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Screening and Monitoring for Presymptomatic Type 1 Diabetes: A Time for Action

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Abstract

Background: Historically, type 1 diabetes (T1D) has been diagnosed following symptoms of overt hyperglycemia. However, the autoimmune processes driving the progression of the disease start years prior to the appearance of symptomatic disease. Early stages of T1D can be detected by screening individuals, including young children, for islet autoantibodies. ***Summary:*** The goal of this review is to discuss the benefits of early detection for individuals with presymptomatic T1D as well as discuss barriers that currently prevent a more widespread implementation of screening programs. Early detection of T1D can reduce the occurrence and severity of complications associated with clinical onset of T1D, including life-threatening diabetic ketoacidosis. It also facilitates the use of approved novel therapeutics that can delay the progression to clinical T1D and allows individuals to participate in clinical trials for other disease-modifying therapies in development. Despite these benefits, there are knowledge gaps that should be addressed before screening can be implemented optimally in practice. ***Key Messages:*** Diagnosis of presymptomatic stages of T1D offers several benefits to individuals and their caregivers. Given the multifaceted benefits screening can provide, this review offers expert perspective on the importance of adopting early-detection strategies to identify presymptomatic stages of T1D as part of clinical care.

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Clinical Type 1 Diabetes Is Preceded by Presymptomatic Type 1 Diabetes

Type 1 diabetes (T1D) is caused by autoimmunity that destroys beta cells of the islets of Langerhans, eventually leading to impaired glucose regulation and symptomatic (clinical) disease [1, 2]. The current standard of care for T1D treatment is insulin replacement therapy. However, individuals presenting with symptomatic new-onset T1D frequently undergo weeks to months of disruptive clinical symptoms, such as polydipsia, polyuria, tiredness, and weight loss, and often present in life-threatening diabetic ketoacidosis [3, 4]. The incidence and prevalence of T1D have increased and continue to grow worldwide, fastest in young children, with diabetic ketoacidosis events at diagnosis on the rise [5–8]. Thus, there is a pressing clinical need for identification of people in the early stages of T1D by screening before they present with clinical symptoms. The goal of this review is to share the perspective from experts on the importance of early detection of T1D as well as to discuss the barriers currently preventing more widespread implementation of screening strategies.

Although T1D historically has been diagnosed following symptoms of hyperglycemia, it is now known that the underlying autoimmunity starts months to years earlier and gradually progresses to overt hyperglycemia [3]. Extensive research has shown that the early stages of T1D can be detected by screening for circulating autoantibodies directed against 4 major islet autoantigens: insulin, glutamic acid decarboxylase (GAD), insulinoma-associated antigen 2 (IA-2), and zinc transporter 8 (ZnT8) [3]. In children and adolescents from families with T1D and children in the general population, once 2 or more islet autoantibodies are detected, the likelihood of developing clinical T1D over the course of their lifetime approaches 100% [9, 10]. Consequently, the presence of multiple autoantibodies is diagnostic of presymptomatic T1D and is further staged according to blood glucose levels [3]. The International Classification of Diseases (ICD)-10 defines stage 1 (ICD-10 E10.A1) as the presence of multiple islet autoantibodies and normal glucose levels (normoglycemia), i.e., no impaired glucose tolerance, no impaired fasting glucose, and a normal hemoglobin A1c (HbA1c < 39 mmol/mol [<5.7%]). Stage 2 (ICD-10 E10.A2) is defined as the presence of elevated glucose levels (dysglycemia) in a person previously or currently positive for multiple islet autoantibodies, with dysglycemia defined as impaired glucose tolerance (2-h plasma glucose 7.8–11.0 mmol/L [140–199 mg/dL]), impaired fasting glucose (fasting plasma glucose 5.6–6.9 mmol/L [100–125 mg/dL]), HbA1c 39–47 mmol/mol (5.7–6.4%), or ≥10% increase in HbA1c. Lastly, stage 3 (ICD-10 E10.9) is defined by the presence of overt hyperglycemia (2-h plasma glucose ≥11.1 mmol/L [≥200 mg/dL], fasting plasma glucose ≥7.0 mmol/L [≥126 mg/dL], or HbA1c ≥ 48 mmol/mol [≥6.5%]) and at least one islet autoantibody [11, 12]. Clinical symptoms secondary to hyperglycemia may not be initially apparent in persons at stage 3 T1D [11]. Of note, ICD-10 E10.A0 recognizes presymptomatic T1D in the presence of a single confirmed islet autoantibody.

Our understanding of the association of antibody types, number, and affinities with the rate of progression to clinical T1D for different age groups is evolving, resulting in varying predictive values [10, 13]. For example, insulin autoantibody (IAA) positivity is mostly prevalent in young children, and their early appearance – followed by GAD and IA-2 autoantibodies – was associated with the highest rates of progression to stage 3 T1D in one study [11, 14]. IA-2 autoantibody positivity has also been associated with an increased rate of disease progression, particularly in pediatric populations [15, 16]. ZnT8 autoantibody positivity has similarly been associated with increased risk of progression to T1D [15]. In contrast, GAD autoantibody positivity detected as a single antibody, which is often seen in adult-onset cases of T1D, has been associated with slower progression to T1D [11, 15].

The Benefits of Early Detection of T1D

Early detection of T1D (i.e., during its presymptomatic stages) can impact the burden associated with clinical T1D onset, with reduced severity of metabolic decompensation and hospitalization rates and duration [17]. Children diagnosed with presymptomatic T1D receiving basic diabetes education and monitoring have lower rates of life-threatening diabetic ketoacidosis at clinical onset of T1D compared to those unscreened [17–19]. In addition to acute complications and healthcare costs, the presence of diabetic ketoacidosis at clinical diagnosis is associated with worse glycemic control long term, increased risk of cognitive impairment, and psychological distress in children and their caregivers [20, 21].

Less is known about the impact of early T1D diagnosis on diabetic ketoacidosis rates in adults, even though they account for more than half of the individuals diagnosed

with T1D. Several studies showed that the rate of diabetic ketoacidosis in newly diagnosed adults ranges from 19 to 24% [22–24]. Therefore, reduced diabetic ketoacidosis at diagnosis has potential to improve short-term and long-term health outcomes for both children and adults. Modeling has suggested that the potential impacts of reducing diabetic ketoacidosis events on other subsequent outcomes (e.g., HbA1c and diabetes complications) may make early screening cost-effective, although the long-term impact of early detection on such outcomes is not yet known in detail [25, 26]. Early detection of T1D has the additional benefit of providing individuals with more time to prepare and learn the disease management strategies needed to cope, allowing opportunities for education for individuals with T1D and their families [1, 27].

With the advent of novel disease-modifying therapies, early detection of T1D now allows for the opportunity to potentially intervene in preclinical disease progression. Teplizumab, approved in the USA and several other countries, is a therapy that targets the autoimmune-mediated destruction of beta cells by acting on several subpopulations of T cells and, as a result, delays the onset of clinical T1D in individuals with stage 2 T1D by a median of 24.9–32.5 months [28–30]. It is important to note that teplizumab is approved to delay stage 3 T1D onset rather than for T1D prevention or cure; the long-term durability of its effect and impact on lifetime disease burden, including long-term complications, remain to be determined and are subject to ongoing studies. Nonetheless, individuals diagnosed with stage 2 T1D aged 8 and older can use this therapy to gain more disease-free years and prepare for life with the disease [1]. In addition to a delayed need for insulin therapy, prolonged periods of better residual insulin secretion and tight glycemic control could theoretically reduce diabetes-associated long-term complications [31]. While currently available only in certain regions worldwide, teplizumab is under review for approval in other countries.

Finally, diagnosis of presymptomatic T1D can also facilitate participation in clinical trials of other disease-modifying therapies. Participation in trials could not only potentially yield personal benefits for individuals receiving active study drug but also benefit the field as a whole as it could help bring other therapies to market, allowing for future clinical approval of alternative treatments or combination therapy approaches [1, 32].

Barriers to Early Detection of T1D

Despite the potential benefits of early T1D detection, some barriers remain, including accurate quantification of harms in screening (such as overdiagnosis [false positive] and underdiagnosis [false negative]), impact of uncertainty of risk and timing of progression to clinical disease, healthcare system and clinician readiness, reimbursement, and the clinical practice status quo [33, 34]. Challenges related to practical implementation further compound these barriers. These include the standardization and harmonization of autoantibody assays across laboratories and countries to ensure consistent and reliable screening results; the establishment of clearly defined care coordination pathways from primary care screening to specialist referral and follow-up; and the considerable variability across healthcare systems in infrastructure, reimbursement frameworks, and clinical capacity [33, 35]. General pediatricians may also find implementation of screening strategies to be challenging considering the time required to learn about early-stage T1D detection and monitoring as well as to incorporate screening and anticipatory guidance into busy clinical visits.

Some studies have demonstrated that early detection of T1D in its presymptomatic phase is associated with some parental anxiety and stress, whereas other research has shown that these negative feelings dissipate rapidly and early diagnosis is associated with reduced stress overall for those individuals and their families who ultimately receive a clinical diagnosis of T1D (i.e., a "soft landing") [36, 37]. Because parental anxiety can vary widely in real-world clinical practice, as screening efforts expand, it is important to consider cultural and other individual characteristics because they may influence a parent's anxiety levels as well as their decision to screen. The impact of screening on stress and anxiety in the general population is being investigated in depth in the early T1D detection program European Action for the Diagnosis of Early Non-Clinical Type 1 Diabetes for Disease Interception (EDENT1FI) (https://www.edent1fi.eu) and in the Early Surveillance for Autoimmune Diabetes (ELSA) study (https://www.elsadiabetes.nhs.uk/).

Beyond the early-stage disease period, the psychological and lifestyle impact post-T1D diagnosis should be considered for individuals identified through screening [37]. Because screened individuals who progress to stage 3 T1D more often do not present in diabetic ketoacidosis and have greater residual beta-cell function, they are more likely to experience a prolonged partial remission

phase characterized by low insulin requirements and relatively stable glycemic control [17, 20]. Although this is clinically beneficial in the short term, it may pose unique challenges, particularly for adolescents, who may underestimate the seriousness of their condition during remission and adopt a more lenient approach to diabetes self-management [27, 38]. When remission eventually wanes and insulin demands increase, these individuals could face difficulty adapting to the intensified treatment regimen required to maintain glycemic control. A related consideration is whether individuals diagnosed with T1D through screening, who may not have experienced overt symptoms prior to diagnosis, might face reduced motivation to engage with the demands of lifelong insulin therapy and disease management. When the perceived severity of a condition is low, treatment adherence may be affected, particularly in adolescents and young adults [27]. To mitigate these risks, structured education and psychological support should be integrated into the care of screened individuals, with particular attention to preparing patients and their families for eventual transitions, such as the transition to stage 3 and out of remission [27, 38]. To date, limited published data directly compare the long-term clinical course – including glycemic control, psychosocial outcomes, and treatment engagement – in individuals diagnosed through screening versus those presenting with clinical symptoms or those who have received disease-modifying therapy such as teplizumab. Available evidence from the Fr1da study suggests that children diagnosed with presymptomatic T1D through population-based screening have milder metabolic decompensation at clinical manifestation, including lower HbA1c and higher C-peptide levels at stage 3 onset [20]. However, whether these early benefits translate into sustained improvements in long-term glycemic control and self-management behaviors remains to be established. Several ongoing initiatives are positioned to address these knowledge gaps: the EDENT1FI program (https://www.edent1fi.eu) is investigating psychosocial outcomes across the screening-to-diagnosis trajectory; the European pre-T1D registry (https://www.pre-t1d-registry.eu/) aims to compile longitudinal metabolic and clinical data from individuals with presymptomatic T1D across multiple European cohorts; and long-term follow-up, including within TrialNet (https://www.trialnet.org/), will continue to yield data on outcomes in teplizumab-treated individuals [28, 39, 40]. As screening programs expand, comparative studies evaluating the clinical course and psychological adaptation of screened versus symptomatically diagnosed individuals – as well as those receiving disease-modifying therapies – should be prioritized. In the interim, incorporating motivational support and psychological care into post-diagnosis disease management pathways will be important to optimize engagement and outcomes for all individuals identified through early detection.

Current Scientific State of Screening Tests and Programs Available

Current variation regarding the predictive value of a single autoantibody highlights the importance of the choice of detection method. Although some assays detect both low-affinity (nonpredictive) and high-affinity (predictive) autoantibodies, newer assays are more specific by detecting only high-affinity (predictive) autoantibodies. Confirmation of single higher affinity antibodies in separate tests further increases predictability [35]. However, it is likely that the risk of progression to stage 3 T1D in these individuals does not reach that which is observed in people with multiple islet autoantibodies.

To improve diabetes education and screening participation, several T1D early-detection programs are underway that are investigating optimal screening strategies in the general population and their impact. One such program is the Innovative Health Initiative-funded project EDENT1FI, mentioned previously. The online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000552602) lists this study and additional screening programs that are ongoing or recruiting to date. The European pre-T1D registry compiles a database of autoantibody, metabolic, and metadata collected from individuals with presymptomatic stage 1 and stage 2 T1D who have not yet progressed to stage 3 T1D, with the goal of harmonizing guidelines and disseminating information to improve care in diabetes and facilitate clinical trial execution and access to disease-modifying therapy (https://www.pre-t1d-registry.eu/). This registry aims to collect data from ongoing participating screening initiatives in Europe, like EDENT1FI and its component studies, e.g., the Fr1da studies, βetty or ELSA, INNODIA, DiaUnion, the Global Platform for the Prevention of Autoimmune Diabetes (GPPAD), and BabyDiab. The Screen to Prevent Type 1 Diabetes (STOPT1D) program is also available to provide educational resources for healthcare providers, enabling individuals with T1D and their families to learn more about T1D screening and monitoring programs (https://www.stopt1dprogram.org/).

Table 1. Wilson and Jungner's principles of screening

Wilson and Jungner's principles of screening [41]	Does screening for T1D satisfy this principle?	Comments
The condition sought should be an important health problem	Yes	Incidence and prevalence of T1D and occurrence of life-threatening DKA events at diagnosis are increasing worldwide
The natural history of the condition, including development from latent to declared disease, should be adequately understood	In progress	Development from latent to declared disease in both pediatric and adult populations is not fully understood
There should be a recognizable latent or early symptomatic stage	Yes	Presymptomatic stages of T1D have been well defined
There should be a suitable test or examination	Yes	Early stages of T1D can be detected by screening for circulating autoantibodies directed against major islet autoantigens
The test should be acceptable to the population	In progress	Although parental anxiety and stress associated with early detection of T1D dissipates rapidly and early diagnosis is associated with reduced stress overall for those individuals who develop clinical T1D and their families, acceptability of the test in the general population is being ascertained in more detail as part of ongoing screening studies
There should be an agreed policy on whom to treat as patients There should be an accepted treatment for patients with recognized disease	Yes	Teplizumab has been approved for use in individuals diagnosed with stage 2 T1D aged 8 and older
Facilities for diagnosis and treatment should be available	Yes	Diagnosis and treatment can be done in medical practices
The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole	In progress	A limited number of studies have investigated the cost-effectiveness of large-scale T1D screening
Case-finding should be a continuing process and not a "once and for all" project	Yes	Several screening programs have been initiated globally and their impacts are being assessed (online supplementary Table)

DKA, diabetic ketoacidosis; T1D, type 1 diabetes.

How Early T1D Detection Satisfies the Wilson and Jungner Principles

The Wilson and Jungner principles of screening published in 1968 are a list of principles that have been used to help guide screening decisions for decades (Table 1) [41]. Early T1D detection satisfies most of the criteria in this list. However, a criterion that has not yet been completely satisfied is understanding the natural history of the condition as the development specifically from presymptomatic disease to symptomatic disease is not fully understood, particularly in adult populations [22]. Furthermore, although studies have reported that approximately 70% of children with ≥2 islet autoantibodies persistently develop clinical T1D within 10 years from seroconversion, individual rates of progression differ, and the factors that drive this are not well known [4, 10]. Additionally, the cost of case-finding should be economically balanced in relation to expenditure on medical care as a whole [41]. Only a limited number of studies have investigated the cost-effectiveness of large-scale T1D screening [25, 26].

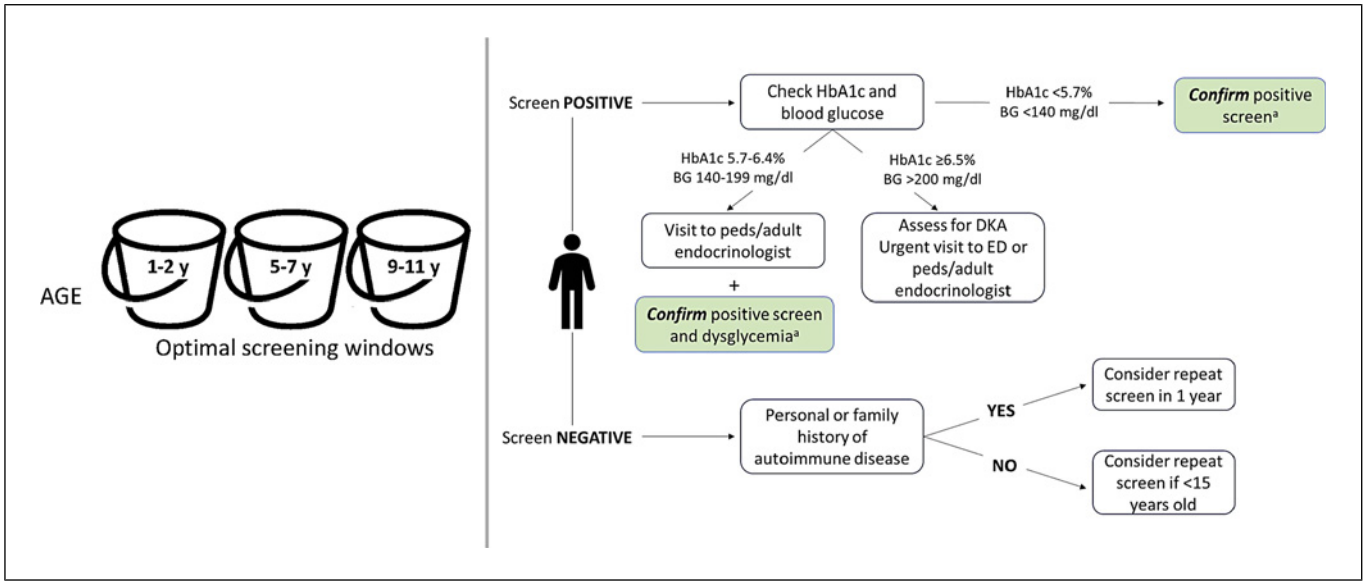

Fig. 1. Algorithm for management of a person screened for T1D. Confirmation of a positive screening test (i.e., positive screen for one or more islet autoantibodies) by measuring all four biochemical islet autoantibodies (GADA, IA-2A, IAA, and ZnT8A) and excluding acute hyperglycemia are critical. Figure adapted from Simmons et al. [45] with permission. [a]Education on the importance of monitoring for the prevention of DKA and metabolic monitoring should be provided for individuals with confirmed positive screens with normoglycemia or dysglycemia, with monitoring performed as recently outlined in the consensus guidelines by Phillip et al. [11]. BG, blood glucose; DKA, diabetic ketoacidosis; ED, emergency department; GADA, glutamic acid decarboxylase autoantibody; HbA1c, hemoglobin A1c; IA-2A, insulinoma-associated antigen 2 autoantibody; IAA, insulin autoantibody; T1D, type 1 diabetes; ZnT8A, zinc transporter 8 autoantibody.

Early Detection of Islet Autoantibodies in Clinical Practice

Employing early detection in clinical practice should be aimed at identifying individuals with T1D as early as possible. An initial screening for 3 autoantibodies may be adequate for identifying individuals currently positive for multiple autoantibodies (i.e., presymptomatic T1D). Screening for all 4 autoantibodies would allow for the more sensitive identification of individuals positive for just one autoantibody, potentially identifying additional individuals at risk for developing clinical T1D who would otherwise be missed. For example, single IAA positivity has been associated with increased risk of T1D development in youths and would be missed if IAA happens to not be included in the 3 autoantibodies for which screening is being done [42, 43]. However, a large proportion of people with low-affinity single islet autoantibodies detected by widely used radiobinding or other assays lose their autoantibodies over time and have no increase in risk of developing clinical T1D [44].

Since islet autoantibodies can be found in anyone at any age, individuals regardless of age (or other factors, such as race or family history) can be considered for early detection of presymptomatic T1D [22, 45]. Various strategies have been suggested to optimize sensitivity, specificity, and feasibility of screening. Islet autoantibodies may begin to appear in the first year of life with seroconversion to newly formed islet autoantibodies peaking in early childhood and decreasing with age. Screening early in life is optimal to capture young children presenting with new-onset T1D, who have particularly high rates of severe diabetic ketoacidosis at diagnosis. However, given that maternal islet autoantibodies can persist in the infant's circulation up to the second year of life, detection of islet autoantibodies in neonates may not always be accurate [46]. Importantly, autoantibody-based screening at a single age earlier in life will miss individuals that seroconvert at later ages. We believe that optimally, all children should be screened 2–3 times before the age of 15 years, beginning ideally within the second year of life to capture early-onset cases of T1D [47, 48]. Subsequent rescreening at 5–7 years of age and again at 9–11 years of age in those who were negative up to that point could improve diagnostic sensitivity (Fig. 1) [45, 47–49]. Others have proposed genetic screening of neonates to identify newborns genetically at increased risk for T1D, with

follow-up antibody testing only in individuals at increased risk. Depending on the country, healthcare system, and antibody testing strategy, a combined genetics/autoantibody-based approach could be a feasible strategy [50]. This approach would require long-term follow-up of genetically at-risk individuals from birth, which is currently not integrated into routine healthcare and may greatly reduce sensitivity [51].

Importantly, screening and monitoring strategies should take into consideration the differences between pediatric and adult populations. In children, particularly young children, progression from seroconversion to clinical T1D tends to be more rapid, with the highest rates of progression observed in those who develop multiple autoantibodies early in life [10, 14, 47]. Accordingly, current recommendations suggest screening children two to three times before the age of 15 years, ideally starting in the second year of life, with metabolic monitoring at relatively frequent intervals as outlined in recent international consensus guidelines [11, 47, 48]. In contrast, adults generally exhibit slower rates of progression from stage 1 to stage 3 T1D, particularly those with single GAD autoantibody positivity, which is more commonly observed in adult-onset cases than in childhood-onset cases [22, 52]. Consequently, less intensive monitoring may be appropriate for adults, although the optimal screening ages, intervals, and follow-up strategies for this population remain to be defined. An important caveat is that adults who test positive for islet autoantibodies and are in stage 2 T1D exhibit a risk of clinical progression comparable to that of children in stage 2. This is likely related to a long duration of pre-existing stage 2 T1D [53]. These differences underscore the need for age-adapted approaches to both screening and post-screening surveillance.

To date, the majority of adult screenings have occurred in at-risk relatives, and less is known about the incidence and natural history of new islet autoantibodies and progression to T1D in adults [22]. Furthermore, it has been demonstrated that in a population of children and adults with T1D, autoantibody positivity (for one or more autoantibodies) decreased with an increase in age at T1D onset [52]. A complexity of screening adults for T1D is the much higher incidence of T2D in adults compared to children (~96% of all diabetes in adults and ~26% in children) such that the process of T1D identification involves consideration of T2D as a cause for dysglycemia at older ages [54, 55]. Another added complexity is that many adults are positive for only one islet autoantibody prior to or at diagnosis of T1D, and that autoantibodies to GAD, which have been shown to be present in as many as 90–92% of autoantibody-positive adults in one study, do not necessarily confer increased risk for T1D. Of note, adults with persistent single GAD positivity who ultimately progressed to clinical diabetes appeared to exhibit high genetic risk for T2D, but not T1D [53]. Application of assays that detect only high-affinity GAD autoantibodies may be helpful to limit monitoring to only those at risk of T1D progression [56]. Additionally, approximately 10–12% of women with gestational diabetes, including those above the age of 30 years at the time of pregnancy, have been shown to be islet autoantibody positive and subsequently develop T1D, suggesting pregnant women may benefit from screening [57, 58].

The proposed process of repeat testing for T1D can be streamlined by combining T1D screening with screening for other autoimmune diseases that often co-occur with T1D, such as celiac disease or autoimmune thyroid disease, and has been explored in children in the TRIAD study [59–63]. Other large-scale screening efforts for T1D in children with celiac disease (and vice versa) have already been implemented in the Autoimmunity Screening for Kids (ASK) study, Diabetes Autoimmunity Study in the Young (DAISY), and The Environmental Determinants of Diabetes in the Young (TEDDY) [60, 61]. For practical purposes, early screening for T1D can also be combined with other routine laboratory screenings (e.g., for anemia or lead), vaccination, or primary wellness visits [32]. Novel tools for collecting blood for screening for presence of autoantibodies in T1D are being explored, such as dried blood spot collections [64, 65]. These could reduce the logistic burden and allow combination with other screening efforts. However, these novel approaches need further validation before they can be widely implemented.

Populations That Should Be Screened

Relatives of individuals with T1D have up to a 15-fold increased risk of developing T1D compared to the general population [49]. Despite this, 85–90% of individuals with T1D have no first-degree relative with the disease [4, 66]. Furthermore, once individuals develop multiple islet autoantibodies, the time it takes to progress to clinical T1D appears to be similar regardless of whether they have family members with T1D [36]. As a result, we believe that early detection should not be limited to first-degree relatives of individuals with T1D.

Although people of European ancestry are the most affected, individuals of any race can develop T1D.

Moreover, the incidence rates of T1D among Hispanic, non-Hispanic Black, and non-Hispanic Asian or Pacific Islander young adults are increasing faster than in non-Hispanic White young adults in the USA [67]. Therefore, we are of the opinion that individuals of all races should be considered for early detection.

Individuals with other autoimmune conditions have an increased risk of developing a second autoimmune disorder, including T1D [68]. Autoimmune conditions commonly associated with T1D include celiac disease, autoimmune thyroid diseases, Addison's disease, autoimmune gastritis, and vitiligo [59, 69]. Screening in individuals with these conditions would theoretically enrich rates of positive screens. Official consensus on the specific implementation of screening practices remains to be determined.

Staging and Monitoring in Individuals with Presymptomatic T1D

International consensus guidelines endorsed by societies have been published to guide clinicians on best monitoring practices for individuals with positive autoantibody screening [11]. For those who have a positive test at screening, detection should be followed up with an assessment of any clinical symptoms and the individual's blood glucose levels and HbA1c to determine whether immediate medical attention is needed. A measurement of all 4 islet autoantibodies from a separate blood sample should be taken to confirm the results [11]. Individuals with confirmed positive screens for 2 or more out of 4 autoantibodies should be staged by performing an oral glucose tolerance test (OGTT) (gold standard) or assessing their HbA1c. As mentioned above, normoglycemic individuals (most of the cases) will be classified as having stage 1, dysglycemia will define stage 2, and frank hyperglycemia will identify those with stage 3, allowing timely introduction of insulin therapy (Fig. 1) [3, 11]. In the Fr1da study of 220 children with presymptomatic T1D, 196 were in stage 1, 17 were in stage 2, and 7 were in stage 3 [36]. This staging should be followed by treatment if indicated and available [11]. As mentioned previously, individuals positive for a single autoantibody, also defined as pre-stage 1, are considered at lower risk of progression: in these cases, the proposed frequency of repeated autoantibody testing and glucose measurements over time is less stringent than in those with multiple autoantibodies [11].

Screening and identification of presymptomatic T1D should be followed by education on the symptoms of clinical diabetes and diabetic ketoacidosis and by monitoring, with the goal of limiting the possibility of the individual experiencing a severe and sudden onset of symptomatic T1D and diabetic ketoacidosis [11]. The recent international consensus outlined recommended steps [11]. Depending on the age of the individual and their stage of T1D, different intensity of metabolic monitoring, including glucose and HbA1c measurements, as well as the offer of continuous glucose monitoring (CGM), in the context of education should be proposed [11]. Several studies have demonstrated that the use of CGM in presymptomatic T1D can help identify individuals likely to rapidly progress to stage 3 T1D. Specifically, spending more than 5–10% of time with glucose levels ≥7.8 mmol/L (≥140 mg/dL) was associated with progression to stage 3 T1D [70, 71]. While these results were not entirely reproduced in some studies and others suggest that OGTT is a better predictor of stage 3 T1D than CGM, given that CGM is less invasive, it should be considered an alternative option to OGTT as mass screening programs expand rapidly worldwide [72].

Conclusion

The diagnosis of presymptomatic T1D can offer a softer landing for patients and caregivers, with time to prepare for insulin therapy and for education and monitoring to help avoid diabetic ketoacidosis and other associated complications. T1D does not begin when a person is hyperglycemic; the autoimmune process driving the disease begins much earlier. The approach to detecting and treating T1D is undergoing a much-needed paradigm shift due to the development of novel therapeutics that can potentially modify disease progression [32, 49]. However, the crux of this movement is that individuals with presymptomatic T1D must first be identified via detection of islet autoantibodies in order to take advantage of these therapies. Therefore, early detection of T1D is critical.

To effectively accomplish these goals, significant knowledge gaps need to be addressed. First, diagnostic and early-detection strategies for early-stage T1D should be adopted as part of clinical and medical curricula. Specifically, these topics could be taught in medical school as well as to pediatricians in postgraduate training programs such as during residency, fellowships, and continuing medical education (CME) programs. This would enable more ubiquitous implementation of early-detection efforts. Second, a consensus on an ideal early-detection strategy needs to be reached to develop clear guidelines on the ages at which screening should be performed, how

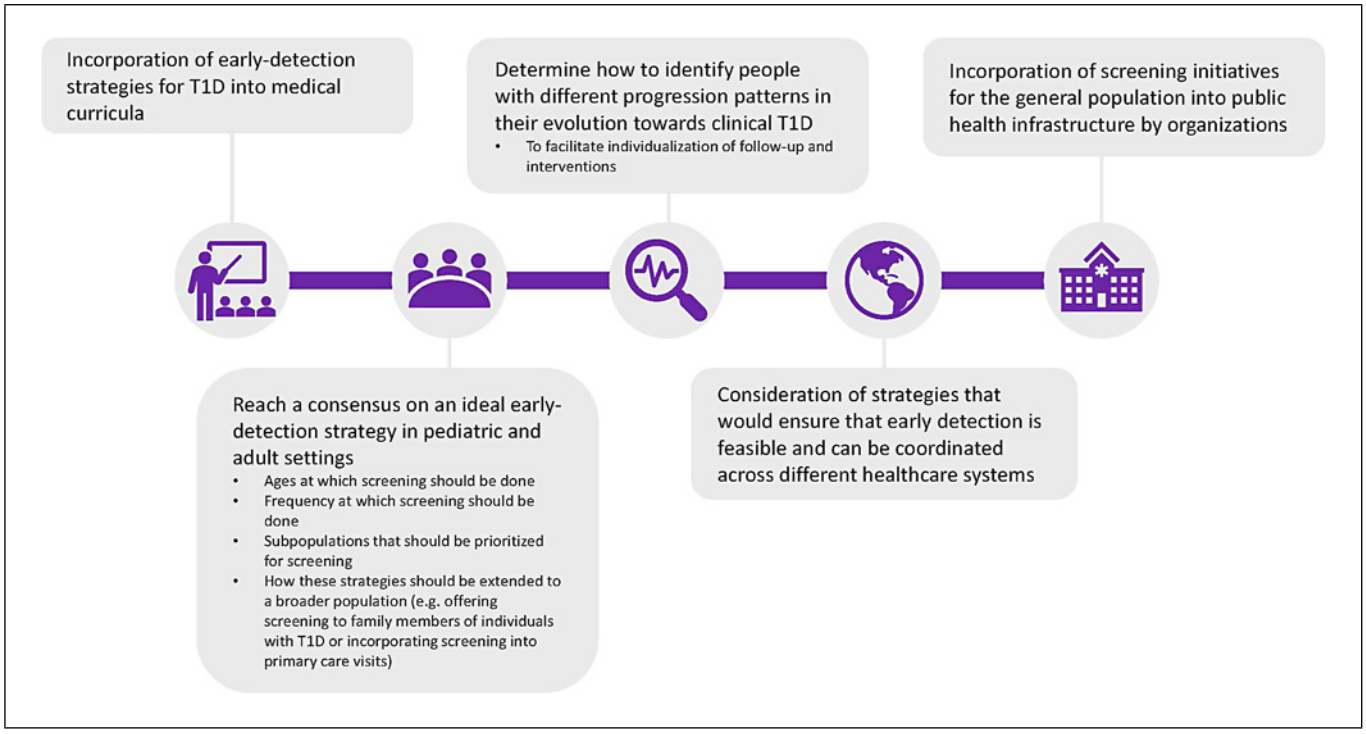

Fig. 2. Measures that need to be taken to ensure appropriate implementation of screening for presymptomatic T1D. Several measures need to be taken for widespread implementation of screening for presymptomatic T1D to take place. Healthcare systems can use a quality improvement approach to address implementation barriers and optimize workflows. T1D, type 1 diabetes.

often it should be done, and who should be offered screening – in both the pediatric and adult settings. There is also a need to clearly define for clinicians how early-detection strategies should be extended to a broader population, such as potentially offering screening to all family members of individuals with T1D or incorporating screening into primary care visits to increase participation [49]. Further, more research is needed to identify risks for different progression patterns in T1D, thus allowing individualization of follow-up. Third, the organizational structures in healthcare should also be considered to ensure early detection across diverse settings. From a laboratory perspective, standardization and harmonization of autoantibody assays across sites and countries are essential as variability in assay platforms, cutoff values, and performance characteristics can lead to inconsistent results and complicate the interpretation of screening outcomes [35, 44]. Efforts such as the Islet Autoantibody Standardization Program (IASP) are critical in this regard, and their continued support should be a priority as screening programs scale up [73]. Additionally, clear care coordination pathways – from initial screening in primary care to confirmatory testing, staging, and specialist referral – need to be established to ensure that individuals with positive screens are not lost to follow-up and receive timely and appropriate management [11, 25, 26, 33]. Another potential way to help mobilize efforts for early detection would be for public health organizations to incorporate screening initiatives for the general population into standard practice (Fig. 2). Such efforts would work toward championing education on the benefits of early T1D detection and facilitate a commitment to improving clinical outcomes of this serious disease.

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Conflict of Interest Statement

Emily Sims has received research funding from Sanofi; she has also received compensation for educational lectures on diabetes screening from Medscape, the American Diabetes Association,

Sanofi, and Health Matters CME, for serving as the Chair of the Steering Committee for Clinical Advances in T1D: Screening, Staging, and Treatment, serving on the Sanofi Drug Agnostic T1D Screening Committee, and consulting for DRI Healthcare and Sanofi. Chantal Mathieu serves or has served on the advisory panel for Novo Nordisk, Sanofi, Eli Lilly and Company, Novartis, Dexcom, Boehringer Ingelheim, Bayer, Roche, Abbott, Medtronic, Insulet, Biomea Fusion, SAB Bio, and Vertex. Financial compensation for these activities has been received by KU Leuven. KU Leuven has received research support for Chantal Mathieu from Medtronic, Novo Nordisk, Sanofi, and ActoBio Therapeutics. Chantal Mathieu serves or has served on the speakers' bureau for Novo Nordisk, Sanofi, Eli Lilly and Company, Medtronic, Dexcom, Abbott, Vertex, and Boehringer Ingelheim. Financial compensation for these activities has been received by KU Leuven. Anette-Gabriele Ziegler is a member of the Data Monitoring Committee for 2 clinical trials for Sanofi and serves on an advisory board for Sanofi. Marian Rewers is a consultant for Sanofi US, Janssen R&D, and Provention Bio and has received educational grants from Sanofi US. Osagie Ebekozien has received research support through his organization from Abbott Diabetes, Lexicon, Lilly, Medtronic, Sanofi, Tandem, and Vertex. He has served on advisory boards for Medtronic and Sanofi. Daniel Agardh has received research grants and consultant fees from Sanofi. Emanuele Bosi has served on advisory boards and has received consultancy and lecture fees from Abbott, Medtronic, Sanofi, and Roche. Lucienne Chatenoud is a consultant for Sanofi. Richard Oram has received research grants or contracts from Randox and Sanofi. He has also received royalties and license from Randox, consulting fees from Sanofi, Provention Bio, and Janssen and payment or honoraria from Sanofi and Novo Nordisk. He has served on data safety monitoring board or advisory board for Sanofi. Sanjoy Dutta has no conflicts of interest to disclose.

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Author Contributions

E.S., C.M., A.Z., M.R., O.E., D.A., E.B., L.C., R.O., and S.D. were all involved in the conception, drafting and review of this work, approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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