Consensus guidance for monitoring persons with islet autoantibody-positive pre-Stage 3 type 1 diabetes

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Abstract
Given the proven benefits of screening to reduce diabetic ketoacidosis (DKA) likelihood at the time of stage 3 type 1 diabetes (T1D) diagnosis and emerging availability of therapy to delay disease progression, T1D screening programs are being increasingly emphasized. Once broadly implemented, screening initiatives will identify significant numbers of islet autoantibody positive (IAb+) children and adults who are at risk of (confirmed single IAb+) or living with (multiple IAb+) early-stage (stage 1 and stage 2) T1D. These individuals will need monitoring for disease progression; much of this care will happen in non-specialized settings. To inform this monitoring, the JDRF in conjunction with international experts and societies developed consensus guidance. Broad advice from this guidance includes: 1) Partnerships should be fostered between endocrinologists and primary care providers to care for persons with IAb. 2) When persons who are IAb+ are initially identified there is a need for confirmation on a second sample. 3) Single IAb+ individuals are at lower risk of progression than multiple IAb+ individuals. 4) Individuals with early-stage T1D should have periodic medical monitoring, including regular assessments of glycemia, regular education about symptoms of diabetes and DKA, and psychosocial support. 5) Interested persons with stage 2 T1D should be offered trial participation or approved therapies. 6) All health professionals involved in monitoring and care of individuals with T1D have a responsibility to provide education. The guidance also emphasizes significant unmet needs for further research on early-stage T1D to increase the rigor of future recommendations and inform clinical care.
Overview
Currently, screening of individuals for islet autoantibodies (IAb) is undertaken as part of programs to detect children, adolescents and adults who are at higher risk of developing type 1 diabetes (T1D) due to having a first-degree relative with T1D or having a known high-risk HLA genotype. Periodic monitoring of persons who have screened positive for one or more autoantibodies (IAb+) is largely, but not always, conducted within these cohort studies. However, up to 90% of people who develop T1D are not part of at-risk groups. Thus, screening programs within the general population are being initiated and guidance for monitoring in non-specialist settings is urgently needed. The guidance provided here was developed by a series of expert working groups, convened as part of a JDRF initiative to document the aims, scope and purpose of monitoring for children, adolescents and adults with IAb+, along with recommended frequencies of monitoring and actions for healthcare professionals when risk of progression towards symptomatic T1D is high. This includes expert clinical advice for educational and psychosocial support for IAb+ individuals, including for their families and caregivers. The expert clinical advice for adults reflects available data but it is important to note that there are very limited data in adults aged 45 years and older who are IAb+. It is also important to note that this consensus document does not encompass screening for IAb, and only provides expert clinical advice for monitoring of individuals who have screened positive for at least one IAb.

Introduction and rationale
The presence of islet autoantibodies (IAb) for a pre-symptomatic period of variable duration in first-degree relatives of individuals with type 1 diabetes T1D has been known for more than 40 years (1), with recommendations for IAb screening appearing soon after (2). Decades of subsequent research and monitoring of individuals with IAb+ has led to the paradigm shift that T1D is a continuum of stages, from genetic risk through to autoimmunity and then metabolic disease. This has been accompanied by the evolution of descriptive terminology that reflects these stages (Table 1). Similarly, treatment options have moved on from monitoring and managing metabolic disease to include options for modulating the autoimmune response (3,4).

Screening programs have developed to the point that large numbers of at-risk children and adults have been intensively followed in longitudinal cohort studies (5–15) centered on understanding the natural history of progression to symptomatic T1D (see Table 2). Of note, many entry criteria for individuals with presymptomatic T1D into these studies require a family history of T1D or HLA genetic risk and most are focused on pediatric populations. Based on the outcomes of these and other studies, stages of presymptomatic and symptomatic T1D are now clinically defined (Table 1) to a degree of clinical consensus (16–18), although regulatory agencies and research studies may differ in definitions. Using these classifications, individuals can be monitored, diagnosed with diabetes and even, at times, started on insulin replacement therapy early in the disease course, based on meeting ADA (18), ISPAD (16) or AACE (19) diagnostic criteria. To date, the ISPAD guidelines have provided metabolic and autoantibody monitoring recommendations for children with presymptomatic T1D (16), but do not make specific recommendations for education or psychosocial support in IAb+ individuals, monitoring of single IAb+ individuals, or when to start insulin. The Fr1da study has suggested and introduced specific recommendations for children (21). A separate set of recommendations based on a Delphi-survey of expert opinion has provided guidance on
metabolic and autoantibody monitoring, with recommendations for education and psychosocial support, but does not specifically address adults with early-stage T1D (20). Consequently, to date there is no available guidance on monitoring in adults, or in individuals with a single IAb+, nor on when insulin therapy is indicated.

Consensus on evidence-based expert clinical advice for monitoring is an important unmet need, since a positive test for IAb (Table 3) is a condition for access to disease-modifying therapies, such as teplizumab (22), and IAb screening is anticipated to become more common (7,23–25), highlighting the need for clear monitoring advice.

These efforts are identifying an ever-growing number of IAb+ people who warrant education and ongoing monitoring for progression towards clinical diabetes. Evidence shows that such monitoring in research studies can significantly reduce the incidence of diabetes-related ketoacidosis (DKA) at diagnosis (24,26–33), occurring in up to 70% of unmonitored individuals, which is greatly lowered for individuals participating in follow-up studies (26,34–39). The impact of monitoring in general clinical practice on DKA rates is not known. DKA is a life-threatening condition that requires hospital admission, with significant associated costs for critical care (40–42). Additionally, in a number of studies, DKA at presentation of T1D in youths has been associated with higher HbA1c that was sustained for up to 11 years after diagnosis (43–45)(44). Other studies have however not found such an association between DKA at presentation of T1D and poorer long-term glycemic control (46). The lack of DKA at onset of T1D is also predictive of fewer severe hypoglycemic events after 10 years following diagnosis (47). In this context, the overall goals of monitoring are described in Table 4.

Monitoring of persons with IAb+ outside of research settings will require expert clinical advice that is clear and actionable by healthcare professionals (HCPs) who have limited expertise in diabetes. As indicated, current insights into monitoring progression to clinical T1D are largely derived from research studies of individuals known to be at risk of T1D, and general population data are less extensive. With this caveat, knowledge on best practices is particularly important for primary-care and secondary-care physicians who may not frequently see people known to be at risk of T1D, and yet who will be tasked with the initial aspects of monitoring following a positive autoantibody screen. Other persons who may assist with care of these individuals will include nurse practitioners, physician assistants, diabetes care and education specialists, psychologists and other mental and behavioral health professionals, all of whom have a role in supporting IAb+ individuals and their families within the monitoring environment. Clear expert clinical advice for monitoring by these groups of HCPs increases the likelihood that individuals at risk for or in early stages of T1D and their families can receive accurate and actionable education about presymptomatic T1D and their individual status.

The requirement for monitoring
Islet autoantibodies against four major pancreatic autoantigens are currently clinically available: insulin autoantibody (IAA); GAD autoantibody (GADA); insulinoma antigen-2 autoantibody (IA-2A, also called ICA512) and; zinc transporter-8 autoantibody (ZnT8A) (48). These are often considered ‘biochemical autoantibodies’ and are the screening targets recommended by the most-recent ADA Standards of Care (25). A further islet autoantibody assay, for islet-cell autoantibody (ICA), using indirect immunofluorescence
on pancreatic tissue, has been used for screening purposes, but it is less available outside of research studies and the antigenic targets are not fully known. Considerable evidence in multiple populations supports the concept that the number and type of biochemical autoantibodies can be used to predict risk for progression to clinical disease (Stage 3, Table 1). These autoantibodies and their characteristics are described in Table 3. However, it must be noted that these attributes are derived from observations made in known IAb+ populations in the research environment. Further data from studies in general population IAb+ groups are needed.

Confirmation of IAb+ status is important to identify the persistence of the underlying autoimmune response and the validity of the target antigen, although the accuracy of autoantibody tests can vary between laboratories and between target antigens. Therefore, the first positive test should be confirmed within 3 months (49), and where possible in a laboratory that meets the performance standards set by the Islet Autoantibody Standardization Program (IASP) (50). Persistent IAb+ status on 2 or more different samples is needed, using sensitive and specific assays with high predictive value for disease progression (51). Several research programs have tested for IAb status using capillary sampling to obtain serum or dried blood spots for assessment. However, venous samples are preferred (due to reduced interference from hemolysis) and should be used as confirmation whenever capillary testing has been performed initially.

Predicting when an individual with T1D-related autoantibodies may progress to Stage 3 T1D is difficult. However, in children and adolescents, persistent multiple IAb+ status confirms early-stage (Stage 1 or Stage 2) T1D with higher rate of progression to Stage 3 T1D compared to single IAb+ status (52). For the same reasons as discussed for single IAb+ status, confirmation of multiple IAb+ status is important, as it indicates early-stage T1D, and should adhere to the ‘rule of twos’ – i.e. the presence of two different autoantibodies, confirmed in two tests from two separate samples (51–54). Subsequent loss of individual antibodies is not associated with a slower rate of progression. The type of positive autoantibody (Table 3) is also of importance – since as children age, relative risks for progression with each antibody type will change (55,56), with some evidence that this is also true for adults (55,57). Consideration of these data, along with autoantibody titres, may aid risk stratification (58). Although fewer data are available to date, Type 1 Diabetes TrialNet cohort data indicate that the rate of progression to T1D in IAb+ adults is slower than in children (59).

Misdiagnosis of T1D as type 2 diabetes (T2D) in adolescents and adults can lead to DKA (60), as this misdiagnosis means that these individuals are often not started on insulin (61). Latent autoimmune diabetes of adults (LADA) can also be misdiagnosed as T2D (62), with a risk of delayed insulin initiation. These observations emphasize the value of autoantibody testing for newly-diagnosed adults with diabetes, particularly when they have features of T1D (e.g., younger age, non-obese, sudden weight loss, mild acidosis, DKA, hyperglycemia >300 mg/dL[16.7 mmol/L]) (63) to make an accurate diagnosis and start appropriate treatment. It is, however, important to recognize that some individuals with new onset T1D have a phenotype that does not differ substantially from persons with T2D, particularly given the increased prevalence of obesity (60,64). Misdiagnosis of maturity onset diabetes of the young (MODY) is also reported (65), suggesting that islet autoantibody screening can be valuable at presentation of all forms of diabetes.
An important outcome of monitoring individuals with IAb+ is to inform the decision to initiate insulin therapy, and this is an area of evolving practice. In some centers, individuals with hyperglycemia (see Table 5) but with hemoglobin A1c (HbA1c) <6.5% (48 mmol/L) might not be started on insulin without the presence of symptoms. Sequential HbA1c monitoring has been productive in this context in pediatric studies on individuals with IAb+, as an absolute ≥10% increase from baseline, even if the HbA1c test reading stays below 6.5% (48 mmol/L), is predictive of disease progression (66,67) within a median of 1 year. Risk of progression within 2 years following a confirmed ≥10% increase in HbA1c is lower for older individuals. This aspect of Stage 3 T1D (i.e. when to start insulin once hyperglycemia is confirmed) is one on which further evidence to support clinical practice is needed, to better understand the metabolic and mental health outcomes.

**What should be monitored?**

It is acknowledged that the practice of monitoring of individuals with IAb+ must accommodate different settings with diverse healthcare resources. In this context, there are multiple available tools for monitoring, including self-monitored blood glucose (SMBG), periodic continuous glucose monitoring (CGM), a standard oral glucose tolerance test (OGTT), random venous glucose, HbA1c and repeat IAb monitoring. In this context, serial stimulated C-peptide measurement during an OGTT can be used to assess deterioration of β-cell function and to predict risk development of T1D (70). Since individuals who present with clinical T1D (Stage 3) often have significant residual β-cell function (68), they may benefit from therapies that can optimize prolongation of insulin secretion (69).

The pros and cons of each monitoring method are documented in Table 5. Identification of an increase in sequential HbA1c values from a baseline reading can be as informative as 2-h OGTT values in predicting risk of stage 3 in youth with genetic risk and diabetes-associated autoantibodies (66,67). Ongoing research continues to evaluate the role of CGM (including professional CGM, which is blinded to the user) in aiding in the identification of individuals, including those with a normal OGTT, who are likely to rapidly progress to stage 3 T1D (71–73). To date, use of CGM metrics in individuals who have multiple IAb+ status has been shown to be predictive of progression to T1D, but CGM measures are not yet as sensitive as OGTT testing (74).

**Where should monitoring take place?**

In practice monitoring should be carried out wherever the skills and resources exist to perform the appropriate tests (Table 5). However, since many people will be monitored in primary care, there is a need to consider different intensities of monitoring consistent with resources available. The capabilities of primary-care HCPs and other care providers should be applied to monitoring of early-stage T1D without the need to refer to an expert practitioner, until clinically appropriate. In primary care, this may help specify basic education about symptoms and glycemic signposts. It is understood that, compared to Stage 1, monitoring in Stage 2 T1D may require more-expert practitioners.

**Objectives and methodology**

The aim of this international consensus report is to formulate expert clinical advice, based on current evidence and expert opinion, that specifies the required monitoring and management approach for persons who have been identified as having IAb+ status and pre-Stage 3 T1D, and can be used in daily
clinical practice. Overall, these key principles should encompass: (a) who should be monitored; (b) which endpoints to monitor; (c) the frequency and duration of monitoring; (d) initiation of insulin during Stage 3 T1D, and; (e) how to provide psychosocial and educational supports for affected individuals and families.

We acknowledge that monitoring of IAb+ individuals will occur in diverse settings, with variable resources to support effective monitoring of IAb+ individuals. Thus, a guiding principle of this consensus report is to provide advice that is straightforward and actionable within the landscape of available clinical skills and resources, wherever the monitoring will take place. The audience for this consensus document therefore includes: (a) primary-care providers; (b) endocrinologists and diabetologists; (c) diabetes care and education specialists (DCES); (e) mental and behavioral health professionals, and; (f) individuals at risk for or in early stages of T1D and their families.

Methodology
The consensus process was initiated by the JDRF with a conference held on 21st February 2023 at the 16th International Conference on Advanced Technologies & Treatments for Diabetes (ATTD) in Berlin, Germany, with in-person or virtual attendance. A mission statement was created and the attendees were invited by email from JDRF and the consensus project leadership. The initial working group comprised 61 internationally-recognized physicians, nurse practitioners, clinical psychologists and diabetes care and education specialists, with expertise in the diagnosis and care of people with early-stage T1D. The conference was centered on monitoring of IAb+ people in early-stage T1D, including discussions of current guidance on current best practice for monitoring, as applied by several prospective T1D prevention trials.

Following a moderated discussion, expert participants were offered the opportunity to join at least one of four working groups, each focused on key aspects of monitoring. Each working group was chaired by two expert contributors, as noted below, and was tasked with self-organized review of the available evidence, participation in serial online discussions and development of core principles. The working groups were; (1) monitoring in children and adolescents (Rachel Besser, Kurt Griffin chairs); (2) monitoring in adults (Rifka Schulman-Rosenbaum, John Wentworth chairs); (3) educational needs (Kirstine Bell, Brigitte Frohnert chairs), and; (4) psychosocial interventions (Kimberly Driscoll, Laura Smith chairs). This subsequently generated 21 separate group online discussions. Each aspect of these discussions was documented with support from JDRF team members and a medical writer. It must be noted that this document is not intended or structured as a systematic review.

On a weekly basis from 3rd May 2023 onwards, evidence-based statements and expert interpretations were drafted for review and revision. At the end of this iterative process, an agreed narrative review of the available evidence was compiled along with the expert clinical advice. Each bulleted principle was assigned a level of supporting evidence (A, B, C or E, see Supplementary Table 1), that adheres to the evidence-grading system for “Standards of Care in Diabetes”, published by the American Diabetes Association (ADA) (75). The process concluded with a conference to review and endorse the penultimate consensus report at the ADA 83rd Scientific Sessions in San Diego, USA. Following this meeting, a revised draft was made available for public comment, after which the consensus document was finalized. The outcomes of this process are also summarized in an algorithm that details the decision path for monitoring of IAb+ persons as part of screening protocols for any reason (Figure 1).
1. Terminology
Precise and consistent language is important to facilitate clear communication and education. As the field has evolved, so has the language around multiple IAb+ status, the stages of T1D and associated risk of progression. It was once commonplace to refer to ‘risk of’ and ‘prevention of’ T1D in individuals with multiple IAb+ status. However, the staging criteria recognize seroconversion to multiple IAb+ status as the onset of the early-stage T1D and thus it is not possible to both have a condition and be ‘at risk’ for it.

Therefore, Stage 1 T1D and Stage 2 T1D (Table 1) should be referred to by their defined names or collectively referred to as either ‘early-stage T1D’ or pre-Stage 3 T1D. While the staging criteria are still becoming widely known, it may be appropriate to refer to these stages as ‘presymptomatic T1D’ for some audiences, to highlight that these early stages exist prior to traditional, symptomatic (i.e. Stage 3 T1D) disease. Individuals with a genetic risk (based on genetic screening and/or family history) or with only single IAb+ status are pre-Stage 1 T1D and can be referred to as ‘at-risk’, but individuals with multiple IAb+ status are confirmed as having early-stage T1D. It must also be clear what the focus of prevention is, e.g., prevention of seroconversion, progression to dysglycemia, or of Stage 3 T1D.

2. Partnership between primary care and specialist healthcare professionals
There is a need for primary care to take on some of the early-stage monitoring and managing IAb+ children and adults. However, staging criteria are relatively new and are unlikely to be widely known among primary care HCPs. Therefore, educational steps and materials must facilitate the partnership between primary care HCPs and secondary care. Primary care HCPs in some regions (e.g., US, Europe) are involved in screening and monitoring tasks for hypercholesterolemia and other metabolic syndromes, so the expectation is that this is possible for early-stage T1D. A critical need is that all HCP stakeholders recognize that some IAb+ individuals can progress rapidly, whereas others may not develop symptoms for decades. In this context, the following expert clinical advice is suggested:

Clinical roles and responsibilities
- Primary care HCPs should understand the stages of T1D, as well as methods for and suggested frequency of metabolic monitoring that can be used to prevent DKA at onset of clinical T1D. [E]
- Primary care HCPs with a specific interest in managing persons with early-stage T1D can serve as a local referral resource for other primary care HCPs when specialist care providers are not readily accessible. [E]
- The primary care provider, specialty care provider, along with the at-risk single IAb+ individual or the multiple IAb+ early-stage T1D individual and their family, should determine which provider will have primary responsibility for metabolic monitoring and what degree of collaboration is desired. [E]
- The level of specialist engagement will need to be reassessed and may shift over time as the IAb+ individual progresses through the stages of T1D, as well as when other needs and circumstances change. [E]

Communication and co-ordination of care
Within a medical practice, HCPs should ensure that the medical record for a child, adolescent or adult, who is single or multiple IAb+, reflects their status and their individual plan for routine metabolic follow up and for urgent evaluation if symptoms of hyperglycemia develop. [E]

If an IAb+ individual meets the criteria for Stage 2 T1D (Table 1), a referral should be made to a diabetologist/endocrinologist to discuss early treatment options and individualized risk of progression to clinical T1D. [E]

If an IAb+ individual develops symptomatic hyperglycemia, an immediate consultation with, and referral to, a multidisciplinary diabetes team comprising specialists with training and expertise in diabetes is necessary. [E]

Training and skills development

Both monitoring and education require a broader understanding of early-stage T1D across the medical community. Inclusion of an understanding of the continuum of T1D into all levels of medical and nursing education will require development of competencies appropriate to the role (Figure 2). [E]

3. Monitoring in children and adolescents

The current landscape of monitoring children and adolescents in early-stage T1D

The following section encompasses monitoring of children and adolescents aged up to 17 years. The overall algorithm is summarized in Figure 1. For a young person who has screened positive for multiple IAb+ status, monitoring recommendations are also provided by the International Society for Pediatric and Adolescent Diabetes (ISPAD) (16) and by the Fr1da study (21).

This expert clinical advice emphasizes the need to benchmark the glycemic stage of disease and to offer ongoing monitoring for disease progression, which should be appropriate to the needs of the affected person and their family. At present, standard 2-hour OGTT (1.75g per kg of body weight up to 75g maximum) is the preferred modality, particularly for inclusion in a Stage 3 prevention trial, whereas less-intensive methods are suggested for children or adolescents who decline to undertake OGTT or participate in a research protocol. Even in a clinical study setting, adherence with OGTT monitoring can be low (Germany, US) (76). Given the diverse settings and resources available, amongst the monitoring tools identified (Table 5), HbA1c testing is not suitable outside of the clinical setting and only random glucose assessments, routine SMBG and CGM, that do not require venipuncture, can be self-managed at home. Studies using CGM in small cohorts of children and youth with Stage 1 or Stage 2 T1D have suggested that glucose levels ≥140 mg/dL (7.8 mmol/L) for >10% of each day is associated with an 80% risk of progression to T1D within 12 months of the CGM assessment period (72,77). In this context, risk of progression to Stage 3 T1D within 2 years of baseline CGM assessment was 40% in individuals with early-stage T1D who spent ≥5% of each day with glucose ≥140 mg/dL (7.8 mmol/L) (71). These outcomes indicate a need for more evidence to confirm the emerging value of CGM in monitoring individuals with early-stage T1D and to understand the disease-predictive value of additional CGM metrics. This need is more pressing given that home use of CGM systems and CGM-derived glycemic metrics is being evaluated for risk stratification for healthy relatives of people with T1D (78,79).
Monitoring at a 6–12 monthly cadence has been used for participants in prevention trials, depending on risk stratification. More-frequent monitoring can be indicated for children who screen positive before 3 years of age and are at high risk of progression (24,51), e.g. at 3- to 6-monthly intervals, depending on staging (24). It should be noted that, amongst monitoring tools, not all CGM systems are generally available in all regions, or for use in very young children. For all individuals outside of the research setting, reducing the frequency of monitoring can be considered as part of a minimally burdensome approach and modelling studies suggest this can be achieved whilst meeting the goal of DKA prevention on a population level (80). In this context, youths of Black race and/or Hispanic ethnicity are less likely to participate with monitoring in this context\(^\text{110}\).

**Monitoring for single islet autoantibody positive at-risk children**

Evidence from cohort studies indicates that up to 50% of children with single IAb\(^+\) status revert to negative (81,82). Children with confirmed persistent single IAb\(^+\) status are not at high risk for progression compared to those with multiple IAb\(^+\) status, with one population-based study indicating that the 10-year risk of progression to T1D for persistent single IAb\(^+\) children is 14.5%, with most of that progression (10%) happening in the first 2 years after becoming IAb\(^+\) (51). This analysis also showed that the progression rate is higher for young children who have single IA-2\(^-\) (40.5%), compared with GADA\(^+\) (12.9%) or IAA\(^+\) (13.1%) (51), however it must be noted that fewer than 10% of children with single IAb\(^+\) status are IA-2\(^-\). Younger age (<5 years) at first IAb\(^+\) confirmation is a risk factor for progression to multiple IAb\(^+\), particularly during the first 2 years after seroconversion (83,84). As children age, relative risks for progression with each antibody subtype change (56), with an increased effect for GADA with increasing age and a reduced effect for IAA (85).

For young children, evidence indicates that metabolic and autoantibody monitoring frequency in the first 2 years after first detection of an autoantibody is the key, as this is when spread from at-risk single to early-stage T1D multiple IAb\(^+\) is most-likely. Following confirmed single IAb\(^+\) status, the IAb\(^+\) evolution after 2 years predicts development of clinical T1D (86). Progression to multiple IAb\(^+\) status or reversion is also highest in the first 2 years in single IAb\(^+\) pre-school children, with a hazard rate of 0.3 in the first 2 years, versus 0.05 for children who have been single IAb\(^+\) for >2 years (83). Among children with increased genetic risk, those who remain single IAb\(^+\) have a risk for T1D of 1.8 per 100 person years, children who revert to negative status have a risk of 0.14 per 100 person years, and children who have never been IAb\(^+\) have a risk of 0.06 per 100 person years (82). The rate of progression to multiple IAb\(^+\) status also declines with age (87).

**Expert Clinical Advice for Monitoring of Single IAb\(^+\) (at risk) Children**

- Confirm persistent single IAb\(^+\) status after first detection in a second sample, preferably in a laboratory that meets IASP standards, using two independent methods (88), and also confirming negative status for other islet autoantibodies. [B]
- IAb status and metabolic monitoring during the first 2 years after seroconversion is most critical (51,83,84,89). Ongoing metabolic monitoring is not essential beyond this 2 year period. [B]
- Children who develop T1D at very young age have more-rapidly progressing and aggressive disease. For children aged ≤3 years who are single IAb\(^+\), monitor their IAb\(^+\) status every 6 months for 3 years, then...
annually thereafter for 3 more years. Metabolic monitoring in children ≤3 years should include random venous or capillary blood glucose (BG) and HbA1c values at the same frequency (51,83,84,86,89). If no progression, stop autoantibody and metabolic monitoring, and counsel for risk of clinical disease. [B]

- For children aged >3 years at first positive test, monitor IAb+ status annually for 3 years. Metabolic monitoring should include annual random venous or capillary BG and HbA1c testing for 3 years (51,83,84,89). If no progression after 3 years, stop autoantibody and metabolic monitoring, and counsel for risk of clinical disease (51,83,84,89). [C]

- For children with single IAb+ who revert to seronegative during autoantibody monitoring, or do not progress (see above), education should be provided to their families emphasizing potential symptoms and awareness of DKA (33,90,91). [C]

**Limitation.** Many data on single IAb+ children are derived from groups with extended prospective follow-up and known genetic risk profiles or first-degree relatives with T1D with limited racial/ethnic diversity. Data on individuals in the general population are more limited, particularly in those with a single screening event.

**Monitoring for multiple autoantibody positive children (early-stage T1D)**

Children with confirmed multiple IAb+ status are at very high risk for progression to Stage 3 T1D within 15 years. Combined data from five prospective studies indicate that the 15-year risk for Stage 3 T1D is 85% for children with two IAb and 92% for those with three IAb, and >99% lifetime risk (86). In children with multiple IAb+, younger age at first IAb detection predicts more-rapid progression to stage 3 T1D (51,92). Although data on children with multiple IAb+ identified from general population screening are derived from shorter follow-up durations, progression rates appear to be similar to those observed in the family members T1D research cohorts (24,93).

The detection of multiple autoantibodies should be confirmed in a venous sample, within three months (49). However, this should not be a rate-limiting step in the monitoring or treatment process, as progression can happen rapidly in young children. Confirmation is critical, since without it there is a risk of delivering a false diagnosis of multiple IAb+ status, with consequent anxiety and distress for the individual. Conversely, although loss of confirmed multiple IAb+ status is rare and may be associated with reduced risk of progression to T1D (94), monitoring should not be discontinued in this group.

**Expert Clinical Advice for Monitoring of Multiple IAb+ Children (early-stage T1D)**

Monitoring of glucose metabolism among children with multiple IAb+ status is necessary to predict time to Stage 3 diagnosis, identify those who may be eligible for intervention, and prevent DKA. Options for metabolic assessments include: home SMBG monitoring, periodic CGM assessment and lab testing for HbA1c, random venous or capillary BG, and OGTT (with stimulated C-peptide assessments). It is acknowledged that there is variable access to high-quality laboratory-testing facilities outside of the research setting. Where possible, the opportunity to undertake monitoring at home or in the primary care setting should be considered (Table 5).

**Expert Clinical Advice for Monitoring of Multiple IAb+ Children (early-stage T1D)**
- Education must be provided to reinforce the need for and value of longitudinal monitoring to prevent DKA (33,90,91). Written instructions with relevant emergency contact details should be provided in case of T1D symptoms and/or hyperglycemia. [E]
- Confirm persistent multiple IAb⁺ status after first detection in a second sample, preferably in a laboratory that meets IASP standards, following the ‘rule of twos’ (52), preferably using two independent methods (88). [B] Where a two-test confirmation is not possible, a single blood-test positive for multiple IAb status identifies a person with sufficient risk for metabolic monitoring. [E]
- In infrequent cases, for a child with previously confirmed multiple IAb⁺ status and who has reverted to single or negative IAb⁺ status (94), monitoring should also follow the advice below. [E]
- Metabolic monitoring should be conducted based on the staging criteria and modalities described in Table 1 and Table 5. This should be undertaken when the child is healthy and not experiencing intercurrent illness. [E]
- SMBG meters and strips can be provided to all children with multiple IAb⁺ or their parents. [E]
- During intercurrent illness, SMBG can be used to detect hyperglycemia. [A]
- For children with recent confirmation of multiple IAb⁺ status, an SMBG test can be performed on 2 different days over a two-week period (on each day, test either fasting or postprandial), and again thereafter once every 1-3 months. See also advice below. [E]
- In children with Stage 1 T1D, HbA1c should be measured once every 3 months for children ≤3 years old, at least every 6 months for children 3-9 years old, and at least every 12 months for children >9 years old (92). [E] Increase in longitudinal HbA1c of ≥10%, even in the normal range (e.g. from 5.0% to 5.5%) indicates increased risk of disease progression to Stage 3 T1D within a median of 1 year (66,67). [B]
- In children with Stage 2 T1D, measures of glucose regulation should be monitored every 3 months, as above. [E]
- Longitudinal change in HbA1c of ≥10% from date of confirmed islet autoantibodies may indicate dysglycemia and disease progression (66,67), and requires the performance of an OGTT to assess T1D stage (Table 1) in order to determine eligibility for therapy. [E]
- Random venous or capillary BG should be measured at the same time as HbA1c. Rise in venous glucose in children with multiple IAb⁺ status predicts time to Stage 3 T1D, see Table 1 (95). [E]
- OGTT is the established gold standard to diagnose Stage 2 or Stage 3 T1D [A], but if not possible, obtain a 2-hour postprandial capillary blood glucose after a carbohydrate-rich meal (85).[E]
- Monitor objective weight trends in a growing child using a growth chart, [C] which may be below the normal range during progression of T1D. Ensure that a healthy meal plan has been maintained, to preclude disordered eating behaviors as a cause of weight change. [E]
- 10-14 day CGM can be used periodically to monitor glucose metabolism at a similar frequency as HbA1c measurement. [E] CGM should ideally be blinded to the individual wearing it and must interpreted by trained HCP, with education for the user and their family. [E] Criteria for CGM metrics to diagnose Stage 2 or Stage 3 T1D are proposed (Table 1) and require further research.
- Stage 2 T1D warrants referral to specialists in T1D progression for discussion of risk and options for monitoring, wherever feasible. [E]
— In countries with approved therapeutic options for early-stage T1D or locations with access to intervention studies (3,96), referral to a clinical center with expertise in the specific treatment should be done when Stage 2 T1D is suspected or diagnosed. [E]

4. Monitoring in adults

The current landscape of monitoring adults who are at risk or with early-stage T1D

The following guidance encompasses monitoring of adults aged 18 years and over, although they are based on outcomes data that typically reflects adults younger than 45 years of age. Data specific to adults older than this are an important unmet need. Epidemiological data show that, overall, T1D is diagnosed more-frequently in adulthood than in childhood (97–100), at a median more-than 35 years of age (101,102). Despite this, misdiagnoses of T1D in adults remain common and are increasingly likely with age (60), setting the scene for development of DKA. In common with childhood-onset T1D, adult-onset T1D is associated with the presence of islet-specific autoantibodies (103–106). Although TrialNet cohort data indicate that the rate of progression to T1D in IAb+ adults is slower than in children, many adults with multiple IAb+ status and early-stage T1D still develop Stage 3 disease (59). While it has been suggested that progression in some adults may not occur and that some of those who do progress have only a single IAb+, further long-term follow-up data are needed to better characterize the long-term implications of persistent autoimmunity in adults (107). For example, recent data highlight the frequent presence of islet autoimmunity in cohorts presenting with phenotypic T2D (108).

Guidance to inform clinical monitoring practices in adults represents a considerable unmet need. There are many evidence base gaps, including a lack of information about risk of disease progression in IAb+ adults without a family history of T1D, particularly in individuals with non-European ancestry. Data on suggested monitoring protocols, including effectiveness in preventing DKA and adherence with monitoring, are substantially based on children and adolescents. The frequency of DKA among adults at diagnosis with T1D is unknown but believed to be lower than for children, given that adults may recognize and respond to symptoms of hyperglycemia, often have higher C-peptide levels at clinical diagnosis and a slower decline in β-cell function over time (109). Yet, incorrect assumptions leading to underdiagnosis of T1D in adults mean many develop DKA before starting insulin therapy.

DKA incidence at clinical diagnosis can be reduced by participation in active monitoring (24,26,27). Regarding frequency of monitoring, modelling based on TrialNet data suggest that conducting approximately half the number of visits involved in a research setting (typically once every 12 rather than every 6 months), is likely to be effective in substantially reducing the incidence of DKA to the levels seen in research studies both for children and adults (80). However, data from the TrialNet study indicate that adults 18 years and older are less likely than pediatric participants to engage with recommended monitoring using 6- to 12-monthly OGTT in the early phases after screening positive for autoantibodies (110). As with youths, adults of Black race and/or Hispanic ethnicity are less likely to participate with monitoring in this context (110). Regarding frequency of monitoring, modelling based on TrialNet data suggest that conducting approximately half the number of visits involved in a research setting is likely to be effective in substantially reducing the incidence of DKA on a population level to that seen in research studies, both for children and adults (73).
Most endocrinologists and primary-care HCPs will not be trained in monitoring adults with single IAb\(^+\) status or early-stage T1D. Thus, the educational need will be significant. As with children and adolescents, monitoring in IAb\(^+\) adults must be realistic and actionable across diverse regions, with different resources. HCPs are significantly burdened such that additional tasks for monitoring in pre-Stage 3 T1D must be clinically useful.

**Monitoring for single autoantibody positive at-risk adults**
Frequency of monitoring can be based on the stage at which an individual with IAb\(^+\) is diagnosed. Single IAb\(^+\) adults with dysglycemia should be monitored more-frequently than those with normoglycemia. Additional risk stratification may also be possible based on other characteristics, such as age, or modifiable factors, such as abdominal obesity.

**Expert Clinical Advice for Monitoring Single IAb\(^+\) (at risk) Adults**
- Confirm persistent single IAb\(^+\) status after first detection in a second sample, preferably in a laboratory that meets IASP standards, using two independent methods (88), and also confirming negative status for other islet autoantibodies. [B]
- Annual metabolic monitoring should be considered for single IAb\(^+\) adults if there are additional risk factors, including one or more of: first-degree relative with T1D; elevated genetic risk for T1D if tested; dysglycemia (e.g. impaired fasting glucose or impaired glucose tolerance) or; history of stress hyperglycemia (111,112). [E]
- Although single IAb\(^+\) adults are at lower risk of progression to T1D compared to children (59), and this risk continues to fall with increasing age, there remains a residual risk for progression. The approach to metabolic monitoring for single IAb\(^+\) adults can be informed by that applied for screening for T2D, which is advised every 3 years for normoglycemic adults aged >35 years, or who are overweight/obese with one or more additional risk factors (18). A similar 3 year frequency is proposed for single IAb\(^+\) adults, to monitor for risk of progression, which may be increased to annual monitoring with the additional risk factors identified for T2D. [E]
- No T1D monitoring is indicated in individuals with transient, single IAb\(^+\) who then revert to seronegative. Screening for diabetes in this group of adults should thereafter follow standard of care guidelines for T2D (18). [C]

**Monitoring for multiple autoantibody positive adults (early-stage T1D)**
As with monitoring in single IAb\(^+\) adults, more-frequent monitoring is proposed for persons with multiple IAb\(^+\) status if they are diagnosed with Stage 2 T1D compared to Stage 1 T1D. Risk stratification based on age, abdominal obesity and other modifiable factors, also applies.

**Expert Clinical Advice for Monitoring Multiple IAb\(^+\) (early stage T1D) Adults**
- Education must be provided to reinforce the need for and value of longitudinal monitoring to prevent DKA (33,90,91). Written instructions with relevant emergency contact details should be provided in case of T1D symptoms and/or hyperglycemia. [E]
- Confirm persistent multiple IAb\(^+\) status after first detection in a second sample, following the ‘rule of twos’ (52) and preferably using two independent methods (88). [B] Where a two-test confirmation is
not possible, a single blood-test positive for multiple IAb status identifies a person with sufficient risk for metabolic monitoring. [8]

- In infrequent cases, for adults with previously confirmed multiple IAb+ status who have reverted to single or negative IAb+ status (94), monitoring should also follow the advice below. [E]
- All multiple IAb+ adults can be provided with SMBG meters and strips, to be used during illness or when symptoms may be present. [E]
- In adults with Stage 1 T1D and normoglycemia (Table 1), glycemic status should be monitored using HbA1c every 12 months, as part of routine primary care visits. Modify frequency of monitoring based on individual risk assessment, based on age, number and type of IAb, and glycemic metrics (4). [E]
- If duration of normoglycemia extends to 5 years, metabolic monitoring every 2 years may be sufficient. [E]
- In adults with confirmed Stage 2 T1D (Table 1), metabolic status should be monitored using HbA1c every 6 months, in conjunction with one other monitoring modality, either: blinded CGM (applied and interpreted by trained HCP), higher-frequency of SMBG or 2-h plasma glucose following 75g OGTT. [E]
- Longitudinal change in HbA1c of ≥10% from date of confirmed islet autoantibodies may indicate dysglycemia and disease progression (66,67), and requires the performance of an OGTT to assess T1D stage (Table 1) in order to determine eligibility for therapy. [E]
- When dysglycemia or hyperglycemia occurs, C-peptide monitoring should be considered where the diagnosis of T1D vs T2D is unclear. Meta-analysis indicates that a C-peptide level of ≤0.20 nmol/L with IAb+ status can be associated with a diagnosis of T1D rather than T2D (113); however, many adults presenting with T1D will have C-peptide above this level (109). [B] Note that C-peptide levels can be falsely low in hypoglycemia (<70 mg/dL [3.9 mmol/L]), after fasting or in severe hyperglycemia/DKA, so concomitant plasma glucose concentration should be checked and interpreted in combination with the clinical state.
- In countries with approved therapeutic options for early-stage T1D or locations with access to intervention studies (3,96), referral to a clinical center with expertise in the specific treatment should be done when Stage 2 T1D is suspected or diagnosed. [E]

**Monitoring during pregnancy for IAb+ women**

Evidence on the progression of T1D in IAb+ women is limited and research data on this aspect of managing risk in early-stage T1D is a significant unmet need (Table 7). With that said, a high risk for postpartum T1D has been indicated (114), and the guidance below is primarily based on expert opinion. Pregnancy demands increased pancreatic β-cell function and may result in diabetes, as it does in gestational diabetes mellitus (GDM) (115). Given that 60% of babies born to women with diagnosed T1D are large for gestational age (LGA), which is associated with increased rates of obstetric and neonatal complications (116,117), it is important to avoid a missed early diagnosis and promote normal fetal development.

**Expert Clinical Advice for Monitoring in Pregnancy for IAb+ Women**

- Women with confirmed IAb+ who become pregnant should have an OGTT or HbA1c test or application of CGM soon after pregnancy is confirmed (by 8 weeks if possible) (18,118). [C]
- Women with confirmed IAb+ who are not already diagnosed with diabetes mellitus, should receive OGTT tests at 24-28 weeks as standard for all pregnancies (18). [A]
- Glucose monitoring for women with confirmed IAb+ status who are diagnosed with diabetes mellitus: once post-partum, women should be assessed prior to discharge from hospital, in consultation with a specialist endocrinologist, to determine continued need for insulin (114). [C]
- Women with confirmed IAb+ status should be monitored for 6-12 months post-partum to assess any changes in insulin requirement. [E] Where available, follow-up both with the gestational care provider and an insulin-initiation specialist should be provided. [E]

5. When to start insulin
At some point, monitoring will reveal a person with persistent and/or recurrent hyperglycemia prompting a decision on whether to start insulin, along with associated education and support for affected individuals and their families. As screening programs identify more people with early-stage T1D, more people are being assessed as meeting classic diagnostic criteria for Stage 3 (Table 1), but who might not yet require insulin therapy. Decisions about how and when to initiate insulin will be based on a range of factors, many of which do not have a body of evidence. Therefore, consideration of starting insulin should trigger a referral to a specialist center with expertise in initiating and managing people with T1D on insulin.

6: Education
The primary goals of education for the care of IAb+ individuals and their families are outlined in Table 6. Given the paucity of evidence on education for persons with early-stage T1D, extensive experience in education for Stage 3 T1D can be extrapolated to this population. National standards for diabetes self-management education and support (DSMES) have been published by the ADA and the Association of Diabetes Care & Education Specialists (ADCES) and are broadly applicable in this context (119). When appropriate, evidence from studies in Stage 3 T1D are used to support grading of evidence.

Experience in clinical studies can also inform education for persons with early-stage T1D and their families/caregivers. The TEDDY prospective study protocol emphasizes parental education regarding symptoms and signs of diabetes. For families new to T1D this education provides foundational skills for diabetes management that are a component of reduced parenting stress at the time of Stage 3 diagnosis compared to community controls (120). Similarly, families of children with early-stage T1D in the Fr1da study are invited to participate in an educational program of blood glucose monitoring and symptoms of hyperglycemia/DKA. They are also provided with a guidebook, specifically designed for children with early-stage T1D and assigned a contact person to answer questions at any time. Children who take part in this program alongside metabolic monitoring have a lower rate of DKA and reduced HbA1c at Stage 3 T1D presentation, compared to children who declined education and follow up (33). Over 50% had no symptoms at the clinical presentation of stage 3 T1D, 93.5% had no weight loss, and length of stay in hospital was shorter (90,91).

Basic community awareness campaigns not associated with monitoring and centered on the early symptoms of T1D that target teachers, pediatricians and parents, have been effective in reducing DKA rates
in children in regional settings (Parma in Italy (121) and Newcastle in Australia (122)). However, national campaigns in Italy and Austria, with the same objectives, have not seen the same impact (123,124). The content and delivery of these campaigns were not similar, so it is hard to draw conclusions about the effectiveness of this education.

Education topics and intensity for persons with early-stage T1D and their families should be staged based on T1D stage, age, rate of progression, etc. First degree relatives may have different needs for support and guidance from the general population, as they have an established awareness of the implications and impact of IAb+ status. Education topics should be linked to specifically-timed action plans and include the topics below. Education can be specified applicable to each stage of presymptomatic T1D (Table 1). Clinical practitioners with experience in early-stage T1D should be involved in the later steps of education.

**When should education be provided?**
- At the point of a positive autoantibody screen, at diagnosis of each stage, when monitoring tasks are performed, and annually for review and maintenance.
- During life transitions and milestones, and when care needs change.

**Key education topics**

Education and self-care behaviors for individuals at risk for, or with early-stage diabetes (Table 1), can be derived from the overall framework of self-management skills for diabetes and related conditions, including prediabetes. These are described in the ADCES7 self-care behaviors (125). Those relevant for at-risk individuals or those with early-stage T1D focus on understanding the implications of their single (at risk) or multiple IA+ (early-stage T1D) status, and the benefits of regular monitoring. Symptom awareness is also important, to reduce the risks of hospitalization for DKA, as well as the value of glucose monitoring. If other family members have T1D, do not assume pre-existing awareness and knowledge. The most-current education should always be mandated, as summarized below

**Educational topics of highest value for IAb+ individuals and family members**
- Understanding autoimmunity and the confirmation of single (at risk) or multiple IAb+ (early-stage T1D) status.
- Definition of at-risk or early-stage T1D.
- Risk perception - accurate risk perception is linked with staying engaged in monitoring and with DKA prevention (126).
- Risks and benefits of individual participation in research studies.
- Awareness of hyperglycemia episodes for introducing insulin at the right time.
- Strategies for healthy coping.
- Symptom awareness and prevention of DKA.
- Glucose monitoring (SMBG, CGM), if clinically recommended.
- Healthy behaviors, including meal planning and physical activity.
- Risks and benefits of intervention therapies.
- Monitoring planning, with descriptions of lab tests and devices that may be used (Table 5).
Where should education be provided?
Education for all stakeholders can be accessed in multiple media and settings, and should be crafted with the specific audience communities in mind. For education aimed at HCPs, a key requirement is for professional associations in all regions to be aligned with the educational program and curriculum, preferably compatible with their educational platforms and with accreditation. For education aimed at people with pre-Stage 3 T1D, in-person options associated with clinical appointments or in group sessions are important, and strong evidence supports DSMES delivery through virtual, telehealth, telephone, text messaging, and web-based/mobile phone apps (127–131).

Who should provide education?
The competencies that must be addressed in education are outlined in Figure 2. There is a need for diabetes professional associations to endorse the educational goals, educational tool and educational content, as described. The groups indicated in the pyramid sections on the left-hand side of the graphic should have the competencies described and participate as appropriate.

**Expert Clinical Advice for Education of Single IAb+ (at risk) and Multiple IAb+ (early-stage T1D) Individuals**
- Education is the responsibility of all health professionals involved in the monitoring and care of individuals with T1D. [E]
- Persons at risk or with early stage T1D may participate in monitoring education programs to reduce the rate of DKA at diagnosis (33,90,91). [B]
- Education should be provided: (1) at the point of a positive autoantibody screening; (2) at diagnosis of each stage; (3) annually for review and maintenance; (4) during life transitions. [E]
- Education should accompany the implementation of all monitoring plans. This includes home glucose testing and any monitoring devices. [E]
- Education should be culturally, linguistically and socioeconomically congruent. [E]
- Education topics and intensity should be based on T1D stage and risk of progression, and include the risks and benefits of intervention therapies, when appropriate. [E]
- Diabetes education should be accessible, engaging and person-centred. This includes consideration of the developmental, social, emotional, cultural, linguistic needs of the individual and/or family. [E]

7: Psychosocial Support

What is the current landscape regarding psychosocial support for people with T1D-related autoantibodies?
Persons who learn that they or a loved one have T1D-related autoantibodies often experience significant stress (132). This is in part because events that are unpredictable, uncontrollable and threatening may be highly stressful. People who have IAb+, particularly those who have multiple IAb+, will very likely develop T1D in the future. However, disease progression is impossible to predict precisely and having IAb+ status
does not mean imminent T1D onset [133,134]. Stage 3 T1D, with associated insulin administration and glycemic monitoring, could be months or even years away [17].

When learning they have T1D-related autoantibodies, individuals of all ages and their family members can experience a range of emotional and behavioral reactions (135,136), including shock, grief, guilt, anger, depression, and anxiety. If time passes with no diagnosis of Stage 3 T1D, cognitions about T1D may change and individuals may become convinced they will never get the disease or have reduced risk, despite evidence to the contrary [137]. Parents often engage in behaviors in attempts to prevent T1D when faced with the news that their child is at increased risk, even when not provided with recommendations to do so, though more recent data has shown that lower physical activity and meal plans with a higher glycemic index are associated with faster progression to T1D (138–140). Meal-planning changes are most commonly reported, with extra monitoring at home (including blood glucose checking) being particularly common in families with someone who already has T1D (141,142).

Research has documented the psychosocial impact of newborn screening (143), as well as genetic and IAb screening for T1D (132,136). Failure to understand the screening and risk information presented is common. For example, more than a third of participating mothers and over half of participating fathers in the TEDDY study stated that their child was not at increased risk for T1D, despite being clearly informed of their child’s increased genetic risk [137]. To date, no data are available on how children screened positive for IAb perceive or react to their risk.

Emotional distress in response to a positive IAb screen is also common. Many parents of children in the TEDDY study experienced anxiety after learning that their child was at increased risk for developing T1D with mothers reporting higher anxiety than fathers [132]. Although anxiety decreased across time for parents of IAb+ children who never develop additional autoantibodies, anxiety remained elevated in many parents of children with multiple autoantibodies for years after the child’s first IAb+ test result. Mothers who experienced negative interpersonal life events and post-partum depression, but who were accurate about their child’s T1D risk, were particularly vulnerable to heightened anxiety [144]. In the ASK Study, which conducted IAb screening in the general population, 74.4% of parents reported significant levels of anxiety about their child’s T1D risk at the first follow-up visit; parents with lower educational attainment were more likely to exhibit higher levels of anxiety [145].

Around 40% of mothers and 20% of fathers in the Fr1da study reported clinically elevated symptoms of depression after learning that their child was at increased risk for T1D as compared with around 18% of mothers and fathers of children who were islet autoantibody negative [24]. Depressive symptoms declined across one year, with scores in mothers remaining slightly elevated as compared to mothers of islet autoantibody negative children; scores in fathers did not remain elevated.

Although both the ADA and ISPAD have published recommendations about the psychosocial care of individuals with Stage 3 T1D (146–148), these are limited to general principles for care of those with early stage T1D [149]. Thus, there is an urgent need to provide guidance on psychosocial support for individuals with T1D-related autoantibodies and their families.
We recognize regional differences in healthcare resources may limit mental health resources for care of persons with diabetes. In most areas, there are insufficient mental and behavioral health professionals with expertise in the psychosocial aspects of T1D who can provide the care recommended by ADA and ISPAD (146–148).

What is the purpose of psychosocial support?
The overall goal of providing psychosocial support for individuals identified as having early stage T1D and their families is to assist them in successfully managing the psychosocial impacts associated with this life-changing news. To accomplish this goal, emotional, cognitive, and behavioral functioning need to be assessed and addressed, not only in individuals with T1D-related autoantibodies but in their family members as well, when appropriate.

What type of support should be provided?
The essential first step is to ask the individual who is at risk for T1D and/or their caregivers and family members about their reactions upon receiving the news that they have T1D-related autoantibodies. However, asking once is not enough as adjustment to autoantibody status may change over time (132). Inquiring about how individuals are coping with the news and their current needs should be conducted at every monitoring visit. Examples of questions to include in the conversation include:

1. How do you feel about this news?
2. Others have said this news brings feelings of sadness or worry, what are your feelings?
3. What is your understanding about having multiple autoantibodies?
4. What type of things are you doing to try to prevent T1D?
5. What are your thoughts about talking with a counselor about your feelings from this news?

Providers can also assess global symptoms of anxiety and depression using use age-appropriate standardized and validated questionnaires, such as the PHQ9 for depression (150) or the Hamilton Anxiety Scale (151). However, global measures of anxiety and depression may not be sensitive to the emotional impact specifically associated with learning they – or a loved one - have T1D autoantibodies. In such cases, measures that assess emotional reactions to the IAb⁺ status, such as the State component of the State-Trait Anxiety Inventory (152) may be more appropriate. At a minimum, providers should have conversations with individuals about their reactions to IAb⁺ results rather than relying solely on global measures of psychosocial functioning. Assessments should occur at regular intervals, since reactions are likely to change over time. Additional measures for both depression and anxiety in diabetes are provided in the ADA Psychosocial Position Statement (147), along with the associated directory of mental health providers https://my.diabetes.org/health-directory.

It is also important to consider developmental and family-specific factors when assessing psychosocial needs. For example, children and adolescents with T1D autoantibodies may experience varied emotional, cognitive, and behavioral impacts as they develop. This further emphasizes the need for ongoing, regular assessment of psychosocial needs. Additionally, individuals with a family history of T1D may react differently to learning about T1D-related autoantibodies (141), compared to those who are unfamiliar with
disease; family context and prior experience with T1D are important considerations when assessing psychosocial impact and the need for additional support.

Although increased anxiety and depression can occur in individuals with T1D-related autoantibodies and their family members, this can be reduced by monitoring for the potential development of T1D (120). Providing individuals with regular monitoring for T1D, depending on stage, as outlined in earlier sections of this statement can help individuals manage some of the unpredictability of T1D development (120,132).

Based on the extant literature, diabetes-focused organizations, such as the ADA and ISPAD, have provided recommendations on the importance of individuals with diagnosed T1D receiving psychosocial care (146–148), that is preferably integrated into routine diabetes visits and delivered by providers with diabetes-specific training (153). While the same level of evidence does not yet exist in those individuals with T1D-related autoantibodies, the well-documented emotional, cognitive, and behavioral impacts of autoantibody status certainly suggests that a similar standard for psychosocial care should be available for all individuals who are at risk for developing T1D and their families. For individuals with early-stage T1D and their parents or caregivers, there are well-developed models of managing psychosocial reactions to risk status, including age-specific education and assigned contact persons to answer questions that can serve as models (9,145).

Ideally, psychosocial care should be integrated with routine monitoring visits and delivered by health care professionals using a collaborative, person-centered, culturally informed approach. When available, refer to mental and behavioral health professionals with expertise in T1D for additional assessment and treatment. For individuals residing in the US, the ADA publishes the Mental Health Provider Directory, which lists providers with expertise in diabetes.

**Expert Clinical Advice for Psychosocial Support for Single IAb⁺ (at risk) and Multiple IAb⁺ (early-stage T1D) individuals**

- Emotional, cognitive, and behavioral functioning should be assessed in persons at risk or with early-stage T1D and their family members, when appropriate. Specifically: Anxiety; Risk perception; Behavior changes. [E]
- As an essential first step to providing psychosocial support, HCPs should ask the individual at risk or with early stage T1D and/or their caregivers and family members about their reactions upon receiving the news that they have T1D-related autoantibodies. This can be accomplished using guiding questions and standardized and validated questionnaires. [E]
- At each monitoring visit, there should be enquiries into current needs, particularly coping. [E]
- Psychological care should be integrated into routine medical visits and, whenever possible, delivered by providers with diabetes-specific training. [E]

**8. Unmet needs for further research**

This consensus document for monitoring individuals with single (at risk) and multiple IAb⁺ (early-stage T1D) covers key principles based on existing evidence and agreed expert opinion. It also highlights the significant unmet need for further research on early-stage T1D, to further increase the rigor for future guidance and recommendations and drive the evolution of clinical care for people who have tested positive for islet
autoantibodies. The key principles in this consensus document will be subject to updating once additional evidence becomes available, as indicated in Table 7.

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Conflicts of interest
M.P. has received honoraria for participation on advisory boards for Medtronic Diabetes, Pfizer and Sanofi, and as a speaker for Eli Lilly, Medtronic Diabetes, Novo Nordisk, Pfizer, Sanofi and Ascensia. MP owns stocks of DreaMed Diabetes and his institution has received research grant support from Dexcom, Medtronic Diabetes, Pfizer, Sanofi, NG Solutions, Lumos, Opko, Eli Lilly, Novo Nordisk, Roche Diagnostics, DreaMed Diabetes, Dompe, GWave and Provention Bio, travel expenses from Medtronic Diabetes and Sanofi and consulting fees from Qulab Medical and Provention Bio. T.B. has received honoraria for participation on advisory boards for Novo Nordisk, Sanofi, Eli Lilly, Medtronic and Indigo Diabetes, and as a speaker for AstraZeneca, Eli Lilly, Novo Nordisk, Medtronic, Sanofi and Roche. His institution has received research grant support and travel expenses from Abbott Diabetes Care, Medtronic, Novo Nordisk, Sanofi, Sandoz and Novartis. R.E.J.B has received a Programme Development Grant from NIHR and her institution has received speaker fees from EASD and consulting fees from Provention Bio and travel expenses from JDRF. H.M.C. has received research grant support from IQVIA, JDRF, Diabetes UK, UK Medical Research Council and the European Union Commission. H.M.C has received speaker fees from Novo Nordisk and has participated on advisory boards for Novo Nordisk and Bayer AG, and owns shares in Roche Pharmaceuticals and Bayer AG. T.D. has received consulting fees and honoraria from Sanofi. O.E. has received research support through the T1D Exchange from Abbott, Dexcom, Eli Lilly Pharmaceuticals, Janssen Pharmaceuticals, MannKind Pharmaceuticals, Sanofi, Vertex Pharmaceuticals and Medtronic Diabetes. O.E. has also participated on advisory boards for Medtronic and Sanofi. D.J.F. is a Board Member for the Children’s Diabetes Foundation. K.J.G. has received reimbursement for attending meetings and travel expenses from JDRF and is on the Advisory Council for Early Check Screening Program and Canadian T1D Screening Program. R.W.L. has received consulting fees from Cigna Insurance and is an employee of the Endocrine Society. A.L. has received grants or contracts from JDRF, National Institutes of Health/National Institute of Diabetes and Digestive and Kidney diseases, Vinnova, the Swedish Research Council, Swedish Diabetes Fund and the Helmsley Charitable Trust, consulting fees from Diamyd Medical AB, and as a paid member of the Scientific Advisory Board of the TEDDY study group, including Travel reimbursement. A.L. has planned patents at the Fred Hutchinson Cancer Center, and has participated in advisory boards for NextCell Pharma AB, Better Diabetes Diagnosis Study,
Sweden, TEDDY Study Steering Committee and is the TEDDY Study Immune Markers Committee Chair. D.M.M. has received reimbursement from Abbott, Lifescan, Sanofi, Medtronic, Provention Bio, BioSpex, Kriya and Bayer and received payment to his institution from NIDDK, the Helmsley Charitable Trust, the National Science Foundation, along with research support from Dexcom. D.M.M. has participated in data-safety monitoring boards or observational Study monitoring boards for GO MOMS, National Institute of Diabetes and Digestive and Kidney diseases, ATTEMPT and REMODEL and has an unpaid role as ISPAD President. C.M. has received honoraria from Medtronic, Boehringer Ingelheim, Eli Lilley and Company, Vertex, Novo Nordisk, Sanofi, ActoBio Therapeutics and Insulet, and participated in data safety monitoring boards or advisory boards for ActoBio Therapeutics, AstraZeneca, Vertex, Boehringer Ingelheim, Eli Lilly and Company, Imcyse, Insulet, Sanofi, Medtronic, Novo Nordisk, Roche and Sanofi. R.P.-B. has accepted grants or contracts from NIDDK, JDRF, Novo Nordisk, Medtronic and Lexicon Pharmaceuticals and consulting fees from Bayer, Averitas Pharma, Lexicon Pharmaceuticals, Novo Nordisk, Roche, Procter & Gamble, Reata Pharmaceuticals and Nevro Inc. R.P.-B. has also received payment or honoraria from Roche and travel support from Lexicon Pharmaceuticals. R.P.-B. is on the Board of Directors for The American Diabetes Association and has participated on a data safety monitoring boards or advisory boards for Reata Pharmaceuticals. M.J.R. and has received grant or contract support from JDRF, the Helmsley Charitable Trust and Sanofi, as well as consulting fees from Provention Bio, Sanofi and JDRF. M.J.R. has also received travel expenses from Sanofi and JDRF, and has participated on data safety monitoring boards or advisory boards for Sanofi. K.M.S. has received grants or contracts from Provention Bio, Sanofi and Novartis, as well as consulting fees from Provention Bio, Sanofi and JDRF, and has participated on data safety monitoring boards or advisory boards for Sanofi. K.M.S. has a leadership and fiduciary role with the Diabetes Training Camp. E.K.S. has received grant funding from National Institutes of Health, JDRF and is the chair of Clinical Advances in T1D Screening Committee and has received consulting fees from Sanofi and DRI Healthcare. E.K.S. has received payment for lectures from Health Matters CME, Medscape, American Diabetes Association and Children with Diabetes and has received payment and travel reimbursement from Sanofi. K.M.S. is a member of data safety monitoring boards and advisory boards, and is the Treasurer for the Immunology of Diabetes Society. K.M.S. has a patent on extracellular vesicle cargo as a biomarker in T1D. J.S.S. has received grants or contracts from Diabetes Research Institute Foundation and consulting fees from 4Immune, AbbVie, Abvance, ActoBiotics, Adocia, Aerami/Dance Biopharma, AiTA, Altheia, Applied Therapeutics, Arecon, Astra-Zeneca, Avotres, Bayer, Biomea Fusion, COUR Pharmaceuticals, Dexcom, Diasome, Dompe, Enthera, Imcyse, Immunomolecular Therapeutics, Kriya Therapeutics, Levicure, Novo Nordisk, Oramed, Orgenesis, Provention Bio, Quell Therapeutics, Remedy Plan Inc., Sanofi, Signos, Vertex, Viacyte, vTv Therapeutics, and WiNK. J.S.S. has received payment or honoraria from Sanofi and Medscape and support for attending meetings or travel from Dexcom, Sanofi and Medscape. J.S.S. has US Patent #11,434,291 - Methods and Composition for Preventing Type 1 Diabetes and has participated on data safety monitoring boards or advisory boards for Provention Bio, Imcyse, INNODIA, University of Paris. J.S.S. is the Chair of the Strategic Advisory Board, for INNODIA, has been on the Board of Directors for Applied Therapeutics and Dexcom Inc, and has stock or stock options in 4Immune, Abvance, AiTA, Applied Therapeutics, Avotres, Dexcom, Immunomolecular Therapeutics, Oramed, Orgenesis, Signos, vTv Therapeutics, and WiNK. LAD has received Research Support to their institution from Dompe, Lilly, Mannkind, Medtronic, Provention/Sanofi and Zealand and Consulting fees from Vertex, Abata. L.A.D. has a patent pending on the actions of difluoromethylornithine in diabetes. P.A., A.A., A.A-O., K.J.B., E.B., J.J.C., M.E.C.,
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<table>
<thead>
<tr>
<th>Stage of T1D</th>
<th>Islet autoantibody status</th>
<th>Glycemic status</th>
<th>Symptoms</th>
<th>Insulin required</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk</td>
<td>Single autoantibody or transient single autoantibody</td>
<td>Normoglycemia&lt;br&gt;FPG &lt;5.6 mmol/L (&lt;100 mg/dL)&lt;br&gt;120-min OGTT &lt;7.8 mmol/L (&lt;140 mg/dL)&lt;br&gt;HbA1c &lt;5.7% (&lt;39 mmol/mol)</td>
<td>No symptoms</td>
<td>Not required</td>
</tr>
<tr>
<td>(Pre-stage 1 T1D)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1 T1D</td>
<td>≥2 autoantibodies&lt;br&gt;Also referred to as:&lt;br&gt;  - Early-stage T1D&lt;br&gt;  - Presymptomatic T1D</td>
<td>Normoglycemia&lt;br&gt;FPG &lt;5.6 mmol/L (&lt;100 mg/dL)&lt;br&gt;120-min OGTT &lt;7.8 mmol/L (&lt;140 mg/dL)&lt;br&gt;HbA1c &lt;5.7% (&lt;39 mmol/mol)</td>
<td>No symptoms</td>
<td>Not required</td>
</tr>
<tr>
<td>Stage 2 T1D</td>
<td>≥2 autoantibodies*&lt;br&gt;Also referred to as:&lt;br&gt;  - Early-stage T1D&lt;br&gt;  - Presymptomatic T1D</td>
<td>Glucose intolerance or dysglycemia not meeting diagnostic criteria for Stage 3 T1D, with at least 2 of the following, or a single positive at 2 time points within 12 months:&lt;br&gt;  - FPG 5.6–6.9 mmol/L (100–125 mg/dL)&lt;br&gt;  - 120-min OGTT 7.8 – 11.0 mmol/L (140-199 mg/dL)&lt;br&gt;  - OGTT values ≥11.1 mmol/L (≥200 mg/dL) at 30, 60 and 90 mins&lt;br&gt;  - HbA1c 5.7–6.4% (39–47 mmol/mol) or longitudinal ≥10% increase in HbA1c (66,67) from first measurement with Stage 2 T1D&lt;br&gt;  - CGM values &gt;7.8 mmol/L (&gt;140 mg/dL) for 10% of time over 10 days continuous wear(73)§, and confirmed by at least one other non-CGM glucose measurement test listed.</td>
<td>No symptoms</td>
<td>Not required</td>
</tr>
<tr>
<td>Stage 3 T1D</td>
<td>≥1 autoantibodies</td>
<td>Persistent hyperglycemia with or without symptoms as measured and confirmed by one or more of the following:&lt;br&gt;  - 1x random venous glucose ≥11.1 mmol/L (≥200 mg/dL) with overt symptoms;&lt;br&gt;  - 120-min OGTT ≥11.1 mmol/L (≥200 mg/dL) and/or;&lt;br&gt;  - 2x random venous glucose ≥11.1 mmol/L (≥200 mg/dL) and/or;&lt;br&gt;  - FPG ≥7.0 mmol/L (≥126 mg/dL) and/or;&lt;br&gt;  - Laboratory-tested HbA1c ≥6.5% (48 mmol/mol)&lt;br&gt;  - CGM values &gt;7.8 mmol/L (&gt;140 mg/dL) for 20% of time over 10 days continuous wear(73)§, and confirmed by at least one other non-CGM glucose measurement test listed.</td>
<td>May include**:&lt;br&gt;  - Polyuria&lt;br&gt;  - Polydipsia&lt;br&gt;  - Weight loss&lt;br&gt;  - Fatigue&lt;br&gt;  - DKA</td>
<td>+/- Insulin, based on glycemic status</td>
</tr>
</tbody>
</table>
Some persons with confirmed persistent prior multiple autoantibody positivity may revert to single autoantibody status or negative status in stage 2 (94). ** Stage 3 might not include symptoms. § CGM is ideally blinded and must be applied and interpreted by a trained health care professional. Note, use of CGM-derived criterion did not achieve consensus within the consensus panel and CGM metrics are not part of current ADA or ISPAD guidelines on staging criteria in T1D (16,156).

DKA, diabetic ketoacidosis; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; T1D, type 1 diabetes mellitus
Table 2. Established population-based screening and monitoring studies in early-stage T1D*

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Study name</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASK</td>
<td>Autoimmunity Screening for Kids program⁷</td>
</tr>
<tr>
<td>BABYDIAB</td>
<td>Part of the international Type 1 Data Intelligence (T1DI) project⁰¹⁴</td>
</tr>
<tr>
<td>DAISY</td>
<td>Diabetes Autoimmunity Study in the Young⁶</td>
</tr>
<tr>
<td>DIPP</td>
<td>Type 1 Diabetes Prediction and Prevention Study based in Finland¹¹</td>
</tr>
<tr>
<td>DPT-1</td>
<td>Diabetes Prevention Trial–Type 1¹²</td>
</tr>
<tr>
<td>ENDIT</td>
<td>European Nicotinamide Diabetes Intervention Trial¹³</td>
</tr>
<tr>
<td>Fr1da</td>
<td>Population-based healthcare research study based in Bavaria, Germany⁹</td>
</tr>
<tr>
<td>INNODIA</td>
<td>Global partnership between academic institutions, commercial partners and patient organizations¹⁴</td>
</tr>
<tr>
<td>PLEDGE</td>
<td>Population Level Estimation of T1D Genes in Children¹⁵⁵</td>
</tr>
<tr>
<td>TEDDY</td>
<td>The Environmental Determinants of Diabetes in the Young Study⁵</td>
</tr>
<tr>
<td>TrialNet</td>
<td>US-based research network centred on delaying or preventing T1D¹⁰</td>
</tr>
<tr>
<td>Type1Screen</td>
<td>Australian screening and monitoring program open to relatives and IAb+ people identified through other screening pathways (ACTRN12620000510943)</td>
</tr>
</tbody>
</table>

* Note, these are major research networks but this is not an exhaustive list.

IAb+, islet autoantibody positive; T1D, Type 1 diabetes
**Table 3. Autoantibodies against islet autoantigens detected in Stage 1-3 type 1 diabetes**

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Islet specificity</th>
<th>Typical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin autoantibody (IAA)</strong></td>
<td>Insulin</td>
<td>Common as a first detected autoantibody in young children ([157,158])&lt;br&gt;Appearance is more common in younger children ([159])&lt;br&gt;Frequency of appearance declines with age.&lt;br&gt;Not informative for individuals treated with insulin, who often develop antibodies in response to injected insulin.</td>
</tr>
<tr>
<td><strong>GAD autoantibody (GADA)</strong></td>
<td>Glutamic acid decarboxylase</td>
<td>Common as a first detected autoantibody in childhood, up until age 15 years ([157,158,160])&lt;br&gt;Adult-onset cases most often present with GADA ([161])&lt;br&gt;Is associated with slower progression to T1D ([162]) and is often found as a single IAb*, especially in adults</td>
</tr>
<tr>
<td><strong>Insulinoma antigen-2 autoantibody (IA-2A), also known as ICA512</strong></td>
<td>Tyrosine phosphatase islet antigen-2</td>
<td>Presence is associated with more-advanced islet autoimmunity and faster progression to stage 3 T1D ([55,163])</td>
</tr>
<tr>
<td><strong>ZnT8A autoantibody (ZnT8A)</strong></td>
<td>Zinc transporter type 8, a transmembrane protein in the β granule</td>
<td>Presence can improve risk stratification in individuals with single GADA*, IAA* or IA-2* status ([164])</td>
</tr>
<tr>
<td><strong>Islet-cell autoantibody (ICA)</strong></td>
<td>Multiple antigens, undefined</td>
<td>Detected by indirect immunofluorescence on islet-cell tissue. While not frequently measured other than in research studies, it does add to risk determination in the presence of other biochemical autoantibodies.</td>
</tr>
</tbody>
</table>
Table 4. Purpose of monitoring in IAb⁺ children, adolescents and adults

1. Primary purpose is to prevent DKA and to minimize the risk of requiring emergency care or hospital admission.

2. Identification for and monitoring of therapeutic intervention(s) to delay Stage 3 onset (where available) and prolong β-cell function.

3. To provide advice for the start of insulin in Stage 3 T1D, when glucose is sufficiently elevated and before symptoms develop, to minimize HbA1c and avoid the consequences of hyperglycemia on long-term glycemic outcomes.

4. To avoid misdiagnosis of T2D and delayed commencement of insulin therapy.

5. Referral for participation in research studies.

IAb⁺, islet autoantibody positive; DKA, diabetic ketoacidosis; HCPs, healthcare professionals; T1D, Type 1 diabetes; T2D, Type 2 diabetes.
<table>
<thead>
<tr>
<th>Method</th>
<th>Pros</th>
<th>Cons</th>
<th>Metrics obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference OGTT†</td>
<td>• Gold standard in research settings</td>
<td>• Requires glucose load and 2-5x blood draws over 2 hrs</td>
<td>• Glycemic staging</td>
</tr>
<tr>
<td></td>
<td>• Used to stage disease and predict progression</td>
<td></td>
<td>• Risk scores for progression (DPTRS, DPTRS60, Index60, M60, M120, PLS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(93,165–169)</td>
</tr>
<tr>
<td>Standard OGTT‡</td>
<td>• Similar to test for GDM, OGTT with 2x blood draws (compared to 3x</td>
<td>• Requires 2x blood draws, fasting and at 2 hrs</td>
<td>• 120 min OGTT-derived glucose</td>
</tr>
<tr>
<td></td>
<td>draws in GDM test), performed routinely in clinical care</td>
<td></td>
<td>• M120</td>
</tr>
<tr>
<td>Random glucose</td>
<td>• One-off sample</td>
<td>• Requires a blood draw or fingerstick test</td>
<td>• Similar to 120 min OGTT-derived glucose(95) if obtained 2 hours postprandially.</td>
</tr>
<tr>
<td></td>
<td>• Low cost</td>
<td>• Less sensitive than 120-min OGTT</td>
<td></td>
</tr>
<tr>
<td>Standard HbA1c test</td>
<td>• Highly specific for clinical diagnosis of Stage 3 T1D</td>
<td>• Indicates 3-month average glucose. Often normal in asymptomatic or</td>
<td>• Risk of progression to “clinical disease”: HbA1c &gt;5.7%(170)</td>
</tr>
<tr>
<td></td>
<td>• Can use capillary sample</td>
<td>recent-onset Stage 3 T1D</td>
<td>• 10% rise from baseline (at first IAb*) over 3-12 months (66,67), suggests</td>
</tr>
<tr>
<td></td>
<td>• Longitudinal HbA1c may be as informative as OGTT(66)</td>
<td>• May be affected by age, non-diabetes disease states (e.g., renal,</td>
<td>dysglycemia and progression to Stage 2 T1D.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• hemotological syndromes)</td>
<td>• Consider use of CGM if 10% rise in HbA1c is confirmed, or higher-frequency</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>of SMBG, to monitor risk for progression</td>
</tr>
<tr>
<td>CGM†</td>
<td>• Can be used at home</td>
<td>• Risk of anxiety for unblinded user seeing CGM fluctuations and</td>
<td>• Sensitive in detecting individuals with asymptomatic Stage 3 T1D and...</td>
</tr>
<tr>
<td></td>
<td>• Can be blinded for physician review only in some regions</td>
<td>experiencing alarms</td>
<td>• Risk of progression to ‘clinical disease’: i.e., 10% of time with glucose...</td>
</tr>
<tr>
<td></td>
<td>• Optimal duration of CGM wear is validated in adults and children &gt;2</td>
<td>• Requires appropriate education on use and interpretation</td>
<td>• ≥5% time with glucose ≥140 mg/dL (7.8 mmol/L) has been associated with a 40%</td>
</tr>
<tr>
<td>yrs with diagnosed T1D, at all glycemic levels(171).</td>
<td>• Many primary care HCPs are unfamiliar with interpretation</td>
<td>• Duration of wear not validated in early-stage T1D</td>
<td>risk of progression to T1D within 2 years (71)</td>
</tr>
<tr>
<td></td>
<td>• Cost and access issues</td>
<td></td>
<td>• Other positive predictive value (PPV) metrics not tested.</td>
</tr>
<tr>
<td>SMBG</td>
<td>• Simple to use at home</td>
<td>• Uncomfortable for users, can affect accuracy and use</td>
<td>Immediate capillary blood glucose test result.</td>
</tr>
<tr>
<td></td>
<td>• Comparatively low cost</td>
<td>• Optimal timing and frequency have not been determined</td>
<td>2-hour postprandial measure likely of most value.</td>
</tr>
<tr>
<td>C-Peptide</td>
<td>• Validated measure of β-cell function.</td>
<td>• Can be falsely low in hypoglycemia &lt;70 mg/dL (&lt;3.9 mmol/L), in...</td>
<td>A stimulated postprandial C-peptide value ≤0.2 nmol/L with IAb* status can assist</td>
</tr>
<tr>
<td></td>
<td>• Stimulated C-peptide in research settings is valuable to assess</td>
<td>• Wide range of values at clinical diagnosis, including &gt;0.2 nmol/L,</td>
<td>with appropriately classifying diabetes type.</td>
</tr>
<tr>
<td></td>
<td>insulin production and distinguish between T1D (or stages of T1D)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>and T2D</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
persistent, but low levels of secretion can be seen long after diagnosis
• Presence of C-peptide does not exclude T1D and on its own is not useful for staging or diagnosis of T1D

<table>
<thead>
<tr>
<th>Repeat antibody testing</th>
<th>Confirms initial IAb⁺ test result and progression to multiple IAb⁺ status</th>
<th>None</th>
<th>Autoantibody type and single IAb⁺ or multiple IAb⁺ status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td>Provides awareness of diabetes symptoms and signs</td>
<td>None</td>
<td>Person-reported outcomes for possible progression to Stage 3 T1D</td>
</tr>
</tbody>
</table>

* Used in research settings for staging progression of impaired glucose tolerance as the C-peptide provides important predictive value. § Used in clinical practice to detect impaired glucose tolerance in prediabetes and GDM. † Use of CGM-derived criterion did not achieve consensus within the consensus panel, with further evidence required to confirm findings to date.

CKD, chronic kidney disease; CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; DPTRS, Diabetes Prevention Trial-Type 1 Risk Score; GDM, gestational diabetes mellitus; M60/120, 60 minute or 120 minute test result; OGTT, oral glucose tolerance test; PLS, partial least squares; SMBG, self-monitored blood glucose
Table 6. The primary goals of education for care of IAb+ individuals and their families

1. To prevent DKA and promote safe monitoring practices and reduce the occurrence of symptoms of diabetes.

2. To minimize the requirement for emergency care, hospital admission and need for intensive care at diagnosis of T1D.

3. To improve appropriate risk perception at each monitoring milestone.

4. To understand specific outcomes – e.g., prevention of DKA versus initiation of insulin therapy.

5. To understand available interventions.

6. To explore and understand the benefits of individual participation in research studies.

7. To provide education that support psychosocial interventions to optimize general and mental health for affected individuals and families.

IAb+, islet autoantibody positive; DKA, diabetic ketoacidosis; T1D, Type 1 diabetes
Table 7. Selected unmet needs for further research and clinical development

**Unmet research needs** *

- Long-term rates of progression to Stage 3 diabetes in IAb⁺ individual without a family history of T1D, and progression rates in adults and persons of non-European ancestry.
- The impact of pregnancy in women who are IAb⁺ and the glycemic changes that may be evident during pregnancy and in the post-partum period, along with risks for progression to Stage 3 T1D during and after pregnancy.
- Neonatal outcomes for infants of women who are IAb⁺ and the association with glycemic changes during pregnancy.
- Cost-effectiveness of monitoring strategies for individuals with early-stage T1D.
- Timing of insulin initiation in persons with presymptomatic T1D, including short and long term metabolic and mental health outcomes of different strategies.
- Impact of education alone, independent of other monitoring activities, on frequency of DKA at diagnosis and presentation of T1D.
- Methods of identifying and monitoring behavioral health needs in early-stage T1D.

**Unmet clinical needs**

- Comprehensive and consistent educational materials that use consistent language and vocabulary when referring to diabetes stages and risks, including translation into region-specific languages. This applies to all stakeholders, from affected individuals to expert providers.
- Validated tools to measure the anxiety, depression and other mental-health behaviors that are specific to early-stage T1D.
- Sufficient availability of mental health professionals with expertise in T1D, including early-stage T1D in youth and adults.
- Knowledge and coverage of appropriate monitoring by stakeholders (insurers, clinicians, etc...)
- Timely access to expert HCPs and centers of expertise for intervention(s) to delay onset of Stage 3 T1D.

* The key principles in this consensus document will be subject to updating once additional evidence becomes available.

IAb⁺, islet autoantibody positive; DKA, diabetic ketoacidosis; HCPs, healthcare professionals; T1D, Type 1 diabetes
Figure 1. Algorithm for monitoring of persons screened positive for one or more islet autoantibodies
*Monitoring frequency and methodology depends on age, length of time since first detection of IAb, number of IAb detected and presence of symptoms of T1D (see Tables 1-3).

Ab, antibody; IAb, islet autoantibody; PRN, pro re nata (as needed); Sx, symptoms; T1D, type 1 diabetes
Figure 2. The continuum of educational needs and competencies – what does one need to know?
The graphic represents the anticipated skills that must be developed within the continuum of stakeholders in monitoring presymptomatic T1D. The need is for unified, consistent, globally applicable language at all levels.

HCP, Healthcare professionals; T1D, Type 1 diabetes
Supplementary Table 1. ADA evidence-grading system for Standards of Care in Diabetes*

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Description</th>
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| A                 | Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including:  
- Evidence from a well-conducted multicenter trial  
- Evidence from a meta-analysis that incorporated quality ratings in the analysis  
Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including:  
- Evidence from a well-conducted trial at one or more institutions  
- Evidence from a meta-analysis that incorporated quality ratings in the analysis |
| B                 | Supportive evidence from well-conducted cohort studies  
- Evidence from a well-conducted prospective cohort study or registry  
- Evidence from a well-conducted meta-analysis of cohort studies  
Supportive evidence from a well-conducted case-control study |
| C                 | Supportive evidence from poorly controlled or uncontrolled studies  
- Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results  
- Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls)  
- Evidence from case series or case reports  
Conflicting evidence with the weight of evidence supporting the recommendation |
| E                 | Expert consensus or clinical experience |