Improving Lives

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. 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 JDRF 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 JDRF 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 and DR. Even though we emphasize product development, JDRF will continue to support discovery research that has the potential to ultimately benefit people with T1D; historic JDRF 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 JDRF'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, JDRF 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. JDRF 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 fully closed loop Artificial Pancreas (AP) systems. 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. 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, JDRF supports development of insulin-pramlintide co-formulations so people can benefit from pramlintide without any extra burden; moreover, these co-formulations may enable fully 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.

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 fully automated systems for glucose control to reduce the burden of T1D self-management; this can be achieved through automated 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. For this reason, we support development of pumps with “user-centric” features such as miniaturized form factor, which will improve user experience and increase adoption of devices, allowing more people with T1D to reap the clinically demonstrated benefits of AP systems. 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.

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

The IL program supports development of drugs and other therapies for DN and DR. The risk of these long-term complications can be significantly, but not entirely, reduced by tight glucose control, and targeted

treatments for DN and DR 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.

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. JDRF, 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. JDRF strongly encourages and supports the inclusion of people with T1D in DN 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 DR and DN therapies. As the leading cause of mortality in adults with T1D, cardiovascular disease (CVD) is also clearly an important unmet clinical need. While financial resources for this area are limited, we will use strategic partnerships, including with pharmaceutical companies and other funders, and non-financial resources, to accelerate development of therapies to prevent or treat CVD in T1D, whose pathophysiology is likely distinct from CVD in T2D.

Mental health disorders remain an under-researched aspect of T1D. There is evidence that clinical depression, for example, is suffered disproportionately by people with T1D, and that among people with T1D it is associated with poor clinical diabetes outcomes like high HbA1c. The IL program supports the development of diabetes-focused behavioral health interventions that improve the mental health of people with T1D by targeting outcomes that include but are not limited to clinical depression, disordered eating, and diabetes

distress, particularly in high-risk groups such as adolescents and young adults. Behavioral health interventions may also improve clinical endpoints such as HbA1c, DKA, and severe hypoglycemia events requiring medical intervention. JDRF prioritizes development of interventions that offer sustained health benefits, are scalable, and are supported by strong clinical data; we also encourage collection of health economic data to better capture the full value of interventions. In clinical trials testing non-behavioral interventions (drugs, devices), psychosocial measures to capture patient reported outcomes (PROs), including quality of life (QoL) assessments, should be included. JDRF will work toward the development of standardized psychosocial measures for T1D across the T1D disease continuum.

Deprioritized

The IL program has deprioritized select areas that JDRF has supported in the past. Now, JDRF will only be able to support projects in this area that are exceptional and highly translational:

- Hypoglycemia unawareness (HU): While hypoglycemia unawareness (HU) is a significant cause of hypoglycemia, we will refocus our resources on therapies that prevent hypoglycemia through broadly applicable mechanisms independent of the specific physiology associated with HU. This will include device and drug approaches that reduce hypoglycemia.
- Biomarkers: JDRF has previously invested significantly in biomarker studies in DN and DR; we are now transitioning resources to develop therapeutic interventions for these long-term complications with the aim of ensuring inclusion of people with T1D in clinical trials.
- Device subpopulation studies: In the device space, we have deprioritized evaluation of HCL systems in defined subpopulations of people with T1D. Instead, we are now prioritizing the development of new and improved devices that will reduce burden, improve clinical outcomes, and broadly increase adoption of HCL systems.
- Open protocol: We have deprioritized research to support open protocol projects because recent accomplishments in the field, including the establishment of pathways for regulatory approval of products for each component of an AP system, have created a healthy ecosystem that will continue to develop without direct JDRF support through market trends and industry efforts.
- Alpha cell physiology: Alpha cell physiology has been deprioritized because the field, while promising, is relatively far from clinical translation. In general, JDRF prioritizes mature opportunities over early discovery; however, we recognize that basic research plays a critical role in the ultimate development of therapies and improvements to clinical care, and we will continue to support gap-filling basic research.

Partnerships

The JDRF 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, JDRF 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, JDRF partnership allows companies to include people with T1D in DR clinical trials primarily investigating other populations (e.g., non-T1D DR). Similarly, JDRF 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. JDRF 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, JDRF 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

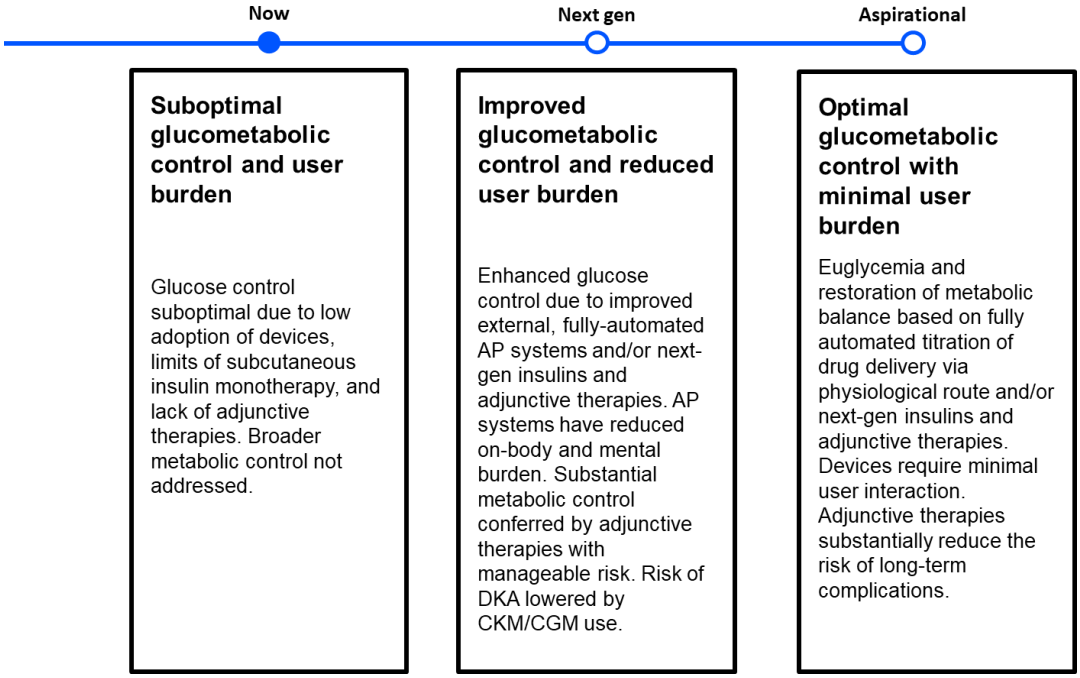
with other governmental and non-profit organizations. Through these partnerships, JDRF leverages significant financial and non-financial resources for T1D research, accomplishing far more than we could as a sole contributor.

Beyond providing funding, JDRF 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. JDRF 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 JDRF partners on regulatory strategy. JDRF Research works in lockstep with the JDRF T1D Fund, JDRF's venture philanthropy arm, who can advise our partners on business strategy and consider providing financial investment where appropriate. JDRF policy experts work to ensure that T1D therapies achieve payer coverage. Taken altogether, JDRF 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

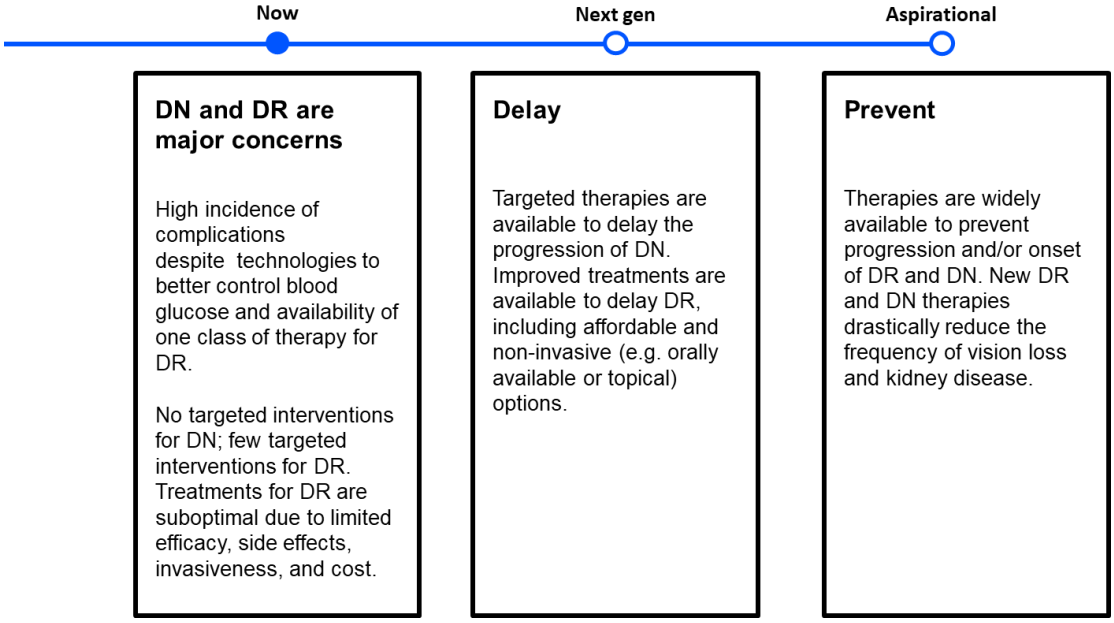
Glucometabolic control

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.



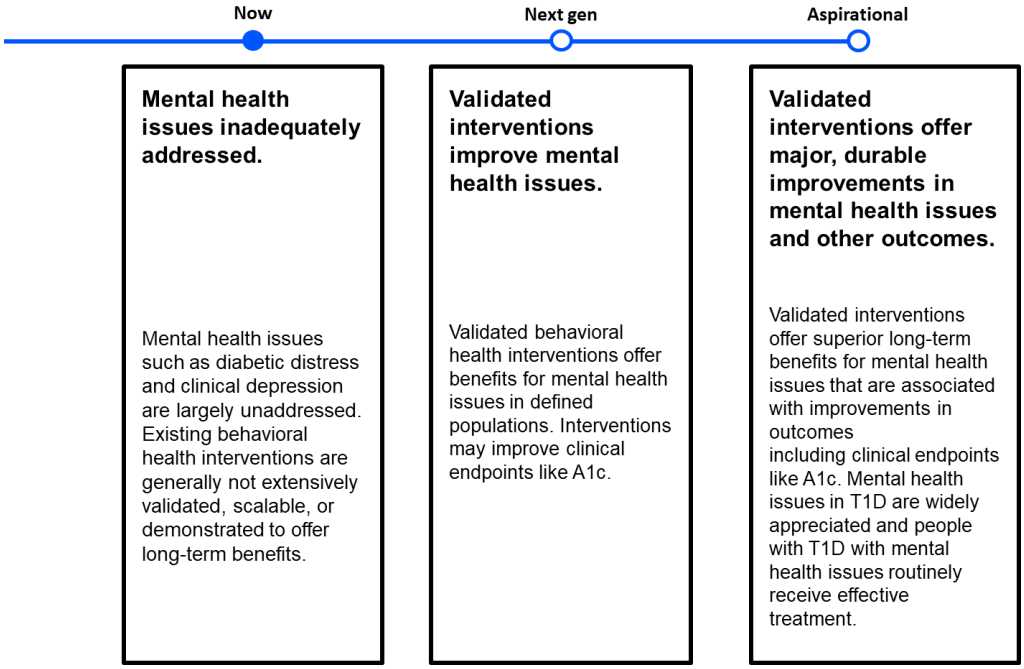
Complications

The Complications roadmap charts a path forward for therapies for DN and DR. Envsioned “next-gen” therapies for DN 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 JDRF’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. Only one GRI candidate (MK-2640, licensed by Merck from Smart Cells Inc.) has completed a clinical trial to date. Several biotechnology and pharmaceutical companies are currently working on GRI and seek JDRF 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 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 three HCL systems commercially available in the U.S.: MiniMed 670G, MiniMed 770G, and Control-IQ, and more are expected to be commercially available in the near future. Multiple approaches to transition from HCL to fully 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, a member of the SGLT2 inhibitor class has recently been FDA-approved to improve renal outcomes in adults with T2D and kidney disease, as well as in heart failure, where T1D remains excluded. The benefits of these drug classes 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 JDRF 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:

Fully Closed-Loop AP Systems

Goal: To develop fully-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: JDRF supports development of technologies that can be employed to create fully closed loop AP systems that demonstrate superiority in efficacy and/or safety. Promising approaches to close the loop 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. JDRF 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: JDRF 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, JDRF 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, JDRF 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.

Barrier: The clinical base of evidence necessary to widely implement a diabetes-focused behavioral health intervention is insufficient.

Strategy: JDRF 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.

Long-Term Complications

Goal: To have therapies that protect against DN and DR progression available to people with T1D.

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

Strategy: JDRF 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 JDRF 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.

Policy and Reimbursement Considerations

For each goal and the related products, JDRF is focused on how research can advance product development with regulatory and reimbursement considerations in mind so that JDRF's work accelerates products through

the pipeline and into the hands of people with T1D. Our strategy and priorities in the US in these areas by type of product follow. Global strategies and priorities are planned in parallel and will be expanded in the future.

One area of focus that will enhance regulatory and reimbursement pathways for both medical devices and drugs is incorporation of outcomes in addition to HbA1c and a favorable benefit to risk profile. There is community consensus that outcomes such as hypoglycemia, hyperglycemia, time in range, and DKA are clinically meaningful, especially for those measured by CGM. A JDRF and Helmsley Charitable Trust funded patient preference study, published in the journal Patient Adherence and Outcomes (Marinac et al) on outcomes beyond HbA1c showed that adult patients with T1D and caregivers of children with T1D prioritize decreases in the weekly number and severity of non-severe hypoglycemic events (Level 1, defined as between 54 and 70 mg/dL, and Level 2, defined as less than 54 mg/dL) and hyperglycemic events. Ongoing efforts by JDRF and our partners are working to ensure that regulators and payers adopt and utilize these outcomes, with emphasis on hypoglycemia and other metrics measured by CGM, in their decision-making for T1D therapies. Notably, JDRF is working closely with a coalition around hypoglycemia and there has been a recent advance that reflects acceptance of the clinical meaningfulness of Level 2 hypoglycemia by the U.S. Food and Drug Administration (FDA). JDRF is also working with FDA, the Critical Path Institute (C-Path), a non-profit working in the regulatory space, and the Jaeb Center for Health Research, a non-profit clinical coordinating center, on an effort related to the use of CGM metrics in regulatory decision making for drug therapies.

Medical Devices

Artificial pancreas systems are regulated as medical devices by FDA in the U.S. JDRF has been interacting on a regular basis with FDA on AP systems for over 10 years. There is an FDA guidance document that provides the general framework for testing and approval of AP systems that device manufacturers have relied upon to guide the development of their systems. The unit at FDA that has oversight of AP systems, the Diabetes Branch within Centers for Devices and Regulatory Health (CDRH), is engaged with JDRF, commercial entities developing AP systems, and the larger T1D community, which results in interactive and streamlined regulatory interactions. Miniaturized devices will likely have similar regulatory considerations as existing components of AP systems. Systems with implantable components will present new considerations although the fundamental functioning of the device remains the same. JDRF will continue to engage with regulators, industry, and researchers, monitoring progress and anticipating and addressing issues proactively.

Reimbursement for medical devices, including AP systems, is distinct in the public and private insurance programs in the U.S. JDRF works with the largest private payers to inform them of the benefits of new devices in an effort to gain coverage and as a result, CGMs and the current AP systems have wide coverage in the private insurance market. It is expected that innovative systems demonstrating similar benefit will also achieve wide coverage. As an example, the first implantable CGM is quickly gaining coverage in this sector. Public insurance programs, specifically Medicare, have a somewhat fragmented approach to device coverage. Any new device needs to have a proactive strategy to gain Medicare coverage with close consideration of the benefit categories. JDRF works closely with the Centers for Medicare & Medicaid Services (CMS) to ensure that all diabetes devices, including new devices, gain swift coverage so people with T1D have timely access. Extensive advocacy by JDRF staff and advocates led to initial Medicare coverage of CGMs in 2017 and a recent proposed expansion to all FDA-authorized CGMs as well as recent Medicare coverage of one of the AP systems currently on the market, with a proposed expansion to the others soon. Leadership by JDRF in getting new device coverage has increased access to devices via public and private insurers and we will continue to work with payers to gain coverage for any new devices.

Drugs

Regulatory authorities, namely the FDA in the U.S., make decisions about which medical products can be made available to the public and bases its decisions on an assessment of whether the benefits of the product outweigh the risks, as demonstrated in clinical trials. For traditional development of a novel drug, FDA requires a development program that culminates in at least two adequate and well-controlled phase III clinical trials with the expectation of a sufficient number of people exposed to assess benefits and risks. To expand the indications of an already approved drug to a new patient population or disease indication, such as is being researched for some adjunct therapies, FDA will generally require two adequate and well-controlled phase III clinical trials. Some earlier stage clinical and preclinical work from the previous approval(s) can sometimes be relied upon for approval of the new indication, but it will depend on the specific situation. Specifics about the development program including the duration of study, number of subjects enrolled, and efficacy/safety endpoints depend on the exact product, the patient population and the indication for use being sought. As specific products are being researched and pursued, JDRF explores the possible development pathway to discuss regulatory strategies and identify potential challenges for that specific product class as needed.

Before any new therapy can be covered by public or commercial payers, certain standard steps must be taken. A code identifying the product must be obtained from the CMS for a product approved by the FDA as a drug or biologic. For products that are sold by pharmacies to patients, the list price is set by the manufacturer and then the pharmacy benefit manager (PBM) acting on behalf of a commercial insurer or a Medicare Part D plan negotiates a post-sale rebate in return for favorable formulary placement. Where competitors exist that are used to treat the same condition, PBMs may demand higher rebates to maintain favorable formulary placement, strongly motivating the manufacturer to increase prices to pay rebates.

Things to consider when approaching a payer to request coverage include the efficacy of the product in terms of its ability to modify the target disease, the cost of the present standard of care for the disease and how the new product or service may change that picture, the safety profile of the new product or service, and the size of the population that will potentially be treated using the new product or service. Payers give most credence to peer reviewed literature from an independent source. They will generally want to see randomized controlled trials (in preference to observational studies). Multiple studies and studies with larger numbers of participants, and those that include a range of participants, such as children or older adults, will be helpful.

Behavioral Health Interventions

Coverage for behavioral health interventions is usually outside of the medical benefit and part of a behavioral health benefit. By statute, behavioral health benefits must be covered at parity with physical health benefits, including equal copays and similar restrictions on access. However, many insurers will put limits on the number and frequency of mental health visits or require proof of improvement to continue coverage. For T1D focused behavioral health interventions that aim to improve physical and mental wellbeing, an additional improvement in diabetes outcomes may make it easier to show that the intervention will lead to improved overall health outcomes. As these interventions are developed, generating evidence of physical and mental benefits along with economic considerations will facilitate consideration by payers.

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 control from novel insulins and adjunctive therapies
Target Population	People with type 1 diabetes, all ages Possibly 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 Possibly 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: o**ral 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, Fully-Closed Loop AP System

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

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) for all situations. 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 nondiabetic 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

This therapeutic concept captures drug approaches to delay, prevent, and reverse DN.

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