TYPE 1 DIABETES PREVENTION LANDSCAPE

A GUIDE FOR NAVIGATING EMERGING OPPORTUNITIES | NOVEMBER 2014

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HEALTH ADVANCES

Strategy Consultants for the Healthcare Industry

Commissioned by:

THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST

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FOREWARD

Since our inception in 2008, The Helmsley Type 1 Diabetes (T1D) Program has had four core areas of focus – research, technology, systems and outreach. We did not have any programs in T1D prevention. As we move into the next phase of our Program, we want to reconsider the area of prevention. Over the past few years, we have learned about some interesting prevention programs through our collaborations within the T1D community and we want to expand our knowledge of these and other ongoing efforts. We have also seen the continued struggle to achieve meaningful results with disease-modifying approaches in new-onset and established T1D. We recognize that opportunities still exist in these areas, but now we know more about the hurdles that will take time and significant resources to overcome, and we want to be able to compare these to the opportunities and risks in T1D prevention. To inform our review, we conducted a comprehensive landscape evaluation in T1D prevention to fully understand the state of the research, what will be required to make meaningful advancements, and where critical gaps exist. Our team had a particular interest in primary prevention, today defined as the period before autoantibody formation, based on a hypothesis that it may be easier to prevent T1D with interventions prior to the beginning of any known immune or beta cell changes. In addition to evaluating the landscape in T1D, we also looked at prevention research in other related diseases to see if any insight or approaches could be relevant.

We engaged Health Advances to conduct the prevention landscape evaluation. Health Advances is a healthcare consulting company with a diabetes practice led by Marie Schiller and Sheela Hegde. Marie and Sheela have worked extensively with diabetes companies and nonprofit organizations to provide comprehensive evaluations and define research and development strategies. In addition to diabetes, Health Advances covers a wide range of diseases in its other practices, and this expertise was leveraged to assess the broader prevention landscape. The evaluation was conducted over a six-month period beginning in January 2014.

Based on this evaluation, we have decided to incorporate primary prevention as part of our goal to better understand the disease with an emphasis on looking at intervention approaches that could potentially alter the pre-T1D autoimmune course and disease onset. As we initiate our program, we want to share the prevention landscape evaluation that has been done by Health Advances in order for the T1D community to benefit from this comprehensive review. This white paper is not meant to be a scientific publication but rather an overview of the scientific literature and a summary of the commentary from the scientific community described through the lens of a prospective funder or strategic contributor.

We want to personally thank the researchers who took the time to speak with Health Advances in order to share their views on the research and offer thoughts on how best to move forward with various aspects of prevention research. We would not have been able to achieve such a rich repository of knowledge without all these contributions. In particular we would like to thank the researchers listed in Figure 3 for their review of this white paper.

We are excited to share more about our program as we push forward and look for opportunities to collaborate with the T1D community. We are cautiously optimistic about the progress that collectively we can make within the prevention field.

David Panzirer,
Trustee

Eliot Brenner,
Program Director T1D

Gina Agiostratidou,
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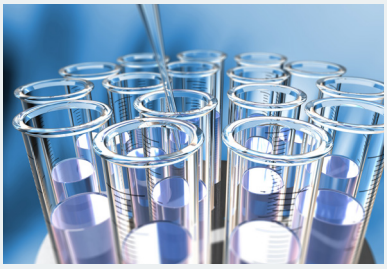

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EXECUTIVE SUMMARY

The T1D prevention landscape evaluation validated that numerous efforts to date have resulted in many important advances that will set the stage for future progress. Over 25 observational and intervention studies have been completed or are ongoing across primary and secondary prevention, with the majority of these in secondary prevention (Figure 1).

Figure 1: T1D Prevention Trial Landscape

SIGNIFICANT GAPS AND HURDLES EXIST

- Despite research efforts to date, T1D etiology and the mechanisms leading to the disease are still not understood.
- Primary prevention has not been the core focus for many of the intervention studies despite the fact that this might be the ideal time to try to prevent disease onset; to date, the results in secondary prevention have not been favorable.
- Studies take an extraordinary amount of time and capital to plan, recruit, monitor, analyze and summarize.
- A lack of understanding about the pancreas or ways to evaluate its role in disease formation is slowing the progress that can be made in prevention research.
- Studies tend to focus on single hypotheses or single interventions versus evaluating the interplay between factors or agents.
- Historically, government has been one of the sole funders for many prevention-related studies; given the large investment to date and ongoing funding pressures, there may be more limited funding moving forward.
- Industry is not actively funding T1D primary prevention as they perceive the science as too early; companies are increasingly interested in secondary prevention but acknowledge “de-risking” this area could fuel more activity.

NEW OPPORTUNITIES EMERGE

- Initiation of more prevention studies in the genetic at-risk population with interventions initiated shortly after birth using islet autoantibody seroconversion as a relevant endpoint in order to shorten trial timelines
- A greater emphasis on sub-populations to identify more insight on disease causation and potential targets (e.g. markers of protection including protective alleles and mothers with T1D during pregnancy)
- Validation of associations found with environmental triggers and novel pre-autoantibody biomarkers
- Expanded biomarker research using DNA, RNA, protein and small molecule discovery approaches to identify more markers of susceptibility, disease initiation and intervention response
- Development of new, more cost-effective research tools and diagnostics
- Enhanced design of studies to include better ways to assess the interplay between causative factors, including the beta cell and microbiome, and to study the effect of a combination of intervention measures
- Collaboration with researchers involved in non-T1D autoimmune prevention and vaccine research to leverage the expanded body of prevention research and expertise
- Inclusion of other relevant autoimmune or inflammatory diseases in primary prevention studies to maximize the benefit of these large and expensive studies
- Development of improved, system-level analytics required to optimize the large data sets being generated from ongoing observational studies
- Evaluation of new models of collaborative research that encourage parallel research paths and extensive data sharing

REVIEW OBJECTIVES

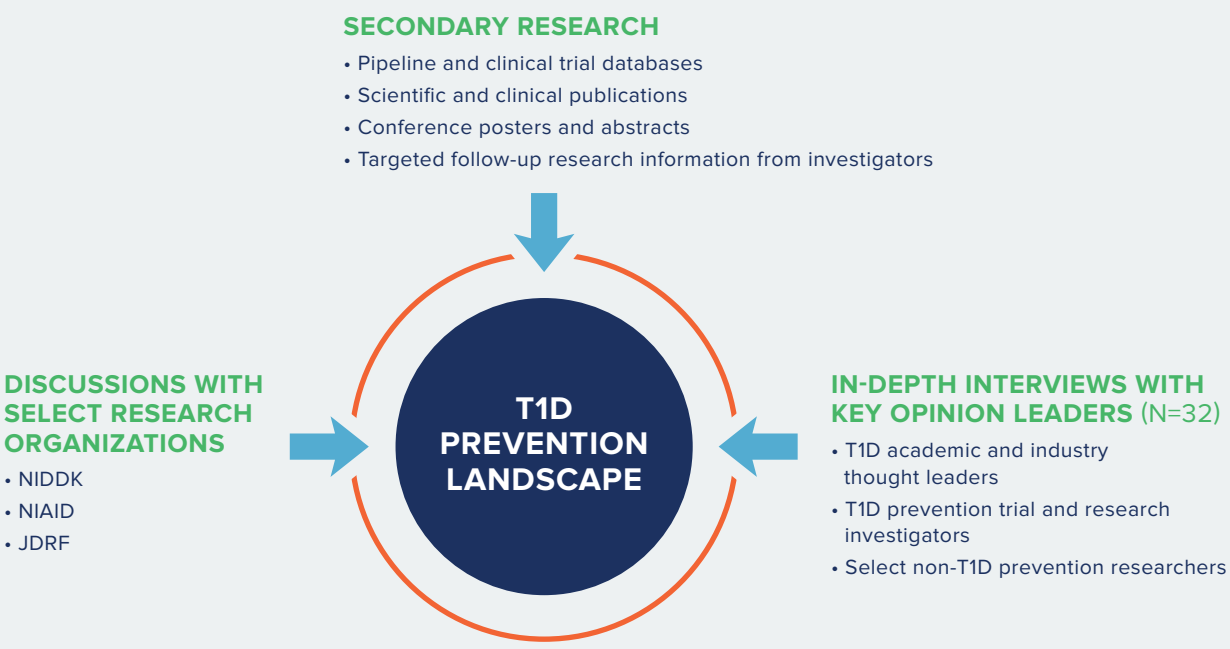
The overall objective of this evaluation was to identify emerging opportunities within T1D prevention that could help bring the field closer to identifying a universal intervention which one day could prevent all cases of T1D. More specifically, the review was designed to:

- Document what is known today about the etiology of T1D and highlight key gaps that could be the focus of future research efforts.
- Provide an overview of past and current observational and intervention prevention studies, including pre- and post-autoantibody populations; provide detailed summaries for a subset of these studies in order to highlight important elements of trial design and results.
- Profile the prevention landscape outside of T1D and identify areas that may be relevant to consider as part of a T1D prevention program.
- Identify key insights from past and current studies and outline the gaps and roadblocks that should be addressed in future prevention funding.
- Summarize future funding opportunities that expand on existing efforts or provide novel approaches based on insights captured in the field to date.

RESEARCH METHODOLOGY

Health Advances used a combination of secondary and primary research to conduct its evaluation (Figure 2). The secondary research was used to generate a list of basic, translational and clinical research programs within both T1D and other related diseases. Diseases with either a known autoimmune or inflammatory component were also included. Examples include allergy, multiple sclerosis, celiac disease, asthma, and inflammatory bowel disease.

Figure 2: Landscape Research Methodology



**It should be noted that other NIH organizations are actively involved in some of the research areas covered in this report. Examples included NICHD, NIAMS, and NINDS.*

The literature research included a screen of scientific papers published over the past 20+ years. The focus within basic research was on studies using human samples versus mouse models. Based on this list of research publications, Health Advances identified over 150 experts with relevant experience. From this list, Health Advances selected a subset of experts for individual in-depth interviews to capture additional information on particular studies, especially those that are still underway, and to capture insight on what lessons have been learned to date, what results should be available from ongoing studies in the future, and where opportunities exist for continued or new research. Health Advances conducted additional secondary research to fill any gaps and to investigate additional areas of interest that surfaced from its primary research.

Following this final stage of the review, Health Advances compiled the key findings and drafted a summary document that captured the details of the landscape evaluation. This draft was reviewed by a subset of experts that comprised The Prevention Landscape Review Committee (Figure 3). The mix of experts on this committee is representative of the experts included in the primary research with members from academia, government agencies, disease organizations and industry.

Figure 3: Prevention Landscape Review Committee

NAME	TITLE
Beena Akolkar, Ph.D.	Senior Advisor, Immunopathogenesis and genetics of Type 1 Diabetes
Mark Atkinson, Ph.D.	American Diabetes Assocation Eminent Scholar for Diabetes, Research Jeffrey Keene Family Professor, Director, Diabetes Institute at UF Health Departments of Pathology and Pediatrics
Ezio Bonifacio, Ph.D.	Professor for Preclinical approaches to stem cell therapy / Diabetes, CRTD, Technical University of Dresden
Len Harrison, D.Sc.	Professor, Molecular Medicine, Walter+Eliza Hall Institute of Medical Research
Richard Insel, M.D.	Chief Scientific Officer, JDRF
Jeff Krischer, Ph.D.	Professor, Department of Pediatrics, University of South Florda College of Medicine
Desmond Schatz, M.D.	Professor and Associate Chairman of Pediatrics, Medical Director of the Diabetes Center and Associate Director of the GCRC at the University of Florida
Jay Skyler, M.D., M.A.P.C.	Professor of Medicine, Pediatrics and Psychology at the University of Miami Miller School of Medicine and Deputy Director for Clinical Research and Academic Programs at the Diabetes Research Institute
Murray Stewart, M.D.	Chief Medical Officer (Pharmaceuticals), GSK
Anette Ziegler, Univ-Prof. Dr. med.	Director of the Institute for Diabetes Research, Helmholtz Zentrum Munich, Director of the Research Group for Diabetes at TUM, Chairperson of the Forschergruppe Diabetes e.V.

T1D DISEASE MAPPING

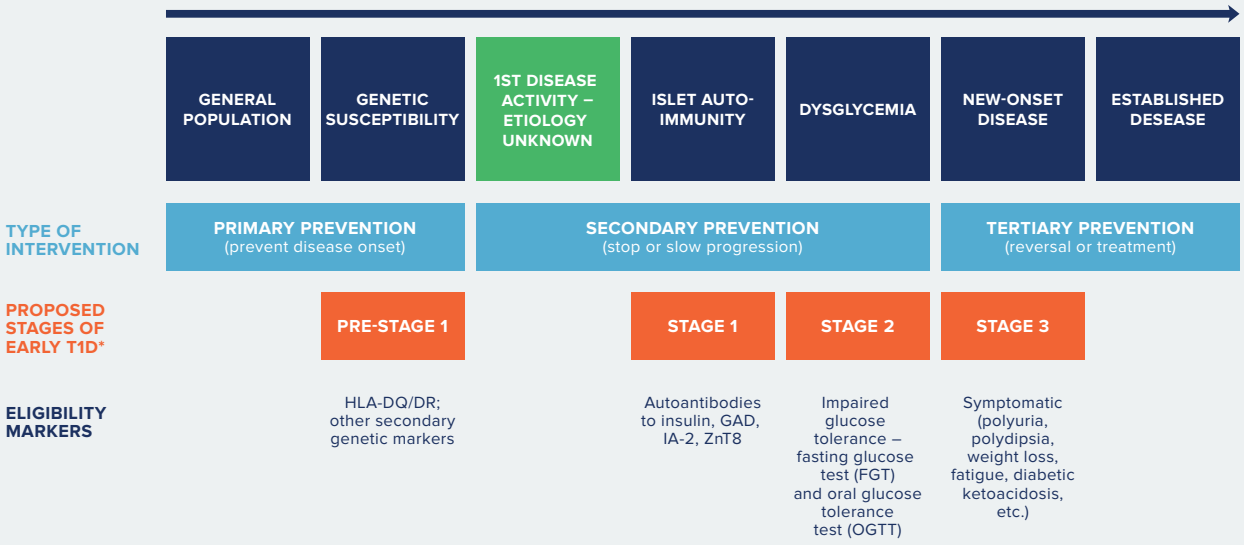
T1D PREVENTION INTERVENTION APPROACHES AND STAGING METHODOLOGY

With the research that has been performed to date in what used to be referred to as the pre-disease onset period, it is now commonly accepted that the damage to beta cells is occurring years before an individual is diagnosed with T1D. This has created a need for better disease staging in the pre-symptomatic period. Historically, the terms primary prevention and secondary prevention were used to define these early stages. Primary prevention intervenes before the onset of specific diseases via modifying the susceptible environment or eliminating the exposures that lead to the disease. A classic example is vaccination. In T1D, primary prevention is defined by genetic susceptibility, identified by family history or genetic testing and the absence of any evidence of immune activation directed against the islets, which today is primarily measured by the appearance of islet autoantibodies. Secondary prevention measures are those that detect and treat pre-clinical pathological changes to prevent the establishment or progression of a disease once a person has already been exposed to it. In T1D, secondary prevention is characterized by the period post-autoantibody detection, as today this is the earliest validated marker of immune activation.

Recently, JDRF and five other organizations involved in T1D care, research and access presented to the FDA a mutually agreed upon staging methodology that captures the early disease period to the FDA (1). This is a critical step as more clinical trials are initiated before individuals may be defined as having T1D based on current diagnosis criteria. In addition to this staging methodology, the International Society for Pediatric and Adolescent Diabetes (ISPAD) has also proposed a staging methodology that expands from early disease through symptomatic disease with complications (2).

The period pre- and post-autoantibody formation is recognized by experts as an important inflexion point for intervention approaches, as the risk-benefit ratio is substantially different in these two populations. In addition to this inflection point, some experts believe that the period of new onset symptomatic disease represents another period for potential intervention, and they have used the term tertiary prevention to distinguish this period from the period in which symptoms become more established. It should be noted that tertiary prevention could also be used to define any period following T1D diagnosis. In new onset, a realistic outcome of tertiary prevention trials is to preserve the production of endogenous insulin secretion rather than to reverse the damage that has already occurred. Benefits may include simpler insulin regimen, lower HbA1c, and reduced risk of hypoglycemia and microvascular complications (3). For purposes of this evaluation, tertiary prevention studies were not included. Figure 4 outlines these critical inflexion points and summarizes the new proposed T1D staging methodology.

Figure 4: T1D Intervention Approaches and Staging



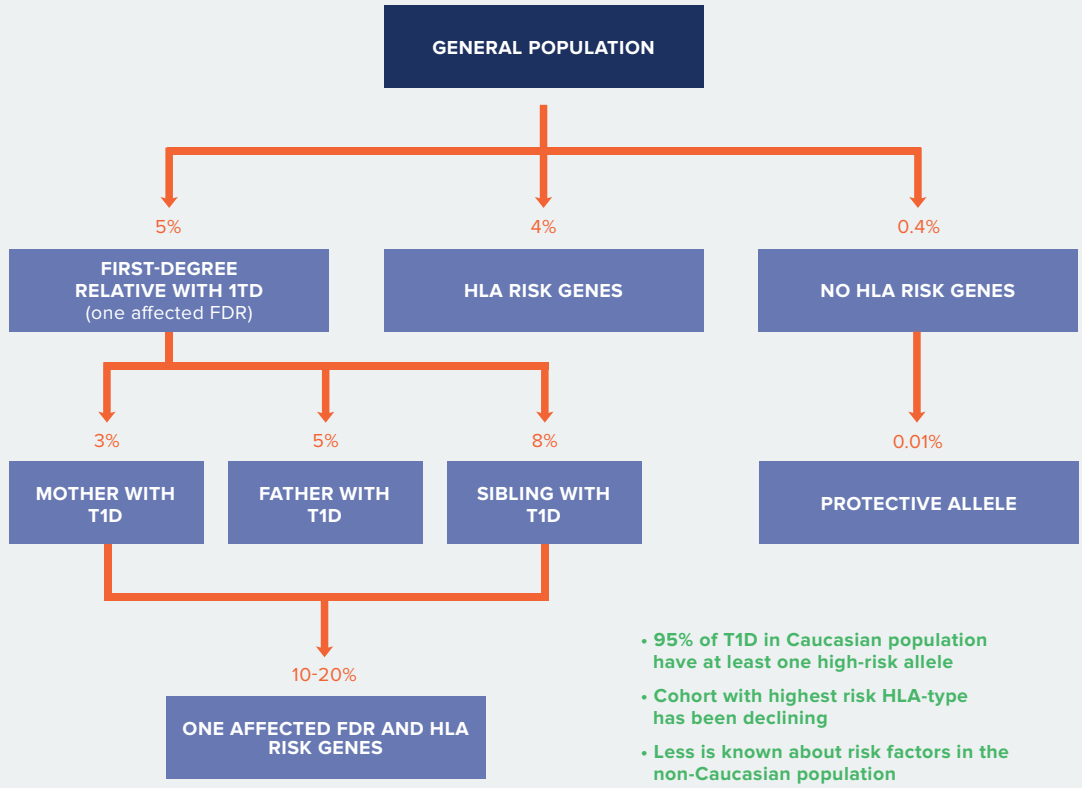
**This is a new staging methodology that has been recommended by seven different organizations with significant involvement in T1D research, care and access (ACE, ADA, Endocrine Society, Helmsley Charitable Trust, ISPAD, and JDRF; other staging methodologies have also been outlined, including one from ISPAD that includes staging of established disease.*

Citation Number: 1,2

T1D GENETIC RISK

One of the most robust areas of T1D disease mapping research has been in the area of disease genetics. Through initial observations of the role of Human Leukocyte Antigen (HLA) associations made in the 1970s (4) (5) (6) and more recent findings in genome-wide association studies, more than 50 genetic loci have been found to be associated with T1D (7) (8). The largest study, completed in 2010, was the Type 1 Diabetes Genetics Consortium (TIDGC) that included the collection and genotyping of over 14,000 samples (9). However, the HLA region remains the greatest contributor to the genetic susceptibility to T1D. Figure 5 depicts a map of the risk from the general population and first-degree relatives through T1D diagnosis (10).

Figure 5: T1D Disease Risk



Citation Number: 9

This risk stratification does provide value for targeting primary prevention research to a susceptible population, but the low predictive value relative to the current cost of genetic screening and the risk of an intervention have some experts concerned about the feasibility of an intervention in this population. As genetic screening costs, efficacy and safety improve, these concerns could dissipate, and primary prevention measures could become justified. The majority of research conducted to date has been in family members of individuals with T1D given the higher conversion rate to T1D in this population. In recent years, research has continued in the area of non-HLA genetic factors that could increase the predictive risk value. More work is needed to further validate how much the predictive risk can increase using additional genetic markers and to potentially identify non-genetic susceptibility markers that could also increase the predictive risk (see section on Novel Pre-Autoantibody Biomarkers).

In addition to acquiring knowledge on T1D genetic risk markers, researchers have also uncovered protective HLA alleles, including DR2 and DQB1*0301 and 0602 (11) (12). It may be possible to study subjects with the protective genes to identify what differences exist in areas such as the immune system or microbiome. It is also interesting to note that the risk of diabetes in children with T1D mothers is lower than with T1D fathers, suggesting that some potential tolerization mechanism may exist between some mothers with T1D and their offspring (13). This increased risk for children with T1D fathers could also be caused by T1D susceptibility genes being preferentially transferred from fathers to children who subsequently get the disease.

GENETIC RISK FACTORS IN OTHER RELEVANT DISEASES

HLA associations and other genetic markers have also been identified for other autoimmune diseases. Figure 6 provides details on the HLA allele, the affected disease and the relative risk (14). As mentioned earlier, gaining more knowledge on the role of non-HLA genes in T1D susceptibility could increase the relative risk percentage. An example is in celiac disease where work has been done to develop genomic risk scores (GRS) based on multiple SNPs that can more accurately predict celiac disease risk across several populations (15). This increased predictability could potentially narrow the group of individuals who need to be followed in a primary prevention study and increase the risk-to-benefit ratio. Understanding how researchers are using this information to map disease etiology and/or design intervention approaches in other diseases could open the door to new approaches in T1D. An example of such an approach is in ankylosing spondylitis, where a strong homology has been found between the klebsiella infection and HLA B27; as antibodies are formed to fight klebsiella infections, these antibodies could react to HLA B27 sparking the autoimmune attack (16).

Given the higher incidence of certain autoimmune diseases in people with T1D, such as celiac disease and autoimmune thyroid disease, it is likely that common mechanisms could be found by studying these diseases in a T1D prevention study. There is also rationale to include diseases that have no direct link to T1D except that the diseases occur at roughly the same time.

Figure 6: Defining Disease Risk in T1D and Other Autoimmune Diseases

HLA ALLELE	DISEASES WITH INCREASED RISK	RELATIVE RISK
HLA-B27	Ankylosing spondylitis Postgonococcal arthritis Acute anterior uveitis	12x 14x 15x
HLA-B47	21-hydroxylase deficiency	15x
HLA-DR2	Systemic lupus erythematosus	2 to 3x
HLA-DR3	Autoimmune hepatitis Primary Sjogren's syndrome Diabetes mellitus type 1 Systemic lupus erythematosus	14x 10x 5x 2 to 3x
HLA-DR4	Rheumatoid arthritis Diabetes mellitus type 1	4x 6x
HLA-DR3 and –DR4 combined	Diabetes mellitus type 1	15x
HLA-DQ2 and HLA-DQ8	Coeliac disease	7x

Citation Number: 14

ISLET AUTOANTIBODY – ENTERING SECONDARY PREVENTION

The subsequent, definable stage in the course of T1D development following the genetic at-risk stage is formation of T1D-related autoantibodies. Antibodies to islet cells, including insulin, glutamic acid decarboxylase 65 (GAD65), the IA-2 protein, and zinc transporter (ZnT8) predict development of T1D with the presence of multiple autoantibodies, indicating a substantially higher risk. Indeed, individuals with three to four antibodies have a 60%-90% risk of developing T1D when followed over a 10-year period (17). Clinically defined T1D, however, is still diagnosed by abnormal glucose levels and defined disease symptoms (American Diabetes Association criteria), and it is also possible to have T1D without having any autoantibodies (recent T1Dx data; and studies of fulminant T1D). More focus is also being placed on the affinity levels of autoantibodies, in particular when only a single autoantibody is present, to understand how the relative risk changes relative to affinity levels.

Based on the information available today, it is unclear if efforts to prevent T1D in the pre- or post-antibody stage will be more successful. Most interviewed academic researchers believe that once autoantibodies are detectable, the course of the disease is set and may be challenging to reverse. However, given the relative higher risk of developing T1D in the autoantibody positive population versus the at-risk populations, the options for potential interventions are much broader. For example, an immune-based therapy may be an ethically acceptable approach in secondary prevention but not yet in primary prevention. A subset of academic researchers and industry R&D teams believe intervening with a secondary prevention measure could provide clinically meaningful results even if it does not completely eliminate the disease and that this is a better approach than attempting primary interventions without more knowledge of the disease etiology. The outcome of delaying onset could change the long-term outcomes of individuals with T1D.

It is important to note that as more is learned about the process of autoantibody formation (seroconversion), new opportunities may arise for shortening the time of primary prevention studies using rate of seroconversion as a trial endpoint. The timing of seroconversion will also influence at what age a prevention measure will need to be administered, as it is now known that many children who develop youth-onset T1D will have detectable islet autoantibodies by the age of 3 (18).

Starting in the early 1980s, researchers in Australia, Germany, Sweden, Finland, Germany and the U.S. have been screening both T1D relatives and the general population for islet autoantibodies and following the natural history of pre-T1D in those who are autoantibody positive. TrialNet, sponsored by NIH NIDDK, has been conducting a similar program in relatives since 2000. Many of these at-risk individuals have been recruited into secondary prevention trials. Moving forward, efforts to expand this approach to include non-familial T1D subjects will be important, given that only 10% of T1D diagnoses are familial in nature. Expansion to non-familial populations, however, greatly increases the size and cost of trials.

Measuring autoantibodies as part of clinical studies or registries is a large expense and requires a blood draw from participants. As researchers try to capture more comprehensive longitudinal data, particularly around the point of seroconversion, the frequency of testing is also increasing. Reducing the total cost and burden of autoantibody testing and follow-up would help accelerate more primary and secondary prevention research and ultimately allow for screening to occur if and when a secondary prevention is found. Several screening initiatives are currently being considered in different regions across the globe. These early efforts could be instrumental in defining the most valuable and cost-effective screening approaches, especially as more is learned about the relative risk of single and multiple antibodies.

Preclinical diagnosis of T1D based on autoantibody detection has a benefit outside of research that many experts feel is underappreciated. It is associated with a marked decrease in the frequency of severe metabolic decompensation and ketoacidosis at clinical presentation of T1D (19) (20). This classic presentation of T1D in children is associated with increased mortality, longer hospitalization and greater cost, fewer partial remissions in the first year after diagnosis, lower residual beta cell function, worse metabolic control, and a higher insulin requirement.

NOVEL PRE-AUTOANTIBODY BIOMARKERS

Many experts interviewed believe that once autoantibodies can be detected, it may be too late to try and prevent the disease in its entirety, as these antibodies are markers of a disease process that has already been initiated. Therefore, identifying highly predictive, pre-autoantibody markers could be critical for better assessing disease risk and progression, or as surrogate endpoints in prevention studies. As one example, if no additional biomarkers are found, a T1D vaccine would have to be either given to the entire population or to those who are genetically at risk shortly after birth, assuming a vaccine is no longer viable after seroconversion. This puts tremendous cost and safety requirements on any potential vaccine approach. Little is known today about the period before autoantibody formation, but research is ongoing in the areas of genomics, transcriptomics, proteomics and metabolomics.

Two examples demonstrate the ongoing progress in this area. The first example is the Type 1 Diabetes Prediction and Prevention (DIPP) study in Finland (21) (22), in which children who later progressed to T1D had decreased phosphatidylcholines (PCs) in cord blood and diminished levels of ether phospholipids during the follow-up. Decreased PCs in cord blood may be pathogenically important because choline, which is mainly incorporated in PCs in a non-free form, is in particularly high demand during pregnancy as a substrate for building cellular membranes (23). Furthermore, choline is a major provider of methyl groups needed for DNA methylation, and is therefore essential for developmental processes, including genomic imprinting and the maintenance of genome stability (23) (24). In the same DIPP metabolomic study, the appearance of first islet autoantibodies was preceded by increased levels of pro-inflammatory lysophosphatidylcholine (lysoPC), glutamate, and branched chain amino acids (BCAAs), as well as decreased levels of several TCA cycle metabolites. Interestingly, the appearance of autoimmunity normalized the metabolic profiles to the levels found on average in control children (25).

The second and more recent example is of two studies in Europe, in which researchers found that expression of the IFN signature was increased in genetically predisposed children prior to the development of autoantibodies but not in established T1D patients. These findings identify transient increased expression of type I IFN genes in pre-clinical diabetes as a risk factor for autoimmunity in children with a genetic predisposition to T1D (26) (27). While these findings need to be validated further, they do point to the potential to identify and screen for pre-autoantibody markers. In all likelihood, it will be a combination of markers versus a single marker that is required to better predict autoantibody formation and ultimately the onset of symptomatic disease.

The inability to directly study the pancreas in prevention research significantly limits the knowledge that can be gained regarding the cause of the disease, particularly in susceptible individuals before and after the formation of autoantibodies. Being able to evaluate the pancreas during the pre-dysglycemic period could answer critical questions on how and when issues with the pancreas arise and how this affects the rate of seroconversion and incidence of T1D. Studying the organ allows evaluation of the system instead of beta cells alone – for example, evaluating the interaction with both the entire endocrine and exocrine parts of the pancreas and the overall vasculature. JDRF's Network for Pancreatic Organ Donors with diabetes (nPOD) is focused on studying cadaveric organ donors with T1D as well as those who are islet autoantibody positive to better understand the role of beta cells in disease formation (28). Expanding this effort or others to include more early-stage participants could provide significant value to the field of prevention research. This will not be an easy effort, and therefore continuing to invest in finding better beta cell imaging approaches is critical.

ENVIRONMENTAL TRIGGERS

No definitive causations have yet been identified, but associations have emerged in the areas of viral, bacterial, dietary, nutritional and growth causes. It is important to note that the disease trigger could be the result of not a single trigger but the interaction between multiple factors including genetic-environment and environment-environment interactions (29). In some areas, such as vitamin D and viruses, evidence exists to support a positive association with T1D, whereas other data shows no association (see Sidebar). Several ongoing environmental determinant studies should provide significantly more data points (see details in Landscape of T1D Observational Studies section). Despite the discrepancy in data, viral vaccines and vitamin D therapy are areas of active interest as potential prevention interventions (see details in Landscape of T1D Prevention Intervention Studies section).

Examples of Conflicting Evidence on T1D Triggers

VIRUSES

In the area of viral triggers, an association has been found between certain viruses and beta cell autoimmunity, including coxsackie B and rotavirus. Causation has not yet been demonstrated at this point, as some at-risk children without viral infection ultimately developed T1D, while a portion of the infected group did not develop T1D (29) (30). In addition, other studies have not seen the same association (31) (32). Differences in cohort size and frequency of testing have been implicated as factors driving the variance in results.

VITAMIN D

With vitamin D, some studies have shown vitamin D levels to be lower in children with multiple autoantibodies and T1D as compared to autoantibody negative children but in other studies no difference was found. Vitamin D is prescribed in infants in many regions in Europe yet some of the highest rates of T1D incidence exist in these regions. The doses used today are often lower than historical levels which could be influencing the discrepancies (29).

LANDSCAPE OF T1D OBSERVATIONAL STUDIES

BACKGROUND

Historically, diseases that have been successfully prevented have had causes of known origin; this makes intuitive sense given it is difficult to prevent a process that is not understood. The bulk of successful prevention strategies have been geared toward infectious diseases, with successful vaccines produced after scientific breakthroughs discovered and defined the causative agents. Particularly well-known examples are the measles and polio vaccines produced within 10 years of discovering the viruses responsible for the diseases. At a recent industry conference in Boston, the Chief Scientific Officer of Sanofi Aventis, Dr. Gary Nabel, ended his talk with a simple slide illustrating that if we know the cause of a disease, his team could find ways to modify the disease progression. He was referring to several genetic diseases that have been successfully eliminated with enzyme replacement therapy. In T1D, the disease etiology and the environmental causes are still not known, and unlike many genetic disorders, several different etiologies could be involved.

Over the course of the last 30 years, a number of studies geared mainly toward identifying the environmental trigger(s) and potential mechanisms leading to T1D have been initiated. Figure 7 provides a list of most of these studies. The majority have focused on identifying the environmental triggers versus understanding how the genetic risks translate into pathophysiological abnormalities that lead to autoantibody formation and then the ultimate progression for some individuals to hyperglycemia. BABYDIAB in Germany, DAISY in Colorado, DIPP in Finland and DiPiS in Sweden have been the four, longest-standing cohorts. These studies have been instrumental in establishing the foundation of knowledge that we continue to build on today. Most of the studies to date have focused on screening familial T1D cohorts, as the number of subjects that need to be screened is lower and the recruitment is more targeted given the established infrastructure from within existing diabetes centers. In countries that have established general birth cohort studies, such as Norway, ancillary studies geared at screening for T1D have become more standard given the increasing incidence of T1D. Finland has done an extraordinary amount of research in T1D prevention given the high incidence rate of T1D in Finland relative to any other country at 64.2 cases per 100,000 for children under 15 (33). The increasing rate of T1D across the globe is raising awareness, but the extreme cost and daunting timelines for observational studies continue to slow progress. Although genetic susceptibility allows for some segmentation, the low predictive rate requires large studies to capture enough subjects that seroconvert and then ultimately advance to T1D.

Figure 7: List of T1D Pathomechanism and Environmental Studies

STUDY NAME (CITATION #)	SUBJECTS	STATUS	YEAR INITIATED	REGIONS	DESCRIPTION
DiMe (34)	Siblings with genetic risk	Completed	1986	Finland	• The aim was to evaluate the role of genetic, environmental and immunological factors in the development of T1D.
BABY DIAB (35)	Newborns of T1D parents with genetic risk	Ongoing, recruitment completed	1989	Germany	• 2,000 children of parents with T1D followed from birth in order to identify when islet autoimmunity occurs along with genetic and environmental determinants of the process. • TEENDIAB is another study that is specifically looking at genetic factors during puberty period.
DAISY (36)	Newborns with genetic risk	Ongoing, recruitment completed	1993	Colorado	• The primary goal is to learn how genes and the environment interact to trigger the onset of T1D. • 35,000 babies have been screened for generic markets, 1,500 actively enrolled.
DIPP (37)	Newborns with genetic risk	Ongoing	1994	Finland	• The project aims to clarify the pathomechanism of T1D development; to date, over 150,000 children have been screened for T1D risk alleles. Of those, over 8,500 children carrying increased genetic risk for T1D have participated in the study; over 300 of them have progressed to clinical T1D.
PANDA (38)	Newborns with genetic risk	Completed	1996	Florida	• This study was designed to identify people at risk for developing T1D, based on their genetics, family history and autoimmunity status, and to understand the role genetics plays in the development of the complications associated with T1D in patients already affected by T1D.
Pathway to Prevention Study (TrialNet) (39)	T1D family members with autoantibodies	Ongoing	2000	Global	• International network of researchers who are exploring ways to prevent, delay and reverse the progression of T1D. • This cohort is followed and used to recruit for intervention studies.
DIPIS (40)	Newborns with genetic risk	Ongoing	2000	Sweden	• Stage I (recruitment) started in September 2000 and ended in September 2004; Stage II represents a longitudinal follow-up of children with increased genetic risk for T1D.
MIDIA (41)	Newborns from T1D mothers	Ongoing, recruitment completed	2001	Norway	• Around 47,000 children were genetically tested for T1D risk genes throughout Norway through 2007. Almost 1,000 children were diagnosed with a high genetic risk for T1D.
TEDDY (42)	Newborns from general population and T1D parents with genetic risk	Ongoing, recruitment completed	2002	Global	• See Figure 8.
DEW-IT/ DEW-IT 2 (43)	Children with genetic risk	Ongoing	2002	Washington	• The DEW-IT Study offered free genetic screening to children in Washington State to find their future risk of getting T1D. With parental permission, left-over blood from their child's heel poke from the newborn screening tests already done by the Washington State Department of Health; the goal of the DEW-IT study is to find the best methods to allow T1D risk screening to become part of normal healthcare.
DIABIMMUNE (44)	Newborns and 3-5 yr old with genetic risk	Ongoing	2008	Finland, Estonia and Russia Karelia	• The project aims at testing the hygiene hypothesis in T1D and other immune-mediated diseases; Screened 3,000 newborns for genetic susceptibility for cohorts of 330 newborn infants in each country and 1,500 three year olds for autoantibodies for T1D and celiac disease.
ENDIA (45)	Mothers with T1D or T1D 1st degree relative and their infants	Ongoing	2014	Australia	• See Figure 9.

THE LARGEST ONGOING OBSERVATIONAL STUDY – TEDDY

The massive efforts going into the global TEDDY trial provide the field hope that the trigger or triggers will be found soon, but with large data sets come new complexities. While the study has been well supported, significant resources will be needed to conduct the ancillary studies required to investigate the numerous hypotheses surrounding potential disease pathways and triggers. Figure 8 provides a synopsis of the TEDDY study. The NIH, through NIDDK and other agencies, has contributed more than $275 MM for TEDDY. Other organizations are also contributing. TEDDY, a multi-center, global study, has screened over 400,000 newborns for the T1D high-risk HLA-DR, DQ genotypes, with an estimated total of 8,000 children now enrolled. To date, several valuable findings have been released, but it is a long study that will take many years to complete and publish the results. As an example of early results, TEDDY, like several of its predecessor studies (BABYDIAB, DIPP, DAISY), looked at celiac disease and showed a very high risk of celiac disease (46). This overlap in disease risk and timing of disease onset provides an additional opportunity to learn from a diet-related autoimmune disease. The TEDDY study will generate one of the largest birth cohort data sets ever collected, creating new challenges surrounding ways to qualify, analyze and share the data sets. It will be a number of years before key findings can be released with a scheduled completion date of 2023. Finding ways to bring big data expertise and additional funding to the table may help accelerate the evaluation.

Figure 8: The Largest T1D Observational Study

NAME	The Environmental Determinants of Diabetes in the Young
TIMELINES	2002 – Start Date, 2023 – Expected Completion Date
ENROLLMENT	~425,000 screened newborns, of which ~8,000 have been expected to be enrolled
REGIONS	Finland, Germany, Sweden and three centers in North America (Colorado, Florida, Georgia and Washington) (University of South Florida is Data Coordinating Center)
INCLUSION CRITERIA	Newborns from general population and T1D parents with genetic risk (high-risk HLA-DR, DQ genotypes); roughly 10% in the T1D familial group
EVALUATION SCHEDULE	Every 3 months from birth through 4 years old, subsequently every 6 months until age 15
STUDY OBJECTIVE	The long-term goal of the TEDDY study is the identification of infectious agents, dietary factors, or other environmental agents, including psychosocial factors which trigger T1DM in genetically susceptible individuals or which protect against the disease.
STUDY OUTCOMES	Appearance of one or more islet cell autoantibodies (GADA, IAA, IA-2A) confirmed on two consecutive visits and the development of T1D
ADDITIONAL FACTORS BEING EVALUATED	• Genes within and outside the HLA region • Infectious agents (particularly viruses), dietary factors, psychosocial factors, and other factors such as toxins, immunizations, and allergies • Microbiome
FUNDING	NIH NIDDK (>$275 MM from the Special Statutory Funding Program for Type 1 Diabetes Research)

Citation Number: 42

A RECENT STUDY – ENDIA

The Environmental Determinants of Islet Autoimmunity (ENDIA) study is modeled in many ways after TEDDY with some important refinements. Figure 9 provides a synopsis of this study. The ENDIA study is enrolling 1,400 Australian children with mothers or a first-degree relative with T1D who will be evaluated for development of T1D autoantibodies and T1D every 3 months from early pregnancy through age 2, then subsequently every 6 months. It is important to point out that this study starts examining environmental impacts on the higher-risk individuals prior to pregnancy. It is known that innate immunity is established at a very early age, so the impact of microbiome, nutrition, body weight and composition, metabolome/lipidome, insulin resistance, immune function, and viral infections will be monitored pre- and post-pregnancy.

Figure 9: A Recently Initiated T1D Observational Study

ENROLLMENT	1,400 mothers and their infants
REGIONS (Start Date)	Australia (2014)
INCLUSION CRITERIA	Pregnant women who have T1D or who have a 1st degree relative
EVALUATION SCHEDULE	Every 3 months from early pregnancy through 2 years old, subsequently every 6 months
PRIMARY OUTCOME MEASURE	Presence of at least 1 autoantibody
SECONDARY OUTCOME MEASURE	Development of T1D
ADDITIONAL OUTCOMES BEING EVALUATED	Microbiome, bodyweight/composition, metabolome/lipidome, insulin resistance, innate and adaptive immune function (T cell populations, cytokine/chemokines), viral infections.

STUDY HYPOTHESIS

The overarching hypothesis of ENDIA is that environmental factors in pregnancy and early childhood differ between children who develop autoimmunity and T1D and those who do not.

SPECIFIC HYPOTHESIS:

- The maternal microbiome in pregnancy and lactation differs between the two groups
- The child's microbiome differs between those who develop autoimmunity and T1D and those who do not
- Accelerated weight gain during pregnancy and in early childhood increases risk of autoimmunity
- Early viral infection increases the risk of autoimmunity

Citation Number: 45

ENDIA, TEDDY, and all of the other studies attempting to determine the environmental cause or causes of T1D are complex, long-term undertakings that will hopefully provide valuable insights into T1D development. The tremendous amount of data accrued over the course of these extensive studies provides a solid foundation on which to build future research efforts with the goal of elucidating the etiology of the disease.

LANDSCAPE OF T1D PREVENTION INTERVENTION STUDIES

Despite the lack of understanding of the disease pathophysiology or definitive evidence on the environmental triggers, a select number of primary and secondary prevention intervention studies have been completed or are underway. The majority have been in secondary prevention; overall, the results to date have not been encouraging, as many failed to hit the primary endpoints. Figure 10 provides a list of many of these studies.

Figure 10: List of T1D Prevention Intervention Studies

STUDY NAME (CITATION #)	PRIMARY OR SECONDARY	INCLUSION CRITERIA	INTERVENTION	STATUS	YEAR INITIATED	REGIONS	DESCRIPTION
ENDIT (34)	Secondary	Family members with ICA positive but OGTT negative	Nicotinamide	Completed	1997	18 EU Countries, Canada and US	• The aim to assess whether high dose nicotinamide prevents or delays onset of diabetes in people with a first degree family history of T1D.
DIABETES PREVENTION TRIAL TYPE 1 (48)	Secondary	ICA-positive T1D siblings with impaired OGTT	Parenteral Insulin	Completed	2000	Belgium	• Hypothesis: Prophylactic administration of metabolically active insulin can prevent or delay clinical onset of T1D in a high risk group of non-diabetic siblings. • The parenteral insulin regimen utilized did not delay or prevent the development of T1D.
DIABETES PREVENTION TRIAL TYPE 1 (49)	Secondary	ICA and IAA positive T1D siblings (3-45 year olds)	Oral insulin	Completed	2000	North America	• Oral insulin study was based on the hypothesis that insulin taken orally might suppress the immune system's destructive attack on beta cells. • Failed to hit primary endpoint of a delay or prevention of T1D in people at moderate risk (25 to 50 percent likelihood) of developing T1D in 5 years.
BABYDIET (35)	Primary	1st degree relatives w/ high risk HLA type	Gluten free diet for first 12 months	Ongoing	2001	Germany	• The objective was to determine whether delaying the introduction of gluten in infants with a genetic risk of islet autoimmunity is feasible, safe, and may reduce the risk of T1D–associated islet autoimmunity. • Study has found no evidence yet of a benefit with respect to reducing the risk for islet autoantibodies.
FINDIA (50)	Primary	Newborns with genetic risk	Insulin-free cow's milk formula	Completed	2002	Finland	• Study compared the intestinal microbiota composition in children with at least two diabetes-associated autoantibodies and matched controls. • Results: weaning to an insulin-free CMF reduced the cumulativ incidence of autoantibodies by age 3 years in children at genetic risk of T1D mellitus.
TRIGR (51)	Primary	Up to 7 days old with familial risk	Hydrolyzed vs. Non-Hydrolyzed infant formula	Completed	2002	US, Europe, Australia	• The hypothesis for this study is that weaning to an extensively hydrolyzed infant formula will decrease the incidence of T1D in subjects with risk-associated HLA genotypes and a first degree relative with T1D, as it does in all relevant animal models for the disease. • Results: no effect was seen in treated arm.
Pilot Trial of Vitamin D for the Prevention of T1D (52)	Primary	Newborns with genetic risk	Vitamin D3	Completed	2005	Canada	• Primary endpoint – feasibility of recruitment. • Results: A primary prevention trial in infants using vitamin D is feasible.

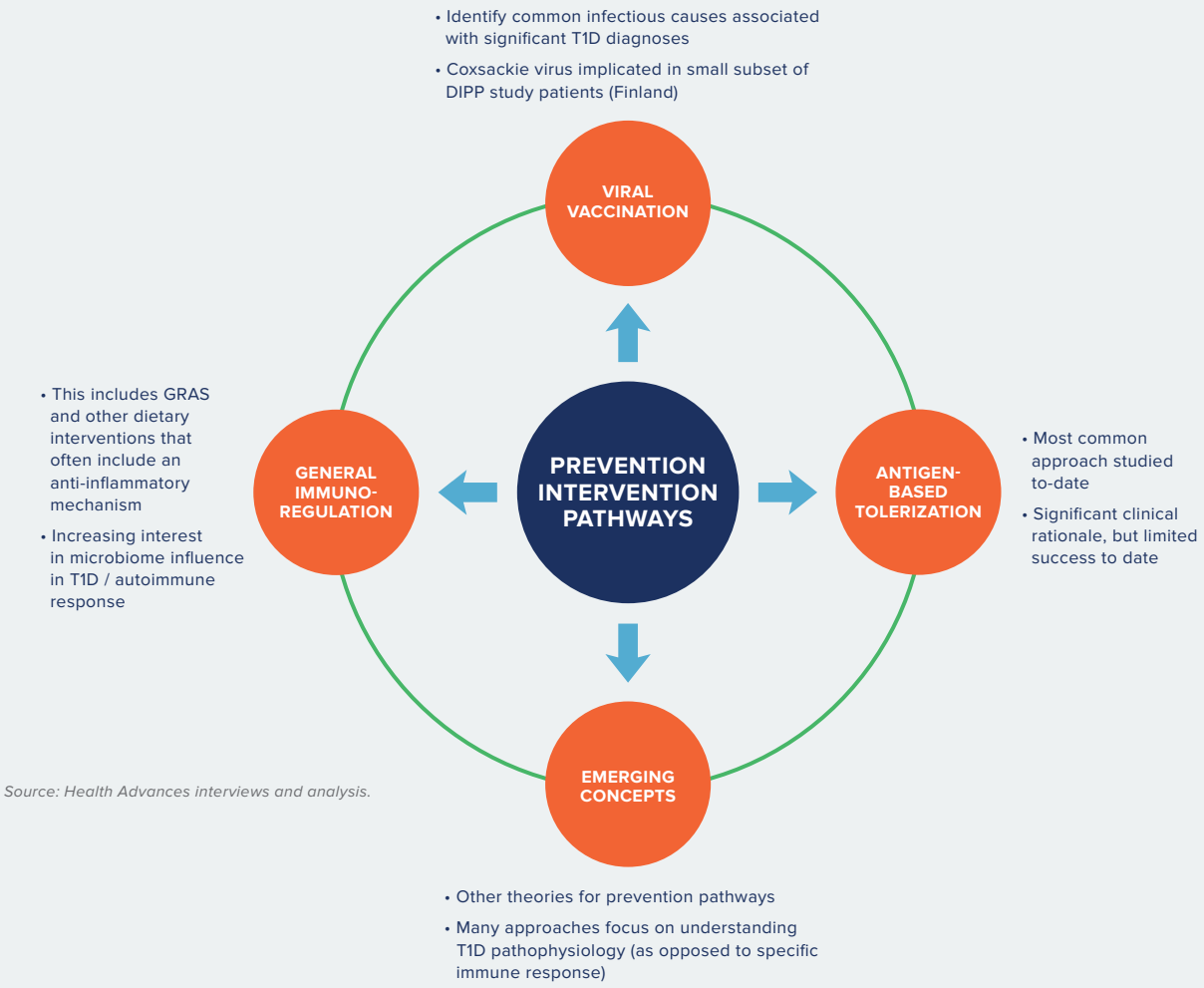
Figure 10: List of T1D Prevention Intervention Studies *(cont.)*

STUDY NAME (CITATION #)	PRIMARY OR SECONDARY	INCLUSION CRITERIA	INTERVENTION	STATUS	YEAR INITIATED	REGIONS	DESCRIPTION
INIT (53/54)	Secondary	Immediate or extended family members with T1D and 2 or more autoantibodies	Intranasal Insulin	Completed	2006	Australia and New Zealand	• Primary endpoint – to evaluate whether intranasal insulin can delay or prevent the onset of T1D in at-risk children. • No results yet reported.
Nutritional Intervention to Prevent Diabetes (NIP) (55)	Primary	Pregnant mother's (>24 weeks) with familial history Newborns up to 5 months with familial history	DHA	Completed	2006	US	• Docosahexaenoic acid (DHA) is important for brain and eye development and has also helped people with autoimmune diseases that are similar to diabetes. • 20% higher level of plasma and/or red blood cell membrane phospholipid DHA achieved in the treatment group; At least a 20% reduction in the level of the major inflammatory cytokine, IL1-beta, achieved in the plasma of the treatment group. • 95% of families will continue to attend follow-up visits.
Oral Insulin for Prevention of Diabetes in Relatives at Risk for T1D (56)	Secondary	Immediate or extended family members with T1D and 2 or more autoantibodies	Oral Insulin	Ongoing	2007	US, Au, Italy, UK, Canada, Finland	• Effect of treatment with oral insulin versus placebo in individuals in the primary stratum (ICA+ confirmed or GAD65 and ICA512 positive on the same sample with confirmation of at least one of these autoantibodies). • Secondary analyses will be done to assess the effects of oral insulin versus placebo in other categories of subjects defined using different combinations of autoantibodies and metabolic status.
PRE-POINT (57)	Primary	2-7 years old with familial risk and IA-2 autoantibody negative	Oral Insulin	Completed	2008	Austria, Germany, Italy, UK, US Switzerland	• The preventative treatment with insulin is intended to stop the development of T1D autoantibodies in children with high genetic risk; the aim of the study is to find the most appropriate dose of the insulin to do this. The study showed that a relatively high dose of daily oral insulin (67.5 mg) is safe and appears to change the immune response to insulin.
DIAPREV-IT (58/59)	Secondary	4-18 years old w/ GAD + 1 other autoantibodies and not T1D	GAD65 Vaccine	Ongoing	2009	Sweden	• Primary endpoint: the onset of T1D. • Multiple T1D related secondary measures.
Teplizumab for Prevention of T1D In Relatives "At-Risk" (60)	Secondary	8-25 years old with familial history and autoantibody positive	Anti-CD3 antibody	Ongoing, recruiting	2010	North America	• Results of previous studies indicate that Anti-CD3 antibody reduces the loss of insulin production during the first year after diagnosis in individuals with T1D. The purpose of this study is to determine if an Anti-CD3 antibody can interdict the immune process that causes the destruction of insulin secreting beta cells in the pancreas during the "pre-diabetic" state and thereby prevent or delay the onset of T1D.
EDIA (61)	Primary	Newborns (<12 months) who's parents agreed to HLA testing	Hydrolysed casein-based infant formula	Ongoing	2012	Finland	• The proposed mechanistic formula feeding study sets out to identify the mechanism(s) by which an extensively hydrolyzed casein formula is able to protect children at risk for T1D from beta-cell autoimmunity.
CTLA4-Ig (Abatacept) for Prevention of Abnormal Glucose Tolerance and Diabetes in Relatives At-Risk for T1D (62)	Secondary	1st degree relatives and w/ greater than 2 autoantibodies and normal glucose function	Abatacept	Ongoing	2013	North America	• The primary objective is to determine whether intervention with Abatacept will prevent or delay the development of AGT in at-risk autoantibody positive non diabetic relatives of patients with T1DM. • Secondary and primary outcomes include: the effect of Abatacept on the incidence of T1DM; analyses of C-peptide and other measures from the OGTT; safety and tolerability; and mechanistic outcomes.

DESCRIPTION OF T1D PREVENTION INTERVENTION APPROACHES

In general, three types of interventions may be used to prevent T1D, with other hypotheses emerging through observational studies and preclinical research (Figure 11).

Figure 11: Potential Intervention Pathways for T1D Prevention



Source: Health Advances interviews and analysis.

ANTIGEN-SPECIFIC

As seen in Figure 10, many of the completed and ongoing studies have used insulin, administered either through parenteral, oral or intranasal routes. Insulin represents an antigen-specific approach focused on presenting the antigen in a more tolerant environment such as the gut in order to tolerize an individual and either prevent the autoimmune attack before it occurs or arrest it once the cascade has begun. Insulin has been used in these studies because of its clear role as a target antigen and its strong safety record. Proinsulin, the inactive precursor to insulin, may be a better choice because studies have shown that T cells, the ultimate immune effectors of beta-cell destruction in T1D, also react to regions outside of insulin in the parent protein (64) (65) (66).

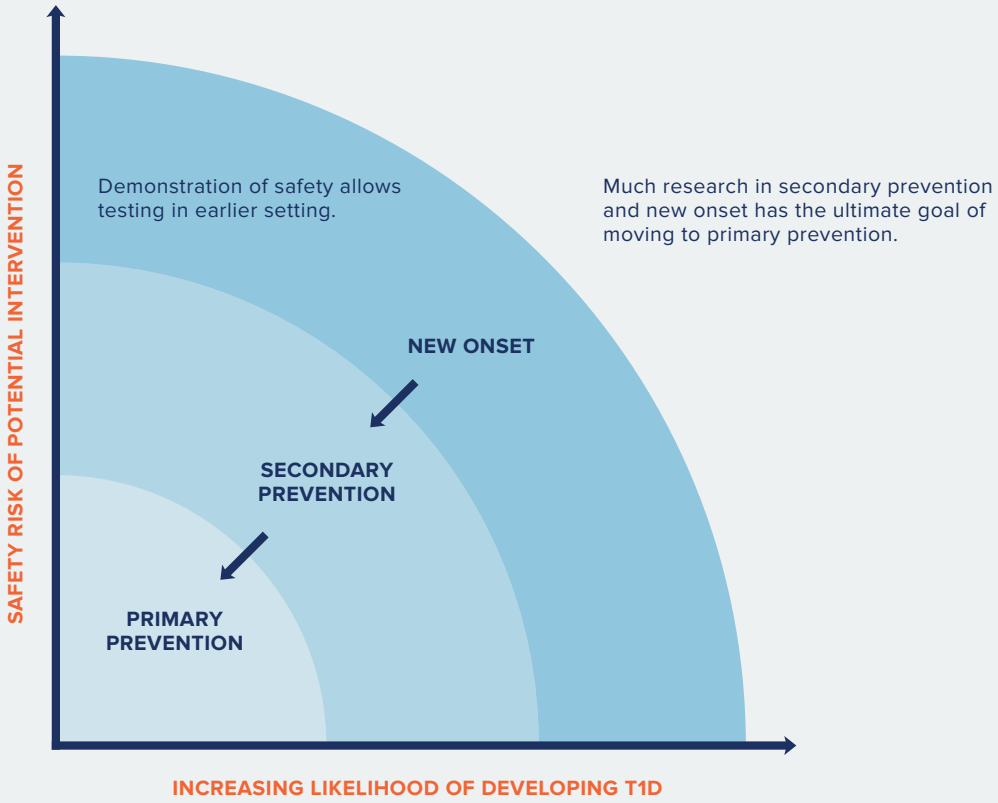
The DPT-1 Trial evaluated the impact of oral and parenteral insulin administration on T1D development and progression in a secondary prevention population. Over 100,000 individuals were screened, and 372 subjects were randomized between treatment and placebo arms. The study failed to hit its primary endpoint of delaying disease onset, but a retrospective secondary analysis showed that the subpopulation with multiple autoantibodies exhibited a delay in T1D onset (48) (49). These results may indicate that an antigen-based strategy may ultimately be most successful in the highest risk segments. Importantly, the initial trial did demonstrate it was possible to successfully recruit family members of those with T1D for an interventional clinical trial (66). Even though intervention studies bear more risk than observational studies, evidence to date supports that conducting intervention studies is easier from a recruitment and retention perspective as it gives subjects greater motivation based on the potential for a positive effect. An oral insulin study recruiting 400 high-risk insulin autoantibody-positive individuals has been initiated to further test the hypothesis (56).

Pre-POINT is an example of a prevention intervention study first being tested in secondary prevention and then moving to the primary setting following demonstration of an acceptable safety profile. In an effort to address one of the outstanding questions from prior antigen-based studies, the major goal of the study is to determine optimal oral insulin dosing in genetically at-risk children. The children, all between 2 and 7 years old, received oral insulin once daily for between 3 and 18 months. The study showed safety at all doses and evidence of inducing a change in the immune response to insulin at the highest dose (67.5 mg) (57). Follow-up to validate this in a younger set of infants is required.

A GAD65 study is also underway in secondary prevention (58) (59) despite the failure in the initial Diamyd study to preserve beta cell function in new onset patients (67). Another study in new onset patients has also been initiated.

The T1D community continues to wrestle with the question on the optimal timing of antigen-based therapies and how relevant results in one population are to another (i.e., new onset to secondary prevention). Currently, most experts believe the earlier the tolerization the better, but they also acknowledge that clinical development safety requirements may force a natural progression of studies from new onset to secondary prevention to primary prevention. The rationale supporting this theory is that autoantibodies (and probably T cell responses) to the antigen are not yet present, and a protective effect could be achieved by teaching the immune system not to make a strong response to beta cell antigens when beta cells may be damaged (e.g., due to viral infection). However, it is also possible that administration of an antigen in the primary prevention setting may not show an effect, as the disease process or trigger has not yet been initiated, making the approach more efficacious in secondary prevention. For nasal insulin, a study was first done in new onset patients not yet on insulin (68). The study failed to show a delay to insulin starts, but it did identify some immune effects without any safety issues that would justify moving upstream to secondary prevention (68). Until safety is demonstrated, the greater risk aversion of the pre-autoantibody population will necessitate starting trials further in the course of disease. Figure 12 depicts the strategy of starting in new onset, moving to secondary and ultimately translating to primary prevention interventions.

Figure 12: Progression of Clinical Development for Potential Prevention Interventions



Source: Health Advances interviews and analysis.

VIRAL VACCINE

Based on the results out of Finland regarding the increased incidence of coxsackie B viruses in children who go on to develop T1D, this team is pushing forward with the development of a viral vaccine. Other investigators are working to confirm the results before pursuing further. Companies involved with vaccine research and development noted that they would be hesitant to initiate work in T1D until more is known about potential targets. It will be important to keep the broader community of vaccine experts integrally involved as these programs move forward. Their experience from work with vaccines in other fields could be invaluable.

GENERAL IMMUNE APPROACHES THROUGH DIETARY MEASURES OR NUTRITIONAL SUPPLEMENTS

From a practical standpoint, the optimal prevention measure would not have to rely on identification of at-risk individuals through HLA or autoantibody testing. Incorporation of screening methods would place additional cost and logistical complexity into already strained healthcare systems. As a result, adoption may be significantly limited. The most optimistic scenario is one in which the entire population could be administered an agent or combination of agents that would completely prevent development of T1D. This idea, of course, presents its own difficulties. The intervention would have to be extremely safe and administered at a very early age, or even at birth, because T1D and/or seroconversion can develop at a young age. Finally, and not a trivial consideration, any intervention administered to the general population must be cost-effective.

Various compounds falling under the Food and Drug Administration's Generally Recognized as Safe (GRAS) designation, such as Vitamin D, omega-3 fatty acids, and probiotics, have all been considered. Probiotics could be interesting given the focus on the microbiome and its role in disease causation. Dietary supplements have also been tested. Only a few studies have been completed in the primary and secondary prevention populations with this category of interventions.

Examination of the effect of these agents on T1D development represents a highly practical approach, as most of the therapies are safe and inexpensive, two prerequisites for any intervention that would be used as a primary prevention measure. A secondary benefit of including safe interventions in primary prevention studies is improving trial recruitment and compliance. It has been demonstrated that individuals prefer to participate in studies where there is an intervention that may provide a benefit versus taking time to participate in an extended observational study.

EARLY CONCEPTS AND HYPOTHESES

A number of early stage intervention concepts surfaced from this prevention landscape evaluation that could provide opportunities for future trials. Some of the most noted include:

COMBINATION THERAPIES

Most agents have been studied as monotherapies, and most experts believe a combination will likely be necessary given the complexity of the disease mechanisms. For example, Vitamin D affects the TH1/TH2 pathway and could provide an adjuvant affect when used in combination with another agent (69). This hypothesis may warrant further investigation. It should be noted that the role of vitamin D has been a topic of heated debate, both within the T1D research community and the community at large (70).

THE PROTECTIVE ALLELE POPULATION

Evaluating the protective allele population could provide insight into a pathway to reduce the disease risk in patients with susceptible genetics.

TOLERIZATION DURING PREGNANCY

Capturing more knowledge on the interaction between T1D mothers and their offspring during the gestational period could further elucidate any potential tolerization mechanisms. This research may start by evaluating potential cell-based therapies that allow this tolerization to be achieved on a more predictable basis. No trials have been initiated, and more research is likely required before any are initiated.

THE MICROBIOME

The focus on the microbiome has been steadily increasing over the past few years, mostly looking at the gut microbiome. Although minimal information exists today about the role of the microbiome in T1D development, this is an extensive area of research for the diabetes community (71). In both TEDDY and ENDIA, information should be forthcoming over the next few years. From a theoretical perspective, the gut microbiome is established at birth and rapidly changes for about one year, and the very wide variability between individuals indicates there is a considerable environmental impact on its formation. An imbalance in the microbiome perturbs development of the innate immune system, and has been associated with many autoimmune diseases. The microbiome appears to be responsible for inducing tolerance to certain antigens at an early age, which indicates it could have a role in producing autoimmunity to T1D-associated antigens, ultimately leading to beta cell death. Not surprisingly, the bulk of microbiome work has been focused on gut-specific diseases such as Crohn's disease, ulcerative colitis, and *Clostridium difficile* infection (CDI). The most advanced areas are in CDI where microbiome transplants are being performed in refractive patients with early success. Within T1D, the knowledge is not nearly mature enough to start considering therapeutic options, but experts believe the microbiome should be integrally mapped with immune and beta cell research.

SUMMARY OF ADVANCES, CRITICAL GAPS AND EMERGING OPPORTUNITIES

The point made most often by experts within and outside of T1D is that until the etiology of T1D is more fully understood, efforts to delay or prevent T1D are going to be challenging. With that said, these same experts are quick to admit that reversing a disease after symptomatic onset will be even more challenging. Efforts to date in T1D prevention research have uncovered some critical pieces of the puzzle that open the door to future opportunities. As compared to other autoimmune diseases, a significant amount of research has been funded, including many ongoing studies that will hopefully generate some breakthrough insights over the next 10 years. A sustained focus is going to be necessary to ultimately translate this research into interventions that will delay and ultimately prevent the disease. Even after more is known about the pathomechanisms and environmental triggers, it will take many years to translate from pathway understanding to therapeutic targets to safe interventions. Conducting intervention studies that also capture knowledge about the pathomechanisms of T1D will accelerate the path to discovering T1D prevention.

ADVANCES IN T1D PREVENTION RESEARCH

- Given the current knowledge of genetic risk factors and autoantibody formation, long-term observational and intervention studies that screen the general population are feasible; intervention studies may be even easier to complete given the potential benefits that could come to study participants; the cost is still extremely high, driven by the size, complexity, follow-up period and diagnostic monitoring requirements.
- Children born from fathers with T1D have a higher relative risk than those from mothers with T1D; both have a higher risk than the general population.
- Individuals with certain HLA allele types are protected against developing T1D.
- For many individuals who go on to develop T1D in youth, seroconversion occurs early (between the ages of 1 and 3).
- Growing evidence exists that T1D could be a heterogeneous disease with multiple etiologies.
- Associations have been identified between environmental factors and beta cell autoimmunity and T1D incidence rates, but these have not yet been confirmed as causative; in addition, for many factors, there is evidence both supporting and contradicting the association; viral triggers and vitamin D deficiency are two areas noted frequently by experts.
- Pre-autoantibody markers, in particular inflammatory markers, have been identified but not yet validated.
- Screening for genetic susceptibility and autoantibodies can improve the symptoms of T1D at diagnosis and improve glucose control for at least the first few years.
- T1D patients have a higher rate of celiac disease than the general population; this could suggest dietary interventions or disease homology that should be further investigated.
- None of the prevention intervention studies have hit their primary endpoints. Antigen-based therapies, in particular insulin, have been proven safe in primary and secondary prevention; efficacy has not been demonstrated although sub-population analyses have identified patient segments that did have a positive response, and these populations are now being studied in follow-on trials.

CRITICAL GAPS AND HURDLES IN PREVENTION RESEARCH

- Despite all the advances to date, T1D disease etiology remains unknown.
- New pre-antibody markers and environmental triggers need to be validated.
- Research has been limited in the familial, susceptible, and autoantibody-positive populations.
- Prevention studies are long and expensive, particularly when including non-familial subjects.
- Lack of understanding of ways to evaluate the role of the pancreas in disease formation is slowing down many aspects of prevention research.
- Assessment of the interplay between the multiple factors likely involved in disease formation has been limited.
- Intervention studies have not used a combination of measures that target the multiple aspects and potential heterogeneity of T1D.
- More collaboration with other early childhood and autoimmune researchers is needed.
- Moving forward, the gap in T1D prevention funding is likely to expand given the overall reduction in government funded research and the extensive resources already devoted to large observational studies; diabetes public charities have also seen a reduction in charitable donations; industry is not actively funding T1D primary prevention as it perceives the science as too early.

EMERGING OPPORTUNITIES

- Novel primary prevention trial designs that initiate intervention close to birth and leverage the early seroconversion rate to shorten trials for primary prevention
- Greater emphasis on sub-populations to increase insight on disease causation; examples include the protective allele and mothers with T1D
- Additional biomarker research using DNA, RNA, protein and small molecule discovery approaches to determine additional markers of susceptibility, disease initiation, and intervention response
- Development of more accurate, less expensive research tools and diagnostics
- Establishment of screening for T1D as a standard practice
- Confirmatory studies to help validate emerging biomarkers and environmental triggers
- Inclusion of other autoimmune diseases to expand knowledge of disease etiologies
- Better system-level analytics and data management to accurately assess the interplay between the confounding factors likely involved in disease formation (see next page)
- Enhanced design of studies to include better ways to assess the interplay between causative factors, including the beta cell and microbiome, and to study the effect of a combination of interventions
- Collaboration with researchers involved in non-T1D autoimmune prevention and vaccine research to leverage the expanded body of prevention research and expertise
- Inclusion of other relevant autoimmune or inflammatory diseases in primary prevention studies to maximize the benefit of these large and expensive studies
- Evaluation of new models of collaborative research that encourage parallel research paths and extensive data sharing

Trial Design, Data Management and Collaboration Models

TRIAL DESIGN

T1D prevention studies have taken many years to complete, making it hard to incorporate new findings as they occur in the field. A number of examples exist, such as where new research techniques or new pathways should be examined but static trial designs make it challenging. An alternative approach may be accelerating the recruitment period in large populations and using the appearance of islet autoantibodies at around 1 to 3 years of age as the primary endpoint.

DATA MANAGEMENT

Massive amounts of data are being generated throughout the T1D prevention field. In particular, TEDDY is going to generate one of the largest datasets ever created through an NIH grant. The T1D community will need to collaborate with big data experts and create the infrastructure to ensure the data being captured is effectively and efficiently analyzed and shared. This challenge is not unique to T1D prevention as other areas of T1D research will need similar data sharing and management strategies.

COLLABORATION MODELS

The T1D prevention field has many examples of collaborative programs but sometimes these collaborations come at an expense. To gain consensus, the most conservative path is often taken on trial design or on the types of interventions to be studied. Trying to evaluate new ways of sharing data and collaborating may allow for better science and innovation. Reaching out to experts in other diseases could bring in complementary knowledge on how to use unique approaches to address the critical gaps in T1D prevention research.

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