*

Screening should include the measurement of ≥ 2 aAbs among IAA, anti-GAD and anti-IA-2. Given their frequency, IAA and anti-GAD may be prioritized. However, as IAA is the most difficult to measure, anti-GAD and anti-IA-2 may be a first-line option. Anti-ZnT8 is not essential for first-line screening. Simplified assays (2Screen/3Screen ELISA, ADAP IAA/anti-GAD or IAA/anti-GAD/IA-2) compatible with capillary blood sampling are particularly suitable for screening. "Secondary" anti-GAD aAb screening in individuals with impaired fasting glucose values on a routine laboratory assessment without FDRs and without risk factors for type 2 diabetes, may also be considered, as this is currently a major path of diagnosis of preclinical T1D and of subsequent referral for specialized follow-up.

Whichever assay is chosen, any positivity must be confirmed by a second measurement of all 4 individual aAbs performed by an expert center on a venous blood sample within 3 months of the positive screening. A negative confirmation test [83] is equivalent to a negative screening. To obtain additional information for stratification into stages 1, 2 or 3, this confirmatory venous sample should also measure a post-prandial glycemia (2 h after a carbohydrate-containing meal) and HbA1c [29,30,37].

*Requirements for a screening laboratory*

aAb assays should be performed by laboratories meeting 3 quality criteria:

1). Use of an assay validated by the international Islet Autoantibody Standardization Program (IASP) [84].
2). IASP validation of the laboratory performance with the chosen assay and positivity threshold. Workshops are regularly organized for this purpose [84].
3). Use of a positive threshold specific to the target population and age group (pediatric and adult), defined as the 98th-99th percentile of values measured in an age-matched non-diabetic population. The corollary of this criterion is that, by definition, 1–2 % of results will be false positives, particularly for low values.

*Report of negative screening results*

The laboratory should report negative screening results (~95 % of cases) to the prescriber, who will then inform the FDR/family, explaining the interpretation of the result and the proposed follow-up (i.e. whether repeated screening is needed). An appropriate information support with contacts of regional expert centers should be provided.

Screening guidelines are summarized in Fig. 2.

## Guidelines for care of preclinical T1D in FDRs of PwT1D

*Definition of an expert center for preclinical T1D*

While screening can be offered in both in- and out-hospital settings

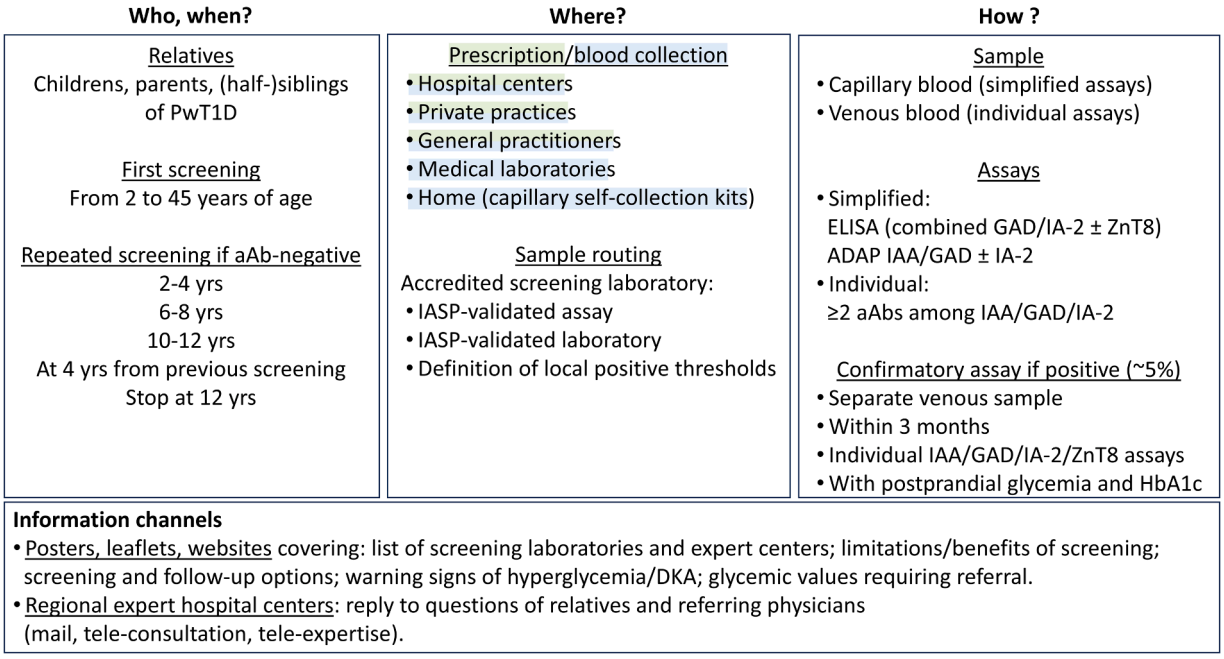


**Fig. 2.** Screening guidelines for relatives of PwT1D.

(the latter with the support of an expert center), follow-up of stage 1, and more particularly stage 2, requires specific expertise covering the entire patient journey: information, interpretation of a positive result and follow-up. Regional expert centers must be clearly identified to enable smooth referral of multiple-aAb+ FDRs. While these expert centers may not necessarily be the same as those caring for the affected FDR(s), they will liaise with these adult/pediatric centers if different. As the percentage of positive FDR screenings is ~5 %, those requiring follow-up by an expert center will be limited. As an example specific to the French population, 679 FDRs (55 % aged < 18-year-old) underwent initial screening as part of the INNODIA study deployed in the Paris region. Of these, 632 (93.1 %) screened negative, 39 (5.7 %) were single-aAb+ (pre-stage 1) and 8 (1.2 %) were multiple-aAb+. The 6 requirements for an expert center are summarized in Table 4.

*Diagnostic announcement of a positive screening test*

The diagnostic announcement should be made, or reviewed (if already made by a referring physician), by the physician of the expert center in charge of subsequent follow-up. This will often be the first contact with the FDR/family and is just as important as the announcement of a stage 3 diagnosis. It must be carried out by an experienced professional in order to establish a relationship of trust. For pediatric FDRs, this announcement should be made in the presence of the child, with age-appropriate explanations.

The doctor should set aside time to listen and discuss the emotional situation; referral to the team psychologist can be proposed. After this initial exchange on the understanding, feelings and representations of the situation by the FDR/family, the diagnostic announcement should integrate therapeutic education actions covering:

- Reminders about T1D and the notion of disease stages;
- Current risk stratification according to the individual age and aAb profile (Table 2);
- The need to refine prognostic stratification by OGTT, or other glucose metrics when OGTT is not accepted or feasible;
- The proposed follow-up, according to stage, age and organization of the center;
- Warning signs of hyperglycemia (polyuria, polydipsia, fatigue, weight loss) and DKA (nausea, abdominal pain, vomiting, acetone breath odor);
- Capillary blood glucose threshold values that should prompt contacting the center (fasting blood glucose ≥ 126 mg/dl; postprandial or random blood glucose ≥ 200 mg/dl);
- Use of a blood glucose meter;
- Specific lifestyle measures (diet, physical activity) to be implemented;
- Information on how to contact the center.

These notions should be regularly reviewed throughout follow-up. Therapeutic education and support (availability of a reference person) are critical for managing the stress of announcement and limiting the risk of hyperglycemia, DKA and prolonged hospitalizations, and can prevent the onset of hyperglycemic symptoms (stage 3b) [11]. In the case of children, the diabetologist of the affected FDR will be informed of the child's entry into follow-up.

**Table 4**
Requirements of an expert center for preclinical T1DM.

| Requirement | Description |
|---|---|
| 1) Expertise and training | Healthcare professionals with an expertise in pediatric or adult diabetology trained in monitoring preclinical T1D. |
| 2) Multidisciplinary healthcare team | Physician, therapeutic education nurse, psychologist, dietician, social worker; ± advanced practice nurse, clinical research infrastructure. |
| 3) Associated medical laboratory | Nearby or remote laboratory proficient in aAb assays and complying with quality requirements. |
| 4) Local link between pediatric and adult centers | To ensure referral between centers according to age and continuity of care at adult transition. |
| 5) Networking with all professionals involved | Regular exchanges with referring physicians and other healthcare professionals. |
| 6) Link to a national registry | GDPR-compliant pseudonymized registry of preclinical T1D case linked with the EU registry (www.pre-t1d-registry.eu), with the aim of regularly evaluating practices and facilitating inclusion in prevention trials. This registry should also include FDRs with a negative screening for epidemiological purposes. |

*Psychological support during screening and follow-up*

Psychological support should be an integral part of the screening process, starting from the information given prior to screening. It should be systematically proposed and integrated into multidisciplinary follow-up visits. Whenever possible, it should be provided by clinical psychologists with specific expertise in diabetes and therapeutic education. The professional will discuss the impact of the announcement and follow-up with the FDR/family, to ensure that the expected benefits outweigh this impact. In the pediatric setting, a separate discussion time should be set aside with parents and children. As emotional adjustment to the diagnosis may change over time, this exchange should be regular, while respecting the requests/needs of the FDR/family.

*Follow-up of FDRs with pre-stage 1 T1D (single-aAb+)*

*Evidence*

In pre-stage 1, the risk of progression is overall low (15 % at 10 years), but highly variable as other aAbs may follow [29,30]. This sequential seroconversion confers the same risk of progression as an initial seroconversion for multiple aAbs [30]. The risk of progression is higher in the short term (10 % at 2 years and 15 % at 10 years) [29,30,37]. It is particularly high before 3 years of age and declines with age [85].

Follow-up should include measurements of the 4 aAbs, if possible combined with postprandial blood glucose and HbA1c [29,30,37], in order to obtain maximum information from a single sample, particularly in children. This follow-up can be directly provided by the referring physician with the support of an expert center [27].

*Guidelines for children*

In children > 3-year-old who are single-aAb+, a 3-year annual follow-up should be proposed. In the absence of progression (persistence of a single aAb or seroreversion), follow-up can subsequently continue as for aAb-negative FDRs (aAb rescreening every 4 years up to 12 years of age). A follow-up every 2 years may be considered in case of a persistent single aAb in the presence of other risk criteria for rapid progression (Table 3), particularly in the uncommon situation of single anti-IA-2 aAbs [29] or in the presence of autoimmune comorbidities.

In children ≤ 3-year-old who are single-aAb+, a more frequent and prolonged follow-up is required (bi-annually for 3 years, then annually for 3 additional years). If still single-aAb+ after this time, further follow-up may be proposed every 2 years till 12 years of age. In the case of seroreversion, follow-up can subsequently continue as for aAb-negative FDRs.

*Guidelines for adolescents and adults*

Follow-up should be proposed every 3 years, or annually in the presence of other risk factors for rapid progression: obesity, predisposing HLA Class II genotypes (combined DQ2/DQ8) if assessed, or a history of stress hyperglycemia or autoimmune comorbidities. Follow-up can stop in the absence of progression after 2 visits (i.e. 6 years).

*Follow-up of FDRs with stage 1 T1D (≥ 2 aAb+)*

Stage 1 marks the onset of disease, albeit asymptomatic. From stage 1 onwards, follow-up should be carried out by expert centers wherever possible (geographical proximity). If this is not possible or not desired, follow-up can be provided by the referring physician or by a diabetologist/pediatrician from a local center, with remote support from an expert center.

*Initial metabolic stratification*

This initial assessment enables to classify preclinical T1D into stage 1 or 2 and to guide subsequent follow-up. It should be carried out in the weeks following confirmation of a positive screening. It will include venous blood sampling for an OGTT (oral glucose load equivalent to 1.75 g/kg up to a maximum of 75 g) with glucose measurements at 0, 30, 60, 90 and 120 min and for HbA1c, in the absence of intercurrent illnesses. Stage 1 and 2 diagnostic criteria are detailed in Table 3. Concomitant C-peptide measurements during OGTT have little added value in routine care.

*Stage 1 follow-up*

*Evidence*

Follow-up should include [27]: OGTT (or postprandial blood glucose measurements, see "OGTT: practical considerations"), HbA1c [63], annual aAb monitoring to detect any additional seroconversion or seroreversion, and capillary self-monitoring of blood glucose (SMBG). It should be noted that seroreversion of some aAbs (with persistence of ≥ 1 aAb) is not associated with slower progression, and actually predicts faster progression in triple-aAb+ children if one aAb disappears [86]. Follow-up should therefore remain the same, as the risk of progression persists even in the case of complete seroreversion [87], which probably explains a proportion of clinical stage 3 onset cases without aAbs [88]. Since the progression rate from stage 1 to stage 3 decreases with age (5-year risk of 35 % in < 12-year-old, 22 % in 12–17-year-old, and 15 % in adults) [44], follow-up should be more frequent in children and less so in adolescents/adults. A more frequent follow-up can be proposed in the presence of other risk factors for rapid progression (Table 2), of autoimmune comorbidities, and based on glycemic parameters.

Depending on their needs, the FDR/family can benefit from a nutritional and psychological follow-up and from training on SMBG and current treatments for preclinical and clinical T1D, in order to acquire the necessary autonomy, promote a healthy lifestyle, manage psychological burden, and better cope in case of progression to stages 2 and 3. The guidelines below should be adapted to practical conditions of acceptability and feasibility. When such conditions are not met, mitigation strategies should be considered, including OGTT omission (see "OGTT: practical considerations").

*Guidelines for children*

Follow-up should ideally include:

1). At home: pre- and postprandial SMBG after a carbohydrate-containing meal, monthly and in case of warning signs or intercurrent illnesses.
2). At the hospital: at stage 1, a younger age at seroconversion is also associated with a faster clinical progression [29,78]. Follow-up will therefore be more or less frequent according to age [78]:

- ≤ 3-year-old: HbA1c and postprandial glycemia after a carbohydrate-containing meal every 3 months; and OGTT/HbA1c every 6 months;
- 3–8-year-old: OGTT/HbA1c every 6 months;
- ≥ 9-year-old: OGTT/HbA1c every 12 months;
- With annual aAb monitoring irrespective of age.

*Guidelines for adolescents and adults*

Follow-up should ideally include:

1). At home: pre- and postprandial SMBG after a carbohydrate-containing meal, only in case of warning signs or intercurrent illnesses.
2). At the hospital: OGTT/HbA1c every 12 months for 5 years, then every 2 years; with annual aAb monitoring.

*Pregnant women*

Despite the absence of specific studies, the additional β-cell stress imposed by pregnancy suggests an increased risk of clinical progression [89]. Considering the risk of macrosomia and obstetrical/neonatal complications in case of unrecognized clinical T1D, a closer surveillance is mandatory, even in single-aAb+ women. This should include an OGTT/HbA1c or CGM once pregnancy is confirmed, before 8 weeks of amenorrhea [90], followed by the usual OGTT screening for gestational diabetes at 24–28 weeks. In the case of diabetes during pregnancy, glycemic status should be reevaluated in the days after delivery and then at 6 and 12 months [89].

*Follow-up of FDRs with stage 2 T1D (asymptomatic dysglycemia)*

*Evidence*

Follow-up should include [27]: OGTT (or postprandial blood glucose measurements, see "OGTT: practical considerations"), HbA1c and CGM or SMBG, with a different frequency according to age (see below). aAb monitoring has no added value at this stage. Warning signs of hyperglycemia and DKA and the blood glucose thresholds requiring referral should be reviewed. The same multidisciplinary care described for stage 1 follow-up should be proposed.

The care center for stage 3, if different from the expert center, should be clearly identified to avoid any delay in transition. As short- or medium-term progression to clinical stage 3 becomes certain, the patient can be given a care protocol for the management of long-term illness (*affection de longue durée*, ALD).

*Guidelines for children, adolescents and adults*

Follow-up should include:

1). At home: intermittent CGM (10–14 days every 3 months), with an objective of time in tight range (TITR; 70–140 mg/dl) >80 % [27]; or pre- and postprandial SMBG after a carbohydrate-containing meal, monthly and in case of warning signs or intercurrent illnesses.
2). At the hospital: OGTT/HbA1c every 6 months.

*OGTT: practical considerations*

OGTT with venous blood sampling at the hospital is currently the most sensitive test to detect clinical progression, even in comparison with CGM [91]. However, such intensive follow-up can sometimes be difficult (e.g., young age, difficult venipuncture, acceptance, availability of frequent follow-up visits). In this case, OGTT (and concomitant HbA1c measurement) can be replaced with home postprandial capillary blood glucose measurements (1 or 2 h after a meal/OGTT for stage 1 or 2 follow-up, respectively), or alternated with OGTT/HbA1c testing, e.g. at the occasion of venous blood draws for annual aAb monitoring for stage 1. These capillary measurements should however be regarded as follow-up rather than diagnostic tests, and confirmed on venous samples when positive. Since the objective is not to miss an early diagnosis of stage 2 or 3 T1D, when disease is still asymptomatic, these capillary measurements should not be limited to situations of warning signs of hyperglycemia or intercurrent illnesses. In the absence of adherence to intensive monitoring even with capillary blood glucose tests, it is critical to emphasize vigilance for warning signs and a thorough knowledge of the care pathway for rapid management in the event of clinical progression. The diagnostic performance of CGM-based metrics is the focus of intensive research and is expected to improve in the future; the influence of over-restrictive dietary modifications should also be considered when interpreting CGM results. The advantages and drawbacks of follow-up by OGTT or capillary glucose measurements are summarized in Table 5.

**Table 5**
Advantages and drawbacks of follow-up strategies based on OGTT or postprandial capillary blood glucose measurements.

| | OGTT | Postprandial capillary blood glucose |
|---|---|---|
| Advantages | • More sensitive<br>• Standardized<br>• Multiple measures over 2 h<br>• More effective early diagnosis | • At home<br>• Short, light procedure<br>• Lower cost<br>• Possibility of more frequent follow-up |
| Drawbacks | • At the hospital<br>• Lengthy, burdensome procedure<br>• Higher cost<br>• Possibility of less frequent follow-up<br>• Risk of missed appointments | • Less sensitive<br>• Not standardized<br>• Single measure at 1 or 2 h<br>• Less effective early diagnosis<br>• Risk of missed tests |

*The entry into clinical stage 3*

The entry into stage 3 through preclinical follow-up occurs most often with an asymptomatic stage 3a [11]. There is currently no consensus on when to initiate insulin therapy. It should preferably be initiated before onset of hyperglycemic symptoms, depending on the glycemic profile.

Follow-up guidelines are summarized in Fig. 3.

## Therapeutic perspectives

The age of T1D clinical onset has a major impact on life expectancy and co-morbidities [92], even under strict glycemic control [93]. The risk of coronary heart disease and heart attack is 5-fold higher for patients diagnosed between 0 and 10 years of age than for those diagnosed between 25 and 30 years, corresponding to a reduction in life expectancy of 14–18 years versus 9–10 years [92]. Although new insulin delivery technologies are expected to improve prognosis, the medical stakes remain high. Hence, the availability of novel therapeutics that may preserve endogenous insulin secretion and delay clinical progression provides an additional rationale for screening and follow-up.

*Teplizumab*

Teplizumab, a humanized anti-CD3 monoclonal antibody not binding the Fc receptor, is the first disease-modifying agent that delays progression from stage 2 to stage 3 T1D [23]. It provides a reference treatment that will accelerate the development of other drugs and broaden therapeutic options available in clinical trials or routine care. The cost of teplizumab (~116,000 € for the 14-day treatment course) is another factor to consider for its introduction into routine care.

The pivotal phase 2 trial in stage 2 T1D (median age 14 years, 72 % < 18-year-old) with a single 14-day course reported a median delay of progression to stage 3 of 24 months at 5 years (48.4 vs. 24.4 months in the teplizumab vs. placebo arm) [23] and of 32.5 months at 6 years (59.6 vs. 27.1 months) [94]. Teplizumab has also been tested in several randomized trials in adults and children ≥ 8-year-old with stage 3 T1D. A meta-analysis of five of these trials has documented its benefit on residual stimulated C-peptide (mean +0.08 and +0.12 nmol/l at 1 and 2 years, respectively) and on exogenous insulin requirements (−0.08 and −0.10 U/kg/d at 1 and 2 years, respectively) [95].

When aggregating patients studied at stages 2 and 3 (1500 patient-years in total) [95], the safety profile has been reassuring. The main adverse effects, generally early and spontaneously resolving, are cytopenia (mainly lymphopenia), ALT elevations; skin rash and moderate flu-like syndrome (fever, fatigue) due to cytokine release; and, more rarely, Epstein-Barr virus reactivation, usually asymptomatic. The long-term impact of this treatment is still unknown, but the transient nature of lymphopenia and the preservation of antiviral responses do not

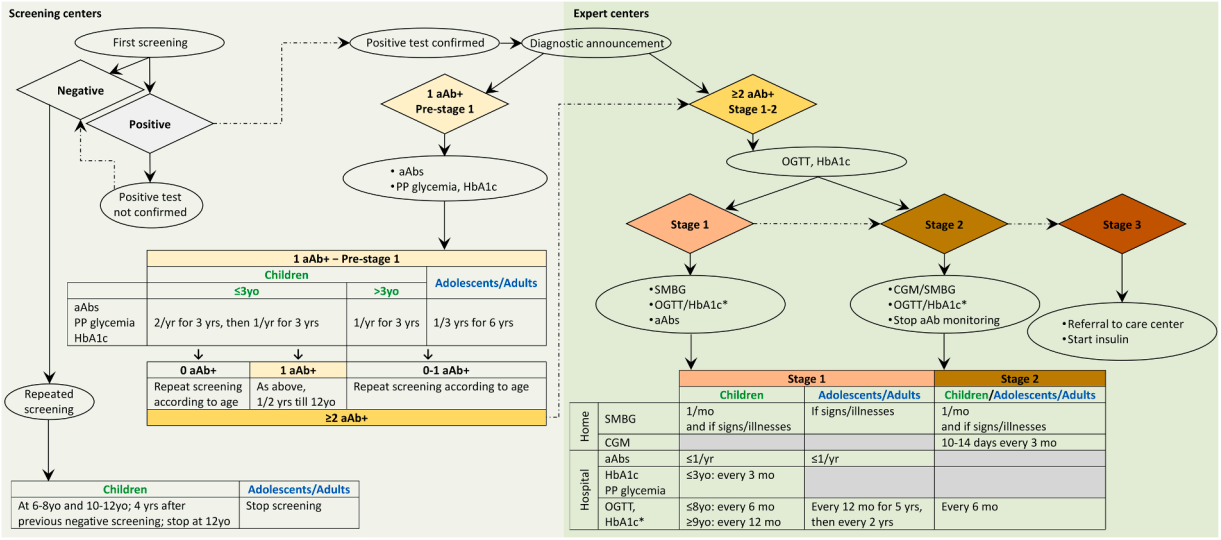


**Fig. 3.** Follow-up guidelines for FDRs. CGM, continuous glucose monitoring; PP, postprandial; SMBG, self-monitoring of blood glucose. *Home PP capillary glucose measurements can be considered as an alternative to in-hospital OGTT/HbA1c (see Table 5). Note that blood glucose should be measured 1 hour after meal for stage 1 follow-up and at 2 h after meal for stage 2 follow-up.

raise any particular warning so far.

### *Agents in clinical trials*

Several molecules have already demonstrated a benefit on C-peptide preservation at clinical stage 3 in randomized, double-blind, placebo-controlled phase 2 trials. They often require less demanding treatment regimens and they have sometimes achieved other secondary endpoints compared with teplizumab (HbA1c, insulin doses, hypoglycemic events). Moreover, most of them are already marketed in France for other indications, with a reassuring safety record in both children and adults. They are therefore being considered for trials in preclinical T1D. They can be classified into immunomodulatory and β-cell protective agents and are summarized in Table 6. Abatacept has also been tested in a phase 2 trial in stage 1 T1D [96]: despite an improvement in stimulated C-peptide, it did not delay progression to stage 2 or 3. Combination therapies provide a third therapeutic option, either using molecules with dual immunomodulatory/β-cell-protective effects (e.g. baricitinib) or by combining agents with distinct therapeutic mechanisms (e.g. anti-IL-21/liraglutide). This is similar to what has been achieved in the oncology field, by combining immunotherapies to boost immune responses against tumor cells, and chemotherapies to decrease tumor mass and increase its vulnerability. Based on the hypothesis of a pathogenic role of low-grade enteroviral infections in islets, a fourth class of antiviral agents is also under consideration [97]. A growing number of multicenter clinical trials, coordinated in Europe by the INNODIA network (www.innodia.org), is currently being developed to test several of these molecules, either as monotherapy or in combination [98,99,100]. These trials will extend the therapeutic options for stage 1 or 2 T1D.

## Conclusions

A more or less pro-active attitude towards preclinical T1D screening is debated among both FDRs of PwT1D and healthcare professionals. Areas of uncertainty requiring further research include diagnostic criteria for stage 2 T1D, trial evidence of the cost effectiveness of screening programs and long-term outcome assessment. Nonetheless, renewed interest is motivated by the demonstrated short/medium-term benefits of early management outside the usual emergency setting (DKA avoidance, better glycemic control), easier access to aAb assays, and new treatment options to delay clinical onset. PwT1D, FDRs and their families should be informed that these novel screening and early management pathways exist, that there are both potential harms and benefits, and that this is therefore a personal choice that caregivers should accompany and respect to minimize harms and maximize benefits. This is also a new area of expertise for healthcare professionals, who need to learn how to inform, listen and respond to questions of PwT1D and their

**Table 6**
Therapies with proven benefit on C-peptide preservation at clinical onset of stage 3 T1DM. All data, including for teplizumab, refer to trials at stage 3 T1DM.

| Class | Molecule | Age | Treatment regimen | Secondary outcomes | Reference |
|---|---|---|---|---|---|
| Immunomodulatory therapies | Teplizumab, Anti-CD3 | 8–17 yrs | IV, daily for 12 days; 2 cycles for 1 yr | No | [99] |
| | Abatacept, CTLA-4-Ig | 6–36 yrs | IV, days 1, 14, 28; then monthly for 2 yrs | HbA1c, insulin doses | [100] |
| | Alefacept, LFA-3-Ig | 16–35 yrs | IM, weekly for 12 wks; 2 cycles for 1 yr | Insulin doses, hypoglycemias | [101] |
| | Golimumab, Anti-TNF-α | 6–21 yrs | SC, weekly for 2 wks; then bimonthly for 1 yr | Insulin doses | [102] |
| | Rituximab, Anti-CD20 | 8–40 yrs | IV, weekly for 4 wks | HbA1c, insulin doses | [103] |
| | Low-dose thymoglobulin Anti-thymocytes Ig | 12–45 yrs | IV, daily for 2 days | HbA1c | [104] |
| β-cell-protective therapies | Verapamil | 7–17 yrs | Oral, daily for 1 yr | No | [105] |
| Combination therapies | Baricitinib JAK1/2 inhibitor | 10–30 yrs | Oral, daily for 48 wks | No | [106] |
| | Anti-IL-21 + liraglutide | 18–45 yrs | IV, every 6 wks; and SC, daily; for 1 yr | No | [107] |
| Antiviral therapies | Pleconaril + ribavirin | 6–15 yrs | Oral, daily for 6 mo | No | [97] |

families, how to interpret and announce positive screening results and manage or refer for subsequent follow-up. An extended version of this expert position statement written in French can be found in [108]. This rapidly evolving field is undergoing a major learning process and will remain open to regular updates and improvements.

## CRediT authorship contribution statement

**Roberto Mallone:** Writing – review & editing, Writing – original draft. **Elise Bismuth:** Writing – review & editing, Writing – original draft. **Charles Thivolet:** Writing – review & editing, Writing – original draft. **Pierre-Yves Benhamou:** Writing – review & editing, Writing – original draft. **Nadine Hoffmeister:** Writing – review & editing, Writing – original draft. **François Collet:** Writing – review & editing, Writing – original draft. **Marc Nicolino:** Writing – review & editing, Writing – original draft. **Rachel Reynaud:** Writing – review & editing, Writing – original draft. **Jacques Beltrand:** Writing – review & editing, Writing – original draft.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: RM serves or has served on advisory panels, speakers' bureaus, research activities for Amarna Therapeutics, Endotope Biosciences, Human Cell Design, King's College London, Immunocore, Lilly, Novo Nordisk, Sanofi; financial compensation for these activities has been received by INNODIA iVZW, APHP Foundation or INSERM. EB has received honoraria and travel funding to participate to congresses, training activities, advisory panels, speakers' bureaus for Abbott, Insulet, Lilly, Medtronic, Novo Nordisk, Sanofi. CT has received honoraria for conferences from Abbott, Glooko, Lilly, Novo Nordisk, Medtronic, Sanofi; and for advisory panels from Insulet and Medtronic. PYB participated in advisory panels for Abbott, Insulet, Lilly, Novo Nordisk; and is medical consultant for Diabeloop. NH has no interest to disclose. FC participated in conference activities for Dexcom and Ypsomed. MN has received honoraria for advisory panels, speakers' bureaus, research activities for Merck, Ipsen, Novo Nordisk, Pfizer, Rhythm, Sanofi. RR participated in advisory panels and speakers' bureaus for Lilly and Medtronic. JB participated in speakers' bureaus for Lilly, Medtronic, Merck Serono, Novo Nordisk, Sanofi, Ypsomed; and in advisory panels for Lilly, Medtronic, Sanofi, Ypsomed.

*Financial support*

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

*Acknowledgements*

We gratefully acknowledge the Review Committee of this position statement for constructive criticism and editing suggestions: Inès Aaron-Popelier (Paris), Marie-Alexandra Alyanakian (Paris), Pascal Barat (Bordeaux), Fréderic Batteux (Paris), Jacques Bringer (Montpellier), Regis Coutant (Angers), Marc De Kerdanet (Rennes), Bruno Fève (Paris), Jean-François Gautier (Paris), Samy Hadjadj (Nantes), Emmanuelle Lecornet-Sokol (Paris), Chantal Mathieu (Louvain), Alfred Penfornis (Corbeil-Essonnes), Sylvie Picard (Dijon), Eric Renard (Montpellier), Jean-Pierre Riveline (Paris), Igor Tauveron (Clermont-Ferrand), Jean-François Thébaut (Paris), Anne Vambergue (Lille).

## References

[1] Jacobsen LM, Vehik K, Veijola R, Warncke K, Toppari J, Steck AK, 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; 45:624–33. https://doi.org/10.2337/dc21-0422.

[2] Donzeau A, Piffaretti C, Jossens A, Levaillant L, Bouhours-Nouet N, Amsellem-Jager J, et al. Time trend in excess mortality in children with type 1 diabetes from 1987 to 2016 in mainland France. Pediatr Diabetes 2022;23:38–44. https://doi.org/10.1111/pedi.13298.

[3] Ghetti S, Kuppermann N, Rewers A, Myers SR, Schunk JE, Stoner MJ, et al. Cognitive function following diabetic ketoacidosis in children with new-onset or previously diagnosed type 1 diabetes. Diabetes Care 2020;43:2768–75. https://doi.org/10.2337/dc20-0187.

[4] Fredheim S, Johannesen J, Johansen A, Lyngsøe L, Rida H, Andersen MLM, et al. Diabetic ketoacidosis at the onset of type 1 diabetes is associated with future HbA1c levels. Diabetologia 2013;56:995–1003. https://doi.org/10.1007/s00125-013-2850-z.

[5] 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: 1249–55. https://doi.org/10.2337/dc17-0558.

[6] Duca LM, Reboussin BA, Pihoker C, Imperatore G, Saydah S, Mayer-Davis E, 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;20:172–9. https://doi.org/10.1111/pedi.12809.

[7] Choleau C, Maitre J, Elie C, Barat P, Bertrand AM, de Kerdanet M, et al. Ketoacidosis at time of diagnosis of type 1 diabetes in children and adolescents: effect of a national prevention campaign. Arch Pediatr 2015;22:343–51. https://doi.org/10.1016/j.arcped.2014.11.001.

[8] Usher-Smith JA, Thompson MJ, Sharp SJ, Walter FM. Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: a systematic review. BMJ 2011;343:d4092. https://doi.org/10.1136/bmj.d4092.

[9] Rickels MR, Evans-Molina C, Bahnson HT, Ylescupidez A, Nadeau KJ, Hao W, et al. High residual C-peptide likely contributes to glycemic control in type 1 diabetes. J Clin Invest 2020;130:1850–62. https://doi.org/10.1172/JCI134057.

[10] Triolo TM, Chase HP, Barker JM, Group DPTS. Diabetic subjects diagnosed through the Diabetes Prevention Trial-Type 1 (DPT-1) are often asymptomatic with normal A1C at diabetes onset. Diabetes Care 2009;32:769–73. https://doi.org/10.2337/dc08-1872.

[11] Hummel S, Carl J, Friedl N, Winkler C, Kick K, Stock J, et al. Children diagnosed with presymptomatic type 1 diabetes through public health screening have milder diabetes at clinical manifestation. Diabetologia 2023;66:1633–42. https://doi.org/10.1007/s00125-023-05953-0.

[12] Steck AK, Larsson HE, Liu X, Veijola R, Toppari J, Hagopian WA, et al. Residual beta-cell function in diabetes children followed and diagnosed in the TEDDY study compared to community controls. Pediatr Diabetes 2017;18:794–802. https://doi.org/10.1111/pedi.12485.

[13] DCCT Research Group. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. The Diabetes Control and Complications Trial Research Group. Ann Intern Med 1998;128:517–23. https://doi.org/10.7326/0003-4819-128-7-199804010-00001.

[14] Jeyam A, Colhoun H, McGurnaghan S, Blackbourn L, McDonald TJ, Palmer CNA, et al. Clinical Impact of residual c-peptide secretion in type 1 diabetes on glycemia and microvascular complications. Diabetes Care 2021;44:390–8. https://doi.org/10.2337/dc20-0567.

[15] Lachin JM, Nathan DM, DCCT/EDIC Research Group. Understanding metabolic memory: the prolonged influence of glycemia during the diabetes control and complications trial (DCCT) on future risks of complications during the study of the epidemiology of diabetes interventions and complications (EDIC). Diabetes Care 2021;44:2216–24. https://doi.org/10.2337/dc20-3097.

[16] Lachin JM, McGee P, Palmer JP, DCCT/EDIC Research Group. Impact of c-peptide preservation on metabolic and clinical outcomes in the diabetes control and complications trial. Diabetes 2014;63:739–48. https://doi.org/10.2337/db13-0881.

[17] DCCT/EDIC Research Group, Aiello LP, Sun W, Das A, Gangaputra S, Kiss S, et al. Intensive diabetes therapy and ocular surgery in type 1 diabetes. N Engl J Med 2015;372:1722–33. https://doi.org/10.1056/NEJMoa1409463.

[18] Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–53. https://doi.org/10.1056/NEJMoa052187.

[19] DCCT/EDIC Research Group. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC study 30-year follow-up. Diabetes Care 2016;39:686–93. https://doi.org/10.2337/dc15-1990.

[20] DCCT/EDIC Research Group, Lachin JM, Genuth S, Cleary P, et al. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000;342:381–9. https://doi.org/10.1056/NEJM200002103420603.

[21] Haute Autorité de Santé. Dépistage: objectifs et condition, 2016 [accessed 01/03/2024].

[22] ADA Professional Practice Committee. Diagnosis and Classification of Diabetes: standards of Care in Diabetes—2024. Diabetes Care 2023;47:S20–42. https://doi.org/10.2337/dc24-S002.

[23] Herold KC, Bundy BN, Long SA, Bluestone JA, DiMeglio LA, Dufort MJ, et al. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. N Engl J Med 2019;381:603–13. https://doi.org/10.1056/NEJMoa1902226.

[24] Bosi E, Catassi C. Screening type 1 diabetes and celiac disease by law. Lancet Diabetes Endocrinol 2024;12:12–4. https://doi.org/10.1016/s2213-8587(23)00354-6.

[25] Ziegler A-G, Kick K, Bonifacio E, Haupt F, Hippich M, Dunstheimer D, et al. Yield of a Public health screening of children for islet autoantibodies in Bavaria, Germany. JAMA 2020;323:339–51. https://doi.org/10.1001/jama.2019.21565.
[26] Diabète, https://sante.gouv.fr/soins-et-maladies/maladies/article/diabete; 2023 [accessed 08/03/2024].
[27] Phillip M, Achenbach P, Addala A, Albanese-O'Neill A, Battelino T, Bell KJ, et al. Consensus guidance for monitoring individuals with islet autoantibody-positive pre-stage 3 type 1 diabetes. Diabetologia 2024;67:1731–59. https://doi.org/10.1007/s00125-024-06205-5.
[28] Mallone R. Considerations for more actionable consensus guidance for monitoring individuals with islet autoantibody-positive pre-stage 3 type 1 diabetes. Diabetologia 2024. https://doi.org/10.1007/s00125-024-06296-0.
[29] Ziegler AG, Rewers M, Simell O, Simell T, Lempainen J, Steck A, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. JAMA 2013;309:2473–9. https://doi.org/10.1001/jama.2013.6285.
[30] Bingley PJ, Boulware DC, Krischer JP. Type 1 Diabetes TrialNet Study G. 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;59:542–9. https://doi.org/10.1007/s00125-015-3830-2.
[31] Hendriks AEJ, Marcovecchio ML, Besser REJ, Bonifacio E, Casteels K, Elding Larsson H, et al. Clinical Care advice for monitoring of islet autoantibody positive individuals with presymptomatic type 1 diabetes. Diabetes Metab Res Rev 2024;40:e3777. https://doi.org/10.1002/dmrr.3777.
[32] Chetan MR, Charlton MH, Thompson C, Dias RP, Andrews RC, Narendran P. The Type 1 diabetes 'honeymoon' period is five times longer in men who exercise: a case-control study. Diabet Med 2019;36:127–8. https://doi.org/10.1111/dme.13802.
[33] Haute Autorité de Santé. Éléments pour élaborer une aide à la prise de décision partagée entre patient et professionnel de santé, https://www.has-sante.fr/jcms/c_2838959/fr/elements-pour-elaborer-une-aide-a-la-prise-de-decision-partagee-entre-patient-et-professionnel-de-sante; 2018 [accessed 09/05/2024].
[34] Smith LB, Liu X, Johnson SB, Tamura R, Elding Larsson H, Ahmed S, et al. Family adjustment to diabetes diagnosis in children: can participation in a study on type 1 diabetes genetic risk be helpful? Pediatr Diabetes 2018;19:1025–33. https://doi.org/10.1111/pedi.12674.
[35] Gargiulo M. C'est arrivé demain. La prédiction d'une maladie et d'un handicap. Handicap et mort. Erès; 2018, p. 13–30.
[36] Sims EK, Besser REJ, Dayan C, Geno Rasmussen C, Greenbaum C, Griffin KJ, et al. Screening for type 1 diabetes in the general population: a status report and perspective. Diabetes 2022;71:610–23. https://doi.org/10.2337/dbi20-0054.
[37] Anand V, Li Y, Liu B, Ghalwash M, Koski E, Ng K, et al. Islet autoimmunity and HLA markers of presymptomatic and clinical type 1 diabetes: joint analyses of prospective cohort studies in Finland, Germany, Sweden, and the US. Diabetes Care 2021;44:2269–76. https://doi.org/10.2337/dc20-1836.
[38] Mathieu C, Lahesmaa R, Bonifacio E, Achenbach P, Tree T. Immunological biomarkers for the development and progression of type 1 diabetes. Diabetologia 2018;61:2252–8. https://doi.org/10.1007/s00125-018-4726-8.
[39] Pociot F, Lernmark A. Genetic risk factors for type 1 diabetes. Lancet 2016;387:2331–9. https://doi.org/10.1016/S0140-6736(16)30582-7.
[40] Redondo MJ, Jeffrey J, Fain PR, Eisenbarth GS, Orban T. Concordance for islet autoimmunity among monozygotic twins. N Engl J Med 2008;359:2849–50. https://doi.org/10.1056/NEJMc0805398.
[41] Hoffmann VS, Weiss A, Winkler C, Knopff A, Jolink M, Bonifacio E, Ziegler AG. Landmark models to define the age-adjusted risk of developing stage 1 type 1 diabetes across childhood and adolescence. BMC Med 2019;17:125. https://doi.org/10.1186/s12916-019-1360-3.
[42] Vehik K, Bonifacio E, Lernmark A, Yu L, Williams A, Schatz D, et al. Hierarchical order of distinct autoantibody spreading and progression to type 1 diabetes in the TEDDY study. Diabetes Care 2020;43:2066–73. https://doi.org/10.2337/dc19-2547.
[43] Frohnert BI, Ide L, Dong F, Baron AE, Steck AK, Norris JM, Rewers MJ. Late-onset islet autoimmunity in childhood: the Diabetes Autoimmunity Study in the Young (DAISY). Diabetologia 2017;60:998–1006. https://doi.org/10.1007/s00125-017-4256-9.
[44] Jacobsen LM, Bocchino L, Evans-Molina C, DiMeglio L, Goland R, Wilson DM, et al. The risk of progression to type 1 diabetes is highly variable in individuals with multiple autoantibodies following screening. Diabetologia 2020;63:588–96. https://doi.org/10.1007/s00125-019-05047-w.
[45] Krischer JP, Lynch KF, Schatz DA, Ilonen J, Lernmark A, Hagopian WA, et al. The 6 year incidence of diabetes-associated autoantibodies in genetically at-risk children: the TEDDY study. Diabetologia 2015;58:980–7. https://doi.org/10.1007/s00125-015-3514-y.
[46] Steck AK, Johnson K, Barriga KJ, Miao D, Yu L, Hutton JC, et al. Age of islet autoantibody appearance and mean levels of insulin, but not GAD or IA-2 autoantibodies, predict age of diagnosis of type 1 diabetes: diabetes autoimmunity study in the young. Diabetes Care 2011;34:1397–9. https://doi.org/10.2337/dc10-2088.
[47] Parikka V, Nanto-Salonen K, Saarinen M, Simell T, Ilonen J, Hyoty H, et al. Early seroconversion and rapidly increasing autoantibody concentrations predict prepubertal manifestation of type 1 diabetes in children at genetic risk. Diabetologia 2012;55:1926–36. https://doi.org/10.1007/s00125-012-2523-3.
[48] Bosi E, Boulware DC, Becker DJ, Buckner JH, Geyer S, Gottlieb PA, et al. Impact of age and antibody type on progression from single to multiple autoantibodies in type 1 diabetes relatives. J Clin Endocrinol Metab 2017;102:2881–6. https://doi.org/10.1210/jc.2017-00569.
[49] Leslie RD, Evans-Molina C, Freund-Brown J, Buzzetti R, Dabelea D, Gillespie KM, et al. Adult-Onset type 1 diabetes: current understanding and challenges. Diabetes Care 2021;44:2449–56. https://doi.org/10.2337/dc21-0770.
[50] So M, O'Rourke C, Ylescupidez A, Bahnson HT, Steck AK, Wentworth JM, et al. Characterising the age-dependent effects of risk factors on type 1 diabetes progression. Diabetologia 2022;65:684–94. https://doi.org/10.1007/s00125-021-05647-5.
[51] Ilonen J, Hammais A, Laine AP, Lempainen J, Vaarala O, Veijola R, et al. Patterns of beta-cell autoantibody appearance and genetic associations during the first years of life. Diabetes 2013;62:3636–40. https://doi.org/10.2337/db13-0300.
[52] Vehik K, Lynch KF, Schatz DA, Akolkar B, Hagopian W, Rewers M, et al. Reversion of beta-cell autoimmunity changes risk of type 1 diabetes: TEDDY study. Diabetes Care 2016;39:1535–42. https://doi.org/10.2337/dc16-0181.
[53] Decochez K, De Leeuw IH, Keymeulen B, Mathieu C, Rottiers R, Weets I, et al. IA-2 autoantibodies predict impending type I diabetes in siblings of patients. Diabetologia 2002;45:1658–66. https://doi.org/10.1007/s00125-002-0949-8.
[54] Achenbach P, Warncke K, Reiter J, Naserke HE, Williams AJ, Bingley PJ, et al. Stratification of type 1 diabetes risk on the basis of islet autoantibody characteristics. Diabetes 2004;53:384–92. https://doi.org/10.2337/diabetes.53.2.384.
[55] Achenbach P, Lampasona V, Landherr U, Koczwara K, Krause S, Grallert H, et al. Autoantibodies to zinc transporter 8 and SLC30A8 genotype stratify type 1 diabetes risk. Diabetologia 2009;52:1881–8. https://doi.org/10.1007/s00125-009-1438-0.
[56] Weiss A, Zapardiel-Gonzalo J, Voss F, Jolink M, Stock J, Haupt F, et al. Progression likelihood score identifies substages of presymptomatic type 1 diabetes in childhood public health screening. Diabetologia 2022;65:2121–31. https://doi.org/10.1007/s00125-022-05780-9.
[57] Ziegler AG, Bonifacio E. Why is the presence of autoantibodies against GAD associated with a relatively slow progression to clinical diabetes? Diabetologia 2020;63:1665–6. https://doi.org/10.1007/s00125-020-05175-8.
[58] Barker JM, Barriga KJ, Yu L, Miao D, Erlich HA, Norris JM, et al. Prediction of autoantibody positivity and progression to type 1 diabetes: diabetes Autoimmunity Study in the Young (DAISY). J Clin Endocrinol Metab 2004;89:3896–902. https://doi.org/10.1210/jc.2003-031887.
[59] Erlich H, Valdes AM, Noble J, Carlson JA, Varney M, Concannon P, et al. HLA DR-DQ haplotypes and genotypes and type 1 diabetes risk: analysis of the type 1 diabetes genetics consortium families. Diabetes 2008;57:1084–92. https://doi.org/10.2337/db07-1331.
[60] Onengut-Gumuscu S, Chen WM, Robertson CC, Bonnie JK, Farber E, Zhu Z, et al. Type 1 diabetes risk in african-ancestry participants and utility of an ancestry-specific genetic risk score. Diabetes Care 2019;42:406–15. https://doi.org/10.2337/dc18-1727.
[61] Luckett AM, Weedon MN, Hawkes G, Leslie RD, Oram RA, Grant SFA. Utility of genetic risk scores in type 1 diabetes. Diabetologia 2023;66:1589–600. https://doi.org/10.1007/s00125-023-05955-y.
[62] Sosenko JM, Skyler JS, Beam CA, Krischer JP, Greenbaum CJ, Mahon J, et al. Acceleration of the loss of the first-phase insulin response during the progression to type 1 diabetes in diabetes prevention trial-type 1 participants. Diabetes 2013;62:4179–83. https://doi.org/10.2337/db13-0656.
[63] Helminen O, Aspholm S, Pokka T, Hautakangas MR, Haatanen N, Lempainen J, et al. HbA1c predicts time to diagnosis of type 1 diabetes in children at risk. Diabetes 2015;64:1719–27. https://doi.org/10.2337/db14-0497.
[64] Vehik K, Boulware D, Killian M, Rewers M, McIndoe R, Toppari J, et al. Rising hemoglobin A1c in the nondiabetic range predicts progression of type 1 diabetes as well as oral glucose tolerance tests. Diabetes Care 2022;45:2342–9. https://doi.org/10.2337/dc22-0828.
[65] Steck AK, Dong F, Geno Rasmussen C, Bautista K, Sepulveda F, Baxter J, et al. CGM metrics predict imminent progression to type 1 diabetes: autoimmunity screening for kids (ASK) Study. Diabetes Care 2022;45:365–71. https://doi.org/10.2337/dc21-0602.
[66] Sosenko JM, Palmer JP, Greenbaum CJ, Mahon J, Cowie C, Krischer JP, et al. Patterns of metabolic progression to type 1 diabetes in the Diabetes Prevention Trial-Type 1. Diabetes Care 2006;29:643–9. https://doi.org/10.2337/diacare.29.03.06.dc05-1006.
[67] Ferrannini E, Mari A, Nofrate V, Sosenko JM, Skyler JS. Progression to diabetes in relatives of type 1 diabetic patients: mechanisms and mode of onset. Diabetes 2010;59:679–85. https://doi.org/10.2337/db09-1378.
[68] Pauley ME, Geno Rasmussen C, Dong F, Simmons KM, Rewers M. 1294-P: prevalence of islet autoantibodies in adults from the general population. Diabetes 2023;72:1294. https://doi.org/10.2337/db23-1294-P.
[69] Leete P, Mallone R, Richardson SJ, Sosenko JM, Redondo MJ, Evans-Molina C. The Effect of age on the progression and severity of type 1 diabetes: potential effects on disease mechanisms. Curr Diab Rep 2018;18:115. https://doi.org/10.1007/s11892-018-1083-4.
[70] Hao W, Gitelman S, DiMeglio LA, Boulware D, Greenbaum CJ. Fall in c-peptide during first 4 years from diagnosis of type 1 diabetes: variable relation to age, HbA1c, and insulin dose. Diabetes Care 2016;39:1664–70. https://doi.org/10.2337/dc16-0360.
[71] Carré A, Richardson SJ, Larger E, Mallone R. Presumption of guilt for T cells in type 1 diabetes: lead culprits or partners in crime depending on age of onset? Diabetologia 2021;64:15–25. https://doi.org/10.1007/s00125-020-05298-y.
[72] Gregory GA, Robinson TIG, Linklater SE, Wang F, Colagiuri S, de Beaufort C, et al. Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. Lancet Diabetes Endocrinol 2022;10:741–60. https://doi.org/10.1016/S2213-8587(22)00218-2.

[73] Greenbaum CJ, Beam CA, Boulware D, Gitelman SE, Gottlieb PA, Herold KC, et al. Fall in C-peptide during first 2 years from diagnosis: evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. Diabetes 2012;61:2066–73. https://doi.org/10.2337/db11-1538.

[74] Munoz C, Floreen A, Garey C, Karlya T, Jelley D, Alonso GT, McAuliffe-Fogarty A. Misdiagnosis and diabetic ketoacidosis at diagnosis of type 1 diabetes: patient and caregiver perspectives. Clin Diabetes 2019;37:276–81. https://doi.org/10.2337/cd18-0088.

[75] Ziegler AG, Bonifacio E, Group B-BS. Age-related islet autoantibody incidence in offspring of patients with type 1 diabetes. Diabetologia 2012;55:1937–43. https://doi.org/10.1007/s00125-012-2472-x.

[76] Naserke HE, Bonifacio E, Ziegler AG. Prevalence, characteristics and diabetes risk associated with transient maternally acquired islet antibodies and persistent islet antibodies in offspring of parents with type 1 diabetes. J Clin Endocrinol Metab 2001;86:4826–33.

[77] Koczwara K, Bonifacio E, Ziegler AG. Transmission of maternal islet antibodies and risk of autoimmune diabetes in offspring of mothers with type 1 diabetes. Diabetes 2004;53:1–4. https://doi.org/10.2337/diabetes.53.1.1.

[78] Ghalwash M, Dunne JL, Lundgren M, Rewers M, Ziegler AG, Anand V, et al. Two-age islet-autoantibody screening for childhood type 1 diabetes: a prospective cohort study. Lancet Diabetes Endocrinol 2022;10:589–96. https://doi.org/10.1016/S2213-8587(22)00141-3.

[79] Ghalwash M, Anand V, Lou O, Martin F, Rewers M, Ziegler A-G, et al. Islet autoantibody screening in at-risk adolescents to predict type 1 diabetes until young adulthood: a prospective cohort study. Lancet Child Adolesc Health 2023;7:261–8. https://doi.org/10.1016/S2352-4642(22)00350-9.

[80] So M, Speake C, Steck AK, Lundgren M, Colman PG, Palmer JP, et al. Advances in type 1 diabetes prediction using islet autoantibodies: beyond a simple count. Endocr Rev 2021;42:584–604. https://doi.org/10.1210/endrev/bnab013.

[81] Cortez FJ, Gebhart D, Robinson PV, Seftel D, Pourmandi N, Owyoung J, et al. Sensitive detection of multiple islet autoantibodies in type 1 diabetes using small sample volumes by agglutination-PCR. PLoS One 2020;15:e0242049. https://doi.org/10.1371/journal.pone.0242049.

[82] Lind A, Freyhult E, de Jesus, Cortez F, Ramelius A, Bennet R, Robinson PV, et al. Childhood screening for type 1 diabetes comparing automated multiplex Antibody Detection by Agglutination-PCR (ADAP) with single plex islet autoantibody radiobinding assays. EBioMedicine 2024;104:105144. https://doi.org/10.1016/j.ebiom.2024.105144.

[83] Karl FM, Winkler C, Ziegler A-G, Laxy M, Achenbach P. Costs of public health screening of children for presymptomatic type 1 diabetes in Bavaria, Germany. Diabetes Care 2022;45:837–44. https://doi.org/10.2337/dc21-1648.

[84] Marzinotto I, Pittman DL, Williams AJK, Long AE, Achenbach P, Schlosser M, et al. Islet autoantibody standardization program: interlaboratory comparison of insulin autoantibody assay performance in 2018 and 2020 workshops. Diabetologia 2023;66:897–912. https://doi.org/10.1007/s00125-023-05877-9.

[85] Bonifacio E, Weiss A, Winkler C, Hippich M, Rewers MJ, Toppari J, et al. An age-related exponential decline in the risk of multiple islet autoantibody seroconversion during childhood. Diabetes Care 2021;44:2260–8. https://doi.org/10.2337/dc20-2122.

[86] Frohnert BI, Ghalwash M, Li Y, Ng K, Dunne JL, Lundgren M, et al. Refining the Definition of stage 1 type 1 diabetes: an ontology-driven analysis of the heterogeneity of multiple islet autoimmunity. Diabetes Care 2023;46:1753–61. https://doi.org/10.2337/dc22-1960.

[87] So M, O'Rourke C, Bahnson HT, Greenbaum CJ, Speake C. Autoantibody reversion: changing risk categories in multiple-autoantibody-positive individuals. Diabetes Care 2020;43:913–7. https://doi.org/10.2337/dc19-1731.

[88] Patel SK, Ma CS, Fourlanos S, Greenfield JR. Autoantibody-negative type 1 diabetes: a neglected subtype. Trends Endocrinol Metab 2021;32:295–305. https://doi.org/10.1016/j.tem.2021.02.001.

[89] Lobner K, Knopff A, Baumgarten A, Mollenhauer U, Marienfeld S, Garrido-Franco M, et al. Predictors of postpartum diabetes in women with gestational diabetes mellitus. Diabetes 2006;55:792–7. https://doi.org/10.2337/diabetes.55.03.06.db05-0746.

[90] Simmons D, Immanuel J, Hague WM, Teede H, Nolan CJ, Peek MJ, et al. Treatment of gestational diabetes mellitus diagnosed early in pregnancy. N Engl J Med 2023;388:2132–44. https://doi.org/10.1056/NEJMoa2214956.

[91] Ylescupidez A, Speake C, Pietropaolo SL, Wilson DM, Steck AK, Sherr JL, et al. OGTT metrics surpass continuous glucose monitoring data for t1d prediction in multiple-autoantibody-positive individuals. J Clin Endocrinol Metab 2023;109:57–67. https://doi.org/10.1210/clinem/dgad472.

[92] Rawshani A, Sattar N, Franzen S, Rawshani A, Hattersley AT, Svensson AM, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. Lancet 2018;392:477–86. https://doi.org/10.1016/S0140-6736(18)31506-X.

[93] Lind M, Svensson AM, Kosiborod M, Gudbjornsdottir S, Pivodic A, Wedel H, et al. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med 2014;371:1972–82. https://doi.org/10.1056/NEJMoa1408214.

[94] Sims EK, Bundy BN, Stier K, Serti E, Lim N, Long SA, et al. Teplizumab improves and stabilizes beta cell function in antibody-positive high-risk individuals. Sci Transl Med 2021;13:eabc8980. https://doi.org/10.1126/scitranslmed.abc8980.

[95] Herold KC, Gitelman SE, Gottlieb PA, Knecht LA, Raymond R, Ramos EL. Teplizumab: a disease-modifying therapy for type 1 diabetes that preserves beta-cell function. Diabetes Care 2023;46:1848–56. https://doi.org/10.2337/dc23-0675.

[96] Russell WE, Bundy BN, Anderson MS, Cooney LA, Gitelman SE, Goland RS, et al. Abatacept for delay of type 1 diabetes progression in stage 1 relatives at risk: a randomized, double-masked, controlled trial. Diabetes Care 2023;46:1005–13. https://doi.org/10.2337/dc22-2200.

[97] Krogvold L, Mynarek IM, Ponzi E, Mørk FB, Hessel TW, Roald T, et al. Pleconaril and ribavirin in new-onset type 1 diabetes: a phase 2 randomized trial. Nat Med 2023;29:2902–8. https://doi.org/10.1038/s41591-023-02576-1.

[98] Mallone R, Sims EK, Achenbach P, Mathieu C, Pugliese A, Atkinson MA, et al. Emerging concepts and success stories in type 1 diabetes research: a roadmap for a bright future. Diabetes 2024. https://doi.org/10.2337/db24-0439.

[99] Ramos EL, Dayan CM, Chatenoud L, Sumnik Z, Simmons KM, Szypowska A, et al. Teplizumab and beta-cell function in newly diagnosed type 1 diabetes. N Engl J Med 2023;389:2151–61. https://doi.org/10.1056/NEJMoa2308743.

[100] Orban T, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R, et al. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. Lancet 2011;378:412–9. https://doi.org/10.1016/S0140-6736(11)60886-6.

[101] Rigby MR, DiMeglio LA, Rendell MS, Felner EI, Dostou JM, Gitelman SE, 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;1:284–94. https://doi.org/10.1016/S2213-8587(13)70111-6.

[102] Quattrin T, Haller MJ, Steck AK, Felner EI, Li Y, Xia Y, et al. Golimumab and beta-cell function in youth with new-onset type 1 diabetes. N Engl J Med 2020;383:2007–17. https://doi.org/10.1056/NEJMoa2006136.

[103] Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, Becker DJ, Gitelman SE, Goland R, et al. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. N Engl J Med 2009;361:2143–52. https://doi.org/10.1056/NEJMoa0904452.

[104] Haller MJ, Schatz DA, Skyler JS, Krischer JP, Bundy BN, Miller JL, et al. Low-dose anti-thymocyte globulin (ATG) preserves beta-cell function and improves hba1c in new-onset type 1 diabetes. Diabetes Care 2018;41:1917–25. https://doi.org/10.2337/dc18-0494.

[105] Forlenza GP, McVean J, Beck RW, Bauza C, Bailey R, Buckingham B, et al. Effect of verapamil on pancreatic beta cell function in newly diagnosed pediatric type 1 diabetes: a randomized clinical trial. JAMA 2023;329:990–9. https://doi.org/10.1001/jama.2023.2064.

[106] Waibel M, Wentworth JM, So M, Couper JJ, Cameron FJ, MacIsaac RJ, et al. Baricitinib and β-cell function in patients with new-onset type 1 diabetes. N Engl J Med 2023;389:2140–50. https://doi.org/10.1056/NEJMoa2306691.

[107] von Herrath M, Bain SC, Bode B, Clausen JO, Coppieters K, Gaysina L, et al. Anti-interleukin-21 antibody and liraglutide for the preservation of beta-cell function in adults with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Diabetes Endocrinol 2021;9:212–24. https://doi.org/10.1016/S2213-8587(21)00019-X.

[108] Mallone R, Bismuth E, Thivolet C, Benhamou P-Y, Hoffmeister N, Collet F, et al. Dépistage et prise en charge du diabète de type 1 préclinique, stade 1–2. Prise de position d'experts français. Médecine des Maladies Métaboliques 2024;18:405–32. https://doi.org/10.1016/j.mmm.2024.06.003.