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Screening for Type 1 Diabetes in the General Population: a Status Report and Perspective

Emily K Sims MD[1], Rachel EJ Besser MD PhD[2,3], Colin Dayan MD PhD[4], Cristy Geno Rasmussen, PhD[5] Carla Greenbaum MD[6], Kurt J Griffin MD PhD[7], William Hagopian MD PhD[8], Mikael Knip MD[9-11], Anna E. Long[12], Frank Martin PhD[13], Chantal Mathieu MD PhD[14], Marian Rewers MD PhD[5], Andrea K. Steck MD[5], John M Wentworth MD[15], Stephen S. Rich PhD[16], Olga Kordonouri MD[17], Anette-Gabriele Ziegler MD PhD[18], and Kevan C. Herold MD[19], for NIDDK Type 1 Diabetes TrialNet Study Group

[1]Department of Pediatrics, Indiana University School of Medicine
[2] Department of Paediatrics, NIHR Oxford Biomedical Research Centre, John Radcliffe Hospital,
[3]Welcome Centre for Human Genetics, University of Oxford, Oxford, UK
[4]Cardiff University School of Medicine, Cardiff, UK.
[5] Barbara Davis Center for Diabetes, University of Colorado-Anschutz, School of Medicine, Aurora, CO USA
[6]Benaroya Research Institute, Seattle, WA
[7]Sanford Health, Sioux Falls, SD
[8] Pacific Northwest Research Institute, Seattle WA USA
[9]Pediatric Research Center, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland;
[10]Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Helsinki, Finland; and
[11]Tampere Center for Child Health Research, Tampere University Hospital, Tampere, Finland
[12]Bristol Medical School, University of Bristol, Bristol UK
[13]JDRF, New York, NY
[14]Department of Endocrinology, UZ Gasthuisberg, KULeuven, Leuven, Belgium
[15]Departments of Diabetes and Endocrinology and Population Health and Immunity, Royal Melbourne Hospital and Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia
[16] Center for Public Health Genomics, University of Virginia, Charlottesville, VA USA
[17] Kinder- und Jugendkrankenhaus AUF DER BULT, Hannover Germany
[18]Institute of Diabetes Research, Helmholtz Zentrum München, German Research Center for Environmental Health, Munich-Neuherberg, Germany. Technical University Munich, School of Medicine, Forschergruppe Diabetes at Klinikum rechts der Isar, Munich, Germany.
[19]Department of Immunobiology and Department of Internal Medicine, Yale University, New Haven, CT

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Direct Correspondence to:
Kevan C. Herold, MD
Departments of Immunobiology and Internal Medicine
Yale University
300 George St, #353E
New Haven, CT 06520
Email: Kevan.herold@yale.edu
Phone Number: 203-785-6507

Abstract

Most screening programs to identify individuals at risk for type 1 diabetes have targeted relatives of people living with the disease to improve yield and feasibility. However, ~90% of those who develop type 1 diabetes do not have a family history. Recent successes in disease modifying therapies to impact the course of early-stage disease have ignited the consideration of the need for and feasibility of population screening to identify those at increased risk. Existing population screening programs rely on genetic or autoantibody (AA) screening, and these have yielded significant information about disease progression and approaches for timing for screening in clinical practice. At the March 2021 Type 1 Diabetes TrialNet Steering Committee meeting, a session was held in which ongoing efforts for screening in the general population were discussed. This report reviews the background of these efforts and the details of those programs. Additionally, we present hurdles that need to be addressed for successful implementation of population screening and provide initial recommendations for individuals with positive screens so that standardized guidelines for monitoring and follow-up can be established.

Introduction

Combined with work by multiple groups over the past decades to identify those at high risk, the recent positive results of the Phase 2 randomized controlled TrialNet TN10 “Anti-CD3 (teplizumab) prevention trial” have opened opportunities for prevention of type 1 diabetes (1). The TN-10 trial reported that a single 14-day course of teplizumab drug therapy delayed the clinical diagnosis of type 1 diabetes in 76 multiple islet autoantibody (AA) positive non-diabetic relatives by a median of 24 months, and in a subsequent analysis up to 32.5 months (1; 2). The relatively rapid time to clinical diabetes in the placebo group fulfilled the predictions from trial planning: a 75% risk of clinical diagnosis in 5 years in the AA+, non-diabetic, dysglycemic relatives, and validated methods used in that trial to identify individuals at-risk for disease. In addition to teplizumab, prevention trials with other therapies are underway (NCT01773707 and NCT03428945).

Type 1 diabetes frequently presents with preventable life-threatening complications (diabetic ketoacidosis or DKA), and the diagnosis of type 1 diabetes affects longevity, morbidity, and the quality of life for patients and their families (3-6). These and other data highlight an urgent unmet need to develop programs to identify those at risk, with or without a relative with type 1 diabetes, who may benefit from these treatments (7).

Relatives of patients with type 1 diabetes have a ~15-fold increased risk of disease as compared to those without a relative with type 1 diabetes (8-10). Siblings of patients have, on average, a 6-7% lifetime risk of type 1 diabetes and offspring of mothers and fathers with type 1 diabetes have a 1.3-4% and 6-9% lifetime risk, respectively, compared to 0.4% in the general population (8-10). Because of the enriched risk in relatives, screening programs and clinical trials have often targeted this group.

However, ~90% of those who will present with new type 1 diabetes do not have a positive family history (11; 12). The treatment effects of teplizumab and other immune therapies after the diagnosis of type 1 diabetes, in patients without affected family members, illustrates the efficacy of these therapies in the general population. Therefore, to identify the most individuals who would benefit from therapies to prevent type 1 diabetes, those without a positive family history must be identified. Several groups have initiated screening of the general population and there has been interest on the part of academics, advocacy organizations, policy groups, pharma, and others in evaluating the optimal manner in which to proceed with this large endeavor. At the March 2021 TrialNet Steering Committee meeting, ongoing efforts for screening of the general population were reviewed. This report presents the background on these and other screening efforts, clinical recommendations, the details of selected programs, and challenges for implementation of population screening.

<u>Progression of type 1 diabetes in humans</u>: Type 1 diabetes is caused by the destruction of insulin producing β cells by immune mechanisms, involving B, CD4+, and CD8+ T cells, with the latter serving as the postulated effectors (11). Some immune cell targets have been identified, such as proinsulin and insulin, glutamic acid decarboxylase 65 (GAD65), islet antigen 2 (IA-2), islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP), zinc transporter-8 (ZnT8), and chromogranin A (13). In model systems and *in vitro*, T cells that are reactive with peptides from these antigens can elicit β cell killing, yet a direct causal role for these cells remains to be defined.

Despite the primary role of T cells in β cell killing, clues to the immune targets in type 1 diabetes originated by finding AAs that are reactive with these proteins in individuals with and prior to the diagnosis of clinical type 1 diabetes. The earliest observations of anti-islet cell antibodies (ICA), in 1974, entailed immunofluorescent detection of immunoglobulins that reacted with islets from a pancreas from a blood type group O donor. The specific molecular targets of autoantibodies have been progressively discovered with the first being insulin (14; 15). Subsequently, other antigens, including GAD65, were recognized and methods such as radioimmunoprecipitation were used to identify islet cell proteins recognized by antibodies (16-

18). The methods to measure biochemically defined AAs to insulin (IAA), GAD65 (GADA), ZnT8 (ZnT8A), and a protein tyrosine phosphatase (ICA512A or IA2A), have previously been reviewed (19).

AAs can be found prior to clinical disease (20-24) indicating that there is an asymptomatic period before the typical presentation with clinical type 1 diabetes, which is associated with β cell functional loss, hyperglycemia, and, often, ketoacidosis (25). The risk for progression to type 1 diabetes is built on the detection of AAs. Beginning with the appearance of two AAs, Stages of type 1 diabetes are now defined and identify steps during the progression of disease (**Figure 1**)(26). The notions of stages have been useful for identifying cohorts for clinical studies, but there are limitations to their application in the clinical practice setting. First, AAs identify risk but not the speed of progression to clinical type 1 diabetes. The rates of progression for each individual may vary considerably (20-22; 27). Risk is modified by age at seroconversion (to AA positivity) and the number of the AAs present in an individual's serum, although which AAs are found may differ by age. Younger individuals frequently have IAA initially, whereas in teen-age years, GADA are frequently found. Second, the stages do not include direct measures of the immune process or β cell decline (28; 29). Finally, discrete stages may not be identified in all individuals. For example, some individuals, particularly for children < 5 yrs in Stage 1, may progress to overt clinical disease without a period of dysglycemia (i.e., Stage 2). This may reflect infrequent glucose monitoring or alternatively a more rapid progression compared to older individuals (30).

At-risk individuals typically harbor a genetic predisposition to autoimmunity. The strongest genetic determinants of risk are the human leukocyte antigen (HLA) genotypes, but other non-HLA susceptibility loci have also been identified. Genetic risk scores (GRS), incorporating multiple loci have been developed and shown to predict islet autoimmunity (31). After development of islet autoimmunity, metabolic features, including body mass index and more subtle analyses of β cell function and insulin secretion can inform risk and evolution of progression from early-stage disease (32). Other risk indices (e.g. Index 60, Diabetes Prevention Trial – Type 1 Risk Score

(DPTRS)) that incorporate these metabolic data can greatly enhance prediction of progression from early-stage disease. Reviews that detail the pathophysiology of type 1 diabetes, including AA, genetics and metabolic measures in type 1 diabetes prediction are available (19; 31-33).

Technological performance and improvements in AA measurements:

Most contemporary studies of type 1 diabetes progression have use radiobinding assays (RBA), but newer methods and assays may improve prediction. These are reviewed in (19) and summarized in **Table 1.** In addition to new AA targets, new technologies have improved specificity and sensitivity and may be multiplexed, minimizing the blood volumes needed, and enhancing the throughput and accessibility of tests. Some newer assays selectively measure AAs with high binding affinities or truncated peptides (e.g., GAD 96-585), and have shown improved assay specificity and type 1 diabetes prediction (19; 34; 35). The validation of these methods has been supported by the Islet AA Standardization Program (IASP) workshop, which compares assay performance across different methods (19). The results from this program indicate that the assays are sensitive and sufficiently specific to distinguish patients with type 1 diabetes from nondiabetic controls but the program was not designed to evaluate specificity at the level required for population-based screening. In an ongoing comparator study, TrialNet will evaluate the prediction of type 1 diabetes within 5 years with these new assays. Minimization of false positive rates in nondiabetic individuals is a particularly important consideration to minimize risks of unnecessary testing and anxiety in the context of broader screening.

Ongoing screening programs (**Table 2a)**:

a) In relatives of individuals with type 1 diabetes: Both TrialNet (a US based consortium) and INNODIA (a European private/public partnership) began by screening relatives to maximize efficiency for enrollment in clinical studies. However, both have begun to include monitoring or screening of at-risk individuals from the general population. The Type 1 Diabetes TrialNet Pathway to Prevention Study, initiated in 2004, has screened over 220,000 relatives. Initially, assays for ICA and IAA, IA2A, and GADA (by RBA) were performed. In 2019, after an internal review of data from this study to improve cost and efficiency, screening was changed to GADA and IAA by on-line consenting and optional at-home test kits. Those individuals who test positive for either AA then underwent testing for ZnT8A, IA2A, and ICA. Overall, TrialNet identified ~5% of nondiabetic relatives to have at least one AA, and about half of these with multiple AA (i.e., Stage 1 or Stage 2). INNODIA, a European private/public partnership, screens for four AAs by RBA and has screened more than 4400 first-degree relatives. Consistent with the TrialNet data, the most frequently found AAs are GADA and IAA, with 2.6% of the individuals tested having multiple AAs.

b) In the general population: In total, the number of individuals without a relative with T1D who have been screened is greater than the number of relatives. **Table 2b** summarizes data from selected programs ongoing and under-development for the general population. The **Supplemental Table** describes completed programs. These generally fall into the categories of birth cohorts or AA-based screening programs. Some differences in positive screen rates between programs exist; these are likely multifactorial and related to background prevalence, overall screening strategy, inclusion of individuals with relatives with type 1 diabetes, and the assays utilized.

<u>Birth cohorts:</u> Birth cohorts use a combined approach to initially identify individuals at increased genetic risk for type 1 diabetes. Genetic screening can enrich for individuals who are appropriate for targeted AA screening. Using screening for HLA, the TEDDY study (The Environmental Determinants of Diabetes in Youth) is gathering data from > 8,000 HLA genetically at-risk newborns, most (~90%) without a known type 1 diabetes relative (22)(**Supplemental Table 1**). These newborns are followed for 15 years for the appearance of AAs and diabetes, with documentation of environmental factors that could contribute to disease. The Type 1 Diabetes Prediction and Prevention Study (DIPP) has been active in three Finnish university hospitals since

1994, screening >250,000 infants (36). All newborn infants from these hospitals (~25% of the national birth cohort) are screened for HLA-conferred susceptibility to type 1 diabetes, with parental consent, using cord blood. Almost 10% of those screened carry such HLA genotypes and are invited for follow-up until 15 years of age or type 1 diabetes diagnosis. The BABYSCREEN study initiated 2018 in Helsinki, Finland, screens cord blood cells for HLA alleles conferring high-risk for type 1 diabetes and celiac disease. Participants carrying increased risk for either disease are invited to AA testing at 1, 2 and 3 years of age. Of the 9000 children screened, 6.0% were considered at high genetic risk for type 1 diabetes, 15.0% at high genetic risk to celiac disease, and 4.1% at high genetic risk to both diseases. The Global Platform for the Prevention of Autoimmune Diabetes (GPPAD) tests newborn blood spots collected from cord blood or at primary care provider (PCP) visits and calculates GRS to identify those at ≥10% risk for multiple AAs by 6 years of age. Those at increased genetic risk are offered the opportunity to enroll in a primary prevention study (37). Over 279,000 infants have been screened as of July 2021, with a positive AA screen rate of 1.1% with increased genetic risk.

Three recently initiated programs in the US, the CASCADE program, the Sanford PLEDGE project, and the PrIMeD program also utilize GRS (38) from dried blood spots or saliva. Those with “positive” GRS screens are offered AA screening (39). In follow-up of the newborn and study entry samples for GRS testing, the PLEDGE study performs AA testing at 2 years and pre-kindergarten visits, with an emphasis on integrating study processes into routine pediatric care, and integration with the electronic health record system. Children with positive AAs are offered ongoing monitoring according to principles described in **Table 3** or offered the opportunity to participate in a TrialNet clinical trial for at-risk individuals (www.trialnet.org).

Screening after the neonatal period: Several programs use AAs for primary screening in children after the neonatal period, including ASK (Autoimmunity Screening for Kids, Colorado), T1Detect

(US), Fr1da and Fr1dolin (Germany) (**Table 2b**)(40-44). Relatives are not excluded from participating in these programs. AA screening alone is more costly when conducted without genetic pre-screening, but it is specific for Stage 1 or Stage 2 disease. Multiple methods for AA detection have been used (40-44). Unique approaches to optimize enrollment and follow-up have been employed (40-44).

The goals of the US-based ASK program, available to residents of Colorado aged 1-17 years, are early diagnosis, DKA prevention, prevention study enrollment, and referral. Diabetes AA testing is combined with screening for celiac disease by measuring tissue transglutaminase antibodies (tTGA) and, more recently, SARS-CoV-2 antibodies. Children who have a positive test are invited for confirmatory testing. Of 25,738 participants: 3.4% were positive for any AA on the initial screening, 0.52% were positive for multiple islet AA, and 0.58% were positive for a single high-affinity AA (Rewers M, personal communication, 2021).

The T1Detect program was initiated by the JDRF in 2020 (42). T1Detect provides online links for individuals ≥1 years of age to a commercial laboratory (Enable Biosciences). That laboratory uses an online portal to provide screening at home with a blood spot testing approach. Participants receive test kits for collection of dried blood spots that are mailed for measurement of GADA, IA2A, and IAA using the ADAP assay (19). Participants screening AA positive are contacted by the laboratory and offered one-on-one and/or online support. Of the 800 initial screens (of which 74% are first-degree relatives of individuals with type 1 diabetes), 12.0% are positive for 1 AA, 4.0% for 2 AAs, and 1.63% are positive for 3 AAs.

Some programs have successfully established partnerships with community PCPs. The Fr1da program, initiated in 2015, screens for AAs in children 1.75-1.99 years of age in Bavaria at well child visits, and more recently was extended to Saxony and northern Germany, and to include screening for SARS-CoV-2 antibodies (45; 46). Consistent with the predicted frequency, 0.31% of the 90,632 children screened were positive for ≥2 AAs (43). Of the 196 participants found to have Stage 1 disease, 28.7% developed Stage 2 or 3 type 1 diabetes in 3 years of follow-up.

Through this program, factors were identified in this screening program that predicted progression from Stage 1 to Stage 2 or type 1 diabetes, including obesity, IA2A positivity, HbA1c>5.7%, and from 60-minute OGTT glucose levels in the highest tertile. The type 1 diabetes GRS was predictive of AAs but not predictive of progression of Stages (43).

Other programs are in development (**Table 2b**). The Australian General Population Screening Pilot, set to launch in 2022, will compare uptake, feasibility, and cost of screening children using three different strategies: genetic testing at birth, genetic testing in infancy, and AA testing of participants between 2-6 years of age. Recruitment will be through dedicated maternity hospitals and by direct mail-out to defined regions. In the T1Early program under development in the UK, AA will be measured in capillary blood at a pre-school vaccination visit (between 3.5-4 years of age) by PCPs. The ADIR program starting in 2021 in Israel will coordinate capillary blood AA screening with scheduled PCP hemoglobin screening.

Considerations for clinical practice (Table 3):

Benefits and risks of screening for early-stage type 1 diabetes: The early identification, monitoring and regular follow-up of high-risk individuals can reduce DKA rates at the time of diagnosis of Stage 3 type 1 diabetes. DKA rates fall from 25%-62% to 4-6% with monitoring, with potential longer-term impacts to reduce HbA1c levels and risk of complications (40; 41; 47).

Some studies have described a risk of negative psychological impact on those who screen AA-positive, but this stress appears to wane over time. Post-diagnosis adjustment for subjects diagnosed through screening and monitoring compares favorably to those diagnosed with clinical symptoms (43; 48; 49). In addition, screening enables access to medical expertise to discuss results and provide ongoing education and monitoring. Importantly, the majority (~95%) of relatives of individuals with type 1 diabetes are AA-negative at screening, which can be reassuring, particularly for families with an affected family member.

Perception of benefit is an important consideration for program success. One study from the US suggested that both parents and pediatricians valued screening programs associated with monitoring that minimize the risk of DKA, and enable treatment options or access to clinical studies to delay the onset of clinical type 1 diabetes (50). Thus, studies should be highlighted as part of outreach.

What is the optimal timing and approach to screening for type 1 diabetes? Genetic-based testing versus AA-based screening has the benefit of enriching for individuals who are most likely to have AAs (**Figure 2**). By selecting these individuals for AA screening, costs may be reduced, yet the potential losses to follow-up, and serologic testing and costs of recontact need to be considered. Analysis of birth cohorts have shown that peak rates of AA seroconversion occur around 1.5 years in those who progress to clinical type 1 diabetes, and most individuals seroconvert by 2-3 years of age (51; 52). Thus, if a single AA test is performed, testing at ages 3-4 should maximize case capture. However, early onset type 1 diabetes, where severe DKA rates are highest, as well as older adolescent and adult seroconverters, would be missed. If two tests can be done, straddling the 3-4 yr age group (i.e., at 2 and 5-7 years of age) has been suggested (52; 53). Most genetically high-risk young children who convert from single to multiple AA positivity do so within 2 years after initial seroconversion, suggesting that a single AA-positive individual should be rescreened after this interval (52). For practical considerations, timing AA screening with primary care visits may expand participation. The optimal strategies for identification of at-risk adults need to be studied. The ASK and T1Detect programs have taken a broader approach to screen older individuals and will capture the smaller proportion of individuals that become AA-positive after early childhood, but may miss children who progress to Stage 3 disease at an early age. Involvement of pediatric and adult PCPs might not only improve initial community engagement but also facilitate follow-up, monitoring, and ultimate care coordination for those that screen positive. Pediatric testing may coincide with other laboratory screening performed routinely, such as for anemia, lead, or lipid levels but because children, in general, infrequently undergo routine laboratory testing in general care, Capillary blood testing with multiplexed or dried blood spot testing can facilitate screening with referral to a diabetes center if the test results are positive (43; 54).

Which tests should be used? AA screening tests need to be standardized, since sensitivities, thresholds for positive tests, and other characteristics may differ between assays. The RBA assay was used in the successful prevention trial (TN10). Many programs use assays that have been validated in the IASP program, but only one assay system (Kronus) is approved by the FDA as a diagnostic and this assay has not been tested for identifying risk for type 1 diabetes. Home testing with dried blood spots or capillary microsamples rather than serum-based assays may enable a much broader outreach and acceptance for patients but like other assays, validation with the RBA assays and their ability to predict Stage 3 disease need to be confirmed.

What is the optimal follow up for positive screens? As noted, the biomarkers of risk do not give information about the rate of progression to type 1 diabetes. Importantly, prevention of DKA and enrollment in clinical trials are not achieved with screening alone – follow-up is needed and requires input from health care professionals familiar with the significance of laboratory findings and the clinical disease (55; 56). Some programs employ monitoring with HbA1c, random glucose levels, or OGTTs for those at high risk. Home glucose meter or CGM have also been suggested as options (57) and CGM has been tested in TrialNet (manuscript in preparation). INNODIA is testing whether repeated home measurements of C-peptide, using dried blood spots, may be useful for assessing β cell loss.

Optimal methods or frequencies for monitoring have not been established. Furthermore, communication of risk associated with positive screens and treatment options is complicated even among those with a family history and baseline knowledge of type 1 diabetes (48). Understanding optimal communication about risk and treatment of early-stage type 1 diabetes is essential. Finally, referral to clinical trials through networks such as INNODIA or TrialNet should be considered. In these consortia, patients will have access to the most advanced and potentially beneficial options for delay or prevention.

How can the general public be made aware of these opportunities? Currently, general population screening requires the participation of PCPs. Screening in the Fr1DA, PLEDGE, PrIMeD and T1Early programs are performed in primary care clinics. In the UK, the T1 Early program is using a creative design agency to inform communication with the general public, and engage leading pediatric diabetologists and the National Children's and Young People's Network to raise awareness about pre-clinical diabetes, aid recruitment, and embed screening within the UK-health system.

Outreach to minority communities is an unmet need. The rates of type 1 diabetes among minority ethnic/racial group members is significant: and in total, comparable to the frequency among non-Hispanic whites (NHW): NHW: 2.55/1000, non-Hispanic black (NHB): 1.63/1000; Hispanic: 1.29/1000; and Non-Hispanic Asian: 0.6/1000 (58). Recent analyses in the US have suggested that type 1 diabetes incidence is increasing most rapidly amongst minority groups (increases of incidence of 4.0%/year in Hispanics, 2.7%/year in NHB, 4.4%/year in Asian/Pacific Islanders *vs.* 0.7%/year in NHW (59). There is a higher frequency of DKA at diagnosis amongst these populations (41), who would, therefore, benefit from early detection and monitoring. However, groups of non-European ancestry are underrepresented in type 1 diabetes research (60). Of the 226,553 initial screens in the TrialNet Pathway to Prevention study, only 3.75% and 13.58% are African American and Hispanic respectively. In the T1Detect program 5.5% (of 800) are Hispanic, and 1.4% are African American. More success has been seen in the ASK program in which more than half are from minority groups (35% are NHW; 51% Hispanic; 8% African American). Obstacles such as engagement with PCPs and specialists in underserved neighborhoods and out of pocket costs remain hurdles that need to be addressed so that all who can benefit have access.

Does screening have economic benefits? Screening costs vary by the types of assays and the expenditures needed to identify participants. Clinical charges for AA tests can range from $131 (ICA) to $528 (ZnT8A) (61) but multiplexing and selective AA measurements (e.g. GADA and IAA) can reduce these costs. The current costs for AA screening in the ASK study is $47 and in the JDRF T1Detect program, $55. Based on the frequencies of positive screenings in the ASK program, the cost of AA screening per case of type 1 diabetes detected before diagnosis is $4700 (62).

A major goal of general population screening, through attentive follow-up of individuals who test positive, is to reduce the rate of life-threatening DKA at the time of diagnosis, a complication which is associated with long term sequalae and outcomes (40; 41; 47). It is estimated that screening and follow-up would be cost effective even if it would reduce the rate of DKA by 20%, which would also lower HbA1c by 0.1% over a lifetime (62). An approved treatment to delay type 1 diabetes would eliminate the cost of insulin, supplies for administration, and glucose monitoring which will also have cost-savings. In addition to impacts on patient outcomes, a clear understanding of cost savings of successful screening programs will be important to achieve buy-in and coverage from medical payers. Further analyses testing cost-effectiveness at multiple levels will be key for payer engagement and long-term integration into health systems.

Summary and conclusions: Criteria have been proposed to be applied for the justification of population screening (**Table 4**) and the programs listed in **Table 2** are working towards fulfilling these criteria. It is now possible to identify the majority of children and adults who will develop type 1 diabetes and to take action to delay or prevent the disease prior to needing insulin. Recently, a report from the Milken Institute identified hurdles and suggested changes needed in US health care policy, recommendations for screening, and a unified framework for policy implementation (https://milkeninstitute.org/reports/diabetes-pediatric-autoantibody-screening). Clearly, a number of logistical uncertainties that remain before screening and monitoring can be applied as part of clinical care (**Figure 3**) (7). Understanding the implications of positive screens from different testing methods on ultimate risk of clinical progression will be important to guide these protocols. Education and partnership with community PCPs will be essential for continued engagement and monitoring of at-risk individuals.

The value of the prevention or even delay of the diagnosis of type 1 diabetes on the lives of families and those who would have otherwise been diagnosed with type 1 diabetes for their development, emotional, physical, and mental health should not be underestimated. The ability to intervene in the disease course during a presymptomatic phase is a key tenant of population screening but likewise, identifying effective therapies and applying them in clinical settings is dependent on identifying those at risk who are most likely to benefit from them. Collaborations between groups involved in screening and therapeutics will be needed to fulfill this objective.

In conclusion, screening for type 1 diabetes for purposes of delay or prevention of clinical disease, has entered a new phase. With the availability of new therapies that can delay or prevent type 1 diabetes, the opportunity for dramatically changing the future of this disease is enormous. Attention to hurdles discussed in **Figures 3 and 4** and the Milken Institute Report should be considered a high priority for stakeholders in our field, taking advantage of knowledge gained from current successful efforts so that thoughtful coordinated larger-scale approaches can be implemented and interventions provided to all who stand to benefit.

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Table 1. Autoantibody Methods (19)

Methods	**Description**
Radiobinding assay (RBA)	Radiolabeled antigens detected in antibody-antigen complexes
Electrochemiluminescence (ECL)	Biotin and Sulfo-TAG labeled ligands that emit light when activated
ELISA	Detection of antigen:antibody complexes by enzyme linked reagents
Luciferase immunoprecipitation (LIPS)	Quantitates serum antibodies by measuring luminescence emitted by the reporter enzyme luciferase fused to an antigen of interest.
ADAP (agglutination PCR)	PCR amplification of DNA in DNA-antigen conjugates bound to antibodies to form aggregates

Table 2: Ongoing Screening programs

A: Selected type 1 diabetes screening programs employing screening of relatives for eligibility to participate in clinical studies.								
Program	**Population screened**	**Location**	**Screening sites**	**Number screened**	**Screening material**	**Screening assays**	**Rates of positive screens**	**Comments**
TrialNet: Pathway to Prevention (TN01)	Relatives ages 3-45 years	US, Canada, Europe, Australia	TrialNet Centers and affiliates	>250,000	Serum or capillary sample	RBA: IAA and GADA, followed by IA-2A, ZnT8A and ICA if positive	• AA+: 5% • ≥2 AA+: 2.5%	• Objective is to identify participants eligible for clinical trials. • Monitors nonrelatives identified through other programs
INNODIA	Relatives and general population	Europe	Academic sites	> 4400	Serum	RBA	AA+: 379 • 1AA+: 6.0% • 2AA+: 1.0% • 3AA+ 0.9% • 4AA+ 0.8% • ≥2 AA+: 2.6%	Of AA+ : • IAA: 184 (49.9%) • GADA 242 (65.2%) • IA-2A 81 (21.8%) • ZnT8A (94 (25.1%)
Bart's Oxford – BOX family study	Relatives	UK	Diabetes clinics/at home	6000	Capillary blood since 2015	RBA: IAA, GADA, IA2A, ZnT8A	470 AA+: • 1AA+ 6% • ≥2 AA+ 2%	Family members are recruited at diagnosis of a proband (<21 years old) in the study area.

Type1Screen	Relatives ages 2 to 30 years	Australia and New Zealand	Community collection centers and in-home collection	>700	Capillary or venous blood	IAA: RBA or ADAP; GADA, IA-2A, ZNT8A: ELISA or ADAP	AA+: 34 (5%)
							• 1AA+: 13 (1.9%)
							• ≥2 AA+: 21 (3.9%)
								• Family members recruited by health professionals, emails, and social media.
								• Of AA+:
								  • IAA 3 (9%)
								  • GADA 25 (74%)
								  • IA-2A 18 (53%)
								  • ZNT8A 22 (65%)

US- United States, UK- United Kingdom, AA- islet autoantibody

B: General Population Screening Programs								
Program	**Population screened**	**Location**	**Screening sites**	**Number screened**	**Screening material**	**Screening assays**	**Rates of positive screens**	**Comments**
1) Genetic prescreening with follow- up for AA								
DIPP	Age 0.25-15 yrs with high-risk HLA genotypes	Finland	Three university hospitals	>250,000	Serum	HLA genotyping followed by RBA: IAA, GADA, IA-2A, ZnT8A	• ~10% of screens with high-risk HLA. • ≥2 AA+: • by 2 yrs: 2.2% • by 5 yrs: 3.5% • by 15 yrs: 5.0%	All newborns with parental consent (~25% of birth cohort) receive cord blood HLA screening. ~19,000 at-risk have agreed to follow-up AA screening at 3-12 mo intervals up to age 15 yrs.
BABY-SCREEN	Newborns-1-3 yrs with high-risk HLA for type 1 diabetes and/or celiac disease	Helsinki, Finland	University Hospital	Target for HLA screening: 30,000; >9000 tested	Serum	HLA genotyping followed by RBA: IAA, GADA, IA-2A, ZnT8A, tTGA	By 1 yr: • 1 AA+: 5.3% • ≥2 AA+: 1.8% By 2 yrs • 1 AA+: 6.5% • ≥2 AA+: 3.7%	• HLA screening from cord blood followed by AA screening at age 1, 2 and 3 yrs. • Type 1 diabetes in first degree relative in 3.1%
GPPAD	Infants< 1 months of age	Germany, UK, Poland, Belgium, and Sweden	Around delivery or primary care physician (PCP) visits	>275,000, (1.72% first degree relatives)	Capillary blood spots	47 SNP GRS to ID those with >10% risk of ≥2 AA+ by age 6 yrs.	1.1% with increased genetic risk	• At-risk infants are offered participation in a primary prevention trial.
PLEDGE	Age < 6y	North and South Dakota and Minnesota, US	Integrated Health System Clinics and Labs	Target= 33,000	Capillary Blood Spot for GRS, serum for AA	GRS, RBA	n/a	• GRS with newborn screen or study entry; AA testing at ~ 2, 5y. • Utilizes EHR for tracking/communication.
CASCADE	Age 1+	Northwest US	Newborn Screens and elementary schools	Target= 60,000	Serum	GRS, RBA: GADA, IAA, ZnT8A, tTGA; LIPS for IA2A	n/a	Initial GRS screen, at-risk followed for type 1 diabetes and celiac disease.
PrIMeD	Age 2-16 yrs	Virginia, US	Pediatric clinics	3477	Saliva for GRS, serum for AA	82-SNP GRS, RBA: IAA, GADA, IA-2A, ZnT8A	• 461 (1.3%) with "high" GRS (10x over expected) • AA testing in progress	AA screening offered to those with high GRS, ≥2 AA+ invited to contact TrialNet or obtain local CGM monitoring.

2) Screening for AA								
Fr1da	Age 1.75-10.99 yrs	Bavaria, then Lower Saxony, Hamburg, Saxony, Germany	PCP clinics	>150,000	Capillary blood	ELISA: GADA, IA2A, ZnT8A/ LIPS: IAA; confirm with RBA: IAA, GADA, IA-2A, ZnT8A	≥2 AA+: 0.3%	Positive screens invited for metabolic staging by OGTT. >80% of these with Stage 1.
Fr1dolin	Age 2-6 yrs	Lower Saxony and Hamburg, Germany	PCP clinics	>15,000	Capillary blood	ELISA: GADA, IA-2A, ZnT8A; confirm with RBA: IAA, GADA, IA2A, ZnT8A	≥2 AA+: 0.35%	• Combined screening for type 1 diabetes risk and familial hypercholesterolemia. • Positive screens invited for staging with OGTT
T1Detect(JDRF)	Age 1yr+	Most US states	At home	Up to 2000/mo	Capillary blood spot	ADAP: GADA, IA-2A, IAA	• Nonrelatives: • 1AA+: 12% • ≥2 AA+: 5.4% • Relatives: • 1AA+: 12% • ≥2 AA+: 5.7%	• Direct access to participants through the JDRF website. • Of the first 800 tests, 203 (25.4%) were from the general population.
ASK	Age 1-17yrs	Colorado, US	PCP and hospital specialty clinics, emergency departments	25738	Serum	RBA with ECL confirmation IA-2A, GADA, IAA, ZnT8A and tTGA	• AA+: 3.4% • ≥2 AA+: 0.52% • Single high affinity AA+: 0.58%	• Screening for type 1 diabetes, Celiac Disease, and SARS-CoV-2 Ab • 4.84% with 1st degree relative with type 1 diabetes.
3) Screening programs in development								
T1Early	Preschool age: 3.5-4 yrs	UK	Pre-school vaccination PCP visit	n/a	Capillary blood	LIPS: GADA, IA-2A, ZnT8A	n/a	Positive screens using the LIPS assay will undergo metabolic staging.
ADIR	Age 9-18 months old, 5 yrs	Israel	PCP visit with hemoglobin screening	Target of up to 50,000	Capillary or venous blood	ADAP: GADA, IA-2A, IAA	n/a	Due to start October 2021.
JDRF Australia General Population Screening Pilot	Newborns, infants, and 2-6 yrs	Australia	Maternity hospitals, general population	Target of 3000 in each cohort	Capillary blood and saliva	GRS, ADAP for IAA,GADA, IA-2A and ZNT8A	n/a	Starting in 2022. Will compare GRS approach to cross-sectional AA

								screening in older children.

* AA= islet autoantibodies GRS= genetic risk score; PCP=primary care physician; EHR= electronic health record; JDRF- Juvenile Diabetes Research Foundation

Study acronyms: DIPP- Type 1 Diabetes Prediction and Prevention Study; BABYSCREEN- Newborn Screening for Genetic Susceptibility to Type 1 Diabetes and Celiac Disease and Prospective Follow-up Study; GPPAD- Global Platform for the Prevention of Autoimmune Diabetes; PLEDGE: General Population Level Estimation for Type 1 Diabetes Risk in Children 0-5 Years Old During Routine Care Delivery; CASCADE: Combined Antibody Screening for Celiac and Diabetes Evaluation; PrIMeD: Precision Individualized Medicine in Diabetes Study; Fr1da: Früherkennung Typ-1 Diabetes (Engl.: Early detection of type 1 diabetes); Fr1dolin: Früherkennung Typ-1 Diabetes und Hypercholesterinämie in Niedersachsen) (Engl.: Early detection of type 1 diabetes and hypercholesterolemia in Lower Saxony)

ASK: Autoimmunity Screening for Kids; ADIR: Screening for Islet Autoantibodies in the Israeli Paediatric General Population for Detection of Pre-symptomatic type 1 diabetes

Table 3: Recommendations for practice

1. When asked about screening for type 1 diabetes risk,
    a. Available screening tools: Genetic, autoantibodies, glucose levels, symptoms
    b. The overall risk for development of type 1 diabetes is greater for those with a relative with type 1 diabetes compared to those without relatives because of shared genetic and environmental factors. However, the risk for type 1 diabetes in children who have 2+ autoantibodies is the same whether or not they have an affected relative.
    c. Screening initiatives are available in North America, Europe, Australia and New Zealand (see Table 3).
    d. There are risks and benefits of screening. The former may involve anxiety about the findings but the latter may include reassurance of a negative test, avoidance of DKA at diagnosis, and access to clinical studies and therapies to delay or prevent type 1 diabetes.
2. Information, with the assurance of privacy, testing for antibodies, and ongoing monitoring or enrollment in trials is available (e.g. through the NIH funded research network TrialNet or through the IMI funded research network INNODIA and other programs in Europe).
    a. For relatives: TrialNet, INNODIA and Type1Screen provide free, confidential AA testing and ongoing monitoring for relatives who are AA positive.
    b. For non-relatives: See regional initiatives (Table 3). If testing shows that they have one or more AA, the test should be confirmed. TrialNet/INNODIA/Type1Screen will provide confirmation of positive AA tests conducted outside of a research study. AA positive individuals can be referred to TrialNet/INNODIA/Type1Screen for a confirmation test whether or not they have a relative with diabetes.
3. The optimal time for cross-sectional screening is ages 2 and 5-7yr but screening school age children, particularly at the time of other laboratory tests may be the most practical.
4. Follow up of positive tests is needed to reduce rates of DKA and avoid the unexpected diagnosis of type 1 diabetes. Follow up may include:
    a. Discuss the results and the implications.
    b. Explain signs and symptoms of diabetes.
    c. Standards for metabolic follow up have not been established but may involve HbA1c levels, random glucose levels, OGTTs, or potentially continuous glucose monitoring.
    d. Clinical studies are available through TrialNet and INNODIA.

Table 4: Wilson and Jungor's guidelines for screening as applied to type 1 diabetes

Principle	Application to screening for type 1 diabetes
1. Identify an important health problem	Type 1 diabetes is one of the most common and consequential chronic illnesses of children but also affects individuals of all ages.
2. There should be an accepted treatment for the condition	Teplizumab was shown to delay or delay the diagnosis of individuals at-risk. Other agents are under evaluation.
3. Facilities for diagnosis and treatment are available	Diagnosis and treatment can be done in medical offices.
4. There should be a recognizable latent or early symptomatic period	Stages of progression of type 1 diabetes in those at genetic risk have been defined. High risk individuals (Stage 2) have a 75% risk of diagnosis within 5 yrs.
5. There should be a suitable test or examination	AAs can define risk. Newer technologies to improve prediction are under study. AAs can be measured in many laboratories.
6. The test should be acceptable to the population	
7. The natural history of the condition should be understood	Although many specifics remain uncertain, results from immune therapy trials indicate that type 1 diabetes is due to immune mediated killing of beta cells.
8. There should be an agreed policy on whom to treat as patients	Children and adolescents, during developmental years have the highest unmet need
9. The cost of case-finding should be economically balanced in relation to expenditure on medical care as a whole	The lifetime costs for type 1 diabetes, after onset in childhood are great, even without the additional costs associated with disease related complications.
10. Case finding should be a continuing process	Projects across the globe are piloting strategies .for case identification

Figure Legends

Figure 1. Definitions of Stages of Type 1 diabetes (26; 63)

Figure 2. Considerations for Approaches to General Population Screening: Combined Genetic/AA-Based Screening Versus an AA-Based Approach.

Figure 3. Logistical needs and uncertainties that remain to be answered for optimal implementation and sustainability of large-scale general population screening for type 1 diabetes.

Screening for Type 1 Diabetes in the General Population: a Status Report and Perspective

Emily K Sims MD[1], Rachel EJ Besser MD PhD[2,3], Colin Dayan MD PhD[4], Cristy Geno Rasmussen, PhD[5] Carla Greenbaum MD[6], Kurt J Griffin MD PhD[7], William Hagopian MD PhD[8], Mikael Knip MD[9-11], Anna E. Long[12], Frank Martin PhD[13], Chantal Mathieu MD PhD[14], Marian Rewers MD PhD[5], Andrea K. Steck MD[5], John M Wentworth MD[15], Stephen S. Rich PhD[16], Olga Kordonouri MD[17], Anette-Gabriele Ziegler MD PhD[18], and Kevan C. Herold MD[19], for NIDDK Type 1 Diabetes TrialNet Study Group

[1]Department of Pediatrics, Indiana University School of Medicine
[2] Department of Paediatrics, NIHR Oxford Biomedical Research Centre, John Radcliffe Hospital,
[3]Welcome Centre for Human Genetics, University of Oxford, Oxford, UK
[4]Cardiff University School of Medicine, Cardiff, UK.
[5] Barbara Davis Center for Diabetes, University of Colorado-Anschutz, School of Medicine, Aurora, CO USA
[6]Benaroya Research Institute, Seattle, WA
[7]Sanford Health, Sioux Falls, SD
[8] Pacific Northwest Research Institute, Seattle WA USA
[9]Pediatric Research Center, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland;
[10]Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Helsinki, Finland; and
[11]Tampere Center for Child Health Research, Tampere University Hospital, Tampere, Finland
[12]Bristol Medical School, University of Bristol, Bristol UK
[13]JDRF, New York, NY
[14]Department of Endocrinology, UZ Gasthuisberg, KULeuven, Leuven, Belgium
[15]Departments of Diabetes and Endocrinology and Population Health and Immunity, Royal Melbourne Hospital and Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia
[16] Center for Public Health Genomics, University of Virginia, Charlottesville, VA USA
[17] Kinder- und Jugendkrankenhaus AUF DER BULT, Hannover Germany
[18]Institute of Diabetes Research, Helmholtz Zentrum München, German Research Center for Environmental Health, Munich-Neuherberg, Germany. Technical University Munich, School of Medicine, Forschergruppe Diabetes at Klinikum rechts der Isar, Munich, Germany.
[19]Department of Immunobiology and Department of Internal Medicine, Yale University, New Haven, CT

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Direct Correspondence to:
Kevan C. Herold, MD
Departments of Immunobiology and Internal Medicine
Yale University
300 George St, #353E
New Haven, CT 06520
Email: Kevan.herold@yale.edu
Phone Number: 203-785-6507

Abstract

Most screening programs to identify individuals at risk for type 1 diabetes have targeted relatives of people living with the disease to improve yield and feasibility. However, ~90% of those who develop type 1 diabetes do not have a family history. Recent successes in disease modifying therapies to impact the course of early-stage disease have ignited the consideration of the need for and feasibility of population screening to identify those at increased risk. Existing population screening programs rely on genetic or autoantibody (AA) screening, and these have yielded significant information about disease progression and approaches for timing for screening in clinical practice. At the March 2021 Type 1 Diabetes TrialNet Steering Committee meeting, a session was held in which ongoing efforts for screening in the general population were discussed. This report reviews the background of these efforts and the details of those programs. Additionally, we present hurdles that need to be addressed for successful implementation of population screening and provide initial recommendations for individuals with positive screens so that standardized guidelines for monitoring and follow-up can be established.

Introduction

Combined with work by multiple groups over the past decades to identify those at high risk, the recent positive results of the Phase 2 randomized controlled TrialNet TN10 "Anti-CD3 (teplizumab) prevention trial" have opened opportunities for prevention of type 1 diabetes (1). The TN-10 trial reported that a single 14-day course of teplizumab drug therapy delayed the clinical diagnosis of type 1 diabetes in 76 multiple islet autoantibody (AA) positive non-diabetic relatives by a median of 24 months, and in a subsequent analysis up to 32.5 months (1; 2). The relatively rapid time to clinical diabetes in the placebo group fulfilled the predictions from trial planning: a 75% risk of clinical diagnosis in 5 years in the AA+, non-diabetic, dysglycemic relatives, and validated methods used in that trial to identify individuals at-risk for disease. In addition to teplizumab, prevention trials with other therapies are underway (NCT01773707 and NCT03428945).

Type 1 diabetes frequently presents with preventable life-threatening complications (diabetic ketoacidosis or DKA), and the diagnosis of type 1 diabetes affects longevity, morbidity, and the quality of life for patients and their families (3-6). These and other data highlight an urgent unmet need to develop programs to identify those at risk, with or without a relative with type 1 diabetes, who may benefit from these treatments (7).

Relatives of patients with type 1 diabetes have a ~15-fold increased risk of disease as compared to those without a relative with type 1 diabetes (8-10). Siblings of patients have, on average, a 6-7% lifetime risk of type 1 diabetes and offspring of mothers and fathers with type 1 diabetes have a 1.3-4% and 6-9% lifetime risk, respectively, compared to 0.4% in the general population (8-10). Because of the enriched risk in relatives, screening programs and clinical trials have often targeted this group.

However, ~90% of those who will present with new type 1 diabetes do not have a positive family history (11; 12). The treatment effects of teplizumab and other immune therapies after the diagnosis of type 1 diabetes, in patients without affected family members, illustrates the efficacy of these therapies in the general population. Therefore, to identify the most individuals who would benefit from therapies to prevent type 1 diabetes, those without a positive family history must be identified. Several groups have initiated screening of the general population and there has been interest on the part of academics, advocacy organizations, policy groups, pharma, and others in evaluating the optimal manner in which to proceed with this large endeavor. At the March 2021 TrialNet Steering Committee meeting, ongoing efforts for screening of the general population were reviewed. This report presents the background on these and other screening efforts, clinical recommendations, the details of selected programs, and challenges for implementation of population screening.

Progression of type 1 diabetes in humans: Type 1 diabetes is caused by the destruction of insulin producing β cells by immune mechanisms, involving B, CD4+, and CD8+ T cells, with the latter serving as the postulated effectors (11). Some immune cell targets have been identified, such as proinsulin and insulin, glutamic acid decarboxylase 65 (GAD65), islet antigen 2 (IA-2), islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP), zinc transporter-8 (ZnT8), and chromogranin A (13). In model systems and *in vitro*, T cells that are reactive with peptides from these antigens can elicit β cell killing, yet a direct causal role for these cells remains to be defined.

Despite the primary role of T cells in β cell killing, clues to the immune targets in type 1 diabetes originated by finding AAs that are reactive with these proteins in individuals with and prior to the diagnosis of clinical type 1 diabetes. The earliest observations of anti-islet cell antibodies (ICA), in 1974, entailed immunofluorescent detection of immunoglobulins that reacted with islets from a pancreas from a blood type group O donor. The specific molecular targets of autoantibodies have been progressively discovered with the first being insulin (14; 15). Subsequently, other antigens, including GAD65, were recognized and methods such as radioimmunoprecipitation were used to identify islet cell proteins recognized by antibodies (16-

18). The methods to measure biochemically defined AAs to insulin (IAA), GAD65 (GADA), ZnT8 (ZnT8A), and a protein tyrosine phosphatase (ICA512A or IA2A), have previously been reviewed (19).

AAs can be found prior to clinical disease (20-24) indicating that there is an asymptomatic period before the typical presentation with clinical type 1 diabetes, which is associated with β cell functional loss, hyperglycemia, and, often, ketoacidosis (25). The risk for progression to type 1 diabetes is built on the detection of AAs. Beginning with the appearance of two AAs, Stages of type 1 diabetes are now defined and identify steps during the progression of disease (**Figure 1**)(26). The notions of stages have been useful for identifying cohorts for clinical studies, but there are limitations to their application in the clinical practice setting. First, AAs identify risk but not the speed of progression to clinical type 1 diabetes. The rates of progression for each individual may vary considerably (20-22; 27). Risk is modified by age at seroconversion (to AA positivity) and the number of the AAs present in an individual's serum, although which AAs are found may differ by age. Younger individuals frequently have IAA initially, whereas in teen-age years, GADA are frequently found. Second, the stages do not include direct measures of the immune process or β cell decline (28; 29). Finally, discrete stages may not be identified in all individuals. For example, some individuals, particularly for children < 5 yrs in Stage 1, may progress to overt clinical disease without a period of dysglycemia (i.e., Stage 2). This may reflect infrequent glucose monitoring or alternatively a more rapid progression compared to older individuals (30).

At-risk individuals typically harbor a genetic predisposition to autoimmunity. The strongest genetic determinants of risk are the human leukocyte antigen (HLA) genotypes, but other non-HLA susceptibility loci have also been identified. Genetic risk scores (GRS), incorporating multiple loci have been developed and shown to predict islet autoimmunity (31). After development of islet autoimmunity, metabolic features, including body mass index and more subtle analyses of β cell function and insulin secretion can inform risk and evolution of progression from early-stage disease (32). Other risk indices (e.g. Index 60, Diabetes Prevention Trial – Type 1 Risk Score

(DPTRS)) that incorporate these metabolic data can greatly enhance prediction of progression from early-stage disease. Reviews that detail the pathophysiology of type 1 diabetes, including AA, genetics and metabolic measures in type 1 diabetes prediction are available (19; 31-33).

Technological performance and improvements in AA measurements:

Most contemporary studies of type 1 diabetes progression have use radiobinding assays (RBA), but newer methods and assays may improve prediction. These are reviewed in (19) and summarized in **Table 1.** In addition to new AA targets, new technologies have improved specificity and sensitivity and may be multiplexed, minimizing the blood volumes needed, and enhancing the throughput and accessibility of tests. Some newer assays selectively measure AAs with high binding affinities or truncated peptides (e.g., GAD 96-585), and have shown improved assay specificity and type 1 diabetes prediction (19; 34; 35). The validation of these methods has been supported by the Islet AA Standardization Program (IASP) workshop, which compares assay performance across different methods (19). The results from this program indicate that the assays are sensitive and sufficiently specific to distinguish patients with type 1 diabetes from nondiabetic controls but the program was not designed to evaluate specificity at the level required for population-based screening. In an ongoing comparator study, TrialNet will evaluate the prediction of type 1 diabetes within 5 years with these new assays. Minimization of false positive rates in nondiabetic individuals is a particularly important consideration to minimize risks of unnecessary testing and anxiety in the context of broader screening.

Ongoing screening programs (**Table 2a)**:

a) In relatives of individuals with type 1 diabetes: Both TrialNet (a US based consortium) and INNODIA (a European private/public partnership) began by screening relatives to maximize efficiency for enrollment in clinical studies. However, both have begun to include monitoring or screening of at-risk individuals from the general population. The Type 1 Diabetes TrialNet Pathway to Prevention Study, initiated in 2004, has screened over 220,000 relatives. Initially, assays for ICA and IAA, IA2A, and GADA (by RBA) were performed. In 2019, after an internal review of data from this study to improve cost and efficiency, screening was changed to GADA and IAA by on-line consenting and optional at-home test kits. Those individuals who test positive for either AA then underwent testing for ZnT8A, IA2A, and ICA. Overall, TrialNet identified ~5% of nondiabetic relatives to have at least one AA, and about half of these with multiple AA (i.e., Stage 1 or Stage 2). INNODIA, a European private/public partnership, screens for four AAs by RBA and has screened more than 4400 first-degree relatives. Consistent with the TrialNet data, the most frequently found AAs are GADA and IAA, with 2.6% of the individuals tested having multiple AAs.

b) In the general population: In total, the number of individuals without a relative with T1D who have been screened is greater than the number of relatives. **Table 2b** summarizes data from selected programs ongoing and under-development for the general population. The **Supplemental Table** describes completed programs. These generally fall into the categories of birth cohorts or AA-based screening programs. Some differences in positive screen rates between programs exist; these are likely multifactorial and related to background prevalence, overall screening strategy, inclusion of individuals with relatives with type 1 diabetes, and the assays utilized.

Birth cohorts: Birth cohorts use a combined approach to initially identify individuals at increased genetic risk for type 1 diabetes. Genetic screening can enrich for individuals who are appropriate for targeted AA screening. Using screening for HLA, the TEDDY study (The Environmental Determinants of Diabetes in Youth) is gathering data from > 8,000 HLA genetically at-risk newborns, most (~90%) without a known type 1 diabetes relative (22)(**Supplemental Table 1**). These newborns are followed for 15 years for the appearance of AAs and diabetes, with documentation of environmental factors that could contribute to disease. The Type 1 Diabetes Prediction and Prevention Study (DIPP) has been active in three Finnish university hospitals since

1994, screening >250,000 infants (36). All newborn infants from these hospitals (~25% of the national birth cohort) are screened for HLA-conferred susceptibility to type 1 diabetes, with parental consent, using cord blood. Almost 10% of those screened carry such HLA genotypes and are invited for follow-up until 15 years of age or type 1 diabetes diagnosis. The BABYSCREEN study initiated 2018 in Helsinki, Finland, screens cord blood cells for HLA alleles conferring high-risk for type 1 diabetes and celiac disease. Participants carrying increased risk for either disease are invited to AA testing at 1, 2 and 3 years of age. Of the 9000 children screened, 6.0% were considered at high genetic risk for type 1 diabetes, 15.0% at high genetic risk to celiac disease, and 4.1% at high genetic risk to both diseases. The Global Platform for the Prevention of Autoimmune Diabetes (GPPAD) tests newborn blood spots collected from cord blood or at primary care provider (PCP) visits and calculates GRS to identify those at ≥10% risk for multiple AAs by 6 years of age. Those at increased genetic risk are offered the opportunity to enroll in a primary prevention study (37). Over 279,000 infants have been screened as of July 2021, with a positive AA screen rate of 1.1% with increased genetic risk.

Three recently initiated programs in the US, the CASCADE program, the Sanford PLEDGE project, and the PrIMeD program also utilize GRS (38) from dried blood spots or saliva. Those with "positive" GRS screens are offered AA screening (39). In follow-up of the newborn and study entry samples for GRS testing, the PLEDGE study performs AA testing at 2 years and pre-kindergarten visits, with an emphasis on integrating study processes into routine pediatric care, and integration with the electronic health record system. Children with positive AAs are offered ongoing monitoring according to principles described in **Table 3** or offered the opportunity to participate in a TrialNet clinical trial for at-risk individuals (www.trialnet.org).

<u>Screening after the neonatal period:</u> Several programs use AAs for primary screening in children after the neonatal period, including ASK (Autoimmunity Screening for Kids, Colorado), T1Detect

(US), Fr1da and Fr1dolin (Germany) (**Table 2b**)(40-44). Relatives are not excluded from participating in these programs. AA screening alone is more costly when conducted without genetic pre-screening, but it is specific for Stage 1 or Stage 2 disease. Multiple methods for AA detection have been used (40-44). Unique approaches to optimize enrollment and follow-up have been employed (40-44).

The goals of the US-based ASK program, available to residents of Colorado aged 1-17 years, are early diagnosis, DKA prevention, prevention study enrollment, and referral. Diabetes AA testing is combined with screening for celiac disease by measuring tissue transglutaminase antibodies (tTGA) and, more recently, SARS-CoV-2 antibodies. Children who have a positive test are invited for confirmatory testing. Of 25,738 participants: 3.4% were positive for any AA on the initial screening, 0.52% were positive for multiple islet AA, and 0.58% were positive for a single high-affinity AA (Rewers M, personal communication, 2021).

The T1Detect program was initiated by the JDRF in 2020 (42). T1Detect provides online links for individuals ≥1 years of age to a commercial laboratory (Enable Biosciences). That laboratory uses an online portal to provide screening at home with a blood spot testing approach. Participants receive test kits for collection of dried blood spots that are mailed for measurement of GADA, IA2A, and IAA using the ADAP assay (19). Participants screening AA positive are contacted by the laboratory and offered one-on-one and/or online support. Of the 800 initial screens (of which 74% are first-degree relatives of individuals with type 1 diabetes), 12.0% are positive for 1 AA, 4.0% for 2 AAs, and 1.63% are positive for 3 AAs.

Some programs have successfully established partnerships with community PCPs. The Fr1da program, initiated in 2015, screens for AAs in children 1.75-1.99 years of age in Bavaria at well child visits, and more recently was extended to Saxony and northern Germany, and to include screening for SARS-CoV-2 antibodies (45; 46). Consistent with the predicted frequency, 0.31% of the 90,632 children screened were positive for ≥2 AAs (43). Of the 196 participants found to have Stage 1 disease, 28.7% developed Stage 2 or 3 type 1 diabetes in 3 years of follow-up.

Through this program, factors were identified in this screening program that predicted progression from Stage 1 to Stage 2 or type 1 diabetes, including obesity, IA2A positivity, HbA1c>5.7%, and from 60-minute OGTT glucose levels in the highest tertile. The type 1 diabetes GRS was predictive of AAs but not predictive of progression of Stages (43).

Other programs are in development (**Table 2b**). The Australian General Population Screening Pilot, set to launch in 2022, will compare uptake, feasibility, and cost of screening children using three different strategies: genetic testing at birth, genetic testing in infancy, and AA testing of participants between 2-6 years of age. Recruitment will be through dedicated maternity hospitals and by direct mail-out to defined regions. In the T1Early program under development in the UK, AA will be measured in capillary blood at a pre-school vaccination visit (between 3.5-4 years of age) by PCPs. The ADIR program starting in 2021 in Israel will coordinate capillary blood AA screening with scheduled PCP hemoglobin screening.

Considerations for clinical practice (Table 3):

Benefits and risks of screening for early-stage type 1 diabetes: The early identification, monitoring and regular follow-up of high-risk individuals can reduce DKA rates at the time of diagnosis of Stage 3 type 1 diabetes. DKA rates fall from 25%-62% to 4-6% with monitoring, with potential longer-term impacts to reduce HbA1c levels and risk of complications (40; 41; 47).

Some studies have described a risk of negative psychological impact on those who screen AA-positive, but this stress appears to wane over time. Post-diagnosis adjustment for subjects diagnosed through screening and monitoring compares favorably to those diagnosed with clinical symptoms (43; 48; 49). In addition, screening enables access to medical expertise to discuss results and provide ongoing education and monitoring. Importantly, the majority (~95%) of relatives of individuals with type 1 diabetes are AA-negative at screening, which can be reassuring, particularly for families with an affected family member.

Perception of benefit is an important consideration for program success. One study from the US suggested that both parents and pediatricians valued screening programs associated with monitoring that minimize the risk of DKA, and enable treatment options or access to clinical studies to delay the onset of clinical type 1 diabetes (50). Thus, studies should be highlighted as part of outreach.

What is the optimal timing and approach to screening for type 1 diabetes? Genetic-based testing versus AA-based screening has the benefit of enriching for individuals who are most likely to have AAs (**Figure 2**). By selecting these individuals for AA screening, costs may be reduced, yet the potential losses to follow-up, and serologic testing and costs of recontact need to be considered. Analysis of birth cohorts have shown that peak rates of AA seroconversion occur around 1.5 years in those who progress to clinical type 1 diabetes, and most individuals seroconvert by 2-3 years of age (51; 52). Thus, if a single AA test is performed, testing at ages 3-4 should maximize case capture. However, early onset type 1 diabetes, where severe DKA rates are highest, as well as older adolescent and adult seroconverters, would be missed. If two tests can be done, straddling the 3-4 yr age group (i.e., at 2 and 5-7 years of age) has been suggested (52; 53). Most genetically high-risk young children who convert from single to multiple AA positivity do so within 2 years after initial seroconversion, suggesting that a single AA-positive individual should be rescreened after this interval (52). For practical considerations, timing AA screening with primary care visits may expand participation. The optimal strategies for identification of at-risk adults need to be studied. The ASK and T1Detect programs have taken a broader approach to screen older individuals and will capture the smaller proportion of individuals that become AA-positive after early childhood, but may miss children who progress to Stage 3 disease at an early age. Involvement of pediatric and adult PCPs might not only improve initial community engagement but also facilitate follow-up, monitoring, and ultimate care coordination for those that screen positive. Pediatric testing may coincide with other laboratory screening performed routinely, such as for anemia, lead, or lipid levels but because children, in general, infrequently undergo routine laboratory testing in general care, Capillary blood testing with multiplexed or dried blood spot testing can facilitate screening with referral to a diabetes center if the test results are positive (43; 54).

Which tests should be used? AA screening tests need to be standardized, since sensitivities, thresholds for positive tests, and other characteristics may differ between assays. The RBA assay was used in the successful prevention trial (TN10). Many programs use assays that have been validated in the IASP program, but only one assay system (Kronus) is approved by the FDA as a diagnostic and this assay has not been tested for identifying risk for type 1 diabetes. Home testing with dried blood spots or capillary microsamples rather than serum-based assays may enable a much broader outreach and acceptance for patients but like other assays, validation with the RBA assays and their ability to predict Stage 3 disease need to be confirmed.

What is the optimal follow up for positive screens? As noted, the biomarkers of risk do not give information about the rate of progression to type 1 diabetes. Importantly, prevention of DKA and enrollment in clinical trials are not achieved with screening alone – follow-up is needed and requires input from health care professionals familiar with the significance of laboratory findings and the clinical disease (55; 56). Some programs employ monitoring with HbA1c, random glucose levels, or OGTTs for those at high risk. Home glucose meter or CGM have also been suggested as options (57) and CGM has been tested in TrialNet (manuscript in preparation). INNODIA is testing whether repeated home measurements of C-peptide, using dried blood spots, may be useful for assessing β cell loss.

Optimal methods or frequencies for monitoring have not been established. Furthermore, communication of risk associated with positive screens and treatment options is complicated even among those with a family history and baseline knowledge of type 1 diabetes (48). Understanding optimal communication about risk and treatment of early-stage type 1 diabetes is essential. Finally, referral to clinical trials through networks such as INNODIA or TrialNet should be considered. In these consortia, patients will have access to the most advanced and potentially beneficial options for delay or prevention.

How can the general public be made aware of these opportunities? Currently, general population screening requires the participation of PCPs. Screening in the Fr1DA, PLEDGE, PrIMeD and T1Early programs are performed in primary care clinics. In the UK, the T1 Early program is using a creative design agency to inform communication with the general public, and engage leading pediatric diabetologists and the National Children's and Young People's Network to raise awareness about pre-clinical diabetes, aid recruitment, and embed screening within the UK-health system.

Outreach to minority communities is an unmet need. The rates of type 1 diabetes among minority ethnic/racial group members is significant: and in total, comparable to the frequency among non-Hispanic whites (NHW): NHW: 2.55/1000, non-Hispanic black (NHB): 1.63/1000; Hispanic: 1.29/1000; and Non-Hispanic Asian: 0.6/1000 (58). Recent analyses in the US have suggested that type 1 diabetes incidence is increasing most rapidly amongst minority groups (increases of incidence of 4.0%/year in Hispanics, 2.7%/year in NHB, 4.4%/year in Asian/Pacific Islanders *vs.* 0.7%/year in NHW (59). There is a higher frequency of DKA at diagnosis amongst these populations (41), who would, therefore, benefit from early detection and monitoring. However, groups of non-European ancestry are underrepresented in type 1 diabetes research (60). Of the 226,553 initial screens in the TrialNet Pathway to Prevention study, only 3.75% and 13.58% are African American and Hispanic respectively. In the T1Detect program 5.5% (of 800) are Hispanic, and 1.4% are African American. More success has been seen in the ASK program in which more than half are from minority groups (35% are NHW; 51% Hispanic; 8% African American). Obstacles such as engagement with PCPs and specialists in underserved neighborhoods and out of pocket costs remain hurdles that need to be addressed so that all who can benefit have access.

Does screening have economic benefits? Screening costs vary by the types of assays and the expenditures needed to identify participants. Clinical charges for AA tests can range from $131 (ICA) to $528 (ZnT8A) (61) but multiplexing and selective AA measurements (e.g. GADA and IAA) can reduce these costs. The current costs for AA screening in the ASK study is $47 and in the JDRF T1Detect program, $55. Based on the frequencies of positive screenings in the ASK program, the cost of AA screening per case of type 1 diabetes detected before diagnosis is $4700 (62).

A major goal of general population screening, through attentive follow-up of individuals who test positive, is to reduce the rate of life-threatening DKA at the time of diagnosis, a complication which is associated with long term sequalae and outcomes (40; 41; 47). It is estimated that screening and follow-up would be cost effective even if it would reduce the rate of DKA by 20%, which would also lower HbA1c by 0.1% over a lifetime (62). An approved treatment to delay type 1 diabetes would eliminate the cost of insulin, supplies for administration, and glucose monitoring which will also have cost-savings. In addition to impacts on patient outcomes, a clear understanding of cost savings of successful screening programs will be important to achieve buy-in and coverage from medical payers. Further analyses testing cost-effectiveness at multiple levels will be key for payer engagement and long-term integration into health systems.

Summary and conclusions: Criteria have been proposed to be applied for the justification of population screening (**Table 4**) and the programs listed in **Table 2** are working towards fulfilling these criteria. It is now possible to identify the majority of children and adults who will develop type 1 diabetes and to take action to delay or prevent the disease prior to needing insulin. Recently, a report from the Milken Institute identified hurdles and suggested changes needed in US health care policy, recommendations for screening, and a unified framework for policy implementation (https://milkeninstitute.org/reports/diabetes-pediatric-autoantibody-screening). Clearly, a number of logistical uncertainties that remain before screening and monitoring can be applied as part of clinical care (**Figure 3**) (7). Understanding the implications of positive screens from different testing methods on ultimate risk of clinical progression will be important to guide these protocols. Education and partnership with community PCPs will be essential for continued engagement and monitoring of at-risk individuals.

The value of the prevention or even delay of the diagnosis of type 1 diabetes on the lives of families and those who would have otherwise been diagnosed with type 1 diabetes for their development, emotional, physical, and mental health should not be underestimated. The ability to intervene in the disease course during a presymptomatic phase is a key tenant of population screening but likewise, identifying effective therapies and applying them in clinical settings is dependent on identifying those at risk who are most likely to benefit from them. Collaborations between groups involved in screening and therapeutics will be needed to fulfill this objective.

In conclusion, screening for type 1 diabetes for purposes of delay or prevention of clinical disease, has entered a new phase. With the availability of new therapies that can delay or prevent type 1 diabetes, the opportunity for dramatically changing the future of this disease is enormous. Attention to hurdles discussed in **Figures 3 and 4** and the Milken Institute Report should be considered a high priority for stakeholders in our field, taking advantage of knowledge gained from current successful efforts so that thoughtful coordinated larger-scale approaches can be implemented and interventions provided to all who stand to benefit.

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Table 1. Autoantibody Methods (19)

Methods	Description
Radiobinding assay (RBA)	Radiolabeled antigens detected in antibody-antigen complexes
Electrochemiluminescence (ECL)	Biotin and Sulfo-TAG labeled ligands that emit light when activated
ELISA	Detection of antigen:antibody complexes by enzyme linked reagents
Luciferase immunoprecipitation (LIPS)	Quantitates serum antibodies by measuring luminescence emitted by the reporter enzyme luciferase fused to an antigen of interest.
ADAP (agglutination PCR)	PCR amplification of DNA in DNA-antigen conjugates bound to antibodies to form aggregates

Table 2: Ongoing Screening programs

A: Selected type 1 diabetes screening programs employing screening of relatives for eligibility to participate in clinical studies.								
Program	**Population screened**	**Location**	**Screening sites**	**Number screened**	**Screening material**	**Screening assays**	**Rates of positive screens**	**Comments**
TrialNet: Pathway to Prevention (TN01)	Relatives ages 3-45 years	US, Canada, Europe, Australia	TrialNet Centers and affiliates	>250,000	Serum or capillary sample	RBA: IAA and GADA, followed by IA-2A, ZnT8A and ICA if positive	• AA+: 5% • ≥2 AA+: 2.5%	• Objective is to identify participants eligible for clinical trials. • Monitors nonrelatives identified through other programs
INNODIA	Relatives and general population	Europe	Academic sites	> 4400	Serum	RBA	AA+: 379 • 1AA+: 6.0% • 2AA+: 1.0% • 3AA+ 0.9% • 4AA+ 0.8% • ≥2 AA+: 2.6%	Of AA+ : • IAA: 184 (49.9%) • GADA 242 (65.2%) • IA-2A 81 (21.8%) • ZnT8A (94 (25.1%)
Bart's Oxford – BOX family study	Relatives	UK	Diabetes clinics/at home	6000	Capillary blood since 2015	RBA: IAA, GADA, IA2A, ZnT8A	470 AA+: • 1AA+ 6% • ≥2 AA+ 2%	Family members are recruited at diagnosis of a proband (<21 years old) in the study area.

Type1Screen	Relatives ages 2 to 30 years	Australia and New Zealand	Community collection centers and in-home collection	>700	Capillary or venous blood	IAA: RBA or ADAP; GADA, IA-2A, ZNT8A: ELISA or ADAP	AA+: 34 (5%)
							• 1AA+: 13 (1.9%)
							• ≥2 AA+: 21 (3.9%)
								• Family members recruited by health professionals, emails, and social media.
								• Of AA+:
								  • IAA 3 (9%)
								  • GADA 25 (74%)
								  • IA-2A 18 (53%)
								  • ZNT8A 22 (65%)

US- United States, UK- United Kingdom, AA- islet autoantibody

B: General Population Screening Programs								
Program	**Population screened**	**Location**	**Screening sites**	**Number screened**	**Screening material**	**Screening assays**	**Rates of positive screens**	**Comments**
1) Genetic prescreening with follow- up for AA								
DIPP	Age 0.25-15 yrs with high-risk HLA genotypes	Finland	Three university hospitals	>250,000	Serum	HLA genotyping followed by RBA: IAA, GADA, IA-2A, ZnT8A	• ~10% of screens with high-risk HLA. • ≥2 AA+: • by 2 yrs: 2.2% • by 5 yrs: 3.5% • by 15 yrs: 5.0%	All newborns with parental consent (~25% of birth cohort) receive cord blood HLA screening. ~19,000 at-risk have agreed to follow-up AA screening at 3-12 mo intervals up to age 15 yrs.
BABY-SCREEN	Newborns-1-3 yrs with high-risk HLA for type 1 diabetes and/or celiac disease	Helsinki, Finland	University Hospital	Target for HLA screening: 30,000; >9000 tested	Serum	HLA genotyping followed by RBA: IAA, GADA, IA-2A, ZnT8A, tTGA	By 1 yr: • 1 AA+: 5.3% • ≥2 AA+: 1.8% By 2 yrs • 1 AA+: 6.5% • ≥2 AA+: 3.7%	• HLA screening from cord blood followed by AA screening at age 1, 2 and 3 yrs. • Type 1 diabetes in first degree relative in 3.1%
GPPAD	Infants< 1 months of age	Germany, UK, Poland, Belgium, and Sweden	Around delivery or primary care physician (PCP) visits	>275,000, (1.72% first degree relatives)	Capillary blood spots	47 SNP GRS to ID those with >10% risk of ≥2 AA+ by age 6 yrs.	1.1% with increased genetic risk	• At-risk infants are offered participation in a primary prevention trial.
PLEDGE	Age < 6y	North and South Dakota and Minnesota, US	Integrated Health System Clinics and Labs	Target= 33,000	Capillary Blood Spot for GRS, serum for AA	GRS, RBA	n/a	• GRS with newborn screen or study entry; AA testing at ~ 2, 5y. • Utilizes EHR for tracking/communication.
CASCADE	Age 1+	Northwest US	Newborn Screens and elementary schools	Target= 60,000	Serum	GRS, RBA: GADA, IAA, ZnT8A, tTGA; LIPS for IA2A	n/a	Initial GRS screen, at-risk followed for type 1 diabetes and celiac disease.
PrIMeD	Age 2-16 yrs	Virginia, US	Pediatric clinics	3477	Saliva for GRS, serum for AA	82-SNP GRS, RBA: IAA, GADA, IA-2A, ZnT8A	• 461 (1.3%) with "high" GRS (10x over expected) • AA testing in progress	AA screening offered to those with high GRS, ≥2 AA+ invited to contact TrialNet or obtain local CGM monitoring.

2) Screening for AA								
Fr1da	Age 1.75-10.99 yrs	Bavaria, then Lower Saxony, Hamburg, Saxony, Germany	PCP clinics	>150,000	Capillary blood	ELISA: GADA, IA2A, ZnT8A/ LIPS: IAA; confirm with RBA: IAA, GADA, IA-2A, ZnT8A	≥2 AA+: 0.3%	Positive screens invited for metabolic staging by OGTT. >80% of these with Stage 1.
Fr1dolin	Age 2-6 yrs	Lower Saxony and Hamburg, Germany	PCP clinics	>15,000	Capillary blood	ELISA: GADA, IA-2A, ZnT8A; confirm with RBA: IAA, GADA, IA2A, ZnT8A	≥2 AA+: 0.35%	• Combined screening for type 1 diabetes risk and familial hypercholesterolemia. • Positive screens invited for staging with OGTT
T1Detect(JDRF)	Age 1yr+	Most US states	At home	Up to 2000/mo	Capillary blood spot	ADAP: GADA, IA-2A, IAA	• Nonrelatives: • 1AA+: 12% • ≥2 AA+: 5.4% • Relatives: • 1AA+: 12% • ≥2 AA+: 5.7%	• Direct access to participants through the JDRF website. • Of the first 800 tests, 203 (25.4%) were from the general population.
ASK	Age 1-17yrs	Colorado, US	PCP and hospital specialty clinics, emergency departments	25738	Serum	RBA with ECL confirmation IA-2A, GADA, IAA, ZnT8A and tTGA	• AA+: 3.4% • ≥2 AA+: 0.52% • Single high affinity AA+: 0.58%	• Screening for type 1 diabetes, Celiac Disease, and SARS-CoV-2 Ab • 4.84% with 1st degree relative with type 1 diabetes.
3) Screening programs in development								
T1Early	Preschool age: 3.5-4 yrs	UK	Pre-school vaccination PCP visit	n/a	Capillary blood	LIPS: GADA, IA-2A, ZnT8A	n/a	Positive screens using the LIPS assay will undergo metabolic staging.
ADIR	Age 9-18 months old, 5 yrs	Israel	PCP visit with hemoglobin screening	Target of up to 50,000	Capillary or venous blood	ADAP: GADA, IA-2A, IAA	n/a	Due to start October 2021.
JDRF Australia General Population Screening Pilot	Newborns, infants, and 2-6 yrs	Australia	Maternity hospitals, general population	Target of 3000 in each cohort	Capillary blood and saliva	GRS, ADAP for IAA,GADA, IA-2A and ZNT8A	n/a	Starting in 2022. Will compare GRS approach to cross-sectional AA

								screening in older children.

* AA= islet autoantibodies GRS= genetic risk score; PCP=primary care physician; EHR= electronic health record; JDRF- Juvenile Diabetes Research Foundation

Study acronyms: DIPP- Type 1 Diabetes Prediction and Prevention Study; BABYSCREEN- Newborn Screening for Genetic Susceptibility to Type 1 Diabetes and Celiac Disease and Prospective Follow-up Study; GPPAD- Global Platform for the Prevention of Autoimmune Diabetes; PLEDGE: General Population Level Estimation for Type 1 Diabetes Risk in Children 0-5 Years Old During Routine Care Delivery; CASCADE: Combined Antibody Screening for Celiac and Diabetes Evaluation; PrIMeD: Precision Individualized Medicine in Diabetes Study; Fr1da: Früherkennung Typ-1 Diabetes (Engl.: Early detection of type 1 diabetes); Fr1dolin: Früherkennung Typ-1 Diabetes und Hypercholesterinämie in Niedersachsen) (Engl.: Early detection of type 1 diabetes and hypercholesterolemia in Lower Saxony)

ASK: Autoimmunity Screening for Kids; ADIR: Screening for Islet Autoantibodies in the Israeli Paediatric General Population for Detection of Pre-symptomatic type 1 diabetes

Table 3: Recommendations for practice

1. When asked about screening for type 1 diabetes risk,
    a. Available screening tools: Genetic, autoantibodies, glucose levels, symptoms
    b. The overall risk for development of type 1 diabetes is greater for those with a relative with type 1 diabetes compared to those without relatives because of shared genetic and environmental factors. However, the risk for type 1 diabetes in children who have 2+ autoantibodies is the same whether or not they have an affected relative.
    c. Screening initiatives are available in North America, Europe, Australia and New Zealand (see Table 3).
    d. There are risks and benefits of screening. The former may involve anxiety about the findings but the latter may include reassurance of a negative test, avoidance of DKA at diagnosis, and access to clinical studies and therapies to delay or prevent type 1 diabetes.
2. Information, with the assurance of privacy, testing for antibodies, and ongoing monitoring or enrollment in trials is available (e.g. through the NIH funded research network TrialNet or through the IMI funded research network INNODIA and other programs in Europe).
    a. For relatives: TrialNet, INNODIA and Type1Screen provide free, confidential AA testing and ongoing monitoring for relatives who are AA positive.
    b. For non-relatives: See regional initiatives (Table 3). If testing shows that they have one or more AA, the test should be confirmed. TrialNet/INNODIA/Type1Screen will provide confirmation of positive AA tests conducted outside of a research study. AA positive individuals can be referred to TrialNet/INNODIA/Type1Screen for a confirmation test whether or not they have a relative with diabetes.
3. The optimal time for cross-sectional screening is ages 2 and 5-7yr but screening school age children, particularly at the time of other laboratory tests may be the most practical.
4. Follow up of positive tests is needed to reduce rates of DKA and avoid the unexpected diagnosis of type 1 diabetes. Follow up may include:
    a. Discuss the results and the implications.
    b. Explain signs and symptoms of diabetes.
    c. Standards for metabolic follow up have not been established but may involve HbA1c levels, random glucose levels, OGTTs, or potentially continuous glucose monitoring.
    d. Clinical studies are available through TrialNet and INNODIA.

Table 4: Wilson and Jungor's guidelines for screening as applied to type 1 diabetes

Principle	Application to screening for type 1 diabetes
1. Identify an important health problem	Type 1 diabetes is one of the most common and consequential chronic illnesses of children but also affects individuals of all ages.
2. There should be an accepted treatment for the condition	Teplizumab was shown to delay or delay the diagnosis of individuals at-risk. Other agents are under evaluation.
3. Facilities for diagnosis and treatment are available	Diagnosis and treatment can be done in medical offices.
4. There should be a recognizable latent or early symptomatic period	Stages of progression of type 1 diabetes in those at genetic risk have been defined. High risk individuals (Stage 2) have a 75% risk of diagnosis within 5 yrs.
5. There should be a suitable test or examination	AAs can define risk. Newer technologies to improve prediction are under study. AAs can be measured in many laboratories.
6. The test should be acceptable to the population	
7. The natural history of the condition should be understood	Although many specifics remain uncertain, results from immune therapy trials indicate that type 1 diabetes is due to immune mediated killing of beta cells.
8. There should be an agreed policy on whom to treat as patients	Children and adolescents, during developmental years have the highest unmet need
9. The cost of case-finding should be economically balanced in relation to expenditure on medical care as a whole	The lifetime costs for type 1 diabetes, after onset in childhood are great, even without the additional costs associated with disease related complications.
10. Case finding should be a continuing process	Projects across the globe are piloting strategies .for case identification

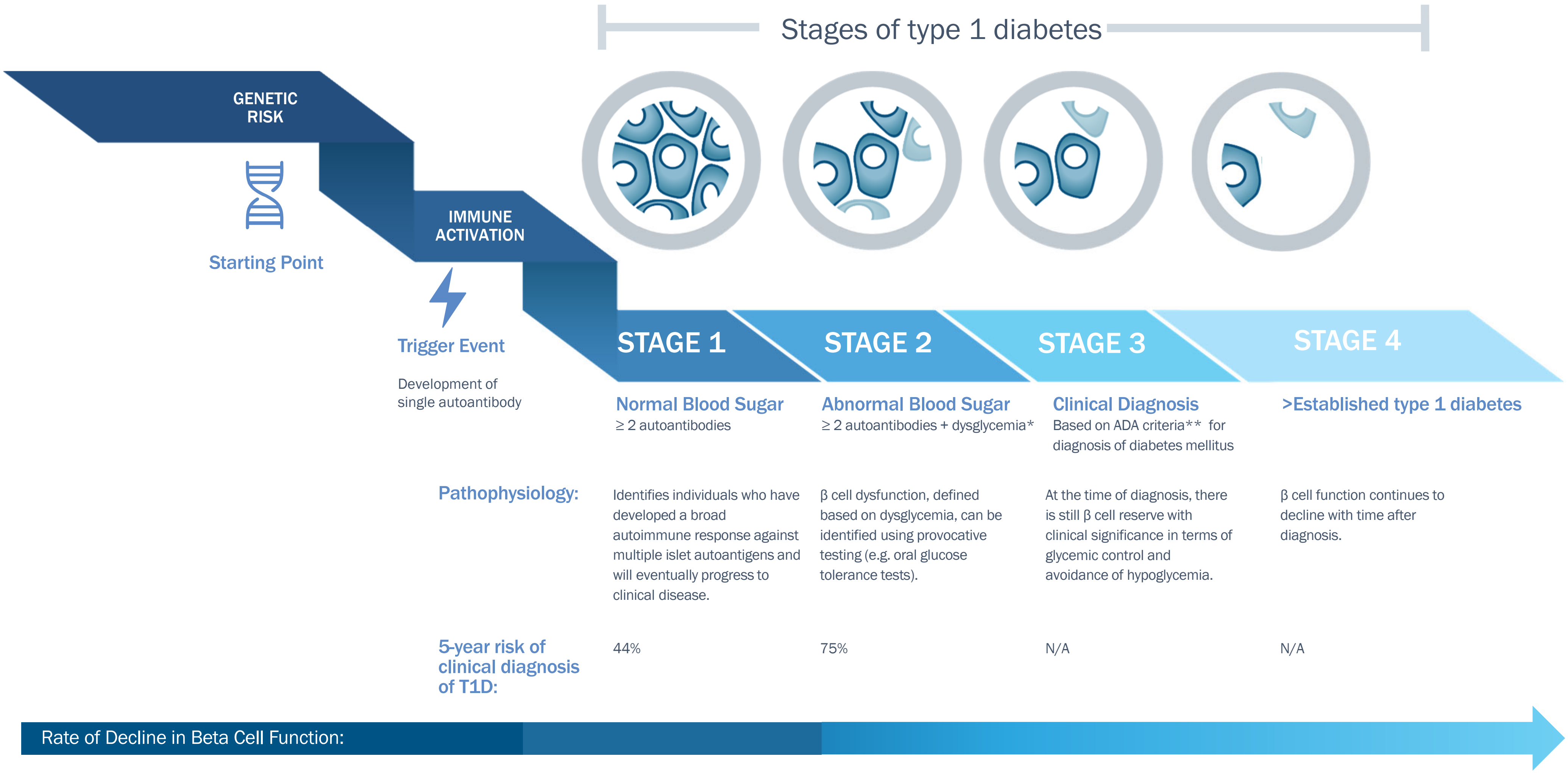
Figure Legends

Figure 1. Definitions of Stages of Type 1 diabetes (26; 63)

Figure 2. Considerations for Approaches to General Population Screening: Combined Genetic/AA-Based Screening Versus an AA-Based Approach.

Figure 3. Logistical needs and uncertainties that remain to be answered for optimal implementation and sustainability of large-scale general population screening for type 1 diabetes.

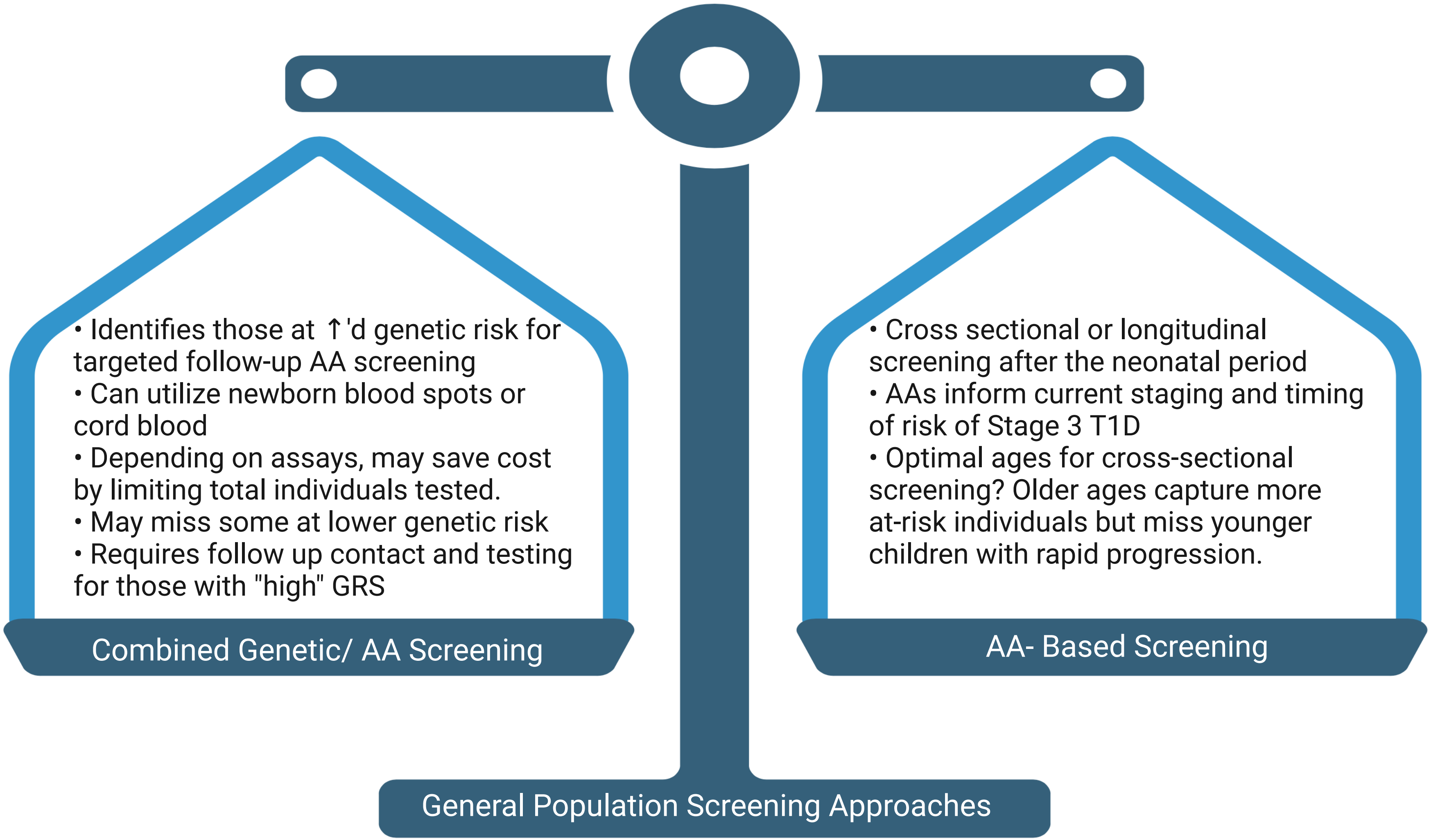
Figure 1



*Dysglycemia defined as fasting glucose level of 110-125 mg/dL, or 2-hour post-prandial plasma glucose of ≥ 140 and < 200 mg/dL, or an intervening glucose value at 30, 60, or 90 minutes > 200 mg/dL during an oral glucose tolerance test (OGTT). A Hemoglobin A1c (HbA1c) of 5.7-6.4% or a 10% increase in HbA1c levels in those with multiple AAs has also been suggested as criteria for Stage 2 (26). However, in general, increased HbA1c levels has variable performance as a predictive marker for type 1 diabetes.

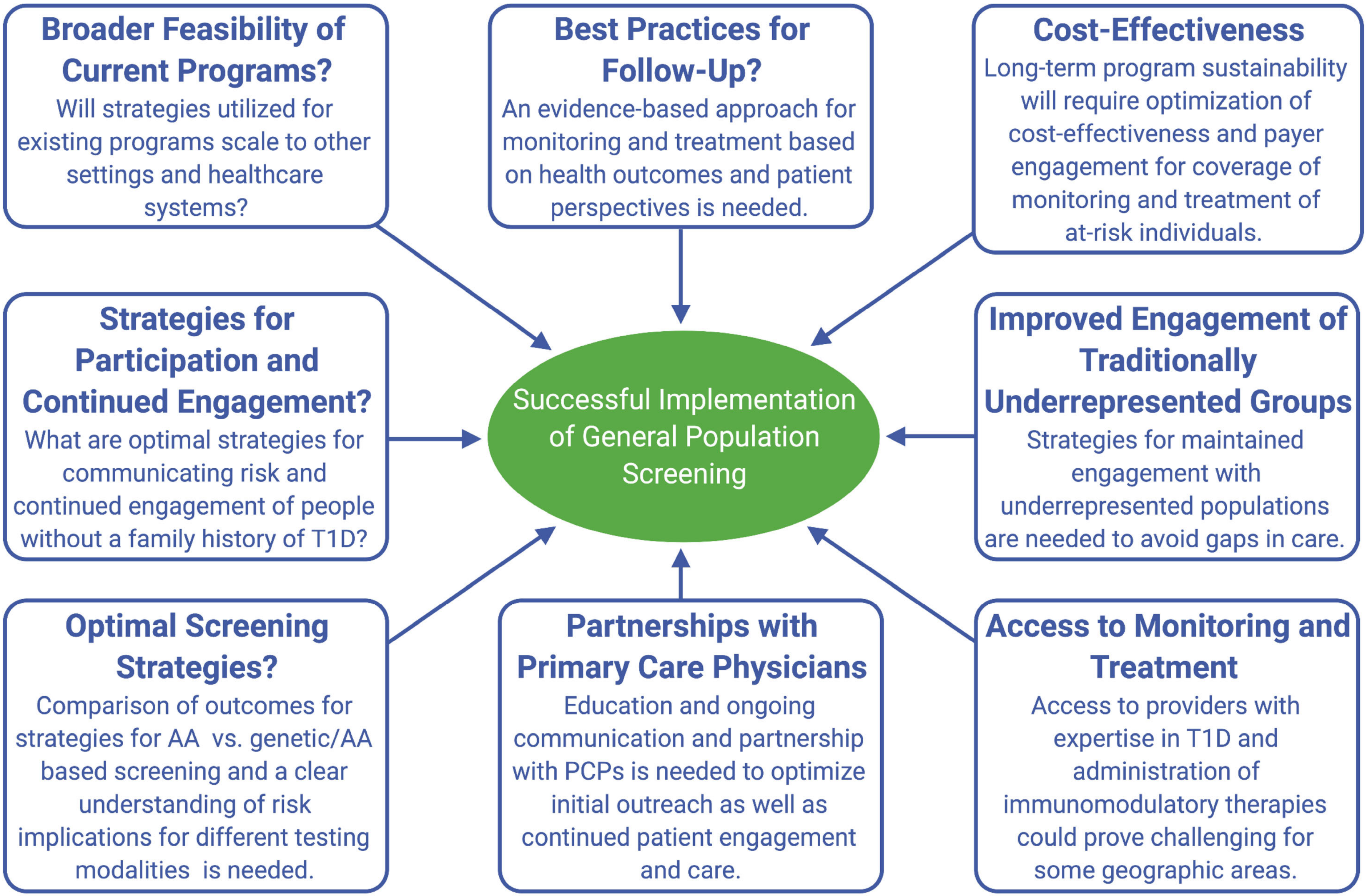
**Because some patients are actually asymptomatic at the time they cross the threshold for glucose-based criteria for T1D, some investigators have proposed 3a and 3b subtypes of Stage 3 based on the presence of clinical symptoms, which may be useful in guiding degree of clinical intervention (i.e. insulin dosing).

Figure 2



• Identifies those at ↑'d genetic risk for targeted follow-up AA screening
• Can utilize newborn blood spots or cord blood
• Depending on assays, may save cost by limiting total individuals tested.
• May miss some at lower genetic risk
• Requires follow up contact and testing for those with "high" GRS
Combined Genetic/ AA Screening
• Cross sectional or longitudinal screening after the neonatal period
• AAs inform current staging and timing of risk of Stage 3 T1D
• Optimal ages for cross-sectional screening? Older ages capture more at-risk individuals but miss younger children with rapid progression.
AA- Based Screening
General Population Screening Approaches

Figure 3


Broader Feasibility of Current Programs?
Will strategies utilized for existing programs scale to other settings and healthcare systems?
Best Practices for Follow-Up?
An evidence-based approach for monitoring and treatment based on health outcomes and patient perspectives is needed.
Cost-Effectiveness
Long-term program sustainability will require optimization of cost-effectiveness and payer engagement for coverage of monitoring and treatment of at-risk individuals.
Strategies for Participation and Continued Engagement?
What are optimal strategies for communicating risk and continued engagement of people without a family history of T1D?
Successful Implementation of General Population Screening
Improved Engagement of Traditionally Underrepresented Groups
Strategies for maintained engagement with underrepresented populations are needed to avoid gaps in care.
Optimal Screening Strategies?
Comparison of outcomes for strategies for AA vs. genetic/AA based screening and a clear understanding of risk implications for different testing modalities is needed.
Partnerships with Primary Care Physicians
Education and ongoing communication and partnership with PCPs is needed to optimize initial outreach as well as continued patient engagement and care.
Access to Monitoring and Treatment
Access to providers with expertise in T1D and administration of immunomodulatory therapies could prove challenging for some geographic areas.

Supplemental Materials

Supplemental Table: Selected completed birth cohorts – relatives and general population now completed or in follow up*							
Program: Location	Population screened	Location	Number screened	Screening material	Screening assays	Rates of positive screens	Comments
BABYDIAB 1989-2000 (1)	Newborn children of those with T1D	Germany	2364	Cord blood then venous blood	ICA and RBA: IAA, GADA, IA-2A, ZnT8A and TTG AA	• AA+: 220(9%) • ≥2 AA+: 123(5%)	• AA screening in cord blood, at 9 months and 2, 5, and 8 years • From 3 yrs, yearly oral glucose tolerance test monitoring if AA+
DAISY 1993-2004	Newborn general population (GP) and relatives <4 yrs	Colorado, US	Newborns : 32,114	Cord blood for HLA and serum for AA	• RBA and ECL: IAA, GADA, IA-2A, ZnT8A, tTGA	• 1,424 GP newborns and 1,123 relatives identified and followed • AA+: 8% • ≥2 AA+: 5%	• Genetically at-risk newborns based on HLA genotyping and relatives followed at 9, 15, 24 months and annually thereafter until age 20 y • AA+ followed q3-6 mo until 30 y
DEW-IT (2) 1995-2001 2010-2012	GP newborn blood spots	Washington, US	42000 blood spots tested (3)	Dried new born screening blood spots, then serum for AA	HLA genotyping; RBA: IAA, GADA, IA-2A, and later, ZnT8A	• 14.2% of children eligible for AA surveillance(3) • 3748 followed over time (3) • AA+: 173 (5%) • ≥2 AA+: 170 (5%)	Cover letter and consent form mailed to Washington families. Consenting families received HLA genotyping of dried newborn blood spots followed by AA monitoring of at-risk individuals.
DiPiS (4) 2000-2004	GP newborns	Sweden	35688	Cord blood for HLA, blood spots for GADA and IA2A, serum for IAA and ZnT8	HLA genotyping; RBA: IAA, GADA, IA-2A, ZnT8A	• 7826 positive screens(3) • 4359 followed over time •AA+: 184 (4%) •≥2 AA +: 100 (2%)	• Children identified for surveillance based on risk score that include HLA genotype and environmental, demographic, and historical risk factors. • Positive screens with yearly follow up. Those with ≥2 AA+ followed every 3 months.
TEDDY (5) 2004-2010	Newborns in both relatives and GP	Clinical centers in US Finland, Germany, Sweden	424,788	Capillary blood spots	HLA genotyping; RBA: IAA, GADA, IA-2A, tTGA	21589 (0.05%) of screens with high-risk HLA; 8676 parents consented to follow up.	• High-risk newborns followed every 3-6 months for 15 yrs for AAs and T1D, with documentation of potential environmental contributors. • 90% without a known relative with T1D

Recent follow up data obtained from recent published references (3; 5) and personal communications (M Rewers)

GP=general population; AA- autoantibody; Study Acronyms: DAISY: Diabetes Autoimmunity Study in the Young; DEWIT: Diabetes Evaluation in Washington Study; DiPiS: Diabetes Prediction in Skane; TEDDY: The Environmental Determinants of Diabetes in Youth

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