

Is It Time to Screen the General Population for Type 1 Diabetes?

Kimber M Simmons, MD, MS¹ and Aaron W Michels, MD²

1. Pediatric Endocrinology and Diabetes Fellow, Children's Hospital Colorado, Aurora, Colorado, US;

2. Assistant Professor of Pediatrics & Medicine, Barbara Davis Center for Childhood Diabetes, University of Colorado, Denver, US

Abstract

Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by destruction of insulin-producing β cells in the pancreas. The incidence of T1D is increasing dramatically, and the prevalence has doubled in the last 2 decades, further increasing the morbidity and mortality associated with the disease. T1D is now predictable with the measurement of antibodies directed against β cell proteins. Islet autoantibodies (IAs) are detectable from the peripheral blood months to years before clinical diagnosis. With the presence of two or more antibodies, the risk for developing T1D is nearly 100 % given enough time. Targeted screening for T1D risk has been carried out in first-degree relatives and those with a significant genetic risk. However, more than 85 % of individuals who are diagnosed with T1D do not have a family history. In light of the predictability of T1D and recent advances in IA measurement, general population screening is on the horizon. We provide an overview of the history of general population screening and discuss the rationale for and arguments against screening the general population for T1D risk.

Keywords

Type 1 diabetes, screening, islet autoantibodies, risk, prediction, general population

Disclosure: Kimber M Simmons, MD, MS, and Aaron W Michels, MD, have no conflicts of interest to declare. No funding was received for the publication of this article.

Open Access: This article is published under the Creative Commons Attribution Noncommercial License, which permits any noncommercial use, distribution, adaptation, and reproduction provided the original author(s) and source are given appropriate credit.

Received: February 27, 2015 **Accepted:** April 10, 2015 **Citation:** *US Endocrinology*, 2015;11(1):10–6 DOI: <http://doi.org/10.17925/USE.2015.11.1.10>

Correspondence: Kimber M Simmons, MD, MS, Children's Hospital Colorado, 13123 E 16th Ave B265, Aurora CO 80045, US. E: kimber.simmons@childrenscolorado.org

Type 1 diabetes mellitus (T1D), also referred to as insulin-dependent, childhood-onset, or juvenile diabetes, is an autoimmune disease that occurs when insulin-producing β cells in the pancreas are aberrantly targeted and destroyed by a person's immune system, usually leading to an absolute insulin deficiency.¹ A diagnosis of T1D is made when a patient has glycemic abnormalities, which often result in clinical symptoms. The American Diabetes Association annually publishes guidelines for diagnosis of T1D using these metabolic measurements, which are widely accessible for use. Of importance, the autoimmune disease process begins long before clinical onset of T1D and can be identified by the presence of serum islet autoantibodies (IAs) that are directed against proteins in insulin-producing β cells. Currently four major antibodies are measured, including insulin, glutamic acid decarboxylase (GAD), islet antigen 2 (IA-2), and zinc transporter 8 (ZnT8). The ability to accurately measure multiple IA makes T1D a predictable disease. To date, targeted screening for IA has been performed in first-degree relatives (FDRs) of people having T1D or those having high-risk human leukocyte antigen (HLA) genes. *HLA* genes confer more than 50 % of the genetic risk for T1D. After the development of two or more IAs, an individual will almost always develop clinical T1D given enough time.² The incidence of developing clinical T1D after ≥ 2 IAs are present is 11 % each year and approximately 70 % in the ensuing 10 years. With the ability to measure IA and predict T1D risk, the next step in disease prevention is screening the general population. There are a number of reasons to screen the general population for T1D

risk by measuring IA but also an equal number of arguments against screening. This article discusses the history of screening the general population for IAs and assesses the pros and cons of screening the general population for T1D risk in the 21st century.

Natural History and Predictability of T1D

The natural history of T1D as a chronic autoimmune disorder, initially described by George Eisenbarth, holds true today (see *Figure 1*).³ Genes predispose risk, as linkage studies and genetic association studies in families having T1D and case-control collections have consistently identified linkage between the HLA region on chromosome 6p21 and T1D. Genome-wide association studies have confirmed that *HLA* genes and major histocompatibility complex (MHC) class II genes confer more than half the genetic risk for T1D. More than 50 genetic loci that provide increased susceptibility for T1D development (www.t1dbase.org) have also been identified, most of which have some known function in cellular immunity and only contribute minor genetic risk for T1D development. Of importance, only about 5 % of individuals having high-risk *HLA* genes go on to develop T1D, so HLA has a low positive predictive value when used alone to assess risk for T1D in the general population.^{4,5} In individuals with increased genetic risk, an unidentified trigger initiates an abnormal immune response, leading to destruction of pancreatic β cells. Antibodies targeted against pancreatic islet cells and insulin can be measured in serum and are present in individuals from months to years before clinical onset of T1D occurs.^{2,6–8}

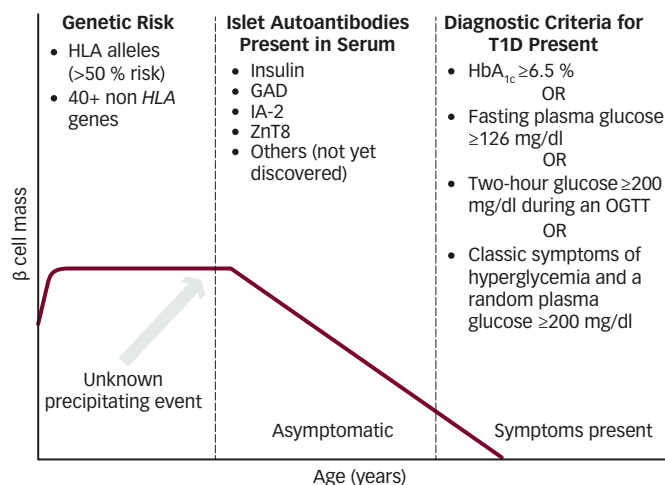
In the early 1970s, an antibody to islet cell antibodies (ICAs) was identified in a section of frozen pancreas, establishing the first autoantibody in T1D.⁹ Although highly sensitive, ICA lacks specificity, having many target molecules. The four major autoantibodies present in autoimmune diabetes (insulin, GAD, IA-2, ZnT8) are well characterized and can be measured by validated and highly sensitive and specific radioimmunoassays. The Diabetes Antibody Standardization Program occurs biannually and is focused on improving the sensitivity and specificity of IA testing globally. Importantly, the measurement of IA have greatly improved over the last decade, and assays are now available that do not use radioactivity and that have the potential to measure all four antibodies in a single well using small blood volumes.^{10–12} Insulin is the only β cell-specific autoantibody that has been identified and is often the first antibody to appear in young children who develop T1D, making it an important antibody to measure when determining risk.¹³ Concordance of insulin autoantibody measurements between laboratories and assays has historically been poor, but recent workshops have focused on this problem and improved the sensitivity of the assay.^{14,15}

Autoantibody positive individuals lose β cell mass over time and, when approximately 10–20 % of β cells remain, not enough insulin can be produced to transport glucose from the bloodstream into the body's cells for energy. Blood glucose levels rise, protein and fat stores are broken down and converted into glucose by the liver, and glucose and ketone levels rise in the blood and are subsequently excreted in the urine. Without incidental discovery of blood glucose abnormalities or screening, patients go on to develop clinical signs and symptoms of T1D, which include polyuria, polydipsia, and weight loss. Metabolic deterioration can only be detected 12 to 18 months before clinical diagnosis with the measurement of glycated hemoglobin (HbA_{1c}) or blood glucose.^{16,17} With a delayed diagnosis, diabetic ketoacidosis (DKA), a condition characterized by a combination of abdominal pain, vomiting, severe dehydration, and altered mental status, occurs. Sadly, the prevalence of DKA at diagnosis has not decreased in recent years and remains present in more than 30 % of individuals at the time of T1D diagnosis in developed countries.¹⁸ Infants and toddlers are at greatest risk for DKA, for they often have delayed diagnosis when their symptoms are attributed to other illnesses. After diagnosis, people having T1D rely on subcutaneous insulin via multiple daily injections or insulin pump for survival. Although insulin therapy continues to improve, achieving glycemic targets in T1D is challenging, and patients are at risk for retinopathy, neuropathy, nephropathy, cardiovascular disease, and life-threatening hypoglycemia. Retention of β cell function has been an ongoing focus of T1D research and continues to be important to lessen the burden of daily T1D management and complications. Despite our continued understanding of the pathogenesis of T1D, incidence has dramatically increased in the last 2 decades, especially in children younger than 5 years, and no interventions are present to delay or prevent the onset of clinical disease.^{19–23}

History of Screening

In the US, IA screening has been limited to first-degree relatives (FDRs) or people having high-risk HLA genotypes.^{8,24} In FDRs, the presence of two or more IA predicts that 70 % of such patients will develop T1D within 10 years and that all such individuals will develop T1D given enough time.² A limited number of studies have screened the general population for T1D risk. Few have used multiple IA to predict risk, and none have used

Figure 1: Natural History of Type 1 Diabetes



GAD = glutamic decarboxylase; HbA_{1c} = glycated hemoglobin; HLA = human leukocyte antigen; IA-2 = islet antigen 2; IAA = insulin; OGTT = oral glucose tolerance test; ZnT8 = zinc transporter.

all four major IAs to assess T1D risk (see Table 1). Most studies completed have used a school-based setting to screen the general population. IA development at a young age and higher levels of insulin autoantibodies predispose patients to develop T1D earlier in life, so children younger than school age need to be screened.^{25,26} Yearly well child visits with a pediatrician or family doctor would provide an opportunity to screen young children. None of the studies completed have had a large enough sample size to be statistically powered owing to the low prevalence rate of T1D in the general population, estimated at 1/300.²⁷ This should become easier in the future, for the prevalence of T1D is increasing.²⁸ ICA is relatively common in the general population, but antibodies for GAD and IA-2, the major antigens recognized by ICA, are much less prevalent. Studies report ICA frequency in the general population that far exceeds the prevalence of T1D in the population. However, studies not using ICA to indicate IA-positivity have found IA prevalent in numbers that would be expected based on known disease incidence in the general population. From these studies, it is estimated that the prevalence of multiple IA-positive children in the general population is 1/200 to 1/300. It is reasonable to consider screening for T1D with the measurement of blood glucose or HbA_{1c} , but these metabolic abnormalities only begin to slightly increase 12 to 18 months before meeting the clinical diagnostic criteria for diabetes and, moreover, can be intermittent.²⁹ Oral glucose tolerance tests aid in defining time to diagnosis but are too laborious and invasive for large-scale screening.^{30,31}

More than 85 % of people who develop T1D have no family history of disease, so the ability to predict T1D with IA measurement makes screening the general population for antibody positivity important.^{32,33} With a disease prevalence of 1/300, genotyping for HLA-DR and HLA-DQ loci, which confer significant genetic risk for T1D, should be considered as part of a program for T1D. Genotyping would help stratify risk. For example, children not having a family history of T1D but who carry both DR3/DQ2 and DR4/DQ8, the two highest-risk HLA haplotypes, have a 1/20 risk for developing T1D by age 15.³⁴ Another consideration of HLA screening is that a specific HLA gene, DQ6 (DQB*06:02) confers dominant protection from the development

Table 1: Studies Screening the General Population for T1D Risk

Location and Date	n	Age (Years)	IA Measured	IA Prevalence	T1D Incidence	Sensitivity	Specificity	PPV	NPV	References
Florida 1985	1,445	5–15	ICA	0.8 %	No follow-up	ND	ND	ND	ND	37
Florida 1986	9,698	5–18	ICA first, then GAD, IA-2, IAA	<ul style="list-style-type: none"> ICA: 0.6 % GAD: 0.1 % IA-2: 0.2 IAA: 0.2 	0.1 % over 6–12 years	ND	ND	<ul style="list-style-type: none"> ICA: 20 % GAD: 56 % IA-2: 69 % IAA: 46 % 	ND	38
Spain 1987	2,291	14–17	ICA and IAA	<ul style="list-style-type: none"> ICA: 0.4 % IAA: 0.4 % 	No follow-up	ND	ND	ND	ND	39
Netherlands 1989	3,383	5–19	ICA	0.2 %	0.2 % over 11.5 years (n=2805)	57 %	100 %	50 %	100 %	40
Finland 1990	1,212	3–18	ICA	4.1 %	0.3 % over 8 years	100 %	96 %	6 %	100 %	41
Germany 1991	4,257	6–21	ICA	1.1 %	No follow-up	ND	ND	ND	ND	42
Netherlands, 1994	3,383	5–19	ICA, then GAD	0.3 %	0.3 % over 11.5 years (n=2,805)	ICA: 57 %	ICA: 100 %	ICA: 50 %	ICA: 100 %	43
Florida 1994	9,696	5–17	ICA and IAA	0.6 %	0.1 % over 2–8 years	<ul style="list-style-type: none"> ICA: 100 % IAA: 50 % 	<ul style="list-style-type: none"> ICA: 99 % IAA: 99 % 	<ul style="list-style-type: none"> ICA: 18 % IAA: 16 % 	<ul style="list-style-type: none"> ICA: 100 % IAA: 100 % 	44
Sweden 1995	415	0–15	ICA < GAD < IAA	<ul style="list-style-type: none"> ICA: 4.1 % GAD: 4.1 % IAA: 2.8 % 3 IA: 0.3 % 	No follow-up	ND	ND	ND	ND	4
France 1995	13,380	6–17	ICA and IAA	ICA: 1.5 %	ND	ND	ND	ND	ND	45
England 1997	2,855	9–13	ICA, GAD, IA-2, IAA	<ul style="list-style-type: none"> ICA: 2.4 % GAD: 2.2 % IA-2: 2.1 % IAA: 2.0 % ≥2 IA: 0.7 % 	0.1 % over 27 months	ND	ND	ND	ND	46
Germany 1999	9,419	6–17	ICA, GAD, IA-2, IAA	<ul style="list-style-type: none"> ICA: 0.9 % GAD: 3.0 % IA-2: 2.4 % IAA: 3.0 % ≥2 IA: 0.8 % 	0.1 % over 10–28 months	ND	ND	ND	ND	47
Finland 2001	3,652	>6	ICA, GAD, IA-2, IAA	<ul style="list-style-type: none"> ICA: 2.8 % GAD: 0.5 % IA-2: 0.6 % IAA: 0.9 % ≥2 IA: 0.6 % 	0.1 % over 5.3 years	ND	ND	ND	ND	48
Sweden 2001	1,031	7–13	ICA, GAD, IA-2	<ul style="list-style-type: none"> ICA: 1.4 % GAD: 2.4 % IA-2: 1.8 % 	0.6 % over 10 years	<ul style="list-style-type: none"> ICA: 67 % GAD: 83 % IA-2: 33 % ≥3 IA: 33 % 	<ul style="list-style-type: none"> ICA: 99 % GAD: 98 % IA-2: 98 % ≥3 IA: 100 % 	<ul style="list-style-type: none"> ICA: 29 % GAD: 21 % IA-2: 11 % ≥3 IA: 50 % 	ND	49
Washington state 2002	4,504	12–18	GAD, IA-2, IAA	<ul style="list-style-type: none"> GAD: 0.9 % IA-2: 0.5 % IAA: 0.9 % ≥2 IA: 0.3 % 	0.1–0.2 % over 8 years	≥2 IA: 100 %	ND	≥2 IA: 50 %	ND	50
Florida 2003	9,698	5–18	ICA, then GAD, IA-2, IAA	≥2 IA: 0.3 %	0.3 % over 6–12 years	ICA: 92 %	ICA 100 %	ICA 20 %	ICA 100 %	51
Germany 2004	11,840	6–17	ICA, GAD, IA-2, IAA	<ul style="list-style-type: none"> ≥1 IA: 6.5 % ≥2 IA: 0.6 % *excluding ICA	No follow-up	ND	ND	ND	ND	52
Colorado 2006	122, *organ donors	0–86	GAD, IA-2	<ul style="list-style-type: none"> GAD: 0.8 % IA-2: 0.8 % 2 IA: 0.8 % 	No follow up	ND	ND	ND	ND	53

Table 1: Studies Screening the General Population for T1D Risk (Cont.)

Location and Date	n	Age (Years)	IA Measured	IA Prevalence	T1D Incidence	Sensitivity	Specificity	PPV	NPV	References
Sweden 2008	17,055	Infants	GAD, IA-2	ND	0.2 % over 6–7 years	ND	ND	≥2 IA: 11 %	ND	35
Finland 2010	3,475	3–18	GAD, IA-2	<ul style="list-style-type: none"> GAD: 1.0 % IA-2: 0.6 % 	0.5 % over 27 years	<ul style="list-style-type: none"> GAD: 50 % IA-2: 50 % ≥1 IA: 61 % ≥2 IA: 39 % 	<ul style="list-style-type: none"> GAD: 99 % IA-2: 100 % ≥1 IA: 99 % ≥2 IA: 100 % 	<ul style="list-style-type: none"> GAD: 26 % IA-2: 41 % ≥1 IA: 22 % ≥2 IA: 100 % 	<ul style="list-style-type: none"> GAD: 99 % IA-2: 100 % ≥1 IA: 99 % ≥2 IA: 100 % 	54, 55

GAD = glutamic acid decarboxylase; IA = islet autoantibody; IA-2 = islet antigen 2; IAA = insulin autoantibody; ICA = islet cell antibody; ND = not determined due to insufficient data; NPV = negative predictive value; PPV = positive predictive value; T1D = type 1 diabetes.

of T1D. Considering that ~20 % of the general population in the US carries this allele, consideration for genetic testing and excluding these individuals from IA screening is warranted. Importantly, high-risk HLA is not needed to induce IA, suggesting that HLA may be more important in modulating the immune response after an environmental trigger begins the autoimmune process.³⁵ As combinations of genes that confer risk for T1D become better defined and as costs of genetic testing decrease, genetic testing in combination with IA screening may allow better detection of people who are at risk for T1D. At present, the cost of genetic testing is prohibitive for most people, would decrease equity when offering screening, and requires clinical interpretation, which is not a part of routine clinical practice. The American Diabetes Association does not currently recommend widespread screening of low-risk individuals not having any symptoms, owing to a lack of approved therapeutic interventions. However, it does suggest that high-risk individuals be offered screening within the context of a clinical research study.³⁶ The International Society for Pediatric and Adolescent Diabetes, the American Association of Clinical Endocrinologists, and the American College of Endocrinology do not address screening in their published guidelines.

Another important consideration in general population-screening efforts is the sensitivity, specificity, positive predictive value, and negative predictive values used to evaluate the effectiveness of large-scale screening. When screening the general population for IAs, sensitivity is defined as the proportion of people who test antibody-positive and eventually develop T1D, and specificity is the proportion of people who test negative and never develop T1D. Positive predictive value is defined as the proportion of people who test antibody-positive who progress to diagnosis of T1D and negative predictive value as the proportion of people who test antibody negative who never develop T1D. In general, the specificity of IA tests is high, which minimizes false positive results. Sensitivity of IA measurement in general population screening to date has been poor and variable (see *Table 1*),^{4,35,37–55} consistent with the finding that IA measurement varies widely between laboratory and assay used. Because a positive IA screen would generate additional screening and concern regarding disease development, having an initial test with high sensitivity and a confirmatory test with high specificity is important. Interpreting these values is also dependent on each cutoff for IA-positivity, for there are not international standards for positivity in IA assays. The Barbara Davis Center Autoantibody Laboratory measures all four IAs using radioimmunoassays, with each assay being 99 % specific. Recently, Kronus developed a commercial assay for ZnT8 measurement, and now all four major IAs can be measured commercially. To date, no screening effort listed in *Table 1* has measured all four IAs to determine T1D risk.

Table 2: World Health Organization Requirements for Screening

WHO Criteria	Type 1 Diabetes
The condition should be an important health problem	Life-threatening diabetic ketoacidosis Life-threatening hypoglycemia Micro- and macrovascular complications
There should be a treatment for the condition	Insulin
Facilities for diagnosis and treatment should be available	Pediatric and adult endocrine clinics are prominent in the US
There should be a latent stage of the disease	Preclinical phase marked by multiple islet autoantibodies in the serum
There should be a test or examination for the condition	Serum islet autoantibodies
The test should be acceptable to the population	All four major islet autoantibodies are commercially available
The natural history of the disease should be adequately understood	T1D is a chronic progressive autoimmune disease (see <i>Figure 1</i>)
There should be an agreed policy on whom to treat	American Diabetes Association clinical care guidelines
The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole	Screening modalities are improving, such as using dried blood spots to measure IAs Economic burden of T1D is high
Case finding should be a continuous process, not just a "once and for all" project	Risk determination can be incorporated into pediatric well child visits

IAs = islet autoantibodies; T1D = type 1 diabetes; WHO = World Health Organization.

Prevention Trials

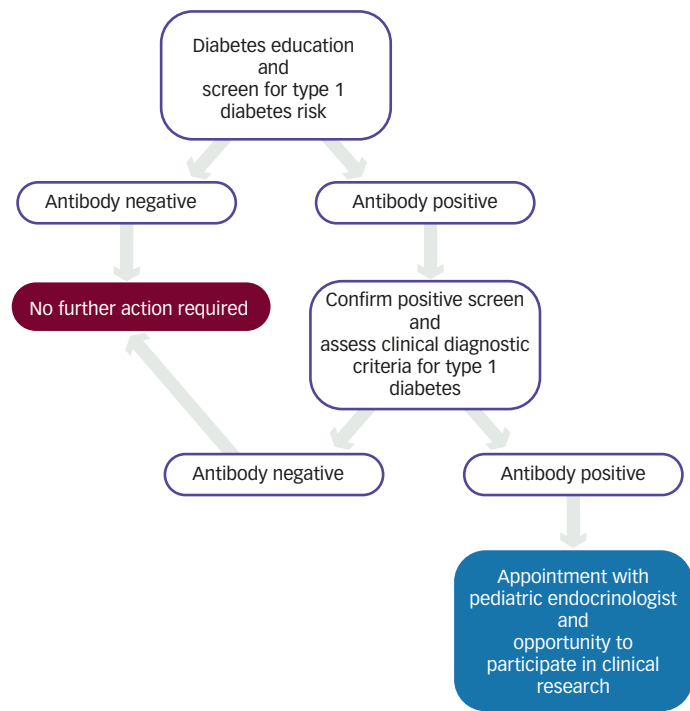
When individuals test IA-positive, there is currently no effective treatment to prevent or delay T1D onset. Before a prevention therapy is accepted, the treatment must be safe and cost-effective and must delay or prevent T1D onset. Furthermore, the treatment should not increase the risks to a patient beyond the risk for being diagnosed and managing T1D with subcutaneous insulin therapy. In the early 1990s, the National Institutes of Health sponsored the first clinical prevention trials network, called Diabetes Prevention Trial–Type 1 (DPT-1), now known as Type 1 Diabetes TrialNet. TrialNet supports clinical research trials aimed at delaying or preventing T1D in IA-positive individuals (secondary prevention) and preserving β cell mass in people recently diagnosed with T1D (tertiary prevention).⁵⁶ Clinical prevention trials to date have shown encouraging but limited success in delaying

Table 3: Pros and Cons of Screening for Type 1 Diabetes Risk

Pros	Cons
<ul style="list-style-type: none"> Meets World Health Organization's screening guidelines⁴⁸ Decrease life-threatening DKA Reliable methods to detect IA Reduced economic burden Clinical prevention trials available Greater understanding of disease natural history from the general population 	<ul style="list-style-type: none"> Preventive treatment not yet available Low prevalence in general population Need to repeat IA testing at regular intervals Cost-benefit analysis not yet performed for multiple screenings in an individual Access to healthcare for screening Concerns for increased anxiety based on test results

DKA = diabetic ketoacidosis; IA/s = islet autoantibody/ies.

Figure 2: Proposed Flowchart for Conducting General Population Screening by Measuring Islet Autoantibodies in Children Younger than 18 Years



the diagnosis of T1D.⁵⁷ Most secondary prevention trials have focused on antigen-specific therapies (predominantly insulin) with the rationale that they will enhance regulatory T cell function and, in turn, limit β cell destruction.⁵⁸ The first clinical trial sponsored by DPT-1 was a randomized, placebo-controlled trial that treated genetically at-risk individuals positive for one or more IA using low-dose subcutaneous or oral insulin. This study showed no effect of insulin in delaying the progression to T1D diagnosis.⁵⁹ However, the rate of progression to T1D diagnosis was faster after stopping oral insulin, and a post-hoc analysis showed that individuals having a persistently high level of insulin autoantibody (≥ 80 nU/ml) had delayed T1D

onset, with an estimated delay of 5 years.⁶⁰ In patients with new-onset T1D anti-CD3 monoclonal antibodies, abatacept, rituximab, and anti-thymocyte globulin and granulocyte colony-stimulating factor (ATG-GCSF) have shown a transient effect in preserving β cell function.⁶¹⁻⁶⁵ With success in new-onset T1D, the next step will be to offer these therapies to IA-positive individuals. Anti-CD3 mAb (Teplizumab) for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus and CTLA4-Ig (Abatacept) for Prevention of Abnormal Glucose Tolerance and Diabetes in Relatives At-Risk (NCT01030861 and NCT01773707, respectively) are both currently enrolling IA-positive FDRs. Another trial available to IA-positive individuals is DIAPREV-IT, a study in which children aged 4 and older who are positive for GAD and one or more additional autoantibodies will receive a GAD alum vaccine at enrollment and 1 month later and then be followed for the development of T1D for 5 years (NCT01122446). It will likely take years for a preventive treatment to become standard in clinical care, but this does not mean that IA screening in the general population should not be performed.

Rationale for General Population Screening

Screening is defined as the systematic application of a test (IA measurement) to identify individuals who are at sufficient risk for a specific disorder (T1D) to benefit from further investigation or direct preventive action, among people who have not sought medical attention because of symptoms of that disorder.⁶⁶ The World Health Organization (WHO) created the first guidelines for screening the general population for a disease in 1968, and they are still used today when establishing screening programs (see Table 2).⁶⁷ Even without having an effective intervention to delay or prevent T1D, T1D arguably meets the WHO's criteria needed to screen the general population, most of which have already been discussed.

T1D is an important health problem, for its economic burden is high, and there remains significant risk for long-term complications and disability. The annual average medical costs for a child who has T1D in the US total \$9,000, approximately six times higher than the annual average medical costs for a child not having T1D. In 2007, \$15 million was spent in the US on T1D.^{68,69} Although the cost for a hospital admission for DKA at onset varies widely, the cost can exceed \$20,000.⁷⁰ The lifetime economic burden of T1D is significant, but to date, a formal cost-benefit analysis of T1D screening has not been completed. This important analysis is ideally required before implementing general population screening, for one of the WHO criteria for disease screening stipulates that the total cost of finding a case should be economically balanced in relation to medical expenditure as a whole. With the cost of IA measurement expected to decrease further upon expansion of individuals screened, the potential exists for screening to reduce the overall expenditure related to T1D.

Despite large medical expenditure and declining rates of medical complications secondary to diabetes, significant risk for morbidity and mortality remains, in part because of an increasing incidence of T1D.⁷¹ Methods such as mass education have failed to reduce the rate of DKA at diagnosis, suggesting that another approach to identifying individuals at risk for T1D is needed. DKA is present in more than 30 % of people having T1D at onset.¹⁸ DKA can cause morphologic and functional brain changes, leading to poor neurocognitive outcomes.^{72,73} DKA also leads to cerebral edema and death, even in developed countries. Screening FDRs for IAs reduces the incidence of DKA dramatically, as only 3.67 % of individuals screened in the DPT-1 presented in DKA.⁷⁴ Because a severe metabolic

phenotype still occurs often at the time of diagnosis, it is likely that early identification of T1D risk in the general population would decrease the rate of complications and death. However, research into a cost-benefit analysis of autoantibody screening and early identification of T1D risk versus patient quality of life years needs to be conducted.

The effect of screening healthy children for a chronic disease raises concerns that knowledge of IA-positivity will have an emotional effect on a patient and family. However, mothers of children in a population-based screening program for T1D had a positive attitude toward screening and desired to optimize the health of their children.⁷⁵ With ongoing research, there will be a time when an intervention is effective at preventing the disease, and an effective screening program needs to be established before this revolution in T1D. Finally, though screening for T1D risk is a goal, measuring IA will allow for T1D surveillance in the general population, which has the potential to greatly contribute to our understanding of T1D epidemiology and pathogenesis. *Table 3* summarizes the pros and cons of screening for T1D risk in the general population.

Proposal for Islet Autoantibody Screening

A screening program for IA in the general population will need to be simple, convenient, and feasible. Individuals who test IA-positive will need to be counseled about the risk for developing T1D, the clinical symptoms that indicate T1D, and how to prevent DKA (see *Figure 2*). We have recently developed the ability to measure IA via dried blood spot (DBS) on filter paper with excellent correlation and no false positive compared with gold-standard fluid-phase radioimmunoassay measurement of IA in serum (unpublished data). DBS screening will allow for widespread screening for IA, for other programs using DBS, such as newborn screening for genetic disorders have been cost-effective and feasible. Ideally, screening would be conducted in a pediatrician's or family doctor's office at well child visits, as there is evidence in FDRs to support the assertion that the majority of people who develop T1D have IAs present at a young age.^{2,25,26}

The use of DBS removes barriers such as venipuncture to obtain blood, shipment of blood samples, and the need for multiple laboratories to conduct technically challenging IA assays. DBS on filter paper are simple

to collect and stable over time before extraction and can be mailed to central laboratories with expertise in measuring IA. One limitation to the use of DBS is the potential loss of specificity in the measurement of an antibody, but this is minimized because four antibodies are measured. A screening test is not meant to be diagnostic. Thus if a person tests positive for IA on DBS, then risk for T1D must be confirmed using the gold-standard determination of IA by measuring serum antibodies with radioimmunoassays. Because IA can become positive over time, interval screening is important. An evaluation for clinical symptoms and glycemic abnormalities would need to occur at the time of confirmation or shortly thereafter. The lifetime risk for T1D development in FDRs or those having high-risk HLA genes with a single autoantibody is 10 % and nearly 100 % if there are two or more antibodies.² If two or more serum IAs are present, then the patient would need an assessment by a pediatric endocrinologist in the community or referred to a tertiary care center. Pediatric and adult endocrinologists are familiar with treating FDRs who are at increased risk for T1D. If an individual is IA-positive, he or she would be followed the same way as a FDR, with close monitoring of fasting blood glucose, HbA_{1c}, and blood glucoses during a two-hour oral glucose tolerance test.

Conclusions

T1D is an immunologic disorder marked by the presence of IAs before onset of metabolic symptoms. The risk for developing T1D has been well defined and characterized in first-degree relatives by measuring serum antibodies directed against insulin, GAD, A-2, and ZnT8. However, approximately 85 % of all newly diagnosed patients with T1D do not have a family history of the disease, and despite having a defined preclinical disease, DKA remains a significant comorbidity. Screening the general population for T1D is rational and becoming possible with the advent of improved IA assays and the ability to measure IA from DBS on filter paper. Integrating this testing into standard pediatric clinical care at well child visits would allow for the detection of T1D risk in the entire pediatric population. However, cost, need for repeated testing, and access to healthcare will need to be addressed. Now that T1D is predictable, we remain hopeful and confident that screening will lessen the burden of disease and eventually lead to prevention. ■

- Atkinson MA, Eisenbarth GS, Michels AW, Type 1 diabetes, *Lancet*, 2014;383:69–82.
- Ziegler AG, Rewers M, Simell O, et al., Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children, *JAMA*, 2013;309:2473–9.
- Eisenbarth GS, Type I diabetes mellitus: a chronic autoimmune disease, *N Engl J Med*, 1986;314:1360–8.
- Hagopian WA, Sanjeevi CB, Kockum I, et al., Glutamate decarboxylase-, insulin-, and islet cell-antibodies and HLA typing to detect diabetes in a general population-based study of Swedish children, *J Clin Invest*, 1995;95:1505–11.
- Rewers M, Bugawan TL, Norris JM, et al., Newborn screening for HLA markers associated with IDDM: diabetes autoimmunity study in the young (DAISY), *Diabetologia*, 1996;39:807–12.
- Nejentsev S, Sjoroes M, Soukka T, et al., Population-based genetic screening for the estimation of type 1 diabetes mellitus risk in Finland: selective genotyping of markers in the HLA-DQB1, HLA-DQA1 and HLA-DRB1 loci, *Diabet Med*, 1999;16:985–92.
- Kimpimaki T, Kulmala P, Savola K, et al., Natural history of beta-cell autoimmunity in young children with increased genetic susceptibility to type 1 diabetes recruited from the general population, *J Clin Endocrinol Metab*, 2002;87:4572–9.
- Barker JM, Barriga KJ, Yu L, et al., Prediction of autoantibody positivity and progression to type 1 diabetes: Diabetes Autoimmunity Study in the Young (DAISY), *J Clin Endocrinol Metab*, 2004;89:3896–902.
- Bottazzo GF, Florin-Christensen A, Doniach D, Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies, *Lancet*, 1974;2:1279–83.
- Yu L, Dong F, Miao D, et al., Proinsulin/insulin autoantibodies measured with electrochemiluminescent assay are the earliest indicator of prediabetic islet autoimmunity, *Diabetes Care*, 2013;36:2266–70.
- Miao D, Guyer KM, Dong F, et al., GAD65 autoantibodies detected by electrochemiluminescence assay identify high risk for type 1 diabetes, *Diabetes*, 2013;62:4174–8.
- Miao D, Steck AK, Zhang L, et al., Electrochemiluminescence assays for insulin and glutamic acid decarboxylase autoantibodies improve prediction of type 1 diabetes risk, *Diabetes Technol Ther*, 2015;17:119–27.
- Vardi P, Ziegler AG, Mathews JH, et al., Concentration of insulin autoantibodies at onset of type 1 diabetes: inverse log-linear correlation with age, *Diabetes Care*, 1988;11:736–9.
- Bingley PJ, Bonifacio E, Mueller PW, Diabetes Antibody Standardization Program: first assay proficiency evaluation, *Diabetes*, 2003;52:1128–36.
- Schlosser M, Mueller PW, Torn C, et al., Participating L, Diabetes Antibody Standardization Program: evaluation of assays for insulin autoantibodies, *Diabetologia*, 2010;53:2611–20.
- Xu P, Beam CA, Cuthbertson D, et al., Prognostic accuracy of immunologic and metabolic markers for type 1 diabetes in a high-risk population: receiver operating characteristic analysis, *Diabetes Care*, 2012;35:1975–80.
- Sosenko JM, Palmer JP, Greenbaum CJ, et al., Patterns of metabolic progression to type 1 diabetes in the Diabetes Prevention Trial–Type 1, *Diabetes Care*, 2006;29:643–9.
- Dabelea D, Rewers A, Stafford JM, et al., Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study, *Pediatrics*, 2014;133:e938–45.
- Group DP, Incidence and trends of childhood type 1 diabetes worldwide 1990–1999, *Diabet Med*, 2006;23:857–66.
- Harjutsalo V, Sjoberg L, Tuomilehto J, Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study, *Lancet*, 2008;371:1777–82.
- Patterson CC, Dahlquist GG, Gyurus E, et al., Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–20: a multicentre prospective registration study, *Lancet*, 2009;373:2027–33.
- Lipman TH, Levitt Katz LE, Ratcliffe SJ, et al., Increasing incidence of type 1 diabetes in youth: twenty years of the Philadelphia Pediatric Diabetes Registry, *Diabetes Care*, 2013;36:1597–603.
- Lawrence JM, Imperatore G, Dabelea D, et al., Trends in incidence of type 1 diabetes among non-Hispanic white youth in the United States, 2002–2009, *Diabetes*, 2014;63:3938–45.
- Elding Larsson H, Vehik K, Gesualdo P, et al., Children followed in the TEDDY study are diagnosed with type 1 diabetes at an early stage of disease, *Pediatr Diabetes*, 2014;15:118–26.
- Steck AK, Johnson K, Barriga KJ, et al., Age of islet autoantibody appearance and mean levels of insulin, but not GAD or IA-2 autoantibodies, predict age of diagnosis of type 1 diabetes: diabetes autoimmunity study in the young, *Diabetes Care*, 2011;34:1397–9.
- Steck AK, Vehik K, Bonifacio E, et al., Predictors of progression from the appearance of islet autoantibodies to early childhood diabetes: the environmental determinants of diabetes in the young (TEDDY), *Diabetes Care*, 2015 [Epub ahead of print].

27. Geographic patterns of childhood insulin-dependent diabetes mellitus, Diabetes Epidemiology Research International Group, *Diabetes*, 1988;37:1113–9.
28. Imperatore G, Boyle JP, Thompson TJ, et al., Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth, *Diabetes Care*, 2012;35:2515–20.
29. Sosenko JM, Palmer JP, Raffkin-Mervis L, et al., Incident dysglycemia and progression to type 1 diabetes among participants in the Diabetes Prevention Trial–Type 1, *Diabetes Care*, 2009;32:1603–7.
30. Sosenko JM, Skyler JS, Beam CA, et al., Acceleration of the loss of the first-phase insulin response during the progression to type 1 diabetes in diabetes prevention trial-type 1 participants, *Diabetes*, 2013;62:4179–83.
31. Sosenko JM, Skyler JS, Herold KC, Palmer JP, Type 1 Diabetes T, Diabetes Prevention Trial–Type 1 Study G: the metabolic progression to type 1 diabetes as indicated by serial oral glucose tolerance testing in the Diabetes Prevention Trial–Type 1, *Diabetes*, 2012;61:1331–7.
32. Veijola R, Reijonen H, Vahasalo P, et al., HLA-DQB1–defined genetic susceptibility, beta cell autoimmunity, and metabolic characteristics in familial and nonfamilial insulin-dependent diabetes mellitus, Childhood Diabetes in Finland (DiMe) Study Group, *J Clin Invest*, 1996;98:2489–95.
33. Dahlquist G, Blom L, Holmgren G, et al., The epidemiology of diabetes in Swedish children 0–14 years—a six-year prospective study, *Diabetologia*, 1985;28:802–8.
34. Aly TA, Ide A, Humphrey K, et al., Genetic prediction of autoimmunity: initial oligogenic prediction of anti-islet autoimmunity amongst DR3/DR4-DQ8 relatives of patients with type 1A diabetes, *J Autoimmun*, 2005;25 Suppl:40–5.
35. Gullstrand C, Wahlberg J, Ilonen J, et al., Progression to type 1 diabetes and autoantibody positivity in relation to HLA-risk genotypes in children participating in the ABIS study, *Pediatr Diabetes*, 2008;9(3 Pt 1):182–90.
36. Standards of medical care in diabetes—2015: summary of revisions, *Diabetes Care*, 2015;Suppl. 38:S4.
37. Maclaren NK, Horne, G, Spillar, RP, et al., Islet cell autoantibodies (ICA) in US school children, *Diabetes*, 1985;34(Suppl. 1):84A.
38. Atkinson MA, Maclaren NK, Riley WJ, et al., Are insulin autoantibodies markers for insulin-dependent diabetes mellitus?, *Diabetes*, 1986;35:894–8.
39. Bergua M, Sole J, Marion G, et al., Prevalence of islet cell antibodies, insulin antibodies and hyperglycaemia in 2291 schoolchildren, *Diabetologia*, 1987;30:724–6.
40. Bruining GJ, Molenaar JL, Grobbee DE, et al., Ten-year follow-up study of islet-cell antibodies and childhood diabetes mellitus, *Lancet*, 1989;1:1100–3.
41. Karjalainen JK, Islet cell antibodies as predictive markers for IDDM in children with high background incidence of disease, *Diabetes*, 1990;39:1144–50.
42. Boehm BO, Manfras B, Seissler J, et al., Epidemiology and immunogenetic background of islet cell antibody–positive nondiabetic schoolchildren, Ulm–Frankfurt population study, *Diabetes*, 1991;40:1435–9.
43. Aanstoot HJ, Sigurdsson E, Jaffe M, et al., Value of antibodies to GAD65 combined with islet cell cytoplasmic antibodies for predicting IDDM in a childhood population, *Diabetologia*, 1994;37:917–24.
44. Schatz D, Krischer J, Horne G, et al., Islet cell antibodies predict insulin-dependent diabetes in United States school age children as powerfully as in unaffected relatives, *J Clin Invest*, 1994;93:2403–7.
45. Levy-Marchal C, Dubois F, Noel M, et al., Immunogenetic determinants and prediction of IDDM in French schoolchildren, *Diabetes*, 1995;44:1029–32.
46. Bingley PJ, Bonifacio E, Williams AJ, et al., Prediction of IDDM in the general population: strategies based on combinations of autoantibody markers, *Diabetes*, 1997;46:1701–10.
47. Strebelow M, Schlosser M, Ziegler B, et al., Karlsburg Type I diabetes risk study of a general population: frequencies and interactions of the four major Type I diabetes-associated autoantibodies studied in 9419 schoolchildren, *Diabetologia*, 1999;42:661–70.
48. Kulmala P, Rahko J, Savola K, et al., Beta-cell autoimmunity, genetic susceptibility, and progression to type 1 diabetes in unaffected schoolchildren, *Diabetes Care*, 2001;24:171–3.
49. Samuelsson U, Sundkvist G, Borg H, et al., Islet autoantibodies in the prediction of diabetes in school children, *Diabetes Res Clin Pract*, 2001;51:51–7.
50. LaGasse JM, Brantley MS, Leech NJ, et al., Successful prospective prediction of type 1 diabetes in schoolchildren through multiple defined autoantibodies: an 8-year follow-up of the Washington State Diabetes Prediction Study, *Diabetes Care*, 2002;25:505–11.
51. Maclaren NK, Lan MS, Schatz D, et al., Multiple autoantibodies as predictors of type 1 diabetes in a general population, *Diabetologia*, 2003;46:873–4.
52. Schlosser M, Strebelow M, Rjasanowski I, et al., Prevalence of diabetes-associated autoantibodies in schoolchildren: the Karlsburg Type 1 Diabetes Risk Study, *Ann N Y Acad Sci*, 2004;1037:114–7.
53. Gianani R, Putnam A, Still T, et al., Initial results of screening of nondiabetic organ donors for expression of islet autoantibodies, *J Clin Endocrinol Metab*, 2006;91:1855–61.
54. Knip M, Korhonen S, Kulmala P, et al., Prediction of type 1 diabetes in the general population, *Diabetes Care*, 2010;33:1206–12.
55. Siljander HT, Veijola R, Reunanen A, et al., Prediction of type 1 diabetes among siblings of affected children and in the general population, *Diabetologia*, 2007;50:2272–5.
56. Skyler JS, Greenbaum CJ, Lachin JM, et al., Type 1 Diabetes TrialNet—an international collaborative clinical trials network, *Ann N Y Acad Sci*, 2008;1150:14–24.
57. Simmons K, Michels AW, Lessons from type 1 diabetes for understanding natural history and prevention of autoimmune disease, rheumatic diseases clinics of North America, 2014;40:797–811.
58. Michels AW, von Herrath M, 2011 update: antigen-specific therapy in type 1 diabetes, *Curr Opin Endocrinol Diabetes Obes*, 2011;18:235–40.
59. Diabetes Prevention Trial–Type 1 Diabetes Study G: Effects of insulin in relatives of patients with type 1 diabetes mellitus, *N Engl J Med*, 2002;346:1685–91.
60. Vehik K, Cuthbertson D, Ruhlrig H, et al., Long-term outcome of individuals treated with oral insulin: diabetes prevention trial-type 1 (DPT-1) oral insulin trial, *Diabetes Care*, 2011;34:1585–90.
61. Herold KC, Gitelman SE, Masharani U, et al., A single course of anti-CD3 monoclonal antibody hOKT3gamma1(Ala-Ala) results in improvement in C-peptide responses and clinical parameters for at least 2 years after onset of type 1 diabetes, *Diabetes*, 2005;54:1763–9.
62. Haller MJ, Gitelman SE, Gottlieb PA, et al., Anti-thymocyte globulin/G-CSF treatment preserves beta cell function in patients with established type 1 diabetes, *J Clin Invest*, 2015;125:448–55.
63. Orban T, Bundy B, Becker DJ, et al., Costimulation modulation with abatacept in patients with recent-onset type 1 diabetes: follow-up 1 year after cessation of treatment, *Diabetes Care*, 2014;37:1069–75.
64. Pescovitz MD, Greenbaum CJ, Bundy B, et al., B-lymphocyte depletion with rituximab and beta-cell function: two-year results, *Diabetes Care*, 2014;37:453–9.
65. Keymeulen B, Walter M, Mathieu C, et al., Four-year metabolic outcome of a randomised controlled CD3-antibody trial in recent-onset type 1 diabetic patients depends on their age and baseline residual beta cell mass, *Diabetologia*, 2010;53:614–23.
66. Wald NJ, Guidance on terminology, *J Med Screen*, 2001;8:56.
67. Wilson JM, Jungner YG, Principles and practice of mass screening for disease, *Bol Oficina Sanit Panam*, 1968;65:281–393.
68. Dall TM, Zhang Y, Chen YJ, et al., The economic burden of diabetes, *Health Affairs*, 2010;29:297–303.
69. Dall TM, Yang W, Halder P, et al., The economic burden of elevated blood glucose levels in 2012: diagnosed and undiagnosed diabetes, gestational diabetes mellitus, and prediabetes, *Diabetes Care*, 2014;37:3172–9.
70. Maldonado MR, Chong ER, Oehl MA, Balasubramanyam A, Economic impact of diabetic ketoacidosis in a multiethnic indigent population: analysis of costs based on the precipitating cause, *Diabetes Care*, 2003;26:1265–9.
71. Gregg EW, Li Y, Wang J, et al., Changes in diabetes-related complications in the United States, 1990–2010, *N Engl J Med*, 2014;370:1514–23.
72. Cameron FJ, Scratch SE, Nadebaum C, et al., Neurological consequences of diabetic ketoacidosis at initial presentation of type 1 diabetes in a prospective cohort study of children, *Diabetes Care*, 2014;37:1554–62.
73. Lin A, Northam EA, Werther GA, Cameron FJ, Risk factors for decline in IQ in youth with type 1 diabetes over the 12 years from diagnosis/illness onset, *Diabetes Care*, 2015;38:236–42.
74. Triolo TM, Chase HP, Barker JM, Group DPTS, Diabetic subjects diagnosed through the Diabetes Prevention Trial–Type 1 (DPT-1) are often asymptomatic with normal A1C at diabetes onset, *Diabetes Care*, 2009;32:769–73.
75. Ludvigsson J, Gustafsson-Stolt U, Liss PE, Svensson T, Group AS, Mothers of children in ABIS, a population-based screening for prediabetes, experience few ethical conflicts and have a positive attitude, *Ann N Y Acad Sci*, 2002;958:376–81.