Artificial Pancreas

Vision

The Artificial Pancreas (AP) program's vision is a world in which AP devices/systems are commercially available to effectively and conveniently enable optimal glucose control, improve other metabolic outcomes, and enhance quality of life for people with type 1 diabetes (T1D).

Mission

The AP program will continue to support innovation in research and product/system development efforts to accelerate progress towards our vision. Taking a holistic view of the opportunities and challenges in driving toward our vision, our efforts will span the gamut of technology translation – including driving early-stage research, accelerating and/or de-risking more mature commercial development efforts, and enabling a healthy, competitive, and patient-centric market for AP systems.

Rationale

A robust and ever-growing body of evidence demonstrates that AP systems – also known as automated insulin delivery (AID) systems – meaningfully improve clinical outcomes for people with T1D and simultaneously ease the burden of self-management. While other sectors of the research community work toward a cure, AP systems leverage mature and ever-improving technology and are, in principle, applicable to a large portion of the T1D population today. Although AP systems have improved tremendously over the years in terms of both technology and accessibility, there remain opportunities for significant improvements that are within reach.

Current Clinical Outcomes are Suboptimal

In a recent study by the T1D Exchange Clinic Network (published in early 2019), it was demonstrated that only 17 percent of youth with T1D, and only 21 percent of adults with T1D are achieving the American Diabetes Association's recommended HbA1c target of <7.5%. Overall, mean

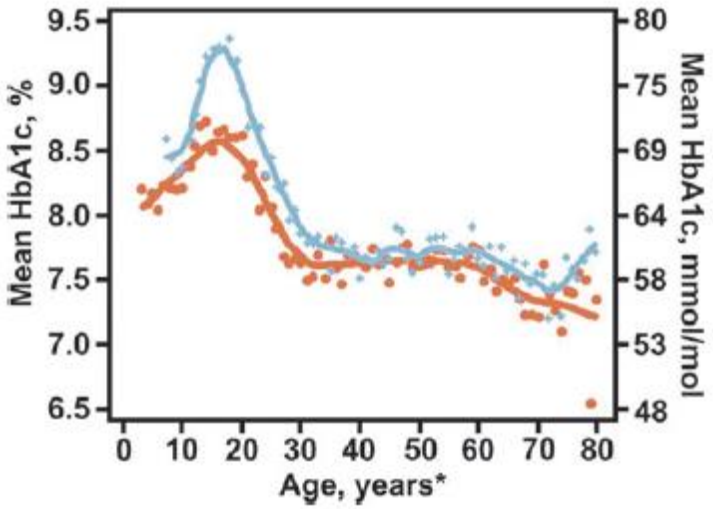


Fig. 1. Average HbA1c by year of age: 2010-2012 (orange line) versus 2016-2018 (blue line). Overall metabolic control as measured by HbA1c has worsened between the two cohorts, with a notable increase in adolescents and young adults. (Source: T1D Exchange Clinic Network)

HbA1c increased from 7.8% in 2010-2012 to 8.4% in 2016-2018, with the largest increase occurring in adolescents and young adults (Fig. 1). Clearly, more effective treatment options are necessary for the T1D community. AP systems have already made a positive impact on the clinical outcomes of many people who use them, but there are significant opportunities to ensure future AP systems achieve tighter glucose control and thus increase users' adoption, adherence, and likelihood to achieve healthy clinical outcomes – HbA1c and beyond.

Available Devices are Burdensome

Characteristics common to the devices/systems in the current generation of hybrid closed-loop AP systems – systems both already approved/marketed and those in commercial pipelines – include requirements for the user to make treatment decisions around meals, exercise, and other situations the algorithm is incapable of handling effectively; frequent finger-sticks to calibrate and/or confirm CGM readings; frequent replacements of consumables like infusion sets and insulin; bulkiness and multiple on-body devices; and user-unfriendly interactions with device interfaces. There are opportunities to drive innovations that reduce all of these burdens, enhancing the quality of life of – and increasing the likelihood of successful utilization by – people who choose them.

Adoption of Systems among People with T1D is lower than Desired

Currently, based on high-level reports from Industry, at most only 12 percent of people in the United States with T1D use a hybrid closed-loop AP system. There are a litany of factors that figure into this relative low rate of adoption, some of which are outside the immediate scope of our Research mandate (e.g., reimbursement issues). There are other factors, though, that strategic research and development initiatives can help address, such as accelerating the delivery to market of new innovations and driving the generation of important gap-filling evidence as to the benefits of AP systems in specialized populations and circumstances. In addition, we are confident that our efforts to improve the effectiveness and user-friendliness of AP systems will lead to wider adoption.

Strategy

The AP program is focused on three goals to realize our ultimate vision:

- Enable **improved outcomes** for people with type 1 diabetes through a drive toward full, effective automation of drug delivery
- **Reduce burden** on users, caregivers, and health care professionals
- Increase **adoption and successful utilization**

Enabling improved outcomes

Enabling meaningful improvements in the clinical outcomes associated with AP systems is the primary objective of the AP program. In order to achieve these improvements, AP systems must be developed that achieve tighter glucose control for a wider range of daily life activities. Strategically, we are focused on the following areas to enable full, effective automation of next-generation AP systems:

Better-inform the algorithms

Algorithms will be more effective if they are better informed of "disturbances" – physiologic activity affecting glucose – and moreover are capable of offsetting these disturbances. Useful information may be obtained from sensors quantifying important activities such as exercise, stress, sleep, and even meal ingestion. The inputs may come from med-tech devices (e.g., accelerometers) and from novel biometric sensors (e.g., lactate sensors). The incorporation of these non-glucose inputs into AP system frameworks and algorithms has the potential to greatly improve the robustness of these systems.

The AP program's strategy in this space is to drive research elucidating what additional inputs are most informative to a next-gen AP algorithm as they relate to disturbances in blood glucose levels (and thus are most likely to result in more effective algorithms), enabling the sensing of non-glucose inputs, and ultimately incorporating both the framework to the capture additional signals and next-gen, better-informed algorithms into future AP devices.

Create "smarter" algorithms

Algorithms will be more effective if they are smarter, i.e., if they can learn to adapt over time, anticipate the future, and/or incorporate contextual information about the user. Applying advanced numerical techniques such as machine learning to AP systems holds the potential to empower an algorithm to learn.

The AP program's strategy in this space is to drive research based on advanced numerical techniques (e.g., machine learning) leveraging large repositories of AP device data and other contextual information (e.g., patient age) to elucidate previously unknown relationships among the data, and moreover incorporate these learnings and/or mathematical constructs into next-generation algorithms. As part of this strategy, the AP program will make efforts to enable the consolidation and harmonization of these valuable data sets, and to enlarge (add more data to) and enrich (add other potentially informative data to) them for future research endeavors. In addition, the AP program has started, and will continue to prioritize, making inroads with data partners, from both generation/management and analysis perspectives.

Use adjunct drugs to enable more effective insulin delivery

Current AP systems are limited by their ability to dose only one drug (insulin) via a subcutaneous route that is associated with significant pharmacokinetic delays. The addition of another adjunct drug into an AP system can enable a more effective delivery of insulin by an AP algorithm. As examples, in one embodiment the incorporation of amylin can enable an algorithm to more effectively offset the effects of meals, while in another embodiment the incorporation of glucagon can empower the algorithm to dose insulin more aggressively.

The AP program's strategy in this area is to continue to understand how effective and/or user-friendly an AP system can be leveraging fixed-ratio co-infusion of insulin and amylin. (A closely related priority in the Metabolic Control program is to drive the development of an insulin-amylin co-formulation, which would translate straightforwardly to this application.) The AP program will also be opportunistic in evaluating applications involving the incorporation of glucagon or other potential adjunct drugs into AP therapy.

Use more physiologic insulin delivery routes to enable more effective insulin delivery

One of the aspirational goals for the AP program is driving the development of AP systems that can more closely mimic natural insulin release by the pancreas through delivery of insulin via a much more physiologic route than the subcutaneous tissue, such as the intraperitoneal space, which has the potential to result not only in very tight glucose control, but also restore more holistic metabolic control in the body.

The AP program's strategy in this area is to continue to perform academic-level research aiming to understand to what degree an AP system leveraging intraperitoneal insulin delivery and glucose sensing can improve outcomes and decrease burden, while simultaneously to drive development efforts of such systems (both more "mature" and novel/early-stage systems) toward clinical studies.

Drive development of ketone-monitoring technology

Robust mitigation strategies against DKA are likely to become a significant need in the near future due in part to the emergence of SGLT inhibitors as adjunctive treatments labeled for T1D. Of course, these strategies will also be meaningful in the context of other treatment regimens. One approach is to develop wearable, continuous ketone monitors akin to continuous glucose monitors. The AP program's strategy in this area will be opportunistic in nature, evaluating the landscape and opportunities as they arise, with the latitude to pursue the most compelling efforts.

Reducing burden

A reduction in the burden associated with AP systems, both on-body and interactional, will drive a direct improvement in the quality of life of the people who use them, and is expected to indirectly lead to improved outcomes by increasing the likelihood of their successful utilization. Meaningful burden reduction is also expected to drive increased adoption. Strategically, we are focused on the following ways to reduce burden:

Reduce the frequency of infusion set/catheter replacements

Current AP systems require replacement, and literally re-placement, of infusion sets/catheters nominally every three days. The development of longer-lasting components can greatly reduce both the on-body and interactional burden associated with these replacements. In parallel, more concentrated and thermostable insulin formulations are needed to reduce the frequency with which insulin reservoirs must be refilled.

The AP program's strategy in this space is to evaluate and support the development of novel technologies in biomaterials, bioactive surface modification, and controlled localized drug delivery to mitigate the inflammatory response to infusion sets at the site of insertion and extend their wear time while effectively delivering insulin. As a complementary effort, the Metabolic Control program will evaluate and support the development of new concentrated and thermostable insulin formulations.

Integrate insulin delivery and glucose sensing sites
A profound reduction in on-body burden can be realized, compared to current systems, if insulin can be delivered and glucose sensed from the same subcutaneously inserted device. The incorporation of a glucose sensing component into an insulin infusion catheter will eliminate a large percentage of device insertions relative to today's standards.

The AP program's strategy in this space is to evaluate the technical implications of sensing glucose at the site of insulin delivery and support the development of solutions that enable the integration of glucose sensing and insulin infusion. Subsequent work will incorporate technology from extended wear infusion sets as described above to better enable synergies with the current and anticipated (longer) durations of glucose sensor wear.

Improve the form factor of AP components/systems
Incorporating user-centric design principles to improve the form factor or wearability of AP components/systems can greatly reduce on-body burden for the users of these devices.

The AP program's strategy in this area is to drive the development of next-generation insulin pumps and AP devices with novel and more efficient pumping mechanisms that enable miniaturization as well as integration of the sensing and pumping components into a single device, thus reducing on-body burden.

Enable more discreet device interactions
Shifting user interactions from the device to a more discreet medium (i.e., a phone) can meaningfully reduce interactional burden. Enabling an open-protocol AP device ecosystem (discussed in further detail below) can drive these types of improved user interactions.

Drive development of decision-support technologies
While not a part of an AP system, per se, decision-support technologies can meaningfully reduce the mental burden of T1D self-management by partially automating the decision-making component of the insulin-dosing process, and in doing so can possibly drive improvements in outcomes.

The AP program's strategy in this area will be opportunistic in nature, evaluating the landscape and opportunities as they arise, with the latitude to pursue the most compelling efforts.

Increasing adoption and successful utilization
Increasing the rate of adoption of AP systems – and moreover the successful utilization of them – is key to realizing the full potential of the benefits of AP systems. To this end, the AP program seeks to ensure scientific rigor in understanding how these systems can be utilized by the disparate populations of people with T1D, each with its own special characteristics. Strategically, the AP program is focused on the following ways to accomplish this goal:

Generate gap-filling evidence of AP system benefits in under-studied and/or under-served sectors of the T1D population
Commercial studies of AP systems often specifically exclude or under-represent certain sub-populations of the T1D community. Studying these populations in a scientifically rigorous manner has the potential to encourage AP system adoption by these people, whether initiated by them or their health care professional.

The AP program's strategy in this area is to direct and fund impactful clinical investigations scrutinizing these under-studied and/or under-served populations, thus adding to the body of evidence demonstrating AP systems' benefits. It is the strategic goal of these studies to increase awareness of AP systems among patients, caregivers, and health care providers so as to drive meaningful increases in the adoption of the devices.

Understand what the barriers/problems are to better inform future development
In the case that there are issues preventing successful utilization of AP systems by certain sub-populations, understanding what these barriers are and how to fix them can lead to future products designed specifically to benefit them, and thus lead to improved adoption.

The AP program's strategy in this area is to understand what the unmet needs of certain populations are with respect to AP systems – through a combination of clinical investigations, psychosocial studies, and big-data analysis – and moreover to address these unmet needs in future AP system development efforts, thereby enabling successful use of AP systems by as many people with T1D as possible.

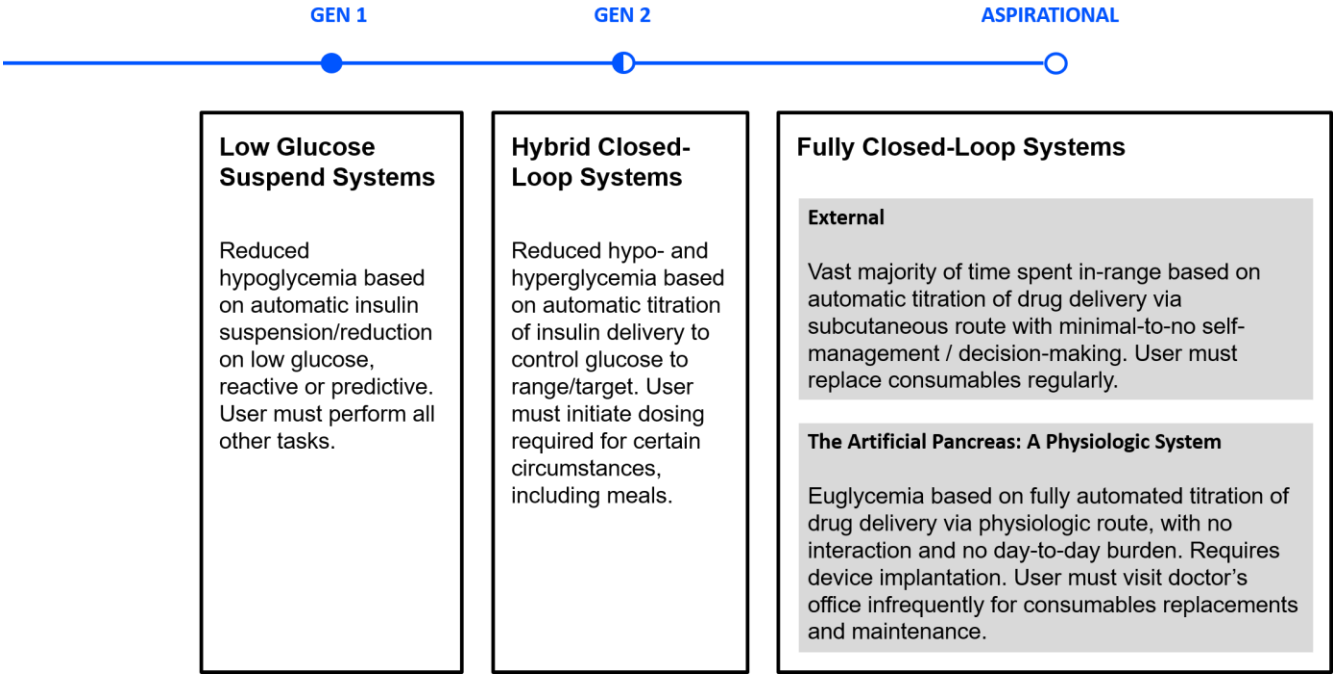
Enable an open-protocol AP ecosystem

In an open-protocol AP ecosystem, component devices from different manufacturers can be safely and conveniently paired with other complementary components to work in concert to form complete AP systems. This impactful new paradigm will enable users of AP systems to choose the components that work best for them, thus improving user satisfaction and – likely increasing the successful utilization of the devices. Importantly, this ecosystem has the potential to grow adoption of AP devices by greatly expanding choice in the marketplace. Other benefits of an open-protocol system include enabling a pathway to market for academic and/or "do-it-yourself" algorithms, which come with life-improving innovations that are currently being used off-label in a small population or otherwise are not being utilized to their full potential. Finally, open-protocol systems lend themselves to discreet, phone-based device interactions.

The AP program's strategic approach to enabling this ecosystem is to both accelerate development efforts of open-protocol AP components as well as, more broadly, to continue to engage with the many key stakeholders – FDA, Industry, legal counsel, non-profits – to ensure the success of this new paradigm.

Roadmap

In 2009, JDRF released an iterative roadmap to achieve a vision of device-based treatment of T1D. This roadmap was revised in 2015 to reflect current thinking. The 2015 roadmap reflected the two achieved milestones of (1) Suspend and (2) Predictive Suspend, and proposed two pathways for future generations: (3a) Automated Insulin Delivery and (3b) Multihormone Systems. These roadmaps were integral to driving the development the first few generations of AP devices. Below we outline a further revised roadmap that is focused on two key factors: achieving improved outcomes and reducing device burden. Currently, we have reached the beginning of a generation of hybrid closed-loop systems, but we expect systems within this category to improve meaningfully in terms of outcome improvements and burden reduction over the foreseeable future. Ultimately, the AP program aspires to enable the realization of fully automated systems in two distinct embodiments, each with advantages and disadvantages that may suit the needs and preferences of different people with T1D: next-generation external systems (i.e., leveraging subcutaneous drug delivery) and true "artificial pancreas" systems which would achieve tight glucose control through full automation of drug delivery, via a physiological route, and simultaneously effectively eliminate the day-to-day user burden.



Current Status

The first hybrid closed-loop system, the Medtronic 670G, is currently available in the United States and other markets, and other similar products are in development and nearing the market. While these systems signify an important achievement of progress along the AP roadmap, there is room for much improvement to be realized within this generation of systems, and much more research/development required to drive future generations of AP systems.

Automation of Drug Delivery in AP Systems

Currently, the most advanced (external) AP systems consist of hybrid closed-loop control, meaning the system can regulate basal insulin delivery autonomously while the user is required to manually intervene to account for particular circumstances that call for more extreme insulin adjustments such as meals, exercise, and stress. JDRF is funding investigators to evaluate the potential for other data inputs, such as med-tech and biometric signals to detect or perhaps predict such events so as to modify insulin delivery accordingly, thus enhancing the predictive capability of control algorithms and increasing the level of automation of these systems. This would represent a significant reduction in burden to users and result in more consistent dosing of insulin which would translate into improved and more consistent clinical outcomes.

Although the improvements to AP systems outlined above for Gen 3 devices represent a significant advancement over current systems, these systems would likely remain limited by the pharmacokinetics and pharmacodynamics of subcutaneously delivered insulin. While significant progress has been made in the development of fast acting insulin formulations, these insulins still suffer from suboptimal onset, peak, and duration of action. Moreover, the subcutaneous route of insulin delivery results in reduced insulin signaling in the liver, which plays a central role in glycemic regulation, and concomitant elevated plasma insulin levels which can result in adverse side effects. Clinical studies have demonstrated that physiologic delivery of insulin (e.g., delivery directly to the intraperitoneal space) results in improved glucose control both after meals and during periods of fasting, and moreover physiologic insulin delivery has been linked to restoration of the counter-regulatory response and other endocrine and metabolic benefits. Delivering insulin in a physiologic manner more closely mimicking the secretion of insulin by the native pancreas could overcome the challenges associated with subcutaneous insulin delivery by improving insulin pharmacokinetics, engaging the liver in glycemic regulation, and enabling complete automation of diabetes management while delivering improved clinical outcomes.

Burden Associated with AP Systems

While the development of hybrid closed-loop systems is a remarkable accomplishment that will drastically improve the lives of many people living with T1D, there is still much room for improvement. The on-body burden resulting from the multiple devices that must be used/worn as well as the requirement for frequent and often asynchronous replacement of consumables is a significant inconvenience to users. As such, Gen 3 devices should address some of these shortcomings by incorporated user-centric design such as integrating different components into a single on-body device with a reduced profile/size which simplifies and reduces the frequency of changes in consumable components, thus reducing the burden to the user.

An ideal AP system would allow users to live their lives as if they didn't have T1D; such a system would free users from dealing with pump settings, on-body devices, and frequent changes of consumables such as infusion sets and CGM sensors. Following the development of Gen 3 systems which mitigate some these concerns, the development of an implantable AP system capable of fully automated insulin delivery has the potential to deliver such a therapeutic solution. An implanted miniaturized device that only requires a few doctor visits each year for insulin refills and sensor/catheter changes would virtually eliminate the on-body and mental burden of day-to-day diabetes management.

Adoption and Utilization of AP Systems

Adoption of the current generation of systems – hybrid closed-loop systems – is increasing but still relatively low. Major unmet market needs responsible for this low adoption include lack of choice in such systems, lack of data demonstrating benefits of using such systems among certain populations, and more systemic effects such as reimbursement issues and resistance or lack of knowledge/awareness on the part of some health care providers to prescribe such systems. Improving adoption rates is a priority area for the AP program, and although some ways to address this area are beyond the scope of research, there are other constructive ways the AP program can drive progress.

Although there is currently only one hybrid closed-loop system (approved by regulatory agencies) on the market, there are others nearing the market, each with its own set of features that may fit the lives of some people with T1D better than others. This imminent improvement in choice should help greatly to expand the reach of AP systems among the T1D population. In addition,

while the usual cadence of corporate-sponsored clinical studies of systems in development typically initially excludes (or at least does not focus on) use of the systems by sub-populations with unique characteristics and needs, e.g., pregnant women or older adults, we are now beginning to focus on these groups. Further adoption increases are expected by performing clinical studies demonstrating the benefits of using these systems – or identifying shortcomings in current design paradigms which can inform future development efforts.

Critical Gaps

Progress toward Next-Gen External Systems

To accelerate progress towards next-generation systems, we are focusing efforts on addressing solutions to these critical gaps:

1. Full, Effective Automation of Drug Delivery

Currently, automation of drug delivery to effectively normalize glucose levels is limited by the lack of data available to the algorithms, the sub-optimal pharmacokinetic and pharmacodynamic properties of current insulin formulations (and the inability of systems to incorporate the delivery of adjunctive drugs), and a lack of advanced algorithms that can learn and adapt to changing conditions.

- Algorithms do not have enough information to automate drug delivery effectively. By incorporating inputs beyond glucose, algorithms will be better informed of physiological activities/states affecting glucose control, and can incorporate these data to more effectively automate drug delivery.
- Drugs used in current AP systems – i.e., rapid-acting insulin formulations – are sub-optimal for achieving normalized glucose levels. Development of faster-acting and/or liver targeted insulins and/or incorporation of adjunctive drugs (whether via a co-formulation with insulin or otherwise) can enable the algorithms to be more effective in controlling glucose effectively.
- Algorithms do not effectively learn from previous data or adapt to changing conditions. Adaptive systems leveraging advanced machine learning techniques can improve the robustness of the algorithms in normalizing glucose levels and ameliorate inter- and intra-patient variability.

2. Minimal User Burden

Current AP systems are associated with a high degree of user burden – both in terms of physical/on-body burden and interactional/mental burden.

- Devices are large/bulky and require frequent replacements of consumables and rotation of infusion sites. Such on-body burden can be significantly lowered by developing miniaturized, more discreet systems, longer-lasting consumables requiring less frequent replacements/rotations, and infusion sets integrating glucose sensors.
- User interactions with devices are currently not discreet, requiring physically interfacing with the AP devices/components. Improved interactional user experiences can be achieved by developing systems which transition functionality to discreet app-based interfaces.
- Even with hybrid closed-loop systems, frequent self-management decision-making is still required of the user. Developing ways to automate decisions or make them easier and/or less time-consuming can reduce this mental burden.

3. Broad Adoption and Successful Utilization

Current AP systems have not yet been widely adopted due to a number of factors.

- There is a dearth of choice in available AP systems, greatly limiting adoption of such systems. Expanding the choices available to users – or more importantly, potential users – in terms of types and features of AP systems/components will help drive adoptions rates significantly, enabling people with type 1 diabetes to choose the device or device configuration that works best for them.
- Current systems are not labeled for and/or under-studied in certain populations of potential users, presenting a barrier to adoption among these people. The generation of clinical evidence demonstrating the benefits of AP systems in these populations – or otherwise the identification of shortcomings of current systems which may be addressed in future systems – can encourage prescriptions and adoption among these important sub-populations.

Progress toward the Artificial Pancreas: A Physiologic System

There are additional gaps to address before the aspirational systems are available:

4. Physiologic Delivery of Insulin to the Peritoneal Cavity

Currently, two systems enable physiologic insulin delivery directly to the peritoneal cavity, but these systems have significant caveats and are – not surprisingly – under-utilized. There is currently a need for a new generation of miniaturized AP systems/devices featuring physiologic insulin delivery that are free of the problems associated with the current systems.

- Current systems are bulky (and aesthetically unappealing) and can exert stresses on tissues causing an inflammatory response. The development of miniaturized, implantable devices capable of pumping insulin with high degrees of accuracy and precision is needed.
- Current systems are prone to occlusions and biological encapsulation effects. Novel technologies addressing these issues are crucial to ensuring proper performance and reliably over long periods of time.
- There do not yet exist ideal insulin formations that will work with these systems. Ultra-concentrated and ultra-stable insulin formulations designed for intraperitoneal delivery are crucial to the success of these devices.
- Algorithms for IP delivery to enable full automation are not mature. Although algorithms for IP delivery of insulin have been developed, these have only been tested to respond to glucose levels and manage increases in glucose levels after meals. Algorithms designed specifically for this purpose must be developed and sufficiently validated to enable full automation.

5. Sensing of Glucose in the Peritoneal Cavity

Research suggests that sensing of glucose in the peritoneal space provides faster kinetics than subcutaneous sensing which could result in improved glycemic control and help enable full automation of insulin delivery. These sensors are in preclinical development; there are no systems developed yet to measure glucose in the peritoneal cavity in humans.

- Continuous intraperitoneal glucose sensors for use in humans do not exist.
- Catheters for IP insulin delivery integrated with continuous IP glucose sensors to enhance usability do not exist.

Regulatory Pathway

Artificial pancreas systems are regulated as medical devices by FDA in the US. 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 CDRH, is very engaged with JDRF, commercial entities developing AP systems, and the larger T1D community which results in interactive and streamlined regulatory interactions.

The overall strategy to ensure that all AP systems continue to have clear and reasonable regulatory pathways is to continue to engage with FDA, Industry, and researchers, monitoring progress and anticipating and addressing issues proactively.

To that end, a focus recently has been on the regulatory framework for open-protocol AP systems where components from individual manufacturers are cleared or approved separately by FDA, enabling the end user to choose from a variety of components to essentially assemble their own AP system. FDA has recently created two new device types, the integrated CGM (or “iCGM”), and the alternate controller-enabled insulin pump (or “ACE pump”), and has steadfastly expressed a willingness to create an analogous device type for an interoperable AP controller. JDRF has been instrumental in fostering this with FDA and will continue to ensure that these additional pathways are clear and reasonable.

Therapeutic Concepts

The below therapeutic concepts, mapped to a generation/embodiment in the AP roadmap, are based on clinical trial data and real-world observations of the systems that have reached the market and/or are approaching the market, and preliminary research and input from key opinion leaders on the future-generation systems.

Gen 1 – Low Glucose Suspend Systems

Parameter	Target
Primary Indication	Reduction of the frequency, severity, and duration of hypoglycemia
Target Population	People with type 1 diabetes, all ages
Features	**Automation**: Insulin reduction/suspension when glucose falls or is predicted to fall below low threshold **Burden**: Frequent user-initiated dosing/interaction; 3-day infusion set replacements and insulin reservoir replacements
Efficacy Targets	Time in range (70-180 mg/dL): >65% Time < 70 mg/dL: <4% Time < 54 mg/dL: <1%
Risk/Side Effect	- Catheter occlusions leading to hyperglycemia and/or DKA - Subcutaneous insulin administration leading to lipohypertrophy - Intermittent CGM inaccuracy leading to algorithm dosing errors - Intermittent interruptions in CGM wireless communication leading to interruptions in closed-loop control

Gen 2 – Hybrid Closed-Loop Systems

Parameter	Target
Primary Indication	Reduction of the frequency, severity, and duration of hypo- and hyperglycemia
Target Population	People with type 1 diabetes, all ages
Features	**Automation**: Partial automation of insulin delivery: basal modulation **Burden**: User-initiated dosing/interaction for meals and other situations; 3-day infusion set replacements and insulin reservoir replacements
Efficacy Targets	Time in range (70-180 mg/dL): >70% Time < 70 mg/dL: <4% Time < 54 mg/dL: <1% Time > 180 mg/dL: <20% Psychosocial improvements leading to enhanced quality of life
Risk/Side Effect	- Catheter occlusions leading to hyperglycemia and/or DKA - Subcutaneous insulin administration leading to lipohypertrophy - Intermittent CGM inaccuracy leading to algorithm dosing errors - Intermittent interruptions in CGM wireless communication leading to interruptions in closed-loop control

Aspirational – External Fully Closed-Loop Systems

Parameter	Target
Primary Indication	Near-normalization of glucose levels
Target Population	People with type 1 diabetes, all ages
Features	**Automation**: Full automation of drug (insulin and possibly other adjunctive drugs) delivery for all situations **Burden**: Infrequent/rare user-initiated dosing/interaction for extraneous circumstances; miniaturized devices; 7-to-10-day infusion set replacements and insulin reservoir replacements; integrated infusion/sensing port; minimal-to-no finger-sticks required (for CGM calibrations or otherwise)
Efficacy Targets	Time in range (70-180 mg/dL): >90% Time < 70 mg/dL: <2% Time < 54 mg/dL: ~0% Time > 180 mg/dL: <5% Significant psychosocial improvements leading to enhanced quality of life
Risk/Side Effect	Subcutaneous insulin administration leading to lipohypertrophy

Aspirational – The Artificial Pancreas: A Physiologic System

Parameter	Target
Primary Indication	Normalization of glucose levels
Target Population	People with type 1 diabetes, all ages
Features	**Automation**: Full automation of drug (insulin and possibly other adjunctive drugs) delivery via physiologic route for all situations **Burden**: No user interaction or day-to-day burden; infrequent (~4x per year) visits to doctor's office for insulin refills and/or sensor changes
Efficacy Targets	Time in **tight** glucose range (80-120 mg/dL): >90% Time < 70 mg/dL: <1% Time < 54 mg/dL: ~0% Time > 180 mg/dL: <5% Significant reduction in glycemic variability Significant psychosocial and metabolic improvements leading to enhanced quality of life
Risk/Side Effect	Surgical procedure required for implantation of device/components; associated complications and recovery time

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