Anette-G. Ziegler,[1,2] Ezio Bonifacio,[3,4,5] Alvin C. Powers,[6,7,8] John A. Todd,[9] Leonard C. Harrison,[10] and Mark A. Atkinson[11]

Type 1 Diabetes Prevention: A Goal Dependent on Accepting a Diagnosis of an Asymptomatic Disease

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Type 1 diabetes, a disease defined by absolute insulin deficiency, is considered a chronic autoimmune disorder resulting from the destruction of insulin-producing pancreatic β-cells. The incidence of childhood-onset type 1 diabetes has been increasing at a rate of 3%–5% per year globally. Despite the introduction of an impressive array of therapies aimed at improving disease management, no means for a practical "cure" exist. This said, hope remains high that any of a number of emerging technologies (e.g., continuous glucose monitoring, insulin pumps, smart algorithms), alongside advances in stem cell biology, cell encapsulation methodologies, and immunotherapy, will eventually impact the lives of those with recently diagnosed or established type 1 diabetes. However, efforts aimed at reversing insulin dependence do not address the obvious benefits of disease prevention. Hence, key "stretch goals" for type 1 diabetes research include identifying improved and increasingly practical means for diagnosing the disease at earlier stages in its natural history (i.e., early, presymptomatic diagnosis), undertaking such efforts in the population at large to optimally identify those with presymptomatic type 1 diabetes, and introducing safe and effective therapeutic options for prevention.

WHAT DOES "AN EARLY, PRESYMPTOMATIC DIAGNOSIS OF TYPE 1 DIABETES" MEAN?

The traditional diagnosis of type 1 diabetes based on persistent hyperglycemia is preceded by a variable (many months to years) period of asymptomatic β-cell autoimmunity (1). Research efforts over the last three decades involving literally millions of individuals have established a paradigm for diagnosing β-cell autoimmunity based on the analysis of type 1 diabetes–associated autoantibodies (AAbs) against insulin, glutamic acid decarboxylase, insulinoma-associated protein 2, and zinc transporter 8 (2,3). These efforts have demonstrated that type 1 diabetes–associated AAbs are diagnostic and that children with multiple AAbs progress to symptomatic diabetes at a rate approximating 11% per year (4).

In contrast to the traditional diagnosis of type 1 diabetes, an emerging concept embraces the impact of the aforementioned high rate of progression to overt hyperglycemia in children with multiple AAbs (5). This proactively posits that these children do, in effect, have type 1 diabetes but it is "presymptomatic" and that type 1 diabetes is primarily an immune disorder and secondarily a metabolic one. Adoption of this concept by the health care community would not only provide a unique opportunity for an earlier diagnosis of type 1 diabetes but also open up new opportunities for prevention-directed therapies.

HOW DO WE IMPLEMENT TYPE 1 DIABETES EARLY DIAGNOSIS FOR PREVENTION?

One key initial question arising from this line of thought is, "What efforts are needed to enable the diagnosis of

[1]Institute of Diabetes Research, Helmholtz Zentrum München, Neuherberg, Germany
[2]Forschergruppe Diabetes, Klinikum rechts der Isar, Technische Universität München, München, Germany
[3]DFG-Center for Regenerative Therapies Dresden, Faculty of Medicine, Technische Universität Dresden, Dresden, Germany
[4]Paul Langerhans Institute Dresden, German Center for Diabetes Research (DZD), Technische Universität Dresden, Dresden, Germany
[5]Forschergruppe Diabetes e.V., Neuherberg, Germany
[6]Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, TN
[7]Division of Diabetes, Endocrinology, and Metabolism, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN
[8]VA Tennessee Valley Healthcare System, Nashville, TN
[9]JDRF/Wellcome Trust Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research, University of Cambridge, Cambridge, U.K.
[10]Walter and Eliza Hall Institute of Medical Research, Department of Medical Biology, University of Melbourne, Parkville, Victoria, Australia
[11]Departments of Pathology and Pediatrics, UF Diabetes Institute, University of Florida, Gainesville, FL

Corresponding author: Mark A. Atkinson, atkinson@ufl.edu.

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type 1 diabetes at the presymptomatic stage beyond the confines of affected families, in other words, in the general population?"

This is an important question because most studies on the prediction and prevention of type 1 diabetes to date have involved "enriched populations," namely, relatives of a type 1 diabetes proband and subjects identified from the general population carrying HLA haplotypes known to confer high type 1 diabetes risk. Although the enriched population approach in relatives has advantages in terms of specificity and the ability to recruit participants, it markedly restricts the number of individuals who might theoretically benefit from early diagnosis because, at best, it only captures 10%–15% of those likely to develop type 1 diabetes (6). Stated another way, by limiting efforts to relatives, we ignore up to 90% of the emerging population with type 1 diabetes—a major missed opportunity where the impact of prevention would be profound (7) (Fig. 1). Even with an exceptional network for type 1 diabetes prevention trials in place (e.g., National Institutes of Health Type 1 Diabetes TrialNet, www.diabetestrialnet.org; EURODIAB European Nictotinamide Diabetes Intervention Trial [ENDIT], http://cordis.europa.eu/project/rcn/38525_en.html), studies of relatives are a challenge as recruitment to a multicenter trial of oral insulin in relatives with β-cell autoimmunity took 7 years to meet its enrollment targets.

This notion of establishing programs that target the general population has been facilitated by an increasing understanding of the presymptomatic phase of type 1 diabetes. TrialNet natural history studies have emphasized the importance of implementing early screening: cumulative autoantibody seroconversion was greatest and costs associated with autoantibody detection were lowest in subjects <10 years of age at the time of the first screening (8). Prospective studies from birth found that β-cell autoimmunity was detectable between 6 months and 5 years of age in around 70% of children diagnosed with type 1 diabetes (9–11). With the logistics of early diagnosis largely laid out by these natural history studies, we believe it is timely, and indeed obligatory, to expand screening for asymptomatic type 1 diabetes in young children from relatives into the general population in order to translate potential preventative therapies. For the smaller

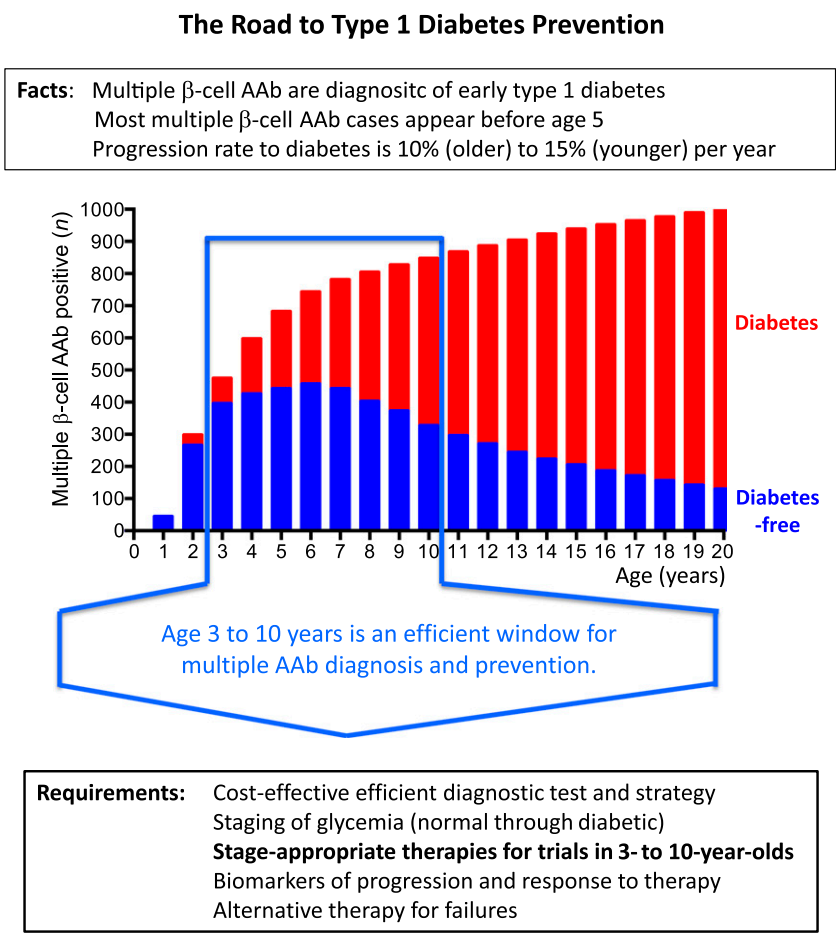

Figure 1—Infographic of the road to type 1 diabetes prevention. Data presented in the graph were modeled on published studies on multiple β-cell AAb incidence and progression to diabetes (2,9,10) and refer to 1,000 multiple β-cell AAb-positive cases expected to occur by age 20 years. Blue bars indicate the number of multiple β-cell AAb-positive children identified at each age who have not developed diabetes, and red bars indicate the number of children who have developed diabetes.

fraction of patients who develop autoimmunity during the teenage years, repeat screening may be beneficial, but further discussions of cost and equipoise would likely be needed.

THE CHALLENGE OF HAVING A DIAGNOSIS BUT NO TREATMENT

Type 1 diabetes researchers are faced with a dilemma. Through screening for AAbs, we can identify children with impending disease but currently cannot stop the progression to type 1 diabetes. Why then would one diagnose presymptomatic type 1 diabetes? We would argue that it is the first and essential step in reaching effective treatment. Through studies of immunometabolism in AAb-positive subjects, it is possible—perhaps even likely— that novel targets for prevention will be identified given the intrinsic nature of the disease occurring at the intersection of metabolism and immunity. Rather than debating the screening of relatives versus the general population, we propose that we should make a sustained effort to screen for presymptomatic type 1 diabetes in both groups. With careful and ethical approaches to screening and testing possible interventions and avoidance of raising expectations that prevention and "cure" are just around the corner, we argue for diagnosis of presymptomatic type 1 diabetes in the general population and attempts to find a means to delay or prevent the need for insulin treatment.

There are indications that therapeutic intervention in presymptomatic type 1 diabetes may have a higher likelihood of success than at the time of clinical diagnosis. Results from an anti-CD3 antibody trial, although in recently diagnosed type 1 diabetes, suggest that those with a higher concentration of plasma C-peptide at study entry are more likely to be therapeutic "responders" (12). By extrapolation, we surmise that individuals at the presymptomatic stage with presumably even greater β-cell function may be more responsive to immunotherapeutic approaches. Moreover, the rate of progression to type 1 diabetes is considerably faster in children than adults, implying that trials in childhood will require fewer participants or at least similar numbers where the statistical power will be much greater. A child is not a "little adult," and therapies should not necessarily be evaluated in adults in order to be applied in children, either for safety or efficacy. The provision of careful and informed counseling for participating children and their families is crucial.

Coming to terms with the concept that clinical presentation of type 1 diabetes is the end stage of pathology and that effective intervention for prevention must occur in early, presymptomatic disease is the important challenge. Current state-of-the-art medicine may not yet allow us to provide the patient with presymptomatic type 1 diabetes a credible offer to accept experimental treatment, given the possibility that the individual may be among the minority who have multiple AAbs but never develop symptomatic disease and the potential side effects of therapy. Thus, we need to implement a new approach to developing experimental therapies and methods that could form the basis for disease mechanism–based clinical research trials through which could we understand in much greater detail than previously the on-target and off-target effects of potential therapeutics, drug pharmacokinetics and pharmacodynamics, appropriate dosing regimens, and long-term effects of drug(s) on the immune system and β-cell health. To achieve this, we must commit ourselves to identifying therapies that are appropriate for testing in presymptomatic children, in whom a therapy should preserve β-cell mass and function while maintaining immune defenses against infection and not adversely affecting the efficacy of vaccination. It therefore behooves us to make the case that presymptomatic type 1 diabetes is the time for participation in clinical trials. This will have to be accepted by the type 1 diabetes community of families, caregivers, support organizations, and researchers before regulatory bodies can be expected to play their part in facilitating trials in presymptomatic disease and before industry sees the feasibility and potential rewards.

While we wait for a treatment that prevents or delays the onset of clinical type 1 diabetes, we should be reminded of one largely underestimated, beneficial clinical outcome that early diagnosis of type 1 diabetes offers, namely, the prevention of metabolic decompensation and diabetic ketoacidosis (DKA) (13–15). DKA occurs in 30% of children with acute onset of type 1 diabetes. Natural history studies have demonstrated that testing for asymptomatic type 1 diabetes can significantly reduce the prevalence of ketoacidosis and may also reduce the depression, anxiety, and burden that is associated with acute-onset symptomatic type 1 diabetes (16–18). Additionally, early intensive insulin treatment has been shown to beneficially affect subsequent glycemic control and reduce risk of long-term microvascular and macrovascular disease (19). Although the societal benefits of saving lives and preventing DKA are without question, the economic benefits are uncertain (20), and in the absence of diabetes prevention, formal studies to assess the economic benefit of early diagnosis are required. To this end, the ability to implement affordable point-of-care measurement at childhood visits would improve the cost efficiency of screening (Table 1).

THE WAY FORWARD

Although the established systems for presymptomatic type 1 diabetes diagnosis are clearly essential, how do we raise awareness and acceptance of their implementation into more routine clinical care and, at the same time, increase the likelihood that type 1 diabetes prevention will be achieved? First, given the aforementioned arguments, we would propose that screening efforts be broadened beyond first-degree relatives to the general population. This could be achieved either by large-scale AAb screening of individuals in specific age ranges or through an approach that uses a combination of genetic analysis and AAb testing. Emerging technologies involving blood spot

Table 1—Raise acceptance for testing and early presymptomatic diagnosis

Obstacle	Action
Psychological burden of knowing disease risk	Extend prediabetes expertise, teams, and teaching, including psychological counseling beyond research centers
Costs • Who should pay? • Equipoise	Economic modeling
Inability to accurately predict time to clinical disease	Identify markers for rapid disease progression
Burden of blood draw	Minimize test volume
Test quality • Accreditation • Certified status	Commercialize and certify high-throughput risk testing methods
Acceptance by health care providers • Will they advise in favor of screening?	Increase lay and general practitioners' knowledge about type 1 diabetes
Fear of employment/occupational discrimination	Address antidiscrimination laws

or capillary blood collection (21), as well as improvements in type 1 diabetes AAb detection and genetic typing (4,22–25), render this feasible. Indeed, the recently formed Fr1da (Typ 1 Diabetes: Früh erkennen – Früh gut behandeln) study involving population-based screening for AAbs in Bavarian children provides an example (26,27). The manner in which testing in the general population would be introduced will vary from country to country. In Germany, it has been added to routine yearly pediatric visits that occur between the ages of 2 and 5 years. Screening is optional and by informed consent, and the cost is as small as $20 per tested child (26). The optimal age for a single type 1 diabetes AAb screen will be a compromise between the sensitivity of detecting a large number of children who have already developed multiple AAbs (increased if screening is in older children) and the loss of sensitivity by missing cases of diabetes that occur prior to screening (Fig. 1). In the U.S., the well-child visits scheduled at times after the peak AAb incidence seen around 1 to 2 years of age (9–11) may be the best and most practical to identify children with presymptomatic type 1 diabetes, and there may be additional opportunities to combine testing for asymptomatic type 1 diabetes with screening for other chronic childhood diseases such as celiac disease or familial hypercholesterolemia. Repeated screening at more than one time point (i.e., a second screening after school admission) is costly but would increase the sensitivity of the approach, as perhaps up to one-third of children and adolescents who develop presymptomatic type 1 diabetes may be missed by a single test.

Next, authoritative bodies in the type 1 diabetes community (e.g., American Diabetes Association, European Association for the Study of Diabetes, JDRF, and National Institutes of Health) should be encouraged to standardize and implement guidelines for staging presymptomatic type 1 diabetes as a framework for prevention. Awareness for the threat of acute-onset type 1 diabetes with the risk and complications of metabolic decompensation and DKA and the clinical benefits of an early diagnosis should be emphasized. Industry should be encouraged to position presymptomatic type 1 diabetes in their immune disorder portfolios. Indeed, efforts need be directed at improving the attractiveness of type 1 diabetes prevention to different stakeholders, be they industry, public health, or insurance providers.

BIOMARKER NEEDS

Staging

We have biomarkers that are able to identify and stage presymptomatic type 1 diabetes (2,4). However, we need to translate these into tests that can be applied cheaply in large numbers. Although current assays are sensitive, specific, and standardized (28–30), they are expensive and labor intensive or require large sample volumes limiting their utility. Two-stage AAb testing that uses a cheap and sensitive screening assay followed by more elaborate confirmation assays in 1%–2% of those screened is one approach that could be considered (27). Subsequent development of sensitive, cheap point-of-care assays that can be performed locally on capillary blood could increase application of screening and could reduce costs as the majority of samples would not require further processing, including shipping to central laboratories. With the commercial development of various rapid single-sample ELISA-based assays, this goal seems increasingly feasible. Similarly, simplification of metabolic assessment is required, as well as standardization of some of the measurements. Metabolic assessment is an important component of management as it not only informs us whether β-cell function is impaired but also stratifies time to symptomatic disease. Furthermore, we should aim to accurately assess if β-cell function is improving or declining, independent of extrinsic influences. Metabolic assessment currently requires clinic visits and invasive methodology and is, therefore, relatively expensive and performed infrequently. Measurements that can be applied frequently or even in real time should be considered and developed to increase our knowledge of metabolic function variation, trends, and changes in children with AAbs.

Heterogeneity

Evidence continues to accumulate that type 1 diabetes is a heterogeneous disorder with respect to its immunogenetics and pathology (31–37), accounting for different autoantigen specificities, rate of loss of β-cell function, and age at clinical presentation. Thus, biomarkers that define heterogeneity with respect to genetic susceptibility, target autoantigens, immune signature, β-cell function, and metabolic stress may all help in the eventual goal of precision therapy.

Assessing Therapy

Perhaps the most needed set of biomarkers are those that will assess whether there is a metabolic or immunological change induced by therapy. First, these biomarkers should be able to define whether the therapy is achieving its mechanistic objectives. For example, we should be able to measure whether antigen-based therapies achieve a quantitative and/or qualitative change in the immune response to the antigen in a manner presumed to be beneficial. Second, biomarkers must be able to determine whether there is a reversal or stabilization of β-cell autoimmunity and whether β-cell stress has been alleviated. These biomarkers, once established, must secure regulatory qualification as diagnostic or prognostic markers for disease progression in presymptomatic type 1 diabetes. These considerations are important if we expect industry to engage in trials. Although the notions of extended screening will reduce enrollment time, industry must be able to see that there are reliable short-term outcome measures on which to base decisions for longer-term investment that appropriately powered efficacy trials require.

IMPLEMENTING A SUSTAINABLE PROGRAM

Although it is relatively straightforward to propose what is needed, it is always a challenge to successfully achieve it. We recommend that model testing programs for presymptomatic type 1 diabetes that are integrated into regular clinical care of children are commenced as a means to prevent metabolic decompensation and DKA, as well as depression, anxiety, and burden associated with the acute onset of type 1 diabetes. This can be facilitated by formally recognizing the multiple type 1 diabetes AAb-positive state as a disease. Prevention and reversal of asymptomatic

Table 2—Raise acceptance for type 1 diabetes prevention and broaden the scope for how it may occur

Obstacle	Action
Insufficient awareness • Short- and long-term risk of DKA and that DKA can be prevented • DKA prevention can be an outcome of early screening	Increase awareness of • DKA acute and long-term risk • DKA prevalence Develop education program for early diagnosis and DKA prevention
No evidence for efficient preventive therapy (except for DKA prevention by monitoring)	Develop path for faster trials and combinatorial treatments (faster recruitment, shorter trial duration, authority acceptance of combinations)
Insufficient understanding for need of randomized trials and placebo treatment (encountered among the general practice pediatrician)	Explore cross-over design, at least for mechanistic studies
Insufficient pipeline of therapies that could be tested in children	Engage pharma and expertise from other autoimmune disease areas
Lack of reproducible/universally acceptable biomarkers suggesting success in terms of pharmaceutical intervention	Develop programs for biomarker development paralleling trial conduction
Potential impact of disease heterogeneity on methods for prevention • Within a given population • Across different populations	Address specific age-groups and populations and develop more personalized therapies
Standard challenges associated with controlled trials • Compliance • Dropout • Use of agents in control subjects	Improve trial • Infrastructure • Culture • Expertise
Limited interest by big pharma and other agencies in trials whose outcomes take extensive periods of time	Interest pharma • Identification of a market for prevention
Need for large populations to identify a statistically significant effect • Not enough identified prediabetes cases for rapid trial recruitment	Broaden population-based screening beyond first-degree relatives
Lack of guidelines for standard care of prediabetes outside research setting	Implement guidelines for early stages and prevention
Costs of large trials and long-term commitment	Develop sustainable long-term programs

type 1 diabetes requires sustainable long-term programs and commitment to the funding of an intensive research portfolio, along with a firm investment by industry. The latter will also be facilitated by recognizing the disease status presymptomatic type 1 diabetes (Table 2).

CONCLUDING THOUGHTS

At present, the means for presymptomatic diagnosis and prediction of type 1 diabetes are largely established, but prevention remains a challenge. Researchers active in the adoption of population-based screening efforts, as well as individuals who have been screened and their family members, will need to understand the current inability to prevent the disease while undergoing presymptomatic diagnosis. The way forward is, therefore, to significantly expand the concept and practice of early presymptomatic diagnosis and develop and apply existing therapeutic agents that can be tested in rationally designed pilot (mechanistic and safety) and efficacy trials. The goal is to diagnose type 1 diabetes at its earliest detectable stage and intervene to prevent symptomatic disease. Such actions will, without question, have a dramatic impact on the clinical management of this disease.

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