WHITE PAPER

Modeling the Total Economic Value of Novel Type 1 Diabetes (T1D) Therapeutic Concepts

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JDRF T1D Fund

HEALTH ADVANCES

JDRF is the leading global organization funding type 1 diabetes (T1D) research. Our mission is to accelerate life-changing breakthroughs to cure, prevent, and treat T1D and its complications. To accomplish this, JDRF has invested more than $2.2 billion in research funding since our inception. We are an organization built on a grassroots model of people connecting in their local communities, collaborating regionally for efficiency and broader fundraising impact, and uniting on a national stage to pool resources, passion, and energy. We collaborate with academic institutions, policymakers, and corporate and industry partners to develop and deliver a pipeline of innovative therapies to people living with T1D. Our staff and volunteers throughout the United States and our six international affiliates are dedicated to advocacy, community engagement, and our vision of a world without T1D.

200 Vesey Street
28th floor
New York, NY 10281
212-785-9595
www.jdrf.org

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50 Milk Street
Boston, MA 02109
617- 910-7542
www.t1dfund.org

HEALTH ADVANCES

Health Advances is a healthcare strategy consulting firm based in Newton, Massachusetts. With over 150 professional staff, a team of 12 partners, and offices in San Francisco, Zug, and Hong Kong, the company advises life sciences companies, including biopharmaceutical, medical device, diagnostic, and information technology companies, as well as organizations that invest in, service, and collaborate with those companies, on product innovation and corporate strategy.

275 Grove St, Suite 1-300
Newton, MA 02466
781-647-3435
www.healthadvances.com

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Lutz Heinemann, PhD
Managing Director
Journal of Diabetes Science and Technology
Düsseldorf, Germany

Paolo Pozzilli, MD
Professor of Endocrinology and Metabolism
University Campus Bio-Medico
Rome, Italy

John Wentworth, MD
Clinician Scientist
Walter and Eliza Hall Institute of Medical Research
Parkville, Australia

Mark Peakman, PhD
Professor of Clinical Immunology
King's College London
London, England

Marian Rewers, MD, PhD
Professor of Pediatrics, Executive Director
Barbara Davis Center for Diabetes
University of Colorado
Boulder, Colorado

Henk Veeze, MD
Founder and Senior International Medical Director
Diabeter Nederland
Rotterdam, Netherlands

Pratik Choudhary, MD
Senior Lecturer
King's College London
London, England

Thomas Danne, MD
Director, Department of General Pediatrics and Endocrinology/Diabetology
Children's Hospital at Hannover Medical School
Hannover, Germany

James Markmann, MD, PhD
Chief, Division of Transplantation
Massachusetts General Hospital
Boston, Massachusetts

Zachary Bloomgarden, MD
Clinical Professor
Mount Sinai
New York, NY

This report was written by Katelyn Ward, Chelsea Pan, PhD, Mansi Shinde, PhD, Jean Rieuthavorn, Sheela Hegde, and Julia A. Gaebler, PhD. For more information, please contact Sheela Hegde at shegde@healthadvances.com.

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Foreword

In early 2019, JDRF and the JDRF T1D Fund recognized the need to characterize the full economic value of novel therapies for T1D. Currently, despite at least 18MM people living with the disease globally and an estimated 1.6MM in the US, the investment in new technologies and therapies for T1D lags relative to other chronic or autoimmune diseases as measured by resources invested or number of trials in the clinic. There are also an estimated 2.3MM people globally at risk for T1D, in stage 1 or 2 of the disease. We believe that traditional approaches to market analysis underestimate the true value of T1D therapies (where a number of recent market studies predict the *global* T1D market to be anywhere from $2.8B up to $25B by 2025). T1D is a chronic condition that requires constant attention from the individual and their caregivers, whose burden is on top of the unmet medical need, acute cost of care, and the cost of long-term morbidity and mortality from complications from the disease. We sought a comprehensive and quantitative burden of illness (BOI) assessment to provide stakeholders developing, funding, and approving therapies for T1D a better understanding of their potential.

Indeed, the results of the analysis show that the large scale of the annual economic burden of T1D, >$30B in the US and >$90B globally, has been historically underestimated. This is driven by productivity costs that far exceed direct medical costs, the traditional way of sizing the disease impact. As reported here, the full picture exceeds even these figures: due to limited data sources, they do not account for the psychological burden or other intangible costs of the disease for people with T1D and their families. Further psychosocial studies are needed to produce evidence and data to account for these burdens in future analyses.

The report finds that there is substantial economic benefit to a range of T1D therapy innovations. Disease modifying therapies (there are none approved for T1D today) represent substantial improvements in patient health and reduce significant costs associated with the economic burden of disease. This will be true even for therapies that are steps along the way to a cure. Several therapeutic concepts, whether slowing progression of T1D or delaying T1D onset for 1-2 years, or developing truly closed-loop artificial pancreas systems, have multibillion dollar annual economic impact in the US alone. Furthermore, several of these concepts and innovations are relatively near-term as new therapies enter the clinical phase. Our message is reinforced: investment in T1D therapies must be made today to reap these benefits.

Important to note, this report is based on an updated prevalence number of T1D in the US: 1.6MM, up from the 1.25MM prevalence JDRF has previously referenced. This is based on CDC estimates of 1.4MM adults >20 years[1] and 187,000 youth with T1D in 2018[2]. The following report rigorously quantifies BOI for the US, and then extrapolates to most other regions based on gross domestic product (GDP). JDRF will continue to invest and encourage other efforts to better quantify the burden of T1D for geographic regions worldwide.

The following economic analysis is not intended to demonstrate the market size of any one specific therapy for T1D, but rather to illuminate the magnitude of societal costs borne by governments, payers, employers, and of course, people with T1D and their families. This report can inform any organization or company considering investment in T1D research and therapy development, including JDRF and the JDRF T1D Fund as we build our Cure, Prevent, and Treat portfolios. Our hope is that this more comprehensive approach to assessing the value of therapeutic innovations spurs more attention and interest, and ultimately catalyzes more investment into new modalities and tools for T1D.

[1] Based on 2013-2016 NHANES, 2017 NHIS, and the 2018 Census
[2] Based on SEARCH prevalence data, 2017-2018 NHIS, and the 2018 Census

Executive Summary

Objectives

The purpose of this evaluation is two-fold: 1) to identify and assess previously unrecognized costs associated with type 1 diabetes (T1D) and quantify the full economic burden and 2) to fully estimate the potential economic value of several novel T1D therapeutic concepts.

Previous analyses of T1D disease burden typically only consider the direct medical costs associated with T1D, i.e. the costs of insulins and health care visits, but underestimate the full disease burden felt by patients and caregivers. This assessment focuses on also assessing indirect costs, in particular productivity costs, and qualitatively evaluating intangible quality of life impact, in order to derive a global T1D BOI.

This analysis then quantifies how the introduction of seven novel therapeutic concepts for T1D would address the global T1D economic burden. The overall concepts, as well as sequential generations of each concept that achieve increasing therapeutic value, were rigorously defined by JDRF in collaboration with the academic, clinical, and research communities. The concepts tie to three distinct T1D research goals: to **prevent** progression of the disease in those at risk or recently diagnosed; to **cure** the body's inability to control glucose, thereby reversing insulin dependence; and to **treat** T1D patients with new drugs, therapies, and devices that make it easier to manage the disease until a cure is found.

As shown in Table 1, the evaluation includes three prevention concepts: delaying onset of Stage 3 (clinical T1D diagnosis), preventing diabetic ketoacidosis (DKA) at diagnosis, and delaying progression within Stage 3; two cure approaches: replacing beta cell function and restoring beta cell function; and two adjunctive treatments: both medication and device adjuncts to insulin to increase HbA1c and/or time in range (TIR). All concepts are assessed in sequential generations with improvements in efficacy, safety, or route of administration, along the path to achieving increasingly meaningful therapeutic benefits. For some of the concepts, HbA1c improvements are defined, for others TIR improvements, and for others, both. These are meant collectively to reflect improvements in glucose control and the expectation that in the future HbA1c and TIR will both be available as efficacy measures of glycemic control.

Table 1: Therapeutic Concept Overview

Sequential Therapeutic Improvement →

Category	Therapeutic Concept	Gen 1	Gen 2	Gen 3+	Potential MOAs
Prevent	**Delaying Onset of Stage 3**	• Delay onset of Stage 3 by 2 years in at least 30% of the population, IV	• Delay onset of Stage 3 by 2 years in at least **70%** of the population, IV	• Delay onset of Stage 3 by **5 years** in at least **70%** of the population, IV, **then SC**	• Immunotherapies (e.g., teplizumab) • Beta cell survival agents
	Prevent DKA at Diagnosis at Stage 3	• Reduced DKA at conversion to insulin dependence to 20% (from 30-40%)	• Reduced DKA at conversion to insulin dependence to **15%** (from 30-40%)	• Reduced DKA at conversion to insulin dependence to **10%** (from 30-40%)	• Childhood monitoring program
	Preserve Beta Cell Function at Stage 3	• <20% increase per year in insulin requirements, 50-70% TIR, IV	• **<10% increase** per year in insulin requirements, **>70%** TIR, IV	• **50-70% reduction** per year in insulin requirements, **>95% TIR**, IV then **oral or SC**	• Beta cell survival agents • Regenerative therapies • Immunotherapies
Cure	**Beta Cell Replacement**	• 50-100% reduction in insulin needs with broad immunosuppression, 12-24 months duration of efficacy	• **70-100%** reduction in insulin needs and **no broad immunosuppression**, **12-24 months** duration of efficacy	• **Insulin independence** with **no immunosuppression** required, **>24 months** duration of efficacy	• Renewable cell source • Encapsulation / protection of beta cells • Immunosuppression
	Restore Beta Cell Function	• Halts loss in insulin production, improves TIR to 50-70%, achieves HbA1c <7.5%	• **Modest Increases** in insulin production, improves **TIR to 70-90%**, achieves **HbA1c levels <6.5%**	• **Restores durable insulin independence**, achieves **TIR of 100%** and **HbA1c levels <4-5.6%**	• Combination of regenerative therapies and immunotherapies
Treat	**Improve Metabolic Control**	• Reduction of HbA1c by 0.5%, improves TIR to 55%, no additional risk of hypoglycemia, but increased incidence of DKA requires mitigation strategy	• Reduction of **HbA1c by 1.0%**, improves **TIR to 65%, no additional side effects**	• Reduction of **HbA1c by 1.5%** and **75% TIR**, no additional side effects	• Novel insulins • Adjunctive therapies (SGLT inhibitors)
	Artificial Pancreas	• Hybrid closed loop with partial automation of insulin delivery, TIR 80%	• **Fully closed-loop** with full automation of drugs, TIR 95%	• "Artificial pancreas", physiologic system with **full automation**, time in tight glucose range 95%	• Integrated CGM-Insulin Pump systems

Key Findings - T1D Burden of Illness

Global T1D Burden of Illness Nears $100B When Factoring in Productivity Losses

There are significant "hidden" costs associated with the economic burden of T1D. Annual productivity costs *exceed* direct medical costs associated with adult T1D and even have meaningful impact in pediatric T1D, where caregiver productivity is affected. As shown in Figure 1, while the annual direct medical cost burden of T1D in the US in 2018 is $4,429 for a pediatric patient and $8,136 for an adult patient, the total annual cost burden is $5,960 and $20,320 per pediatric and adult patient, respectively, when factoring in productivity losses. Accounting for the 1.6MM annual prevalence in the US, the cumulative economic burden for all T1D patients in the US is ~$30B per year. Extrapolating to global regions suggests a worldwide annual T1D cost burden of ~$90B.

Figure 1a: Annual T1D Per Patient Burden (US)

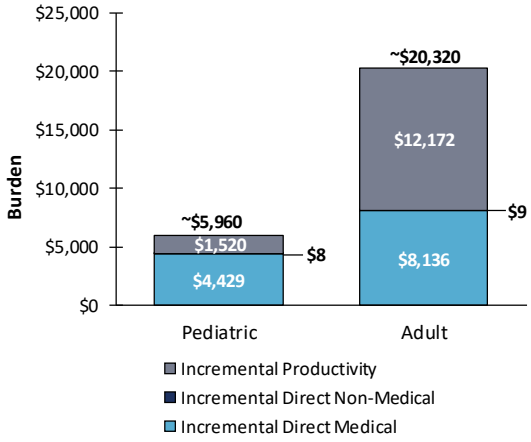
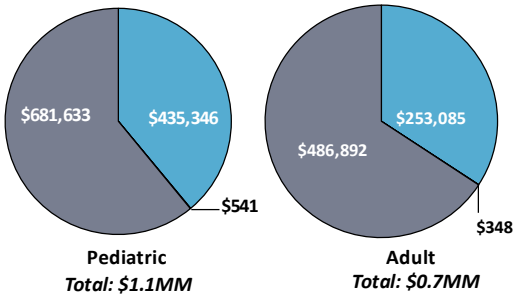
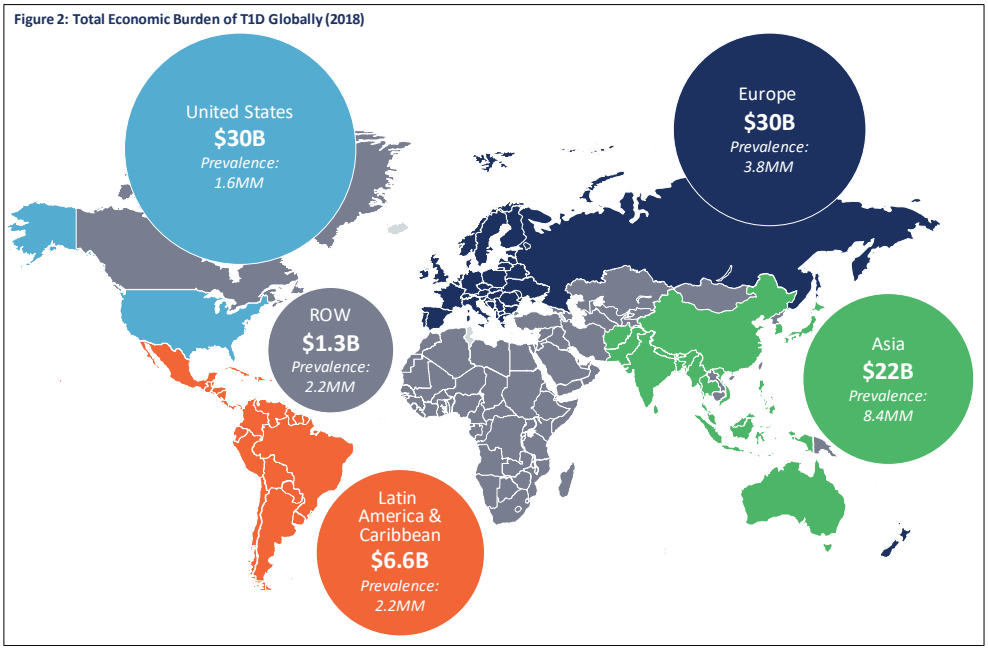


Figure 1b: Lifetime T1D Burden for a Newly Diagnosed Patient (US)



Source: Health Advances Burden of Illness Analysis, Diabetes 2012

Figure 2: Total Economic Burden of T1D Globally (2018)



Key Findings - Economic Value of Therapeutic Concepts

Improvements to Today's Treatments Would Address Global Cost Burden

As the field works towards a cure, there are opportunities to address the needs of people living with the disease today. Adjunct therapies that reduce HbA1c and improve TIR beyond the rates patients are achieving with insulin therapy would have meaningful economic benefits. These adjuncts may be medications or improved delivery devices. Medications that reduce HbA1c by 1.0%-1.5% and improve TIR to 65%+, without significant safety risks, would achieve $5B-$10B of annual economic impact in the US, depending on the level of efficacy achieved. Future fully closed-loop pumps, which achieve TIR of 95% and minimize user burden, would achieve $18B in US annual economic impact. These innovations would also provide intangible benefits, not captured in these figures, by alleviating the day-to-day burden of disease management and the associated psychosocial challenges.

Delaying Disease Onset to, or Preserving Beta Cell Function at Stage 3 Has $3B-$6B in US Economic Benefit

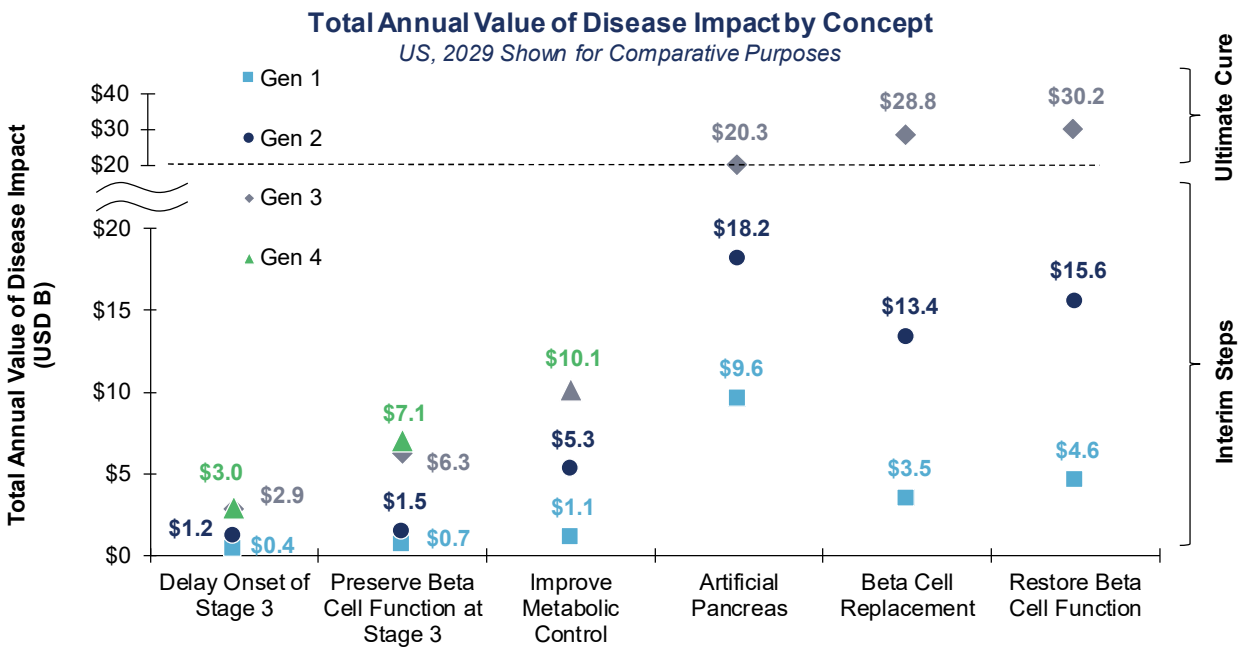
T1D prevention drives value by delaying insulin needs, reducing acute events, and reducing longer term complications. While the direct medical cost savings associated with a therapy that achieves 70% response and delays disease for two years is $12,262 for a pediatric patient and $22,525 for an adult patient, factoring in productivity gains and lifetime benefits increases the total value to $71,675 for a child and $74,799 for an adult in the US. Therapy with 5 years of durability increases these values to $151,596 and $177,721 for each pediatric and adult patient respectively. Accounting for early disease prevalence suggests $3B in annual economic impact for a prevention therapy with 5 year durability and 70% response. There is also value in slowing disease progression upon the onset of T1D. Beta cell preservation therapies that reduce insulin needs by 50-70% would have $6B in annual US economic impact.

Interim Developments Towards a Cure Have Multibillion Dollar Impact in the US Alone

With 18MM people living worldwide with T1D and a global disease cost burden of ~$90B, the need for a cure is significant. The ideal therapeutic cure would achieve durable insulin independence and normal A1c levels with a clean safety profile, and address the full ~$90B global and ~$30B US annual cost burden. However, our evaluation revealed that interim developments towards the cure also have significant economic impact. For example, a beta cell preserving therapy that halts loss in insulin production and allows patients to achieve HbA1c levels <7.5% would provide $4.6B of economic value in the US annually. A beta cell replacement therapy that reduces insulin requirements by 50%+, even if it requires broad immunosuppression and provides 1-2 years of effect, would still generate $3.5B in annual US economic value. These interim developments have a strong place in the market and meaningfully address disease burden by reducing the direct and indirect costs associated with high A1c and insulin requirements.

Overall, this evaluation shows that while a full cure would address the total $30B US annual T1D cost burden, adjunct therapies and interim steps would still address several billion dollars of economic burden in the near-term, as summarized in Figure 3 below.

Figure 3: Total Annual Value of Disease Impact by Therapeutic Concept and Generation



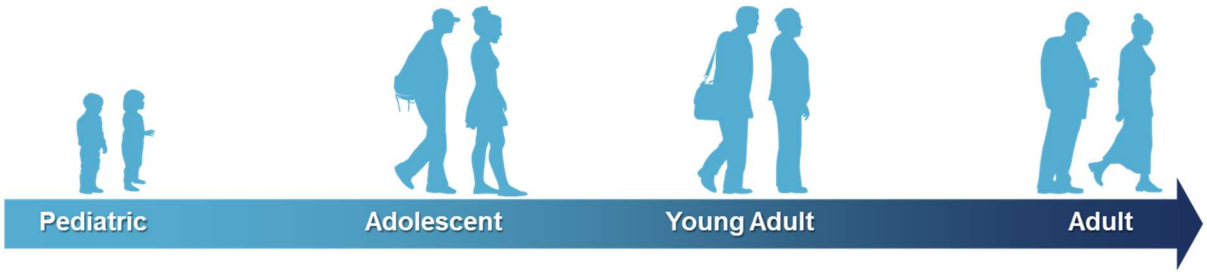
Impact shown can be achieved in 5 years for certain concepts and early generations (e.g. delay onset of stage 3, artificial pancreas), and in 10 years or more for later generations.

Note: Prevent DKA at diagnosis (stage 3) concept not included above

Further Efforts Are Imperative to Quantify Intangible Burden of Disease

It is important to note that the economic analysis does not account for several "intangible" burdens of T1D that patients and caregivers experience throughout the T1D patient lifespan, because of limitations in the disease economic literature. Numerous psychosocial challenges associated with T1D have not yet been quantified. While these challenges across the lifespan of T1D are described below, dedicated research is needed to fully quantify and characterize the pain, suffering, and reduced quality of life that T1D patients and their caregivers experience.

Figure 4: Intangible Burdens Across the T1D Lifespan



"The parent tends to take on the stress and anxiety, and as a result the family relationship becomes challenged, and the child will often act out too."

"There is often a power struggle between parents and teens with T1D that can affect their relationship in the long term."

"You often see the struggle to regain control manifested in eating disorders in adolescents."

"Young adults often make decisions about career and life advancement based on diabetes."

"You're constantly thinking, 'is anyone going to take on the burden of my disease with me', and it's a significant stressor when looking for a partner."

"Making the choice to become a parent when you have T1D comes with decisions around whether you want a child to have this disease as well, and caring for your own body differently during pregnancy."

Source: Health Advances interviews.

Starting with pediatric T1D, caregivers of pediatric patients experience high psychosocial burden due to the stress and anxiety of caring for a sick child. This burden often leads to strained relationships within the family, as well as tensions that can affect the child. In addition, as many as 22% to 33% of mothers of T1D patients experience clinically-significant levels of depressive symptoms [1].

In the adolescent phase of T1D, teens often struggle with a sense of self identity and strive to regain control from their disease. This can manifest in a power struggle between parents and adolescents that can affect relationships in the long-term. Eating disorders and depression are common in adolescents with T1D [2]. Studies show that one in five teenagers with T1D experience depressive symptoms, regardless of how well they manage their A1c [3, 4].

When patients transition to young adulthood, planning for their own care and decisions about career bring up new challenges. In adulthood, patients with T1D may struggle with feeling comfortable with a partner and see their disease as a barrier when seeking a lifelong partner. As T1D patients look to become parents and start a family, they worry about their genetics, and carry the guilt of potentially passing on T1D to a child.

If the psychosocial issues experienced by both caregivers and patients were fully measured and quantified from an economic standpoint, the burden of illness of T1D and the associated value of new interventions would be even higher than what can be estimated today.

Conclusion and Call to Action

This evaluation uncovered significant hidden and underappreciated costs associated with T1D beyond the direct medical costs of insulins, health care services, and other interventions. Productivity losses for both patients and caregivers carry tremendous societal cost. Furthermore, there are concerning intangible costs to the disease

throughout the lifespan, which have yet to be quantified and accounted for in the economic literature. While it was not within the remit of this evaluation to pursue quantification of these intangible costs, this is an urgent need and no BOI study will be complete without this analysis. Investing in robust psychosocial studies would generate valuable data and address this critical gap in the health economic literature.

Based on the key findings, government entities, private payers, and employers should consider the broader disease burden in their calculus for coverage and reimbursement for T1D therapies. Only factoring in cost offsets from insulin, for example, does not consider the burden of insulin management, the related suboptimal HbA1c and TIR outcomes, and the subsequent costs of longer term complications and productivity losses. Payers and regulators can further support innovation by recognizing clinical measures beyond HbA1c, in particular TIR, that better reflect total glycemic control and disease burden, relate to clinical outcomes, and can be differentially addressed by newer innovations.

All parties ultimately have an interest in incentivizing innovations that improve T1D outcomes. Increased recognition of the full burden of T1D by key stakeholders would spur more investment in T1D, where today there is underinvestment relative to other autoimmune diseases. As this evaluation shows, there are multiple market opportunities to address T1D burden, from adjuncts to insulin to treatments that delay disease onset to regenerative approaches that reduce insulin requirements. Efforts to develop novel therapies for T1D have strong economic value and should be rewarded.

Situation Analysis

Today, 18MM people live with type 1 diabetes (T1D) globally, and 1.6MM have been diagnosed with T1D in the US [5-11].[3] Lacking disease modifying therapies, patients are managed with insulin today, and many patients continue to experience suboptimal outcomes. Nonetheless, the investment in new technologies and therapies for T1D is limited relative to other similarly-sized autoimmune diseases. In rheumatoid arthritis, multiple sclerosis, and Crohn's disease, there are already several classes of disease-modifying therapies available and development pipelines continue to be highly active [12]. This underinvestment in T1D is driven in part by the perception that T1D is well managed with established insulin regimens. Additionally, traditional analyses of T1D disease burden typically only consider the direct medical costs associated with T1D and underestimate the full disease burden felt by patients and caregivers. This incomplete understanding of T1D disease burden contributes to the underinvestment in T1D in the US and globally by the biopharmaceutical and investor communities.

Suboptimal Outcomes from Insulin

Despite the standard of care of insulin therapy, most patients with T1D are not at optimal glycemic control, even with use of insulin pumps and continuous glucose monitoring (CGM) which are today's most advanced tools for insulin management [8, 13]. An HbA1c test is the most commonly accepted metric by which physicians, payers, and patients understand an individual's degree of metabolic control today [14]. HbA1c is considered "controlled" for T1D when it is lower than 7.0% in adults and lower than 7.5% in children[15-17]. However, for all patients with T1D today, the average HbA1c hovers around 8.2% [18]. The vast majority of patients do not reach their target HbA1c levels despite their arduous efforts, with a recent study finding that only 17% of pediatric patients and 21% of adult patients meet American Diabetes Association (ADA) recommendations [19].

Furthermore, studies have shown that an average individual with T1D experiences nearly two episodes of symptomatic hypoglycemia per week [20, 21]. Severe hypoglycemia is defined as untreated hypoglycemia that results in intervention from another person or healthcare professional [22]. On average, about 20% of T1D patients in the US experience one or more severe hypoglycemic events annually [20, 21].

Finally, long-term complications associated with T1D are significant. For example, more than 50% of T1D patients experience complications related to polyneuropathy [23], 25% experience nephropathy-related complications [24], and 36% experience retinopathy-related complications.

Underinvestment in T1D

Investment by biopharmaceutical companies in T1D is low relative to the investment in other similarly-sized autoimmune diseases [28]. In rheumatoid arthritis, Crohn's Disease, and multiple sclerosis—autoimmune diseases with roughly 1MM US prevalence—there already are numerous available disease-modifying therapies that address underlying pathophysiology [29-31]. Patients have multiple biologic treatment options, such as anti-TNFs and interleukin blockers for rheumatoid arthritis and Crohn's disease. If one line of therapy does not work, patients can trial several other options.

Furthermore, even with available treatments, the development pipelines in these autoimmune disease are more active than that for T1D. There are ~150 programs in preclinical through Phase 3 development for T1D. In comparison, there are ~220 programs and ~250 programs in development for multiple sclerosis and rheumatoid arthritis respectively. While there are 8 late-stage programs in T1D, many of these insulin related, there are ~20 Phase 3 programs each in multiple sclerosis and rheumatoid arthritis, all focused on disease modifying therapies [12]. Given the high unmet need in T1D, this relative underinvestment is striking. [32].

Incomplete Economic Estimates of T1D Disease Burden

Today, economic estimates of T1D disease burden focus largely on direct medical costs, with payers, budget holders, and Health Technology Assessment (HTA) decision-makers in mind; they fail to consider important and costly indirect, productivity, and intangible burdens shouldered by patients, caregivers, and society. Factors less often considered include lost income due to disease, productivity costs felt by employers and society from missed or inefficient workdays, and intangible costs of disease such as pain and suffering, which are felt by both patients and caregivers.

Research Methodology

T1D Burden of Illness Methodology

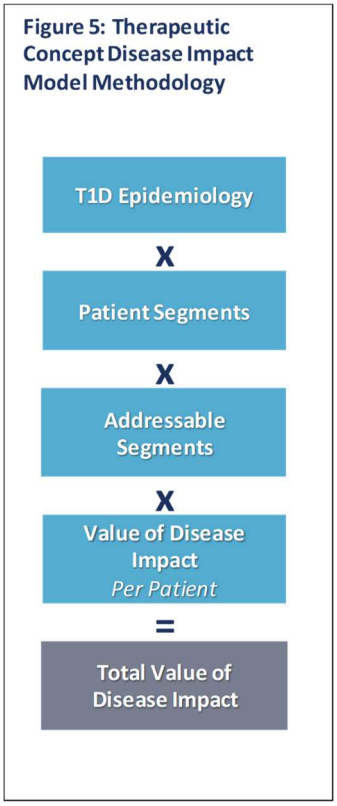
Health Advances completed a comprehensive literature review to estimate the global burden of T1D, drawing on all relevant published literature to define the economic costs that contribute to patient, caregiver, employers, healthcare system, and societal burden [33, 34]. While previous economic analyses focus mainly on direct medical costs, this analysis covers direct medical, direct non-medical, and productivity costs to better reflect the full burden of disease. This evaluation was not able to quantify several intangible burdens of T1D related to pain and suffering that patients and caregivers experience, because of limitations in the disease economic literature.

Direct medical costs include all costs due to resource use that are attributable to the delivery of a health care intervention for T1D, e.g., insulin, testing supplies, and all follow-up costs for other medications and/or health care interventions and complications in ambulatory, inpatient, and nursing care. *Direct non-medical costs* include transportation costs to access care, trained caregiver time, and specialized and/or frequent daycare. *Productivity costs* can result from both presenteeism (presence of a worker who experiences reduced productivity due to illness) and absenteeism (the physical absence of a worker, in which case the employer must also absorb the cost and time of worker replacement) [35]. Productivity costs include the loss in gross income to the patient [35]. In addition, costs to support disability payments for absent workers, and life insurance costs for workers that die are included in the productivity cost calculus [36-38].

This analysis focused on the global costs associated with T1D as well as the net change in these costs associated with the introduction of a novel intervention compared to the cost of care for an otherwise healthy individual.

Impact of Disease Concept Methodology

To examine how novel therapeutic concepts for T1D could address the global T1D economic burden, Health Advances developed a quantitative model that estimates the value of disease impact of seven therapeutic concepts that cure, prevent, or treat T1D. The total impact of each therapeutic concept factored in global T1D epidemiology, patient segmentation, and addressable population sizes, and the change in economic costs associated with each intervention based on anticipated clinical efficacy (Figure 5).



To inform the relevant patient segments and addressable population (i.e. patients who are eligible and likely to be treated) for each concept, Health Advances conducted in-depth interviews with 20 US and European key opinion leaders (referred to as "experts" throughout this paper) and payers. These discussions provided deep insights on each concept's anticipated clinical impact and adoption, and factors that would drive prescribing. Health Advances then designed and fielded a quantitative survey of 72 US endocrinologists, to gain a broader sample of perspectives on each concept, and more inputs on the addressable patient population and adoption potential for each concept.

The value of each therapeutic concept was determined by applying economic estimates to improvements in the following four specific efficacy outcomes: 1) reduction in HbA1c and/or improvement (or increases) in TIR; 2) reduction in DKA events; 3) reduction in severe hypoglycemic events; and, 4) achieving insulin

independence.[3] For each efficacy measure, we attributed savings in direct medical costs relative to the T1D baseline outcome today. We then applied the economic value from savings in direct non-medical and productivity costs. Specifically, we allocated a proportion of the sum of these other economic costs to each therapeutic concept based on the average improvements seen across the key efficacy outcomes compared to healthy baselines.

Finally, while we provide detailed descriptions of the model output for each therapeutic concept on the following pages, there are two important caveats. First, because we did not test and model specific *product* concepts, or the commensurate price potential, the model results presented here do not represent manufacturer revenue potential. Rather, the model results represent the total annual economic value of each concept's impact on T1D at a single point in time. Second, the model estimates the economic impact of each therapeutic concept in isolation; it does not compare across therapeutic concepts nor does it indicate the combined or net impact should several concepts become available.

More details on both the BOI methodology and concept impact modeling are provided in the appendix.

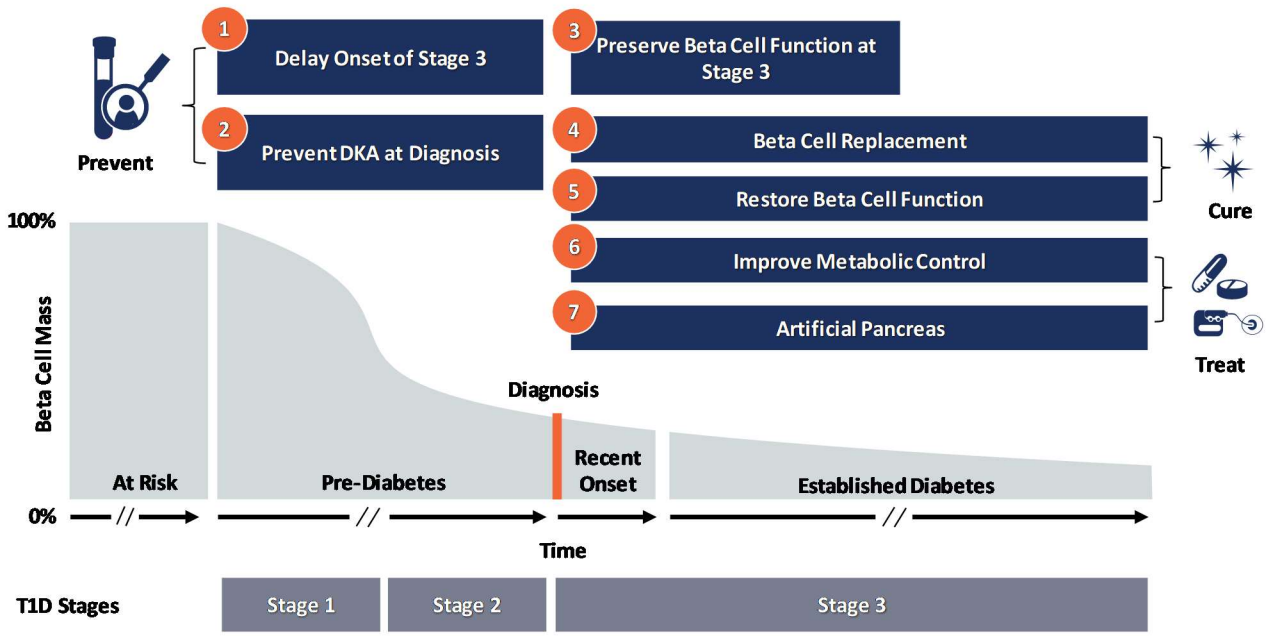
[3] For all such economic outcomes, we applied a 3% growth rate to all future years to account for increasing per-capita health expenditure in the US, as averaged between 2007-2016

Therapeutic Concept Evaluation

Overview

The following sections provide detailed evaluations for each of the seven novel therapeutic concepts (Figure 6). For each concept, the market need, current development status, drivers of adoption, and modeled per-patient and US-level impact on T1D disease costs are described for several concept generations.

Figure 6: Therapeutic Concepts Overview



1. Delay Onset of Stage 3

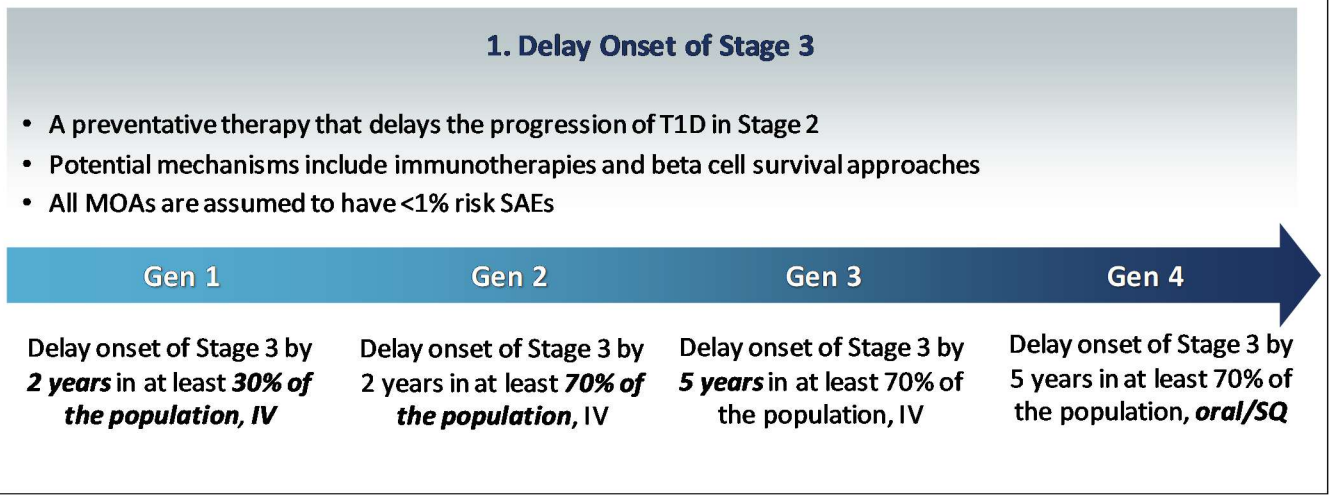
There are at least 300K people with Stage 1 and Stage 2[4] disease in the US and 2.3MM worldwide, based on disease incidence and a 5-year seroconversion rate of 44%[5] [39]. Past research has shown that most Stage 1 and 2 patients progress to Stage 3 within 10 years and that disease progression is even faster in patients younger than 3 years old or with the DR3/DR4-DQ8 HLA genotype [40]. By delaying disease progression, patients not only gain disease-free years but also realize long-term benefits. In particular, studies have shown that prevention of early stage progression could forestall diabetic complications and potentially improve life expectancy [41]. Finally, as T1D incidence continues to increase at 2-4% annually [8, 42], more and more patients will benefit from preventative treatments.

Figure 7 on the following page defines potential generations in therapies that could be developed to prevent Stage 2 T1D from progressing to Stage 3.

[4] Stage 1 is defined as the presence of β-cell autoimmunity as evidenced by the presence of two or more islet autoantibodies with normoglycemia and is presymptomatic, stage 2 as the presence of β-cell autoimmunity with dysglycemia and is presymptomatic, and stage 3 as onset of symptomatic disease.

[5] As there are no studies on seroconversion rates in adults, we simply applied a rate found in pediatric studies to our estimate. However, we recognize that the at-risk population in adults is likely larger as disease progression is slower in the adult population.

Figure 7: Delay Onset of Stage 3



Development Environment

Broad use of preventative therapy relies on the timely identification of early-stage patients. Supporting this goal, early-stage presymptomatic disease definitions formally introduced by JDRF, the Endocrine Society, ADA, AACE, Helmsley Charitable Trust, and others in 2015 have been broadly accepted by the T1D field [41]. Islet autoantibodies are increasingly recognized as key T1D biomarkers. While screening for islet autoantibodies remains limited to first degree relatives (FDRs) today, pilots for broader screening efforts are underway in both the US and Europe. For example, in the US, the ASK Research Program at the Barbara Davis Center for Diabetes is screening for islet autoantibodies in the general childhood population. In Europe, the Fr1da study was designed as a model to introduce public health screening of multiple islet autoantibodies in Bavaria, Germany. [43, 44]. Supporting both of these pilots, JDRF is committed to leading the implementation of population-based screening. Over the next five years, JDRF will support expansion of global screening networks, infrastructure, and protocols, making population-based screening more feasible [45].

In addition to progress in the staging and screening of early-stage disease, recent clinical trials have demonstrated the feasibility of delaying clinical diagnosis in high-risk patients. In 2017, results from a Phase 2 trial with oral insulin provided the first clinical evidence showing feasibility of delaying Stage 2 progression by about one year [43]. More recently, the Teplizumab Prevention Study sponsored by the National Institute of Diabetes and Digestive and Kidney Disorders (NIDDK) and conducted by TrialNet demonstrated delay of clinical T1D diagnosis by a median of two years in both high-risk children and adults who received one course of teplizumab (now owned by Provention Bio) [46]. This outcome has renewed excitement in the field in developing interventions that delay progression of disease before diagnosis, and in including stage 2 disease as part of drug development paths.

Potential Drivers of Adoption

The most important adoption drivers for a preventative therapy are safety and response rate. The safety risks should not outweigh potential disease burden, especially as patients do not yet have symptomatic disease and some may never develop T1D. The therapy should be effective in a broad population, i.e. show a response rate higher than 50%. Based on the supporting endocrinologist survey, physician stated adoption increases from50% to 70% when response rate increases from 30% to 70%.

While current FDA guidance for registration trials states that sponsors should demonstrate at least one year of prevention for high risk patients, longer delay (e.g., 5 years) in symptomatic disease onset is preferred. Given the substantial disease burden of T1D, experts and survey respondents confirmed that 2 years of efficacy duration is highly valuable. Industry sponsors may weigh the choice to seek regulatory approval with one (or two) years of efficacy data and then generate additional post market durability data. Intravenous (IV) therapy will be tolerated given the lack of disease modifying therapies.

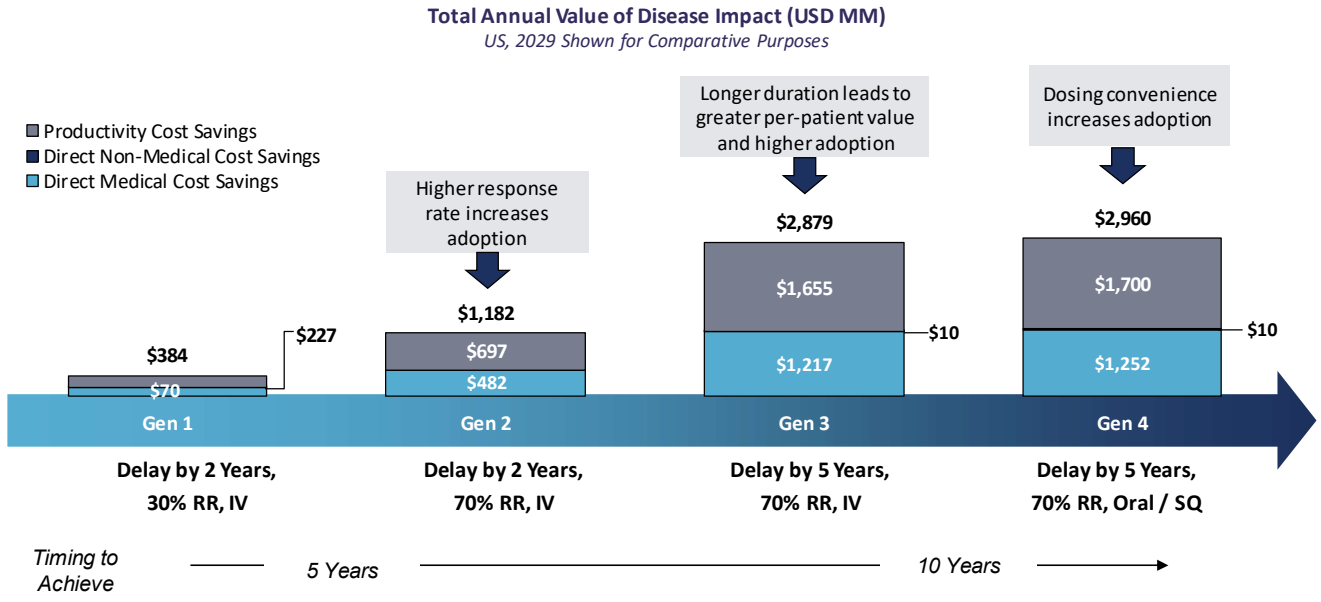
Economic Value of Disease Impact

Based on the per-patient model projections, an IV-formulation therapy that achieves a 70% response rate and delays progression for 2 years yields direct medical cost savings of $12,262 for a pediatric patient and $22,525 for an adult patient in the US.

The value of disease impact includes near term benefits from delayed onset of disease and the longer-term benefits from an improved disease state. For a therapy that delays disease onset by 2 years, the total per-patient economic impact on T1D could reach ~$71,675 and ~$74,799 for each pediatric and adult patient in the US, respectively. If a therapy can demonstrate five years of insulin independence, its potential economic impact on T1D increases to ~$151,600 and ~$177,700 for pediatric and adult patients, respectively.

Figure 8 shows the total annual US economic impact of a preventative therapy that delays the onset of Stage 3, by therapy generation. The model hypothesizes that by 2029, childhood screening rates for T1D increase to 15% of the pediatric population, expanding the population of patients identified and eligible for therapy. The model also assumes an acceptable safety profile, with <1% of serious adverse events (SAEs) in all patients.

Figure 8: Total Annual Economic Impact – Delay Onset of Stage 3



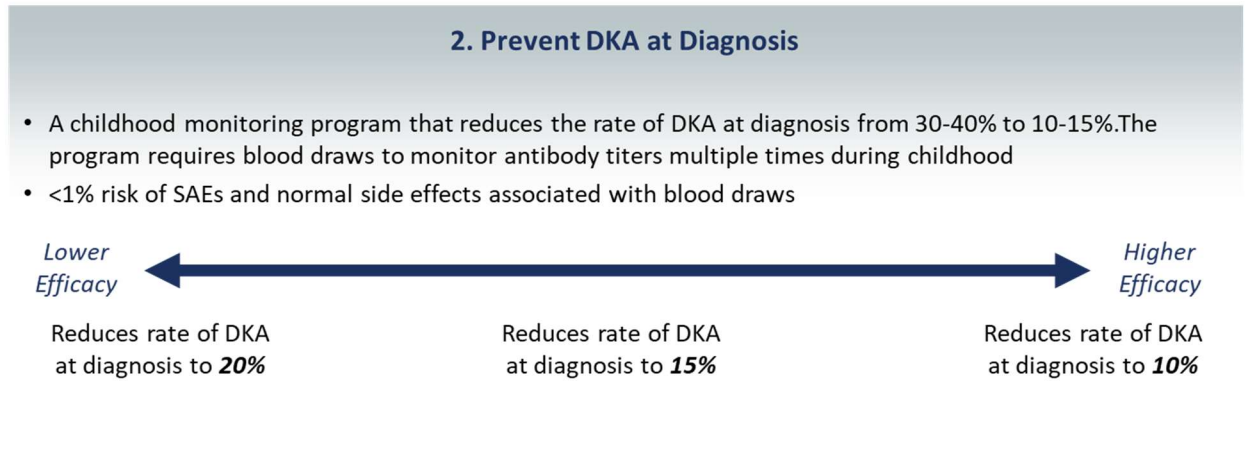
2. *Prevent Diabetic Ketoacidosis (DKA) at Diagnosis*

DKA affects 30-46% of children with newly diagnosed T1D in the US and the rate is likely even higher outside Western regions due to lower awareness and delayed care [47, 48]. These events are life threatening and can

lead to detrimental neurocognitive outcomes and affect long-term care [49]. In recent years, rates of this life-threatening condition increased 6% per year in the US between 2009-2014 [50]. Preventing DKA at diagnosis has immediate and longer-term benefits. Payers today broadly recognize the high cost burden of these DKA events (~$18,000 direct medical cost per DKA event in the US) and appreciate the value of reducing DKA rates [75]. In addition, DKA has been demonstrated in clinical studies to be a preventable event with appropriate screening [51, 52].

Figure 9 defines a monitoring program that reduces DKA at diagnosis.

Figure 9: Prevent DKA at Diagnosis



Development Environment

Multiple studies have already demonstrated strong feasibility for a monitoring program to prevent DKA at diagnosis, including the TEDDY study that showed a 13% DKA rate at diagnosis, compared to 36% in SEARCH and 32% in the German DPV register [52]. Follow up studies of the TEDDY population are even more compelling, showing 4-5% DKA rates [45]. Similarly, the German BABYDIAB and the Munich Family Study showed that proactive follow up of screened children with positive islet autoantibodies reduced DKA rates from 29% to 3% [51]. The need for a monitoring program that reduces DKA at diagnosis is high, and development risk is relatively low.

Potential Adoption and Key Drivers

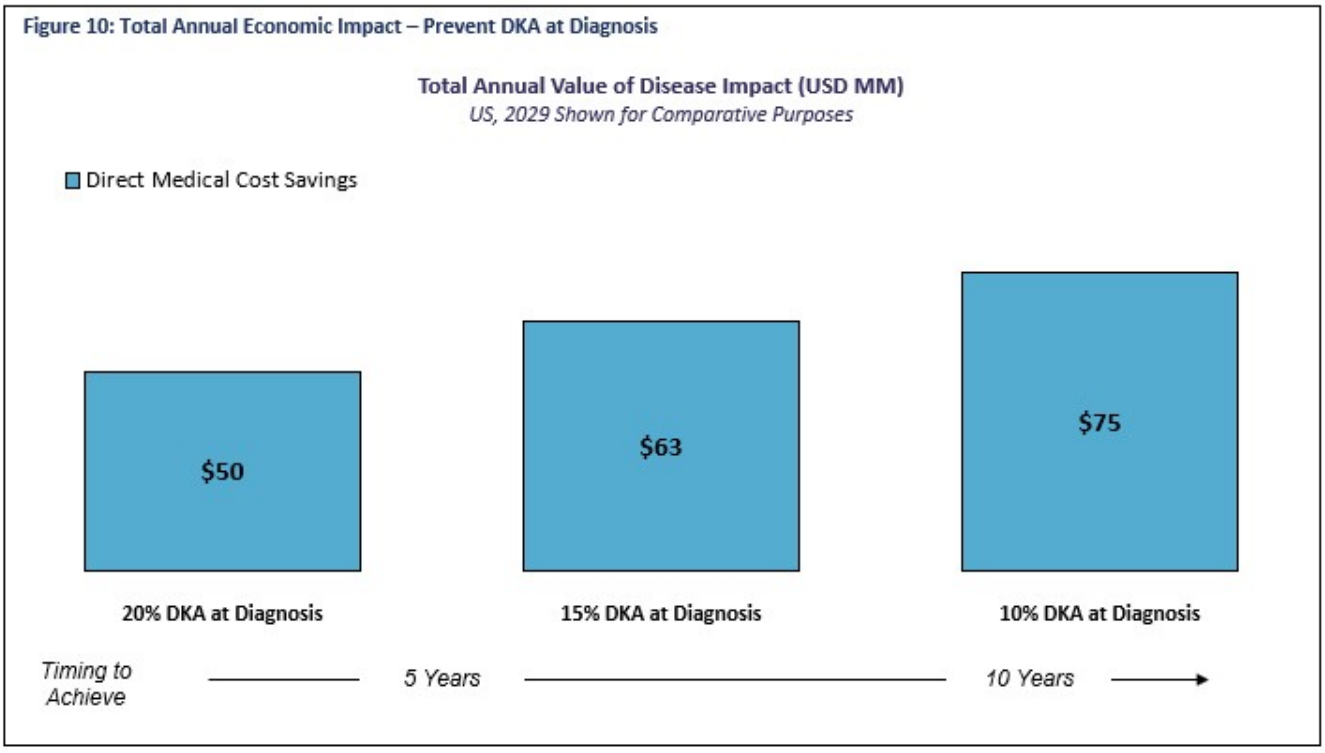
The concept of a monitoring program to prevent DKA at diagnosis resonates strongly with both physicians and payers. A reduction in DKA at diagnosis from 30-40% to 10% is viewed as highly achievable without complex technology or therapies; a simple monitoring program involving multiple blood draws throughout childhood to monitor antibody titers would be effective. Based on the endocrinologist survey, reported physician adoption for such a test is estimated at ~40% of all pediatric T1D patients.

Economic Value of Disease Impact

The value of a DKA monitoring test is directly linked to the number of events that can be avoided and the potential long-term benefits. A program that reduces the rate of DKA to 20% of patients at diagnosis would incur direct medical cost savings of ~$3,310 per patient. If DKA rates fell to 10%, direct medical cost savings would be ~$4,970 per patient. The model hypothesizes broader childhood screening rates in the future, given ongoing pilots and JDRF investment, expanding the population of patients eligible for the monitoring program.

Figure 10 shows the total US annual economic impact of preventing DKA at diagnosis, by therapy generation. These estimates represent the cost impact of a childhood monitoring program alone, and do not account for any potential synergies with a therapy that could prevent early-stage progression.

Figure 10: Total Annual Economic Impact – Prevent DKA at Diagnosis

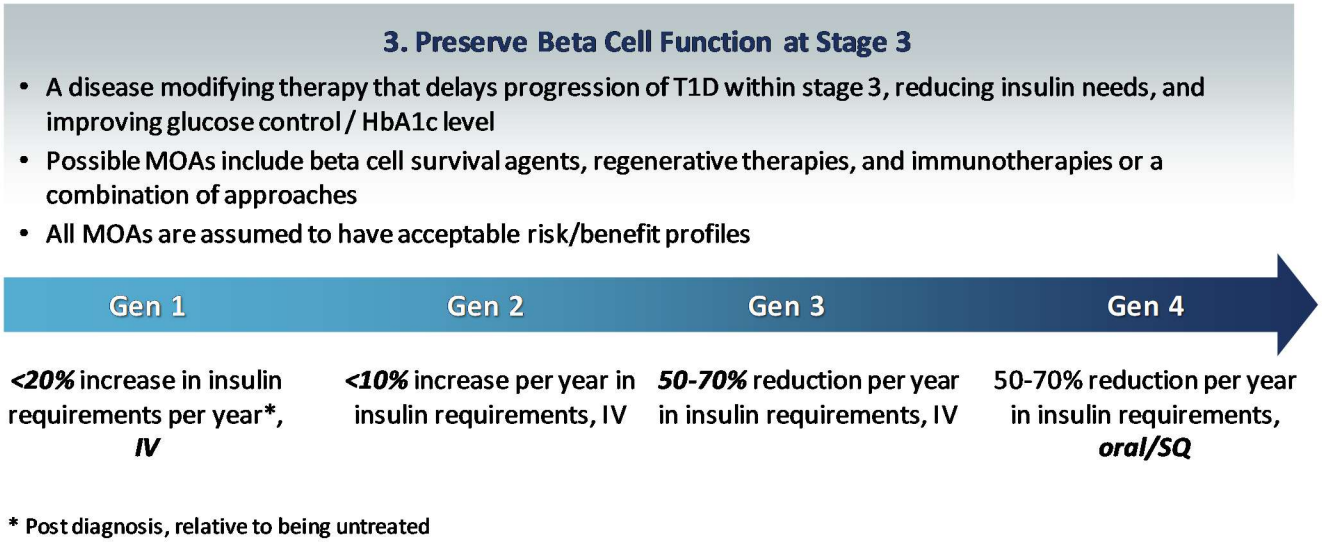


3. *Preserve Beta Cell Function at Stage 3*

Studies have shown that loss of beta cell function occurs early in the disease process [53], and that a disease modifying therapy that delays disease progression at onset of Stage 3 can reduce insulin requirements and reduce risk of long-term complications [54, 55].

Figure 11 defines potential generations for a therapy that preserves beta cell function by reducing the increase in insulin requirements post diagnosis, relative to being untreated.

Figure 11: Preserve Beta Cell Function



Development Environment

There are multiple ongoing T1D trials with immunotherapies and beta cell survival agents to delay loss of beta cell function, with several trials expected to report results in 2020 and 2021. These studies build off previous work in immunotherapy and survival agents, leveraging prior results to inform dosing regimens and target study populations [56, 57]. For example, previous studies identified pediatric patients, patients with higher inflammation index, and subjects with a baseline B-cell signature as subgroups who respond to select beta cell preserving therapies [58]. Preliminary data show potential reduction in the incidence of hypoglycemia and daily insulin burden, as well as improvements in TIR [59-61].

The development environment for immunotherapies and beta cell survival agents is also supported by regulatory and health policy stakeholders. For instance, FDA and EMA published clear guidances, defining C-peptide measurement at 1 year compared to control as the primary efficacy endpoint for Phase 3 trials for products intended to preserve endogenous beta-cell function in newly diagnosed T1D patients. [62, 63]. In order for this endpoint to provide convincing evidence of endogenous preservation, clinically meaningful effects need to be assessed, such as mean daily insulin requirements and glycemic control compared to the control arm. A favorable effect on these endpoints should be balanced against the risks of the particular intervention being tested. Subjects should continue to be monitored for an extended period (2 to 4 years or longer) to investigate both the durability of the effect and rates of hypoglycemia, diabetic ketoacidosis, and long-term complications. Other biomarkers, including composite markers of different clinical and/or immune parameters, are being actively explored as surrogate end points, to further shorten trial duration and reduce study costs.

Potential Adoption and Key Drivers

The adoption of a therapy that preserves beta cell function will be driven by the level of reduction in insulin requirements. The endocrinologist survey indicates that reducing insulin requirements in patients by at least 50% will support the greatest adoption, but even slowing the need for increases in insulin will generate clinical interest. The safety profile for this concept cannot be life-threatening or require hospitalization; if safety issues are significant, restrictions to high severity patients and adult onset patients would be required. Modeled concepts assume a safety profile with <1% risk of SAEs. For most physicians, IV therapy is acceptable.

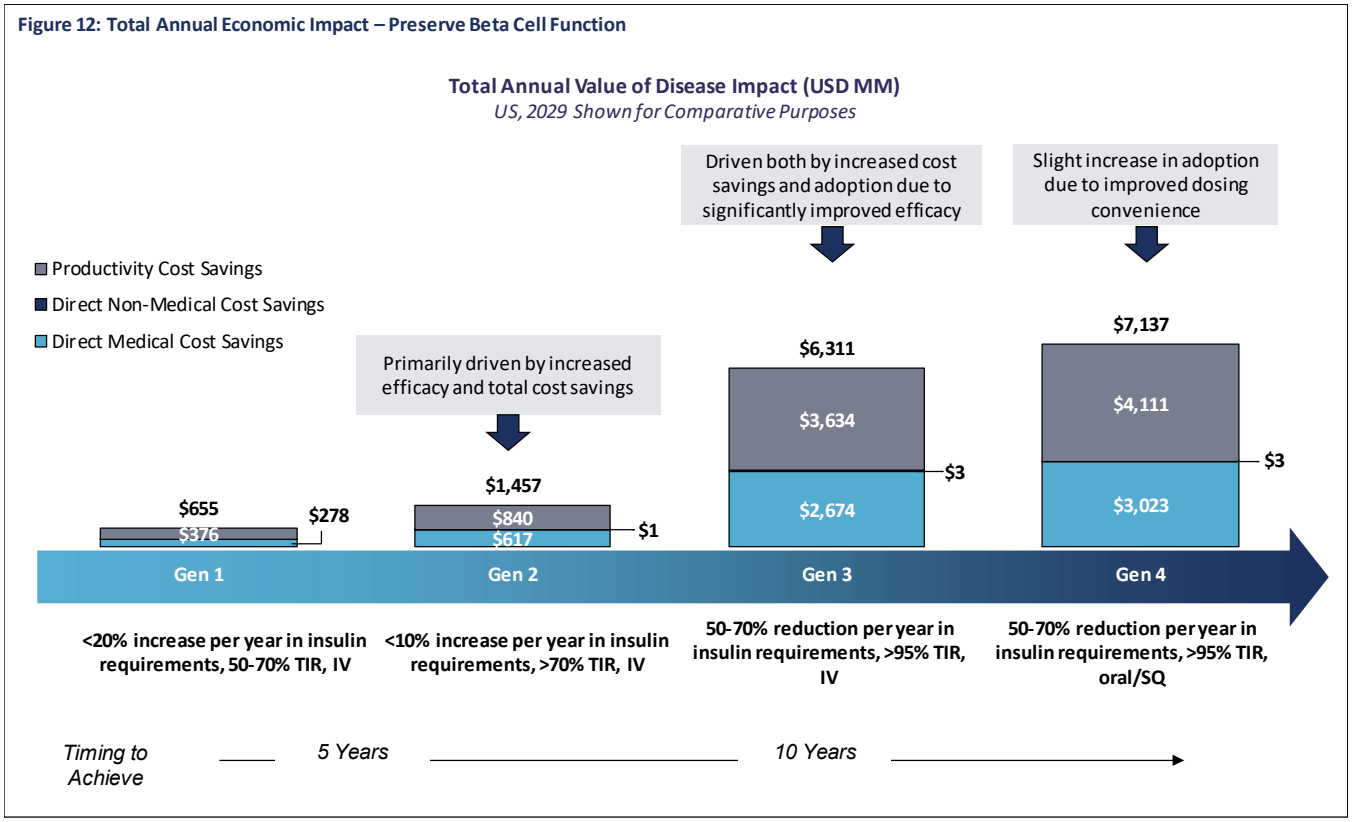
Economic Value of Disease Impact (US)

In an early concept generation, in which increased insulin requirements are less than 20% per year, the model projects that an IV therapy would achieve $830 in total annual cost savings per pediatric patient and $2,810 per adult patient. These cost savings are driven by a 10% reduction in annual insulin requirements and a commensurate 10% reduction in other cost categories.

In a second generation of the therapy, where insulin increases are reduced to <10% per year, the value of disease impact per patient would double. An IV therapy generates annual per-patient cost savings of $1,650 and $5,630 for pediatric and adult patients respectively. A third generation, in which the therapy achieves a reduction in insulin requirements of 50-70% per year, generates annual per-patient cost savings of $4,950 and $16,870 for pediatric and adult patients in the US, regardless of the formulation.

Figure 12 shows the total annual economic impact of preserving beta cell function for the combined US pediatric and adult population, by therapy generation.

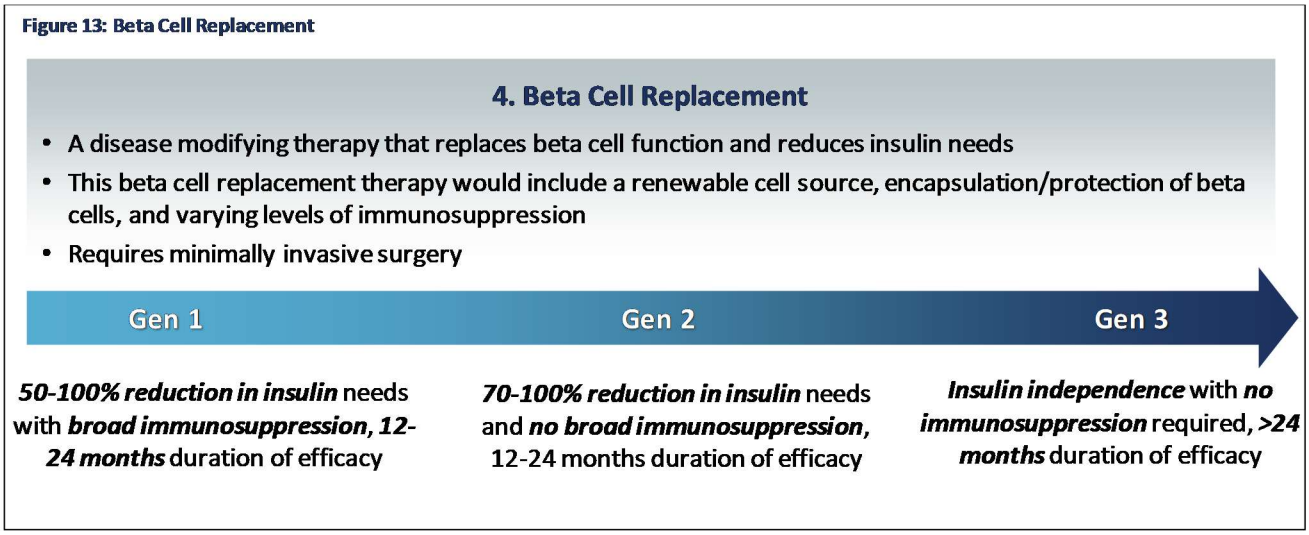
Figure 12: Total Annual Economic Impact – Preserve Beta Cell Function



4. Beta Cell Replacement

Islet cell transplantation using cadaveric human islets has demonstrated durable glycemic control and reversal of hypoglycemia unawareness in patients who undergo the procedure, achieving 50-100% reduction in insulin requirements and durable impact on hypoglycemia unawareness. However, due to limitations in cell source and risks of broad immunosuppressive side effects, only high-risk patients receive islet transplantation, in particular adults with severe hypoglycemia unawareness [64-66]. Given the established efficacy and limited use of islet cell transplantation today, there is significant opportunity for a therapy with a more favorable safety profile and/or unlimited cell source. [67, 68].

Figure 13 defines potential generations for a therapy that replaces beta cell function and reduces insulin requirements. This therapy would apply to people with established stage 3 T1D.



Development Environment

Promising advances in cell sources, beta cell protection, and more targeted immunosuppression contribute to a more favorable development environment for beta cell replacement. The generation of alternative beta cell sources that can be replenished would address limitations that have previously restricted access to this therapy. Both allogenic human stem cells (hSC) and induced pluripotent stem cells (iPSC) are being studied as surrogate beta cells [69, 70]. Similarly, xenotransplantation using porcine islets is gaining acceptance as a potential cell source [71].

There are also new mechanisms to enable protection of beta cells, with the development of delivery systems to protect cell sources and optimize implantation sites. Advances in biomaterial research, 3D medical printing, immunomodulation, and drug delivery strategies are all enabling better protection of beta cells [72]. These new technologies could also allow for development of both device and device-less approaches to protect beta cells after implantation [73].

More targeted immunosuppression will enable more patients to have access to beta cell replacement therapies. Scaffold devices that provide a permeable barrier are being evaluated to implant cells without a full encapsulation device [74]. Such devices could offer localized protection from the immune system or could be used to release immunosuppressive agents [75].

Potential Adoption and Key Drivers

Immunosuppression is one of the greatest challenges in beta cell replacement therapies for T1D, particularly in pediatric patients. The need of broad immunosuppression would limit adoption to ~15% of adult patients based on the endocrinologist survey. While elimination of immunosuppression would increase adoption to 80%, a more targeted approach could still achieve ~50% adoption. Efficacy is also a key adoption driver. Of note, novel therapies that reduce insulin requirements by 50% are considered highly valuable, for which an annual minimally invasive procedure (1 year durability) would be acceptable.

Economic Value of Disease Impact (US)

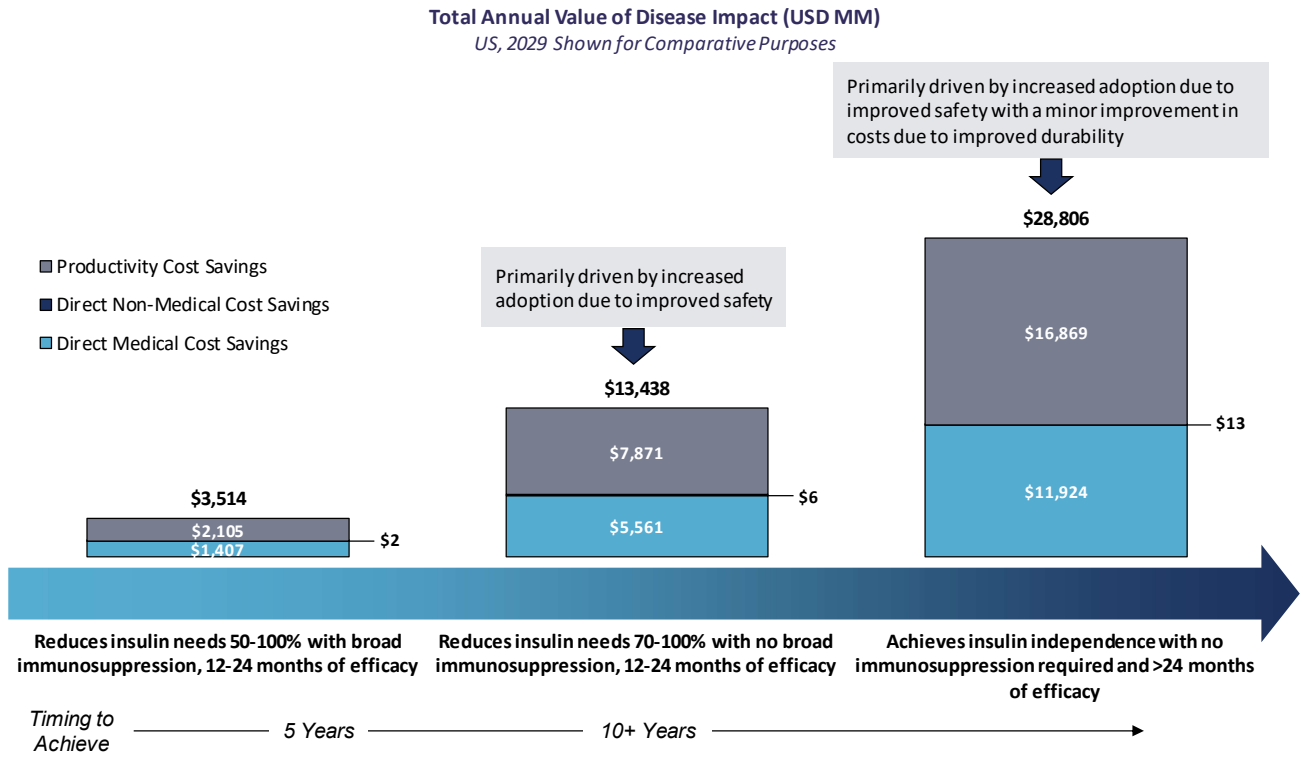
In an early-generation of a beta cell replacement therapy, in which insulin requirements are reduced by 50-100% and broad immunosuppression is still required, a therapy would achieve direct medical cost savings of $5,630 for an adult patient in the US. The total annual economic impact, factoring in direct non-medical and

productivity costs, would reach $14,060 in an adult patient in the US. Given regulatory feedback that broad immunosuppression for pediatric patients would not be acceptable, these savings are excluded from our analysis for the early generation of therapies.

In a second generation of the therapy, in which insulin needs are reduced by 70-100% and no broad immunosuppression is required, total annual economic impact could reach $5,770 in a pediatric patient and $19,690 in an adult patient in the US. In a third generation, in which patients achieve insulin independence on the therapy with no immunosuppression and duration of efficacy is >24 months, the therapy could generate annual total cost impact of $8,250 in a pediatric patient and $28,120 in an adult patient in the US.

Figure 14 shows the total annual economic impact of beta cell replacement for T1D for the combined US pediatric and adult population, by therapy generation.

Figure 14: Total Annual Economic Impact – Beta Cell Replacement

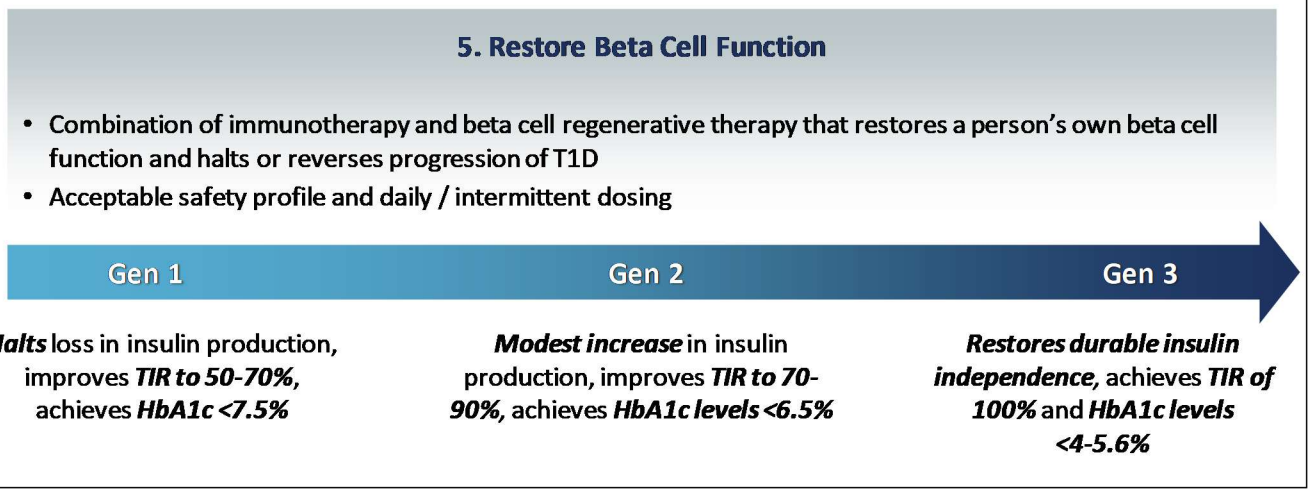


5. Restore Beta Cell Function

There are currently no therapies available that address the underlying pathology of T1D. Therapies that directly modify beta cell biology can stop and even reverse the loss of function that occurs in T1D. The implementation of such disease modifying therapies could return patients to a disease-free, healthy state, which would unlock full economic value and completely eliminate the burden of illness.

Figure 15 below defines potential generations for a combination therapy that halts or reverses progression of T1D.

Figure 15: Restore Beta Cell Function



Development Environment

While there are no approved disease-modifying treatments for T1D, research efforts are exploring pathways that may increase beta cell function, control autoimmune destruction, and ultimately reduce or eliminate insulin need. Mechanisms across multiple autoimmune diseases are being studied to provide insight into the pathogenesis of T1D, including the influence of kinase inhibitors and modifiers of cellular stress pathways [76, 77].

Innovative trial designs will accelerate research into curative therapy options. Identification of novel biomarkers that reflect beta-cell function and/or effective modulation of the autoimmune response can be used to develop trials in targeted patient populations [78]. Advances in targeted drug delivery will be important. Cell or tissue directed drug delivery, such as those used in oncology, may be used to improve targeted drug delivery to beta cells or to sites of immune activity [79-81].

Potential Adoption and Key Drivers

Restoring beta cell function should provide broad benefits across HbA1c, TIR, and insulin requirements. Therapies that show incremental benefits across these key measures see strong clinical interest. Physicians would prescribe an early generation of a regenerative therapy that improves TIR to 50-70%, HbA1c <7.5% and halts loss in insulin production to 50% of patients.

Based on the safety profile, manufacturers may need to focus on patients for whom potential benefits outweigh risks, such as adult patients with uncontrolled disease and frequent severe hypoglycemia events. Therapy dosing would be acceptable as a monthly IV treatment; daily or weekly IV treatments would be considered too demanding for patients.

Economic Value of Disease Impact

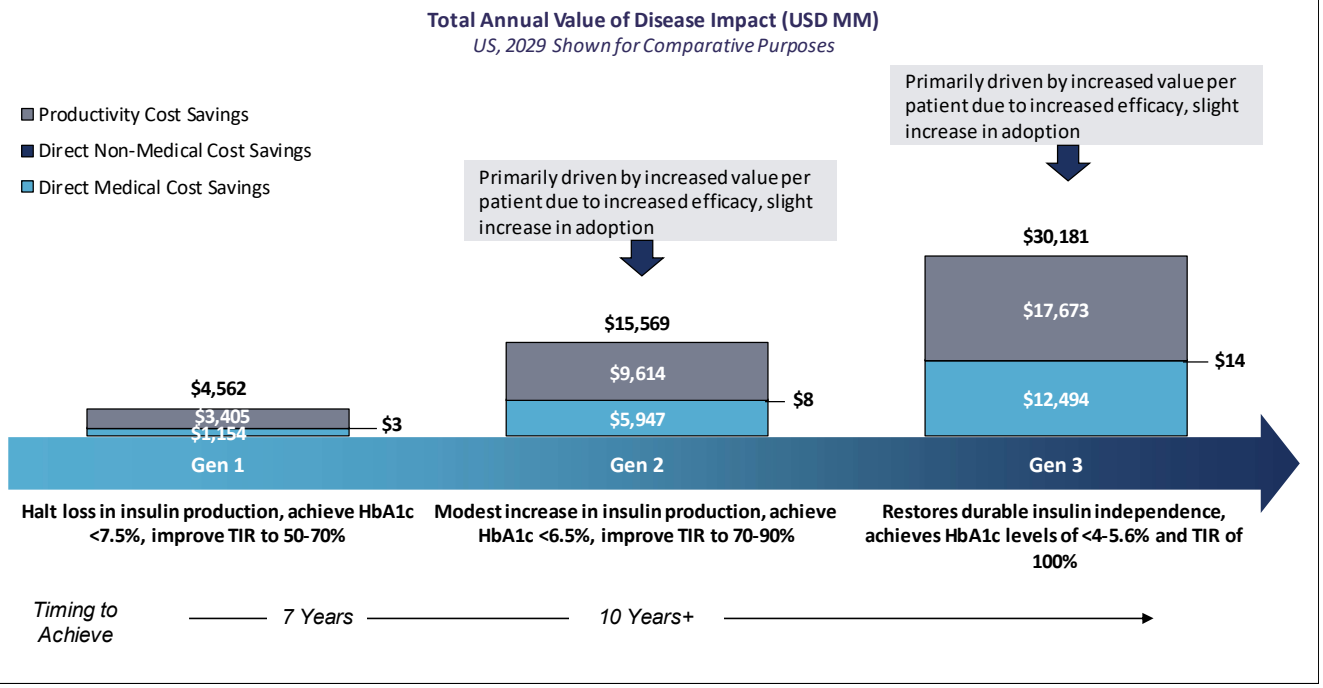
In an early generation of a combination therapy that results in HbA1c <7.5%, TIR in the range of 50-70% and a halt in the loss of insulin production, the therapy could have direct medical cost impact of $1,310 for both pediatric and adult patients in the US in 2029. The total annual economic impact of T1D factoring in direct non-medical and productivity costs could reach $1,860 in a pediatric patient and $5,680 in an adult patient in the US. This value impact is driven by a 0.7% improvement in A1c compared to the baseline value of 8.2%, as reported in the literature, and a 26% reduction in other annual costs based on the ratio of HbA1c improvement to normal HbA1c levels.

In a second generation of the therapy, in which HbA1c levels are <6.5%, TIR is in the range of 70-90%, and modest increases in insulin production are achieved, a therapy would have total annual economic impact of $6,050 in a pediatric patient and $16,620 in an adult patient in the US. This value impact is driven by a 1.7% improvement in A1c over the first generation therapy and 25% reduction in annual insulin requirements, as well as 63% reduction in other annual costs, based on the ratio of HbA1c improvement to normal HbA1c levels.

In a third generation, in which HbA1c levels reach 4-5.6% and TIR reaches 100%, with restored durable insulin independence, a therapy would reach total annual economic impact of $8,250 in a pediatric patient and $28,120 in an adult patient in the US. This value is driven by the achievement of 100% reduced insulin requirements, ultimately curing disease and eliminating all annual costs.

Figure 16 shows the total annual economic impact of restoring beta cell function for the combined US pediatric and adult population, by therapy generation.

Figure 16: Total Annual Economic Impact – Restore Beta Cell Function

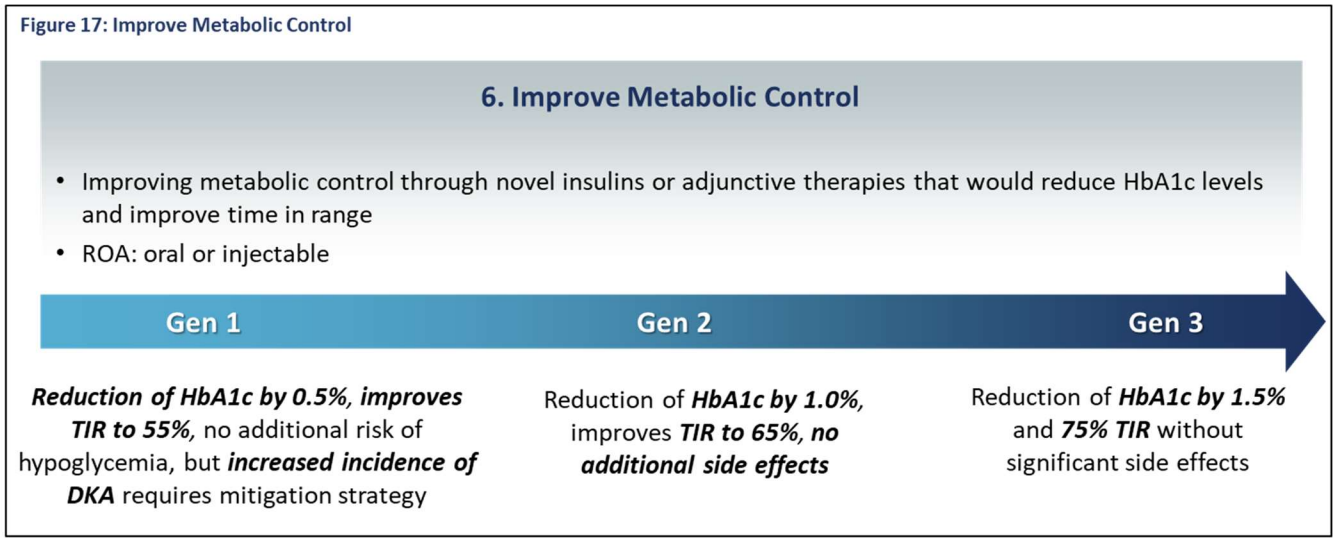


6. *Improve Metabolic Control*

Despite the standard of care of insulin therapy, only 17% of pediatric patients and 21% of adult patients achieve their respective targets of HbA1c < 7.5% and HbA1c < 7.0% [82]. Recent studies also indicate that average HbA1c levels have been rising across patient populations over the past few years [83]. Novel insulin formulations with enhanced functionality and therapies that can augment insulin's efficacy and/or simplify its dosing regimen are needed.

The benefits of achieving improved metabolic control can be realized in both the short-term and long-term. Unit reductions in HbA1c levels have been linked to long-term cost savings from avoiding complications related to depression, cardiovascular disease, nephropathy, neuropathy, and retinopathy [84-86].

Figure 17 below defines potential generations for a therapy that improves metabolic control through novel insulins or adjunctive therapies.



Development Environment

Inconsistency in patient response to insulin is under study. Poor outcomes in select populations are suspected to be driven by patient T1D heterogeneity and delay of efficacy onset from injection [87]. Ongoing efforts to understand changes in pathophysiology, related biomarkers, and effects on metabolic control will enable better patient selection and treatment optimization.

The recent approval of SGLT inhibitors for T1D in Japan and Europe has generated a surge in development efforts for additional adjunctive therapies [88]. Some of these adjunctive therapies are being repurposed from other disease states, while others are being developed specifically for T1D [89].

With the commercial success of existing insulin products, next generation or "smart" insulins with different action profiles are being actively pursued. Key examples include glucose responsive insulins (GRIs), liver-targeted insulins (LTI), ultra-rapid insulins, and ultra-concentrated insulins [90, 91].

Potential Adoption and Key Drivers

Given the existing data from SGLT inhibitors, adoption of a novel metabolic-control therapy will largely depend on the safety profile and incremental efficacy benefits. If a novel therapy can reduce HbA1c by 0.5%, but increases DKA risk, its use will be likely limited to high-need patients such as adults with frequent severe hypoglycemia, which is estimated to be ~20% of the adult T1D patient population. With a more robust safety profile and reduction of HbA1c of 1.5%, adoption is anticipated to reach ~50%.

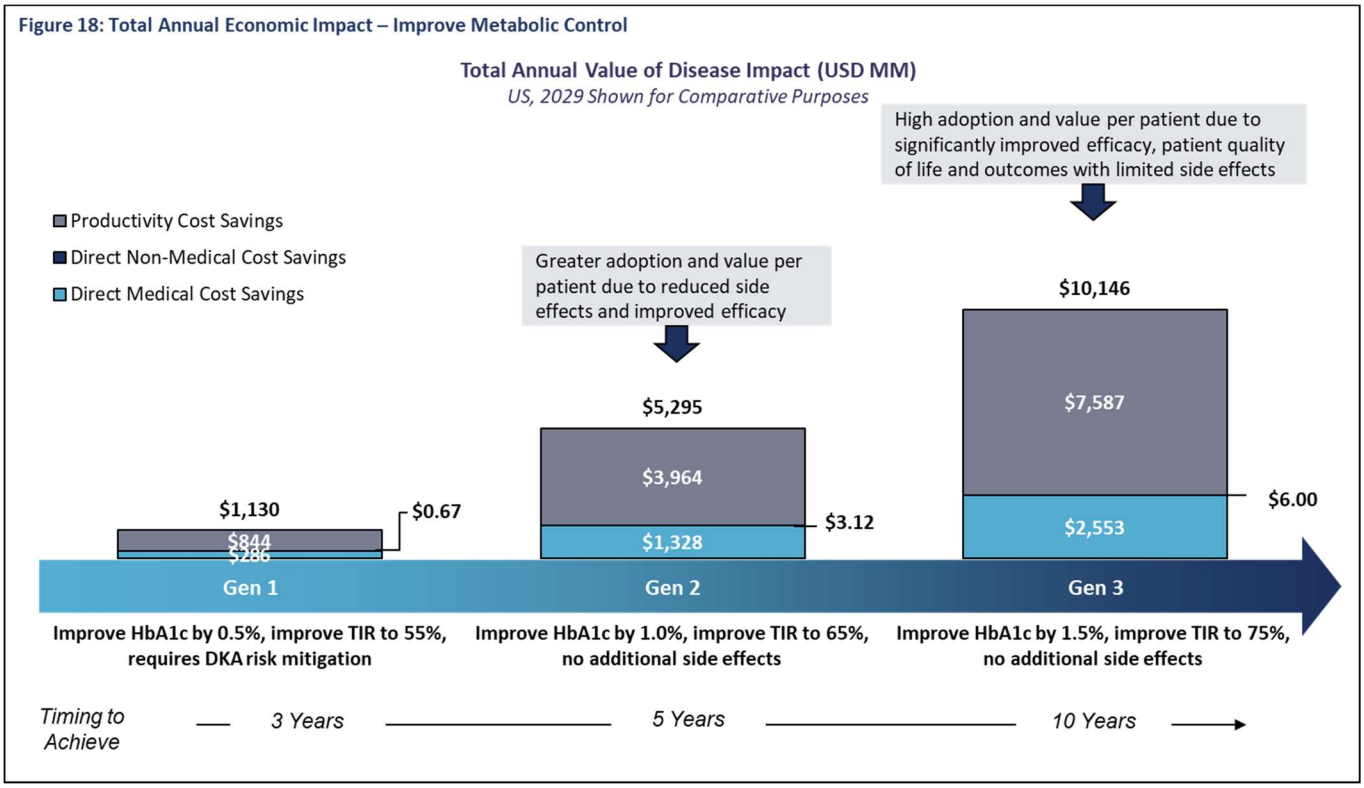
Economic Value of Disease Impact

The value of different generations of metabolic therapies is driven by increases in efficacy and reductions in side effects. In an early generation of the therapy, in which HbA1c is reduced by 0.5% and TIR improves to 55%, but there is increased risk of DKA, a therapy would generate per-patient direct medical cost impact of $940 for both pediatric and adult patients annually in the US in 2029. If direct non-medical and productivity costs are also included, the annual per-patient economic impact of T1D could reach $1,330 in a pediatric patient and $4,060 in an adult patient in the US. This impact is driven by a 19% reduction in annual costs based on the ratio of HbA1c improvement to normal HbA1c level.

In a second generation of the therapy, in which HbA1c levels are reduced by 1.0% and TIR improves to 65%, and there is no additional risk of DKA, the total annual economic impact on T1D could reach $2,660 per pediatric patient and $8,120 per adult patient in the US. This improvement is driven by a 37% reduction in annual costs based on the ratio of HbA1c improvement to normal HbA1c level.

In a third generation, in which HbA1c levels are reduced by 1.5% and TIR increases to 75%, with no significant side effects, the total annual economic impact on T1D could reach $3,990 in a pediatric patient and $12,180 in an adult patient in the US. This increase is driven by a 74% reduction in annual costs based on the ratio of HbA1c improvement to normal HbA1c levels.

Figure 16 below shows the total annual economic impact of improving metabolic control for the combined US pediatric and adult populations, by therapy generation.

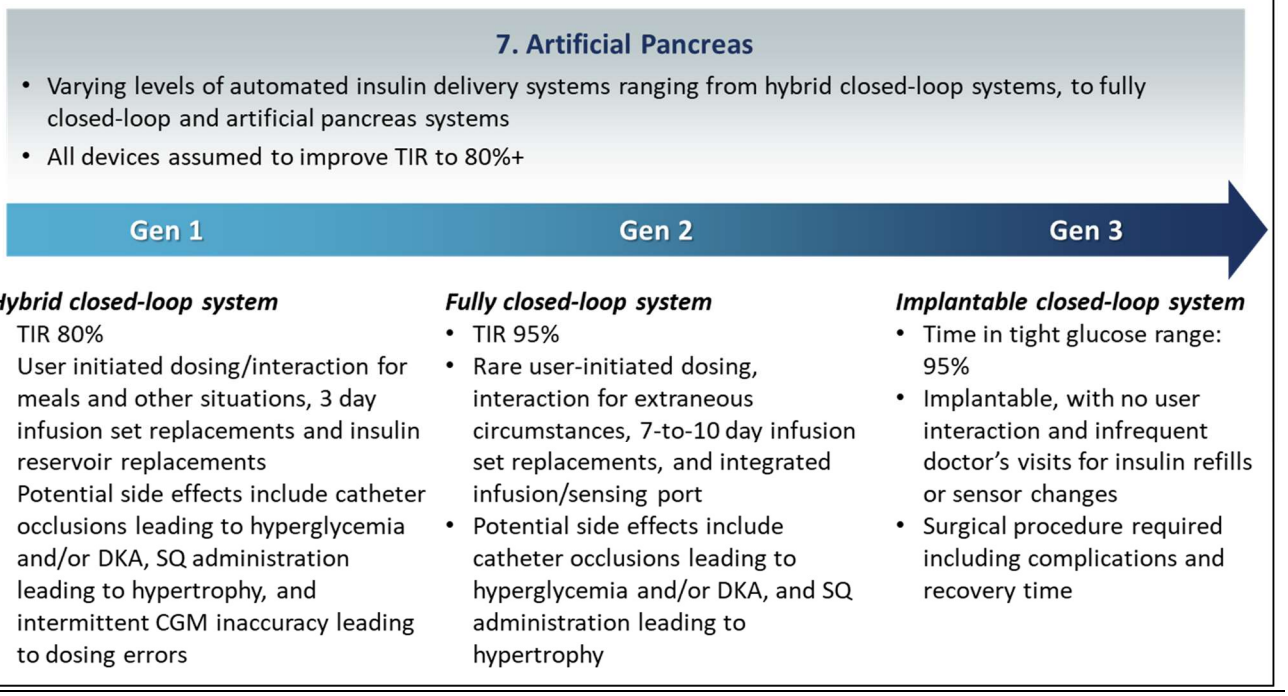


7. Artificial Pancreas

Demand is high for next generation artificial pancreas devices that reduce patient user burden and achieve higher TIR. Today, insulin dosing requires frequent adjustments based largely on physical activity and meals. Even patients who use CGM devices today struggle with self-management, as adequate training is often not provided and dosing algorithms are not optimal [92, 93]. Frequent user intervention is required to make treatment decisions and to calibrate and confirm CGM readings [94]. “Smarter” devices that streamline and automate these processes will improve TIR and relieve the mental burden of self-management.

Figure 19 defines varying levels of automated insulin delivery system improvements.

Figure 19: Artificial Pancreas



Development Environment

Growing acceptance of TIR and advances in technology will support development of artificial pancreas systems. In the past few years, there has been an increase in TIR awareness and acceptance among physicians, recognizing that TIR provides a more holistic view into the patient experience than HbA1c [95, 96]. Advances in data access and advanced analytics are also enabling development of more accurate and predictive dosing calculations, creating better end-user experience for patients, and improved clinical outcomes [97-99] [100].

Potential Adoption and Key Drivers

Reduced patient burden and improved safety will be the main drivers of adoption of artificial pancreas systems. Hybrid closed loop systems are available today, however adoption is relatively low, largely due to the associated user burden and costs, and TIR has only reached 70%. In the future, if hybrid closed loop systems can provide further automation and TIR improvements, the adoption potential could reach ~40% for pediatric and adult patients, based on endocrinologist survey data. If devices evolve to full automation of drug delivery, adoption could reach 50% in pediatric and adult populations. Adoption rates for implantable systems were nearly identical to the rates for external systems, suggesting that there are mixed preferences for these devices. Some patients may favor devices worn externally, while others may prefer implanted devices.

A more robust safety profile demonstrating reduced dosing errors will also be required for broad adoption. In addition, manufacturers will need to show that devices minimize CGM inaccuracy and catheter occlusions, which could lead to hyperglycemia or DKA.

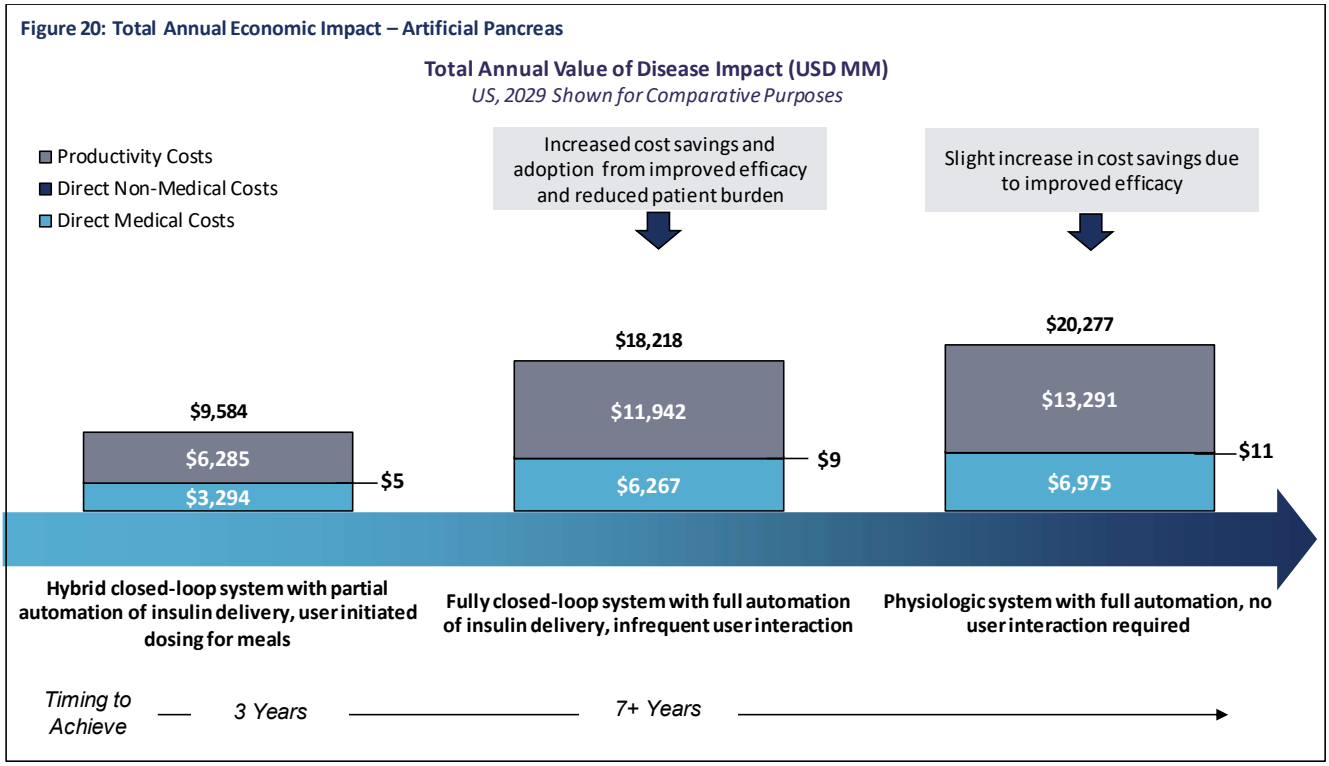
Economic Value of Disease Impact

The impact of different generations of an artificial pancreas system are driven by improving the level of automation, reducing patient burden, and improving TIR. In a hybrid closed-loop system with improved automation and TIR beyond what is available today, a device would achieve annual direct medical cost impact of $4,300 per patient for both pediatric and adult patient populations in the US. The total per-patient annual economic impact on T1D factoring in direct non-medical and productivity costs would reach $5,450 per pediatric patient and $13,500 in an adult patient in the US.

In a fully closed-loop system, the total per-patient annual economic impact on T1D would reach $8,240 in a pediatric patient and $20,420 in an adult patient in the US. This improvement is driven by achieving 95% TIR, and assuming that for every 10% absolute increase in TIR there is an 0.8% improvement in HbA1c. With a fully implantable closed-loop system with no user interaction, the total per-patient annual economic impact would reach $9,180 in a pediatric patient and $22,730 in an adult patient in the US.

Figure 20 shows the total annual economic impact of varying levels of automated insulin delivery system improvements for the combined US pediatric and adult population.

Figure 20: Total Annual Economic Impact – Artificial Pancreas



Appendix: Detailed Methodology

Total Economic Burden of T1D

Definitions of Economic Costs

The global burden of T1D presented here draws on relevant published literature to define the economic costs that contribute to patient, caregiver, employers, healthcare system, and societal burden [33, 34]. Economic Burden of Illness (BOI) or Cost of Illness (COI) studies, for any disease, usually include *direct costs*. These are the costs directly attributed to treating and managing a health condition or disease, such as costs associated with physician, inpatient, outpatient, and Emergency Department (ED) visits and medications. Economic studies of disease burden should also consider *indirect costs*, which include "expenses from the cessation or reduction of work productivity as the result of morbidity and mortality associated with a given disease. Indirect costs consist of work loss, worker replacement, and reduced productivity from illness" [101].

We further segmented these costs into direct medical, direct non-medical, productivity, and intangible costs. Consistent with the health economic literature, *direct medical costs* included all costs due to resource use that are attributable to the delivery of a health care intervention or illness [33, 34]. For this analysis, direct medical costs included the cost of a defined treatment for T1D, e.g., insulin, and all follow-up costs for other medications and/or health care interventions and complications in ambulatory, inpatient, and nursing care. Specialist and physician care, including in the ED, was also included.

Direct non-medical costs included transportation costs to access care, trained caregiver time, and specialized and/or frequent daycare. Direct non-medical costs were estimated based on the frequency of care visits for a T1D patient annually, and the average distance traveled to the site of care [102, 103]. Since the average age of T1D diagnosis is 12 years, and patients are typically able to administer their own medications with the assistance of an adult, specialized care was not considered in this analysis [104]. Instead, we assumed that travel costs associated with outpatient and ED visits for T1D patients were the key component of direct non-medical costs. We identified both direct medical and direct non-medical costs from a comprehensive review of the most recent 10 years of published literature in T1D. Additionally, our analysis focused on the net change in these costs associated with the introduction of a novel T1D therapeutic concept or intervention compared to the cost of care for an otherwise healthy individual.

Economists define *indirect* costs as those generally resulting from the loss of productivity due to illness or mortality. These costs can result from both presenteeism (presence of a worker who experiences reduced productivity due to illness) and absenteeism (the physical absence of a worker, in which case the employer must also absorb the cost and time of worker replacement) [35]. In addition, costs to support disability payments for absent workers, and life insurance costs for workers that die are included in the productivity cost calculus [36-38]. Productivity costs also often include the loss in gross income to the patient [35].

Our analysis accounted for these indirect, or productivity, costs due to disease felt by patients, caregivers, employers and society, and as such, included costs related to income loss, absenteeism, presenteeism, disability payments, and life insurance payments for T1D patients and caregivers. For lost income, we derived the average income of T1D patients compared to otherwise healthy individuals from the published literature and adjusted it for inflation to 2018 estimates [105, 106]. There is a dearth of available data for income loss for T1D caregivers, so we used caregiver surveys to derive the average number of caregiver-missed workdays, estimated average yearly income loss, and then attributed these costs to the pediatric T1D population [107, 108]. Absenteeism costs were based on the unemployment rate of T1D patients and the average time required by employers to replace a lost worker [38, 109]. Presenteeism costs were based on the percent of T1D patients that remained employed but who reported severe difficulty at work leading to reduced productivity [38]. Disability insurance

costs were derived from patient surveys that reported the number of T1D patients eligible for disability and an average T1Dmonthly disability payment [36, 37]. Life insurance costs were taken from T1D mortality rates and average life insurance benefits in the US [110, 111].

Intangible costs are defined in the literature as non-financial costs associated with pain and suffering and reduced health-related quality of life (HRQoL) due to a disease and/or its treatment [112]. The absence of any resource or budgetary impact characterizes intangible costs, where those resources are not released for alternative uses when intangible costs are reduced. Because of this, intangibles are rarely quantified, and our evaluation found that intangible pain and suffering associated with T1D is not accounted for or measured in the health economic literature. Due to these challenges, we excluded intangibles from our quantitative BOI analysis, and instead qualitatively addressed pain, suffering, and reduced QoL associated with T1D.

Analysis of T1D Burden of Illness

After defining and estimating all relevant costs for both the pediatric and adult populations, by country and region, based on the available literature (Table 1), we calculated per-patient annual (2018) and lifetime burden for pediatric and adult patients, respectively, as the sum of the cost categories to arrive at the total economic burden of T1D. We estimated direct medical, direct non-medical, and productivity costs for the US. In Europe, where economic data on T1D are lacking, we estimated direct medical costs only, based on country-specific published literature for the UK [113]. For all countries in Europe, direct non-medical and productivity costs were scaled based on per capita GDP from the UK estimates to each country in Europe [114]. Costs for all other regions, including Latin America, Asia, and ROW, were scaled from the US estimates based on per capita GDP in the US to each region [114]. Per-patient costs were multiplied by the T1D prevalence in each region to determine the total global cost burden. All costs used in the final BOI calculation were adjusted for inflation based on growth in healthcare expenditure in each region. We used per-capita health expenditure growth in each region based on data from the World Bank to calculate 2018 estimates [105].

Table 2: Incremental Medical and Productivity Cost Estimates by Region

Annual Burden per Patient	US		Europe		Asia		Latin America		ROW	
	Ped	*Adult*	*Ped*	*Adult*	*Ped*	*Adult*	*Ped*	*Adult*	*Ped*	*Adult*
Incremental Direct Medical	$4,429	$8,136	$2,957	$3,323	$508	$1,309	$713	$1,309	$143	$263
Incremental Direct Non-Medical	$8	$9	$3	$4	$1	$1	$1	$1	$0.3	$0.3
Incremental Productivity	$1520	$12,172	$653	$5,233	$174	$1,397	$244	$1,959	$49	$393
Incremental Total*	$5,960	$20,320	$3,610	$8,560	$680	$2,710	$960	$3,270	$190	$660

*Total numbers are rounded to the nearest ten.

We calculated the lifetime per-patient burden for newly diagnosed patients by multiplying the annual patient burden by the pediatric and adult lifetimes.

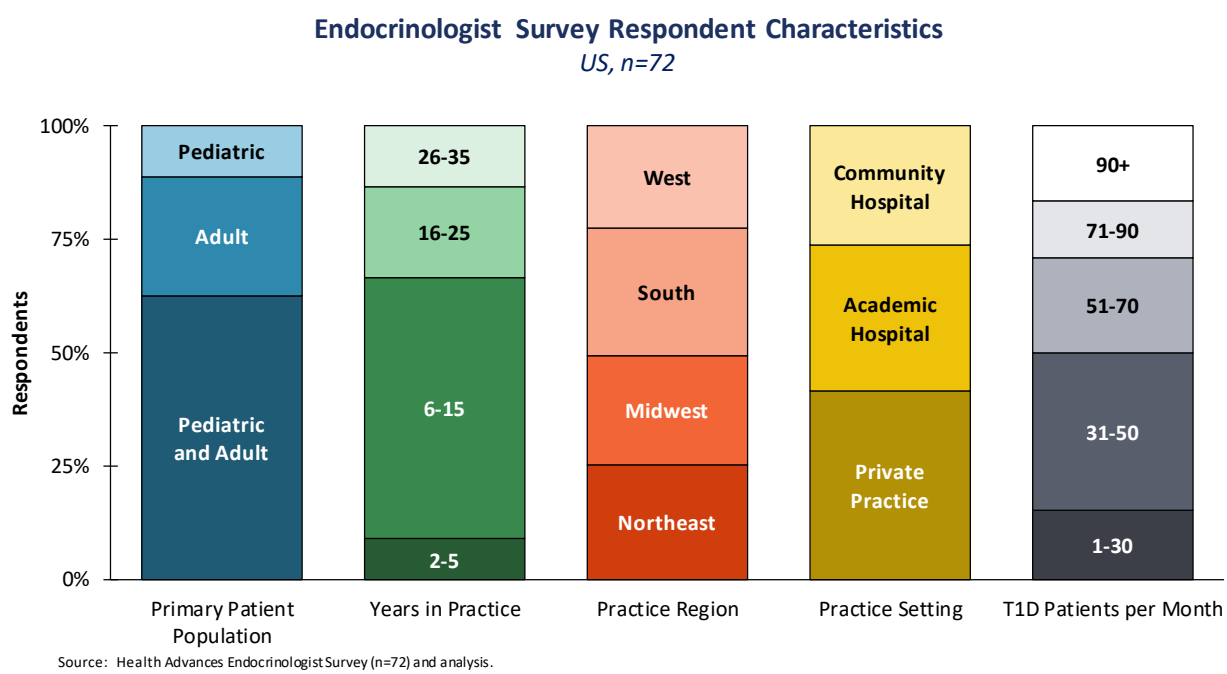
Therapeutic Concept Economic Impact

Addressable Patient Populations and Concept Adoption

Epidemiology data for pediatric and adult populations in the US and globally were derived from the published literature, including 2017 estimates from the International Diabetes Federation (IDF), SEARCH 2014, and the CDC [5, 115, 116]. Patient segmentation considered the populations for which each concept is applicable across pediatric and adult populations, and across Stage 1, Stage 2, and Stage 3 T1D disease. For example, prevention-based concepts are only applicable to patients in Stage 1 and 2 disease, with some prevention concepts targeting solely pediatric populations. Curative- and treatment-based concepts are applicable only to patients with Stage 3 disease. The *addressable* patient population then considers those patients who are eligible and likely to be treated by each concept across different age groups as well as those in different stages of diagnosed disease.

To estimate future adoption rates for each therapeutic concept, expert interviews and a quantitative survey of 72 US endocrinologists were conducted. Survey respondent selection included a diverse group of physicians, varying by practice setting, US region, years in practice, primary patient population, and total number of T1D patients seen per month (shown in graph below). These respondents reviewed each therapeutic concept and generation in detail and then estimated the percent of patients to whom they would prescribe the concept.

Figure 21: Quantitative Survey Research Overview



Source: Health Advances Endocrinologist Survey (n=72) and analysis.

In order to adjust for sample bias of estimates reported by physicians, a market research adjustment was applied to all raw survey adoption data. This market research adjustment was determined by comparing average respondent answers to literature estimates for several T1D metrics that have been well-studied, including DKA at diagnosis, average HbA1c, and percent of patients on insulin pumps today. On average, respondents reported

answers that were 21% higher than the literature reports; therefore, a 21% cut was applied to all adoption data estimates.

The adoption rates for each concept are shown in detail in table 3a and 3b below.

Table 3a: Therapeutic Concept Description and Adoption Model Inputs

Category	Therapeutic Concept	Therapy Profile	Therapy Adoption Model Inputs	
			Pediatric	Adult
Prevent	Prevent Progression in Stage 2	• ***Gen 1***: Delay onset of Stage 3 by 2 years in at least 30% of the population, IV	40%	43%
		• ***Gen 2***: Delay onset of Stage 3 by 2 years in at least 70% of the population, IV	53%	55%
		• ***Gen 3***: Delay onset of Stage 3 by 5 years in at least 70% of the population, IV	60%	62%
		• ***Gen 4***: Delay onset of Stage 3 by 5 years in at least 70% of the population, Subcutaneous	62%	62%
	Prevent DKA at Diagnosis at Stage 3	• ***Gen 1:*** Reduced DKA at conversion to insulin dependence to 20% (from 30-40%) • ***Gen 2:*** Reduced DKA at conversion to insulin dependence to 15% (from 30-40%) • ***Gen 4:*** Reduced DKA at conversion to insulin dependence to 10% (30-40%)	40%	N/A
	Preserve Beta Cell Function at Stage 3	• ***Gen 1***: <20% increase per year in insulin requirements, 50-70% TIR, IV	32%	33%
		• ***Gen 2***: <10% increase per year in insulin requirements, >70% TIR, IV	34%	36%
		• ***Gen 3***: 50-70% reduction per year in insulin requirements, >95% TIR, IV	50%	51%
		• ***Gen 4***: 50-70% reduction per year in insulin requirements, >95% TIR, Oral/ Subcutaneous	56%	58%
Cure	Beta Cell Replacement	• ***Gen 1***: 50-100% reduction in insulin needs with broad immunosuppression, 12-24 months duration of efficacy	14%	16%
			39%	42%
		• ***Gen 2***: 70-100% reduction in insulin needs and no broad immunosuppression, 12-24 months duration of efficacy	59%	63%
		• ***Gen 4***: Insulin independence with no immunosuppression required, >24 months duration of efficacy		
	Restore Beta Cell Function	• ***Gen 1***: Halts loss in insulin production, improves TIR to 50-70%, achieves HbA1c <7.5%	49%	49%
			55%	57%
		• ***Gen 2***: Modest Increases in insulin production, improves TIR to 70-90%, achieves HbA1c levels <6.5%	62%	66%
		• ***Gen 4***: Restores durable insulin independence, achieves TIR of 100% and HbA1c levels <4-5.6%		
Treat	Improve Metabolic Control	• ***Gen 1***: Reduction of HbA1c by 0.5%, improves TIR to 55%, no additional risk of hypoglycemia, but increased incidence of DKA requires mitigation strategy	17%	17%
			36%	40%
		• ***Gen 2***: Reduction of HbA1c by 1.0%, improves TIR to 65%, no additional side effects	48%	51%
		• ***Gen 4***: Reduction of HbA1c by 1.5% and 75% TIR, no additional side effects		

Source: Health Advances Endocrinologist survey (n=72), interviews and analysis.

Table 3b: Therapeutic Concept Description and Adoption Model Inputs

Category	Therapeutic Concept	Burden to Patient	Potential Safety	Efficacy	Therapy Adoption Model Inputs	
					Pediatric	Adult
Treat	Hybrid closed loop with partial automation of insulin delivery	• User initiated dosing/interaction for meals and other situations • 3 day infusion set replacements and insulin reservoir replacements	• Catheter occlusions could lead to hyperglycemia and/or DKA • Subcutaneous insulin administration leading to hypertrophy • Intermittent CGM inaccuracy leading to algorithm dosing errors	• TIR 80%	41%	43%
	Fully closed-loop with full automation of drugs	• Delivery for all situations • Infrequent/rare user-initiated dosing, interaction for extraneous circumstances • Miniaturized devices 7-to-10 day infusion set replacements and insulin reservoir replacements • Integrated infusion/sensing port	• Catheter occlusions could lead to hyperglycemia and/or DKA • Subcutaneous insulin administration leading to hypertrophy	• TIR 95%	52%	54%
	"Artificial pancreas", physiologic system with full automation	• Delivery via physiologic route for all situations • No user interaction required, infrequent (4x per year) visits to doctor's office for insulin refills and/or sensor changes	• Surgical procedure required for implantation of device/components as well as associated complication and recovery time	• Time in tight glucose range (80-120 mg/dL) 95%	52%	54%

Estimating the Economic Value of the Therapeutic Concept Efficacy Outcomes

The value of each therapeutic concept was determined by applying economic estimates to improvements in the following four specific efficacy outcomes: 1) reduction in HbA1c and/or TIR; 2) reduction in DKA events; 3) reduction in severe hypoglycemic events; and, 4) achieving insulin independence.[6] For each efficacy measure, we attributed savings in direct medical costs relative to the T1D baseline outcome today. Final direct medical costs for these outcome measures in the US and globally are depicted in Table 4 below.

[6] For all such economic outcomes, we applied a 3% growth rate to all future years to account for increasing per-capita health expenditure in the US, as averaged between 2007-2016

Table 4: Medical Cost Savings per Outcome Improvement Unit

Outcome Improvement (Baseline)		Savings in Direct Medical Cost					Methodology and Source	
		US	EU	LA	Asia	ROW	*US*	*Ex-US*
HbA1c 1% Reduction *(No reduction of HbA1c levels)*		$1,354 *(per year)*	$565	$211	$151	$42	• Literature-reported costs • Average value across sources (Grabner 2013, Wagner 2001)	• Ex-US: US literature-reported costs extrapolated by GDP
Avoiding One DKA Event at Diagnosis *(Having one event)*		$18,482 *(per event)*	$7,714	$2,887	$2,059	$580	• Literature-reported cost (Maldonado 2003)	• Ex-US: US literature-reported costs extrapolated by GDP
Avoiding One DKA Event in Stage 3 *(Having one event)*		$7,837 *(per event)*	$1,491	$1,224	$873	$246	• Literature-reported costs • Average value across sources (Tieder 2013, Shrestha 2010)	• EU: Literature-reported costs for UK (Dhatariya 2017), extrapolated by GDP • Other regions: US literature-reported costs extrapolated by GDP
Avoiding One Severe Hypoglycemic Event *(Having one event)*		$16,278 for all events *(per event)*	$5,251	$2,543	$1,813	$511	• Literature-reported costs • Average value across sources (Bronstone 2015, Shrestha 2010)	• EU: Literature-reported costs for DE, extrapolated by GDP (Holstein 2002) • Other regions: US literature-reported costs extrapolated by GDP
One Insulin Independence Year *(Insulin usage due to T1D)*	**Pediatric**	$4,429 (per year)	$1,849	$692	$493	$139	• Sussman 2020	• EU: Literature-reported costs for FR, extrapolated by GDP (Chevreul 2014) • Other regions: US literature-reported costs extrapolated by GDP
	Adult	$8,136 (per year)	$3,396	$1,271	$906	$255		
Growth rate of per-capita health expenditure (3% in the US) applied, to adjust literature estimates into 2018 value from the study year								

* Including hospitalized and non-hospitalized hypoglycemic events.
Source: Health Advances analysis, details as outlined on supporting slides.

1. *Reduction in HbA1c and/or TIR*

   From the published literature, we derived a corresponding economic value of $1,354 per-patient per-year in the US for each 1% reduction in HbA1c [117, 118]. As no robust estimates quantifying HbA1c costs outside of the US were identified, we used costs from the US to scale to all other geographies based on per capita GDP in the US to other regions, including Europe, Latin America, Asia, and ROW countries [114].

   The economic value of TIR is less studied in the literature, but we estimated the impact of TIR based on its correlation with HbA1c. Vigersky et al. has shown that for every absolute 10% change in % TIR, there is a 0.8% change in HbA1c [119]. We converted TIR improvements to HbA1c decreases, and estimated the economic value using this method.

2. *Reduction in DKA Events*

   A literature review identified direct medical savings in the US of $18,482 and $7,837 per DKA event avoided at diagnosis and in Stage 3, respectively [120-122]. The economic value of avoiding one DKA event in Europe was derived from Dhatariya et al who reported direct medical costs of $2,312 associated with a DKA event in established T1D patients in the UK [123]. Cost estimates of DKA events were not generally reported across countries or regions. Therefore, we used costs from Dhatariya et al. to scale to the rest of Europe based on per capita GDP. For all other geographies including Latin America, Asia, and ROW countries, estimates for both DKA at diagnosis and DKA in Stage 3 were scaled from the US estimate based on per capita GDP [114].

3. *Reduction in Severe Hypoglycemic Event*
   From the published literature, we estimated direct medical costs of $16,278 per event in the US, for both hospitalized and non-hospitalized patients [121, 124]. Cost savings for an avoided hypoglycemic event in Europe were estimated based on the literature for direct medical costs of an event in adults in Germany [125]. These costs were scaled to all of Europe based on per capita GDP for Germany versus all other European countries. For all other geographies including Latin America, Asia, and ROW countries, estimates for one avoided hypoglycemic event were scaled from the US based on per capita GDP in the US to other regions [114].

4. *Insulin Independence*
   To ascribe an economic value to the outcome of living insulin-free, we identified all direct medical costs associated with T1D. Sussmann, et al., reported the average yearly direct medical expenditure related to T1D as $4,429 and $8,136 for pediatric and adult patients, respectively [106]. We used the direct medical costs of adult T1D patients in France, as reported by Chevreul et al, to estimate the economic value of living one year insulin-free in Europe [126]. These costs were scaled from France to the rest of Europe based on per capita GDP for France and all other European countries. For all other geographies including Latin America, Asia, and ROW countries, estimates for one year of insulin independence were scaled from the US for both pediatric and adult patients based on per capita GDP in the US to other regions [114].

In addition to using direct medical costs to translate clinical benefit from the therapeutic concepts to economic value, we also applied the economic value from savings in direct non-medical and indirect (productivity) costs. Specifically, we allocated a proportion of the sum of these other economic costs to each therapeutic concept based on the average improvements seen across the key efficacy outcomes compared to healthy baselines.

Finally, emerging evidence has shown that there can be lifelong disease impact on glycemic control and long-term complications from poor clinical outcomes that are experienced throughout a T1D patient's lifetime [127]. To address this lifelong impact, we accounted for therapeutic concepts that prevent or delay certain outcome measures by incorporating estimates of the long-term benefit of the delay. We estimated the lifetime economic benefit of delayed onset of Stage 3 T1D from the results of the BOI analysis described above, and modeled the delayed cost intervals of T1D based on patient age of onset [106]. We applied this lifetime cost to the relevant therapeutic concepts for both pediatric and adult populations. For pediatrics, we assumed a percentage of the total lifetime cost based on age of diagnosis and average life expectancy, and applied that across the duration for which the therapeutic concept was effective [26]. However, we did apply an eligibility cut to account for low residual beta cell function when patients are diagnosed as children. Conversely, for patients diagnosed as adults, while there is more residual beta cell function, there are fewer years of lifetime benefit.

DKA events are also known to lead to detrimental neurocognitive outcomes and affect long-term care [49]. While the degree of this impact long-term is not known, we conservatively assumed no additional efficacy impact for therapeutic concepts that result in averted DKA events. We assumed this is achieved over a patient's lifetime, and applied this to the estimates from the BOI analysis of cost savings based on patient age of disease onset.

Collectively, these estimates represent the total economic impact of novel T1D therapeutic concepts, across innovations.

Estimating Regional and Global Values for Therapeutic Concepts

This evaluation focused most rigorously on the US for the BOI analysis and concept valuation, given the higher amount of supporting health economic literature. To estimate the value of concepts globally and by region, the analysis extrapolates calculations to other regions at a high level based on relative GDP. Regional and total global values of each concept and generation are summarized in the table below.

Table 5: Total Annual Economic Impact of Product Concepts by Geography

Category	Therapeutic Concept	Generation	Total Annual Economic Impact (USD MM)					
			US	EU	LA	Asia	ROW	Total
Prevent	Delay Onset of Stage 3	*Gen 1*	$384	$215	$29	$82	$15	$726
		Gen 2	$1,182	$660	$90	$252	$46	$2,231
		Gen 3	$2,879	$1,599	$221	$626	$114	$5,439
		Gen 4	$2,960	$1,644	$226	$640	$117	$5,588
	Prevent DKA at Diagnosis (Stage 3)	*Low*	$50	$25	$3	$10	$2	$91
		Med	$63	$32	$4	$12	$2	$113
		High	$76	$38	$5	$14	$3	$136
	Preserve Beta Cell Function at Stage 3	*Gen 1*	$655	$464	$132	$501	$25	$1,777
		Gen 2	$1,458	$1,033	$294	$1,118	$57	$3,959
		Gen 3	$6,311	$4,474	$1,271	$4,839	$246	$17,141
		Gen 4	$7,137	$5,061	$1,438	$5,475	$278	$19,389
Cure	Beta Cell Replacement	*Gen 1*	$3,514	$2,553	$724	$2,809	$135	$9,736
		Gen 2	$13,438	$9,627	$2,733	$10,490	$520	$36,809
		Gen 3	$28,806	$20,634	$5,859	$22,482	$1,116	$78,896
	Cure Disease – Restore Beta Cell Function	*Gen 1*	$4,562	$3,275	$930	$3,564	$177	$12,507
		Gen 2	$15,569	$11,122	$11,122	$12,009	$604	$42,542
		Gen 3	$30,181	$21,619	$6,138	$23,554	$1,169	$82,660
Treat	Improve Metabolic Control	*Gen 1*	$1,130	$812	$230	$883	$44	$3,099
		Gen 2	$5,295	$3,808	$4,148	$1,081	$206	$14,537
		Gen 3	$10,146	$7,291	$2,069	$7,939	$394	$27,840
	Artificial Pancreas	*Gen 1*	$9,584	$6,843	$1,942	$7,433	$372	$26,174
		Gen 2	$18,218	$13,005	$3,692	$14,124	$707	$49,745
		Gen 3	$20,277	$14,475	$4,109	$15,720	$787	$55,367

References

1. Armstrong, B., E.R. Mackey, and R. Streisand, *Parenting behavior, child functioning, and health behaviors in preadolescents with type 1 diabetes.* J Pediatr Psychol, 2011. **36**(9): p. 1052-61.
2. Martyn-Nemeth, P., et al., *Diabetes distress may adversely affect the eating styles of women with type 1 diabetes.* Acta diabetologica, 2014. **51**(4): p. 683-686.
3. Ehrmann, D., et al., *Longitudinal relationship of diabetes‐related distress and depressive symptoms: analysing incidence and persistence.* Diabetic Medicine, 2015. **32**(10): p. 1264-1271.
4. Roy, T. and C.E. Lloyd, *Epidemiology of depression and diabetes: a systematic review.* Journal of affective disorders, 2012. **142**: p. S8-S21.
5. Cho, N., et al., *IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045.* Diabetes research and clinical practice, 2018. **138**: p. 271-281.
6. Control, C.f.D. and Prevention, *National diabetes statistics report, 2017*. 2017, Atlanta, GA: Centers for Disease Control and Prevention.
7. Fagot-Campagna, A., et al., *Prévalence et incidence du diabète et mortalité liée au diabète en France-Synthèse épidemiologique.* Institut de veille sanitaire, 2010: p. 1-12.
8. Patterson, C., et al., *Diabetes in the young–a global view and worldwide estimates of numbers of children with type 1 diabetes.* Diabetes research and clinical practice, 2014. **103**(2): p. 161-175.
9. Roglic, G., *WHO Global report on diabetes: A summary.* International Journal of Noncommunicable Diseases, 2016. **1**(1): p. 3.
10. Tamayo, T., et al., *The prevalence and incidence of diabetes in Germany: an analysis of statutory health insurance data on 65 million individuals from the years 2009 and 2010.* Deutsches Ärzteblatt International, 2016. **113**(11): p. 177.
11. Xu, G., et al., *Prevalence of diagnosed type 1 and type 2 diabetes among US adults in 2016 and 2017: population based study.* bmj, 2018. **362**: p. k1497.
12. PharmaProjects, *Pipeline.* Citeline, 2019.
13. Rosenbauer, J., et al., *Improved metabolic control in children and adolescents with type 1 diabetes: a trend analysis using prospective multicenter data from Germany and Austria.* Diabetes care, 2012. **35**(1): p. 80-86.
14. Agiostratidou, G., et al., *Standardizing clinically meaningful outcome measures beyond HbA1c for type 1 diabetes: a consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange.* Diabetes Care, 2017. **40**(12): p. 1622-1630.
15. Association, A.D., *Standards of medical care in diabetes—2014.* Diabetes care, 2014. **37**(Supplement 1): p. S14-S80.
16. ADA, *12. Children and Adolescents.* Diabetes Care, 2017. **40**(Supplement 1): p. S105-S113.
17. ADA, *6. Glycemic Targets: Standards of Medical Care in Diabetes—2019.* Diabetes Care, 2019. **42**(Supplement 1): p. S61-S70.
18. Miller, K.M., et al., *Current state of type 1 diabetes treatment in the US: updated data from the T1D Exchange clinic registry.* Diabetes care, 2015. **38**(6): p. 971-978.
19. Idelbrook, C., *A Large Study Finds Most People with Type 1 Diabetes Don't Meet HbA1c Goals.* Glu, 2019.
20. McCrimmon, R.J. and R.S. Sherwin, *Hypoglycemia in type 1 diabetes.* Diabetes, 2010. **59**(10): p. 2333-2339.
21. Frier, B.M., *The incidence and impact of hypoglycemia in type 1 and type 2 diabetes.* International Diabetes Monitor, 2009. **21**(6): p. 210-218.
22. Desouza, C.V., G.B. Bolli, and V. Fonseca, *Hypoglycemia, diabetes, and cardiovascular events.* Diabetes care, 2010. **33**(6): p. 1389-1394.

23. Dyck, P.J., et al., *The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population ‐based cohort: the Rochester Diabetic Neuropathy Study.* Neurology, 1993. **43**(4): p. 817-817.
24. Bjornstad, P., D. Cherney, and D.M. Maahs, *Early diabetic nephropathy in type 1 diabetes: new insights.* Curr Opin Endocrinol Diabetes Obes, 2014. **21**(4): p. 279-86.
25. Jonker, J.T., et al., *Physical Activity and Life Expectancy With and Without Diabetes.* Life table analysis of the Framingham Heart Study, 2006. **29**(1): p. 38-43.
26. Rawshani, A., et al., *Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study.* The Lancet, 2018. **392**(10146): p. 477-486.
27. Miller, R.G., et al., *Improvements in the Life Expectancy of Type 1 Diabetes: The Pittsburgh Epidemiology of Diabetes Complications Study Cohort.* Diabetes, 2012. **61**(11): p. 2987-92.
28. Research, G., *Research: Type 2 Diabetes Mellitus Market Ripe for Investment.* R&D Magazine, 2016.
29. Foundation, C.a.C.
30. Rheumatology.org.
31. Society, N.M.
32. ClinicalTrials.gov, *Type I Diabetes.* NIH, 2019.
33. CDC, *Economic Impact Analysis: Cost of Illness.* Heart Disease & Stroke Prevention, 2017.
34. WHO, *Analysing Disrupted health Sectors - A modular Manual.* 2019. **Module 6**: p. 185-188.
35. Pritchard, C. and M. Sculpher, *Productivity costs: principles and practice in economic evaluation.* Monographs, 2000.
36. Laurence, B., *Social Security Disability for Diabetes (Type I or Type II).* NOLO, 2019.
37. Laurence, B., *How Much in Social Security Disability Benefits Can You Get?* NOLO, 2019.
38. Von Korff, M., et al., *Work disability among individuals with diabetes.* Diabetes care, 2005. **28**(6): p. 1326-1332.
39. Ziegler, A.G., et al., *Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children.* Jama, 2013. **309**(23): p. 2473-9.
40. Ziegler, A.G., et al., *Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children.* Jama, 2013. **309**(23): p. 2473-2479.
41. Insel, R.A., et al., *Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association.* Diabetes care, 2015. **38**(10): p. 1964-1974.
42. Maahs, D.M., et al., *Epidemiology of type 1 diabetes.* Endocrinology and Metabolism Clinics, 2010. **39**(3): p. 481-497.
43. Battaglia, M., et al., *Understanding and preventing type 1 diabetes through the unique working model of TrialNet.* Diabetologia, 2017. **60**(11): p. 2139-2147.
44. Diabetes, B.D.C.f., *ASK: Autoimmunity Screening for Kids.* 2019.
45. JDRF, *JDRF Prevention Program.*
46. ADA, *Teplizumab Delays Clinical Diagnosis of Type 1 Diabetes, an Average of Two Years, According to Study Presented at ADA's Scientific Sessions.* 2019.
47. Rewers, A., et al., *Presence of diabetic ketoacidosis at diagnosis of diabetes mellitus in youth: the Search for Diabetes in Youth Study.* Pediatrics, 2008. **121**(5): p. e1258-e1266.
48. Rewers, A., et al., *Incidence of diabetic ketoacidosis at diagnosis of type 1 diabetes in Colorado youth, 1998-2012.* Jama, 2015. **313**(15): p. 1570-1572.
49. Ghetti, S., et al., *Diabetic ketoacidosis and memory dysfunction in children with type 1 diabetes.* The Journal of pediatrics, 2010. **156**(1): p. 109-114.
50. Benoit, S.R., et al., *Trends in diabetic ketoacidosis hospitalizations and in-hospital mortality—United States, 2000–2014.* Morbidity and Mortality Weekly Report, 2018. **67**(12): p. 362.
51. Winkler, C., et al., *Markedly reduced rate of diabetic ketoacidosis at onset of type 1 diabetes in relatives screened for islet autoantibodies.* Pediatric diabetes, 2012. **13**(4): p. 308-313.

52. Larsson, H.E., et al., *Reduced prevalence of diabetic ketoacidosis at diagnosis of type 1 diabetes in young children participating in longitudinal follow-up.* Diabetes care, 2011. **34**(11): p. 2347-2352.
53. Couper, J., et al., *Phases of type 1 diabetes in children and adolescents.* 2014.
54. Saraiya, S., *Is It Possible to Prevent or Delay Type 1 Diabetes?* AJMC, 2015.
55. Cernea, S. and M. Dobreanu, *Diabetes and beta cell function: from mechanisms to evaluation and clinical implications.* Biochemia medica: Biochemia medica, 2013. **23**(3): p. 266-280.
56. Herold, K.C., et al., *Increased T cell proliferative responses to islet antigens identify clinical responders to anti-CD20 monoclonal antibody (rituximab) therapy in type 1 diabetes.* The Journal of Immunology, 2011. **187**(4): p. 1998-2005.
57. National Institute of, D., et al., *Intravenous CTLA4-lg Treatment in Recent Onset Type 1 Diabetes Mellitus*. 2012.
58. Hu, C., et al., *Combination treatment with anti-CD20 and oral anti-CD3 prevents and reverses autoimmune diabetes.* Diabetes, 2013. **62**(8): p. 2849-2858.
59. Janssen, R. and L.L.C. Development, *A Study of SIMPONI® to Arrest Beta-cell Loss in Type 1 Diabetes*. 2019.
60. National Institute of, A., D. Infectious, and N. Immune Tolerance, *Tocilizumab (TCZ) in New-onset Type 1 Diabetes*. 2019.
61. University of Alabama at, B. and F. Juvenile Diabetes Research, *Verapamil for Beta Cell Survival Therapy in Type 1 Diabetes*. 2017.
62. Agency, E.M., *Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus.* 2018.
63. FDA, *Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention.* CDER, 2008.
64. Bruni, A., et al., *Islet cell transplantation for the treatment of type 1 diabetes: recent advances and future challenges.* Diabetes, metabolic syndrome and obesity: targets and therapy, 2014. **7**: p. 211.
65. Rother, K.I. and D.M. Harlan, *Challenges facing islet transplantation for the treatment of type 1 diabetes mellitus.* The Journal of clinical investigation, 2004. **114**(7): p. 877-883.
66. Shapiro, A.J., *Islet transplantation in type 1 diabetes: ongoing challenges, refined procedures, and long-term outcome.* The review of diabetic studies: RDS, 2012. **9**(4): p. 385.
67. AACE, *The Burden of Type 1 Diabetes.* AACE Diabetes Resource Center, 2019.
68. Robert, T., et al., *Functional beta cell mass from device-encapsulated hESC-derived pancreatic endoderm achieving metabolic control.* Stem cell reports, 2018. **10**(3): p. 739-750.
69. Corritore, E., et al., *β-cell replacement sources for type 1 diabetes: a focus on pancreatic ductal cells.* Therapeutic advances in endocrinology and metabolism, 2016. **7**(4): p. 182-199.
70. Sykes, M., *Immune Response to iPSC-Derived Beta Cells in Type 1 Diabetes.* National Institutes of Health, 2015.
71. Matsumoto, S., et al., *Clinical benefit of islet xenotransplantation for the treatment of type 1 diabetes.* EBioMedicine, 2016. **12**: p. 255-262.
72. Song, S. and S. Roy, *Progress and challenges in macroencapsulation approaches for type 1 diabetes (T1D) treatment: Cells, biomaterials, and devices.* Biotechnology and bioengineering, 2016. **113**(7): p. 1381-1402.
73. Skrzypek, K., et al., *Pancreatic islet macroencapsulation using microwell porous membranes.* Scientific reports, 2017. **7**(1): p. 9186.
74. Salvatori, M., et al., *Extracellular matrix scaffold technology for bioartificial pancreas engineering: state of the art and future challenges.* Journal of diabetes science and technology, 2014. **8**(1): p. 159-169.
75. Berman, D.M., et al., *Bioengineering the endocrine pancreas: intraomental islet transplantation within a biologic resorbable scaffold.* Diabetes, 2016. **65**(5): p. 1350-1361.
76. Khan, D., et al., *Influence of neuropeptide Y and pancreatic polypeptide on islet function and beta-cell survival.* Biochimica et Biophysica Acta (BBA)-General Subjects, 2017. **1861**(4): p. 749-758.

77. Zhu, R., et al., *Defective endoplasmic reticulum export causes proinsulin misfolding in pancreatic β cells.* Molecular and cellular endocrinology, 2019: p. 110470.
78. Novo Nordisk, A.S., *An Observational Study to Assess Longitudinal Variation of Immune Biomarkers in Subjects at Risk for Development of Type 1 Diabetes*. 2015.
79. Mohsen, A., *Nanotechnology Advanced Strategies for the Management of Diabetes Mellitus.* Current drug targets, 2019.
80. Peloso, A., et al., *Regenerative medicine and diabetes: targeting the extracellular matrix beyond the stem cell approach and encapsulation technology.* Frontiers in endocrinology, 2018. **9**.
81. Yamada, Y., *A Nanocarrier System for Mitochondrial Delivery Targeted to a Pancreatic Beta Cell.* Yakugaku zasshi: Journal of the Pharmaceutical Society of Japan, 2019. **139**(1): p. 41-45.
82. McDonald, T., *Heterogeneity of type 1 diabetes.* Pathology, 2017. **49**: p. S14.
83. Foster, N.C., et al., *State of type 1 diabetes management and outcomes from the T1D Exchange in 2016–2018.* Diabetes technology & therapeutics, 2019. **21**(2): p. 66-72.
84. Baxter, M., et al., *Estimating the impact of better management of glycaemic control in adults with Type 1 and Type 2 diabetes on the number of clinical complications and the associated financial benefit.* Diabetic Medicine, 2016. **33**(11): p. 1575-1581.
85. Gilmer, T.P., et al., *Predictors of health care costs in adults with diabetes.* Diabetes care, 2005. **28**(1): p. 59-64.
86. Nathan, D.M. and D.E.R. Group, *The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview.* Diabetes care, 2014. **37**(1): p. 9-16.
87. Chontong, S., S. Saetung, and S. Reutrakul, *Higher sleep variability is associated with poorer glycaemic control in patients with type 1 diabetes.* Journal of sleep research, 2016. **25**(4): p. 438-444.
88. McCrimmon, R.J. and R.R. Henry, *SGLT inhibitor adjunct therapy in type 1 diabetes.* Diabetologia, 2018. **61**(10): p. 2126-2133.
89. Pettus, J.H., et al., *Adjunct Therapy in Type 1 Diabetes: A Survey to Uncover Unmet Needs and Patient Preferences Beyond HbA1c Measures.* Diabetes technology & therapeutics, 2019. **21**(6): p. 336-343.
90. Liu, Y., et al., *Biodistribution, activation, and retention of proinsulin-transferrin fusion protein in the liver: Mechanism of liver-targeting as an insulin prodrug.* Journal of controlled release, 2018. **275**: p. 186-191.
91. Zhang, Y., et al., *High drug-loading gold nanoclusters for responsive glucose control in type 1 diabetes.* Journal of nanobiotechnology, 2019. **17**(1): p. 74.
92. Tauschmann, M., et al., *Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial.* The Lancet, 2018. **392**(10155): p. 1321-1329.
93. Trief, P.M., et al., *Incorrect insulin administration: a problem that warrants attention.* Clinical Diabetes, 2016. **34**(1): p. 25-33.
94. Bergenstal, R.M., et al., *Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes.* Jama, 2016. **316**(13): p. 1407-1408.
95. Zaccaro, M., *Appropriateness of TIme in Range as a Measure of Diabetes Outcomes.* Diabetes in Control, 2018.
96. Runge, A.S., et al., *Does time-in-range matter? Perspectives from people with diabetes on the success of current therapies and the drivers of improved outcomes.* Clinical Diabetes, 2018. **36**(2): p. 112-119.
97. Castle, J.R., J.H. DeVries, and B. Kovatchev, *Future of automated insulin delivery systems.* Diabetes technology & therapeutics, 2017. **19**(S3): p. S-67-S-72.
98. Kovatchev, B.P., et al., *Assessing sensor accuracy for non-adjunct use of continuous glucose monitoring.* Diabetes technology & therapeutics, 2015. **17**(3): p. 177-186.
99. Trevitt, S., S. Simpson, and A. Wood, *Artificial pancreas device systems for the closed-loop control of type 1 diabetes: what systems are in development?* Journal of diabetes science and technology, 2016. **10**(3): p. 714-723.

100. Deshpande, S., et al., *Design and clinical evaluation of the Interoperable Artificial Pancreas System (iAPS) Smartphone App: interoperable components with modular design for progressive artificial pancreas research and development.* Diabetes technology & therapeutics, 2019. **21**(1): p. 35-43.
101. Bocuzzi, S.J., *Indirect health Care Costs.* Cardiovascular Health Care Economics, 2003.
102. McEwen, *Health Care Utilization and Costs of Diabetes.* Diabetes in America, 2015. **3**.
103. Rosenthal, M.B., A. Zaslavsky, and J.P. Newhouse, *The geographic distribution of physicians revisited.* Health services research, 2005. **40**(6p1): p. 1931-1952.
104. Clinic, M., *Type 1 Diabetes.* 2019.
105. WorldBank, *Current Health Expendiutre (% of GDP).* World Health Organization Global health Expenditure Database, 2016.
106. Sussman, M.B., Jennifer; Haller, Michael; Rewers, Marian; Griffiths, Robert, *Estimated Lifetime Economic Burden of Type 1 Diabetes.* 2020. **22**(2).
107. Guzman, G.G., *Household income: 2016*. 2017: US Department of Commerce, Economics and Statistics Administration, US ….
108. Schwartz, F.L., et al., *Experiences of children and adolescents with type 1 diabetes in school: survey of children, parents, and schools.* Diabetes Spectrum, 2010. **23**(1): p. 47-55.
109. Allen, K., et al., *Potential of trans fats policies to reduce socioeconomic inequalities in mortality from coronary heart disease in England: cost effectiveness modelling study.* Bmj, 2015. **351**: p. h4583.
110. Secrest, A.W., Raynard; Orchard, Trevor, *Mortality in Type 1 Diabetes.* Diabetes in America, 2014. **3rd Edition**.
111. Statistics, B.o.L., *May 2018 National Occupational Employment and Wage Estimates.* Occupational Employment Statistics, 2018.
112. Isfeld-Kiely, H. and S. Balakumar, *Framing Burden*. 2015: National Collaborating Centre for Infectious Diseases.
113. Hex, N., et al., *Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs.* Diabetic Medicine, 2012. **29**(7): p. 855-862.
114. Bank, T.W., *GDP per Capita.* 2017.
115. Hamman, R.F., et al., *The SEARCH for Diabetes in Youth study: rationale, findings, and future directions.* Diabetes care, 2014. **37**(12): p. 3336-3344.
116. CDC.
117. Grabner, M., et al., *Estimated Cost Savings Associated With A1c Reductions In A Large Us Commercial Health Plan.* Value in Health, 2013. **16**(3): p. A160.
118. Wagner, E.H., et al., *Effect of improved glycemic control on health care costs and utilization.* Jama, 2001. **285**(2): p. 182-189.
119. Vigersky, R.A. and C. McMahon, *The Relationship of Hemoglobin A1C to Time-in-Range in Patients with Diabetes.* Diabetes Technol Ther, 2019. **21**(2): p. 81-85.
120. Maldonado, M.R., et al., *Economic impact of diabetic ketoacidosis in a multiethnic indigent population: analysis of costs based on the precipitating cause.* Diabetes care, 2003. **26**(4): p. 1265-1269.
121. Shrestha, S.S., et al., *Medical expenditures associated with diabetes acute complications in privately insured US youth.* Diabetes Care, 2010. **33**(12): p. 2617-2622.
122. Tieder, J.S., et al., *Variation in resource use and readmission for diabetic ketoacidosis in children's hospitals.* Pediatrics, 2013. **132**(2): p. 229-236.
123. Dhatariya, K., C. Skedgel, and R. Fordham, *The cost of treating diabetic ketoacidosis in the UK: a national survey of hospital resource use.* Diabetic Medicine, 2017. **34**(10): p. 1361-1366.
124. Bronstone, A. and C. Graham, *The potential cost implications of averting severe hypoglycemic events requiring hospitalization in high-risk adults with type 1 diabetes using real-time continuous glucose monitoring.* Journal of diabetes science and technology, 2016. **10**(4): p. 905-913.

125. Holstein, A., A. Plaschke, and E.-H. Egberts, *Incidence and costs of severe hypoglycemia.* Diabetes care, 2002. **25**(11): p. 2109-2110.
126. Chevreul, K., K.B. Brigham, and C. Bouché, *The burden and treatment of diabetes in France.* Globalization and health, 2014. **10**(1): p. 6.
127. Jacobson, A.M., et al., *The long-term effects of type 1 diabetes treatment and complications on health-related quality of life: a 23-year follow-up of the Diabetes Control and Complications/Epidemiology of Diabetes Interventions and Complications cohort.* Diabetes care, 2013. **36**(10): p. 3131-3138.