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System Failure in Type 1 Diabetes: What Stakeholders Need to Know to Expedite Therapeutic Options

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Abstract

There has been a systemic failure in type 1 diabetes. Regulatory barriers and clinical trial design challenges discourage development of new type 1 diabetes therapies and can compromise the potential for securing approval of new treatments. As a result, there continues to be a pervasive unmet need for those living with type 1 diabetes, resulting in long-term complications, extreme disease management burdens, and psychosocial consequences. People with type 1 diabetes continue to make multiple daily decisions about dosing insulin, a drug that can kill with a single mistake and that at best only manages symptoms without changing the underlying progression of the disease. Further, beyond regulatory challenges, gaps in health care professionals' knowledge and understanding of the disease affect quality of care. The goal of this paper is to educate stakeholders on the extent of this systemic failure and to encourage consideration and dialogue among industry, regulatory agencies, patients, and health care providers to expedite approval of breakthrough therapies that fundamentally change the equation in type 1 diabetes.

Introduction

The discovery of insulin in 1922 vastly changed the prognosis for type 1 diabetes. In the intervening century, management of type 1 diabetes has continued to improve with extensive research and technological advances. But neither insulin nor technology can cure or prevent type 1 diabetes or address its underlying cause or progression. As a result, life with type 1 diabetes continues to be risky and difficult for individuals and their families. The most profound fact to validate this unacceptable reality is this: type 1 diabetes shortens life expectancy by about 12 years, on average (1), largely because patients face enormous difficulty to maintain blood-glucose levels in the recommended target range and thus face life-threatening health complications.

In this paper, we describe the current state of type 1 diabetes through the experiences of three 'personas. Diego, Helen, and Charles are composites of people with different demographics and at different stages of type 1 diabetes. Through their stories, we seek to put a human face on the serious nature of type 1 diabetes and highlight gaps between their needs and the current state of care. Simply put, research, development, and deployment of new therapeutic and curative strategies must be expedited to improve outcomes for the community they collectively reflect.

Impact of Type 1 Diabetes

Complications at onset

As discussed later, long-term health complications from type 1 diabetes can be pervasive and devastating. But type 1 diabetes can have complications right from the start. For example, 9-year-old Diego had been feeling unusually tired for a few days, with excessive

thirst and frequent trips to the bathroom. When his stomach hurt so much he could not get out of bed, his parents brought him to the local emergency room. Testing revealed that Diego had dangerously high blood-glucose levels and diabetic ketoacidosis, a life-threatening complication that requires urgent medical care to avert death. He was diagnosed with type 1 diabetes and admitted for treatment and stabilization. Diego is unfortunately one of many people who experience diabetic ketoacidosis at diagnosis of type 1 diabetes. Diabetic ketoacidosis occurs at or near diagnosis of type 1 diabetes in up to 40–58% of those <18 years old in the US (2,3). It is associated with complications requiring urgent attention, risk of long-term poorly managed diabetes, long-term diabetes-associated complications and comorbidities, and significant health care costs (2). Another common occurrence at the onset of type 1 diabetes is misdiagnosis with type 2 diabetes, which can delay proper treatment.

Challenges of glycemic management

Diego and his family quickly learned that once type 1 diabetes is established, it requires monitoring of blood-glucose levels multiple times throughout the day and administration of exogenous insulin. Glycemic management places an enormous burden on people with type 1 diabetes and those who help care for them. Nineteen-year-old Helen knows this only too well. She has had type 1 diabetes since her early teen years and feels that she can never take a break from even thinking about it, let alone following all the steps necessary to manage it. Although she uses a hybrid closed-loop system in which a continuous glucose monitor and an insulin pump communicate in real time to dose insulin, she still must make numerous diabetes-related decisions throughout the day. She must balance her food intake according to her differing activity levels and always keep snacks on hand, on top of managing her academic, social, and athletic activities and the usual other stresses of everyday life for a young college student. She lives with a persistent fear and concern of low blood sugars or technology failure occurring without warning at any time during her day. She’s constantly either preventing or responding to low alarms on her monitor or having to stop what she’s doing to treat a low blood sugar. Sometimes her insulin pump cannula becomes occluded, and she must stop everything to change her infusion site and respond to the resulting hyperglycemia, and that’s if she has all the supplies needed immediately on hand. All this creates so much anxiety that she doesn’t feel up to having her normal social life. In short, type 1 diabetes is never out of mind, and it can be constantly frustrating and dramatically impact her ability to live her life like her peers.

Charles, who is 53 years old, has lived with type 1 diabetes for much of his life and for decades he has experienced the same fear and anxiety Helen is going through, and that Diego will experience as he grows older. Despite his experience and knowledge, he knows first-hand that the options currently available for glycemic management, while improved, remain frustratingly far from mimicking the body’s natural physiology. Charles uses an automated insulin delivery system , the most advanced treatment currently available, but the technology can be complicated to use and maintain correctly, even for the most sophisticated, knowledgeable, and experienced users. The challenge is even greater when

the technology is used by younger people like Diego who need parental or caregiver support. As a result, many people with type 1 diabetes spend a considerable amount of time every day with blood-glucose levels outside what clinical care guidelines suggest is the safest target range. Registry data demonstrate that only 17% of youth and 21% of adults with type 1 diabetes in the US achieve the average blood-glucose levels recommended by the American Diabetes Association, even with state-of-the-art technology and careful attention to management (4). The challenges of glycemic management put people with type 1 diabetes at greater risk of short- and long-term complications (5), including death.

Short-term complications

Despite their best efforts in managing their diabetes, Diego, Helen, and Charles all regularly experience hypo- or hyperglycemia. Given the considerable improvements in technology and insulins to treat type 1 diabetes, the ability to maintain blood sugars has gotten somewhat less difficult. However, achieving normal blood sugars carries a perpetual risk of hypoglycemia and frequent, multiple daily low blood sugars requiring attention. This means Helen needs to plan before her hockey matches or calculus exams to ensure her blood sugars are optimal and despite best efforts with so many variables to consider (e.g., food intake, hydration, stress, timing of insulin) needs to stop what she's doing and treat before continuing her activities. It will even impact decisions she makes on her future employment choices as the worry about, and the reality of, hypoglycemia and hyperglycemia can affect her during every workday.

Severe hypoglycemia, defined as cases requiring the assistance of another person, can cause seizures, loss of consciousness, and death. Recurrent exposure to hypoglycemia is known to dampen autonomic responses (6) and impair one's awareness of hypoglycemia, as it has for Charles. Being unable to recognize the signs that his blood-glucose level is falling increases his risk of hypoglycemia, unconsciousness, and death. Many people like Charles continue to experience severe hypoglycemia and impaired awareness of hypoglycemia despite using state-of-the-art technology. A recent survey of >2,000 people with type 1 diabetes who use continuous glucose monitors or hybrid closed loop systems found ~20% reported experiencing at least one severe hypoglycemic event and more than 30% reported impaired awareness of hypoglycemia within the prior 12 months (7).

Severe hyperglycemia, on the other hand, can lead to diabetic ketoacidosis, as it did for Diego when he was first diagnosed with type 1 diabetes. But diabetic ketoacidosis can occur in established type 1 diabetes as well. On average, 3% of people with type 1 diabetes reported experiencing at least one diabetic ketoacidosis event in the preceding 3 months[4]. Over 800 Americans with type 1 diabetes die every year from diabetic ketoacidosis (8).

Diabetic ketoacidosis is a real threat for people like Helen. Exhausted by the burden of managing type 1 diabetes and the effort it takes to fit in while living with such a burdensome disease, it can be challenging to keep up with continual infusion set changes,

regularly insert new type 1 diabetes sensors, and remember to order her insulin before it runs out. It's also not uncommon for some people with type 1 diabetes to skip taking insulin altogether – simply because they forgot or in an effort to promote weight loss, as taking insulin can sometimes lead to weight gain. This can raise her risk of developing diabetic ketoacidosis and other serious complications. As discussed below, this behavior reflects some of the psychosocial burdens type 1 diabetes places on people.

Long-term complications

Persistent hyperglycemia contributes to microvascular and macrovascular damage that can lead to longer-term complications, particularly involving the eyes, kidneys, nerves, and cardiovascular system. Between 75% and 82% of people with type 1 diabetes eventually develop diabetic eye disease, which threatens vision in about 30–32% of cases (9); 25–30% develop end-stage kidney disease, which requires dialysis (10); and up to 30% develop peripheral neuropathy, which can result in amputation (11). Charles' hyperglycemia means he is at risk for all these conditions. If he develops end-stage kidney disease, he will likely need to travel to a dialysis center three days per week; each session lasts several hours and could leave him feeling sick and fatigued for hours or days afterward. He is also at risk of developing cardiovascular disease 10 years sooner than if he didn't have type 1 diabetes (12). The bottom line is that current treatments for type 1 diabetes are improved, but many are still facing significant long-term complications. Without continued development of disease-modifying therapies, islet gene editing, or engineered therapies, and better tools and technology, Diego and Helen may face a similar future.

Psychosocial impacts

As mentioned, the burden of managing type 1 diabetes and the risk and occurrence of short- and long-term complications can cause emotional distress along with psychosocial impacts such as anxiety, depression, and disordered eating (13). People with diabetes may feel discouraged, worried, frustrated, tired of dealing with daily diabetes care, or disappointed if their disease management is not yielding the desired results or they experience a diabetes-related health problem despite their best efforts (13). Recently diagnosed Diego desperately wants to be on top of his type 1 diabetes because he knows that keeping his glucose levels within the target range increases his opportunity to play soccer and other sports safely. But every time he sees his endocrinologist, it seems like he is told he needs to do better or is doing something wrong. It can be demotivating. Helen, too, feels she is constantly missing the mark, and she sometimes feels a strong sense of failure. Even Charles, who is most experienced with type 1 diabetes, finds the devices he uses to manage diabetes – and the wealth of data they provide – overwhelming. While they often help him get a handle on his blood-glucose levels, they are also a constant reminder of type 1 diabetes and its implications. These feelings, known as diabetes distress (13), may cause people to slip into unhealthy habits, such as neglecting to monitor their glucose levels or meet with their doctors, like Helen has. Diabetes distress often develops after managing type 1 diabetes for years. In any 18-month period, 33–50% of people with diabetes (type 1 or type 2) have diabetes distress (13).

People with diabetes are 20% more likely to have anxiety and 2–3 times more likely to have depression at some point in their life than people without diabetes (13). Up to 60% of youth with type 1 diabetes report depressive symptoms (14). Several recent studies identify higher rates of suicidal ideation, suicide attempts, and suicide among youth and young adults with type 1 diabetes, as compared with their peers without diabetes (15). Helen has both anxiety and depression related to her type 1 diabetes. Attending college a few hours away from home, she feels isolated and alone. She hides her type 1 diabetes from her classmates and friends to avoid being seen as different. She recently stopped using her insulin pump because it attracted too much attention. She feels anxious about her risk of developing serious complications and thinking about dealing with type 1 diabetes for the rest of her life makes her depressed.

Up to 30% of people with type 1 diabetes are estimated to have disordered eating, making it twice as common in people with type 1 diabetes than people without the condition (16). Deliberate restriction or withholding of insulin to lose weight (a behavior sometimes called diabulimia) is common among individuals with type 1 diabetes (17). Doing this can increase risk of hyperglycemia and its attendant short- and long-term complications.

Obtaining medical care

Italy became the first country to require universal screening of children ages 1-17 for type 1 diabetes, and some screening is also conducted in Australia, the Czech Republic, Denmark, Germany (Fr1da), Poland, Portugal, Sweden, the United States, and the UK (18, 19). Still, in most countries, most children like Diego are diagnosed in the emergency room or, depending on where they live in the world, by a general practitioner, primary care provider or family physician, pediatrician, or endocrinologists after symptoms appear. These symptoms can cause initial misdiagnosis of a stomach illness, flu, or other viral syndrome, increasing the chances of diabetic ketoacidosis. Even after diagnosis, many Americans with diabetes continue to rely on a general practitioner for their care due to the shortage of specialists with experience and expertise in diabetes (20). A significant fraction of people with type 1 diabetes do not receive any care from an endocrinologist (21). One study found that over 50% of people in a specific trial had not seen an endocrinologist over the past year or since diagnosis (21). General practitioners receive little training in complex diabetes care (20). In one survey, health care professionals indicated that current health care in diabetes was inadequate; up to 33% indicated having no formal diabetes training (22). General practitioners typically aren’t familiar with and lack the team support for the latest diabetes technologies and treatments (20), which continue to increase in scale and complexity.

Access to knowledgeable endocrinologists greatly benefits type 1 diabetes management and outcomes. However, it can be difficult for people with type 1 diabetes to find an experienced endocrinologist to help them, due to geography, access challenges, or affordability issues. There is a shortage of endocrine specialists, and many are focused on other areas of endocrinology, not type 1 diabetes, so even they may have gaps in

knowledge as it relates to type 1 diabetes and available therapies and technologies (20). Given the relative shortage of specialists, it can take months to get an appointment. Diego's parents, for example, struggle to find qualified medical professionals with state-of-the-art knowledge about type 1 diabetes and its management and treatment.

Beyond the challenges described above, socioeconomic disparities impact both access to, and quality of, care in the United States and around the world. Lack of health insurance or limited coverage, living in rural areas or areas with low socioeconomic status, limited access to broadband services and digital technologies, are all variables that compromise access to the highest quality care for all forms of diabetes. Looking ahead and anticipating the emergence of more advanced and costly therapies, there is a genuine risk that the socioeconomic obstacles could put these breakthroughs beyond the reach of a substantial part of the type 1 diabetes population (23, 24).

Equally important, access to mental health support professionals familiar with type 1 diabetes is also limited. For example, only 25–50% of people with diabetes who have depression are diagnosed and treated (13). In a survey of health care providers, about 63% indicated that health care systems are poorly equipped to provide psychosocial support for people with diabetes (22). Only 52% of the health care providers indicated that they ask patients how diabetes is affecting their lives (22).

In summary, there remain major gaps in health care providers' understanding, knowledge, and standard of care for type 1 diabetes patients.

Addressing unmet needs in type 1 diabetes

These data about the health and wellbeing of people with type 1 diabetes are sobering and point out how much more could be done to meet their needs. Below, we discuss some of the many opportunities to improve outcomes for this community.

Facilitate early diagnosis

Timely diagnosis of type 1 diabetes is essential to prevent diabetic ketoacidosis. Type 1 diabetes progresses through two predictable presymptomatic stages (Stages 1 and 2) prior to the onset of symptomatic disease in the final clinical stage (Stage 3) (25). These stages are defined by the presence of type 1 diabetes-related autoantibodies and of dysglycemia. Screening for diabetes related autoantibodies and monitoring for dysglycemia can identify those at risk of developing clinical type 1 diabetes very early (19) – like Diego – before they develop any symptoms and thus preventing the need for hospitalization. They can be closely monitored to prevent diabetic ketoacidosis, and they may also be eligible for research to find more therapies, and ultimately a cure, and the opportunity for therapies that can impact the disease progression and delay the onset of symptomatic type 1 diabetes. For Diego, delaying type 1 diabetes would have meant more time without the fear, burden, and the anxiety of type 1 diabetes; a lower risk of complications; and a better

quality of life. Most people living with type 1 diabetes will tell you a day without the disease would be a gift and months or years would be life changing.

Improve treatments and tools

Until the disease can be cured, insulin therapy is essential for people with type 1 diabetes. Insulin is self-administered, and dosing must be carefully matched to metabolic needs to avoid life-threatening complications. It is virtually impossible to continuously achieve this intricate coordination using currently available options for administering exogenous insulin. Although insulins have improved vastly over the years (26), substantial progress is still required. Longer-lasting basal insulins and faster-acting bolus insulins would improve glycemic management. Next-generation drugs like glucose-responsive insulin (27) and liver-targeted insulin (28) are also being investigated. In addition, the potential of combination and adjunct therapies (29), such as pramlintide coformulations, SGLT-2 inhibitors, and GLP-1 inhibitors, to improve glycemic management in people with type 1 diabetes is being tested, although these drugs are not yet approved for use in type 1 diabetes (30). Better insulins and adjunctive therapies could help those like Charles reach and maintain their glycemic targets, improving their quality of life every day and lowering their risk for both hypoglycemia and complications now and in the future. Hurdles for adjunct therapies to reach people with type 1 diabetes are multiple, ranging from industry prioritizing such therapies for the much larger type 2 diabetes population like hesitance of industry to explore the potential in a rather limited market, but also challenges among regulators to allow clinicians and those living with type 1 diabetes to weigh benefits and risks of adjunct therapies themselves.

As insulins have improved, so have tools like continuous glucose monitors, insulin pumps, and hybrid closed loop systems (31). Use of such tools is associated with better glycemic management and lower risks of short- and long-term complications (32). While their use is increasing among people with type 1 diabetes, many with type 1 diabetes still don't use them. In the US, only 37% of adults and 47% of children are using continuous glucose monitors (33).

Despite the technological advances they embody, today's tools are complex and burdensome (34) and carry with them a risk of malfunction or failure (35). Their operation requires technological literacy and a high degree of user involvement (34) to ensure the technology is working appropriately and, in the case of automated insulin devices, communicating effectively. Maintaining coverage and ensuring that supplies are ordered and always on hand is required. Helen struggles to always have backup supplies with her – this is essential when technology fails – no matter where she is or what she is doing. Features that offer additional automation of insulin delivery and improvements to form factor and usability could encourage broader adoption. Helen and others like her would be more likely to use type 1 diabetes options consistently if they were less intrusive and were confident of accessibility and coverage; using these tools would make their daily lives safer

and healthier. In short, assuming that existing management tools are sufficient to ensure optimal outcomes and disease control would be profoundly incorrect.

Pursue a cure

Type 1 diabetes is not yet curable, but various therapeutic pathways that could lead toward a cure are being explored. The historical benefits, limitations, and future directions of using deceased donor sources of islet cells for type 1 diabetes have been well documented (36). Also, the first immune therapy that modifies the underlying disease process and reduces or even eliminates the need for exogenous insulin is now being used in clinical practice. Development of novel therapeutic modalities like cellular and gene therapy and immunotherapies present new opportunities and challenges, and regulatory agencies should ensure their staff include experts who can provide regulatory oversight of clinical studies, along with proactive scientific and regulatory advice to medical researchers and manufacturers to support product development. While safety and efficacy must remain the touchstone of any regulatory approval process, given the overall poor health outcomes of too many people with type 1 diabetes, regulators must work together with sponsors in an open and creative way to overcome potential obstacles to efficiently designing pivotal clinical trials. In particular, full support for research looking for biomarkers that will allow novel trial designs and guide the development of therapies towards personalized medicine would be extremely helpful.

Accelerating pathways to regulatory approval

To reach Diego, Helen, Charles, and everyone with type 1 diabetes, potentially curative therapies and advanced management strategies must move along clear and reasonable pathways to regulatory approval. Regulatory authorities delineate such pathways and, in doing so, have several opportunities to facilitate progress. Specifically, as detailed below, regulators should: a) refocus benefit-risk determinations; b) accept additional benefit measures beyond hemoglobin A1C (HbA1C) levels such as stimulated c-peptide and time-in-range, and c) providing explicit regulatory guidance for novel therapeutics.

Benefit-risk assessment

Assessment of a therapy's benefits and risks is at the crux of regulatory agency review, which ultimately determines its availability to people with type 1 diabetes. Benefit-risk assessments often focus on people who are not meeting glycemic targets and the risk of adverse events related to a therapeutic strategy. Going forward, a broader risk assessment calculation must be adopted that is more deeply informed by the perspectives and preferences of those living with type 1 diabetes, and that takes into account the high rate of unmet need in people with type 1 diabetes, the poor health outcomes they face, the psychosocial effects, and the real risk of dangerous, potentially fatal, complications each person with the disease faces daily. Regulators must also be sensitive to the fact that risk tolerance varies among individuals and can be influenced by disease stage, age, and life circumstances.

New advances in treatment and management will improve health outcomes for people with type 1 diabetes and bring tremendous relief to the overwhelming mental burden that the disease can impact on those who live with it. Thus, considering the risk associated with type 1 diabetes itself and the implications of inhibiting such advances from reaching patients in a timely manner would make benefit-risk assessments fairer, more balanced, and more effective. For Charles, next generation therapies, such as cell replacement, could mean he no longer needs insulin or complicated devices. He may no longer need to live with the sense of failure that he sometimes has when he simply cannot get his blood glucose levels consistently in a safe range, and the accompanying worry about hypoglycemia or diabetic ketoacidosis. Simply put, he can lead a life without constantly worrying about type 1 diabetes, and the voice of Charles and others those living with type 1 diabetes (and their clinicians) should be clearly heard in the regulatory risk assessment.

By rethinking the components of benefit and risk, and the need for different treatment options that cater to the needs of persons living with type 1 diabetes and their differing circumstances, regulatory authorities can better support the type 1 diabetes community and improve outcomes for this population.

Additional benefit measures

The efficacy of a therapeutic strategy is an essential component of a benefit-risk assessment. Measures of efficacy that are typically accepted by regulatory authorities include reductions in hemoglobin A1C (HbA1C) level, risk of hypoglycemia, and risk of complications for strategies intended to improve glycemic control and time to clinical onset of type 1 diabetes for strategies intended to prevent or delay the onset of type 1 diabetes (37).

Use of these endpoints makes sense in some cases, such as insulins or GLP-1s, but has certain drawbacks as more innovative therapies proceed down the developmental pipeline. For example, effect on HbA1C can be difficult if not impossible to determine while insulin is being used (38). Standard of care with advanced insulins and technology allows for both active and placebo treatments to have similar effects on HbA1C. The expectation should be that HbA1C at the end of a trial should be similar in both groups as evidence that proper standard of care was provided, thus allowing for evaluation of other primary endpoints such as stimulated C-peptide in immunotherapy trials. A non-inferior HbA1C, as an indicator of similar standards of care, also allows for secondary endpoints such as type 1 diabetes measure of time in range, insulin use, and hypoglycemia to be fairly compared with both treatment and placebo groups. HbA1C also does not reflect daily variations in glycemic levels that can largely determine what it feels like to live with type 1 diabetes. HbA1C levels that meet recommended targets are not reflective of day-to-day life with diabetes. HbA1C levels reflect average blood-glucose values over ~3 months; large swings of both highs and lows and more steady blood-glucose values can both produce the same HbA1C reading. This variability with such a narrow target time in range (70–180 mg/dL) leads to people having daily challenges with hyperglycemia, and if not there is a perpetual fear of hypoglycemia. Many people with type 1 diabetes may have HbA1C levels within the target range but still experience nighttime hypoglycemia that leaves them and their caregivers terrified and exhausted. Further, HbA1C is less relevant as an endpoint for DMTs that aim to maintain insulin production rather than manage blood-glucose levels. Type 1 diabetes is an autoimmune disease rather than a metabolic disease, but endpoints such as HbA1C offer metabolic information and do not reflect immune status or disease progression. There is the potential for HbA1C to show a difference between treatment and placebo groups as shown in a large meta-analysis of only positive studies with multiple DMTs (39), but these trials would require impractical and potentially prohibitive large numbers and/or duration. Symptomatic type 1 diabetes can take years to develop in those who are at risk, extending the length and cost of clinical trials, and even discouraging the development of therapies that could be used at earlier stages of disease, essentially before end organ failure, that would have to run such a gauntlet (13). Therefore, there is an extreme urgency to agree upon the use of additional criteria as measures of efficacy, including endpoints that provide more insight into daily treatment effects rather than longer-term outcomes.

C-peptide is a byproduct of insulin processing that can be used as a biomarker for beta cell function. A recent review of the evidence concluded that C-peptide is a surrogate endpoint

to predict clinical benefits in clinical trials of DMTs aiming to preserve or replace beta cell function (37). Using C-peptide as the acceptable regulatory endpoint for disease modifying therapies in type 1 diabetes as a measure of beta cell preservation would facilitate availability and further study of combinations with new therapies.

Other measures of efficacy could be derived from the volumes of glycemic data generated by type 1 diabetes. Because they take readings every few minutes, type 1 diabetes can provide detailed glycemic information (40) on much shorter time scales (daily, weekly, or monthly), yielding insights that cannot be gleaned from HbA1C levels. Standardized formats for reporting type 1 diabetes-derived metrics have been developed, and they are considered relevant, reliable outcome measures in type 1 diabetes (41). A recent consensus statement (40) recommended that they be considered for use in all clinical studies in diabetes. Currently, type 1 diabetes measures are not recognized as a primary endpoint for DMTs.

Time in range is one such type 1 diabetes-derived metric – the proportion of time that one's glucose levels are within an optimal glycemic range, which is typically 70–180 mg/dL. Time in range reflects changes in medication, diet, and lifestyle, providing actionable information for people with diabetes and is clinically considered one of the most relevant variables and topics of discussion for goals in the care of patients with type 1 diabetes (37, 41). Almost 60% of people with type 1 diabetes indicated that time in range has a big impact on their daily life, compared with about 30% who said the same for HbA1C (42).

As is evident in the stories of Diego, Helen, and Charles, type 1 diabetes has enormous impacts on people's quality of life. Lessening the burden of living with type 1 diabetes is a laudable goal, and improvements to quality of life should be considered as a benefit when evaluating technologies for managing type 1 diabetes. Considering type 1 diabetes-derived metrics like time in range in benefit-risk assessments would help to incorporate patient perspectives and accelerate the development of therapies that reduce the burden and improve quality of life with type 1 diabetes. These metrics could also lead to a more rapid clinical assessment of therapeutic options.

Offer guidance

Researchers, industry sponsors, and regulatory agencies need a consistent, clear understanding of how to weigh benefits and risks for new and emerging therapies. To create this common understanding, regulatory authorities should develop and share guidance that reflects the agency's thinking and be open to consider adapting as the science evolves. Such guidance is particularly important for novel therapeutic modalities and approaches for which there is no precedent.

Regulatory guidance and open dialogue with experts in early type 1 diabetes are needed for several questions. What approaches and outcomes might be acceptable in early type 1 diabetes for preservation or replacement of beta cells and prevention of further disease progression? What are agencies' expectations and requirements for novel agents such as

immunotherapies and cell therapies? A shared understanding and open dialogue of regulatory authorities' thinking is key to advancing new therapies in a progressing field. The previously mentioned recent approval of the first and only disease modifying therapy for type 1 diabetes has accelerated interest in development of more therapies. This momentum needs to be maintained, and we should work to ensure regulatory barriers are lifted to support incentives for future advancements in the field.

Improve access to tools and education

Many people in the U.S. have difficulty accessing tools and treatments for managing type 1 diabetes (43), including insulin and technology, which can hinder optimal glycemic management and lead to worse outcomes. Access and education can be diminished due to lack of coverage, shortage of primary care access in certain communities and regions, gaps in knowledge about type 1 diabetes, gaps in awareness among providers of available technologies, and limitations among providers in providing training to patients on how to use these technologies. Barriers to access are often greater for underserved and underrepresented populations (44, 45). Diego's parents, for example, are not native English speakers and are overwhelmed by the sheer volume and complexity of information that is now crucial to Diego's health and the limited availability of resources in their native language. They worry about how they will obtain, afford, and maintain supplies important for continued use of technology like type 1 diabetes and insulin pumps, which they have only just learned about.

Even in Europe, where most tools are covered in the health care insurance systems, access remains limited. This limitation ensues mainly from reimbursement barriers, e.g. limiting automated insulin delivery systems to those who already have experienced a severe hypoglycemic attack. Also access to education by specialist teams is an issue in many health care systems. Finally, in emerging economies, access to novel technologies is even more problematic, with access only available to the most economically strong subsections of the population, leaving most with only limited therapeutic options.

Efforts to secure insurance coverage for and affordability of type 1 diabetes tools and treatments must continue to help ensure that everyone with type 1 diabetes has access to them. These efforts should address new and emerging treatments as well, as broad access is essential to encourage their ongoing development.

Conclusion

It is sometimes said that the availability of insulin turned a type 1 diabetes diagnosis from a death sentence into a life sentence. Indeed, more than a century since insulin was first used to treat it, type 1 diabetes remains an incredibly burdensome and high-risk disease. This paper has identified a number of therapeutic advances and practices that are within our sights: a) improved insulins that will act faster and improve glycemic controls, b) more advanced automated insulin delivery systems that can reduce disease burdens, eliminate

the need for meal time boluses, and reduce hypoglycemic events, c) approval of adjunctive therapies, such as GLP-1s for type 1 diabetes, that could improve glycemic controls, reduce insulin needs, contribute to weight loss, and reduce the risks of long-term cardiovascular and kidney complications, d) additional immune therapies that could further delay –or even prevent – disease onset, and e) cell replacement and gene editing therapies that can restore beta cell health and survival, and possibly in combination with immune therapies, offer patients months or even years with dramatically educed burden and risk.

With its incidence increasing, more and more people each year will join Diego, Helen, and Charles in the type 1 diabetes patient community. Investigators, regulatory authorities, and health care stakeholders of all kinds must boldly confront the systemic issues described in this paper to accelerate development and approval of breakthrough therapies that can spare future generations from type 1 diabetes.

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Guarantor Statement
Dr. Colin Dayan is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the paper.

Conflict of Interest Statement

Chantal Matthieu

Chantal Matthieu serves or has served on the advisory panel for Novo Nordisk, Sanofi, Eli Lilly and Company, Novartis, Dexcom, Boehringer Ingelheim, Bayer, Roche, Abbott, Medtronic, Insulet, Biomea Fusion, SAB Bio and Vertex. Financial compensation for these activities has been received by KU Leuven; KU Leuven has received research support for Dr. Matthieu from Medtronic, Novo Nordisk and Sanofi; Dr. Matthieu serves or has served on the speaker's bureau for Novo Nordisk, Sanofi, Eli Lilly and Company, Medtronic, Dexcom, Insulet, Abbott, Vertex and Boehringer Ingelheim. Financial compensation for these activities has been received by KU Leuven. She is president of EASD. All external support of EASD is to be found on www.easd.org.

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Dr. Dayan has lectured for or been involved as an advisor to the following companies: Vielo Bio, Provention Bio, Sanofi, Amarna, Astrazeneca, Shoreline Bio, SAB Therapeutics, Immunocore, Quell, Vertex. Dr. Dayan holds a patent jointly with Midatech plc and Provention Bio/Sanofi.

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