HEALTH ADVANCES

Established T1D Clinical Research Roadmap

Paving a New Path

June, 2012

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Acknowledgements

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Dana Ball
Chief Executive Officer
T1D First
Former Director
The Leona M. and Harry B. Helmsley Charitable Trust

Richard A. Insel, M.D.
Chief Scientific Officer
JDRF

Darlene Deecher, Ph.D.
Senior Vice President
JDRF

Marie Schiller
Managing Director
Health Advances, LLC

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This report was written by Marie Schiller, Donna Hochberg, Ph.D. and Kristen Garner, Ph.D.
For more information or questions, please contact Marie Schiller at mschiller@healthadvances.com

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I. Executive Summary

Several factors have caused a shortfall in established type 1 diabetes (T1D) non-insulin clinical research, despite the fact that T1D is one of the more prevalent autoimmune diseases.[1] First, it has been considered a single hormone deficiency that can be adequately treated with insulin. Although not a perfect remedy, insulin has the potential for enabling individuals with T1D to achieve good control as measured by HbA1c, the most widely recognized surrogate marker of long-term outcomes. Using non-insulin metabolic control agents has been deemed unnecessary by many clinicians given the perceived uniform nature of the disease. Second, most researchers have long believed that trying to reverse T1D once the autoimmune attack has destroyed the majority of pancreatic β-cells was too challenging and would likely require combination approaches with a complex regulatory path and significant safety trade-offs. Although the number of T1D clinical studies has increased over the past five years, the majority of these studies have been for people with new-onset disease, a period when some beta cell function presumably still exists. Notably, this increased interest did not expand into the larger established population who have been living with the disease for many years. Several failures in the new-onset trials have reinforced the challenging nature of stopping the autoimmune attack once the destructive cascade has been initiated. New, emerging data could challenge the current thinking surrounding the potential for therapeutic interventions in people with established T1D. Most notable is increasing evidence largely through the JDRF nPOD initiative that many people with long-standing T1D still have

β-cells present years after diagnosis. Beyond this and quite strikingly, evidence from a variety of efforts (e.g. DCCT, the Joslin Medalist Study) suggests that some individuals with long-standing T1D continue, years after disease onset, to produce small quantities of C-peptide, a marker of endogenous insulin production. In addition to this mounting evidence, the failure of the first-generation studies in new-onset T1D has challenged what was considered the optimal development path for novel T1D immunotherapies. Testing these therapies in people with established T1D, in particular those with some residual levels of C-peptide, may offer a previously untapped opportunity to exploit and challenge current research assumptions. Novel immune modulatory therapies that have been approved for other autoimmune conditions could provide new options for treating established disease as these therapies have more tolerable safety profiles. Some early evidence of benefit from non-insulin metabolic control agents in long-standing disease has also raised interest as more emphasis is placed on the multi-hormonal deficiencies in people with T1D. Some of these metabolic control agents may have a direct or indirect effect on β-cell health alone or in combination with an immune-based therapy.

Lastly, but critical to remember when assessing opportunities for trying new interventions, a large number of individuals with T1D are still not achieving expected glucose control, putting them at higher risk for both micro- and macrovascular complications. The day-to-day management of T1D can be daunting. The T1D Exchange, a clinic-based T1D registry with over 25,000 T1D participants being treated at 67 diabetes centers across the United States, recently released data showing that the average HbA1c for participants is 8.5%.[2] This is more than 20% above the recommended goal for adults of 7% set by the American Diabetes Association (ADA) and other organizations. Better treatments are needed. Ideally, more personalized approaches should be used to systematically and purposefully tailor therapies to the specific of each individual living with T1D.

Based on these findings, a bolder approach to clinical research in people with established T1D is clearly warranted. Near-term clinical development opportunities in established T1D subjects are evident. Industry is seeking a greater level of collaboration with the research community in order to understand and develop well-informed clinical plans. Investment in established clinical research studies is required to build a strong foundation that enables development of therapies that will impact disease management and to increase the probability of novel breakthrough therapies. Clinical research needs to place greater

1. Erika Gebel, "Autoimmune Disorders," *Diabetes Forecast*, Nov (2011).
2. T1D Exchange Clinic Registry, The Jaeb Center for Health Research funded by The Leona M. and Harry B. Helmsley Charitable Trust (2012).

emphasis on disease staging, subject risk stratification, and understanding of population sub-types in order to optimize clinical trial design and increase probability of success. Researchers must establish standards that accurately compare different approaches and include clinically relevant endpoints. Near-term established T1D studies should explore some of the approximately 40 FDA-approved immune-based and non-insulin metabolic control therapies alone or in combination as safety and some mechanistic knowledge is already established for these agents. The exact therapies chosen will depend on how funding organizations and companies weigh the criteria used to prioritize research. Opportunities exist for multiple collaborative research models, including a pre-competitive consortium approach to drive the required observational studies. JDRF and The Helmsley Charitable Trust are both committed to these clinical development initiatives in the established disease population and are excited about the opportunity to partner with the T1D community to address the critical research gaps and accelerate the assessment of potential interventions, which could result in better lives for all people with T1D.

II. Project Background

Traditionally, clinical-stage research in T1D, outside of insulin and accompanying delivery and monitoring systems, has not been a high-priority investment area for most early-stage investors, biotech, or pharma. Over the past five years, a small but meaningful number of companies began to explore immune-based therapies in the newly diagnosed T1D population (new-onset), but with a number of recent failures, this early interest already appears to be waning. This interpretation is based on the failure of pharma to move forward with development agreements for at least three agents (otelixizumab, teplizumab, Diamyd®) that drew significant investment capital. Other therapies that target non-insulin metabolic control and β-cell regeneration have benefited from more investment, fueled in part by the potential of these pathways in the larger type 2 diabetes market. To date, little of this increased interest has translated into any substantial benefit in clinical development activity in the established T1D population—or at least until now.

JDRF and The Leona M. and Harry B. Helmsley Charitable Trust, two of the largest T1D non-profit disease organizations, engaged Health Advances, a firm focused on advising companies and organizations on research, development, and commercialization of new products, to conduct an independent review of what has been evaluated to date in established T1D. More importantly, Health Advances was charged to identify interventions and other supporting activities that could benefit people with established T1D in the near term (next three years).

III. Objectives, Definitions, and Scope

Health Advances' project objectives were to develop an **Established T1D Clinical Research Roadmap** that:

1. Builds from a comprehensive review of the current knowledge of disease etiology and the results of tested interventions.
2. Identifies critical clinical development gating issues.
3. Outlines an actionable path forward that prioritizes human-based learning and near-term, clinically meaningful research, as defined below.

An **Established T1D** population, albeit theoretically, should be comprised of individuals who have reached a steady state of residual β-cell function. However, defining this steady state is challenging given the limit of detection of current C-peptide assays. Another problem is finding subjects who qualify for enrollment in intervention studies aimed at improving disease outcomes with this definition, since a long pre-enrollment period is needed to measure C-peptide and that a steady state of beta cell function has been documented. A logical alternative is to define a steady state based on years since diagnosis, but consensus on this option is lacking given the knowledge gap around the inter- and intra-subject rate and variability of beta cell decline. Thus, the guideline is five years for the purpose of any proposed studies in this report, based on the fact that at two to three years post-diagnosis, 1.) a persistent honeymoon is rare, 2.) exogenous insulin requirements tend to stabilize, and 3.) in almost all cases a period of relatively stable low-to-absent C-peptide function exists. Choosing five years for the guideline incorporates an extra time allowance and is a practical, feasible criteria for selecting subjects for studies.

In addition, other definitions used in this report are defined for clarification purposes and intent. **Near-term**, for purposes of clinical research opportunities, is defined as the 2012-2014 timeframe. **Clinically meaningful** refers to an effect that leads directly to improving an individual's life. A more detailed list of clinically meaningful endpoints will be provided in the report.

The following critical questions were addressed during the development of this T1D established population roadmap:

- What do we know about the underlying disease once a patient progresses beyond the new-onset period?
- Is there a rationale for study disease-modifying therapies in established patients?
- How can trials be optimized for this target population?
- Which therapeutic classes and drug combinations are most promising?
- How should therapies be targeted/tailored based on a predictive profile of disease progression?

It should be noted that islet-cell transplantation, insulin therapies, monitoring and delivery devices, and complication interventions were excluded from this assessment and roadmap.

IV. Research Methodology

In November 2011, JDRF and The Leona M. and Harry B. Helmsley Charitable Trust commissioned Health Advances to conduct a detailed research program spanning a period of three months. Health Advances began the project by establishing a Project Research Committee to provide its core team research guidance.

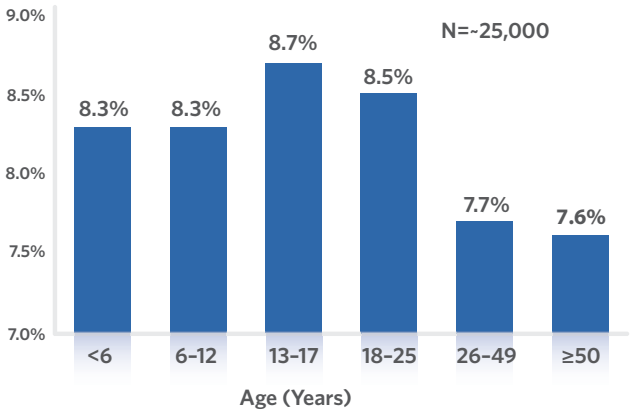
During the course of this research project, Health Advances conducted in-depth interviews with roughly 50 key opinion leaders[3] (referred to as "experts" throughout this paper), across a range of basic and clinical research areas to provide feedback on the existing established T1D landscape and to identify the options for future clinical-stage research. Those interviewed included representatives from government, academic research institutes, non-profit disease organizations, and industry. In addition to conducting primary research, Health Advances utilized secondary research to scan broadly for existing information and to provide details on specific studies. It should be noted that the landscape is limited by what information has been made publically available. Trial results not released or still pending were not included in this report.

3. A more detailed description of the primary research program is available upon request.

V. Introduction to Established Type 1 Diabetes (T1D)

T1D is an autoimmune condition that affects approximately 1.5 million people in the United States.[4] In individuals with T1D, the immune system destroys β-cells, the internal factory for making insulin. When patients are first diagnosed with T1D, they can still have some β-cell activity as measured by C-peptide levels (a byproduct of endogenous insulin production); however, for most patients, β-cell levels decline quickly. In the absence of β-cells, individuals lose control over glucose metabolism and must replace endogenous insulin by injecting or infusing exogenously produced insulin. Although patients are better able to manage their disease because of improvements in insulin and insulin delivery systems, they still run the daily risk of potentially harmful or even fatal hypoglycemic and hyperglycemic events and longer-term risks of morbidity, including retinopathy, neuropathy, nephropathy, and cardiovascular disease, as well as a long list of autonomic complications. The burden of living with a disease that requires people with T1D to make critical treatment decisions each day with a deadly medication is extremely high. Not surprisingly, many people with established T1D are not obtaining the glucose levels set by various organizations, including the American Diabetes Association, which sets its goal at an HbA1c for adults at or below 7%.[5] As seen in Figure 1,[6] recent data released from one of the largest T1D registries show an average HbA1c of 8.5% across all participants, which is approximately 20% above the ADA target. It should be noted that this is not a population-based study and the T1D Exchange population is weighted toward pediatric participants. In addition to the data on HbA1c, data on complications from the T1D Exchange registry have identified a group of participants who are progressing to complications faster than would have been expected based on years since diagnosis. Despite the advancement in therapies made to date, data provides evidence that better treatment options are still needed.

Figure 1: Mean HbA1c by Age Group (T1D Exchange Registry)



4. Boyle, "Projection of Diabetes Burden through 2050," CDC National Diabetes Fact Sheet.
5. "Standards of Medical Care in Diabetes," *Diabetes Care*, 33, suppl.1: S4-5 (2010).
6. T1D Exchange Clinic Registry, The Jaeb Center for Health Research funded by The Leona M. and Harry B. Helmsley Charitable Trust (2012).

VI. Current Established T1D Clinical Research Landscape

Unlike some other autoimmune conditions, no disease-modifying therapies have been approved in T1D.[7] Over the past five years, only a limited number of mostly investigator-initiated, proof-of-concept clinical studies have been conducted in established T1D. Indeed, nearly all clinical studies seeking such a goal have focused on new-onset T1D (defined by C-peptide level or months since diagnosis). This approach is atypical of how clinical researchers usually develop new treatments. Commonly, new therapies target severe or "refractory" patients first, and then apply these learnings to clinical studies that are trialing interventions earlier in the course of the disease. In T1D, the rationale for evaluating putative interventions earlier in the disease process, in combination with insulin, stems from the desire to try to arrest the autoimmune attack to preserve residual β-cells function.

Unfortunately, many of the therapies in development for new-onset patients have failed to hit primary endpoints, although some interesting positive signals have been detected within these overall negative trials. As seen from the evolution of new therapeutic classes in other diseases, progress may be incremental, and over time, dose refinements or more tailored therapies could alter the natural course of disease.

Figure 2[8] lists the majority of interventional studies in established T1D that have been completed or are currently ongoing. It should be noted that some of these studies were conducted in patient cohorts outside of the >5 year definition. In addition, this list is focused on interventional studies that captured C-peptide data. There are a limited number of interventional studies focused solely on glucose control that have not been included. Overall, the interviewed experts agree that it is hard to draw any definitive conclusions from the studies that have been performed to date. Some experts are encouraged by at least a subset of the studies that may demonstrate that C-peptide levels can increase in people with long-standing disease.

Figure 2: Interventional Studies in Established T1D

Intervention (ref number)	Phase	Inclusion Criteria	Endpoints	Outcome	Investigator/ Sponsor
Rapamycin (NCT00372086)	N/A	T1D patients awaiting islet cell transplantation	C-peptide, insulin dose	Slight increase in C-peptide; slight decrease in insulin requirement	Ezio Bonifacio, PhD, San Raffaele Scientific Institute
Rosiglitazone (NCT00372086)	N/A	LADA, C-peptide > 0.3 nmol/L	C-peptide	Fasting C-peptide higher in treated patients	Second Xiangya Hospital
BCG (NCT00607230)	I	T1D, GAD65 Abs	Autoreactive T cells, TNF, C-peptide	Transient increase in C-peptide	Denise Faustman, MD, PhD, Massachusetts General Hospital
Exenatide +/- Daclizumab (NCT00064714)	II	T1D > 5 years, C-peptide 0.3-1.2 ng/mL	C-peptide	Failed to meet endpoint	Amylin Pharmaceuticals
BHT-3021 (proinsulin vaccine) (NCT00453375)	I/II	T1D < 5 years, detectable C-peptide, autoantibodies	C-peptide	Abstract Gottlieb EASD 2008 stabilized C-peptide	Bayhill Therapeutics
Liraglutide (NCT00993720)	II/III	T1D, no complications	Insulin dose	Decrease in insulin dose, accompanied with weight loss in C-peptide negative group	Sten Madsbad, Hvidovre University Hospital
INGAP	I/II	T1D, 18-70 years old	C-peptide, insulin dose	Increase in C-peptide, no change in HbA1c or insulin dose	KM Dungan, Ohio State University School of Medicine
IL-2 and Rapamycin (NCT00525889)	I	3-48 months since diagnosis	Safety measures, stimulated C-peptide, hypoglycemia, insulin requirement, HbA1c	Tregs increased within the first month of therapy, yet clinical and metabolic data demonstrated a transient worsening; transient increase in Tregs; transient β-cell dysfunction	Carla Greenbaum, Benaroya Research Institute - National Institute of Allergy and Infectious Diseases (NIAID) | Immune Tolerance Network (ITN)

7. This evaluation did not cover islet cell therapy.

VI. Current Established T1D Clinical Research Landscape (Ctd.)

Figure 2: Interventional Studies in Established T1D (Ctd.)

Recently Completed, Ongoing, or No Data Identified

Intervention (ref number)	Phase	Inclusion Criteria	Endpoints	Trial Start Date	Investigator/ Sponsor
Estradiol, medroxy-progesterone, hydrocortisone, growth hormone (NCT01265017)	I	Decline in insulin requirement or detectable C-peptide during a previous pregnancy in women with T1D	Stimulated C-peptide, insulin requirement, HbA1c, immunologic and hormonal responses	Jul-12	Lois Jovanovic, Sansum Diabetes Research Institute
Anakinra (NCT00645840)	II	> 5 years since diagnosis, no C-peptide requirement	Insulin sensitivity, HbA1c, fasting glucose	Apr-11	Cees J Tack, Radboud University, Nijmegen, Netherlands
Rilonacept (NCT00962026)	I	< 5 years since diagnosis, stimulated C-peptide > 0.2 nmol/L	Safety measures, HbA1c, insulin requirements	Feb-11	Perrin White, University of Texas Southwestern Medical Center
Tregs (NCT01210664)	I	3 months - 2 years since diagnosis, > 0.1 pmol/mL stimulated C-peptide	Safety measures, stimulated C-peptide, insulin requirement, HbA1c, immunologic markers	Nov-10	Kevan Herold, Yale University, Jeffrey Bluestone and Stephen Gitelman, University of California, San Francisco - Juvenile Diabetes Research Foundation | National Institute of Allergy and Infectious Diseases (NIAID)
Sitagliptin (NCT01227460)	N/A	Adults with T1D	A1c, C-peptide, GLP-1, GIP, and insulin levels.	Nov-10	Satish Garg, Barbara Davis Center
AAT (Aralast) (NCT01319331)	I	100 days - 5 years since diagnosis, >0.2 pmol/mL stimulated C-peptide	Safety measures, stimulated C-peptide, HbA1c	Oct-10	Peter Gottlieb, University of Colorado, Denver - Omni Bio Pharmaceutical, Inc.
ATG + G-CSF (NCT01106157)	I/II	4 months - 2 years since diagnosis, > 0.1 pmol/mL stimulated C-peptide	Glucose control, insulin requirement, c-peptide	April-10	Michael Haller, University of Florida - The Leona M. and Harry B. Helmsley Charitable Trust, Genzyme
Anti IL-1β (Xoma 052) (NCT00711503)	II	> 2 years since diagnosis, > 100pM stimulated C-peptide, HbA1c < 7.0%	Stimulated C-peptide, insulin requirement, HbA1c	Feb-10	Marc Donath, UniversitaetsSpital Zuerich - XOMA/JDRF
Sitagliptin (NCT01159847)	I/II	< 3 years since diagnosis, > 0.2 nmol/L C-peptide (LADA)	Stimulated C-peptide, insulin sensitivity immunomodulatory effects	Jan-10	Zhiguang Zhou, M.D., Ph.D.
INGAP (NCT00995540)	II	2-40 years since diagnosis, < 0.6 ng/mL fasting C-peptide, HbA1c < 7.7%	Adverse events, stimulated C-peptide	Nov-09	Yogish Kudva, Mayo Clinic, George Tsoukas, McGill University - Exsulin Corporation
Autologous Umbilical Cord Blood (NCT00989547)	I	Must have stored cord blood at Vita34, children > 1 year	Not specified	Oct-09	Anette-Gabriele Ziegler, Technische UniversitÃ¤t Munchen
Umbilical Cord Stem Cells (NCT01219465)	I/II	2- 20 years since diagnosis, < 0.1 ng/mL C-peptide	HbA1c, adverse events, fasting glucose, C-peptide, insulin requirements	Jan-09	Fuzhou General Hospital
Autologous Adipose Stem Cells (NCT00703599)	I/II	> 2 years since diagnosis, no C-peptide requirement	Insulin requirement, HbA1c, C-peptide	Nov-07	Emeritta A Barrenechea, Veterens Memorial Medical Centre, Philippines, Florencio Q Lucero, University of Philippines, College of Medicine - Adistem Ltd
IL-2 and Rapamycin (Proleukin and Rapamune) (NCT00525889)	I	3-48 months since diagnosis	Safety measures, stimulated C-peptide, frequency of hypoglycemia, insulin requirement, HbA1c	Aug-07	Carla Greenbaum, Benaroya Research Institute - National Institute of Allergy and Infectious Diseases (NIAID) | Immune Tolerance Network (ITN)

VI. Current Established T1D Clinical Research Landscape (Ctd.)

Figure 2: Interventional Studies in Established T1D (Ctd.)

Recently Completed, Ongoing, or No Data Identified

Intervention (ref number	Phase	Inclusion Criteria	Endpoints	Trial Start Date	Investigator/ Sponsor
Autologous Bone Marrow (NCT00465478)	I/II	> 5 years since diagnosis, 'poor beta cell function'	Insulin requirements, HbA1c, glucose, C-peptide	Mar-06	Beihua Kong, MD PHD, Shandong University
Dietary Fat (NCT01292590)	N/A	T1D using insulin pump and CGM	Insulin requirements, HbA1c, glucose, C-peptide	Sep-10	Howard Wolpert, Joslin
Intensive Physical Activity (NCT00491465)	N/A	Children, > 1 year since diagnosis	HbA1c, fructosamin, QoL measures	Jul-07	Ravital Nimri, Rabin Medical Center
Resistance Training (NCT00410436)	IV	> 1 year since diagnosis	HbA1c, CRP, LDL, ApoA1, ApoB	Oct-06	Ron Sigal, Ottawa Hospital Research Institute, Canadian Institutes of Health Research (CIHR)

However, most of these studies have enrolled small patient numbers and the results are largely inconclusive due to the heterogeneity of participants, the underpowered cohorts, or the single-arm designs. It is hard to define a homogeneous cohort within established T1D, as very little observational research has been completed to help identify key factors that may influence therapeutic response. The endpoints captured in these studies were also less than optimal because the researchers designed protocols that either measured glucose control or β-cell function but usually not both. Therefore, it is hard to know what level of improvement in C-peptide would prove to be clinically meaningful in individuals with long-standing disease.

8. Health Advances interviews and analysis. ClinicalTrials.gov. Paulo Monti et al., "Rapamycin Monotherapy in Patients with Type 1 Diabetes Modifies CD4+CD25+FOXP3+ Regulatory T-Cells," *Diabetes*, September; 57(9): 2341 (2008). Yang Z. et al, Rosiglitazone Preserves Islet Beta-Cell Function of Adult-Onset Latent Autoimmune Diabetes in 3 Years Follow-up Study," *Diabetes Res Clin Pract* Jan; 83(1):54-60 (2009). Faustman D., ADA Abstract (2011) Rother et al., "Effects of Exenatide Alone and in Combination With Daclizumab on β-Cell Function in Long-Standing Type 1 Diabetes," *Diabetes Care* (2009). Gottlieb et al., EASD Abstract (2008). Madsbad S, "Improved Glycemic Control with No Weight Increase in Patients with Type 2 Diabetes," *Diabetes Care*, Jun; 27(6):1335-42 (2004). Kielgast et al., 2011, *Diabetes Care*. Dungan et al., "Effects of Therapy in Type 1 and Type 2 Diabetes Mellitus with a Peptide Derived from Islet Neogenesis Associated Protein (INGAP)," *Diabetes Metab Res Rev*, Sep;25(6):558-65. (2009). S. Alice Long et al., "Rapamycin/IL-2 Combination Therapy in Patients with Type 1 Diabetes Augments Tregs yet Transiently Impairs β-Cell Function," *Diabetes*, June (2012).

VII. Drivers for Change

Historically clinical researchers were skeptical about exploring various approaches in established T1D populations. Today, the perspective of the interviewed experts is changing due to multiple factors highlighted in Figure 3. The most noted rationale for reevaluating opportunities in established disease is the increasing body of evidence on the presence of pancreatic β-cells in at least some individuals with established T1D. Thus, under certain conditions, C- peptide levels can increase, suggesting a potential increase in β-cell mass or function. These data are coming from multiple sources including research using samples from the JDRF nPOD (Atkinson, Univeristy FL) and the Joslin Diabetes Center Medalist Registry (King, Joslin), and several studies performed onpregnant women with T1D. The study of pregnant women by Dr. Jovanovic (Sansum Diabetes Research Institute) demonstrated an increase in C-peptide during the second trimester for both C-peptide positive and negative women, although the increase was much greater in women with some C-peptide at the start of pregnancy.[9] The study of Dr. Nielsen (Aalborg Hospital) demonstrated a median increase in stimulated C-peptide of 50% over the course of pregnancy in 35 women with established T1D. The duration of disease in these women ranged from 1-36 years, and at 33 weeks, 34 of 35 women had detectable C-peptide levels, including women with undetectable C-peptide concentrations in early pregnancy.[10]

Figure 3: Rationale for Clinical Research in Established T1D

- **Many people with T1D are not reaching target HbA1c and are at risk for or already have complications**
- **Solid evidence that β-cells may exist in at least a subset of the established T1D population**
- **Positive efficacy signals from a limited number of clinical studies**
- **The push toward personalizing therapies and recognition that other factors, such as insulin resistance, should drive targeted treatment options**
- **An expanding list of safer therapeutic options that could have positive effects on outcomes**
- **The availability of more resources such as the Helmsley T1D Exchange to facilitate higher-quality studies with potentially accelerated timelines**

As noted previously, nPOD, the network for pancreatic organ donors with diabetes, is a collaborative T1D research project funded by JDRF with a mission of providing characterized cadaveric pancreatic tissue to the research community. The data from nPOD demonstrate the variability in pancreatic damage across the population. It is also important to note that C-peptide levels may be negative when β-cells are still present as seen in Figure 4.[11] The β-cells may be present but not functional. This study found that 67% of the Medalists had random C-peptide levels above 0.3 nmol/l. (reference King) Postmortem examination of pancreases from nine Medalists showed that all had insulin+ β-cells with some positive for TUNEL staining, indicating apoptosis.[12]

Given that β-cells are still present, at least in a subset of individuals with established disease, experts are acknowledging that some previously tested or new disease-modifying approaches may have some utility in established T1D. These data also may provide an explanation for the variability in the few studies that have been done in established disease and the supporting rationale for more personalized approaches to treatment of T1D. It is still unclear what level of C-peptide provides a meaningful clinical benefit for people with established disease. This aspect of research needs to be conducted to gain a better understanding of the significance of C-peptide levels.

9. Jovanovic L, "Declining Insulin Requirement in the Late First Trimester of Diabetic Pregnancy," *Diabetes Care*, Jul; 24(7):1130-6 (2001).
10. Nielsen LR, "Pregnancy-Induced Rise in Serum C-Peptide Concentrations in Women with Type 1 Diabetes," *Diabetes Care*, Jun; 32(6):1052-7 (2009).
11. Atkinson, Presentation given at JDRF Technology Update, Boston (2011).
12. Keenan HA, Sun JK, Levine J, Doria A, Aiello LP, Eisenbarth G, Bonner-Weir S, King GL, "Residual Insulin Production and Pancreatic ß-cell Turnover after 50 Years of Diabetes: Joslin Medalist Study," *Diabetes*, Nov 59(11):2846-53 (2010).

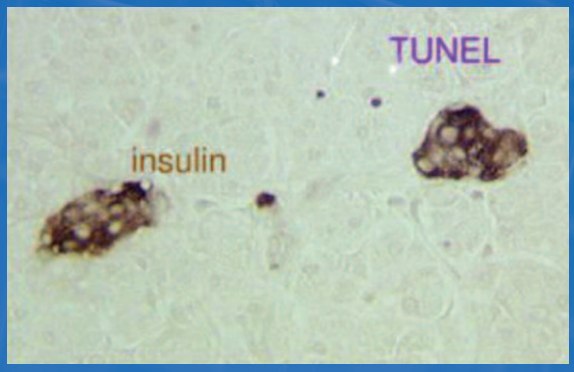
VII. Drivers for Change (Ctd.)

With this increase in knowledge of β-cell biology in established T1D disease, the next logical question is what additional therapies should be considered based on this information? Several immunotherapies that have been approved for other autoimmune diseases over the past 5 to 10 years may be good candidates to test in certain segments of the established T1D population. Many of these new products have better safety profiles than previously available general immunotherapies. With known safety profiles, the ability to accurately predict a risk benefit ratio ahead of time improves the likelihood of a beneficial safety margin in the T1D population. Rationalizing more aggressive approaches in new-onset patients may be challenging based on age and potential outcomes, but in established disease these factors can be optimized. Starting with an approved agent also offers a regulatory advantage and opens the door to combination studies.

Figure 4: nPOD Data Presented by Dr. Mark Atkinson

Beta Cells – Long Standing Type 1

78 year male Medalist (4 at onset) IA2+ Most islets have no insulin+ but half of sections have scattered insulin+ cells (small clusters, singlets or doublets); no TUNEL+ insulin+ cells seen.



C-peptide undetectable

With the ongoing daily struggles to control glucose levels in people with T1D, especially during adolescent ages, experts are considering the utility of non-insulin metabolic control agents being used in type 2 diabetes management. Non-insulin therapies may be of interest for two reasons. First, the best short-acting insulin today still does not match endogenous release insulin profiles, resulting in elevated post-prandial glucose levels if insulin is not dosed ahead of a meal. Second, insulin resistance has historically been considered a type 2 diabetes issue, but more evidence is suggesting it is an issue in certain T1D populations. Several products used in the management of type 2 diabetes may have utility and play a beneficial role in maintaining tighter glucose control in the established T1D population.

Although the scientific rationale and community interest to explore clinical development opportunities in the established T1D population is growing, industry is still raising the question of clinical development feasibility. Conducting proof-of-concept studies in T1D often takes longer than in other autoimmune conditions, driven mostly by a lack of short-term markers of efficacy. Trial recruitment can also be challenging, in particular when looking for specific sub-segments such as C-peptide positive patients. This second hurdle should be lowered with an increasing number of trial networks within the United States and abroad. An example is the recently formed T1D Exchange, which includes a large number of pediatric and adult endocrinology clinics managing roughly 150,000 people with T1D.

VIII. Paving the Path: Observational Research, Standards, and Interventional Studies

Based on a reduction in the many hurdles that have hindered established T1D clinical research, the majority of experts believe efforts in this area should be increased. Figure 5 summarizes the roadmap established based on the project findings.

Figure 5: Established Disease Opportunity Map

Experts agree that more observational research will help build a more robust foundation for a future generation of interventional studies that can be targeted to more homogeneous T1D patient stratification and subject sub-types. Setting clinical development standards across the field will allow researchers to better compare and contrast trial results so they can understand not only the cellular-level impact but also how clinically relevant any of these changes will be. Any increase in C-peptide levels needs to be correlated to clinical improvements, such as a reduction in hypoglycemic events, lower insulin demands, more time in range, better HbA1c, and ultimately a reduction in long-term complications. In parallel with the observational studies and standards development, selective interventional studies could be initiated in the near term, despite the lack of disease understanding. These studies will serve to answer some fundamental questions and provide input into the development of clinical standards.

Observational Research

Experts cite a number of critical gaps in the basic understanding of the progression of T1D over the course of a person's lifetime. The unknowns fall into three general categories: β-cell health, immune system status, and risk stratification. Figure 6[13] shows the critical questions within each of these three areas. It

Figure 6: Key Observational Questions

β-Cell Health What is the status of β-cell mass/function in the established T1D?	• What is the prevalence of residual β-cell mass/function? • How does this change over time? • What factors impact β-cell mass/function over time? • Is β-cell failure reversible? What factors influence regeneration?
Immune System Status What is the status of the immune response in established T1D?	• What immune system markers are perturbed in the periphery of T1D patients? • What is the intra- and inter-individual variability of these markers and how do these relate to β-cell function? • What factors influence variability? • Is T1D a relapsing-remitting disease?
Risk Stratification/ Target Identification What factors other than glucose control and level of C-peptide influence the rate and severity of complications?	• Can biomarkers or other tools predict which individuals will develop complications versus those that will be complication-free over the long-term? • Can protective factors be identified in those individuals remaining complication-free?

13. Health Advances interviews and analysis.

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has been years since the ground-breaking DCCT (Diabetes Control and Complications Trial) was completed, and treatment has improved with better glucose monitoring and improved insulin therapy. Although C-peptide levels were measured during the study, it was not the primary focus. A post-hoc analysis showed those subjects with some level of C-peptide had better outcomes.[14] The follow-up study, called Epidemiology of Diabetes Interventions and Complications (EDIC), is assessing the incidence and predictors of cardiovascular disease events such as heart attack, stroke, or needed heart surgery, as well as diabetic complications related to the eye, kidney, and nerves. The emphasis is on clinical outcomes, not evaluating the impact of control and time on the underlying disease biology or evaluating the intra- or inter-subject variability. A key focus moving forward is deeper characterization of people with T1D over the course of their disease. Figure 6 provides a list of the key questions that observational research should address.

Observational studies that will address these questions come with different levels of complexity, size, time requirements, and cost. Figure 7[15] summarizes study topic areas that align with the list of key questions identified by experts in the field. A comprehensive natural history study would address many of the questions, but it will take researchers many years to read out results from such a large effort. An alternative would be to do a number of smaller, targeted studies that focus on addressing specific questions. An example of one such study would be evaluating residual C-peptide in people with established T1D and tracking how these levels change over time. Another study would be to evaluate "extreme" sub-populations that may help identify critical factors that can lead to potential targets for interventional therapy. An example would be a study of people who have lived with T1D for 50 or more years with few or no complications for the purpose of finding a protective factor that may exist. On the opposite side would be a study of individuals who develop complications faster than would be anticipated given glucose control. Further evaluation of women with T1D during pregnancy could provide more insight into the factors that influence β-cell expansion. A key question is whether the rise in C-peptide is occurring because of the changes in the immune system, hormonal levels, insulin resistance, or demands of the fetus.

Two additional areas that the experts identified as gaps were the lack of knowledge on the impact of T1D on quality of life and the presence of insulin resistance in T1D. Although some quality-of-life scales exist today, experts are questioning whether we need even better

Figure 7: Potential Observational Studies

C-Peptide Prevalence*	Sub-Populations	Relapsing-Remitting	Natural History	Risk Stratification
• Noted by researchers as one of the most important studies	• Pregnancy • Extreme populations - Non-progressors - Early-progressors • Low-insulin dose • Athletes • C-peptide positive	• Understand the intra- and inter-individual variability of C-peptide over time	• Comprehensive study aimed at providing a deep analysis of immune system, β-cell function, and patient demographic markers	• Identifying factors that influence the development of complications over the long term

*This study was initiated by the T1D Exchange in 2012.

14. Steffes MW, Sibley S, Jackson M, Thomas W, "Beta-Cell Function and the Development of Diabetes-Related Complications in the Diabetes Control and Complications Trial," *Diabetes Care*, Mar; 26(3):832-6 (2003).
15. Health Advances interviews and analysis.

tools to truly understand the impact throughout the life of a person with T1D. Understanding this impact will be critically important as researchers study new interventions in T1D. Currently, most emphasis is on achieving glucose control as measured by HbA1c. Some new interventions may help individuals who are already in good glucose control maintain that control while also improving co-morbidities such as depression or improving quality of life and/or productivity. A baseline needs to be in place to measure these types of improvements. On insulin resistance, experts are questioning whether some segments of the T1D population have insulin resistance due to obesity co-morbidities or due to other factors. Understanding these factors could lead to different treatment guidelines for T1D patients with insulin resistance.

As researchers answer these questions on T1D, they can translate the information back into more personalized treatment approaches or more targeted clinical studies. Most experts believe pushing this observational research forward should be the highest priority over the near term.

Standards

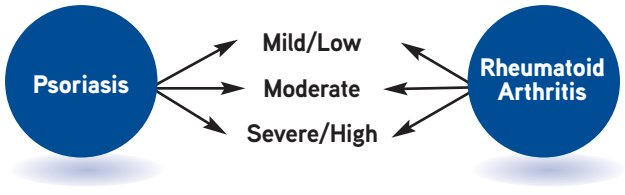
Although this project focused on defining clinical development opportunities for established T1D, what became apparent throughout this assessment is that the lack of standards in the established T1D field. This is a critical gap that needs to be addressed in order to reap the full benefit of any new research efforts.

Interviewed experts agreed that the areas of greatest need are the definition and staging of established T1D and trial endpoints. Some of the clinical trial networks have already initiated efforts to standardize, especially in the new-onset population. These efforts need to be more broadly adopted and expanded into the established T1D population.

The inclusion criterion of "time since diagnosis" used when assessing clinical trials performed to date has varied from one year post-diagnosis to five years post-diagnosis or was defined independently of time and based on C-peptide levels. It is hard to compare across trials without a standard definition. When experts were asked to define "established," the majority talked about a definition in which an individual had reached a steady state of C-peptide with no further decline. For most, this did not mean that C-peptide had to be below a certain level, as they recognized that a small subset of people with T1D may never totally lose C-peptide ("C-peptide positive established disease"). However, no consensus was reached on whether this was likely one year post-diagnosis or five years post-diagnosis. To confirm when steady state is reached, a longitudinal, residual C-peptide study will likely need to be performed. Prior to the release of new data, a field of experts should convene to determine a working definition in order to provide some consistency for the next round of clinical studies.

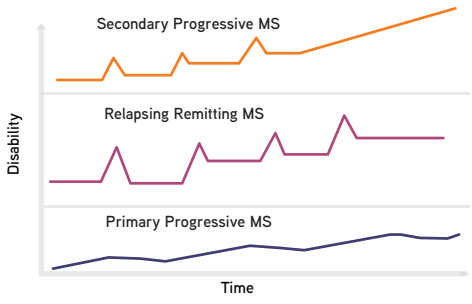
Figure 8: Staging in Other Autoimmune Diseases

RA and Psoriasis Patient Segments: Defined by the Pattern of Disease Activity



- Psoriasis and RA patients are segmented into three groups defined by thresholds of disease activity scales such as DAS28 and PASI, which are primarily comprised of physical signs and symptoms
- Pediatric-onset RA is distinguished from adult-onset

Multiple Sclerosis Patient Segments: Defined by the Pattern of Disease Activity



- EDSS is a composite score used to assess multi-factorial impact of MS

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Over time, experts are hopeful that T1D can be staged similar to what is done in other autoimmune diseases as demonstrated in Figure 8.[16] T1D has always been considered a homogeneous disease, but now the evidence is clearly showing that it is heterogeneous like most autoimmune conditions. The β-cells are always affected, and insulin is always required; however, many other things differ including insulin sensitivity, C-peptide levels, presence of co-morbidities, and hypoglycemic sensitivity. Many of the observational studies mentioned in Figure 7 would provide foundational research to initiative staging.

Other clinical trial standards that should be established largely reside around endpoints. Studies have either been focused on assessing clinical improvements or β-cell functionality; few trials have incorporated both sets of measurements, making it hard to determine what level of β-cell functionality is required to achieve clinically meaningful results. Surrogate markers are not standardized and may not be sensitive enough to provide the full picture of effect. Experts also talked about the need to identify and validate new assays and surrogate markers. The lack of β-cell imaging continues to be a major gap in identification and testing of new therapeutic solutions.

Figure 9: Examples of Disease Measurements and Biomarkers

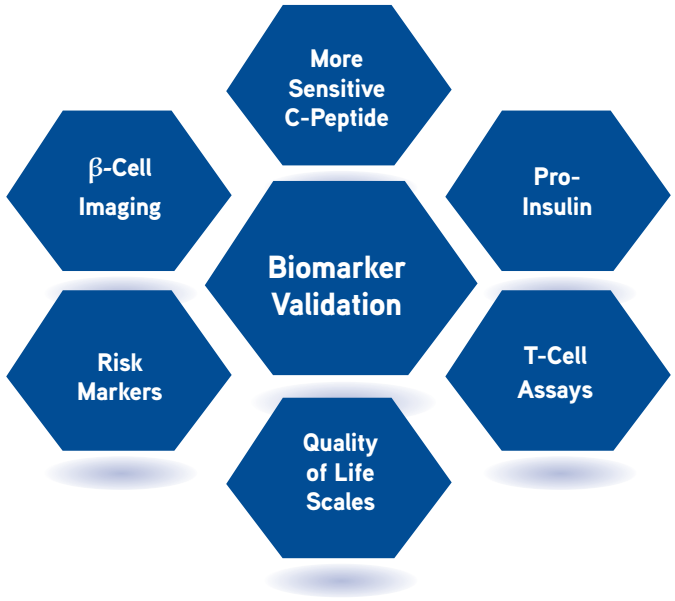

Figure 9[17] provides examples of existing or future biomarkers that researchers should evaluate further. On C-peptide, the questions revolved around the sensitivity of the existing assays. Pro-insulin could be important if for some reason β-cells are producing pro-insulin but the process of cleaving it to produce secreted insulin and its byproduct C-peptide is impaired. Other examples include methods to detect low levels of inflammation and novel T-cell assays. The inability to risk-stratify patients ahead of time restricts the type of interventions that may provide some benefit to high-risk populations.

Interventional Studies

When considering interventional approaches in established T1D, multiple pathways could be targeted, including multiple direct and indirect immune and beta cell pathways. Historically, most researchers believed that in order to increase β-cell mass, a regenerative agent or cell transplant would be required. However, with more data emerging on C-peptide positive established T1D and the ability for people with T1D to increase function under certain conditions, experts are beginning to believe new approaches should be explored.

The critical questions that experts identified as being the focal point for near-term clinical research efforts are listed in Figure 10. These questions revolve around addressing the autoimmune attack and exploring indirect ways to increase mass or function. For example, if you treat C-peptide positive patients with an anti-inflammatory agent, can you increase cell mass and therefore increase function or will function improve for the β-cells that are already there but not producing insulin? The question on metabolic control on β-cell stress is another area that experts want to explore further. What impact does control have on the C-peptide levels? Do individuals with some residual C-peptide have an easier ability to maintain control?

What is the opportune time and pathway to use to stimulate beta cell activity? Without being able to image β-cells, it is challenging to

16. UpToDate, http://www.uptodate.com/index.
17. Health Advances interviews and analysis.

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understand the cause and effect of β-cell injury. The majority of experts do believe a combination approach will be required to see a clinically meaningful result in C-peptide negative established T1D. Although the regulatory hurdles are high, the possibilities are expanding with the growing list of FDA-approved products that could be included as part of a combination regimen.

Experts largely agree that more should be invested to explore disease-modifying and complementary symptomatic therapies, but opinions differ on the exact path to push forward with in the near term given the gap in solid data on risk stratification and the variability in the rate of β-cell decline. It is also important to remember that the scope of this research project was to identify studies that could be initiated and completed over the next three years. This focus eliminated some of the novel preclinical β-cell regenerative therapies. However, as seen in Figure 11,[18] the list of opportunities has grown over the past five years, mostly due to the approval of potential products for other diseases, including type 2 diabetes. Experts also identified a number of products that are food supplements or nutraceuticals that are considered GRAS (generally regarded as safe) therapies.

Experts did agree on some guiding principles when prioritizing potential interventional study. First, safety considerations need to be paramount until patients can be properly risk-stratified and appropriately selected for clinical studies that have a potential therapeutic benefit that matches individual risk. Experts agreed that prioritizing products that had been previously approved for another indication was a logical starting point. Second, while GRAS products could present a great opportunity for new T1D therapies, it is unclear how to best evaluate this class of products and even more challenging to rank these types of interventions against more traditional treatments. Additional planning is required to fully flush out the clinical development plan for this class of agents. Third, when considering combination studies, the emphasis in the short term should be on combining an immune-based therapy with a metabolic control therapy instead of using two immune-based therapies together. When it comes to selecting individual studies to pursue, organizations and companies will need to factor in other criteria specific to their internal goals in order to prioritize their research.

A backbone of the proposed interventional studies is paving a path for combination studies. An example of one of the proposed study designs is shown in Figure 12.[19] This 3- to 4-arm design combining metabolic control and immunotherapy agents could open the door for many more future studies.

Figure 10: Interventional Studies - Key Questions

1	Do non-insulin metabolic control therapies result in clinically meaningful improvements and/or modulation in β-cell function in all established patients or in select sub-segments?
2	Can modulation of the immune system result in changes to β-cell health in established disease? Does this result in clinically meaningful improvements?
3	Does a combination approach result in improved efficacy both clinically and in terms of disease modification?

18. Health Advances interviews and analysis.
19. Health Advances interviews and analysis..

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Figure 11: Potential Therapies for Established T1D

β-Cell Regeneration

- ★ G-CSF
- ★ Pregnancy hormones
- ■ Gastrin
- ■ Human proIslet Peptide (Pancreate)
- ■ INGAP

β-Cell Health

- ★ DPP-IV inhibitors
- ★ GLP-1 R agonists
- ★ Metformin
- ★ PPAR agonists
- ★ Proton pump inhibitors
- ★ TUDCA
- ■ 11 HSD-1 inhibitors
- ■ CB1R antagonist
- ■ Glucokinase activators
- ■ GPR40
- ■ GPR119
- ■ Leptin
- ■ SAHB peptides
- ■ SGLT2 inhibitors
- ■ Sirt1 activators
- ● Almonds
- ● Anti-Oxidants, Resveratrol
- ● Glutathione
- ● Grapefruit Extract
- ● Omega 3 and 6 Fatty Acids
- ● Probiotics
- ● Vitamin D
- ● Vitamin E
- ● Weight loss agents
- ▲ Exercise
- ▲ Diet changes

Anti-Inflammatory

- ★ Anti-IL1 β
- ★ Anti-TNFs
- ★ AAT
- ★ IL-6 antagonist
- ★ Cox-2 inhibitors
- ★ Anti-α-4 integrin (natalizumab)
- ★ Aminosalicylates
- ★ Anti IL-12/23 (ustekinumab)
- ■ Anti-IP10
- ■ Fumarate (BG-12)

Immunomodulation

- ★ Anti-BLyS (belimumab)
- ★ Anti-CD2 * (alefacept)
- ★ Anti-CD20 (rituximab)
- ★ ATG/G-CSF
- ★ BCG vaccine
- ★ CTLA-4
- ★ Fingolimod (Gilenya)
- ★ Glatiramer acetate (Copaxone)
- ★ IL-2
- ★ Imatinib
- ★ Rapamycin
- ■ Anti-CD3
- ■ JNK2 Inhibitors
- ■ Dendritic cells
- ■ GAD65 vaccine
- ■ DiaPep277 (HSP60)
- ■ T-regulatory cells
- ■ Insulin vaccine
- ■ Anti-CD22
- ■ γ-aminobutyric acid (GABA)

Figure 11 Key: ★ Approved ■ Not Approved ● GRAS ▲ Other

*Astellas pulled this product from the market in January, 2012 based on lack of uptake in psoriasis market.

Figure 12: Combination Study Designs

Arm 1	Arm 2	Arm 3	Arm 4 (Optional)
Placebo Control	Immunotherapy	Metabolic Control + Immunotherapy	Metabolic Control
	Critical to see whether any spontaneous increase in β-cell function absent any regenerative agent.	*Gives the immunotherapy a better chance of impacting disease and potentially reduces time to response.*	*Even if there is no disease modifying effect, improvement in symptom management is an advantage.*

Patient Populations and Endpoints

- All patients should have had T1D >5 years
- The study should be powered for patients with residual C-peptide
- Additional patients should be added to the study to test the impact of combination treatment in patients without residual C-peptide
- Trial length is still to be determined
- Key endpoints will include HbA1c, time in range, and C-peptide/proinsulin

IX. A Call to Action

JDRF and The Helmsley Charitable Trust commissioned this project on behalf of all people touched by T1D, with the hope of uncovering opportunities to explore new paths in people living with this disease year after year. The project addressed the key questions raised in developing this roadmap and identified some high-impact opportunities that could be completed over the next few years.

- What do we know about the underlying disease once a patient progresses beyond the new-onset period?

  Evidence on the progression of disease is limited; however the evidence has grown that at least a subset of patients with T1D retain some β-cell function over time. C-peptide has also been shown to increase in certain situations (e.g. pregnancy, following therapeutic intervention).

- Is there rationale to study disease-modifying therapies in established patients?

  Yes, given the thought that β-cells are still present in a subset of patients, potential could exist to stop the autoimmune attack and keep these cells functional. Thus, efforts should be directed at preserving what beta cells are there, restoring their functional activity and possibly, their replication.

- How can trials be optimized?

  Reducing the heterogeneity of subjects and correlating changes in β-cell health to clinically relevant improvements are critical areas that need to be addressed. Combination studies will be critical to achieve substantial improvements in established T1D.

- Which therapeutic classes and drug combinations are most promising?

  Roughly 60 individual drug candidates were identified as having potential benefit in established T1D. The list narrows to 40 if we stay focused on agents already in receipt of regulatory approved for other diseases. Relying on proof of concept T1D efficacy data and relative safety could further narrow the list. Combination studies will be complicated to design but likely necessary to achieve clinically meaningful results.

- How should therapies be targeted/tailored based on a predictive profile of disease progression?

  Unfortunately, not enough is known about the underlying progression of T1D to properly risk-stratify the population. Observational studies are required before therapies can be tailored for individual needs.

To conclude, pushing forward with near-term clinical development opportunities in people with established T1D received support from both the academic research community and companies with existing or potential T1D programs. Industry is asking for more education and the ability to collaborate with the research community. Investment is needed now in order to build a strong foundation for more breakthrough research. Opportunities exist for pre-competitive space collaboration. JDRF and The Helmsley Charitable Trust are both committed to these clinical development initiatives in the established disease population and are excited about the opportunity to partner with the T1D community to address the critical research gaps and accelerate the assessment of potential interventions, which could result in better lives for all people with T1D.