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

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Complete List of Authors:	Ziegler, Annette-G.; Helmholtz Zentrum Munchen Deutsches Forschungszentrum fur Umwelt und Gesundheit, Institute of Diabetes Research bonifacio, ezio; Technische Universitat Dresden, DFG Center for Regenerative Therapies Powers, Alvin; Vanderbilt University, Molecular Physiology and Biophysics Todd, John; University of Cambridge Harrison, Leonard; Walter and Eliza Hall Institute of Medical Research; University of Melbourne, Medical Biology Atkinson, Mark; University of Florida College of Medicine, Pathology

Perspective

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

Anette-G. Ziegler
Institute of Diabetes Research, Helmholtz Zentrum München, Neuherberg, and Forschergruppe Diabetes, Klinikum rechts der Isar, Technische Universität München, München, Germany

Ezio Bonifacio
DFG Center for Regenerative Therapies Dresden, Faculty of Medicine, Technische Universität Dresden; Paul Langerhans Institute Dresden, German Center for Diabetes Research (DZD), Technische Universität Dresden, Dresden, Germany; Forschergruppe Diabetes e.V., Neuherberg, Germany.

Alvin C. Powers
Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, TN Division of Diabetes, Endocrinology, and Metabolism, Department of Medicine, Vanderbilt University, Medical Center, Nashville, TN Veterans Affairs Tennessee Valley Healthcare System, Nashville, Tennessee, United States of America

John Todd
JDRF/Wellcome Trust Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research, University of Cambridge, Cambridge, U.K.

Leonard Harrison
The Walter and Eliza Hall Institute of Medical Research; Department of Medical Biology, University of Melbourne, Parkville, Victoria, Australia.

Mark A. Atkinson
Departments of Pathology and Pediatrics, Diabetes Research Institute, The University of Florida, Gainesville, Florida, United States of America

Correspondence to: Mark Atkinson, PhD., Department of Pathology, University of Florida, 1600 SW Archer Road, Gainesville, FL 32610-0275, USA. atkinson@ufl.edu

Type 1 diabetes (T1D), a disease defined by absolute insulin deficiency, is considered a chronic autoimmune disorder resulting from the destruction of insulin-producing pancreatic β cells (1). The incidence of childhood-onset T1D has been increasing at a rate of 3-5% per year globally (2). Despite the introduction of an impressive array of therapies aimed at improving disease management, no means for a practical "cure" exist (3). This said, hope remains high that any of a number of emerging technologies (e.g. continuous glucose monitoring [CGM], 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 T1D. However, efforts aimed at reversing insulin dependence do not address the obvious benefits of disease prevention. Hence, key "stretch goals" for T1D research include identifying improved and increasingly practical means for diagnosing the disease at earlier stages in its natural history (i.e., early, pre-symptomatic diagnosis), undertaking such efforts in the population at large to optimally identify those with pre-symptomatic T1D, and introducing safe and effective therapeutic options for prevention.

What Does "an Early, Pre-Symptomatic Diagnosis of T1D" Mean?

The traditional diagnosis of T1D 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 analysis of

T1D-associated autoantibodies (AAb) against insulin, glutamic acid decarboxylase, insulinoma-associated protein 2 and zinc transporter 8 (4, 5). These efforts have demonstrated that T1D-associated AAb are diagnostic and that children with multiple AAb progress to symptomatic diabetes at a rate approximating 11% per year (6).

In contrast to the traditional diagnosis of T1D, an emerging concept embraces the impact of the aforementioned high rate of progression to overt hyperglycemia in children with multiple AAb (7). This proactively posits that these children do, in effect, have T1D, but it is "pre-symptomatic," that T1D 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 T1D but in addition, open up new opportunities for prevention-directed therapies.

How Do We Implement T1D Early Diagnosis for Prevention?

One key initial question arising from this line of thought is, *"What efforts are needed to enable the diagnosis of T1D at the pre-symptomatic 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 T1D to date have involved "enriched populations", namely, relatives of a T1D proband, and subjects identified from the general population carrying HLA haplotypes known to confer high T1D risk. While 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 T1D (8). Stated another way, by limiting efforts to relatives, we ignore up to 90% of the emerging T1D population - a major missed opportunity where the impact of prevention would be profound (Figure 1). Moreover, studies of relatives are a challenge as, even with an exceptional network for T1D prevention trials in place (e.g. NIH TrialNet, www.diabetestrialnet.org; EURODIAB ENDIT http://cordis.europa.eu/project/rcn/38525_en.html), recruitment to a multi-center trial of oral insulin in relatives with β cell autoimmunity took seven 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 pre-symptomatic phase of T1D. 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 under ten years of age at the time of first screen (Vehik et al). Prospective studies from birth found that β cell autoimmunity was detectable between six months and five years of age in around 70% of children diagnosed with T1D (9-11). With the logistics of early diagnosis largely laid out by these natural history studies, we believe it is timely, and indeed obligatory, in order to translate potential preventative therapies, to expand screening for asymptomatic T1D in young children from relatives into the general population. For the smaller 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

T1D researchers are faced with a dilemma. Through screening for AAb, we can identify children with impending disease but currently cannot stop the progression to T1D. Why then would one diagnose pre-symptomatic T1D? 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. We propose that rather than debating the screening of relatives versus the general population, we should make a sustained effort to screen for pre-symptomatic T1D in *both* groups. With careful and ethical approaches to screening and testing possible interventions, and as long as we do not raise expectations that prevention and 'cure' are just around the corner, we argue for diagnosis of pre-symptomatic T1D 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 pre-symptomatic T1D 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 T1D, 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 pre-

symptomatic stage with presumably even greater β cell function may be more responsive to immunotherapeutic approaches. Moreover, the rate of progression to T1D 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 T1D is the end-stage of pathology and that effective intervention for prevention must occur in early, pre-symptomatic disease is the important challenge. Current state of the art may not yet allow us to provide the pre-symptomatic T1D patient a credible offer to accept experimental treatment given the possibility that the individual may be among the minority who have multiple AAb but never develop symptomatic disease combined with 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 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 a commitment to understanding the 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 pre-symptomatic 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 pre-symptomatic T1D is *the* time for participation in clinical trials. This will have to be accepted by the T1D community of families, care givers, support organizations and researchers before regulatory bodies can be expected to play their part in facilitating trials in pre-symptomatic disease and before industry sees the feasibility and potential rewards.

While we wait for a treatment that prevents or delays the onset of clinical T1D, we should be reminded of one largely underestimated, beneficial clinical outcome that early diagnosis of T1D offers, namely, the prevention of metabolic decompensation and diabetic ketoacidosis (13, 14). Diabetic ketoacidosis occurs in 30% of children with acute onset of T1D. Natural history studies have demonstrated that testing for asymptomatic T1D can significantly reduce the prevalence of ketoacidosis and may also reduce depression, anxiety and burden in the family associated with the acute onset symptomatic T1D (15-17). Additionally, early intensive insulin treatment has been shown to beneficially affect subsequent glycemic control and reduce risk of long-term micro- and macrovascular disease (Silverstein et al. Diabetes Care 2005. Care of Children and Adolescents with T1D). While the societal benefits of saving lives and preventing diabetic ketoacidosis are without question, the economic benefits are uncertain (18), 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.

The Way Forward

While the established systems for pre-symptomatic T1D diagnosis are clearly key, how do we raise awareness and acceptance of their implementation into more routine clinical care and, at the same time, increase the likelihood that T1D 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 utilizes a combination of genetic analysis and AAb testing. Emerging technologies involving blood spot or capillary blood collection (19), as well as improvements in T1D AAb detection and genetic typing (6, 20-23), render this feasible. Indeed, the recently formed "Früh erkennen – Früh gut behandeln" (Fr1da) study involving population-based screening for AAb in Bavarian children provides an example (24, 25). How testing in the general population would be introduced will vary from country to country. In Germany, this 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 a little of US$20 per tested child (24) The optimal age for a single T1D 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 (Figure 1). In the United States, 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 pre-symptomatic T1D, and there may be additional opportunities to combine testing for asymptomatic T1D 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, since perhaps up to one-third of children and adolescents who develop pre-symptomatic T1D may be missed by a single test.

Next, authoritative bodies in the T1D community (e.g. ADA, EASD, JDRF, NIH) should be encouraged to standardize and implement guidelines for staging of pre-symptomatic T1D as a framework for prevention. Awareness for the threat of acute onset T1D with the risk and complications of metabolic decompensation and diabetic ketoacidosis, and the clinical benefits of an early diagnosis should be emphasized. Industry should be encouraged to position pre-symptomatic T1D in their immune disorder portfolios. Indeed, efforts need be directed at improving the attractiveness of T1D 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 pre-symptomatic T1D (4, 6). However, we need to translate these into tests that can be applied cheaply in large

numbers. While current assays are sensitive, specific, and standardized (26-28), they are expensive and labor intensive, or require large sample volumes limiting their utility. Two stage autoantibody testing that employs 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 (25). 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 since 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 in order to increase our knowledge of metabolic function variation, trends, and changes in children with AAbs.

Heterogeneity. Evidence continues to accumulate that T1D is a heterogeneous disorder, with respect to its immunogenetics and pathology (29-35), 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 required are those that will assess whether there is a metabolic or immunologic 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 pre-symptomatic T1D. These considerations are important if we expect industry to engage in trials. While the notions of extended screening will reduce enrolment 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

While 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 pre-symptomatic T1D that are integrated into regular clinical care of children are commenced as a means to prevent metabolic decompensation and diabetic ketoacidosis, as well as depression, anxiety and burden associated with the acute onset of T1D. This can be facilitated by formally recognizing the multiple T1D AAb positive state as disease. Prevention and reversal of asymptomatic T1D requires sustainable long-term programs and commitment to funding of an intensive research portfolio, along with firm investment by industry. The latter will also be facilitated by recognizing the disease status pre-symptomatic T1D.

Concluding Thoughts

At present, the means for pre-symptomatic diagnosis and prediction of T1D 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 while undergoing pre-symptomatic diagnosis. The way forward is, therefore, to significantly expand the concept and practice of early pre-symptomatic 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 T1D at its earliest detectable stage and intervene to prevent symptomatic disease. Such actions will, without question, have a dramatic impact on clinical management of this disease.

Author Contributions

AZ and MAA co-developed the first draft of the manuscript and contributed through the writing process to the fully developed work. EB, ACP, JT and LCH contributed to development of the final manuscript. Meet the ICMJE criteria for authorship: AZ, EB, ACP, JT, LCH and MAA. Read and agree with manuscript conclusions: AZ, EB, ACP, JT, LCH and MAA The concepts and opinions expressed in the Perspective are presented on behalf of the Type 1 Diabetes Iceland Summit Group (Henry Anhalt, M.D., Mark Atkinson, Ph.D., Ezio Bonifacio, Ph.D., Michael Haller, M.D., Leonard C. Harrison, M.D., Matthias Hebrok, M.D., Jake Kuschner, M.D., Chantal Mathieu, M.D., Gerald Nepom, M.D., Jill Norris, Ph.D., Mark Peakman, M.D., Alvin C. Powers, M.D., John A. Todd, Ph.D., Anette-G Ziegler, M.D.), which met to discuss recent advances in the early diagnosis of type 1 diabetes. The Summit was held between October 1 and October 4, 2015, and was supported by the Leona M. and Harry B. Helmsley Charitable Trust. The Trust had no role in the preparation, review or approval of this manuscript, and was not involved in the decision to submit the manuscript. The authors thank Dr. Andreas Beyerlein for assistance in development of the Figure.

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Guarantor Statement

As the guarantor of this work, Mark Atkinson assumes full responsibility for this work

as a whole and the decision to submit and publish the manuscript.

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Tables

Table 1.

Raise Acceptance for Testing and Early Pre-symptomatic Diagnosis	
Obstacle	**Action**
Psychological burden of knowing disease risk	Extend pre-diabetes 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 T1D
Fear of employment/occupational discrimination	Address anti-discrimination laws

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 it 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 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 amongst 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 • Requires the identification of a market for prevention
Need for large populations to identify a statistically significant effect • Not enough identified pre-diabetes cases for rapid trial recruitment	Broaden population-based screening beyond first degree relatives
Lack of guidelines for standard care of pre-diabetes outside research setting	Implement guidelines for early stages and prevention
Costs of large trials and long-term commitment	Develop sustainable long-term programs

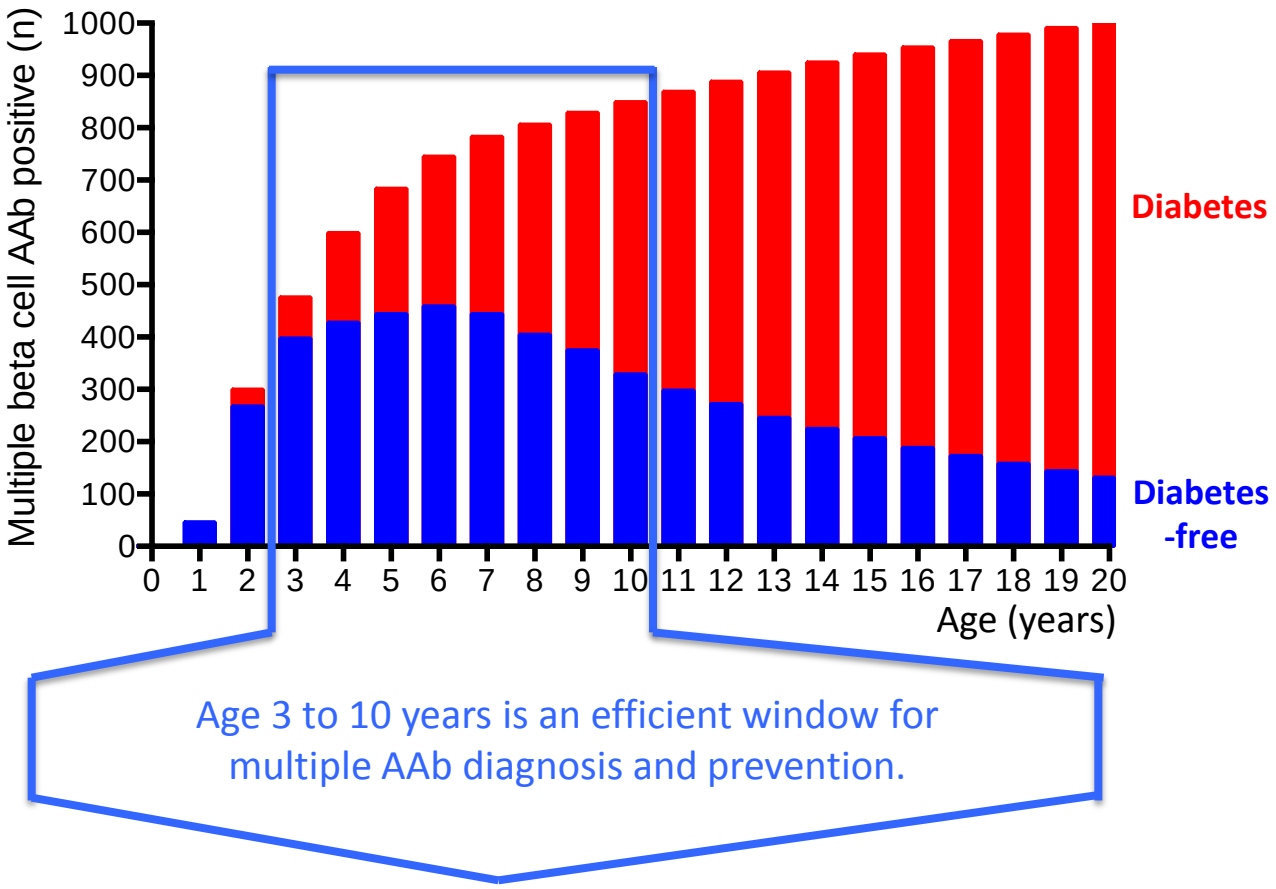
Figure Legend

Figure 1: Infographic of The Road to Type 1 Diabetes Prevention. Data presented in the graph were modeled on published multiple β cell AAb incidence and progression to diabetes studies (4, 9, 10) and refer to 1000 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 who have developed diabetes.

Figure 1

The Road to Type 1 Diabetes Prevention

Facts: Multiple ß-cell AAb are diagnositc of early type 1 diabetes
Most multiple ßa-cell AAb cases appear before age 5
Progression rate to diabetes is 10% (older) to 15% (younger) per year



Requirements: Cost-effective efficient diagnostic test and strategy
Staging of glycemia (normal through to diabetic)
Stage-appropriate therapies for trials in 3 to 10 year olds
Biomarkers of progression and response to therapy
Alternative therapy for failures

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Anette-G. Ziegler
Institute of Diabetes Research, Helmholtz Zentrum München, Neuherberg, and Forschergruppe Diabetes, Klinikum rechts der Isar, Technische Universität München, München, Germany

Ezio Bonifacio
DFG Center for Regenerative Therapies Dresden, Faculty of Medicine, Technische Universität Dresden; Paul Langerhans Institute Dresden, German Center for Diabetes Research (DZD), Technische Universität Dresden, Dresden, Germany; Forschergruppe Diabetes e.V., Neuherberg, Germany.

Alvin C. Powers
Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, TN Division of Diabetes, Endocrinology, and Metabolism, Department of Medicine, Vanderbilt University, Medical Center, Nashville, TN Veterans Affairs Tennessee Valley Healthcare System, Nashville, Tennessee, United States of America

John Todd
JDRF/Wellcome Trust Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research, University of Cambridge, Cambridge, U.K.

Leonard Harrison
The Walter and Eliza Hall Institute of Medical Research; Department of Medical Biology, University of Melbourne, Parkville, Victoria, Australia.

Mark A. Atkinson
Departments of Pathology and Pediatrics, Diabetes Research Institute, The University of Florida, Gainesville, Florida, United States of America

Correspondence to: Mark Atkinson, PhD., Department of Pathology, University of Florida, 1600 SW Archer Road, Gainesville, FL 32610-0275, USA. atkinson@ufl.edu

Type 1 diabetes (T1D), a disease defined by absolute insulin deficiency, is considered a chronic autoimmune disorder resulting from the destruction of insulin-producing pancreatic β cells (1). The incidence of childhood-onset T1D has been increasing at a rate of 3-5% per year globally (2). Despite the introduction of an impressive array of therapies aimed at improving disease management, no means for a practical "cure" exist (3). This said, hope remains high that any of a number of emerging technologies (e.g. continuous glucose monitoring [CGM], 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 T1D. However, efforts aimed at reversing insulin dependence do not address the obvious benefits of disease prevention. Hence, key "stretch goals" for T1D research include identifying improved and increasingly practical means for diagnosing the disease at earlier stages in its natural history (i.e., early, pre-symptomatic diagnosis), undertaking such efforts in the population at large to optimally identify those with pre-symptomatic T1D, and introducing safe and effective therapeutic options for prevention.

What Does "an Early, Pre-Symptomatic Diagnosis of T1D" Mean?

The traditional diagnosis of T1D based on persistent hyperglycemia is preceded by a variable (many months to years) period of asymptomatic β β-cell autoimmunity (1). Research efforts over the last three decades involving literally millions of individuals, have established a paradigm for diagnosing β β-cell autoimmunity, based on analysis of T1D-associated autoantibodies (AAb) against insulin, glutamic acid decarboxylase, insulinoma-associated protein 2 and zinc transporter 8 (4, 5). These efforts have

demonstrated that T1D-associated AAb are diagnostic and that children with multiple AAb progress to symptomatic diabetes at a rate approximating 11% per year (6).

In contrast to the traditional diagnosis of T1D, an emerging concept embraces the impact of the aforementioned high rate of progression to overt hyperglycemia in children with multiple AAb (7). This proactively posits that these children do, in effect, have T1D, …but it is "pre-symptomatic," that T1D 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 T1D but in addition, open up new opportunities for prevention-directed therapies.

How Do We Implement T1D Early Diagnosis for Prevention?

One key initial question arising from this line of thought is, *"What efforts are needed to enable the diagnosis of T1D at the pre-symptomatic 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 T1D to date have involved "enriched populations", namely, relatives of a T1D proband, and subjects identified from the general population carrying HLA haplotypes known to confer high T1D risk.. While 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 T1D (8). Stated another way, by limiting efforts to relatives, we ignore up to 90% of the emerging T1D population - a major missed opportunity where the impact of prevention would be

profound (Figure 1). Moreover, studies of relatives are a challenge as, even with an exceptional network for T1D prevention trials in place (e.g. NIH TrialNet,; www.diabetestrialnet.org; EURODIAB ENDIT http://cordis.europa.eu/project/rcn/38525_en.html), recruitment to a multi-center trial of oral insulin in relatives with β β-cell autoimmunity took seven 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 pre-symptomatic phase of T1D. 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 We now know that in subjects under ten years of age at the time of first screen (Vehik et al). Prospective studies from birth found thata majority of children diagnosed with T1D, β cell autoimmunity was detectable between six months and five years of age in around 70% of children diagnosed with T1D (9-11). With the logistics of early diagnosis largely laid out by these natural history studies, we believe it is timely, and indeed obligatory, in order to translate potential preventative therapies, to expand screening for asymptomatic T1D in young children from relatives into the general population. For the smaller 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

T1D researchers are faced with a dilemma. Through screening for AAb, we can identify children with impending disease but currently cannot stop the progression to T1D. Why then would one diagnose pre-symptomatic T1D? 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. We propose that rather than debating the screening of relatives versus the general population, we should make a sustained effort to screen for pre-symptomatic T1D in *both* groups. With careful and ethical approaches to screening and testing possible interventions, and as long as we do not raise expectations that prevention and 'cure' are just around the corner, we argue for diagnosis of pre-symptomatic T1D 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 pre-symptomatic T1D 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 T1D, 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 pre-symptomatic stage with presumably even greater β β-cell function may be more responsive to immunotherapeutic approaches. Moreover, the rate of progression to T1D 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 T1D is the end-stage of pathology and that effective intervention for prevention must occur in early, pre-symptomatic disease is the important challenge. Current state of the art may not yet allow us to provide the pre-symptomatic T1D patient a credible offer to accept experimental treatment given the possibility that the individual may be among the minority who have multiple AAb but never develop symptomatic disease combined with potential side effects of therapy. ThusNext, 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 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 a commitment to understanding the long-term effects of drug(s) on the immune system and ββ cell health. To achieve this, we must commit ourselves to identifying therapies that are appropriate for testing in pre-symptomatic children, in whom a therapy should preserve ββ 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 pre-symptomatic T1D is *the* time for participation in clinical trials. This will have to be accepted by the T1D community of families, care givers, support organizations and researchers before regulatory bodies can be expected to play their part in facilitating trials in pre-symptomatic disease and before industry sees the feasibility and potential rewards.

While we wait for a treatment that prevents or delays the onset of clinical T1D, we should be reminded of one largely underestimated, beneficial clinical outcome that early diagnosis of T1D offers, namely, the prevention of metabolic decompensation and diabetic ketoacidosis (13, 14). Diabetic ketoacidosis occurs in 30% of children with acute onset of T1D. Natural history studies have demonstrated that testing for asymptomatic T1D can significantly reduce the prevalence of ketoacidosis and may also reduce depression, anxiety and burden in the family associated with the acute onset symptomatic T1D (15-17). Additionally, early intensive insulin treatment has been shown to beneficially affect subsequent glycemic control and reduce risk of long-term micro- and macrovascular disease (Silverstein et al. Diabetes Care 2005. Care of Children and Adolescents with T1D). While the societal benefits of saving lives and preventing diabetic ketoacidosis are without question, the economic benefits are uncertain (18), 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.

The Way Forward

While the established systems for pre-symptomatic T1D diagnosis are clearly key, how do we raise awareness and acceptance of their implementation into more routine clinical care and, at the same time, increase the likelihood that T1D 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 utilizes a combination of genetic analysis and AAb testing. Emerging technologies involving blood spot or capillary blood collection (19), as well as improvements in T1D AAb detection and genetic typing (6, 20-23), render this feasible. Indeed, the recently formed "Früh erkennen – Früh gut behandeln" (Fr1da) study involving population-based screening for AAb in Bavarian children provides an example (24, 25).(24). How testing in the general population would be introduced will vary from country to country. In Germany, this 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 a little of US$20 per tested child (24). The optimal age for a single T1D 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 (Figure 1). In the United States, 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 pre-symptomatic T1D, and there may be additional opportunities to combine testing for asymptomatic T1D 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, since perhaps up to one-third of children and adolescents who develop pre-symptomatic T1D may be missed by a single test.

Next, authoritative bodies in the T1D community (e.g. ADA, EASD, JDRF, NIH) should be encouraged to standardize and implement guidelines for staging of pre-symptomatic T1D as a framework for prevention. Awareness for the threat of acute onset T1D with the risk and complications of metabolic decompensation and diabetic ketoacidosis, and the clinical benefits of an early diagnosis should be emphasized. Industry should be encouraged to position pre-symptomatic T1D in their immune disorder portfolios. Indeed, efforts need be directed at improving the attractiveness of T1D 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 pre-symptomatic T1D (4, 6). However, we need to translate these into tests that can be applied cheaply in large numbers. While current assays are sensitive, specific, and standardized (25-27), they are expensive and labor intensive, or require large sample volumes limiting their utility. Two stage autoantibody testing that employs 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 (25). Subsequent development of sensitive cheapIdeally, we need point of care assays that can be performed locallyquickly on capillary blood could increase application of screening, and could reduce costs since . This is 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.first priority for future T1D

AAb assays. Similarly, simplification of metabolic assessment is required, as well as standardization of some of the measurements. Metabolic Ideally, metabolic assessment is an important component of management as it not would not only informsinform us whether β cell function is impaired, but also stratifiesstratify 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 in order to increase our knowledge of metabolic function variation, trends, and changes in children with AAbs.

Heterogeneity. Evidence continues to accumulate that T1D is a heterogeneous disorder, with respect to its immunogenetics and pathology (28-34), 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 required are those that will assess whether there is a metabolic or immunologic 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 pre-symptomatic T1D. These considerations are important if we expect industry to engage in trials. While the notions of extended screening will reduce enrolment 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

While 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 pre-symptomatic T1D that are integrated into regular clinical care of children are commenced as a means to prevent metabolic decompensation and diabetic ketoacidosis, as well as depression, anxiety and burden associated with the acute onset of T1D. This can be facilitated by formally recognizing the multiple T1D AAb positive state as disease. Prevention and reversal of asymptomatic T1D requires sustainable long-term programs and commitment to funding of an intensive research portfolio, along with firm investment by industry. The latter will also be facilitated by recognizing the disease status pre-symptomatic T1D.

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Concluding Thoughts

At present, the means for pre-symptomatic diagnosis and prediction of T1D 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 while undergoing pre-symptomatic diagnosis. The way forward is, therefore, to significantly expand the concept and practice of early pre-symptomatic 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 T1D at its earliest detectable stage and intervene to prevent symptomatic disease. Such actions will, without question, have a dramatic impact on clinical management of this disease.

Author Contributions

AZ and MAA co-developed the first draft of the manuscript and contributed through the writing process to the fully developed work. EB, ACP, JT and LCH contributed to development of the final manuscript. Meet the ICMJE criteria for authorship: AZ, EB, ACP, JT, LCH and MAA. Read and agree with manuscript conclusions: AZ, EB, ACP, JT, LCH and MAA The concepts and opinions expressed in the Perspective are presented on behalf of the Type 1 Diabetes Iceland Summit Group (Henry Anhalt, M.D., Mark Atkinson, Ph.D., Ezio Bonifacio, Ph.D., Michael Haller, M.D., Leonard C. Harrison, M.D., Matthias Hebrok, M.D., Jake Kuschner, M.D., Chantal Mathieu, M.D., Gerald Nepom, M.D., Jill Norris, Ph.D., Mark Peakman, M.D., Alvin C. Powers, M.D., John A. Todd, Ph.D., Anette-G Ziegler, M.D.), which met to discuss recent advances in the early diagnosis of type 1 diabetes. The Summit was held between October 1 and October 4, 2015, and was supported by the Leona M. and Harry B. Helmsley Charitable Trust. The Trust had no role in the preparation, review or approval of this manuscript, and was not involved in the decision to submit the manuscript. The authors thank Dr. Andreas Beyerlein for assistance in development of the Figure.

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Guarantor Statement

As the guarantor of this work, Mark Atkinson assumes full responsibility for this work as a whole and the decision to submit and publish the manuscript.

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Tables

Table 1.

Raise Acceptance for Testing and Early Pre-symptomatic Diagnosis	
Obstacle	**Action**
Psychological burden of knowing disease risk	Extend pre-diabetes 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 T1D
Fear of employment/occupational discrimination	Address anti-discrimination laws

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 it 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 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 amongst 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 • Requires the identification of a market for prevention
Need for large populations to identify a statistically significant effect • Not enough identified pre-diabetes cases for rapid trial recruitment	Broaden population-based screening beyond first degree relatives
Lack of guidelines for standard care of pre-diabetes outside research setting	Implement guidelines for early stages and prevention
Costs of large trials and long-term commitment	Develop sustainable long-term programs

Figure Legend

Figure 1: Infographic of The Road to Type 1 Diabetes Prevention. Data presented in the graph were modeled on published multiple β cell AAb incidence and progression to diabetes studies (4, 9, 10) and refer to 1000 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 who have developed diabetes.