

Prevention

Vision

The JDRF Prevention Program aims to prevent or delay the onset or progression to insulin-dependent (stage 3) type 1 diabetes (T1D) through the development of therapies that target the triggers, drivers and underlying pathophysiology of T1D. In addition to preventing T1D onset, the Prevention program also aims to prevent the presentation of acute complications at T1D diagnosis, including diabetic ketoacidosis (DKA).

Mission

Through better understanding of disease progression and heterogeneity, the Prevention program aims to delay or prevent the onset of stage 1 (Primary Prevention) or stage 3 (Secondary Prevention) T1D. Delaying progression is an important and impactful step on the path to prevention of T1D as a delay in diagnosis is likely to have long-term benefits on glycemic control and development of acute and long-term complications of T1D. To achieve these goals, we are pursuing development of the following:

- **Environmental triggers:**
Many environmental factors have been implicated in the etiology and pathogenesis of T1D. JDRF has focused on changes in the microbiome and viral infections as two potentially important contributors. A greater understanding of the complex interactions between the intestinal microbiota or viruses associated with risk and several interacting systems in the body is being pursued to provide scientifically rational approaches to prevent development of childhood T1D and biomarkers to evaluate the efficacy of interventions.
- **Universal screening and monitoring for T1D risk and progression:**
Screening for T1D has been shown through earlier clinical research studies to prevent diabetic ketoacidosis (DKA), a life-threatening complication that affects 20–50% of children at the initiation of stage 3 T1D in high-income countries. While the mortality rate in patients with DKA is less than 1% in children, DKA is associated with detrimental neurocognitive outcomes and poor long-term glycemic control. JDRF-supported studies have shown the feasibility of implementation of general population screening studies. Additional research will need to include approaches to broader implementation as well as an understanding of the economic and psychosocial aspects of screening.
- **Biomarkers to refine risk and rate of progression:**
The ability to screen for risk and stage of T1D prior to the appearance of symptoms presents a valuable opportunity to delay, and ultimately prevent, stage 3 T1D. Islet autoantibodies currently allow us to identify those individuals who will likely progress to stage 3 T1D, but the current “gold-standard” assays are not viable for T1D risk detection in the general population, due to considerations about cost, platform and blood volume considerations. Therefore, new approaches, with these considerations in mind, are required to facilitate implementation of screening. In addition, novel biomarkers to further refine the risk and rate of progression will allow better predictions of risk and enable the practice of precision medicine to prevent T1D.

- Understanding disease pathogenesis:**
 There is currently an incomplete understanding of disease progression including identification of mechanisms of human T1D pathogenesis. Triggers, biological pathways, the generation of neoepitopes or cellular targets that contribute to initial autoantibody seroconversion and those that drive progression of T1D from stage 1 through stage 3 T1D will be prioritized. Furthermore, interrogation of existing or novel data sets to understand T1D pathogenesis, disease heterogeneity and risk and rate of progression are of interest.
- Therapies that alter disease course in the early stages of T1D:**
 JDRF is actively partnering with other network, consortia and industry to support therapeutic development to prevent and delay T1D. In addition to supporting these efforts, JDRF will also commit to supporting proof-of-concept, mechanistic-based clinical trials to validate new pathways and targets. Successful completion of these trials will also help identify biomarkers to serve as intermediate study endpoints, enabling intervention earlier in the disease process and shorter trials using fewer subjects.

Rationale

Several developments have increased the importance of prevention of T1D. First, the incidence and prevalence of childhood onset T1D have been increasing over the last several decades in multiple countries with approximately a 2–4% annual increase in incidence, with penetration to low-moderate human leukocyte antigen (HLA) risk groups, suggesting a lowered threshold for its development. In the United States, the SEARCH study has shown a 2.7% increase in annual incidence from 2002 to 2009. In some countries, the disease is also occurring at a much earlier age, with a markedly increased age-incidence in the 1–5 year age range. Recent data also suggest that only a minority of individuals with T1D are achieving their treatment goals, with adolescents faring least favorably. Delaying T1D onset from its current peak incidence range of adolescence to early adulthood or later could have profound long-term benefits of improved outcomes with respect to complications, quality of life and life expectancy. As such, JDRF has made delaying T1D diagnoses a priority for its Prevention program.

90%
T1D individuals with no family history

Designing clinical trials to prevent T1D requires both insights into the natural history of the disease and the ability to detect an at-risk target population for trials. Ongoing efforts to identify individuals at risk through screening of the general population will be a necessary and critical component to the execution of clinical trials in Prevention. Furthermore, there have been recent advances in the field, including increased knowledge of the triggers of T1D that are providing rationale for additional clinical trials in this area. For example, the recent commercial efforts to develop an anti-enteroviral vaccine for the prevention of T1D has been built on years of study to understanding the role enteroviruses play in the initiation and progression of T1D. Additional efforts in the microbiome, neoepitope formation and other environmental triggers may provide additional clues and rationale for designing studies to delay and prevent T1D. In 2017, results from a phase 2 trial with oral insulin provided the first clinical evidence to show feasibility of delaying progression to T1D with a 31 month delay of progression in one of the subgroups. Furthermore, successful screening efforts in first-degree relatives and pilot programs in the general population are beginning to demonstrate the feasibility of identifying large numbers of individuals at early-stages of T1D for clinical studies and eventually for prevention and treatment.

Strategy

In 2015, recognizing that T1D starts with an asymptomatic phase, JDRF, along with key academic partners, funding organizations and patient and professional organizations, defined stages of T1D that are now recognized:

Stage 1 Multiple (two or more) islet autoantibody-positive/normoglycemic

Stage 2 Multiple islet autoantibody-positive/dysglycemic (glucose intolerance)

Stage 3 Clinically defined T1D, insulin-dependence

Individuals identified in stage 1 or stage 2 have a life-long risk for progressing to stage 3 and a clinical T1D diagnosis that approaches 100%. However, the rate of progression is variable and the factors driving progression are not well understood. Both primary prevention of T1D (prevention of stage 1) and secondary prevention (prevention of stage 2 or 3) are priorities for JDRF.

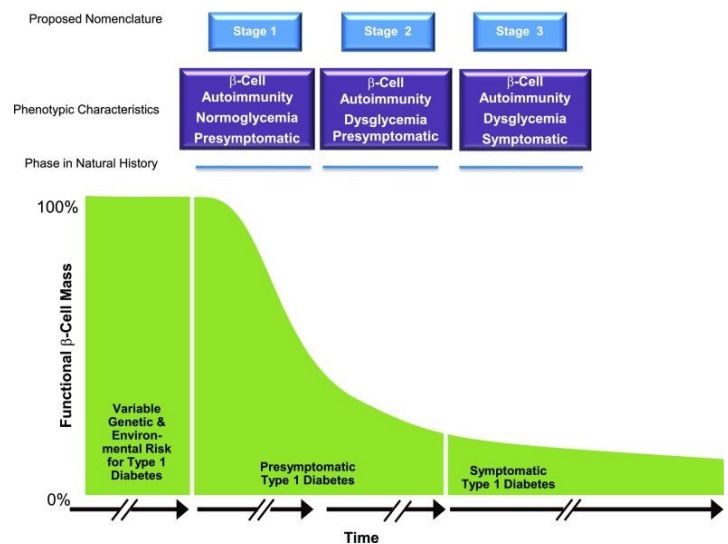


Figure 1. Early Stages of Type 1 Diabetes

For **primary prevention** of T1D, JDRF will support development and testing of three different preventive therapeutic approaches:

1. Anti-viral vaccines: epidemiologic data demonstrating that a limited number of enteroviral serotypes are associated with T1D as well as interrogating the mechanisms associated with enteroviral infection to suggest a pathway for beta cell destruction.
2. Microbiome-based approaches: Vaccines or therapeutic approaches that confer robust immunoregulation early in life based on principles of intestinal microbiota-induced healthy immunoregulation. This approach is based on the hypothesis that the increasing incidence of T1D is arising from altered development or maintenance of healthy microbiota-induced immunoregulation due to changes in the environment.
3. Therapies to induce durable immunoregulation/immune tolerance: This area is shared with JDRF's Immunotherapies program and is further described there.

Diabetes preventive vaccines and/or therapies will carefully need to weigh risks and benefits and, ideally, not require companion diagnostics for their application.

Secondary prevention can be considered early treatment of T1D. JDRF's Prevention Program works in conjunction with both the Immune Therapies and Beta Cell Regeneration Programs to identify targets and strategies for intervention in stage 1 and stage 2 T1D. In addition to providing a means to prevent or delay progression to stage 2 or 3, these strategies may also inform specific primary prevention approaches. The strategy for secondary prevention of T1D is to:

1. Assess and screen for risk of developing T1D, with an intermediate goal of preventing DKA at the time of diagnosis in this population.
2. Precisely predict the rate of progression.
3. Intervene with T1D stage- or pathway-specific therapies to halt progression and prevent or delay stage 2 or 3.

Populations that can be targeted for secondary prevention include (1) relatives of individuals with T1D, who have a 15-fold increased risk of T1D; (2) infants and children who have been screened at birth for high risk genetic markers; and (3) individuals who have been screened for autoantibodies. Because the majority (>90%) of individuals diagnosed with T1D do not have a family history of T1D, cost-effective, rational screening approaches need to be developed to target the wider population.

The current paradigms for predicting risk and rate of progression encompasses a small number of variables that do not account for disease heterogeneity, including accounting for diversity of different populations. By identifying additional biomarkers, or developing composite risk scores, through approaches including machine learning and artificial intelligence, risk and rate of progression can be further refined. These refined approaches will enable clinically meaningful prediction windows to stratify individuals for clinical trials and ultimately, for precision medicine approaches to prevention and treatment of T1D.

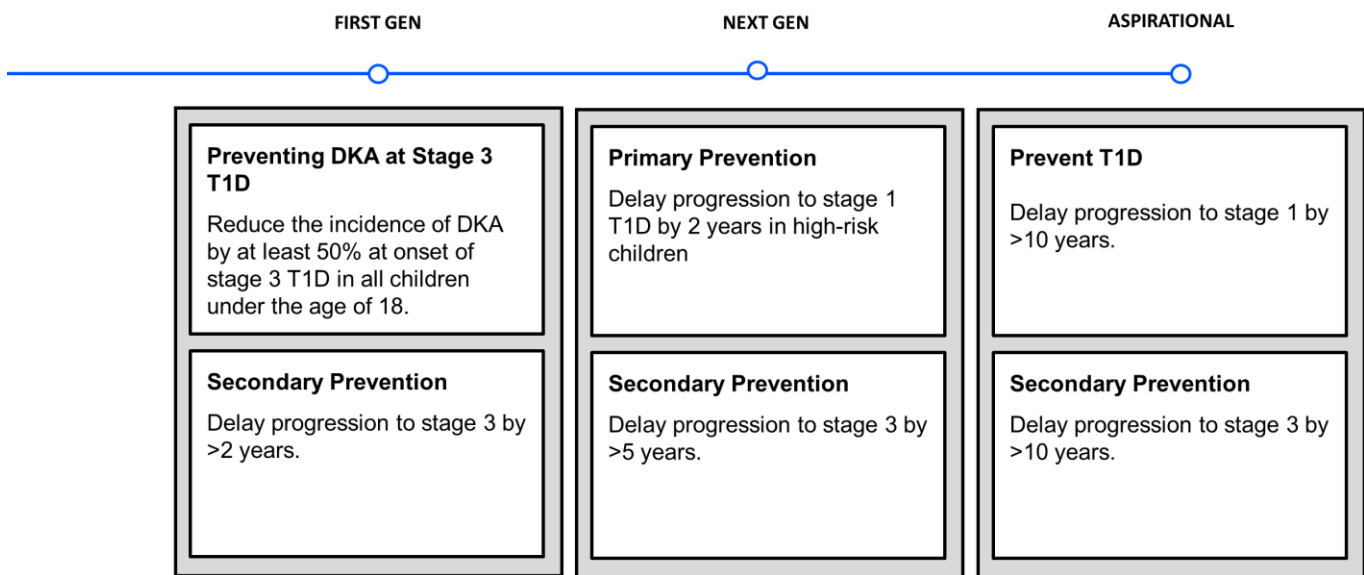
Secondary prevention interventions to robustly arrest disease progression and prevent or delay stage 3 T1D may require combining therapies that target multiple pathways such as beta cell-specific autoimmunity, inflammation, beta cell survival and/or metabolic regulation. Proof-of-concept prevention clinical trials will be prioritized because they can catalyze the field and help garner industry commitment to prevention of T1D.

In adopting a comprehensive prevention strategy, JDRF will need to increase awareness in families of individuals with T1D, the general population, health care providers, regulatory agencies, and payers of the opportunities of risk detection, including prevention of DKA at diagnosis, the continuum of disease progression and inevitability of stage 3 from earlier disease stages, opportunities to participate in natural history and intervention prevention trials, and the benefit/risk of preventive interventions as they develop. Quantitative and qualitative patient and physician studies will be utilized to inform policy decisions and strategy. The psychosocial aspects of screening and intervention in the early stages of T1D will need to be studied and understood. A business model that models economics of prevention, including around general population screening, will need to be developed. It will be important for government, payers and health policy authorities to understand both the economic and individual benefits for screening and prevention of T1D in order to implement the appropriate policies toward prevention of T1D.

Roadmap

Our clinical goals are based upon the steps necessary to achieve treatments to delay or prevent the onset of stage 3 T1D, with a near-term goal of delaying onset to stage 3 and the ultimate goal of long-term delay of stage 1 T1D.

In order to achieve long-term prevention in the population, methods to identify individuals at-risk of developing T1D will need to be implemented. Current clinical studies screen and monitor for risk in high-risk populations (genetically susceptible, relatives) as well as in the general population. Public health screening efforts to identify the vast majority of individuals who will go on to develop T1D will need to be implemented. These efforts will initially be targeted to reduce DKA at diagnosis of stage 3, but will ultimately be necessary for the practical application of T1D preventative therapies.



Current Status

The field has grown considerably over the past five years with a number of major accomplishments:

- Development and acceptance of the stages of T1D, which enable earlier interventions for delaying and preventing T1D
- Widespread acceptance of Islet Autoantibodies as a susceptibility biomarker for T1D and efforts for Qualification with the FDA and EMA are underway
- Initiation of multiple general population-based screening studies for early detection of T1D; DKA rates at diagnosis are dramatically reduced in these studies. In the current feasibility studies, T1D screening widely accepted among the general population.
- An anti-enteroviral vaccine for prevention of T1D is being developed by a commercial entity.
- Multiple prevention trials underway; oral insulin trial provided a benefit in a sub-group demonstrating possibility to delay T1D onset.
- JDRF entered into collaborations to develop and apply machine learning methods to analyze years of global T1D research data and identify factors leading to the onset of T1D in children.
- Multiple T1D microbiome papers published, suggesting a role for microbiome in T1D development.

Viral vaccines

In type 1 diabetes, pancreatic beta cells are targeted by chronic autoimmune responses, resulting in a loss of beta cell mass and function. The disease develops in genetically susceptible individuals, but penetrance is low and environmental factors likely contribute to risk. Viral infections have long been considered as candidates for environmental triggers but, given the lack of evidence for an acute, widespread, cytopathic effect in the pancreas in T1D or for a closely related temporal association of diabetes onset with such infections, a role for viruses in type 1 diabetes remains unproven. Moreover, viruses have rarely been isolated from the pancreas of individuals with T1D, mainly (but not solely) due to the inaccessibility of the organ. It is conceivable that chronic, recurrent and, possibly, persistent enteroviral infections occur in pancreatic beta cells in T1D. There is evidence to suggest that these infections may be sustained by different virus strains over time and that multiple viral hits can occur during the natural history of T1D. The current data suggests that only a minority of beta cells appear to be infected at any given time and that enteroviruses may become replication defective, which could explain why they have been isolated from the pancreas only rarely. Enteroviral infection of beta cells largely depends on the host innate and adaptive immune responses, including innate responses mounted by beta cells. Thus, viruses could play a role in T1D on multiple levels, including in the triggering and chronic stimulation of autoimmunity and in the generation of inflammation and the promotion of beta cell dysfunction and stress, each of which might then contribute to autoimmunity, as part of a vicious circle. Studies into the effects of vaccinations and/or antiviral drugs (some of which are currently on-going) is the next reasonable step to understanding the role of viruses in T1D.

Microbiome

Recent evidence has demonstrated that the intestinal microbiota of young infants at risk for developing childhood-onset autoimmune and allergic disease is altered. Specifically, children who will develop stage 3 T1D have an altered intestinal microbiota with decreased diversity and greater instability to perturbations. The triggers or etiologies of these associations are incompletely understood and the mechanism(s) of their potential contribution to disease have not been elucidated. A greater understanding of the complex interactions between the intestinal microbiota and several interacting systems in the body (immune, intestinal integrity and function, metabolism, beta cell function, etc.) may provide scientifically rational approaches to prevent development of T1D and other childhood immune and allergic diseases and biomarkers to evaluate the efficacy of interventions.

The dynamic cross-talk between the microbiota and the host through signaling from both microbial metabolites and surface molecules leads to development and maturation of healthy immunoregulation. Lessons from animal models have provided some insights into critical signaling pathways activated by metabolites or by microbial associated molecular patterns signaling through conserved pattern recognition receptors. Although there are likely multiple signaling pathways, it is conceivable that signaling through a limited number of conserved pathways are required for induction of healthy immunoregulation in the young host. Vaginal delivery and breast milk likely confer or reinforce these key signaling pathways.

General population screening and mechanistic trials

We have known for some time that the risk of developing T1D can be detected by looking for the presence of islet autoantibodies. Previous studies have shown that approximately 70 percent of asymptomatic individuals with two or more of these autoantibodies progress to stage 3, symptomatic T1D within 10 years and the lifetime risk for progression to stage 3 approaches 100%.

Some protocols initially focused on screening individuals who have close relatives with T1D, but only about 10 percent of people who develop T1D fall into this category. JDRF believes that screening all children for islet autoantibodies during well-child visits is feasible and should be implemented as part of public health policy. This will not only enable enrollment into prevention trials, but in the short-term, aims to reduce hospitalization and life-threatening DKA incidents at onset of stage 3 T1D.

JDRF has and continues to support early screening efforts through its funding of longitudinal studies such as Fr1da and ASK, which offers opportunities for children with no known risk for T1D to be screened for islet autoantibodies during wellness visits. Data from the TEDDY study, which also screened the general population for genetic risk, suggests that early detection can raise awareness and help prevent DKA.

General population screening can also help identify appropriate participants for intervention trials aimed at stopping the progression of T1D and preventing its full onset. These trials could eventually lead to therapies that preserve beta cell function and prevent complications. JDRF is currently supporting proof-of-concept clinical trials using prognostic biomarkers and intermediate biomarker-based trial outcomes/endpoints to inform larger and longer prevention trials.

Finally, a better understanding of disease pathophysiology/etiology will likely contribute knowledge to enable the prevention of T1D through the identification and validation of targets for preventative therapies, informing strategies for effective therapeutic modulation of these targets, and/or development of tools that will allow the identification of patients likely to benefit from preventative therapies. Unraveling and defining disease heterogeneity will be a key piece to stage and/or pathway specific interventions.

Biomarkers

Validated biomarkers that detect risk, stage the disease, and predict its rate of progression in the at-risk setting for T1D are required to provide a framework for clinical trial design, benefit/risk decisions around interventions, and ultimately for the practice of predictive medicine to prevent symptomatic T1D. These biomarkers may include markers of beta cell stress, dysfunction, and damage, functional beta cell mass, autoimmune/inflammatory biomarkers, and/or biomarkers of impaired glucose and metabolic control. While progress has been made in identifying predictive markers for risk of T1D, there may be alternative molecular biomarkers (metabolites, proteomics, gene expression patterns, additional autoantibodies, etc.) that may prove to be expressed earlier, be more highly predictive, and/or more cost effective for detecting risk. Biomarkers that detect activation of innate immunity or of T cells specific for beta cells, islet inflammation or beta cell stress, dysfunction or damage may be demonstrated to serve this role. For prevention approaches to succeed it is also important to develop other biomarkers associated with progression that can be used both as prognostic biomarkers to design trials and tailor therapy and as predictive biomarkers of efficacy of preventive interventions to accelerate clinical development. Biomarkers that detect very early beta cell inflammation or beta cell stress, dysfunction or damage, beta cell specific autoimmune responses, dysglycemia, or insulin resistance may be demonstrated to serve this role. Non-invasive imaging biomarkers to detect islet inflammation and beta cell mass could prove critical for more accurate staging and monitoring progression, may help determine whether the disease can have a relapsing/remitting pattern, and may be used for assessing response to interventions. It is likely that a combination of biomarkers will be required to accurately stage and better predict rate of progression. An emerging area of focus for the Prevention program is the application of artificial intelligence (AI) and machine learning (ML). Initially, existing T1D datasets will be utilized to improve on models for patient stratification and disease heterogeneity and prediction and disease progression modeling. More access to open data and shared data platform for combined analyses and validation of models will be prioritized. In addition, a focus on training bioinformaticians in the T1D space will be emphasized.

Critical Gaps

Launching the First Gen Therapy

To accelerate progress towards prevention or delay of stage 3 disease and DKA incidence, we are focusing efforts on addressing the critical gaps:

1. Screening at risk subjects

- Cost-effective general population screening efforts to increase pool for natural history and intervention trials and to support stage 1 and 2 therapeutic development
- Leveraging trial infrastructure (TEDDY, TrialNet, DIPP, Fr1da, ENDIA, ASK, etc.) networks and building consortia
- Patient and physician preference studies to inform policy decisions around screening
- Economic modeling of screening in the absence of an intervention, for delaying diagnosis and for prevention of stage 3 T1D
- Understanding the psychosocial aspects of screening

2. Biomarkers

- Discovery and validation of refined biomarkers to improve disease stages and progression for conducting clinical trials and serving ultimately as surrogates of efficacy of disease prevention.
- Optimization of autoantibody assays
- Qualification of autoantibodies as biomarkers for use in clinical studies
- Employing machine learning and artificial intelligence techniques to create and inform models of risk prediction

3. Interventions with stage- or pathway-specific therapies

- Pathogenesis and etiology studies to help understand human T1D disease heterogeneity and response to therapy
- Understanding T1D in diverse populations (age, gender, ethnically, genetically, geographically, etc.)
- Ongoing mechanistic trials to assess pathway-specific interventions.
- Continued education of the regulatory agencies of the inevitable progression to symptomatic T1D from early stages of the disease and of the potential benefit/risk of interventions to arrest progression

Towards the Aspirational Therapy

In addition to those gaps listed above, there are additional gaps to address before next generation and aspirational prevention therapies are viable:

4. Viral Vaccines

- Limited epidemiologic studies of enterovirus association with T1D
- Continued engagement with industry partners and regulatory agencies around primary prevention of T1D

5. Microbiome-based therapies

- Incomplete understanding of the basis of healthy microbiota-induced immunoregulation and the specific defects in predisposing to T1D in order to develop scientifically rationally defined sustainable preventive approaches

6. Biomarkers

- Lack of biomarkers that detect risk prior to the development of stage 1
- Lack of prognostic models for the assessment of risk of T1D and its progression prior to development of stage 1
- Validation of surrogate biomarkers to perform clinical trials more efficiently and catalyze commitment of industry to the field.
- Development and validation of low-cost and low-volume assays for predictive screening for T1D risk

Regulatory + Reimbursement Pathway

Regulatory

Regulatory authorities, namely the Food and Drug Administration (FDA) in the U.S., make decisions about which medical products can be made available to the public. FDA bases its decisions on an assessment of whether the benefits of the product outweigh the risks, as demonstrated in clinical trials. For a novel drug or biologic product, FDA requires a development program that culminates in at least two adequate and well-controlled phase 3 clinical trials with the expectation of hundreds to thousands of people enrolled in those trials. Specifics about the development program including the duration of study, number of subjects enrolled, and efficacy/safety endpoints depend on the exact product, the patient population and the indication for use being sought. FDA and EMA (EU regulatory authority) have each developed a guidance document to provide their current thinking on the development of diabetes therapies and each document provides guidance related to products for secondary prevention of T1D. As specific products are being researched and pursued, JDRF explores the possible development pathway with the developer to identify challenges for that specific product as needed.

As identified as a critical gap above, for all types of prevention products, education of regulatory authorities about what is known about the progression of T1D and the inevitability of symptomatic T1D once the early stages are met is happening and should continue. An appreciation of how T1D progresses through the stages will help to ensure that the risks and benefits that are being weighed for interventions to arrest progression are specific and appropriate to the natural history of the disease. To begin this education, JDRF engaged FDA and EMA (EU regulatory agency) in the effort to define early stages of T1D, including attendance at the scientific workshop on the topic in October 2014. Further, the qualification of islet autoantibodies as susceptibility biomarkers that is underway is continuing that education and will make the islet autoantibodies readily available for use in drug development by industry and regulators.

Regarding microbiome-based products, a regulatory assessment of these types of products has been completed. This assessment provided the current regulatory thinking related to these types of products and is being used as a resource for those researching this type of product.

Reimbursement

A sound economic argument for the basis of population screening for T1D antibodies needs to be developed. Such an analysis is being undertaken by the Barbara Davis Center for Childhood Diabetes in conjunction with the ASK study. It should take into account the cost of the disease state that is delayed and/or the cost of incidence of DKA at diagnosis and compare that to a population wide screening effort. The purpose is to convince payers that wide-spread screening is offset by savings generated through that effort.

Once data are available from ongoing studies of population based antibody screening, JDRF should work with the United States Preventive Services Task Force (USPSTF) to have the evidence reviewed for possible recommendation. JDRF should also work with the American Academy of Pediatrics to present study evidence in hopes of having antibody testing included in the recommended screenings for children. The result of such a recommendation would be having it covered under many types of insurance, notably Medicaid.

Therapeutic Concepts

The therapeutic concepts below are based on current evidence about the potential for prevention of T1D. As the science develops and as we understand more about patient preferences, the psychosocial aspects of prevention and the health economics of preventing T1D, these therapeutic concepts will be further refined. It is our belief that the First Generation profile is fairly robust and success here will spur industry to development.

First Gen – Product 1.0

Parameter	Target
Primary Indication	Reduction of DKA at onset of stage 3 T1D.
Target Population	All children under the age of 18
Features	Childhood screening three times during childhood, utilizing a blood draw to measure islet autoantibodies; If the screen is positive for stage 1 T1D, children will be enrolled in a monitoring program to assess dyglycemia and progression to stage 3 T1D
Efficacy	Reduction of the incidence of DKA at stage 3 onset in the general population to below 10%
Risk/Side Effect	Minimal SAEs expected; some redness at the venipuncture site expected. Psychosocial aspects of screening need to be further explored, both for children and parents.

First Gen – Product 2.0

Parameter	Target
Primary Indication	Delay progression from stage 1/2 to stage 3 T1D
Target Population	Adults and children identified through screening programs (FDR and GP) for islet autoimmunity (stage 1)
Features	Initial treatment plus bolus(es) to maintain effect. IV route acceptable; Products may target the immune system and/or the beta cell.
Efficacy	Delay of progression by 2 years in at least 30% of the target population.
Risk/Side Effect	<1% risk of SAEs;

Next Gen – Product 3.0

Parameter	Target
Primary Indication	Delay progression to stage 1 T1D
Target Population	Children identified at birth as having high genetic risk, either through HLA or genetic risk scores (GRS), for developing T1D
Features	IM vaccine (viral) or oral microbiome-based product given shortly after birth plus bolus(es) for additional protection.
Efficacy	Delay progression to stage 1 T1D by 2 years in at least 30% of the target population.
Risk/Side Effect	Redness or swelling at the injection site acceptable; less than 1% risk of SAEs

Aspirational– Product 4.0

Parameter	Target
Primary Indication	Prevention of childhood-onset T1D
Target Population	All children (from birth, or shortly thereafter)
Features	IM vaccine (viral) or oral microbiome-based product given shortly after birth plus bolus(es) for additional protection.
Efficacy	Delay progression to stage 1 T1D by at least 10 years in at least 80% of the target population.
Risk/Side Effect	Redness or swelling at the injection site acceptable; less than 1% risk of SAEs

For more information:

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