Improving Lives Program Research Strategy

Vision

A world where people with type 1 diabetes (T1D) live healthy and burden-free lives.

Mission

To improve the lives of people living with T1D by accelerating the development of advanced drugs, devices, behavioral health interventions, and combinations of these to improve short-term and long-term health outcomes and quality of life.

Rationale

Despite technological advances, substantial unmet clinical needs remain for people with established T1D, the lifelong period of chronic insulin administration where people have little if any detectable beta cell function. Only 17 percent of youth and 21 percent of adults with T1D achieve the American Diabetes Association's recommended HbA1c targets of <7.5 percent and <7.0 percent, respectively; beyond HbA1c, clinically deleterious hyperglycemia and hypoglycemia remain unacceptably high, affecting both short- and long-term outcomes. Increasing scientific evidence indicates that T1D is a disease not only of glucose but also broader metabolic control, with non-glycemic metabolic imbalances such as obesity and insulin resistance endangering short- and long-term health outcomes. In the long-term, it is estimated that half of people with T1D, if not substantially more, will be affected by diabetic nephropathy (DN) in their lifetime; T1D increases the risk of cardiovascular disease (CVD) many-fold and it is a major cause of mortality in adults with T1D. CVD also accounts for the reduced lifespan in people with T1D compared to non-diabetes individuals. Likewise, a large longitudinal study found that after 25 years, the cumulative incidence of diabetic retinopathy (DR), which includes early stages of disease that precede vision loss, was 97 percent; the 25-year cumulative incidence of proliferative DR was 43 percent. Finally, depression and other mental health challenges are common in people with T1D; for example, in the T1D Exchange clinic registry it was found that up to 10 percent of adults had probable major depression, which correlated with worsened diabetes outcomes such as elevated HbA1c and diabetic ketoacidosis (DKA) events. Clearly, more work is urgently needed to address the unmet clinical needs of people with T1D.

In addition to poor outcomes, people with T1D also must deal with therapies and devices that are inconvenient or burdensome throughout the day and their lifetime. This category includes standard insulin therapy, which must be carefully titrated multiple times a day, and devices that are large and obtrusive. The Improving Lives (IL) program exists to develop drugs, devices, and behavioral health interventions that will not only address unmet clinical needs for people with T1D, but also reduce the burden of T1D self-management and improve quality of life.

Recent years have seen major progress in the development of devices and therapies for T1D. Yet we recognize that the benefits from these advances—pioneered by Breakthrough T1D and others—have been unequally distributed across the population of people with T1D, with outcomes having improved in select T1D subpopulations that adopt and adhere to modern treatments, but not in most people with T1D. The IL program recognizes that in the future too, not everyone with T1D will adopt the most cutting-edge diabetes technologies for various reasons, and we will continuously adapt our strategy to support research to improve the lives of all people with T1D.

Strategy

The Breakthrough T1D IL program's strategy is centered on developing products to improve the health and quality of life of people living with established T1D. We support development of drugs, devices, and behavioral health interventions that improve glucose control, broader metabolic control, mental health, and quality of life, and delay or prevent progression of DN, CVD, and DR. Even though we emphasize product development, Breakthrough T1D will continue to support discovery research that has the potential to ultimately benefit people with T1D; historic Breakthrough T1D support for discovery research has helped make possible many of the life-changing products on the horizon, and continued support of creative, innovative, basic science will play a critical role in building the next generation of therapies.

Products developed through the IL program must be safe, effective, and not produce additional user burden that will prevent adoption or adherence. Products that can achieve multiple clinical outcomes will be prioritized. This includes, for example, drugs and drug combinations that have benefits for glucose control, overall metabolic balance, and diabetic complications. As a general principle, the IL program prioritizes work on products that are at a mature stage of development, especially interventional clinical trials, toward our goal of getting products into the hands of people with T1D in an accelerated manner. We support the development of products that were designed specifically for T1D and those repurposed from other indications (e.g., drugs developed for type 2 diabetes).

While Breakthrough T1D's IL strategy is designed to improve outcomes in people with established T1D, drugs, devices and behavioral health interventions developed for this population may also improve outcomes at earlier stages in T1D progression. For example, adjunctive therapies like GLP1 receptor agonists (GLP-1 RAs) and hybrid closed-loop (HCL) systems are being investigated for their ability to preserve beta cells in new onset T1D. Additionally, interventions designed to improve glucose and metabolic control will likely prove beneficial for optimizing the effectiveness of curative treatments like beta cell replacement therapy or drugs that promote beta cell survival and/or regeneration, by creating a metabolic milieu that allows implanted or endogenous beta cells to thrive. Furthermore, disease-modifying therapies target outcomes of glucose control such as

HbA1c, hypoglycemia, and time in range (TIR) as functional measures of preservation of beta cell function. It is noteworthy that the IL program can also benefit people outside of T1D, such as people with type 2 diabetes (T2D), especially those requiring insulin.

The IL program's approach to achieving our mission is to deploy resources in a strategic manner and form and maintain external partnerships to maximize our efforts. Moving forward, Breakthrough T1D will continue to work to address the needs of people living with T1D and remain a leader in this space.

Drugs and Devices for Glucometabolic Control

Achieving adequate glucose control remains a major challenge for most people with T1D and the inability to do so leads to dangerous acute and long-term complications. Breakthrough T1D supports products that will improve HbA1c and other critical aspects of glucose control, including time in range, hyperglycemia, hypoglycemia (severe, symptomatic and non-symptomatic), and glycemic variability. We are also committed to supporting products that will address non-glucose metabolic imbalances that contribute to negative health outcomes in people with T1D, such as insulin resistance, obesity, and hyperketonemia. The IL program emphasizes that T1D is not just an autoimmune disease leading to insulin deficiency, but also a complex metabolic disorder that requires a multi-faceted treatment approach. Indeed, most chronic diseases, including T2D, are treated with multiple drugs for optimal outcomes, but typically people with T1D rely on insulin alone, despite its shortcomings in safety and efficacy. The IL program seeks to fill this critical gap and expand the T1D armamentarium for multiple daily injection (MDI) and pump users alike.

We support development of two categories of drugs for glycemic control: transformative next-generation insulins and adjunctive therapies to complement insulin. Standard-of-care insulin drugs fail to produce optimal outcomes in people with T1D due to non-physiologic pharmacokinetics and biodistribution as well as risks of incorrect dosing and hypoglycemia (necessitating burdensome vigilance on the part of the user), among other challenges. Our efforts in next-generation insulins are focused on glucose-responsive insulin (GRI) and ultra-rapid insulin (URI). GRIs, which are designed to have reduced activity at low blood glucose, will prevent hypoglycemia, enable more aggressive treatment of hyperglycemia by reducing anxiety over hypoglycemia, and reduce the psychological burden of constant blood glucose management, among other benefits. URIs will be designed to have faster onset of activity followed by faster cessation of activity relative to currently available insulins; this will alleviate both early postprandial hyperglycemia and subsequent, delayed hypoglycemia. Further, URIs may enable development of Artificial Pancreas (AP) systems with automated insulin dosing at meals. The IL program will opportunistically consider efforts to develop liver-targeted insulins (LTIs), which can improve blood glucose control, including response to hypoglycemia, by correcting the skewed ratio of hepatic to peripheral insulin distribution that results from subcutaneous insulin administration. LTIs and other approaches that recapitulate non-diabetic physiology and adequately insulinize the liver are postulated to provide non-glycemic metabolic benefits, such as improvement in lipids, as well.

Another way of addressing the limitations of insulin therapy is through development of adjunctive therapies to complement insulin. One reason adjunctive therapies are necessary is that T1D is not just a disease of insulin deficiency; there are numerous other under-appreciated pathophysiologies, such as severe dysregulation of glucagon action and the absence of the metabolic hormone amylin. T1D is a disease not just of glycemic control but also of broader metabolic control, with many

affected people exhibiting metabolic imbalances such as hyperketonemia, insulin resistance, and obesity; indeed, data from the T1D Exchange indicate that approximately two thirds of adults with T1D over the age of 26 live with overweight or obesity, a finding corroborated by data from select geographies outside the US. Insulin resistance in T1D, which is further increased in people with T1D and obesity, is poorly understood but associated with long-term complications, and as such demands more research to inform a mechanistic understanding toward targeted or repurposed therapy development. Adjunctive therapies are needed to improve both glycemic control and other metabolic imbalances, toward the goal of improving long-term health outcomes and closing the gap between T1D and non-diabetes life expectancy. Examples of adjunctive therapies of particular interest include SGLT inhibitors, GLP-1 RAs, and insulin-pramlintide co-formulations, due to their potential near-term impact. SGLT inhibitors are approved for T2D globally and approved for T1D in Europe and Japan. They have clinical efficacy in T1D, where they not only reduce HbA1c, postprandial blood glucose excursions, and glycemic variability by inducing therapeutic glycosuria, but also cause beneficial weight loss and blood pressure reductions. However, use of SGLT inhibitors in T1D is limited by the finding that they increase the risk of DKA; thus, the IL program supports the development of approaches (drug, device, other) that can mitigate the risk of DKA and allow more people to benefit from these drugs. Like SGLT inhibitors, GLP-1 RAs are FDA-approved for T2D and are used by some people with T1D off-label, and the IL program supports studies to build a body of evidence that will guide clinical practice and de-risk private sector investment in GLP-1 RAs for T1D across all age groups. The IL program supports the development of insulin-pramlintide co-formulations to overcome the limitations of currently available pramlintide therapy. Pramlintide, the only FDA-approved adjunctive therapy for blood glucose control in T1D, is a synthetic replacement for the metabolic hormone amylin, which is secreted from beta cells concomitantly with insulin and thus lost in T1D. Pramlintide improves blood glucose control and causes beneficial weight loss, but adoption remains low in part because pramlintide therapy requires multiple extra injections each day. To address this issue, Breakthrough T1D supports development of insulin-pramlintide co-formulations so people can benefit from pramlintide without any extra burden; moreover, these co-formulations may enable increasingly automated insulin delivery systems due to the potential for mealtime glycemic control, which currently requires user intervention through manual meal bolusing. The IL program also supports development of other drugs for glucose and metabolic control in T1D; while we prioritize products in clinical trials, we support earlier development efforts for highly promising therapies and critical discovery research to enable therapy development, such as investigation of the T1D-specific pathophysiology of insulin resistance and identification of T1D metabotypes. In clinical trials, we support the evaluation of quality of life and mental health outcomes toward eventual adoption and improved outcomes.

To facilitate the development and availability of these drugs for glycemic control, Breakthrough T1D supports the optimization of their regulatory and access pathways. This involves supporting the incorporation of newer outcomes, like CGM metrics and specifically time in range, into development programs by regulators. Breakthrough T1D is also performing an assessment of patient reported outcome (PRO) measures used in drug development to understand the gaps and build a strategy for the development of fit for purpose PRO instruments, as needed.

AP systems, also called automated insulin delivery systems, improve glycemic control by employing an algorithm to automatically adjust the rate of insulin delivery from a pump in real time in response to continuous glucose monitoring (CGM) data. These sophisticated systems have made a

major impact on the lives of people with T1D in a short amount of time, but more advances are necessary for them to achieve their full potential. The first issue to address is that available AP systems use HCL technology, which means that insulin delivery is not fully automated. Advance planning and manual regulation of insulin dosing at mealtimes and other periods of glucose change (e.g., exercise, stress) are still required and cause an increase in user burden and potential added risk for human error. As such, we prioritize efforts that aim to advance development of systems providing fully automated mealtime insulin delivery. This can be achieved through delivery of drugs that reduce or delay postprandial hyperglycemia like insulin-pramlintide co-formulations and URI, or other approaches. The second issue is that despite the clinical benefits of AP systems, adoption remains low in part due to on-body burden. In light of achieved and anticipated commercial progress in the development of miniaturized pumps, support of projects to drive forward miniaturized or otherwise "user-centric" insulin pumps is no longer a high Breakthrough T1D priority, with the exception of transformative, novel pumping mechanisms. In parallel, we support efforts to advance toward our ultimate vision of AP care, an AP system consisting of a subcutaneously implanted pump that delivers insulin via catheter into the intraperitoneal space to reach the liver as in endogenous non-diabetes like physiology, providing improved glucose control with minimal user interaction outside of the need to refill the insulin pump. We encourage the development of continuous ketone monitoring (CKM) technology to make combined CGM/CKM devices that will alert the user when ketones rise to a critical, subclinical threshold that indicates short-term risk of DKA. DKA remains a major risk, and in some extreme cases, cause of death for people with T1D; examples of people who may be expected to particularly benefit from CGM/CKM devices include those who engage in intense and prolonged anaerobic exercise, non-diabetic people at high risk of conversion who want to reduce the risk of DKA at diagnosis, and people taking adjunctive therapies that increase the risk of DKA. In recognition of the burden imposed by the need to frequently replace infusion sets, we will consider opportunistic support of efforts in mature product development for longer-lasting consumables and integration of insulin delivery with glucose sensing, i.e. a single device with one or two ports for glucose sensing and insulin delivery. For novel devices, if current regulatory pathways need adjustment or modification, Breakthrough T1D will support this work.

Interventions for T1D Complications: Long-Term Complications and Mental Health

The IL program supports development of drugs and other therapies for DN, CVD, and DR. The risk of these long-term complications can be significantly, but not entirely, reduced by tight glucose control, and targeted treatments for all three remain urgently needed. In DN, the goals of therapy are to prevent, delay, or reverse renal function decline, and reduce proteinuria, risk of end stage renal disease (ESRD), the need for dialysis or transplantation, cardiovascular events due to kidney disease, and death. Currently, DN is treated with drugs to manage hypertension (such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and diuretics that facilitate sodium excretion like hydrochlorothiazides) and lipids (such as statins), but more effective and targeted treatments are needed. Most recently – and for the first time – diabetic kidney disease specific therapies have been approved for T2D, with T1D excluded in the product label. The IL program supports development for T1D of drugs like SGLT inhibitors and GLP-1 RAs, that have shown efficacy in renal outcomes in T2D. We are also interested in evaluating in people with T1D other drugs in clinical development for various stages of chronic kidney disease (CKD) currently being pursued for non-T1D indications. The situation is similar for CVD, where some of the same

drug classes are approved for use in T2D and non-diabetic people but not people with T1D. Breakthrough T1D supports development of novel and repurposed drugs for CVD in T1D. To accelerate development in these areas, Breakthrough T1D is working with regulators such as FDA to help define the regulatory expectations for DN and CVD drugs for people with T1D. Further, it is well established that treatments for DN lead to improvements in CVD outcomes since often prolonged and severe DN leads to CVD outcomes.

For DR, we support development of drugs and other approaches that can prevent, delay, or reverse the progressive decline of visual acuity (an approved measure of functional vision) or DR severity. Current DR staging based on the Early Treatment Diabetic Retinopathy Scale (ETDRS) developed in the 1950s can be significantly enhanced to include peripheral vision, neuronal function, real-time vascular flow, and other functional and structural readouts of the holistic eye, and potentially correlate better with diabetes progression. Breakthrough T1D, along with the Mary Tyler Moore & S. Robert Levine, MD Charitable Foundation, is supporting a DR Moonshot Initiative for reversing vision loss, and an initial step toward that goal is to develop a new DR Staging and Severity Scale to advance diagnostic, prognostic, predictive, and stratification tools for product development. This will also support improved vision related outcomes and research toward accessible solutions for disproportionately affected populations. In contrast to the situation with DN, there is an approved, targeted drug class for DR: anti-VEGF therapy. This drug class was recently approved and follows two other approved DR therapies, intra-vitreal steroid injections and laser photocoagulation, which are partially effective but significantly damage the unaffected retina and are not curative. While anti-VEGF treatments represent a huge advance, they carry risks, are not effective for everyone, and are not widely accessible due to cost and invasiveness. For these reasons, the IL program encourages the development of new DR treatments, especially ones that are less invasive or orally available. It is generally thought that the clinical presentation of DN and DR pathologies are similar in people with T1D and T2D, and that the benefits of DN and DR treatments in T2D can be expected to translate to T1D. Yet people with T1D are too infrequently included in DR trials and, disturbingly, T1D has remained an exclusion criterion in most sponsor-initiated clinical trials in DN; this may result in T1D as an exclusion by regulators – a barrier that the IL strategy aspires to overcome. Breakthrough T1D strongly encourages and supports the inclusion of people with T1D in DN, CVD, and DR trials. While we prioritize support of products at a late stage of development (i.e., in clinical trials), we will also consider supporting earlier stage research efforts on highly promising therapies for long-term complications.

Effective T1D management extends beyond glucose control and encompasses the holistic psychosocial well-being of individuals. The IL program supports the development and implementation of diabetes-focused behavioral health interventions that improve the mental health of people with T1D by targeting outcomes such as depression, anxiety, disordered eating, and diabetes distress. Depression and anxiety are commonly observed disorders amongst people with T1D, with prevalence rates more than 2-3-fold higher in people with T1D compared to the general population. Diabetes distress, which refers to the subclinical emotional burden and stress associated with T1D, affects a significant proportion of individuals with prevalence rates ranging from 18% to 45%. Despite these high prevalence numbers, depression and anxiety in T1D are underdiagnosed and undertreated.

T1D is a demanding condition that requires continuous self-management amidst competing life demands. The presence of comorbid mental health issues can further complicate self-management and act as barriers to achieving treatment goals. Diabetes distress, depression or anxiety, when coexisting with T1D, have all been directly linked with problematic self-care behaviors, lower quality of life, suboptimal glycemia and an increased risk of long-term complications. If left untreated, these mental health conditions often become chronic. Additionally, the constant focus on food and nutrition in the management of T1D, contributes to higher risk of developing disordered eating behaviors (DEB) or clinical eating disorders (ED) among people with T1D. Studies have reported that up to 40% of individuals with T1D engage in some form of disordered eating behavior. Both ED and DEB are associated with sub-optimal glycemic control, a higher incidence of long-term complications, and increased mortality rates when individuals misuse insulin to control their weight. Breakthrough T1D prioritizes development of evidence-based behavioral interventions that are supported by robust clinical data, provide sustained health benefits, and are scalable and implementable in clinical practice.

Psychosocial challenges can affect individuals of all age groups and interventions need to consider age- specific factors and developmental stages to address the unique experiences and needs of each age group. Additionally, social determinants of health such as access to healthcare, socioeconomic factors, education, and cultural influences, can impact diabetes management and outcomes. Breakthrough T1D recognizes systemic issues with access to behavioral health interventions and is working to ensure that those who qualify for diabetes specific behavioral health interventions have ready access to these services. Furthermore, Breakthrough T1D encourages the collection of health economic data to better capture the full value of interventions.

The interaction between emotional disorders and diabetes is complex and bidirectional, with each condition influencing the course of the other. Therefore, early assessment and psychological support are essential components of diabetes care and should be considered a routine part of management. Breakthrough T1D supports research that leads to the implementation of evidence-based interventions in clinical practice.

While validated tools, such as instruments to capture patient reported outcomes (PROs) exist, they are not consistently and routinely used in clinical practice. Also, in clinical trials testing non-behavioral interventions (drugs, devices), PROs, including quality of life (QoL) should be collected. Breakthrough T1D is conducting an assessment of PROs used in drug development to identify gaps and develop a strategy for the refinement, validation or development of fit-for-purpose PRO instruments, if necessary. Breakthrough T1D will work toward refining or developing standardized psychosocial measures for T1D across the T1D disease continuum.

Partnerships

The Breakthrough T1D IL program takes advantage of strategic partnerships with industry, other funders, and academia. Industry partnerships will play a key role in the delivery of products to improve outcomes in people with T1D in an accelerated timeframe. By lowering the hurdles companies face in T1D drug and device development, Breakthrough T1D accelerates the development of products at companies already in the T1D space and incentivizes companies that haven’t previously worked in T1D to join us. For example, Breakthrough T1D partnership allows companies to include people with T1D in DR clinical trials primarily investigating other populations

(e.g., non-T1D DR). Similarly, Breakthrough T1D seeks partnerships with companies pursuing drugs for non-T1D indications (T2D, Nonalcoholic Fatty Liver Disease [NAFLD], obesity, etc.) that have promise as adjunctive therapies for people with T1D due to overlapping pathologies or molecular pathways. Breakthrough T1D partnerships with the private sector often include academic partners as well. Collaborations and partnerships with payers will likely lead to faster access and reimbursement of drugs, devices, and behavioral health interventions.

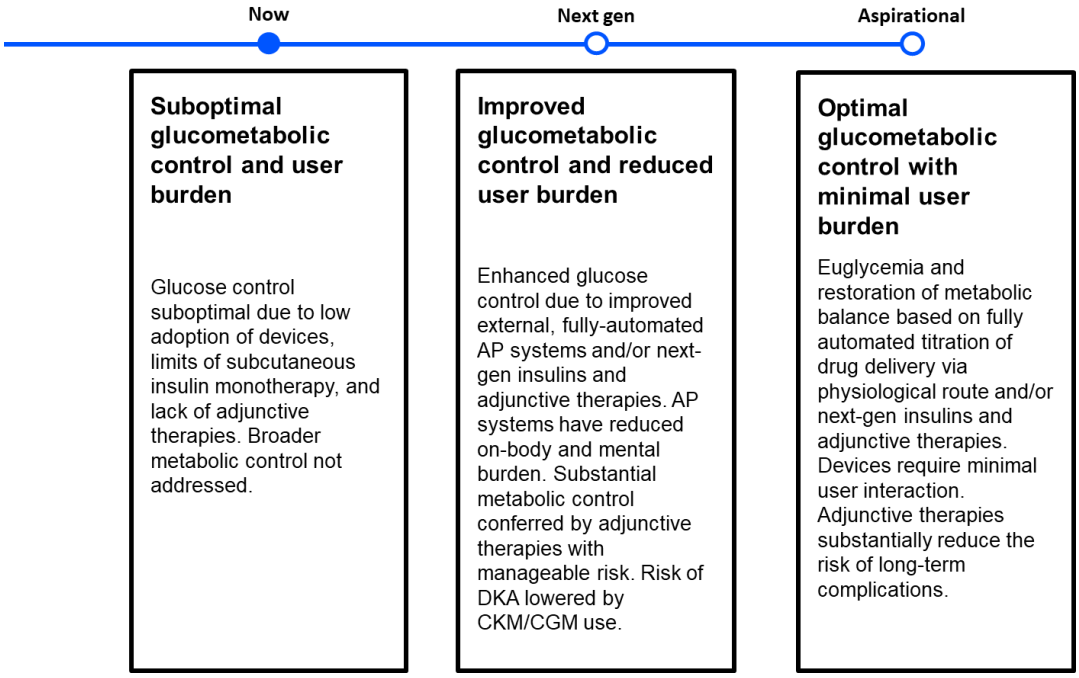
In addition to working with the private sector, Breakthrough T1D has critical partnerships with other funders, including the Helmsley Charitable Trust and National Institutes of Health (NIH), and plays a leadership role in public-private partnerships such as the European Commission's Innovative Medicines Initiative (IMI) and our collaborations with other governmental and non-profit organizations. Through these partnerships, Breakthrough T1D leverages significant financial and non-financial resources for T1D research, accomplishing far more than we could as a sole contributor.

Beyond providing funding, Breakthrough T1D supports our partners with critical non-financial resources. This includes internal scientific expertise and access to clinical trial networks such as the Canadian Clinical Trial Network (CCTN) and Australian Clinical Trial Network (CTN), patient cohorts, clinical trial coordination (through our partnership with the Jaeb Center for Health Research), assistance with clinical trial recruitment, biosamples, and collaboration with existing partnerships and consortia. Breakthrough T1D also provides our partners with regulatory and health policy expertise. Our regulatory affairs team engages with the U.S. Food and Drug Administration (FDA) and other regulatory authorities to ensure policies provide clear and reasonable pathways for T1D research and therapy development and advises Breakthrough T1D partners on regulatory strategy. Breakthrough T1D Research works in lockstep with the Breakthrough T1D T1D Fund, Breakthrough T1D's venture philanthropy arm, who can advise our partners on business strategy and consider providing financial investment where appropriate. Breakthrough T1D policy experts work to ensure that T1D therapies achieve payer coverage. Taken altogether, Breakthrough T1D provides our partners (academic, private sector, other) with support throughout the pipeline, from discovery research through clinical trials to obtaining regulatory approval, payer coverage, and adoption of life-changing products for people with T1D and other insulin requiring diabetes.

Roadmaps

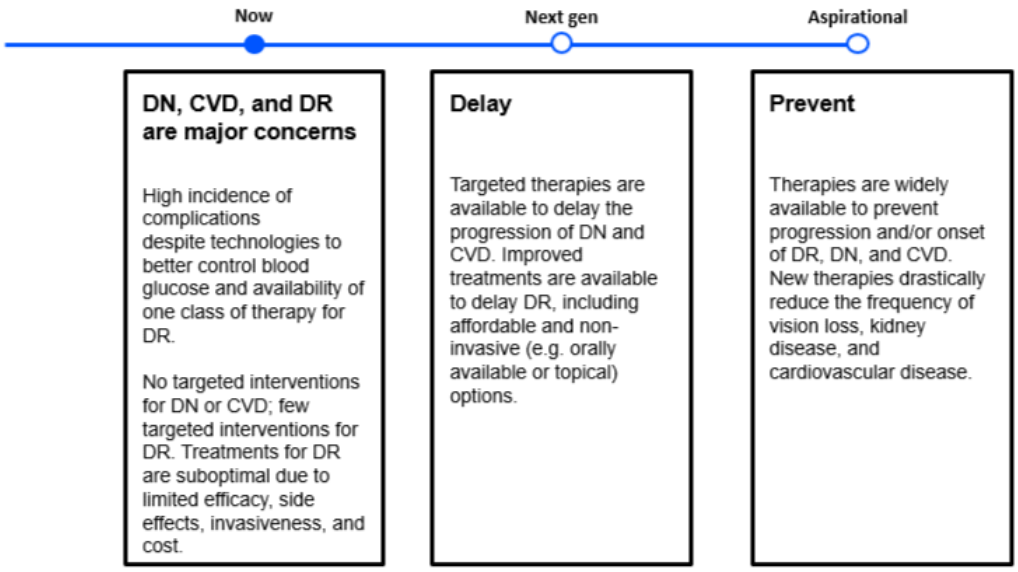
Glucometabolic control

This roadmap provides a staged vision of how drugs and devices will be used jointly to improve glucose and broader metabolic outcomes in T1D. "Next gen" therapies include liver-targeted and faster-acting insulins, and adjunctive therapies that are already in use or are on the near horizon such as SGLT inhibitors and GLP RAs. The "aspirational" generation of therapies includes GRIs and future adjunctive therapies, and/or implantable insulin delivery systems.



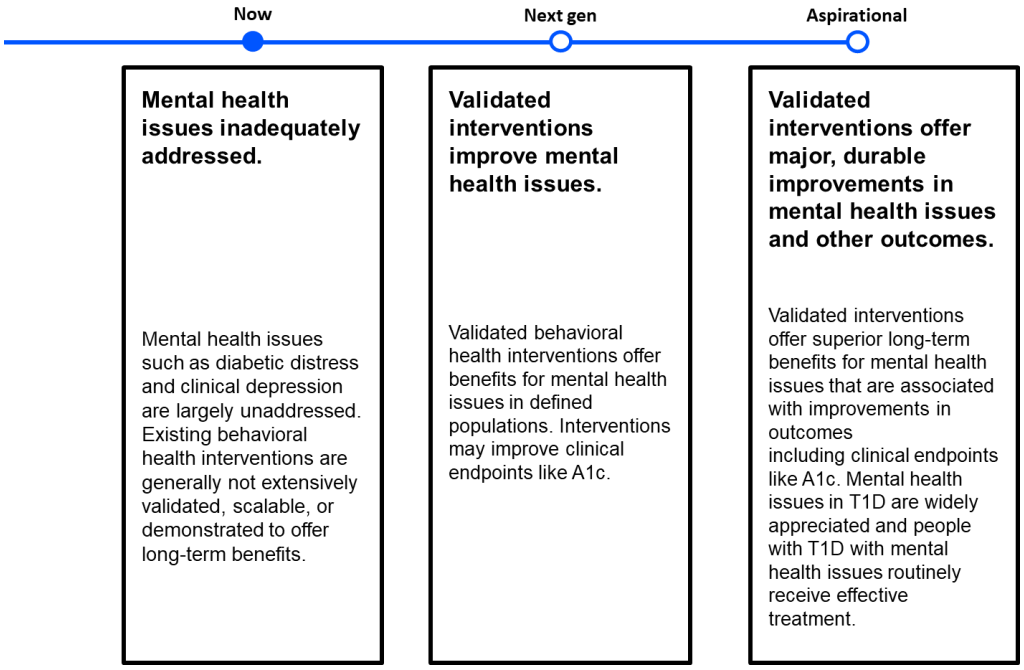
Complications

The Complications roadmap charts a path forward for therapies for DN, CVD, and DR. Envsioned "next-gen" therapies for DN and CVD include drugs approved or in development for non-T1D DKD, such as SGLT inhibitors and GLP1 RAs. Next-gen therapies for DR include orally available and topically administered drugs currently in development. The aspirational generation of therapies will include future drugs for DN and DR.



Psychosocial and Behavioral Health

The Psychosocial and Behavioral Health roadmap displays Breakthrough T1D's vision for the future of psychosocial health care for people with T1D.



Current Status

Several insulins, both basal and fast-acting, are currently available for T1D. Next-generation insulins are in various stages of development. LTIs that preferentially reach the liver by virtue of either oral administration or molecular targeting strategies are in clinical trials. A diverse set of strategies are being pursued for GRI, including development of polymer- or matrix-based systems that release insulin in response to blood glucose, and novel insulin analogs that have glucose-dependent activity. Multiple GRIs are being tested in preclinical T1D models and are poised to enter preclinical development. Two GRI candidates (MK-2640, licensed by Merck from Smart Cells Inc., and a candidate being developed by Novo Nordisk) have completed clinical trials to date. Several biotechnology and pharmaceutical companies are currently working on GRI and seek Breakthrough T1D partnership and leadership to steer the field; however, limited information is available in the public domain. Academics and the private sector are developing URIs using scientific strategies to formulate standard insulin in excipients that enhance its speed of action or to modify the insulin molecule itself. The most rapid insulin currently available is Afrezza, which avoids the rate-limiting step of insulin release from the subcutaneous space by utilizing an alternative route of administration: inhalation through the lungs.

While only one non-insulin drug, pramlintide, is approved by the FDA for glucose control in T1D, several adjunctive therapies are in development. Pramlintide-insulin co-formulations have reached company-sponsored clinical trials. GLP-1 RAs approved for T2D are under clinical investigation in T1D for both glucose control and broader metabolic benefits. The SGLT inhibitors sotagliflozin and

dapagliflozin have been approved in Europe for T1D; dapagliflozin and another SGLT inhibitor, ipragliflozin, have been approved in Japan. To date, no SGLT inhibitor has been approved by the FDA for glucose control in T1D; the major barrier to approval in the United States is the increased risk of DKA associated with SGLT inhibitor use in T1D. Other T2D drugs like bromocriptine, insulin sensitizers, glucokinase activator, and glucagon receptor antagonist are being investigated in clinical trials. There are also drugs being developed against novel targets for T1D metabolic control in earlier stages of research.

Multiple AP devices for glucose control are already on the market. There are currently several HCL systems approved in the U.S.: MiniMed 670G, MiniMed 770G, Minimed 780G, Control-IQ, Omnipod 5, Tidepool Loop (interoperable app), and iLet. Multiple approaches to transition from HCL to more highly automated systems are in development, such as the development of new and improved algorithms. Additionally, investigators are evaluating the potential of non-glucose inputs such as biometric signals to enhance the predictive capability of control algorithms and increase the level of automation. Insulin-pramlintide co-formulations and URI that may help to close the loop are in development as described above. Finally, an implantable system that delivers insulin directly to the intraperitoneal space is under commercial development.

There is also progress in efforts to make the use of AP systems less burdensome in other ways. Devices with "user-centric" features, such as miniaturized form factor, are currently in development in the private sector. Additionally, there is ongoing preclinical and clinical work to increase the longevity of consumables by employing creative scientific strategies like the development of novel biomaterials to resist biofouling and inflammation. Toward the goal of DKA prevention, there are currently efforts underway in the private sector and academic labs to develop CKM technologies. Available therapies for DR include steroids, pan-retinal photocoagulation, and intravitreal anti-VEGF injections. Several drugs are in clinical development for DR, including private sector efforts on a new VEGF inhibitor and drugs against other targets such as plasma kallikrein. There are also trials in people with T1D underway to investigate fenofibrate, a generic medication that has evidence of efficacy in DR in T2D. DN is currently treated with medications to manage hypertension and lipids, but therapies specifically targeting the kidney pathology are lacking. A number of drugs, including but not limited to GLP-1 RAs, mineralocorticoid receptor antagonists, and JAK and SGLT inhibitors, show clinical efficacy in DN in T2D; in fact, SGLT2 inhibitors have been FDA-approved for renal and heart benefits in adults with T2D as well as non-diabetic adults; but people with T1D have largely been excluded from trials. The long-term benefits of GLP-1 RAs and SGLT inhibitors may be expected a priori to translate to T1D, but studies to determine this have not been done.

The existing body of research on T1D and psychosocial health supports the conclusion that mental health issues in people with T1D are associated with negative diabetes outcomes such as poor glycemic control, DKA events, and hospitalizations, and that certain mental health disorders are more common among people with T1D than people without diabetes. The ADA has published a position paper (Young-Hyman et al., 2016) recommending monitoring and screening for diabetes distress and mental health issues in people with T1D and emphasizing the importance of behavioral health services for diabetes care. Several behavioral health interventions (e.g., family-based interventions, cognitive behavioral therapy, others) have been tested in various populations of people with T1D (e.g., adults, adolescents, those recently diagnosed). These studies have provided

evidence that behavioral health interventions can improve mental health issues such as clinical depression and diabetes distress in people with T1D, setting the stage for further research to develop interventions that offer validated, long-lasting, scalable solutions.

Goals and Barriers

The IL program strategy is driven by specific goals related to the development of products for people with established T1D and the key barriers that stand in the way of achieving them. Overcoming these barriers requires Breakthrough T1D leadership; our role is to help lower these hurdles to enable academics and the private sector to move products forward so people with T1D can benefit from novel treatment options. Critical goals and associated barriers in the area of developing interventions to improve outcomes in T1D include but are not limited to the following:

AP Systems with automated dosing at meals
Goal: To develop increasingly automated AP systems that allow people with T1D to have superior glucose control without the burden of manual insulin dosing.

Barrier: No technology has yet demonstrated the ability to enable full insulin automation, and the technologies that must be integrated to close the loop are being developed by discrete companies.

Strategy: Breakthrough T1D supports development of technologies that can be employed to create AP systems with increased automation that demonstrate superiority in efficacy and/or safety. Promising approaches include the development of URIs, adjunctive therapies such as insulin-pramlintide co-formulations that enhance postprandial glucose control, and implantable pumps that deliver insulin into the intraperitoneal space. Other approaches may also be considered. Breakthrough T1D will bring together diverse companies, facilitating interactions that will enable the development of complex products (e.g., drug-device combination products).

Safe, Effective use of Demonstrably Effective Products
Goal: To achieve widespread, safe, effective use of products and technologies that have been demonstrated to improve clinical outcomes in people with T1D, such as AP devices, pramlintide, and SGLT inhibitors.

Barriers: Product class-specific barriers exist for a number of drugs and devices that have been demonstrated to improve key clinical outcomes. FDA-approved AP systems improve glucose control but are not widely used in part due to people's preference for devices with reduced on-body burden and limited access in the general population. Pramlintide is FDA-approved for glucose control in people with T1D but is under-utilized for a number of reasons, including its burdensome treatment regimen of multiple injections per day. SGLT inhibitors, approved for T1D in Europe and Japan but not the US, offer glucose and metabolic benefits; however, their use is limited by an increased risk of DKA.

Strategy: Breakthrough T1D supports focused efforts to overcome defined barriers to the use of product classes that have demonstrated efficacy for T1D. For example, to increase use of AP systems, Breakthrough T1D selectively supports development of miniaturized devices to reduce on-body burden and improve user experience, and advocates for payer coverage; ultimately, these efforts will allow more people to benefit from HCL technology. To improve the onerous treatment regimen of pramlintide, we support development of insulin-pramlintide co-formulations that

eliminate the need for extra injections; this will allow more people to benefit from pramlintide. To reduce the risk of DKA conferred by SGLT inhibitors, we support the development of DKA mitigation strategies like CKM and ketone-suppressing pharmaceuticals, which will lead to wider and safer use of this class of adjunctive therapies. As these examples show, Breakthrough T1D efforts may be deployed either to develop new products in an existing class, or to enable safe, effective use of a currently available product.

Behavioral Health Interventions
Goal: To have safe, effective diabetes-focused behavioral health interventions available to people with T1D to treat mental health issues, while potentially improving clinical outcomes.
Barriers: The clinical base of evidence necessary to widely implement a diabetes-focused behavioral health intervention is insufficient, as is the workforce to provide specialized T1D psychosocial clinical care.

Strategy: Breakthrough T1D supports research to develop behavioral health interventions for T1D that are affordable, scalable, and provide long-lasting benefits. In addition to generating a body of evidence to demonstrate the clinical benefits of interventions, clinical trials should incorporate health economic approaches to allow for analyses of cost effectiveness and sustainability. Breakthrough T1D also prioritizes the training of psychologists with specialization in T1D health.

Long-Term Complications
Goal: To have therapies that protect against DN, CVD, and DR progression available to people with T1D.

Barrier: People with T1D are routinely excluded from clinical trials evaluating drugs for DN and CVD and often excluded from trials for DR.

Strategy: Breakthrough T1D employs strategic partnerships to drive inclusion of people with T1D in definitive clinical trials evaluating therapies for long-term complications that have the potential to change clinical practice and/or regulatory approval. These include private-public partnerships with other private funders, government agencies, and pharmaceutical partners where Breakthrough T1D investment can achieve an outsize result for people with T1D by leveraging the efforts and resources of our partners. Inclusion of people with T1D in clinical trials provides evidence to guide clinical care and support regulatory approvals for T1D.

Therapeutic Concepts

Glucometabolic Control: Drugs
Improved Glucometabolic Control with Drugs on the Near Horizon
This therapeutic concept includes faster-acting insulins and liver-targeted insulins, and adjunctive therapies currently either in use or on the near horizon, such as SGLT inhibitors and GLP1 RAs.

Properties	Improved glucometabolic control with drugs on the near horizon
Primary Product Indication	Improved glucose and metabolic control from novel insulins and adjunctive therapies

Target Population	People with type 1 diabetes, all ages People with other forms of insulin-requiring diabetes
Features	**Novel insulins**: oral or injectable insulins with hepato-preferential activity and/or improved kinetics **Adjunctive therapy**: oral or injectable treatments with low user burden
Efficacy	**Novel insulins**: non-inferiority in HbA1c **Adjunctive therapy**: reduction in HbA1c: 0.5 percent* Clinically meaningful improvements in time in range, time < 70 mg/dL, time < 54 mg/dL, glycemic variability, postprandial glucose, body weight, blood pressure, insulin dose; reduction in burden associated with self-management
Risk/Side Effect	No additional significant insulin-related side effects and only mild to moderate side effects from adjunctive therapies, such as mild nausea at onset of therapy. *

** Relative to today's insulin monotherapy*

Optimal Glucose Control and Metabolic Homeostasis with Future Drugs
This therapeutic concept includes use of faster-acting insulins, liver-targeted insulins, glucose-responsive insulins, and future adjunctive therapies.

Properties	Optimal glucose control and metabolic homeostasis with future drugs
Primary Product Indication	Restoration of euglycemia and other metabolic endpoints from novel insulins and adjunctive therapies
Target Population	People with type 1 diabetes, all ages People with other forms of insulin-requiring diabetes
Features	**Novel insulins: i**nfrequent dosing (maximum 1 dose/day); possibly oral administration; infrequent self-monitoring (up to 1x/day) **Adjunctive therapies:** oral or injectable treatments with minimal user burden
Efficacy	Target HbA1c: <7.0 percent Substantial, clinically meaningful improvement in time in range, near elimination of time < 70 mg/dL and < 54 mg/dL; minimized glycemic variability, postprandial glucose; normalized body weight, blood pressure; minimal burden associated with self-management.
Risk/Side Effect	Tolerable or treatable side effects

Glucometabolic Control: Devices

External, increasingly automated AP System

This therapeutic concept describes an external AP system with automated insulin delivery at meals.

Properties	External, fully-closed loop AP system
Primary Product Indication	Clinically meaningful improvement in glucose control
Patient Population	People with T1D, all ages
Features	Automation: Full automation of drug (insulin and possibly adjunctive therapies) at most situations, including meals. Burden: Infrequent/rare user-initiated dosing/interaction for extraneous circumstances; miniaturized, user-friendly devices; DKA reduction: CGM contains CKM add-on that alerts user when ketones reach subclinical threshold
Efficacy	A1c: non-inferiority relative to SAP Time in range (70-180 mg/dL): >85 percent Time <70 mg/dl: <2 percent Time <54 mg/dL: ~0 percent Time > 180mg/dL: <10 percent Substantial DKA risk reduction Significant psychosocial improvements leading to enhanced quality of life
Risk/Side Effect	Subcutaneous insulin administration leading to lipohypertrophy Intermittent interruptions in CGM wireless communication leading to interruptions in closed-loop control Pump and/or infusion set failures

Implantable, Fully-Closed Loop AP System

This therapeutic concept describes an AP system with an implantable pump that recapitulates non-diabetic physiology by delivering insulin in a fully automated manner into the intraperitoneal space (i.e. to the liver).

Properties	Implantable, fully-closed loop AP system
Primary Product Indication	Normalization of glucose levels
Patient Population	People with T1D, all ages
Features	Automation: Full automation of drug (insulin and possibly other drugs) delivery via physiologic route.

	Burden: Minimal user interaction or day-to-day burden; infrequent (~4x per year) visits to the doctor's office for insulin refills and/or sensor changes DKA reduction: CGM contains CKM add-on that alerts user when ketones reach subclinical threshold
Efficacy	Time in tight glucose range (90-110 mg/dL): >90 percent Time <70 mg/dL: <1 percent Time <54 mg/dL: ~0 percent Time> 180 mg/dL: <5 percent Significant reduction in glycemic variability Minimal DKA Significant psychosocial and metabolic improvements with minimal burden of disease management, leading to greatly enhanced quality of life
Risk/Side Effect	Surgical procedure required for implantation of device/components; associated complications and recovery time

Complications
Diabetic Nephropathy

Properties	Diabetic Nephropathy
Primary Product Indication	Prevent, delay or reverse progressive renal decline in DN
Patient Population	T1D (and T2D, non-diabetic CKD) with DN at CKD stages three and four
Features	Minimally burdensome administration
Efficacy	Reduced proteinuria, eGFR endpoints, ESRD risk (need for dialysis or transplantation), risk of CV events due to kidney disease, and death
Risk/Side Effect	Tolerable or treatable

Cardiovascular disease

This therapeutic concept captures drug approaches to delay, prevent, and reverse CVD. Note that CVD has sub-indications such as heart failure, myocardial infarction and others that require discrete regulatory pathways but have been consolidated here for simplicity.

Properties	Cardiovascular disease
Primary Product Indication	Prevent, delay or reverse CVD
Patient Population	T1D (and T2D, non-diabetic CVD) with established cardiovascular disease or multiple cardiovascular risk factors
Features	Minimally burdensome administration
Efficacy	Reduced risk of major adverse cardiovascular events, cardiovascular death, heart failure and hospitalization for heart failure (while other endpoints may also apply)
Risk/Side Effect	Tolerable or treatable

Diabetic Retinopathy

This therapeutic concept captures interventions to delay, prevent, and reverse DR.

Properties	Diabetic Retinopathy
Primary Product Indication	Prevent, delay or reverse progressive decline of visual acuity or DR severity
Patient Population	Moderate to severe NPDR in T1D (and T2D)
Features	Oral tablet, topical, or other minimally burdensome administration
Efficacy	Clinically significant improvement in ETDRS Best Corrected Visual Acuity (BCVA) or Diabetic Retinopathy Severity Score (DRSS)
Risk/Side Effect	Tolerable or treatable