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COMMENTARY

The Urgent Need for Breakthrough Therapies and a World Without Type 1 Diabetes

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ABSTRACT

Despite significant progress, type 1 diabetes (T1D) still results in premature death, significant complications, and a substantial daily burden for those affected. T1D remains a lifelong condition that demands constant vigilance and resilience and has a significant social and economic impact. Individuals with T1D must walk a tightrope to minimize disease-related complications that result from insufficient insulin while also avoiding adverse effects from too much insulin. Achieving this balance is challenging, as diet, activity, medications, physiology, the environment, stress, and many other aspects of daily living all affect glucose levels, often differently from day to day. Persistent challenges of T1D go beyond maintaining glycemic control and include managing long-term complications and preventing potentially life-threating adverse reactions from insulin therapy, and the emotional and cognitive burdens that often lead to diabetes distress and burnout. The T1D community—researchers, sponsors, clinicians, those living with T1D, and advocates—must look beyond managing symptoms of T1D and aim for better treatments and to bring cures. Emerging therapies need clear and efficient regulatory pathways, and new solutions are needed to address ongoing regulatory challenges. The perspectives of people with T1D must be front and center in research and regulatory decision-making. Through the collective efforts of the T1D community, the urgent needs of those with T1D can be met, and T1D can be made a thing of the past.

Keywords: Diabetes burnout; Diabetes distress; Drug development; Glycemic management; Hypoglycemia; Regulatory; T1D; Type 1 diabetes; Unmet needs

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Key Summary Points

Although progress has been made in managing type 1 diabetes (T1D), the disease still results in premature death, significant complications, and a substantial daily burden for those affected.

Patients diagnosed with T1D face the persistent challenge of relying on subcutaneous insulin to attempt to maintain glycemic levels as close to normal as possible while preventing potentially life-threating adverse events from too much or too little insulin and navigating the emotional, social, and economic burdens of the disease.

Novel therapies, including cures, that greatly reduce or eliminate the burden of T1D are within reach.

The entire T1D community, including researchers, sponsors, clinicians, advocates, those living with T1D, and regulators, must work together to overcome existing scientific, drug development, and regulatory challenges and make these therapies a reality.

TYPE 1 DIABETES: YESTERDAY, TODAY, AND TOMORROW

Breakthrough innovations have dramatically transformed type 1 diabetes (T1D). Over a century of advances in research, therapy, and medical technology have turned T1D from a fatal childhood diagnosis to a challenging chronic condition. Before these advances, children frequently died within days to weeks after diagnosis, and those that did not were subject to severe dietary restrictions, extended bed rest, and often hospitalized for weeks or months at a time. Starvation treatments were commonly employed, combining low-calorie, highly restricted diets with periods of fasting [1]. On average, a 10-year-old diagnosed with "acute-onset diabetes" could expect to live for only 2–3 more years, typically dying from diabetic ketoacidosis (DKA) [2].

Today, more than 100 years after insulin's discovery, steady improvements have been made in available insulins, insulin delivery systems, glycemic monitoring, and overall care. That same 10-year-old child, now diagnosed with type 1 diabetes (T1D), will, on average, live for 61 more years (in a high-income country) [2]. Although it was once thought to primarily afflict children, we now know T1D is not just a childhood-onset disease, with approximately half of US diagnoses occurring after age 30 [3]. The advent of insulin pumps, continuous glucose monitors (CGMs), and automated insulin delivery systems has vastly improved glycemic control and reduced short- and long-term complications [4]. People with T1D are living longer, healthier lives with improved quality of life.

However, the story does not end there. People diagnosed with T1D have an 11-year shorter life expectancy than those without the diagnosis. In upper-middle, lower-middle, or low-income countries, this gap expands to 25, 26, or 46 fewer years of life, respectively, with an overall global average of 24 years of life lost [2]. Mortality rates are 3–18 times higher among individuals with T1D than the general population, attributable largely to diabetes-related cardiovascular and renal disease [5]. Encouraging data show age-standardized mortality rates in T1D have decreased globally by about 21% from 1990–2019. However, the rate of decline was lowest in populations with a lower sociodemographic index, meaning the improvements seen over the last few decades are not equally realized across all T1D populations [6]. Despite these improvements, people with T1D still have shorter life expectancies. This is something that needs to be urgently addressed and in an equitable and global manner.

Decades of research and innovation have made T1D increasingly manageable for the 2 million Americans and more than 9 million people globally who are living with T1D [7, 8]. However, T1D continues to impose a relentless physical and emotional burden. As the incidence of T1D increases worldwide, we cannot stop our march toward overcoming it [2]. While we celebrate yesterday's progress, we must strive for more. A longer life, on its own, is not the final

destination on the road to breaking through T1D.

We envision a world without T1D, where the disease progression is permanently disrupted, insulin independence is restored, and those with the disease lead lives indistinguishable from those without. Achieving this requires re-examining and evolving our current paradigms as well as continuing collaborations across the T1D community. Researchers, clinicians, patients, advocates, sponsors, and policymakers must all work together to accelerate breakthrough progress toward cures.

The information presented in this article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

WHAT IS TYPE 1 DIABETES

T1D is an autoimmune disease in which an individual's immune system destroys insulin-producing beta cells in the pancreas. As the autoimmune attack on beta cells progresses over time, the body is increasingly unable to produce insulin until a critical threshold is crossed and overt clinical symptoms of glucose dysregulation manifest. The resulting complications from the disease and its management can include potentially fatal diabetic ketoacidosis (DKA) and hypoglycemia in the short term and retinopathy (eye), nephropathy (kidney), neuropathy (nerve), and cardiovascular (heart) disease in the long term. The pathophysiology of T1D progresses at variable rates through several distinct stages, ultimately resulting in the requirement for insulin replacement therapy to survive (Fig. 1) [9].

Stage 1 T1D represents the activation of the autoimmune attack against pancreatic beta cells and is marked by the presence of two or more islet autoantibodies. In stage 2, the effects of beta cell destruction are visible as dysglycemia on clinical tests, such as the oral glucose tolerance test. Stage 3 T1D occurs when beta cell destruction has progressed so far that the remaining insulin production capabilities can no longer support normal functions. While some ability to produce insulin typically remains at the onset of stage 3 T1D, exogenously administered insulin is required to survive. Stage 3 T1D is marked by the presence of islet autoantibodies, dysglycemia on clinical tests, and clinical symptoms of

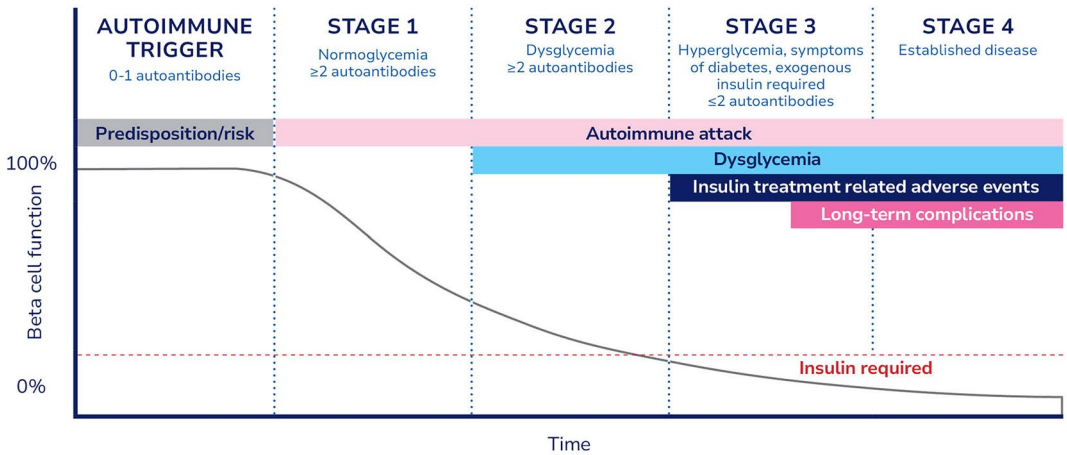

Fig. 1 Decline of beta cell function across stages of T1D. Progression of type 1 diabetes (T1D) resulting from autoimmune attack on pancreatic beta cells. Stage 1 is the presence of two or more islet autoantibodies with normoglycemia; stage 2 is the presence of two or more autoantibodies with dysglycemia; stage 3 involves the presence of two or more autoantibodies, dysglycemia, and the onset of symptomatic disease. Exogenous insulin is required after the onset of stage 3 T1D when remaining beta cell function is no longer able to meet the body's insulin requirements. Established T1D, often with complete insulin deficiency, is commonly called stage 4 T1D [9]

diabetes, including increased urination (polyuria), increased thirst (polydipsia), weight loss, fatigue, DKA, and others. Beta cell destruction continues after onset of stage 3 disease and initiation of insulin therapy, often progressing to complete insulin deficiency, referred to by some as stage 4 T1D [10, 11].

Historically, management of T1D has centered around insulin replacement after the onset of stage 3 T1D. In stages 3 and 4, the goal of insulin replacement therapy is to maintain normal or near-normal blood glucose levels while minimizing the risk of short- and long-term complications due to hypoglycemia (from too much insulin) or hyperglycemia (from lack of insulin). However, the continuous nature of T1D's pathophysiology is evident, and each disease stage reflects progression along the disease continuum. When viewed in this light, therapies that modify the underlying autoimmune disease and/or preserve, restore, or replace beta cell function offer tremendous benefit.

Disease-modifying therapies, like the recently approved teplizumab, and beta cell replacement therapies can prevent, reduce, or eliminate reliance on insulin replacement while supporting improved glycemic outcomes. Blood-glucose management via insulin therapy and glycemic monitoring is demanding and intensive. Individuals must monitor blood glucose levels, administer insulin, and balance how diet, activity, medications, physiology, the environment, stress, and much more affect glucose levels.

Even when considering the availability of modern technologies, managing glucose levels with insulin is an endless task, and the adverse impacts of this disease or its treatment are an inevitability felt by everyone with T1D (Fig. 2).

LIVING WITH TYPE 1 DIABETES

Life with T1D entails significant, persistent, and lifelong challenges. Once diagnosed, management of T1D is physically, mentally, and emotionally demanding and often overwhelming. Care decisions require extreme diligence with little margin for error, as too much or too little insulin, a moving target depending on daily activities and food intake, has dire consequences. Mentally, changes in glucose can affect concentration, memory, overall cognitive function, and more—making everyday life much

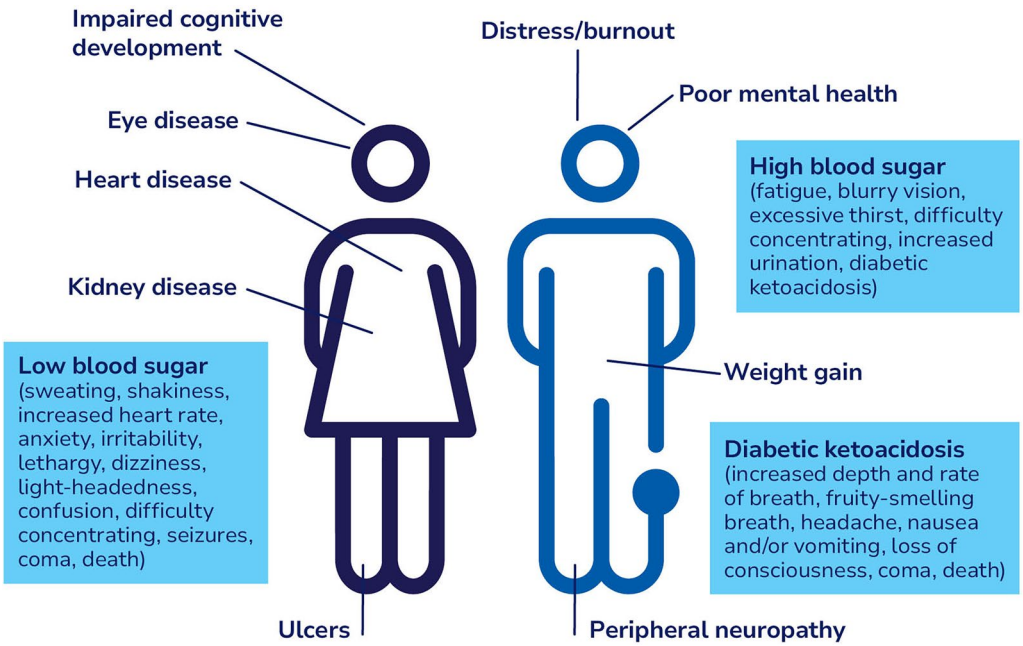

Fig. 2 Important clinical outcomes and effects of type 1 diabetes

more difficult. Emotionally, T1D is associated with fear of hypoglycemia, complications, anxiety, and depression, among others. Socially, T1D directly and indirectly impacts relationships with family, friends, and colleagues. Altogether, life with T1D entails the persistent and lifelong challenges discussed below.

Diagnosis and Diabetic Ketoacidosis (DKA)

While the pathological processes that underlie T1D begin well before the disease is clinically apparent, the lack of widely available screening and early detection programs means the disease is often not recognized until the onset of DKA, an acute uncontrolled hyperglycemic crisis resulting from a lack of insulin. DKA at the time of diagnosis occurs well over 50% of the time and can be a traumatic and even deadly experience [12, 13]. Diagnosis of T1D at the time of a DKA event is associated with higher insulin requirements, adverse neurocognitive outcomes, and worse long-term outcomes [14, 15].

Glycemic Control and Long-Term Complications

Maintaining blood glucose levels as close to normal as possible is critical to minimizing the risk of long-term diabetes-related complications. Diabetic nephropathy is estimated to affect approximately half of individuals with T1D, and the 25-year cumulative incidence of diabetic retinopathy is as high as 97% in some T1D populations [16–18]. Analysis of the Scottish Care Information-Diabetes Collaboration database has shown that men and women < 40 years of age have a 5- and 10-fold relative risk of a cardiovascular disease-related event [19]. Furthermore, by the age of 45, 70% of men and 50% of women with T1D have already developed evidence of atherosclerosis, a predecessor of cardiovascular disease and cardiovascular events [5]. Individuals with T1D also have worse cardiovascular disease outcomes than those with type 2 diabetes [20].

A hemoglobin A1c (HbA1c) of < 7% (53 mmol/mol) is widely recognized to reduce, but not eliminate, the risk of microvascular complications [21]. A 2014 Swedish study found that people with T1D and an HbA1c level of ≤ 6.9% (52 mmol/mol) still had nearly three times the risk of all-cause cardiovascular mortality compared with non-T1D matched controls [22]. From 2021 to 2022, only 26% of individuals with T1D had an HbA1c level < 7% (53 mmol/mol), the clinically recommended target for most adults with diabetes [21]. This inability to achieve glycemic control targets does not reflect a lack of effort for those with T1D. Instead, it directly corresponds to the extremely difficult nature of managing T1D.

Hypoglycemia

Hypoglycemia is one of the most common acute side effects of disease management and is purely iatrogenic, resulting from a too high insulin dose. It is accompanied by a myriad of short-term, intermittent, and persistent effects. Acutely, as blood glucose levels fall, the brain begins to lack adequate glucose (i.e., neuroglycopenia). Hypoglycemia can lead to sweating, shakiness, dizziness, blurred vision, lethargy, weakness, confusion, and, in severe cases, seizures, coma, or death. In children and adolescents, who are at increased risk for hypoglycemic events, long-lasting effects of recurrent hypoglycemia include mild impairments in general intelligence, attention, and visuospatial abilities [23].

Recurrent hypoglycemia can lead to hypoglycemia unawareness, a condition where low blood sugar is not accompanied by physical symptoms. Hypoglycemia unawareness inhibits an individual's ability to recognize the situation and intervene, potentially leading to serious secondary harm depending on when the event occurs, for example, while driving. Hypoglycemia unawareness is reported to occur in approximately 25–40% of individuals with T1D [24].

Managing the constant concern for hypoglycemia is a major focus of care for many with T1D. Patient preference studies have established that avoiding one to five hypoglycemia events per week is five times more important

than having an HbA1c 0.5% (6 mmol/mol) above their target for adults with T1D and seven times more important for caregivers of someone with T1D [25].

Fear of hypoglycemia (FOH), defined as an extreme fear associated with the risk and/or occurrence of hypoglycemia, is reported in as high as 30% of adults with T1D [26]. FOH is associated with lower quality of life, impaired emotional well-being, higher psychological distress, and worse glycemic control [26]. FOH also greatly impacts families and caregivers of individuals living with T1D.

Many people who experience FOH adopt negative hypoglycemia avoidance behaviors that sacrifice long-term health to avoid short-term complications. This includes intentionally keeping glucose levels higher than optimal, reducing or skipping insulin doses, continually snacking, restricting activities, avoiding spontaneity, and often avoiding being alone [27].

It is important to note the increasing availability and capabilities of modern diabetes technologies, including CGMs, insulin pumps, and automated insulin delivery systems. Recent data from the T1D Exchange show an increased utilization of diabetes technologies from 2016–2022 [4]. Further data also demonstrate improvements in HbA1c and hypoglycemia in those using diabetes technologies [28]. While these trends are encouraging, currently available technologies are unable to result in normal glycemic profiles or eliminate hypoglycemia. While devices help reduce the day-to-day burden of care of T1D, improvements in these systems remain an ongoing need.

Diabetes Distress and Burnout

The limitations of today's therapies mean those with T1D continue to have little respite from the demands of this disease. There are no days off from T1D. In one survey, most people with T1D reported that diabetes negatively impacts their ability to plan for the future, manage life challenges, succeed in their schooling or work, and build self-confidence [27].

Given the multitude of factors that can affect blood glucose levels, it is no surprise that managing one's glucose levels is a complex and time-consuming endeavor. In an online survey of over 5000 people with T1D or their caregivers, the overall difficulty of managing blood glucose and the time required to manage blood glucose were the two most cited factors that impact day-to-day life with T1D [27]. Similarly, a recent semi-structured qualitative interview study found many people with T1D struggle with the unceasing nature of the disease. There is simply no aspect of life that is not severely impacted by T1D (Fig. 3).

The American Diabetes Association (ADA) defines diabetes distress as "the emotional distress that results from living with diabetes and the burden of relentless daily self-management" [27]. Diabetes distress has been reported in as high as 61% of adolescents and 42% of adults with T1D and is directly linked to poor glycemic control and higher risks for depression [29]. Notably, diabetes has been shown to more than double the risk of depression, a condition that is itself associated with poor outcomes [30].

Similar to diabetes distress, diabetes burnout is "a state of physical or emotional exhaustion caused by the continuous distress of diabetes (and efforts to self-manage it)" [27]. Diabetes burnout includes understanding the importance of diabetes management but nonetheless being overwhelmed by feelings of mental and physical fatigue, powerlessness, and detachment from self- and diabetes care. It is difficult to measure the rates of diabetes burnout, but some literature suggests that it is a primary barrier to self-care in over one-third of individuals with diabetes [31].

THE PATH TO BREAKING THROUGH T1D

Despite the clear and pressing needs faced by those with T1D, some nonetheless claim that insulin replacement and diabetes technologies are so good that little risk should be tolerated when developing new T1D therapies [32]. We believe the data show otherwise. It is therefore imperative that we continue to bring innovative therapies to address the significant and serious unmet needs of those living with T1D.

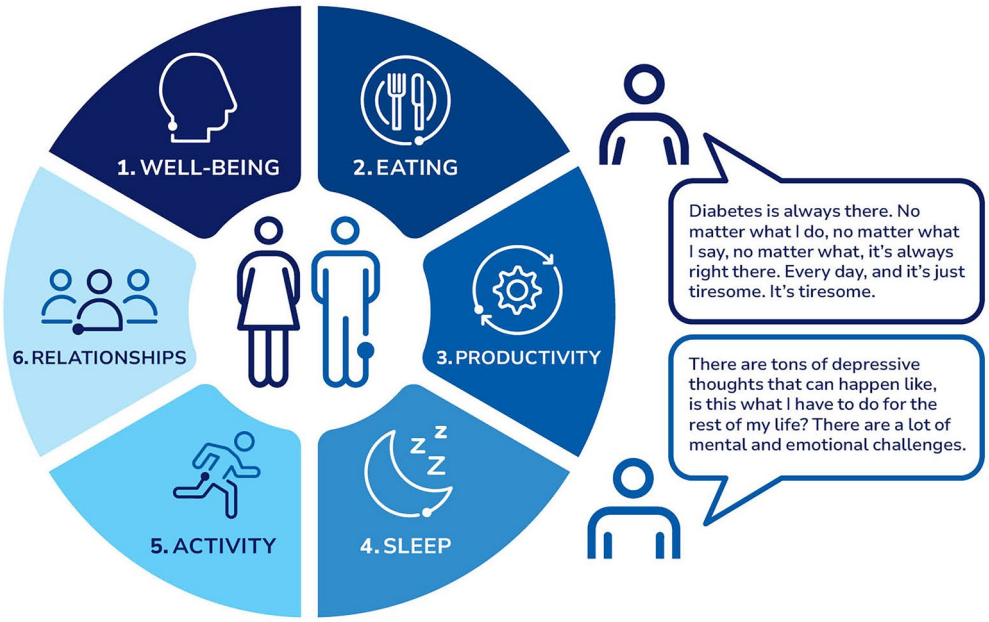

Fig. 3 How type 1 diabetes impacts patients. Semi-structured qualitative interviews identified six domains of life commonly reported to be highly impacted by type 1 diabetes (T1D): well-being (e.g., stress), eating (e.g., carbohydrate counting), productivity (e.g., decreased concentration at work), sleeping (e.g., frequent overnight alarms), activity (e.g., feeling weak), and relationships (e.g., sense of stigma)

Insulin replacement can no longer be seen as the only therapeutic option for T1D. We must aim to modify the overall course of T1D, employing targeted therapeutic strategies for each stage of the disease (Table 1). Ideally, multiple therapeutic options and modalities would be available at each stage, allowing people with T1D more choice in the most appropriate care for them. Some progress has been made in bringing novel types of therapies to market, for example, teplizumab and donislecel.

Teplizumab is an anti-CD3 monoclonal antibody and is the first disease-modifying therapy approved for use in T1D. Teplizumab is indicated to delay the onset of stage 3 T1D in children and adults aged ≥ 8 years with stage 2 T1D [33]. Donislecel is an allogeneic pancreatic cellular therapy indicated for the treatment of adults with T1D who are unable to approach their target HbA1c because of repeated episodes of severe hypoglycemia despite intensive diabetes management and education [34]. Donislecel is the first approved cell therapy available in type 1 diabetes but must be used in conjunction with concomitant immunosuppression. These therapies represent important first steps at moving beyond the insulin-centric paradigm of the last hundred years; however, more is needed to fully meet the needs of people with T1D.

Bringing novel treatments and cures to fruition requires new solutions to long-existing challenges. Researchers and regulators must move beyond the insulin-centric paradigm of the previous 100 years, and the regulatory environment must protect public health without suppressing innovation. Insulin-based treatments cannot remain the status quo—the T1D community can and should do better. We must also foster a health system that allows breakthrough therapies to be available and accessible to all who need them.

Regulatory Opportunities to Advance T1D Cures

Clear and reasonable regulatory pathways are essential components of a healthy, viable, and

Table 1 Treatment strategies beyond targeting glycemic control, therapeutic goals, and ideal treatment characteristics for each stage of type 1 diabetes

Disease stage(s)	Treatment strategy	Overall goals	Ideal treatment/strategy characteristics	Limitations of current therapeutic options
Pre-stage 1	Early detection and prevention	Identify individuals at risk for T1D as early as possible Prevent immune system activation before islet autoantibodies appear Prevent diabetic ketoacidosis	Risk assessment based on islet autoantibody, genetic, and metabolic status, and/or other factors Globally available population level screening programs Point-of-use assays	Risk assessment primarily based on autoantibody status General population screening only available in limited geographies Lack of widespread screening adoption
Stage 1 Stage 2	Prevent, halt, or delay disease progression	Slow or stop autoimmune attack Preserve beta cell function Maintain insulin independence Prevent or delay progression to dysglycemia (i.e., from stage 1 to 2) or symptomatic disease (i.e., from stage 2 to 3)	Sustained or permanent (e.g., > 10 years) treatment effect Simple, available, least invasive administration Low or negligible risk profile Indicated for all ages across pre-symptomatic stages	No therapies available in stage 1 T1D Single therapy available in the US to delay progression to stage 3 by ~ 2 years (teplizumab) 14 day infusion required Indicated for adults and children aged 8 years or older with stage 2 T1D
Recent onset Stage 3	Preserve beta cell function	Preserve residual or restore lost beta cell function Maintain remaining endogenous insulin production Minimize use and burden of care with exogenous insulin Extend honeymoon period, improve glycemic control Reduce risk of treatment related adverse events (e.g., hypoglycemia) Relieve psychological distress	Sustained or permanent treatment effect Simple, available, least invasive administration Low or negligible risk profile Indicated for all ages	No therapies currently available

Table 1 continued

Disease stage(s)	Treatment strategy	Overall goals	Ideal treatment/strategy characteristics	Limitations of current therapeutic options
Stage 4	Restore insulin independence	Provide functioning healthy beta cells Eliminate reliance on exogenous insulin Reduce risk of disease and treatment related complications Prevent autoimmune reactivation	Renewable cell source No broad immunosuppression Provides complete insulin independence Minimal or non-invasive administration Sustained or permanent duration	Single therapy available in the US (donislecel) Therapy available for very limited patient population using non-renewable cell source (deceased donor) Chronic broad immunosuppression required Multiple transplants potentially required Complete and sustained insulin independence not achieved in all patients

T1D type 1 diabetes

inviting product development ecosystem. This has not always existed in T1D, evidenced by the recent history of several sponsors halting or significantly diminishing their T1D programs in response to perceptions of an unfavorable regulatory landscape, in some cases even after positive clinical trial results.

Other autoimmune diseases have well-established regulatory pathways to move beyond treating disease symptoms to modifying the underlying disease itself. In rheumatology, for example, more than a dozen Disease-Modifying Antirheumatic Drugs, or DMARDs, are available. People with rheumatoid arthritis no longer rely solely on painkillers, as was the case in the first half of the twentieth century. Solutions to regulatory challenges in T1D have been identified, and we must work together urgently to implement these solutions.

Assessing Benefits and Risks Through the Eyes of Those with T1D

Decisions to approve any new therapy fundamentally center on whether the benefits of a therapy justify the associated risks. Benefits must be clinically meaningful to people living with the disease, and risks must be tolerable in the short- and long-term when measured against the risks and burden of living with the disease. A product can only be approved when the totality of available evidence, along with the uncertainties in that evidence and risk management strategies, supports a favorable benefit-risk assessment [35].

The benefit/risk paradigms employed by regulators often fail to account for the lived experiences and outcomes of those living with T1D. A product's risks and benefits cannot be weighed against the view that T1D is adequately managed with insulin and technology. This does not reflect the reality for most with T1D and prevents innovation toward new therapeutic regimens. The magnitude of benefits required to outweigh a product's risks should be determined by people living with T1D and no one else.

Incorporating patient perspectives into regulatory decision-making, often called "patient-focused drug development," helps facilitate patient enrollment, reduces patient burden in

clinical trials, and informs the acceptability of tradeoffs between treatment benefits and risks, among other stated benefits [36]. For example, an investigational product may demonstrate equivalent HbA1c effects as standard-of-care therapy but decrease diabetes-related distress or fear of hypoglycemia. It would, therefore, benefit patients and improve the standard of care, assuming all else was equal. Unfortunately, there is currently an absence of validated measures accepted by regulators to inform approvals that capture patient perspectives to inform these decisions.

Providing robust patient preference data on risk tolerance also ensures important regulatory decisions align with the views of patients. A salient example is seen in cell replacement therapies, which often result in complete insulin independence or reliance on little insulin while providing more day-to-day predictability and protection from hypoglycemia. The only available form of this kind of therapy requires using long-term immunosuppression, which is associated with significant adverse events and included as part of the overall risk of cell replacement therapy. However, it is imperative that regulators do not overweigh the risk of immunosuppression in the context of the risks of living with T1D without adequately determining the preferences of those living with T1D.

Another example involves the selection of a clinical trial population. In most cases, the current regulatory perceptions of the risks associated with cell therapies for T1D only allow for participation by those with the most severe cases of T1D—with frequent severe hypoglycemia or hypoglycemia unawareness. However, given the daily lived experience of those in the T1D community, it is reasonable to expect many would welcome the opportunity to join a clinical trial that offered respite from the burdens of insulin, despite the possibility of trading old risks for those associated with novel therapies. Limiting clinical trials to select and small populations lengthens the development pathway, discourages additional innovation and investment, and slows the pace of cures becoming available.

Validation of New Endpoints

HbA1c and hypoglycemic events are the primary measures accepted by regulators to assess therapies targeting glycemic control. These outcomes are well suited for this purpose, but they are not ideal endpoints for trials of novel curative treatment approaches.

For example, disease-modifying therapies aim to preserve existing beta cell function, which is well established to improve T1D outcomes, including lowered hypoglycemia, improved HbA1c, and reduced long-term complications [37]. In trials of disease-modifying therapies, especially in the early period after insulin is required (i.e., new-onset stage 3 T1D), HbA1c and hypoglycemia are not practical or ideal endpoints. With the increasing utilization of diabetes technologies, the heterogeneity of stage 3 T1D, and the variability in insulin requirements across a population, trials using these endpoints must be large and/or lengthy, decreasing feasibility and strongly disincentivizing product development. The established surrogate endpoints are impractical and introduce unnecessary barriers for product developers.

The T1D research community and experts have widely accepted that measuring beta cell function and insulin production, typically via C-peptide levels, is a more appropriate trial endpoint [38, 39]. C-peptide is a direct byproduct of insulin production, produced and secreted in equimolar concentrations to insulin, and is not a component of exogenous insulin formulations. Changes in C-peptide are also easier to assess in the timeframe of a clinical trial. Evidence supporting the validation of C-peptide continues to be published [37], including a recent meta-analysis of participant-level data from 21 randomized control trials [39].

However, the US Food and Drug Administration (FDA) has stated that C-peptide is only acceptable as a "reasonably likely surrogate endpoint," capable of supporting accelerated approval. This requires post-marketing phase 4 studies and limits the viability of some drug programs [40]. Similarly, the European Medicines Agency (EMA) considers C-peptide an unvalidated surrogate endpoint that cannot support marketing authorization. As such, trials must

continue to be designed with endpoints that complicate and lengthen development.

The advent of CGMs has also allowed for more direct and timely measurement of glucose levels than HbA1c can provide. Data collected by CGMs provide significant information regarding glycemic status, standardized CGM-derived metrics are used by patients and clinicians to guide day-to-day management, and CGM data are acknowledged and accepted by patients and healthcare providers as informative for managing T1D [41]. CGM-derived metrics could provide valuable and efficient means to assess the effects of novel therapies, and international consensus has been published on their role in clinical trials [42]. However, most CGM metrics, including those recommended by international consensus, are not currently accepted as primary endpoints by most regulators.

Additionally, patient-reported outcomes (PROs), clinically important aspects of care reported directly by the patient without interpretation or amendment from any others [43], can be used as primary or secondary outcomes in clinical trials to support product approvals if appropriately validated. Of the over 200 T1D PRO measures reported in scientific literature, only the Insulin Dosing Systems Perceptions, Ideas, Reflections, and Expectations (INSPIRE) tool [44] is accepted by regulators as part of medical device development. None of the existing PROs have been validated for use in drug or biologic trials.

Access to Expedited Programs

Finally, the pace of progress is directly related to the number of companies researching T1D and the magnitude of their commitment to the disease. To meet the pressing needs of those with T1D, regulatory pathways intended for products that treat serious and life-threatening diseases must be clearly available. Clearly defined T1D drug development tracks will help entice sponsors and attract increased investment.

The examples discussed here provide a glimpse into a few approaches to improving drug development in T1D, how we measure benefit, and how we benchmark risk. Many other opportunities have been identified that can further streamline the development pipeline, including better screening and early detection, trial enrichment strategies, advancing the role of relevant biomarkers, and increasing clarity on regulatory thinking on these and other topics.

THE FUTURE FOR T1D

In the years before the discovery of insulin, a diabetes diagnosis during childhood was essentially a death sentence. Today, individuals with T1D, especially in high-income countries, can expect to live longer, healthier lives than ever before. However, despite significant progress, T1D still results in premature death, reduced life expectancy, and a substantial daily burden for those affected. T1D remains a challenging, lifelong condition that demands constant vigilance and emotional and mental resilience and has a significant social and economic impact.

The reality of living with T1D is far from "good enough." People with T1D still face the relentless nature of relying on insulin to manage blood glucose as well as constant risks of complications and the social, emotional, and psychological burdens of the disease. For the T1D community, the ultimate goal is no longer just survival but a life free from the daily challenges posed by the disease.

As we look to the future, there is a strong call for more aggressive global action towards curing T1D. This includes exploring disease-modifying therapies and accelerating research into potential cures that go beyond managing symptoms. Regulatory pathways must evolve to support innovation, and widespread screening and early detection are needed to enable prevention or delayed disease onset. A focus on patient-centered approaches, incorporating the experiences and needs of those living with T1D, is essential for driving meaningful change.

The vision of a future without T1D can be achieved but is only possible when we enable innovation and orient regulatory pathways to foster and accelerate development. Through collaboration across the global T1D community, including researchers, sponsors, clinicians,

people living with T1D and their advocates, and policymakers, T1D has the potential to stand out as a shining example of success.

Today, we see a cresting wave of technological advances and innovation that gives us hope for the future. We must accelerate this work. As we look toward the future, we see cures are in reach, and we will not stop until we break through.

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Ethical Approval. The information presented in this article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. Buse JB, Davies MJ, Frier BM, Philis-Tsimikas A. 100 years on: the impact of the discovery of insulin on clinical outcomes. BMJ Open Diab Res Care. 2021;9(1):e002373.

2. Gregory GA, Robinson TIG, Linklater SE, et al. Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. Lancet Diabetes Endocrinol. 2022;10(10):741–60.

3. Fang M, Wang D, Echouffo-Tcheugui JB, Selvin E. Age at diagnosis in US adults with type 1 diabetes. Ann Intern Med. 2023;176(11):1567–8.

4. Ebekozien O, Mungmode A, Sanchez J, et al. Longitudinal trends in glycemic outcomes and technology use for over 48,000 people with type 1 diabetes (2016–2022) from the T1D exchange quality improvement collaborative. Diabetes Technol Ther. 2023;25(11):765–73. https://doi.org/10.1089/dia.2023.0320.

5. Secrest AM, Washington RE, Orchard TJ. Mortality in type 1 diabetes. In: Cowie CC, Casagrande SS, Menke A, et al., editors. Diabetes in America. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases (US); 2018. http://www.ncbi.nlm.nih.gov/books/NBK567986/.

6. Diabetes mortality and trends before 25 years of age: an analysis of the Global Burden of

Disease Study 2019. Lancet Diabetes Endocrinol 2022;10(3):177–92.

7. Global Impact. [cited 2025 Feb 18]. https://dashboard.t1dindex.org/global-impact.

8. Smith R, Eisenberg S, Turner-Pfifer A, et al. We are on the verge of breakthrough cures for type 1 diabetes, but who are the 2 million americans who have it? J Health Econ Outcomes Res. 2024;11(2):145–53.

9. Insel RA, Dunne JL, Atkinson MA, 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):1964–74.

10. Bazile C, Abdel Malik MM, Ackeifi C, et al. TNF-α inhibitors for type 1 diabetes: exploring the path to a pivotal clinical trial. Front Immunol. 2024;15:1470677. https://doi.org/10.3389/fimmu.2024.1470677/full.

11. Aanstoot H-J, Varkevisser RDM, Mul D, et al. Cohort profile: the 'Biomarkers of heterogeneity in type 1 diabetes' study—a national prospective cohort study of clinical and metabolic phenotyping of individuals with long-standing type 1 diabetes in the Netherlands. BMJ Open. 2024;14(6):e082453. https://doi.org/10.1136/bmjopen-2023-082453.

12. Phillip M, Achenbach P, Addala A, et al. Consensus guidance for monitoring individuals with islet autoantibody-positive pre-stage 3 type 1 diabetes. Diabetes Care. 2024;47(8):1276–98.

13. Moffett MA, Buckingham JC, Baker CR, Hawthorne G, Leech NJ. Patients' experience of admission to hospital with diabetic ketoacidosis and its psychological impact: an exploratory qualitative study. Practical Diabetes. 2013;30(5):203–7. https://doi.org/10.1002/pdi.1777.

14. Aye T, Mazaika PK, Mauras N, et al. Impact of early diabetic ketoacidosis on the developing brain. Diabetes Care. 2019;42(3):443–9.

15. Duca LM, Reboussin BA, Pihoker C, et al. Diabetic ketoacidosis at diagnosis of type 1 diabetes and glycemic control over time: The SEARCH for diabetes in youth study. Pediatr Diabetes. 2019;20(2):172–9.

16. Grauslund J, Green A, Sjølie AK. Prevalence and 25 year incidence of proliferative retinopathy among Danish type 1 diabetic patients. Diabetologia. 2009;52(9):1829–35.

17. Perkins BA, Bebu I, de Boer IH, et al. Risk factors for kidney disease in type 1 diabetes. Diabetes Care. 2019;42(5):883–90.

18. Livingstone SJ, Looker HC, Hothersall EJ, et al. Risk of cardiovascular disease and total mortality in adults with type 1 diabetes: Scottish registry linkage study. PLoS Med. 2012;9(10): e1001321.

19. Schofield J, Ho J, Soran H. Cardiovascular risk in type 1 diabetes mellitus. Diabetes Ther. 2019;10(3):773–89.

20. Kristófi R, Bodegard J, Norhammar A, et al. Cardiovascular and renal disease burden in type 1 compared with type 2 diabetes: a two-country nationwide observational study. Diabetes Care. 2021;44(5):1211–8.

21. Lind M, Svensson A-M, Kosiborod M, et al. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med. 2014;371(21):1972–82.

22. Gonder-Frederick L, Nyer M, Shepard JA, Vajda K, Clarke W. Assessing fear of hypoglycemia in children with Type 1 diabetes and their parents. Diabetes Manag (Lond). 2011;1(6):627–39.

23. Lin YK, Fisher SJ, Pop-Busui R. Hypoglycemia unawareness and autonomic dysfunction in diabetes: lessons learned and roles of diabetes technologies. J Diabetes Investig. 2020;11(6):1388–402.

24. Marinac M, Sutphin J, Hutton C, Klein K, Sullivan S, Mansfield C. Preferences for outcomes among adults with type 1 diabetes and caregivers of children with type 1 diabetes. Patient Prefer Adherence. 2020;14:1719–31.

25. Peter ME, Rioles N, Liu J, et al. Prevalence of fear of hypoglycemia in adults with type 1 diabetes using a newly developed screener and clinician's perspective on its implementation. BMJ Open Diabetes Res Care. 2023;11(4):e003394.

26. Diabetes and Emotional Health Workbook | American Diabetes Association. https://professional.diabetes.org/professional-development/behavioral-mental-health/MentalHealthWorkbook.

27. Gopisetty D, Levine B, Liu N, et al. How does diabetes affect daily life? A beyond-A1C perspective on unmet needs. Clin Diabetes. 2018;36(2):133–7.

28. DeSalvo DJ, Noor N, Xie C, et al. Patient demographics and clinical outcomes among type 1 diabetes patients using continuous glucose monitors: data from T1D exchange real-world observational study. J Diabetes Sci Technol. 2023;17(2):322–8. https://doi.org/10.1177/19322968211049783.

29. Fisher L, Hessler D, Polonsky W, Strycker L, Masharani U, Peters A. Diabetes distress in adults with type 1 diabetes: prevalence, incidence and change over time. J Diabetes Complications 2016;30(6):1123–8.

30. Holt RIG, de Groot M, Golden SH. Diabetes and depression. Curr Diab Rep. 2014;14(6):491.

31. Abdoli S, Miller-Bains K, Burr EM, Smither B, Vora A, Hessler D. Burnout, distress, and depressive symptoms in adults with type 1 diabetes. J Diabetes Complications. 2020;34(7): 107608.

32. Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research. Benefit-risk assessment for new drug and biological products. 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-assessment-new-drug-and-biological-products.

33. Provention Bio, Inc. TZIELD (teplizumab-mzwv) injection, for intravenous use. In: FDA.gov. 2022. Silver Spring (MD): US Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761183s000lbl.pdf.

34. CellTrans Inc. LANTIDRA (donislecel-jujn) allogeneic pancreatic islet cellular suspension for hepatic portal vein infusion. In: FDA.gov. 2023. Silver Spring (MD): US Food and Drug Administration. https://www.fda.gov/media/169920/download.

35. The United States Food and Drug Administration. CDER patient-focused drug development. FDA. 2025. https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development.

36. Critical Path Institute. Design of clinical trials in new-onset type 1 diabetes: regulatory considerations for drug development. C-Path.org. 2021. https://c-path.org/design-of-clinical-trials-in-new-onset-type-1-diabetes-regulatory-considerations-for-drug-development/.

37. Latres E, Greenbaum CJ, Oyaski ML, et al. Evidence for C-peptide as a validated surrogate to predict clinical benefits in trials of disease-modifying therapies for type 1 diabetes. Diabetes. 2024;73(6):823–33.

38. Palmer JP, Fleming GA, Greenbaum CJ, et al. C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, 21–22 October 2001. Diabetes. 2004;53(1):250–64.

39. Taylor PN, Collins KS, Lam A, et al. C-peptide and metabolic outcomes in trials of disease modifying therapy in new-onset type 1 diabetes: an individual participant meta-analysis. Lancet Diabetes Endocrinol. 2023;11(12):915–25.

40. Wood Heickman L. APPLICATION NUMBER: 761183Orig1s000. 2022. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/761183Orig1s000MedR.pdf.

41. American Diabetes Association Professional Practice Committee, ElSayed NA, Aleppo G, et al. Diabetes technology: standards of care in diabetes—2024. Diabetes Care. 2024;47(Supplement_1):S126–44.

42. Battelino T, Alexander CM, Amiel SA, et al. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. Lancet Diabetes Endocrinol. 2023;11(1):42–57.

43. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. 2021. https://www.ncbi.nlm.nih.gov/books/NBK326791/pdf/Bookshelf_NBK326791.pdf.

44. MDDT Qualification Program. MDDT summary of evidence and basis of qualification decision for INSPIRE questionnaires. 2019. https://www.fda.gov/media/139432/download?attachment.