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

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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
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. 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). 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. 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.

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. 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. 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. 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 (HbA1c) 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 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 HbA1c, 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 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.

**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). Clinical prevention trials to date have shown encouraging but limited success in delaying the diagnosis of T1D. 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. 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. 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. 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. 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 DIAPREVIT, 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. 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). 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. Although the cost for a hospital admission for DKA at onset varies widely, the cost can exceed $20,000. 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. 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. DKA can cause morphologic and functional brain changes, leading to poor neurocognitive outcomes. 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. 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. 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. DBSs 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 glaceses 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.

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Figure 1: Natural History of Type 1 Diabetes
GAD = glutamic decarboxylase; HbA1c = glycated hemoglobin; HLA = human leukocyte antigen; IA-2 = islet antigen 2; IAA = insulin; OGTT = oral glucose tolerance test; ZnT8 = zinc transporter.
Figure 2:
Proposed Flowchart for Conducting General Population Screening by Measuring Islet Autoantibodies in Children Younger than 18 Years

Diabetes education and screen for type 1 diabetes risk

Antibody negative

No further action required

Antibody positive

Confirm positive screen and assess clinical diagnostic criteria for type 1 diabetes

Antibody negative

Antibody positive

Appointment with pediatric endocrinologist and opportunity to participate in clinical research
### 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 | ICA: 0.6 %  | GAD: 0.1 %    | IAA: 0.2    | ICA: 0.6 %  | GAD: 0.1 % | IAA: 0.2 | 38         |
| Spain 1987        | 2,291 | 14–17       | ICA and IAA | ICA: 0.4 %    | IAA: 0.4 %    | No follow-up | 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 | ICA: 100 %  | ICA: 99 %   | ICA: 18 % | ICA: 100 % | 44         |
| Sweden 1995       | 415   | 0–15        | ICA< GA< IAA | ICA: 4.1 %    | No follow-up  | ND          | ND          | ND   | ND   | 4          |
| Location and Date | n | Age (Years) | IA Measured | IA Prevalence | TID Incidence | Sensitivity | Specificity | PPV | NPV | References |
|-------------------|---|-------------|-------------|---------------|---------------|-------------|-------------|-----|-----|------------|
| 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 | ICA: 2.4 % | GAD: 2.2 % | IA-2: 2.1 % | IAA: 2.0 % | ≥2 IA: 0.7 % | ND | ND | ND | 46 |
| Germany 1999      | 9,419 | 6–17 | ICA, GAD, IA-2, IAA | ICA: 0.9 % | GAD: 3.0 % | IA-2: 2.4 % | IA: 2.4 % | ≥2 IA: 0.8 % | ND | ND | ND | 47 |
| Finland 2001      | 3,652 | >6 | ICA, GAD, IA-2, IAA | ICA: 2.8 % | GAD: 0.5 % | IA-2: 0.6 % | IAA: 0.9 % | ND | ND | ND | 48 |
| Location and Date | n   | Age (Years) | IA Measured | IA Prevalence | T1D Incidence | Sensitivity | Specificity | PPV | NPV | References |
|-------------------|-----|-------------|-------------|---------------|---------------|-------------|-------------|-----|-----|------------|
| Sweden 2001       | 1,031 | 7–13 | ICA, GAD, IA-2 | ≥2 IA: 0.6 % | • ICA: 1.4 % | • GAD: 2.4 % | • IA-2: 1.8 % | • IA: 0.6 % over 10 years | • ICA: 67 % | • GAD: 83 % | • IA-2: 33 % | • IA: 33 % | • ≥2 IA: 100 % | • ≥2 IA: 100 % | • ≥2 IA: ND | ND | 49 |
| Washington state 2002 | 4,504 | 12–18 | GAD, IA-2, IAA | ≥2 IA: 0.3 % | • GAD: 0.9 % | • IA-2: 0.5 % | • IAA: 0.9 % | • ≥2 IA: 0.3 % | • ≥2 IA: 0.3 % over 8 years | • ≥IA: 100 % | ND | ≥2 IA: 50 % | ND | 50 |
| Florida 2003      | 9,698 | 5–18 | ICA, then GAD, IA-2, IAA | ≥2 IA: 0.3 % | • ≥IA: 6.5 % | • ≥IA: 0.6 % excluding ICA | No follow-up | ND | ND | ND | ND | ND | 51 |
| Germany 2004      | 11,840 | 6–17 | ICA, GAD, IA-2, IAA | ≥2 IA: 0.3 % | • GAD: 0.8 % | • IA-2: 0.8 % | No follow-up | ND | ND | ND | ND | ND | 52 |
| Colorado 2006     | 122, *organ donors | 0–86 | GAD, IA-2 | ≥2 IA: 0.8 % | • GAD: 0.8 % | • IA-2: 0.8 % | No follow-up | ND | ND | ND | ND | ND | 53 |
| 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   | • GAD: 1.0 %  | 0.5 % over 27 years | • GAD: 50 % | • GAD: 99 % | • IA-2: 0.6 % | • IA-2: 50 % | 54, 55 |
|                   |       |             |             | • IA-2: 0.6 % |               | • IA-2: 50 % | • IA-2: 100 % | • ≥ IA: 61 % | • ≥ IA: 100 % |            |
|                   |       |             |             |               |               | • ≥ IA: 99 % | • ≥ IA: 100 % | • ≥ IA: 39 % | • ≥ IA: 100 % |            |

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.
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 Figure 1)                |
| 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.
Table 3:

Pros and Cons of Screening for Type 1 Diabetes Risk

| Pros                                                                 | Cons                                                                 |
|----------------------------------------------------------------------|----------------------------------------------------------------------|
| • Meets World Health Organization’s screening guidelines48          | • Preventive treatment not yet available                             |
| • Decrease life-threatening DKA                                      | • Low prevalence in general population                               |
| • Reliable methods to detect IA                                     | • Need to repeat IA testing at regular intervals                     |
| • Reduced economic burden                                           | • Cost-benefit analysis not yet performed for multiple screenings in an individual |
| • Clinical prevention trials available                              | • Access to healthcare for screening                                 |
| • Greater understanding of disease natural history from the general population | • Concerns for increased anxiety based on test results                |

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