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Type 1 Diabetes Autoantibody Screening: A Roadmap for Pediatric Policy Implementation

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The Milken Institute Center for Strategic Philanthropy advises philanthropists and foundations seeking to develop and implement transformative giving strategies.

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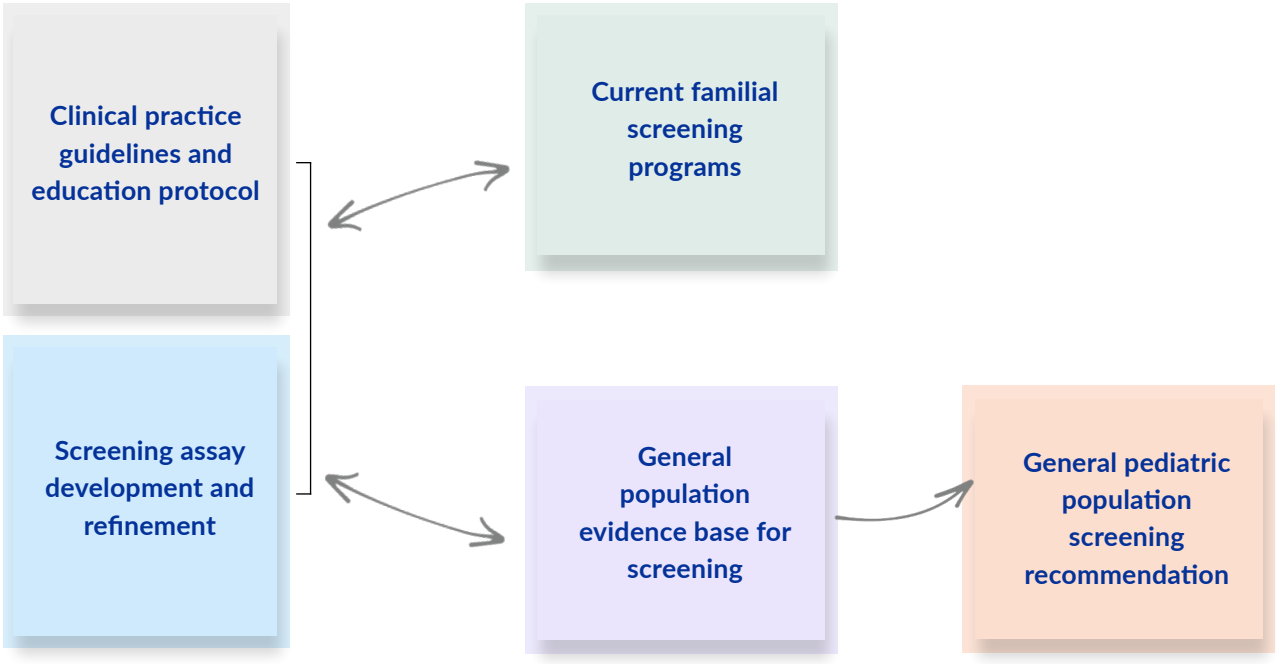
EXECUTIVE SUMMARY

The type 1 diabetes (T1D) community has identified a need to implement autoantibody screening in the general population. To ensure the entire community of T1D stakeholders is working toward this shared objective, the Milken Institute Center for Strategic Philanthropy (CSP) developed an implementation roadmap that outlines a comprehensive framework to balance short- and long-term gains. This framework leverages existing community assets, such as established screening programs, to develop tools and clinical practice guidelines rapidly while stakeholders work to identify the key studies necessary to show the benefits of T1D screening within the US general population. Data generated from these studies can ultimately be used to establish policies for T1D screening in the general pediatric population. Although this roadmap focuses on pediatric screening, many of the learnings and recommendations also apply to adult screening.

FIGURE 1: FRAMEWORK FOR IMPLEMENTING TYPE 1 DIABETES GENERAL PEDIATRIC POPULATION AUTOANTIBODY SCREENING



Source: Milken Institute (2021)

CSP has identified four primary goals and two supporting goals, each with a series of action items. Together, these goals serve as a roadmap to achieve general population screening.

The table below summarizes the essential goals and specific action items for achieving general population screening of T1D autoantibodies in children. While the completion of the action items and achievement of the goals can each influence the field, the goals are not listed in any particular order. Each goal stands on its own and can be undertaken at any point.

TABLE 1: ESSENTIAL GOALS AND SPECIFIC ACTIONS FOR ACHIEVING T1D AUTOANTIBODY SCREENING IN THE GENERAL PEDIATRIC POPULATION

GOAL	ACTION ITEM
Goal 1: Develop and refine ambulatory clinical practice guidelines	1. Initiate quality improvement (QI) for T1D autoantibody screening 2. Strengthen the relationship between clinical communities and groups that issue guidelines 3. Model, develop, and field test clinical practice guidelines
Goal 2: Promote the continued development, validation, and regulatory authorization of screening assays used for ambulatory care	4. Evaluate quality assurance parameters for autoantibody screening assays 5. Initiate key stakeholder assay coalition to prioritize features of diagnostic and screening assays 6. Support development of assay technologies 7. Support refinement of assays through current screening studies
Goal 3: Build the evidence base for general population autoantibody screening design	8. Design and implement a large-scale general population cohort screening study model 9. Coordinate partnerships and develop improved infrastructure for randomized controlled trials (RCTs) for therapeutics
Goal 4: Support efforts to expand the prevention-therapeutic pipeline	10. Support development and refinement of disease-modifying therapeutics for T1D
Supporting Goal 1: Increase clinician knowledge and awareness of T1D screening and care strategies	11. Develop an ongoing T1D clinician awareness campaign 12. Pilot infrastructure to support clinician awareness of screening opportunities 13. Coordinate partnerships between clinician groups and current screening programs
Supporting Goal 2: Improve public knowledge of T1D and develop tools to convey risk accurately	14. Develop consensus on T1D public messaging 15. Implement a comprehensive communication strategy for screening 16. Develop and implement T1D education materials

Source: Milken Institute (2021)

OVERVIEW

Type 1 diabetes (T1D), which used to be commonly known as juvenile diabetes, is an autoimmune disease with a pre-symptomatic stage of variable length. A large proportion of cases onset in childhood, adolescence, and young adulthood, but the disease can develop at any age (Thomas et al. 2018). Symptoms at the clinical onset of the disease in children can resemble other common childhood ailments, such as stomach viruses or urinary tract infections. Prolonged time before a diagnosis can result in people experiencing diabetic ketoacidosis (DKA), a dangerous and sometimes fatal condition. Even when DKA at diagnosis does not lead to death, researchers and clinicians now understand that it is associated with long-term harm for patients (Duca et al. 2017). Screening for T1D autoantibodies, islet cell (ICA), insulin (IAA), glutamic acid decarboxylase (GADA), islet tyrosine phosphatase 2 (IA-2A), and zinc transporter 8 (ZnT8) can offer information on risk for future progression to clinical symptoms and prevent DKA at diagnosis. The presence of two or more T1D autoantibodies indicates a very high likelihood of progression to clinical disease. Eighty-five percent of people who develop T1D have no relatives with the disease. Therefore, to identify the majority of people at risk before clinical disease onset, screening cannot be limited to family members (Tuomilehto 2013).

Screening the general population for T1D autoantibodies has multiple benefits. It can identify people most at risk for progressing to clinical T1D. It can also provide an opportunity to educate and prepare families for disease symptoms and treatment, resulting in a reduction of DKA presentation at diagnosis. Furthermore, therapeutic interventions under clinical development could significantly delay the onset of T1D, further substantiating the potential future benefit of T1D screening in the general population. However, at present, no national policies or recommendations support general population screening for T1D in either adults or children. A national policy or recommendation for autoantibody screening for T1D would enable extensive screening in the general population.

The Need for a Roadmap

Progressive diseases such as T1D can develop undetected, causing symptoms only once the underlying biology has irreversibly changed. The nature of this type of disease trajectory necessitates preventive health screening of asymptomatic individuals. The organizations that vet preventive health policy recommendations for the general population are reluctant to recommend screening for a condition when there is no cure or prevention therapy to offer. These groups also require a large body of evidence showing long-term health outcomes as a result of screening to be included in the review of a topic to make a recommendation. In addition, the considerations required to make a recommendation for pediatric preventive care add additional complexity to the topic.

This roadmap was developed with substantial input from a variety of stakeholder groups across the T1D research, clinical, and nonprofit community, as well as relevant decision makers in preventive health policy. We have identified four goals and two supporting goals with a total of 16 action items that will aid the entirety of the T1D community as it works toward the objective of general population autoantibody screening.

Building the Roadmap

The Milken Institute Center for Strategic Philanthropy (CSP) performed an analysis of the landscape of pediatric preventive health-care policy in the US and the state of autoantibody screening for T1D. We performed a literature review and conducted interviews with 48 key opinion leaders—including researchers, payers, clinicians, industry representatives, and representatives from policy and patient advocacy organizations—to inform scientific and health policy landscape analyses. As the first of many community engagement points, these analyses were shared for feedback and used to develop two discussion sessions held in May 2020. Participants discussed how available methods and programs for T1D autoantibody screening could support general population screening.

As a result of the discussion sessions, CSP identified potential paths, each with unique barriers and differing timelines, to achieving general population screening. Importantly, the discussions helped identify the outstanding questions to be addressed to determine how to achieve general population screening most efficiently. Roadmap frameworks were predicated on the finding that a general pediatric population screening recommendation from a specialist society or national policy organization requires rigorous, published, general population screening study data showing efficacy, as well as long-term benefits and harms.

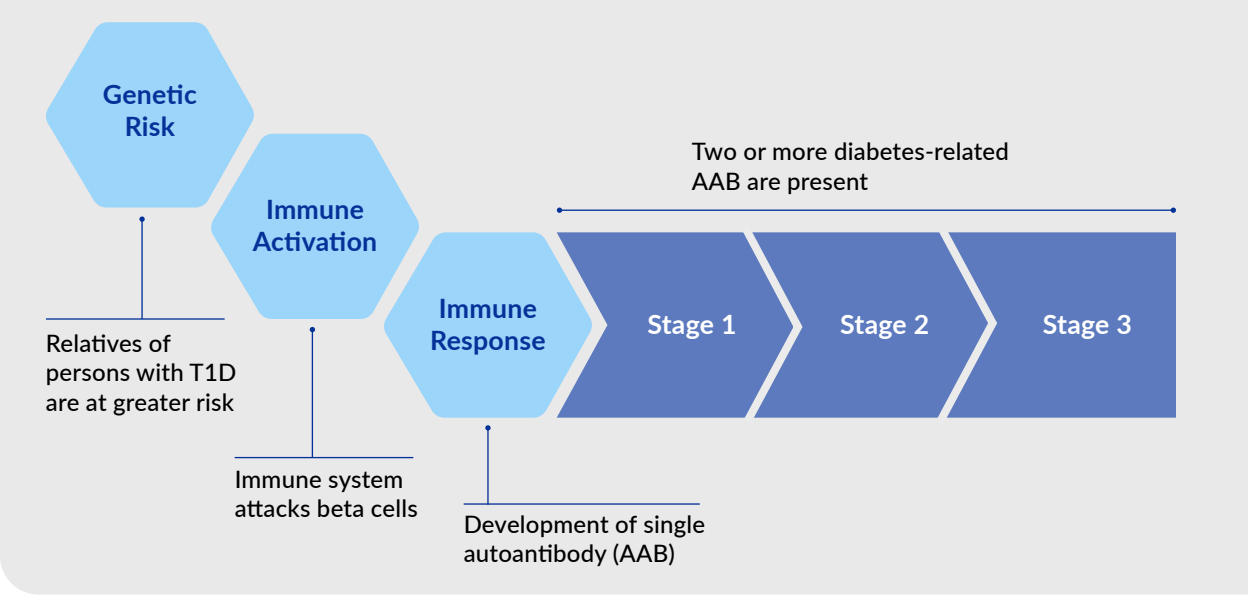
To identify achievable avenues for clinical research and technology development to support policy implementation in the context of T1D autoantibody screening, we brought together the larger T1D community for a three-part webinar and meeting series. Registrants completed a survey whose results served to focus webinar discussions on barriers the field considers to be most challenging. These moderated discussions provided the basis for the unified framework, detailed in this document, that illustrates that expanded familial screening serves an important function and should continue in tandem with activities focused on immediate evidence building for general population T1D autoantibody screening. The identified goals and action items were shared with the community, and its feedback was used to optimize the unified framework for this policy implementation roadmap for T1D general population autoantibody screening.

T1D AUTOANTIBODY SCREENING LANDSCAPE

T1D Background

T1D is an autoimmune disease with a pre-symptomatic stage of variable length. During the pre-symptomatic stage, the person's immune system attacks their pancreatic islet beta cells. Specific proteins in the blood produced by the body in response to its own tissues can be detected in the blood before any symptoms of T1D appear and are a well-established biomarker of early disease. Screening for T1D autoantibodies can identify people most at risk for progressing to clinical T1D and can provide an opportunity to educate and prepare people and their families for disease symptoms and treatment. Known HLA haplotypes confer high genetic risk for the development of T1D, and their presence can be included in determining genetic risk scores for T1D. Evaluating genetic risk scores can be an initial step in identifying people who will develop autoantibodies and, eventually, clinical T1D.

FIGURE 2: STAGES OF TYPE 1 DIABETES



Source: Adapted from TrialNet, https://www.trialnet.org/t1d-facts (2021)

Screening Health Benefits and Harms

Disease prevention screening recommendations and protocols are largely based on the available knowledge of the screening's harms and benefits. As that knowledge base grows and evolves, changes to current screening recommendations and protocols are possible. The current identified benefits and harms of T1D autoantibody screening are outlined below.

DKA Prevention

Autoantibody screening can identify individuals in the early stages of the disease who have a high risk of developing clinical T1D and can provide the opportunity to offer education on the signs and symptoms of diabetes to prevent DKA. A study indicated that children and their families who received close monitoring and education on the symptoms of diabetes and DKA after screening had a reduced likelihood of experiencing DKA upon symptom onset (Elding Larsson et al. 2011). Preventing DKA can yield better long-term health outcomes for people with diabetes. In addition to severe acute illness, DKA at diagnosis is associated with poor long-term glycemic control (measured by HbA1c), resulting in an increased risk for retinopathy, nephropathy, and severe hypoglycemia. HbA1c levels are a key predictor of complications following diagnosis. Specifically, individuals who are diagnosed with T1D in DKA show chronically increased HbA1c (Duca et al. 2017), while interventions focused on reducing HbA1c lead to a significantly decreased risk of retinopathy progression (Group 1995). Researchers believe that DKA at diagnosis is associated with lower residual beta-cell function due to prolonged autoimmune destruction and further depletion of functional pancreatic islets. Lower residual beta-cell function may result in a shorter remission, or "honeymoon" phase, for newly diagnosed T1D patients and a higher risk of developing vascular complications and severe hypoglycemia (Fredheim et al. 2013).

Reduction of DKA requires screening as well as monitoring and education, and for clinical impact, all pieces must be put into place. Individuals who screen positive for two or more T1D autoantibodies and do not receive follow-up education and monitoring visits are likely to remain at the same risk for DKA as those who have not been screened and provided follow-up education and monitoring.

Quality of Life

Monitoring of high-risk individuals has shown an improvement in quality of life after T1D diagnosis. Data from The Environmental Determinants of Diabetes in the Young (TEDDY) Study showed that children with genetic risk for T1D that are enrolled in research monitoring have an improved quality of life, and their parents experience lower stress post-diagnosis compared to children diagnosed without research monitoring (Smith et al. 2018). Further, study participants were prescribed less-intensive diabetes regimens in the time immediately after diagnosis. Early diabetes management is easier for families that participate in screening research studies because children have less severe metabolic decompensation at diagnosis, higher levels of endogenous insulin, better glycemic control, and fewer daily injections. These benefits result in lower parental stress levels (as measured by the State Anxiety Inventory) and better quality of life overall (Smith et al. 2018).

Psychological Stress and Anxiety

A positive islet autoantibody result could lead to additional testing for confirmation and raise concern about disease development, which might require follow-up counseling for the individual and their family. Studies show that parents display a higher anxiety level in response to learning of their child's increased genetic risk as well as when children test positive for one or more T1D

autoantibodies. Anxiety dissipates over time (for general population parents, it can revert back to the same level as for parents of children with no genetic risk factors) when children with increased genetic risk receive repeated negative autoantibody results (Johnson et al. 2017). The unpredictable, uncontrollable, and uncertain nature of the increased genetic risk causes the high anxiety for these parents. Some experts have noted a potential ethical concern surrounding the potential harms of screening because no method for disease prevention or cure exists; however, new therapies in the pipeline and undergoing the US Food and Drug Administration (FDA) approval process may negate this concern. Conversely, other experts have cited the potential for DKA reduction as an ethical reason to screen for autoantibodies.

Clinical Trials and Disease Course Research

More at-risk people need to be identified to participate in clinical trials to support the development of prevention therapies. The current screening of relatives of people with T1D has not yielded enough potential clinical trial participants because of insufficient knowledge of both increased risk in families and the availability of research studies. Because only 5-10 percent of people diagnosed with T1D have a relative with the disease (Tuomilehto 2013), general population screening would help identify a larger pool of participants. However, current general population screening studies are regional and thus not accessible to most US residents. Therefore, most people with T1D are not identified before clinical symptom onset and diagnosis, the window in which preventive therapies could be effective. Endocrinologists see the need for increased screening and suggest that a step-wise targeted screening approach would enrich the population of known autoantibody-positive individuals while the evidence base for a general population screening recommendation is built. In this approach, in addition to relatives, patients with other autoimmune diseases, such as celiac and autoimmune thyroid disease, and their family members, who all have an increased risk for T1D, could be screened for T1D.

In addition to identifying potential clinical trial participants, autoantibody screening can identify individuals with autoantibody profiles linked to faster and/or higher rates of progression to T1D (Achenbach et al. 2004; Giannopoulou et al. 2015). Identification of these individuals can enrich prevention clinical trial participant populations with those most likely to progress to clinical T1D. Enriched participant populations will facilitate prevention study design and execution.

Much remains unknown about the mechanistic link between the specific screened autoantibodies and the clinical onset of T1D. A study population enriched with autoantibody-positive individuals would enable additional research on the heterogeneity of disease progression and diagnosis after seroconversion. Additional research on identifying and understanding environmental factors that impact seroconversion and clinical symptom onset is also needed to inform the field.

Current Screening Assay Technologies

Autoantibodies are immune proteins produced by the body in response to its own tissue. In T1D, autoantibodies are produced in response to beta cell antigens. Currently, four methods are commonly used for autoantibody screening by commercial testing labs and in research studies, each with distinct characteristics.

TABLE 2: PRIMARY CURRENT SCREENING ASSAY TECHNOLOGIES

SCREENING ASSAY	AUTOANTIBODIES DETECTED	USED BY	EASE OF USE
Radio-binding Assay (RBA)	IAA, GADA, IA-2A, ZnT8A	All major screening/testing networks (i.e., TrialNet)	Moderately difficult
Enzyme-linked Immunosorbent Assay (ELISA)	ICA, GADA, IA-2A, ZnT8A	Commercial testing labs	Easy
Electrochemiluminescence-based (ECL)	IAA, GADA, IA-2A, ZnT8A	Research studies	Moderately difficult
Antibody Detection by Agglutination-PCR (ADAP)	IAA, GAD, IA-2A	Research studies	Easy

Source: Milken Institute (2021)

Radio-binding assays (RBA) are currently the gold standard for all four primary islet autoantibodies: IAA, GADA, IA-2A, and ZnT8A. Major screening and testing networks such as Type 1 Diabetes TrialNet (TrialNet), a T1D clinical research network, use these assays, but the process is moderately labor-intensive and technically challenging.

Enzyme-linked immunosorbent assays (ELISA) are used in commercial labs to detect ICA, GADA, IA-2A, and ZnT8A; however, the IAA tests are less sensitive. The sensitivity and specificity seen in known T1D samples are similar to RBA. The tests are relatively quick (approximately two hours) and inexpensive, can be automated for high throughput, and can be used in a multiplex format. An ELISA-based test has been used to perform first-line screening in general population studies where the goal is to identify only children positive for multiple T1D autoantibodies. In these studies, positive results are confirmed via RBA (Kick et al. 2019).

Electrochemiluminescence-based (ECL) assays may have higher sensitivity and higher specificity than RBA or ELISA. One multiplex ECL assay is being developed so that four T1D autoantibodies can be screened simultaneously in a single well. This multiplex format also allows for the inclusion of antibodies associated with other autoimmune diseases, such as celiac and autoimmune thyroid disease. In addition to being a complex, two-day assay, it also requires equipment that is not widely available (Gu et al. 2019).

Another technology in use is the antibody detection by agglutination (ADAP) assay. A multiplex assay using this technology can be performed on dried blood spot samples and has shown high sensitivity when tested on known T1D samples (Cortez et al. 2020). Multiple other assays and technology platforms, such as luciferase immunoprecipitation system (LIPS), are in use and development.

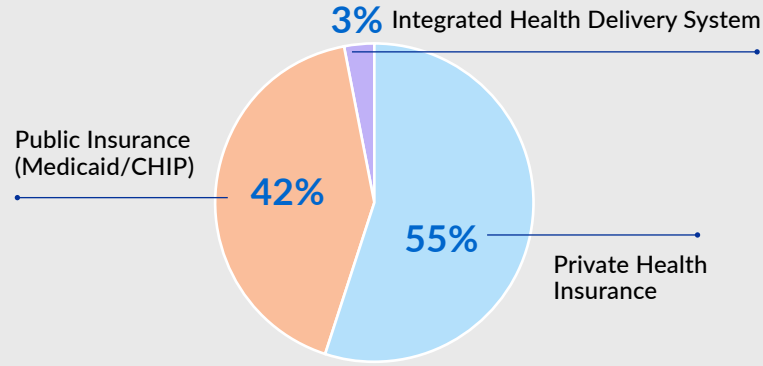
Summary

Screening for T1D autoantibodies provides individuals with important information regarding their risk for developing clinical type 1 diabetes. Currently, there isn't a recommendation for general population screening for T1D autoantibodies. Recommendations for screening are from specialist societies and are limited to individuals with relatives with T1D. Screening is currently available for individuals with relatives with T1D and the general population in small regional research studies in the US. Currently available assays, used in clinical and research settings, all have benefits and technical challenges and will need enhancements to be appropriate for wide-scale general pediatric population screening.

PEDIATRIC US HEALTH CARE POLICY LANDSCAPE

Pediatric preventive care services are typically administered in ambulatory care settings, such as pediatrician offices. These services include well-child visits, immunizations, surveillance screenings, testing, and anticipatory guidance. Children in the US have access to health care via three main channels: government-sponsored programs such as Medicaid, private insurance coverage, and integrated health-care delivery systems.

FIGURE 3: PROPORTION OF US PEDIATRIC POPULATION COVERED BY DIFFERENT INSURANCE TYPES



Source: Centers for Disease Control and Prevention National Center for Health Statistics, https://www.cdc.gov/nchs/fastats/health-insurance.htm (2021)

Pediatric health policy and clinical care guidelines are primarily informed by recommendations and guidelines published by the US Preventive Services Task Force (USPSTF) and the American Academy of Pediatrics (AAP). These recommendations and guidelines are used to guide well-child visits and ensure that all children receive screening and preventive care services. Both organizations specify that these recommendations are for care typically provided by primary care providers to promote health and prevent future disease.

United States Preventive Services Task Force

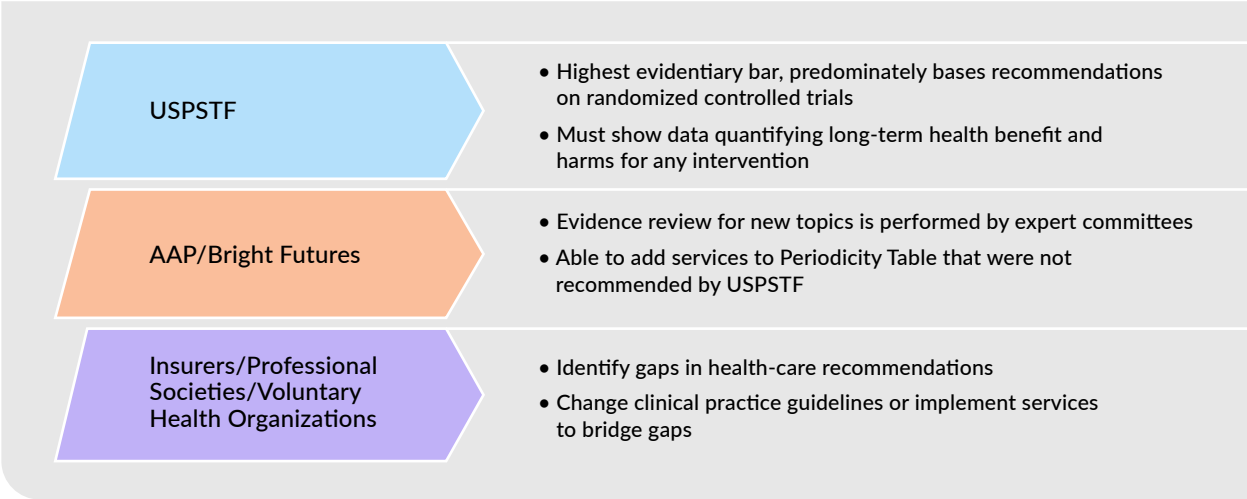
The USPSTF is an independent, volunteer panel of medical professionals with expertise in evidence-based medicine and prevention services. Its goal is to provide evidence-based recommendations for clinical preventive care services for both children and adults. Included in the Affordable Care Act (ACA) list of covered services, these recommendations are adopted by public health-care systems such as Medicaid, which ensures their broad implementation within the United States ("Procedure Manual | United States Preventive Services Taskforce" n.d.). The organization uses an analytic framework to review up to two new topics every year in addition to reviewing a rotating sample of topics from its 90-topic portfolio. The recommendations are designated as screening, counseling, or preventive medicine and are applicable for adults, seniors, or pediatrics. A recommendation may fall into more than one category.

American Academy of Pediatrics

The AAP consists of pediatricians and pediatric medical and surgical subspecialists and is committed to the optimal physical, mental, and social health and well-being of all infants, children, adolescents, and young adults.

The AAP leads Bright Futures, a national health promotion and prevention initiative funded by the US Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau. *The Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents, 4th Edition* is published by the AAP and represents theory-based, evidence-driven guidance for well-child visits, including preventive care screening recommendations.

FIGURE 4: ORGANIZATIONS THAT CREATE AND CHANGE PEDIATRIC HEALTH POLICY RECOMMENDATIONS



Source: Milken Institute (2021)

Making Changes to Health Policy and Clinical Recommendations

Public and private insurers look to the USPSTF and AAP to provide evidence-based recommendations for pediatric preventive care. Both organizations have a thorough and stringent process for reviewing preventive care and screening topics. To be reviewed by the USPSTF and AAP, topics must have high-quality, evidence-based data available that show long-term positive health outcomes for children. Insurers, including integrated health delivery systems, and professional societies play an important role in policy change as they identify gaps in current recommendations and develop new field- or program-specific guidelines. These initial changes in policy lead to changes in clinical practice, which will then yield additional evidence that can be assessed by organizations such as the USPSTF and AAP to affect even greater change in clinical practice.

United States Preventive Services Task Force Policy Review

The USPSTF reviews preventive health science to determine what preventive medical care is appropriate for healthy individuals. Every year the USPSTF reviews up to two new topics in addition to current recommendations already scheduled for re-review. Any individual or group can recommend a topic for review. Topics are prioritized based on

relevance to preventive primary care, the importance for public health, the potential impact of the recommendation, and the availability of new evidence that may change a current recommendation. The USPSTF and researchers from a designated Evidence-based Practice Center, which are institutions designated to review scientific literature and develop evidence reports, use the final plan to gather, review, and analyze evidence on the topic that is published in peer-reviewed journals. The USPSTF members then weigh the potential benefits and harms of the proposed intervention and draft a recommendation that is posted on the USPSTF website for public review and comment. During the public comment period, the draft evidence report undergoes external peer review by five content experts. The report is then finalized and published on the USPSTF website.

The USPSTF sets a high evidentiary bar and prefers to use studies published as a result of randomized controlled trials for its review. Key questions posed for evidence review include:

- Does direct evidence show that providing the service improves health outcomes if implemented in a general primary care setting?
- Can an at-risk population and/or an increased risk population be identified?
- Are accurate (i.e., sensitive and specific) screening tests available?
- Does screening reliably lead to preclinical or earlier detection of disease?
- Does treatment of screening-detected disease lead to improvement in health outcomes, specifically mortality or morbidity?
- What harms are associated with the screening process, including risk identification, screening test, confirmatory diagnosis, and treatment?

Recommendations are given one of five grades: A, B, C, D, or I. Both A and B grades indicate that the USPSTF recommends providing this service to all patients, grade C recommendations should be offered to select patients, grade D recommendations should not be offered to patients, and grade I recommendations require further evidence on harms and benefits of the service ("Procedure Manual | United States Preventive Services Taskforce" n.d.).

TABLE 3: USPSTF RECOMMENDATION GRADES

GRADE	DEFINITION	SUGGESTIONS FOR PRACTICE
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I	The USPSTF concludes that the current evidence is insufficient to assess the balance of the service's benefits and harms. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Source: US Preventive Services Task Force, https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes (2020)

The National Institutes of Health (NIH) Office of Disease Prevention receives supplemental funding to support additional research to build an evidence base for topics graded I. If new evidence for a previously graded topic I emerges, the Task Force will prioritize its re-review. Under the ACA, recommendations that are graded A or B must be covered by all public and private insurers and will thus be available to nearly all individuals in the US.

AAP Policy Review

The AAP publishes a variety of policy documents affirming a position or offering specific guidance. Policy Statements advocate, direct, or detail a public health position of concern to the AAP. Technical Reports are developed based on a review of the literature and data analyses. Clinical Reports guide pediatric health-care professionals in the clinical setting by addressing best practices and state-of-the-art medicine. Clinical Practice Guidelines are based on a comprehensive literature review and data analyses with formal rules of evidence in support of each recommendation made.

Policy inclusion in any of these publications is evaluated and reviewed in the same manner and can take two to five years. First, experts in AAP committees and sections suggest new pediatric preventive care policies. Second, academics in subspecialty groups review and grade

the evidence for the policy using a national rubric. Third, the AAP board of directors reviews the evidence and decides whether to approve or reject it. Approved policies are published in *Pediatrics* and, if applicable, added to the Bright Futures Periodicity Schedule.

The highest level of evidence supports the Periodicity Schedule recommendations. The *Bright Futures Guidelines*, *4th Edition*, provides practitioners with guidance for implementing the recommendations and describes other beneficial preventive care services that lack the same degree of evidence. It also acknowledges that lack of evidence does not mean lack of effectiveness and emphasizes that, sometimes, provision of interventions must continue in the best interests of children's health while the evidence base is improved. The Periodicity Schedule is reviewed annually.

AAP policy and clinical practice guidelines are reviewed by, but not required to be adopted by, private or public insurance (Children's Health Insurance Program) at the state level. States may choose to meet ACA guidelines by developing their own version of the Periodicity Schedule. However, most choose to use the Bright Futures Periodicity Schedule. Therefore, AAP-recommended preventive services become available to the majority of pediatric patients.

Specialist Professional Societies/Voluntary Health Organizations

Professional societies and voluntary health organizations also play a unique role in policy adoption and change. Because it can take a long time to generate and collect enough data to meet the high evidentiary standards of the USPSTF and AAP, professional societies have an opportunity to shape the field. They are typically more aware of current research in specialty topics and can better include data from large cohort studies to assess evidence for specialty clinical practice guidelines. Further, they can often make and update clinical practice guidelines ahead of significant landscape changes from the USPSTF and AAP that depend on necessary general population studies.

Several groups issue guidelines for T1D. The American Diabetes Association (ADA) publishes Standards for Clinical Care Guidelines annually, which insurers consider in their coverage directions. The International Society for Pediatric and Adolescent Diabetics (ISPAD) publishes guidelines similar to the ADA every four years. Generally, researchers and clinicians believe that ISPAD guidelines are more progressive with respect to emerging research, goals for care, and treatment focused on pediatrics. The Pediatric Endocrine Society (PES) does not publish a guidance document but does sponsor the ISPAD guidelines, and many endocrinologists who serve on the committees are members of both societies.

Insurers

For pediatric services, in particular, individual insurers have varying requirements. ACA marketplace insurance plans are required to cover essential pediatric preventive care services outlined in the Periodicity Schedule. Medicaid plans are required to provide Early Periodic Screening, Diagnosis, and Treatment services and follow a nationally recognized pediatric periodicity schedule ("Early Periodic Screening, Diagnosis, and Treatment" 2016). Public and private insurers have the option

to add and cover additional services. Integrated health-care delivery systems look to guidance documents such as those from AAP to inform coverage/treatment decisions, but they also can implement services to bridge gaps in the current guidance and collect data to inform future decisions. This practice has the potential to lead to widespread adoption and a movement to change policy on a topic.

Regulatory Considerations

If a new policy requires implementing a screening tool, regulatory considerations will enable the use of that tool for screening. Depending on how they are distributed, lab tests used as screening tools may be considered medical devices and regulated by FDA's Center for Devices and Radiological Health (CDRH), or they may be considered laboratory-developed tests and regulated by the Clinical Laboratory Improvement Association (CLIA) program. In its review, CDRH considers whether the test usage guidelines are based on data and strongly recommends that assay standardization be achievable with a reference method. CDRH also carefully considers the positive/negative predictive values being set for the test to ensure that false negatives are minimized and that all positives are retested for confirmation.

TABLE 4: PEDIATRIC PREVENTIVE CARE AND DIABETES CARE POLICY DOCUMENTS

Policy Document	How Often Is It Published/ Reviewed?	Impact on Policy Guidelines	Stringency Level	How Are New Topics Proposed?
USPSTF Recommendation	1-2 new topics reviewed each year	Highest	Highest	Anyone
Bright Futures Periodicity Table	Annually	Highest	High	AAP committees
AAP Clinical Practice Guidelines	As needed	High	High	AAP committees
ADA Standards for Clinical Care	Annually	Moderate	Moderate	ADA committees
ISPAD Clinical Practice Guidelines	Every 4 years	Moderate	Moderate	Society members

Source: Milken Institute (2021)

Summary

Because pediatric preventive care policy targets the general population, any potential changes in standard practice are reviewed and assessed with great care and attention.

Policy changes have the potential to affect pediatric care, population-level health outcomes, and payer reimbursement obligations and, therefore, require a high level of evidence and data showing long-term health benefits. The USPSTF and AAP use rubrics and an analytic framework to methodically review the evidence available on a topic before inclusion into the pediatric care setting. In some cases, specialist clinical societies will develop clinical practice guidelines before the USPSTF or AAP. This agility is generally attributed to proximity to the scientific studies, which enables clinical specialists to identify the potential need to adopt a preventive service, as scientific evidence for the service accumulates. Finally, regulatory requirements for screening assays should be considered as the evidence base is built so that the assays are ready for widespread use upon implementation of clinical practice guidelines.

CURRENT T1D SCREENING RECOMMENDATIONS IN THE UNITED STATES

United States Preventive Services Task Force and American Academy of Pediatrics

The USPSTF and AAP use rubrics and analytic frameworks to methodically review the evidence available on a topic before determining a recommendation for inclusion into the regular pediatric care setting. At this time, neither group has a recommendation for T1D screening of any population in any context.

Specialist Professional Societies/Voluntary Health Organizations

The ADA current Standards of Care acknowledges that autoantibody positivity correlates with clinical T1D diagnosis and recommends that relatives of individuals with T1D be offered autoantibody testing in clinical research trial settings. The guidance document specifies that widespread clinical testing of low-risk individuals is not recommended due to a lack of therapeutic interventions (American Diabetes Association 2020).

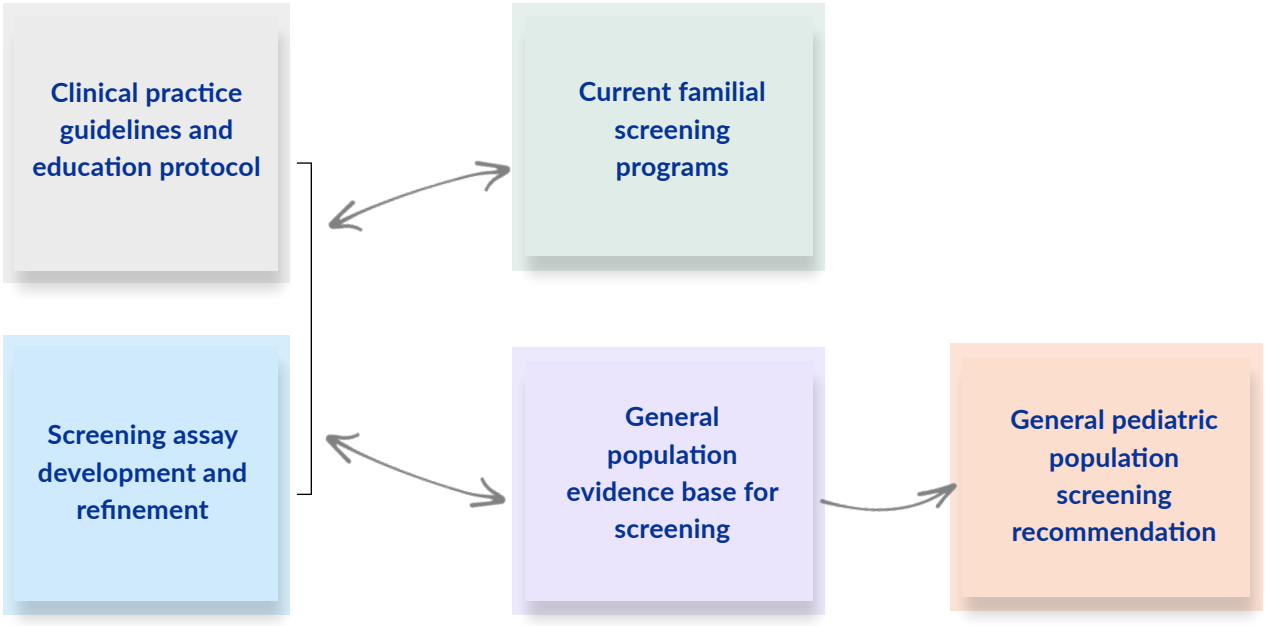
The current ISPAD Clinical Practice Consensus Guidelines acknowledge both the predictive value of autoantibody positivity for progression to clinical T1D diagnosis and the role of autoantibody testing in confirming T1D diagnosis and differentiating between different types of diabetes. The guidelines specify that screening of any population should not occur outside the context of clinical research studies (Couper et al. 2018).

UNIFIED FRAMEWORK FOR T1D AUTOANTIBODY SCREENING POLICY IMPLEMENTATION

A general population screening recommendation from a specialist society or national policy organization in the United States requires rigorous general population screening study data showing the efficacy of the screening assay in US relevant health systems as well as long-term benefits and harms. From a practical perspective, a screening assay must be suitable for use in an ambulatory care setting. The clinical practice guidelines developed to support its use should be based on the prevalence of T1D in the general population as well as the specifications of the assays being used. Finally, clinicians and the public will need access to clear guidance about T1D screening and interpretation of risk, which has been notoriously difficult in other health specialties where the poor understanding of genetic risk profiles has led to harmful health decisions. To help the T1D research and clinical communities navigate this landscape, CSP developed a framework that balances the need for a long-term strategy to achieve general population autoantibody screening with the reality that an expanded set of approved assays and rigorously studied interventions are needed to make measurable progress toward the final goal of universal general T1D autoantibody screening. Broadly, this framework advocates for the simultaneous improvement of assays and protocols through established T1D screening programs, as well as immediate prioritization of large-scale general population study to build evidence necessary for a nationally recognized health-policy recommendation.

The unified framework below illustrates that expanded familial screening serves an important function and should continue in tandem with activities focused on immediate general population evidence building.

FIGURE 5: FRAMEWORK FOR IMPLEMENTING TYPE 1 DIABETES GENERAL PEDIATRIC POPULATION AUTOANTIBODY SCREENING



Source: Milken Institute (2021)

Expanded familial screening provides a mechanism for iterative process improvement and learning that can then be applied to general population study. At the same time, an immediate focus on general population screening will build toward the goal of widespread screening by expanding autoantibody testing and building an evidence base for a screening recommendation for the general US population through the AAP and/or the USPSTF.

TRANSFORMATIVE MILESTONES

While the community can use the goals and action items detailed in the Unified Framework to build a path toward universal general population T1D autoantibody screening, the following milestones will transform the field. Achievement of one or more of these milestones will result in large-scale changes in the recommendations for T1D autoantibody screening in the general population in the United States.

Screening Assay Innovation and Standardization

Currently several assays are in use for the detection of T1D autoantibodies both in research studies and in commercial labs. None of them are ready for widespread use, and most require expensive equipment and significant skill to run. New or improved assays that offer standardized results in an easy-to-use format or that utilize currently available lab equipment will enable the expansion of current screening programs and the refinement of clinical guidelines, resulting in increased screening for T1D autoantibodies.

Insurance Coverage for Screening as Preventive Care

Studies show that autoantibody screening followed by education and monitoring results in a reduction in DKA diagnoses and should, as a result, reduce downstream costs associated with diagnosis. While the USPSTF does not consider cost of services, insurers and states may consider this factor when assessing whether a service should be offered prior to a recommendation from the USPSTF or AAP. Data showing improved health outcomes and savings increase the likelihood that insurers will include a specific preventive service. This inclusion can significantly increase the number of people able to access autoantibody screening.

FDA-Approved Intervention

Currently, autoantibody screening in the general population is not recommended as part of routine care in part because there is no intervention to offer people who screen positive. An FDA-approved therapy for the delay or prevention of T1D will provide a reason for clinicians to offer autoantibody screening. Thus, a single FDA-approved therapeutic for the delay or prevention of T1D could create a ripple effect that will transform the field.

Inclusion in ADA and AAP Guidelines/USPSTF Recommendation

A recommendation for general population T1D autoantibody screening by AAP or a voluntary health organization such as ADA will result in a significant increase in screening. This increase will further build the evidence base needed for a USPSTF recommendation, which in turn will require that the service is offered to everyone and the goal of universal screening will be met.

CSP has identified four primary and two supporting goals that the T1D community should prioritize to move toward the implementation of general population autoantibody screening:

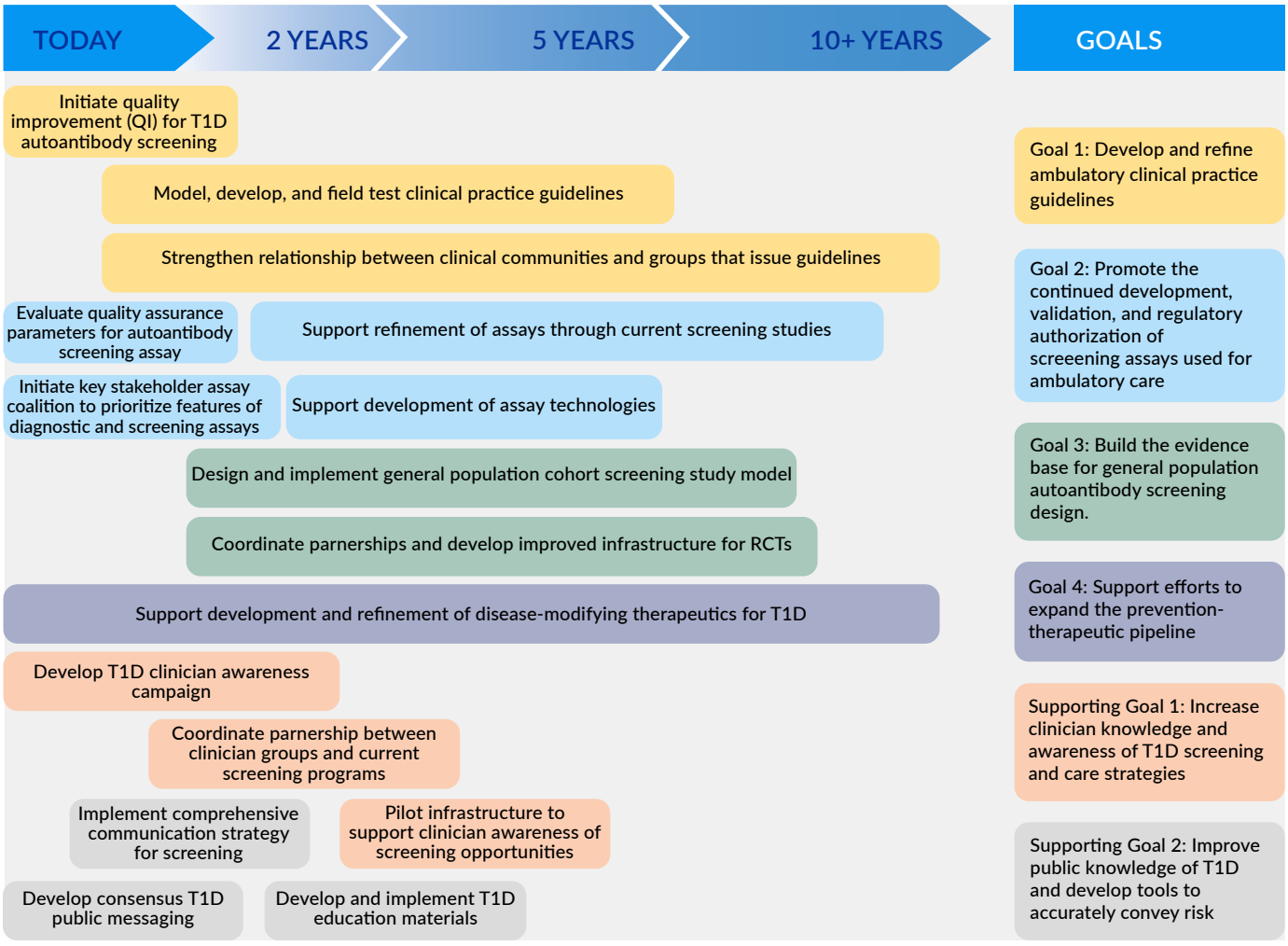
Primary Goals

1. Develop and refine ambulatory clinical practice guidelines.
2. Promote the continued development, validation, and regulatory authorization of screening assays used for ambulatory care.
3. Build the evidence base for general population autoantibody screening design.
4. Support efforts to expand the prevention-therapeutic pipeline.

Supporting Goals

1. Increase clinician knowledge and awareness of T1D screening and care strategies.
2. Improve public knowledge of T1D and develop tools to convey risk accurately.

FIGURE 6: TIMELINE FOR UNDERTAKING ACTION ITEMS



Source: Milken Institute (2021)

Goal 1: Develop and Refine Ambulatory Clinical Practice Guidelines

Clinical practice guidelines, developed through systematic evidence review to optimize clinical care and outcomes, do not exist for routine T1D screening for either familial or general populations. Because autoantibody screening for T1D typically occurs in the context of a research setting, guidelines for screening in ambulatory clinical practice will need to be established to expand current screening and implement widespread general population autoantibody screening. Guidelines should include what age to test, how many times to test, where and how sample collection occurs, how results are communicated to the family, and what happens after results are communicated.

Action Item 1: Initiate Quality Improvement for T1D Autoantibody Screening

Clinical practice guidelines are evidence-based and can take several years to move through the issuance process within organizations such as the AAP. It can help to undertake a quality improvement (QI) process while the service's long-term evidence base is being built. In this process, a group of clinicians develops an evidence-based summary and generates suggested practice guidelines based on the current evidence. This group will implement the guidelines and provide an ongoing review of the process, including patient uptake, results interpretation, follow-up care, and insurance coverage. This QI process allows for iterative refinement of the best practice guidelines and provides an increased opportunity for physicians to offer a service that lacks official clinical practice guidance from a group such as the AAP. A coalition of stakeholders should be formed to assess the field and determine whether additional data or evidence is required and draft suggested clinical practice guidelines to be utilized for QI. An autoantibody screening QI process will provide a vital opportunity to optimize and refine suggested clinical practice guidelines for T1D autoantibody screening and follow-up care.

Action Item 2: Strengthen the Relationship between Clinical Communities and Groups That Issue Guidelines

Voluntary health organizations such as ADA and ISPAD issue detailed guidance documents with specific diabetes diagnosis and care recommendations for pediatric and adult populations. A committee of experts writes each section of the guidance document. The clinical community should strengthen its relationship with these voluntary health organizations to ensure that T1D experts can provide insight during recommendation development, specifically on screening-related topics. Knowing that these guidance documents can be a stepping stone for more significant landscape changes in a field, this relationship is especially important as the field experiences rapid developments in screening assay technology and prevention therapeutics. In addition to belonging to voluntary health organizations as a member or in a leadership role, researchers can participate on specialist committees in a consultant's capacity or via the presentation of current research.

Action Item 3: Model, Develop, and Field Test Clinical Practice Guidelines

Clinicians rely on clinical practice guidelines to inform diagnosis and treatment decisions. These guidelines are typically generated by clinician groups such as the AAP and the American Academy of Family Physicians or public health organizations such as the Centers for Disease Control and Prevention. The guidelines provide an evidence-based framework for clinicians to utilize and standardize diagnosis and treatment across a field. A guidance for a diagnostic or screening service will typically include information on the assay or tool being used, factors that can influence the results, instructions for interpreting the test results, and a follow-up plan if necessary (AAFP 2020).

Without a guideline, pediatricians and ambulatory care clinicians lack access to an optimized procedure to initiate autoantibody screening for T1D and, as a result, may be reluctant to perform screening. This reluctance can result in people not being offered screening, screened at a non-optimum age, or not being offered proper follow-up monitoring and education. To address this need, researchers, clinicians, and organizations that create policy can form a coalition to build on knowledge gained from current screening studies to model, develop, and field test clinical practice guidelines. They can use the findings from previous QI measures and ongoing screening studies to define the guidelines' parameters. To be most effective for use in clinical care, the guidelines should include what age to test, how many times to test, where and how sample collection occurs, how to interpret results, how results are communicated to the family, and how to perform follow-up monitoring and education.

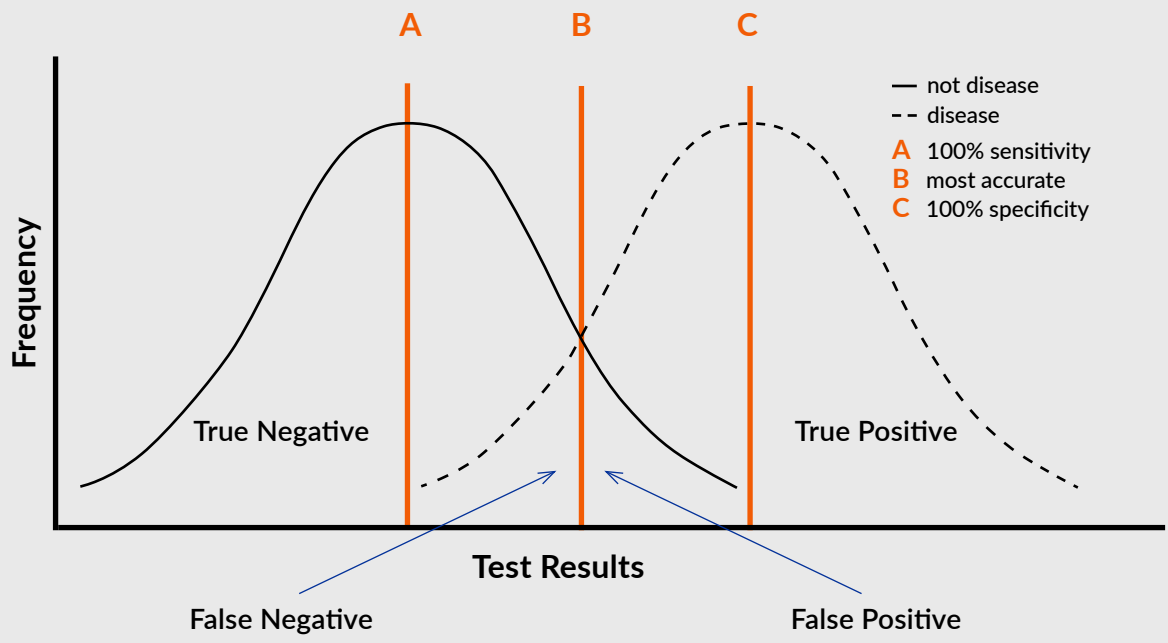
Goal 2: Promote the Continued Development, Validation, and Regulatory Authorization of Screening Assays Used for Ambulatory Care

Major strides are being made in the development of autoantibody screening assays, and efforts to harmonize and standardize these assays are being undertaken by the Islet Autoantibody Standardization Program (IASP), the Critical Path Institute's Type 1 Diabetes Autoantibody Workshop, and other groups. However, while a number of different assays are currently used successfully in screening studies, they all have varying sensitivity and specificity specifications. It is difficult to achieve both high sensitivity and specificity in a single assay because they typically exist in a state of balance, with higher sensitivity resulting in lower specificity and vice versa. Experts believe that the availability of scalable, fit-for-purpose, FDA-authorized assays will greatly further the issuance of a recommendation for pediatric general population screening by policy groups and specialist societies.

The positive predictive value of a test is the proportion of people who test positive for autoantibodies and progress to a clinical T1D diagnosis. Conversely, the negative predictive value is the proportion of people who test negative and do not develop clinical T1D. Because T1D is only prevalent in a small percentage of the general population, an assay with high sensitivity but lower specificity will yield a false-positive rate that will dramatically impact the positive predictive value of the test. Keeping this in mind, developing two distinct tools could improve screening and diagnosis for stage 1 T1D. For example, in the first tool, a high *sensitivity* assay (>99 percent) would identify

all positive cases but likely have lower specificity than would be diagnostically valid, resulting in a higher rate of positive results. This set of positive results would include false positives that would require a second diagnostic test to determine true positives. In the second tool, an assay with exceptionally high *specificity* (>99 percent) could be used in a diagnostic manner because all individuals testing positive will be true positives, and further diagnostic testing will not be required. If the first high-sensitivity assay was low-cost and easily deployable, it could be utilized as a screening assay to identify individuals for additional, more specific diagnostic testing.

FIGURE 7: RELATIONSHIP OF SCREENING ASSAY SENSITIVITY AND SPECIFICITY



Source: Adapted from https://step2.medbullets.com/stats/121625/evaluating-diagnostic-tests (2021)

Action Item 4: Evaluate Quality Assurance Parameters for Autoantibody Screening Assays

Screening assays for type 1 diabetes can be accessed via research programs such as TrialNet, an order for a commercial lab test from a clinician, or, most recently in the community setting, as a mail-order test kit. If an individual is not eligible for participation in TrialNet, they can use the mail-order test kit or work with their clinician to order the commercial lab test. This testing is often not covered by insurance, and the results can be challenging to interpret. Different labs utilize different commercial assays. Each assay has its own sensitivity, specificity, and positive predictive value, making interpreting the results (positivity for T1D autoantibodies and chance of false-positive and -negative results) and explaining them to patients a multi-step process. In addition to limited options for intervention, these conditions can result in general practitioners being hesitant to order the commercial lab test and could challenge the expansion of current screening efforts outside of

research programs. To streamline the process and provide greater confidence in results, a coalition of assay experts and clinicians will need to work together to evaluate standardization efforts for current assays and reach a consensus on interpreting and communicating quality assurance parameters for the commercially used autoantibody screening assays. Although these guidelines will also be applied to future screening tools, this assay performance standardization is especially crucial while the screening process remains variable.

Action Item 5: Initiate Key Stakeholder Assay Coalition to Prioritize Features of Screening and Diagnostic Assays

Many autoantibody screening assay technologies are in use and in development. Each has advantages and disadvantages that include cost, ease of use, specificity, and sensitivity. Screening and diagnostic assays are both used regularly in preventive care. Screening assays are typically chosen for their high sensitivity, low cost, and ease of use and are intended for deployment over large portions of the population to identify the vast majority of individuals who are at risk for a condition. This type of assay will typically have a lower positive predictive value (PPV) and thus a high rate of false positives. Although this high rate of false positives requires additional diagnostic testing to determine true positives, the benefit is that nearly all individuals at risk for the condition are identified for follow-up testing and monitoring. Diagnostic assays typically have a higher specificity and PPV. This type of assay can be useful as a follow-up to a high-sensitivity screening assay to identify the individuals who are truly positive for the condition, or for instances when only one test is possible and having a high PPV is important. Each assay has significant benefits and can be employed to identify individuals who are positive for T1D autoantibodies in the general population. It will be necessary for a coalition of key stakeholders to prioritize the features (i.e., sensitivity, specificity, cost) of both screening and diagnostic assays for this purpose and then identify technology, either existing or under development, that meets the needs of the highest prioritized features. All technology that meets these parameters will be appropriate for screening for T1D autoantibodies.

Action Item 6: Support Development of Assay Technologies

As previously stated, many existing and in-development assays have the potential to meet the T1D community's prioritized needs. Once the features of a screening assay have been prioritized by the coalition and specific technologies have been identified, it will be necessary for the community to support assay development. This includes continued support for proficiency testing of autoantibody assays to ensure that the assays used for screening meet the prioritized features. All assays in use for universal general population screening will be reviewed and regulated by either FDA's CDRH or CLIA. To facilitate this process, assay technology developers must have frequent contact with CDRH and CLIA officials. A strong relationship will ensure that the assays brought forward for review are supported by studies designed with the high level of rigor needed for authorization by the FDA and CLIA.

Action Item 7: Support Refinement of Assays through Current Screening Studies

Assay refinement requires frequent use over time. In the absence of a general population screening recommendation, refinement is most easily achieved via current screening programs both for relatives of people with T1D and the general population. As tools are selected based on the coalition's prioritized features, they should be implemented in current screening programs and iteratively refined. This refinement should be purposeful, focusing on standardization and high-throughput features so that the tools are ready for deployment in the general population. The community can support this effort to refine and standardize screening assays via grant terms and agreements that require data to be shared collaboratively with assay developers and regular assessment of screening tool features such as ease of use, precision, and accuracy.

Goal 3: Build the Evidence Base for General Population Autoantibody Screening Design

A recommendation for general population autoantibody screening from a policy group such as the USPSTF or AAP will require data from the study of the intervention, in this case, screening in the general population in the United States. Although there are large general population cohort studies for screening in Europe and several smaller ongoing studies in the US, current US screening efforts for T1D are focused mainly on screening family members of people with T1D in the context of research studies. These studies have been instrumental in screening and therapeutic research developments in the field. However, they alone are not sufficient for building the evidence base needed for a universal screening recommendation because of the requirement for evidence acquired from the general population. In addition, familial screening is estimated to capture only 15 percent of T1D cases; the other 85 percent are people with no family history of the disease (Tuomilehto 2013). Larger general population screening studies are needed to build the evidence base about the long-term harms and benefits of screening in the general population. Although international efforts can help inform future efforts, data from this type of study performed in the US will receive the strongest weight during review by organizations that issue recommendations for the US.

Action Item 8: Design and Implement a Large-Scale General Population Cohort Screening Study Model

Data on services offered to the general population can be generated in several ways. Randomized controlled trials (RCTs) generate the most stringent type of data. In an RCT for screening, the entire cohort is screened, and some participants are offered the intervention and some are not. Outcomes are observed, and a determination to offer a specific intervention can be made based on the benefits of screening. RCTs in children can be deemed unethical, which is the case for RCTs for autoantibody screening when the current intervention is education and monitoring. Experts agree that counseling and monitoring have proven benefits. Not offering this intervention to the family of an autoantibody-positive child can lead to significant harm and is, therefore, unethical. Another way to generate this type of data is to lobby for implementation on a regional or state level.

Many newborn screening tests were implemented state by state, allowing for comparison across populations in which screening was, and was not, offered. Although it would be cost-effective to compare the data from a state that offers autoantibody screening to the data from a state that does not, the time and effort to get state-by-state uptake is prohibitive largely due to the amount of advocacy work that must take place before state adoption. In addition, this method does not provide a research study-controlled environment to allow for the iterative refinement of assay tools and protocols. Finally, a general population cohort study is designed to screen all participants and offer follow-up care and monitoring to all of them. The outcomes are compared to people not in the study to determine the efficacy of screening as an intervention and long-term harms and benefits. The length of time participants would need to be followed, the ethical concerns of RCTs, and the time and effort required to implement state-by-state screening and to build a population for observation indicate that a large-scale general population cohort study will provide the best vehicle for building an evidence base. Investment in the study infrastructure will be crucial so that the screening assay tools and protocols can be updated and implemented throughout the study.

The actionable goal of investing in general population cohort study infrastructure can be parsed into many smaller action items. To work toward this goal, a coalition led by a neutral leader in the community could design a model for US general population cohort screening studies. This coalition should determine what evidence will be generated by current general population screening studies, what gaps will remain in the evidence base, and how to fill those gaps. A cost analysis will require investigation of implementation strategies for the study and should include exploration of expanding current screening program infrastructure to accommodate additional general population cohort studies.

In addition to the operational specifics of studies such as trial size, time period, and scope, the coalition should identify and prioritize possible results that the USPSTF and others can utilize to inform future screening recommendations for T1D. General population cohort studies for screening should build in a focus on long-term health benefits and harms for the general population that includes emotional and psychological aspects of screening. A long-term cost-benefit analysis for screening and the possibility of bundling screening to reduce costs and increase value should be investigated. Finally, studies should consider a goal to expand knowledge on disease heterogeneity to inform therapeutic trials eventually. Additional understanding of disease heterogeneity and ongoing advances in research can help to refine the trial design and, as a result, eventually develop more targeted prevention therapeutics.

Action Item 9: Coordinate Partnerships and Develop Improved Infrastructure for RCTs for Therapeutics

Although RCTs for screening will not be possible due to ethical concerns, RCTs for therapeutics to prevent or delay T1D will be required as these therapeutics are assessed for efficacy and safety before regulatory review. As therapeutics for T1D move through the research pipeline, the need for clinical trial participants and robust population-based screening will increase. For an indication

in the general population, the pharmaceutical industry will likely require therapeutic testing in the general population. Current screening programs in the US, such as TrialNet and Autoimmunity Screening for Kids (ASK), have collectively identified thousands of individuals who are positive for multiple T1D autoantibodies. Although most of the individuals identified are relatives of individuals with T1D, the programs offer a model of follow-up education, monitoring, and often the opportunity to participate in clinical trials that can be offered to individuals who tested positive for autoantibodies. As the pharmaceutical industry identifies additional prevention targets and therapeutics, investment in and coordination with these current screening programs and any future programs will be crucial to recruiting for clinical trials and building the general population evidence base. One potential approach could leverage the existing academic research infrastructure to conduct platform trials efficiently, allowing multiple therapies to be tested at once with one control arm.

Screening programs also operate smaller phase 1 and 2 clinical trials, typically in the familial population. Along with increased calls for general population screening data, industry researchers have also indicated that well-coordinated, uniform trials and data collection methods at the research level and provisions for participant recontact will enable them to move more efficiently into phase 3 drug development trials. Registration trials require large numbers of participants, and in the case of prevention therapeutics, the participants must be positive for multiple T1D autoantibodies but not yet experiencing clinical symptoms of T1D. Identification of these participants can be a challenge and requires improved infrastructure. Coordination among trial networks, patient groups, hospitals, and clinicians can help identify potential clinical trial participants and increase their awareness of trial opportunities. Clinical and pharmaceutical research communities will benefit from well-populated trials, and at-risk individuals who screen positive for multiple T1D autoantibodies and their families will benefit from additional care options.

Goal 4: Support Efforts to Expand the Prevention–Therapeutic Pipeline

Currently, there are no FDA-approved T1D prevention or cure therapies to offer to people who are positive for multiple T1D autoantibodies. Voluntary health organizations such as the ADA and other groups that write policy have indicated that this lack of prevention or cure therapies prohibits recommending general population screening. Once one or more therapies become available, there will be a greater incentive to recommend screening because disease progression can be halted or significantly delayed.

Action Item 10: Support Development and Refinement of Disease-Modifying Therapeutics for T1D

FDA approval of a therapeutic to prevent or delay a disease can be a transformative milestone for a condition or field. For example, spinal muscular atrophy was added to the Recommended Uniform Screening Panel (RUSP) for newborn screening in 2018 after an FDA-approved therapy became available, enabling the performance of pilot screening studies. Similarly, the availability of therapeutics to prevent or significantly delay the clinical onset of T1D will substantially impact the

implementation of a recommendation for general population screening. The anti-CD3 monoclonal antibody therapeutic, teplizumab, has been shown to delay the onset of clinical T1D symptoms by a median of two years in the initial study, with further follow-up suggesting at least a three-year median delay (Herold et al. 2019). FDA is currently reviewing teplizumab, with a targeted decision date of July 2021. Although this approval can function as a transformative milestone for the community, it is just the beginning. Funding the study and refinement of existing pipeline therapeutics and the development of additional prevention therapeutics will drive innovation, increase the opportunities for RCTs, and support eventual approval of prevention therapeutics in the general population.

Supporting Goals

Goals 1-4, outlined above, will require significant time, attention, and funding and will result in the most significant gains toward achieving general population autoantibody screening for T1D. To support the progression and implementation of these goals, we identified two reinforcing goals that outline the necessity of increased clinician and public awareness of T1D. Having these efforts in place will increase the success of current and future screening initiatives.

Supporting Goal 1: Increase Clinician Knowledge and Awareness of T1D Screening and Care Strategies

Pediatricians and other child health providers currently do not routinely screen or test for T1D or monitor at-risk individuals for disease progression. This reduces the chance of detecting early T1D symptoms, resulting in the possible onset of DKA and severe illness. Increasing clinician awareness of T1D, symptoms, and current screening opportunities would result in a more rapid and less traumatic diagnosis for many patients. In addition, clinicians have a high level of contact with patients and therefore are well poised to identify people with familial risk and educate all families on T1D, screening opportunities, and available therapies.

Action Item 11: Develop an Ongoing T1D Clinician Awareness Campaign

Nonspecific symptoms such as excessive thirst, excessive urination, and fatigue result in frequent misdiagnosis of T1D in both children and adults. Adults are commonly misdiagnosed with type 2 diabetes (T2D), and children are frequently misdiagnosed with bacterial and viral conditions such as urinary tract infections, stomach flu, and strep throat, all conditions with symptoms that overlap with T1D (Dabelea et al. 2014). As previously stated, misdiagnosis of T1D can lead to increased DKA risk, resulting in higher costs and likely lifetime negative health impacts. A recent study found that campaigns that target clinicians, educators, and families and include a focus on the most common early symptoms of T1D (e.g., excessive thirst, increased bedwetting) can reduce the incidence of misdiagnosis and, as a result, reduce the incidence of DKA (Deylami et al. 2018). These past campaigns have been effective in increasing awareness in these groups, and it is essential to continue the momentum they have brought to the field. Bringing together patient advocacy groups,

clinician professional societies, and voluntary health organizations to develop an ongoing T1D awareness campaign targeted to clinicians and community-based health-care services will meet this need. The campaign should focus on the symptoms of T1D in both children and adults, how to differentiate from the more common T2D, and how to diagnosis dysglycemia.

Action Item 12: Pilot Infrastructure to Support Clinician Awareness of Screening Opportunities

As electronic health records (EHRs) have become increasingly common, there has been a move in the health-care system to utilize them to improve patient care management. In addition to many other benefits, EHRs can help providers efficiently diagnose patients because they have access to a patient's complete record of all provider visits. For these systems to be effective, investment is needed to explore clinical support tools specific to T1D awareness and screening opportunities. For example, an ER physician might notice a child was recently diagnosed with a stomach virus in the pediatrician's office, and now they are presenting with worsened symptoms. This, along with knowledge of T1D symptoms, could lead to a simple glucose test. The system could be further developed to include clinical prompts for glucose testing upon entering symptoms consistent with T1D. A sibling of a child diagnosed with T1D might have their chart flagged with a best practice advisory to prompt the provider to discuss T1D familial risk and screening opportunities. Finally, a diagnosis of T2D might include clinical prompts for clinicians to offer patients autoantibody screening to confirm the diagnosis. Modeling this infrastructure in health-care systems with a single EHR system can serve as a framework for implementation in other provider environments.

Action Item 13: Coordinate Partnerships between Clinician Groups and Current Screening Programs

As previously outlined, the current autoantibody screening opportunities for both the general population and relatives of people with T1D exist in a research capacity. There is little connection between these research programs and most primary care facilities. As a result, in addition to not being aware of the benefits of screening for T1D autoantibodies, primary care physicians may not be aware of the screening opportunities available to their patients. Resolving this lack of awareness will require coordination between current screening efforts (such as TrialNet and ASK) and clinician groups, such as the PES and AAP, to raise awareness surrounding current screening opportunities. This awareness should include information on the out-of-pocket cost, benefits, challenges, logistics for screening, and follow-up care.

Supporting Goal 2: Improve Public Knowledge of T1D and Develop Tools to Convey Risk Accurately

General public awareness of diabetes is heavily skewed toward T2D, and as a result, there are many misconceptions about T1D, its causes, and who is affected. General public consciousness and knowledge of screening and monitoring procedures are also needed to increase acceptance of screening.

Action Item 14: Develop Consensus on T1D Public Messaging

There are many common misconceptions about T1D in the general public, such as only children can get it, that you can get it from eating too much sugar, and that you can take a pill to treat it like T2D. The need for additional awareness and education that T1D is an autoimmune disease continues despite ongoing campaigns from patient advocacy groups. An effort to develop consistent messaging aimed at the general public will meet this need. Such an effort will be most effective if it includes diverse input from groups that include current trial centers, patient groups, endocrinologists, primary care physicians, and educators. In addition, community-based health-care providers have opportunities to interact with people who may not have access to or trust another medical provider and can be used to amplify the messaging. This effort can be performed in conjunction with the clinician awareness campaign mentioned above.

Action Item 15: Implement a Comprehensive Communication Strategy for Screening

Part of the reason current education and screening awareness efforts are not reaching the general public is that patient advocacy groups and current screening programs have high rates of interaction with people with T1D and their families but much lower rates with the general public. Dissemination of agreed-on education efforts will require engagement from organizations with a high rate of interaction with the general public, such as general practitioners, health clinics, and schools. For acceptance of autoantibody screening for T1D to be widespread, the general public will need to be already educated and aware of the benefits of screening and the screening procedure. Achieving this awareness will require a comprehensive communication strategy that can be piloted with relatives of people with T1D and a general population audience. This increases the chances that a vetted approach can be in place as larger general population screening initiatives are rolled out.

Action Item 16: Develop and Implement T1D Education Materials

Public awareness campaigns have been used for decades. They are a critical tool for bringing awareness to specific conditions and encouraging the general public to seek more information from their health-care providers. Successful campaigns consider the audience, the message, and the media being used to present the information. For example, the R UV UGLY campaign in the UK on the dangers of tanning beds was targeted to youths ages 16-18. The campaign collaborated with celebrity advocates and used an appearance-based message shown to be effective with young people. Patient advocacy groups such as JDRF and Beyond Type 1 currently utilize public awareness campaigns, but the reach is often limited to people with T1D and their families. Additional collaboration and considerations for campaigns will be needed so the messaging can reach the general public. Accessible education materials should include personal stories of individuals with T1D to engage the public. The languages the materials are offered in and how the public will access them are also important considerations. Materials could be made available in doctor's offices, schools, and on the internet, and each point of access will require specific considerations.

CONCLUSION

As T1D affects people of all ages, can cause numerous negative health effects, and currently cannot be cured or prevented, autoantibody screening in the pediatric population can play an important role in early diagnosis and long-term health outcomes. Preventive health care is complex and requires a high level of evidence for groups that make policy to issue recommendations for a service. Implementing a recommendation for general population autoantibody screening, however, will require a unified approach from the T1D community. Efforts must focus on building the general population evidence base while current screening efforts are continued and expanded. This strategy will allow for iterative improvement of screening assay technology and the establishment of clinical practice guidelines. The outlined goals and action items will help the field achieve this goal and require cooperation and support from the entire T1D community.

Current initiatives must continue to be supported and new ones chosen and funded strategically. Stakeholders can support the goal of universal T1D autoantibody screening in the general pediatric population by supporting the many collaboration opportunities identified above. Support for developing study infrastructure and identifying a neutral coordinating body will ensure that the community's goals are met. As the evidence base for screening in the US general pediatric population grows, data sharing will enable larger strides in the development of cure and prevention therapeutics.

APPENDIX 1: SELECTION OF CURRENT TYPE 1 DIABETES AUTOANTIBODY SCREENING PROGRAMS

Autoantibody testing for T1D is currently performed largely on people who are first-degree relatives of individuals with type 1 diabetes, but there are increasing opportunities for the general population to be screened as well. Several general population screening studies are underway in the US and internationally as well as an opportunity for screening via a JDRF screening education and awareness program. Current studies can be divided into those that screen for T1D autoantibodies in all participants and those that determine a genetic risk score for all participants, then follow and test those with a high genetic risk for developing T1D autoantibodies.

Type 1 Diabetes TrialNet

TrialNet is a research program focused on preventing T1D, with locations in the US, Canada, Australia, and Europe. TrialNet offers risk screening, monitoring, participation in prevention/newly diagnosed studies, and long-term follow-up for people with increased risk for T1D. Pathway to Prevention screening is available to family members of people with T1D ages 2.5-45 years and who have a parent, sibling, or child with T1D and have not yet been diagnosed with T1D. More than 220,000 relatives have been screened. Screening is free and can be performed with an at-home kit, at a TrialNet center, or at a Labcorp or Quest Diagnostics lab location.

People who test positive for one or more T1D autoantibodies are eligible for monitoring; those who test positive for two or more autoantibodies visit a TrialNet location twice a year for follow-up. Follow-up includes diabetes education, a blood test, and an oral glucose tolerance test to determine risk and close monitoring for progression of T1D and eligibility for participation in prevention trials.

Autoimmunity Screening for Kids (ASK)

ASK is a general population research screening program conducted by a team at the Barbara Davis Center for Diabetes in the School of Medicine at the University of Colorado. The program has screened approximately 25,000 children for both T1D and celiac disease-related autoantibodies and is open to all children ages 1-17 years in the state of Colorado. Children with or without a family history of T1D and celiac are eligible to participate in the program. Screening is free, and blood samples are collected at pediatric practices, hospitals, and regional events.

Children who test positive for either disease are offered close monitoring and education on the disease's signs and symptoms. They also potentially have the opportunity to participate in studies for prevention and treatment therapeutics.

Typ-1-Diabetes Früherkennung/Type 1 Diabetes Early Detection (Fr1da Plus)

Fr1da Plus is a general population research screening program in Bavaria, Germany, led by the Institute for Diabetes Research at Helmholtz Zentrum Munchen. To date, this program has screened more than 100,000 children for T1D autoantibodies. Children in two age brackets, ages 1.75–5.99 and then ages 9–10.99, are eligible for screening during primary care visits via capillary finger stick.

Families of children who test positive for T1D autoantibodies are offered follow-up education and support to prevent DKA and to be prepared for symptoms of clinical T1D. These children are eligible for monitoring that includes HbA1c testing, blood, and urine glucose testing, and participation in a clinical trial.

Population-Level Estimation of Type 1 Diabetes Risk GEnes in Children (PLEDGE)

The PLEDGE general population screening program is available to children up to age 6 through Sanford Health. A genetic risk score is determined from a blood sample. Participants are tested for T1D autoantibodies at ages two and five years and for celiac disease-related autoantibodies at age five. Those who are positive for T1D autoantibodies will be referred for clinical care or offered participation in other monitoring or prevention trials. Families are contacted via primary health-care providers.

Precision Individualized Medicine for Diabetes (PRiMeD)

The PRiMeD study is a general population screening program run through the University of Virginia. Children ages 2-16 years are eligible and offered screening for T1D genetic risk. A saliva sample is used for DNA extraction and genotyping, and those with a high genetic risk score (defined by the study) are offered T1D autoantibody screening. Participants are offered retesting, monitoring, and clinical trial participation opportunities depending on autoantibody positivity. To date, this program has screened more than 3,500 children.

T1Detect

T1Detect is a new JDRF-sponsored initiative to offer autoantibody screening to anyone who wants it. Individuals can order a screening test kit for $55, perform the fingerstick at home, and return their sample for testing for three T1D autoantibodies using the ADAP assay by Enable. Participants can opt to share their results with JDRF and be connected to research opportunities via TrialNet and others. Participants are encouraged to share and discuss their results with their health-care providers.

APPENDIX 2: T1D COMMUNITY

The T1D community consists of several types of organizations and fields. Each group has a significant and integral role in how the community moves toward the goal of general population autoantibody screening.

TABLE 5: THE TYPE 1 DIABETES COMMUNITY

Clinicians	Researchers and Research Programs	Industry	Professional Societies/ Voluntary Health Organizations	Nonprofit Patient Advocacy Groups	Funders
Clinicians work directly with patients who have T1D and those who are at risk for the disease. Their role in communicating information about risk and providing care and treatment options is vital to increased autoantibody screening.	Both screening assay and T1D researchers have been instrumental in the great strides the field has seen in the knowledge of T1D autoantibodies and disease progression. Researchers in this field are using this information to develop and investigate potential new therapeutics.	The pharmaceutical industry will ultimately be responsible for the manufacture of prevention and cure therapeutics for T1D. To ensure a business case for developing these therapeutics, pharma will need assurance of at-risk populations for conducting efficient trials and later for a post-approval market for the therapy.	Professional societies are typically responsible for evaluating evidence and determining whether and when a service should be offered to the population in their purview. Members of specialist societies are integrated into the clinical research within a field and can be especially nimble in changing guidance documents to reflect these changes.	Patient advocacy groups work closely with patients and their families to provide information and support during and after diagnosis. These groups have an important role to play in facilitating collaboration among patients, clinicians, and researchers.	Public and private funders work closely with all other groups in the field to understand and prioritize research and community needs. They play an essential role in ensuring the field continues to move forward.
Ex: AAP	Ex: TrialNet, ASK, Sanford Project	Ex: Janssen, Novo Nordisk, Eli Lilly, Provention Bio	Ex: Pediatric Endocrine Society, ISPAD, ADA	Ex: JDRF, Beyond Type 1	Ex: JDRF, NIH, The Leona M. and Harry B. Helmsley Charitable Trust

Source: Milken Institute (2021)

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ACKNOWLEDGMENTS

We are grateful for the generous support of The Leona M. and Harry B. Helmsley Charitable Trust.

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