General population screening for type 1 diabetes: has its time come?

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Purpose of review
The purpose of this review was to describe the potential for general childhood population-based screening of risk of symptomatic type 1 diabetes (T1D)

Recent findings
The earliest stages of T1D can be identified and risk and rate of progression to symptomatic disease can be estimated by the presence of multiple islet autoantibodies and glucose intolerance (dysglycemia) in individuals screened for risk. Screening for human leukocyte antigen risk genotypes in neonates with follow-up detection of islet autoantibodies in childhood has been explored. An alternative approach of general childhood population-based detection of autoantibodies at well child visits provides an approach to detect a high proportion of children who will develop T1D. The Fr1da study was launched in Bavaria in 2015 to explore this concept.

Summary
General childhood population-based screening for risk of T1D will allow detection of an at-risk population that can participate in natural history studies to better understand disease pathogenesis and intervention trials to prevent symptomatic disease and will provide a framework for public health-based prevention of childhood-onset T1D.

Keywords
disease staging, prevention, risk screening, type 1 diabetes

INTRODUCTION

Type 1 diabetes (T1D) is an immune-mediated syndrome associated with loss of functional beta cell mass, lifelong insulin dependence, and risk of diabetic complications [1▪]. The disease arises from a contribution of both genetics, which have been relatively well defined [2], and environmental etiologies, which have not been well elucidated but are contributing an increasing role in disease susceptibility. T1D unfolds with progression from onset of islet autoimmunity, as detected by the presence of autoantibodies to islet antigens (proinsulin, insulin, GAD, IA-2, ZnT8), to loss of functional beta cell mass that results in detectable glucose intolerance, or dysglycemia, which progresses to symptomatic disease when functional beta cell mass reaches a critically low level.

Over the last 5 decades, the incidence of childhood-onset T1D has been increasing in many countries at a rate of ~2–4% annually [3]. In addition, an earlier age of onset of childhood-onset T1D has been observed in several countries [4]. The increasing incidence and prevalence of childhood-onset T1D has catalyzed urgency for its prevention. Designing clinical trials to prevent T1D requires both insights into the natural history of the disease and the ability to detect an at-risk target population for trials.

Presymptomatic type 1 diabetes has distinct stages with variability in rates of progression

Distinct early stages of T1D are now recognized [5▪▪]:

(1) Stage 1 – multiple (two or more) islet autoantibody positive/normoglycemic/asymptomatic;

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KEY POINTS

- Islet autoantibody screening can detect risk of T1D.
- Multiple islet autoantibodies are associated with high risk of developing symptomatic T1D.
- Risk detection can be conducted on a childhood-wide population and thus not be limited to relatives of individuals with T1D, representing a small proportion of newly diagnosed cases of T1D.
- The Fr1da Model Project Diabetes 2015 is offering islet autoantibody screening to 200 000 children at well child visits at 3 and 4 years of age, and has the potential to decrease the risk of developing diabetic ketoacidosis at diagnosis, preserve residual beta cell function, and enroll children in natural history and intervention trials to decrease the risk of disease progression.

(2) Stage 2 – multiple islet autoantibody positive/dysglycemic (glucose intolerance)/asymptomatic; and
(3) Stage 3 – symptomatic disease.

Although T1D progresses quite consistently through these stages, the rate of progression from stage 1 to stage 3 is quite variable – from months to decades. Stage 1 has a 5-year risk of 30–50% developing symptomatic disease that increases to 75–80% at stage 2 [5▪▪]. This ability to stage presymptomatic T1D creates a framework for clinical trials to delay and prevent the onset of clinical symptoms and lifelong insulin dependence.

Target populations for risk screening

Our current understanding of the natural history of T1D has arisen from screening for risk of disease with follow-up longitudinally of at-risk populations. Several populations have been targeted for screening. First and second-degree relatives of individuals with T1D, who have an approximately 10–20-fold increased disease risk compared with background population, have been screened for the presence of islet autoantibodies (stage 1) in several studies, including the Diabetes Prevention Trial-Type 1 trial [6] and in the pathway to prevention natural history trial of TrialNet [7]. Because only 10–15% of newly diagnosed individuals with T1D have an affected relative, this approach to risk screening has limited potential to capture the majority of susceptible patients.

An alternative approach to increase detection of the at-risk population is to screen for genetic risk and then follow that population for onset of islet autoantibodies (stage 1). The ready access to blood samples collected routinely from neonates and the major contribution to susceptibility to T1D from human leukocyte antigen (HLA) genotypes, which confers approximately 50% of the genetic risk, have been leveraged to screen for risk in neonates from the general population. An example of this type of screening is The Environmental Determinants of Diabetes in the Young (TEDDY) natural history study in which over 8000 children were enrolled from screening of over 400 000 neonates recruited from primarily the general population and also from families with a first-degree relative affected by T1D. The at-risk children are being followed for 15 years to identify environmental etiologies and track the development of islet autoantibodies and clinical disease [8]. Children from the general population were eligible if they had one of four at-risk HLA genotypes, which has an overall prevalence of about 5%, confers an expected risk of disease of 3%, and represents around 40% of all cases of symptomatic T1D occurring by age 15 years. Risk in the remaining 95% of the population is less than 0.1%.

To expand the pool of at-risk children beyond high-risk HLA genotypes, a general childhood population can be screened for islet autoantibodies (stage 1). Recent insights into the timing of islet autoantibody seroconversion in childhood and the predictive value of multiple autoantibodies, noted above, have provided a framework to apply this approach experimentally on a childhood population-wide basis as detailed below for the Fr1da Model 2015 Diabetes Project, which represents the first general population-based screening for islet autoantibodies.

Progression to type 1 diabetes is inevitable once multiple islet autoantibodies (stage 1) are detected in children from the general population with HLA-genotype risk or with a family history of type 1 diabetes

Combining the data from three long-term prospective studies in Germany (BABYDIAB), Finland (DIPP), and Colorado (DAISY) that have followed at-risk children from birth generated a dataset of 13 377 children with 20 years prospective follow-up and over 300 cases of T1D and has provided true estimates of time of disease progression from the onset of islet autoantibody seroconversion [9]. The analysis demonstrated that children whether initially identified from the general population based on HLA risk genotypes or based on a prior family history of T1D who subsequently develop two or more islet autoantibodies are destined to develop clinical symptomatic diabetes. The progression to diabetes after multiple autoantibody

seroconversion is 43.5% (95% confidence interval, 39.4–47.8%), 69.7% (65.1–74.3%), and 84.2 (77.7–89.7%) by 5, 10, and 15 years, respectively (Fig. 1), and the risk was similar in children with or without a family history of T1D [9]. The detection of single islet autoantibodies is associated with a markedly lower risk (14.5% by 10 years) to develop T1D [9]. Notably, in children with multiple islet autoantibodies, progression rates to clinical T1D are reasonably constant over time. Approximately 11% of the multiple islet autoantibody positive children develop clinical T1D every year. Progression to symptomatic diabetes is faster for children who have islet autoantibody seroconversion younger than age 3 years (12.5% per year), for children with the HLA genotype *DR3/DR4-DQ8*, and for girls, but the yearly risk remains relatively constant [9].

Screening for stage 1 in the general childhood population: the Fr1da model project diabetes 2015

Routine well child visits are practical opportunities to apply childhood population-based screening for T1D. The Fr1da Model Project Diabetes 2015 (www.typ1diabetes-frueherkennung.de) was launched in Bavaria Germany in January 2015, in which screening for multiple islet autoantibodies is offered at well child visits at 3 and 4 years of age for up to 200 000 children (Fig. 2). With 50% enrollment, there is the potential to detect the earliest stages of T1D in approximately 200–300 children in this cohort. The islet autoantibody screening is performed on capillary blood as a two-step assay with an initial assay for antibodies to GAD, IA-2, or ZnT8 in a multiplex assay. If the multiplex autoantibody assay generates a 'positive' signal, then antibodies to GAD, IA-2, ZnT8 along with insulin are assayed in separate single assays. If any two autoantibodies are positive, a second blood sample is collected and the autoantibodies are reassayed. If two or more autoantibodies are confirmed, then a diagnosis of presymptomatic T1D is made and the family informed. Children with autoantibodies to only a single autoantigen (GAD, IA-2, or ZnT8) are not being followed or rescreened in this initial pilot trial because of cost and relatively low risk of developing T1D compared with multiple islet autoantibody subjects at these ages [9].

The presymptomatic T1D children are offered the opportunity to enroll in a natural history study and potentially in an intervention trial to arrest progression of T1D that is being designed. Although the rate of progression to symptomatic disease in children with multiple autoantibodies who had a family history of T1D was similar to children with HLA-genotype risk [9], the rate of progression of children screened directly from the general population for multiple autoantibodies has not been studied and will be evaluated in the Fr1da project. It is estimated, however, that the Fr1da project could detect up to 60% of childhood-onset T1D occurring before age 20 years in this population.

The optimal age to introduce islet autoantibody general childhood screening is a compromise between the sensitivity of detecting a large number of children who have already developed multiple islet autoantibodies (better with later age screening) and the loss of sensitivity because of children progressing to diabetes (better with earlier age screening). In total, around 0.3–0.5% of children are expected to develop multiple islet autoantibodies

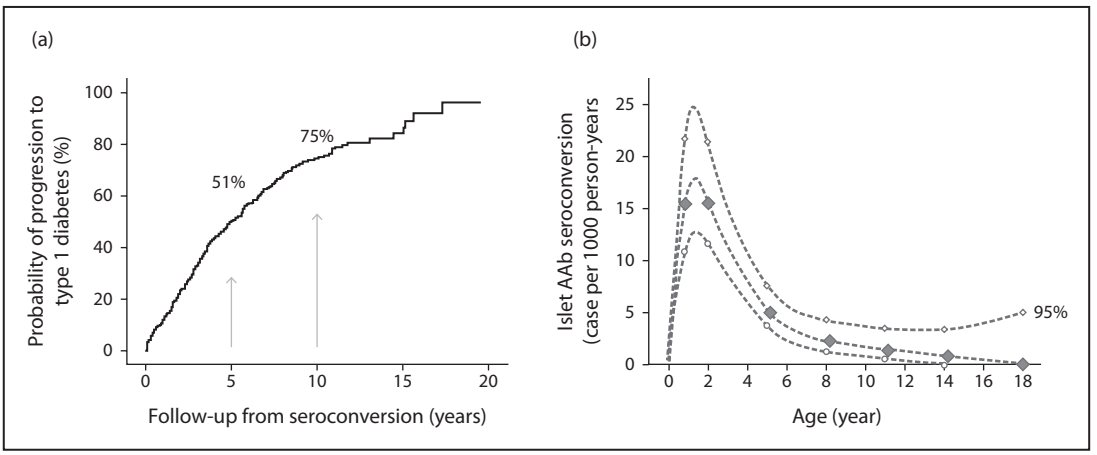

FIGURE 1. Progression to type 1 diabetes (T1D) in children with multiple islet autoantibodies and age incidence of detection of islet autoantibodies. (a) The 5- and 10-year risk of progression to T1D in children with multiple islet autoantibodies age 5 years or less is 51 and 75% (modified from [9]). (b) The incidence of islet autoantibodies peaks around 1–2 years of age. Adapted with permission from [13].

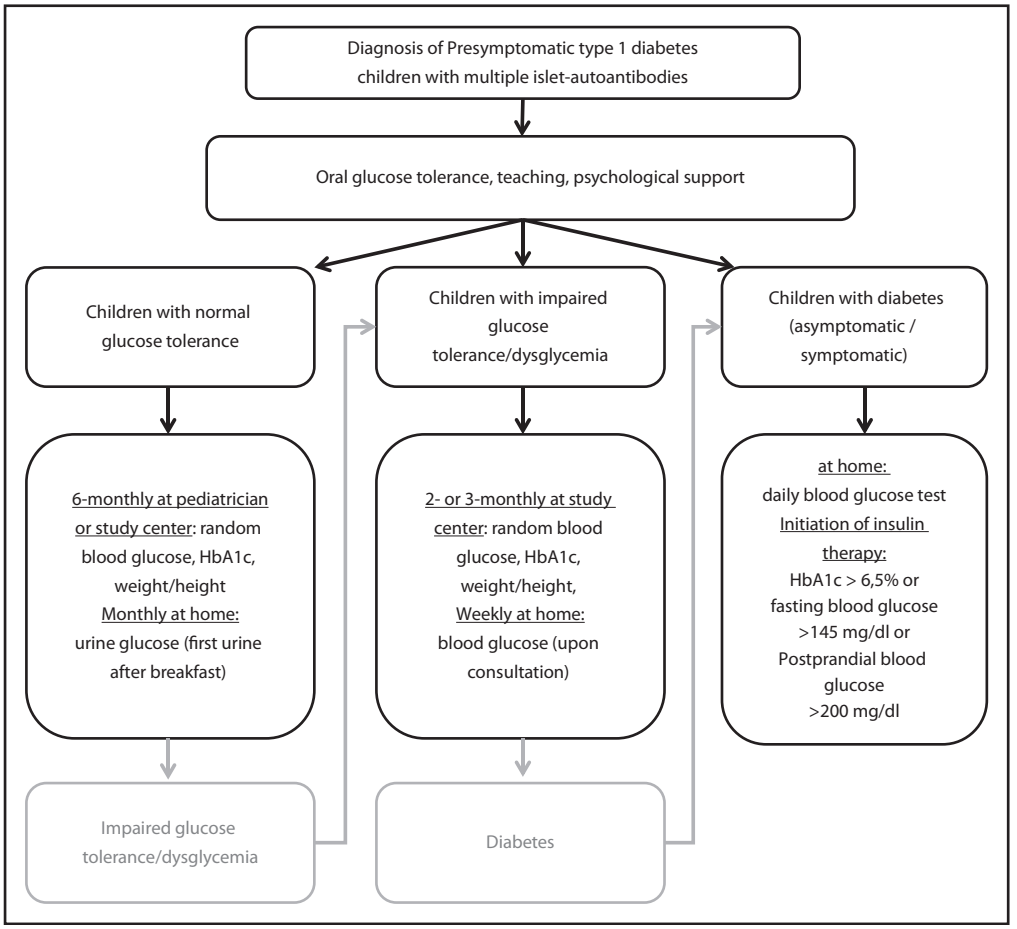

FIGURE 2. Fr1da Model Project Diabetes 2015: recommendation for treatment and care of children with pre type 1 diabetes.

during childhood [10–12]. Islet autoantibody seroconversion is most pronounced in the first 2 years of life (Fig. 1) [13,14,15▪▪]. Furthermore, in children progressing to multiple islet autoantibodies, the progression from single to multiple islet autoantibodies is rapid after seroconversion [16▪]. Of the above-mentioned 13 377 children longitudinally followed from birth [9], 61 and 80% of children developed multiple islet autoantibodies before the age of 3 and 5 years, respectively. On the other hand, 11 and 25% of the children who developed T1D during follow-up (maximum age, 20 years) had done so before the age of 3 and 5 years, respectively. Screening around these ages, e.g., between 2 and 6 years, is likely to yield maximum sensitivity for multiple islet autoantibodies to identify children who will develop T1D before adulthood. Although screening for islet autoantibodies initially at age 2 to 3 years, and rescreening the negatives 2 to 3 years later would have provided more complete identification of children with early asymptomatic T1D, and identified ~50% more cases, the initial Fr1da pilot was designed as a single screening because screening twice in childhood doubled the screening cost.

Current benefits of early screening and detection of type 1 diabetes

General population-based screening is an important component of public health by identifying early disease or predisposition to disease in order to initiate treatment to reduce morbidity and mortality. However, a well tolerated/effective intervention for those determined to be at risk for T1D after screening is not currently available. Nonetheless, there are current potential benefits of screening for T1D risk. Importantly, general childhood population screening can facilitate early diagnosis and decrease morbidity and mortality related to diabetic ketoacidosis (DKA) and cerebral edema at diagnosis. In TEDDY, screening newborns significantly reduced DKA rates in children diagnosed with T1D at ages less than 2 years (16.1% vs. 39.5–54% in diabetes registries) and less than 5 years (13.1% vs. 16.9–36.4%) [17]. Children participating in the

DAISY natural history study had significantly reduced rates of hospitalization (<10% vs. >40%) and lower HbA1c levels at diabetes diagnosis compared with children in the general community [18].

Other advantages of screening may include the establishment of new standards for early diagnosis of T1D, counseling and teaching families prior to onset of clinical diabetes, earlier insulin administration with the potential to preserve greater residual beta cell function, which may lead long-term to decreased hypoglycemia and other complications, the opportunity to learn about the pathogenesis of T1D by recruitment to follow-up studies, and importantly, the opportunity to conduct prevention studies to prevent insulin dependence on a broad population-based level and with relatively rapid recruitment capacity.

Arguments against screening are the potential negative psychological impact of knowledge of risk of developing symptomatic T1D, which the TEDDY study is currently evaluating [19]. It is also useful to consider alternatives to screening for islet autoantibodies to prevent DKA. One alternative is increasing community awareness, but awareness campaigns targeting DKA in the pediatric setting over the last 15–20 years have not durably reduced its prevalence [20].

Although the costs of screening for T1D risk have decreased and the positive predictive value has increased, the costs of follow-up of at-risk patients are large, especially in the absence of an effective intervention. Nonetheless, because the evidence strongly indicates that most of those with multiple autoantibodies will develop T1D in their lifespan, general population screening for multiple autoantibodies currently can be justified experimentally on the basis of preventing acute-onset morbidity and mortality and generating cohorts for evaluating interventions to arrest disease progression.

Costs, benefits, logistics of the Fr1da model project diabetes 2015

The logistical requirements of a simple T1D screening test require easy handling for venipuncture/blood collection and sample transport, and timely reporting of results. For the Fr1da Model Project Diabetes 2015, the primary care pediatrician obtains consent, performs capillary blood collection, and completes a one-page questionnaire. Pediatricians are provided with bar-coded capillary tubes, questionnaires, and addressed prepaid reply envelopes. The cost of a screening program includes costs for islet autoantibody assay (laboratory), obtaining informed consent, sample shipment, result reporting, informing of positive families, and teaching and care of positive children. In the Bavarian Fr1da Study, these costs are estimated to be around 20 Euro per screened child, with the assay cost for a capillary-based three-screen islet autoantibody assay representing only around 10% of the cost. Prevention of DKA and hospitalization in 200 screened children would save approximately 680 000 Euro in healthcare costs, which represents about one-third of the cost of the Fr1da Study. The program thus does not pay for itself without further benefits, which in the future could be prevention or delay of symptomatic diabetes and insulin requirements. Future approaches to reduce screening costs could include a point-of-care screen that immediately excludes the large majority of negatives, compulsory testing to avoid consenting, and less expensive assays for risk screening.

Standard care outside of research of children with stage 1 or stage 2 type 1 diabetes

There are no guidelines or directives for treatment of children with early asymptomatic T1D. Similar to children with overt disease, we suggest that treatment and care must consist of education, self-monitoring, and psychological support. Moreover, standards regarding the timing of initiation of insulin therapy in children with asymptomatic T1D will need to be developed. The American Diabetes Association criteria for laboratory diagnosis of asymptomatic type 2 diabetes may not prove optimum for asymptomatic T1D. Teaching and education should focus on understanding diabetes pathogenesis and symptoms and signs of hyperglycemia and home glucose monitoring. Self-monitoring may consist of urine as well as blood glucose. HbA1c should also be monitored on a regular basis because it is predictive of time to symptomatic disease. A 10% increase in HbA1c levels in samples taken 3–12 months apart or an HbA1c at least 5.9% (41 mmol/mol) predicted the diagnosis of clinical disease [21▪]. Other assays, including C-peptide measurements, are being developed to predict rate of progression to symptomatic disease. Psychological care includes assessment of anxiety and distress associated with an impending chronic disease in childhood (lifelong commitment of blood sugar monitoring, insulin injections, healthy eating, and regular exercise) and individualized support to cope with this knowledge.

As part of the Bavarian Fr1da study, a preventive care plan has been developed that recommends 6 monthly checkups for children with normoglycemia (stage 1), and 2–3 monthly visits for children with dysglycemia (stage 2) (Fig. 2).

Linking risk detection to preventive intervention

An important goal of risk screening is ultimately prevention of symptomatic disease. Screening on a population level will markedly increase the number of children in whom prevention therapy could be applied. This would provide an unprecedented opportunity to design prevention trials to prevent or delay clinical diabetes and insulin dependence on a population-based level. If 100 000 children were screened for asymptomatic T1D in one region within 1 year, and 200–300 children with multiple islet autoantibodies identified, a single clinical efficacy trial could be completed in this one region within a period of 5 years. This is in contrast to current T1D prevention trials that recruit from affected families, and in which recruitment requires several years of multicenter screening and long follow-up. The ability to recruit to prevention trials is also likely to increase the acceptance of screening on a population-based level. This leap in numbers of potential at-risk patients from population screening would allow multiple prevention trials and hopefully speed up the identification of well tolerated, efficacious therapies, leading us to the next phase of precision medicine with personalized intervention strategies that are adapted to the individual at each of the earliest stages of T1D.

CONCLUSION

General childhood population-based approaches to screen for risk of T1D based on detection of islet autoantibodies in children at well child visits have the potential in the short-term to decrease hospitalization and life-threatening DKA at onset of symptomatic disease, and in the long-term, to preserve greater residual beta cell function with decreased risk of complications and provide cohorts to better characterize the natural history of childhood-onset T1D and to conduct secondary prevention trials to delay and ultimately prevent symptomatic disease. The Fr1da Model Project Diabetes 2015 is offering screening to 200 000 children at well child visits at age 3 and 4 years of age in Bavaria over 12 months and represents the first study of general population-based islet autoantibody screening.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet 2014; ■ 383:69–82.

Good current review of pathogenesis of type 1 diabetes and challenges some current T1D dogma.

2. Concannon P, Rich SS, Nepom GT. Genetics of type 1A diabetes. N Engl J Med 2009; 360:1646–1654.
3. Patterson CC, Dahlquist GG, Gyürüs E, *et al.,* EURODIAB Study Group. 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; 373:2027–2033.
4. Harjutsalo V, Sjöberg L, Tuomilehto J. Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study. Lancet 2008; 371:1777–1782.
5. Defining the Early Stages of Type 1 Diabetes, http://cdn.jdrf.org/wp-content/ ■■ uploads/2012/12/Defining-the-Early-Stages-of-T1D-Workshop-Presentations-10-10-2014.pdf. [Accessed 3 May 2015].

Describes a classification of the early stages of T1D that provides a framework for clinical trial design and prevention.

6. Skyler JS, Krischer JP, Wolfsdorf J, *et al.* Effects of oral insulin in relatives of patients with type 1 diabetes: the Diabetes Prevention Trial – Type 1. Diabetes Care 2005; 28:1068–1076.
7. Mahon JL, Sosenko JM, Rafkin-Mervis L, *et al.* TrialNet Natural History Committee; Type 1 Diabetes TrialNet Study Group. The TrialNet Natural History Study of the Development of Type 1 Diabetes: objectives, design, and initial results. Pediatr Diabetes 2009; 10:97–104.
8. Hagopian WA, Erlich H, Lernmark A, *et al.,* TEDDY Study Group. The Environmental Determinants of Diabetes in the Young (TEDDY): genetic criteria and international diabetes risk screening of 421 000 infants. Pediatr Diabetes 2011; 12:733–743.
9. Ziegler AG, Rewers M, Simell O, *et al.* Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. JAMA 2013; 309:2473–2479.
10. 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; 42:661–670.
11. Bingley PJ, Bonifacio E, Williams AJ, *et al.* Prediction of IDDM in the general population: strategies based on combinations of autoantibody markers. Diabetes 1997; 46:1701–1710.
12. LaGasse JM, Brantley MS, Leech NJ, *et al.* Washingtno State Diabetes Prediction Study. Successful prospective prediction of T1D in schoolchildren through multiple defined autoantibodies: an 8-year follow-up of the Washington State Diabetes Prediction Study. Diabetes Care 2002; 25:505–511.
13. Ziegler AG, Bonifacio E. BABYDIAB-BABYDIET Study Group. Age-related islet autoantibody incidence in offspring of patients with T1D. Diabetologia 2012; 55:1937–1943.
14. Parikka V, Näntö-Salonen K, Saarinen M, *et al.* Early seroconversion and rapidly increasing autoantibody concentrations predict prepubertal manifestation of T1D in children at genetic risk. Diabetologia 2012; 55:1926–1936.
15. Krischer JP, Lynch KF, Schatz D A, *et al.,* The TEDDY Study Group. The six- ■■ year incidence of diabetes associated autoantibodies in genetically at-risk children: the TEDDY Study. Diabetologia 2015; 58:980–987.

Characterizes the timing and specificity of the development of islet autoantibodies in the TEDDY childhood cohort (peak seroconversion at 12–24 months of age, autoantibodies detected as early as 3 months of age, insulin autoantibodies predominated early in life, and the order of appearance of specific islet autoantibodies was related to HLA-DR-DQ genotypes).

16. Chmiel R, Giannopoulou EZ, Winkler C, *et al.* Progression from single to ■ multiple islet autoantibodies often occurs soon after seroconversion: implications for early screening. Diabetologia 2015; 58:411–413.

Describes the time course of progression of detection of single to multiple autoantibodies in at-risk children.

17. Elding Larsson H1, Vehik K, Bell R, *et al.,* TEDDY Study Group; SEARCH Study Group; Swediabkids Study Group; DPV Study Group; Finnish Diabetes Registry Study Group. Reduced prevalence of diabetic ketoacidosis at diagnosis of type 1 diabetes in young children participating in longitudinal follow-up. Diabetes Care 2011; 34:2347–2352.
18. Barker JM, Goehrig SH, Barriga K, *et al.,* DAISY Study. Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up diabetes. Care 2004; 27:1399–1404.
19. Roth R, Lynch K, Lernmark B, *et al.,* The TEDDY Study Group. Maternal anxiety about a child's diabetes risk in the TEDDY study: the potential role of life stress, postpartum depression, and risk perception. Pediatr Diabetes 2015; 16:287–298.
20. Dabelea D, Rewers A, Stafford JM, *et al.,* SEARCH for Diabetes in Youth Study Group. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. Pediatrics 2014; 133:e938–e945.
21. ■ Helminen O, Aspholm S, Pokka T, *et al.* HbA1c predicts time to diagnosis of type 1 diabetes in children at risk. Diabetes 2014; 64:1719–1727.
Demonstrates that increasing HbA1c over time and a persistent elevated (≥5.9%) HbA1c can be a useful prognostic biomarker of disease progression to symptomatic disease in children with multiple autoantibodies.