# Closing the Loop on Managing Youth With Type 1 Diabetes: Children Are Not Just Small Adults

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**As hybrid closed-loop (HCL) insulin delivery systems permeate clinical practice, it is critical to ensure all with diabetes are afforded the opportunity to benefit from this technology. Indeed, due to the suboptimal control achieved by the vast majority of youth with type 1 diabetes (T1D), pediatric patients are positioned to see the greatest benefit from automated insulin delivery systems. To ensure these systems are well poised to deliver the promise of more targeted control, it is essential to understand the unique characteristics and factors of childhood. Herein, the developmental and physiological needs of youth with T1D are reviewed and consideration is given to how HCL could address these issues. Studies of HCL technologies in youth are briefly reviewed. As future-generation closed-loop systems are being devised, features that could make this technology more attractive to youth and to their families are discussed. Integration of HCL has the potential to minimize the burden of this chronic medical condition while improving glycemic control and ultimately allowing our pediatric patients to fulfill the primary goal of childhood, to be a kid.**

"Children are not small adults" is a phrase that every pediatric practitioner becomes well aware of during training. Indeed, the developmental changes that are the hallmark of this stage of life will never be recapitulated. In growing children with type 1 diabetes (T1D), the burden of having to constantly adjust insulin needs is a never-ending challenge, especially when growth and development accelerate during puberty. It is not surprising that the summit of suboptimal control of T1D is observed in adolescence (1). Pivotal trials of new drugs and technologies for diabetes are typically carried out first in adults, not only to avoid unnecessary exposure of children to unexpected adverse effects of new therapies but also because near-optimal control of T1D is much more common in adults than in children and adolescents. Thus, it is of utmost importance to consider factors that require special attention during childhood.

In our youngest patients, the inability to communicate needs may lead caregivers to adopt a strategy of constant vigilance (2). Despite such vigilance, it was reported that 90% of hypoglycemic events detected by blinded continuous glucose monitoring (CGM) in infants and toddlers occurred without concomitant symptoms of hypoglycemia detected by their caregivers (3). Due to unpredictable changes in appetite and food intake, many families of young children administer meal boluses after instead of before eating, even at the expense of greater postprandial hyperglycemia and the suboptimal glycemic control that this approach is associated with (4). Nighttime is often the worst time for parents of young children with diabetes due to fears about hypoglycemia, which leads to disturbed sleep patterns secondary to the need to monitor overnight blood glucose levels two or more times per night (5,6).

School-aged children are in the care of numerous adults throughout the day: parents, teachers, coaches, after-school caretakers, and school bus drivers. The competency of

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**See accompanying articles, pp. 1563 and 1579.**

these adults to care for a child with diabetes can be quite variable (7). Furthermore, nearly 45% of parents indicated that their school-aged children themselves were the primary person taking care of their diabetes during school days (7). Fear of hypoglycemia may prompt parents to set higher target blood glucose levels especially during school hours (8,9).

The insulin resistance of puberty is not the only challenge faced by adolescents with T1D (10). Adolescence is a stage of tumultuous emotional upheaval, during which teenagers vie for autonomy. Unfortunately, such autonomy is too often expressed by the refusal to engage in the daily tasks of diabetes treatment, and "diabetes burnout" is all too common in this age-group. This increases the need for continued parental and clinician support to encourage teens to help develop and maintain their commitment to treatment goals (11). While toddlers may not have the communication skills necessary to assist with their care, teenagers often lack desire to communicate with their parents and friends about their condition.

## WHY IS INTEGRATION OF PUMPS AND SENSORS IN YOUTH WITH T1D CRITICAL?

Paradoxically, most advances in diabetes technology that began with the introduction of insulin pump therapy 40 years ago (8,9) have increased rather than decreased the burdens of managing T1D. Despite evidence that these new devices could lower $HbA_{1c}$ levels and reduce the risks of diabetic ketoacidosis and severe hypoglycemia, their uptake in youth with diabetes was markedly delayed (12). It was not until the turn of the century that use of pump therapy became commonplace in the pediatric population. Even now, epidemiological data from T1D registries in the U.S. and Europe indicate that ~50% of youth with T1D use insulin pumps (13). Moreover, a small percentage of youth with T1D were using CGM consistently and effectively until very recently because the burdens and hassles of using these devices outweighed the benefits perceived by parents and children alike (1,14).

Despite the checkered early history of pump and CGM use in pediatrics, there is now clear evidence that times are changing. More recent T1D Exchange registry data indicate a steady increase in pump use and an even more impressive four- to fivefold jump in use of CGM in children and adolescents (15). Why the change? Insulin pumps keep getting smarter, with the integration of bolus calculators and insulin on board features to help prevent stacking of doses, and CGM devices have become so accurate that sensor glucose values can replace the need for confirmatory blood glucose meter measurements. Nevertheless, the most important breakthrough has been the successful integration of both pumps and sensors into a single system that can provide feedback control of the rates of insulin delivery. Pediatric providers now have transformational devices available that can improve clinical outcomes with less effort required by the patient and their families. Furthermore, these devices have the opportunity to minimize human error, such as inaccurate carbohydrate counting, that often occurs in clinical practice.

## WHY HYBRID CLOSED-LOOP RATHER THAN FULL CLOSED-LOOP DELIVERY?

It is important to note that the first generation of artificial pancreas systems will use a hybrid, semiautomatic approach instead of functioning as a fully closed-loop insulin delivery system (16). With hybrid closed-loop (HCL) devices, overnight and between-meal insulin infusion rates are varied automatically in response to changes in sensor glucose values. However, the maximum hourly insulin infusion rate is severely limited in order to mitigate patient injury due to overdelivery of insulin due to a system malfunction. Consequently, as in open-loop treatment, premeal boluses sufficient to cover the carbohydrate content of meals still have to be manually administered by the patient.

## BENEFITS OF HCL CONTROL IN PEDIATRICS

It is clear that many of the special challenges in managing diabetes borne by parents of young children with T1D will be alleviated with the use of the first-generation HCL systems. Importantly, parents can be reassured that automated suspension of basal insulin based on a predicted low sensor glucose level will mitigate the risk of hypoglycemia. Conversely, in older children and adolescents who may forget, whether consciously or subconsciously, to take premeal boluses, the HCL system will automatically increase between-meal insulin infusion rates to minimize postmeal hyperglycemia, albeit to a limited extent. With constant growth and development, a key feature of childhood, use of HCL systems that use adaptive algorithms for changing insulin needs will provide patients with a seamless means of reaching prescribed glycemic targets.

Perhaps the most important feature of HCL systems is their ability to automatically regulate overnight insulin infusion rates based on changes in sensor glucose values. Einstein defined insanity as doing the same thing over and over again and expecting a different result. However, in T1D patients receiving open-loop therapy, insanity is doing the same thing over and over again and always getting a different result. Because so many factors alter insulin requirements during the night, almost every night in the life of a patient with T1D receiving fixed overnight basal rates has been an adventure. In contrast, as illustrated in Fig. 1, HCL systems are able to vary insulin infusion rates from night to night and during different times of the night to mitigate both hyper- and hypoglycemic excursions; namely, doing something different every night but always getting a good result. Moreover, patients and parents may benefit from improved sleep patterns, as the need for intermittent overnight blood glucose meter measurements and sensor alarms will be minimized. Indeed, improved sleep has been endorsed by participants in studies of HCL insulin delivery that assessed the psychosocial impact of system use (17–20).

## STUDIES OF HCL THERAPY IN YOUTH

Over the last decade, studies of HCL devices in youth rapidly progressed from short-term safety and feasibility studies conducted in clinical research facilities to assessments of these investigational devices in more transitional environments afforded by camps and hotels (21–27). The vast majority of these studies demonstrated the superiority of closed-loop insulin delivery as compared with either conventional pump therapy or sensor-augmented pump therapy, with decreased frequency of hypoglycemia and increased time in target range, especially during the night (21,22,24–27). These studies set the stage for testing HCL devices in the real world (21–30). During most of the free-living outpatient studies, there was a 10–20% increase in time in target range with a concomitant reduction in frequency of hypoglycemia.

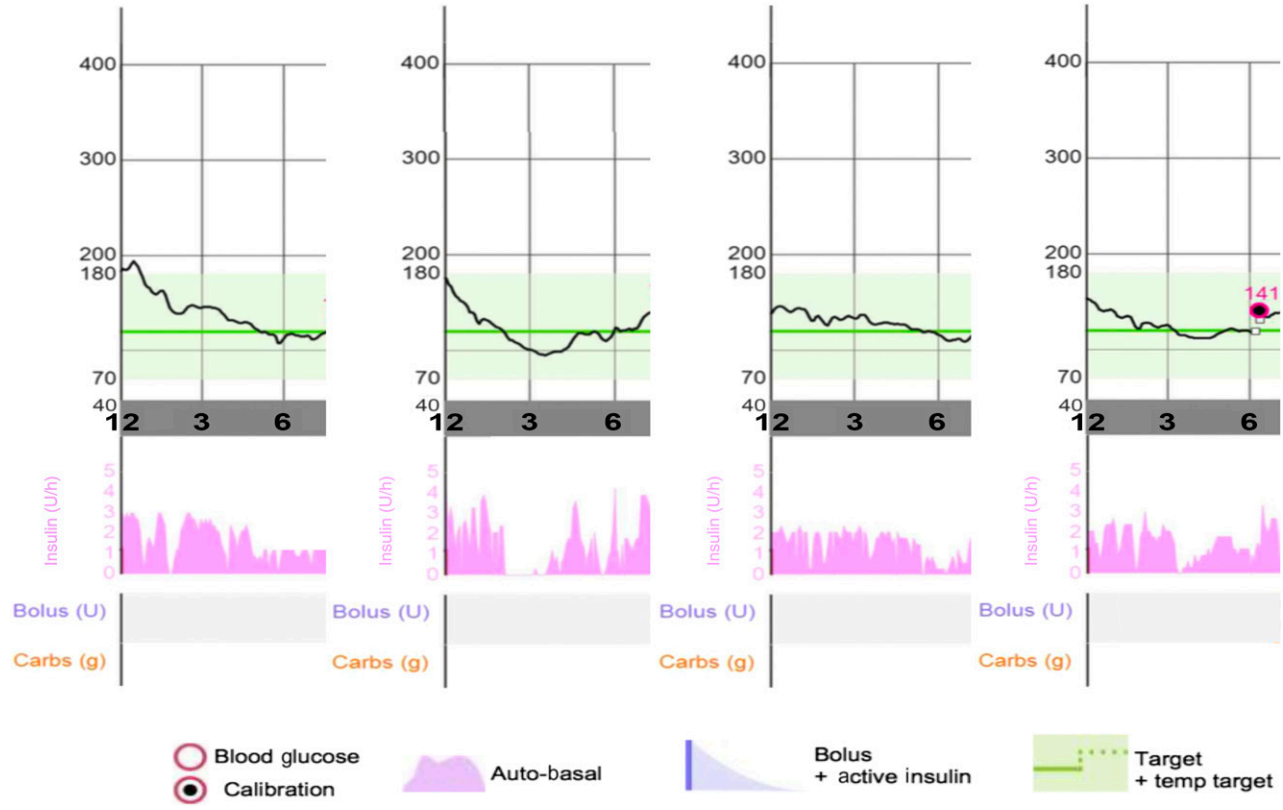


**Figure 1**—Four nights (12 A.M.–7 A.M.) in a single patient using the 670G system. In each panel, sensor glucose tracing is represented as the black line, with the system set point of 120 mg/dL (6.7 mmol/L) denoted by the solid green line. The target range of 70–180 mg/dL (3.9–10 mmol/L) is shaded in light green. The lower panel displays in pink the variable automated basal insulin delivery (Auto-basal) that is driven by the sensor glucose values. Carbs, carbohydrates; temp, temporary; U, units.

In 2016, the U.S. Food and Drug Administration approved the first HCL system, the Medtronic MiniMed 670G system, based on a 3-month, single-arm study that included 30 adolescents (defined as those aged 14–21 years: mean ± SD age 16.5 ± 2.29 years) and 94 adults (defined as age 22–75 years: mean ± SD age 44.6 ± 12.79 years) with T1D (28). In both age-groups, there were no episodes of diabetic ketoacidosis or severe hypoglycemia. Furthermore, time in range increased, and $HbA_{1c}$ was reduced by 0.6% (6.6 mmol/mol) in adolescents and 0.5% (5.5 mmol/mol) in adults ($P < 0.001$ compared with baseline values in both groups) (29). More recently, the same design was used in a pediatric study of 105 participants aged 7–13 years (30). Once again, HCL control in these younger patients resulted in a reduction in $HbA_{1c}$ (from 7.9% [62.3 mmol/mol] to 7.5% [58.8 mmol/mol], $P < 0.001$) and an increase in time in target range (Fig. 2) (30). Ongoing studies will assess the use of this system in 2- to 6-year-olds. Additionally, numerous trials of closed-loop insulin delivery in youth are being conducted (Table 1).

## PERFORMANCE OF THE 670G SYSTEM: INSIGHTS FROM CLINICAL PRACTICE DATA

Ensuring these systems perform well in rigorous clinical trials is essential; yet, the true test of these devices is how they work once integrated into clinical practice. With over 15,000 users identified through CareLink data uploads from 17 March 2017 through 31 December 2017, the effectiveness of this technology could be explored (31). An 8.5% increase in time in target range, defined as 70–180 mg/dL (3.9–10.0 mmol/L) ($P < 0.001$) was observed after switching from open-loop mode to HCL insulin delivery with the 670G, primarily due to a reduction in time spent >180 mg/dL (10 mmol/L) (31). When the data are further parsed based on time of day, the rise in time in target range is 11% for the overnight period (10 P.M.–7 A.M.) and 15% for the early morning hours (3 A.M.–6 A.M.). It is also very revealing that patients in clinical practice used HCL insulin delivery 80% of the time, thus endorsing their desire to have their glucose sensors automatically drive the 670G pump the vast majority of time (31).

## NEW FEATURES TO PROMOTE HCL USE IN PEDIATRICS

To have these devices used by as many youth with T1D as possible, it will be important for manufacturers to incorporate the desires of patients and their families in the next generation of systems. Families have grown accustomed to remote monitoring of CGM data; many will seek closed-loop insulin delivery systems that afford this option (32). Parents of infants and toddlers value insulin pump systems that have incorporated remote bolusing features, and similar functions should be incorporated in HCL systems. While limited access to various system features may be desired for youngsters, as children mature and display greater understanding of their own condition, the use of passcodes or variable access categories may allow the system to "grow" with them (32). Other focus groups have expressed the desire for these devices to be more discreet (33).

In young children being treated with low total daily doses of insulin, use of diluted insulin may improve glycemic control and

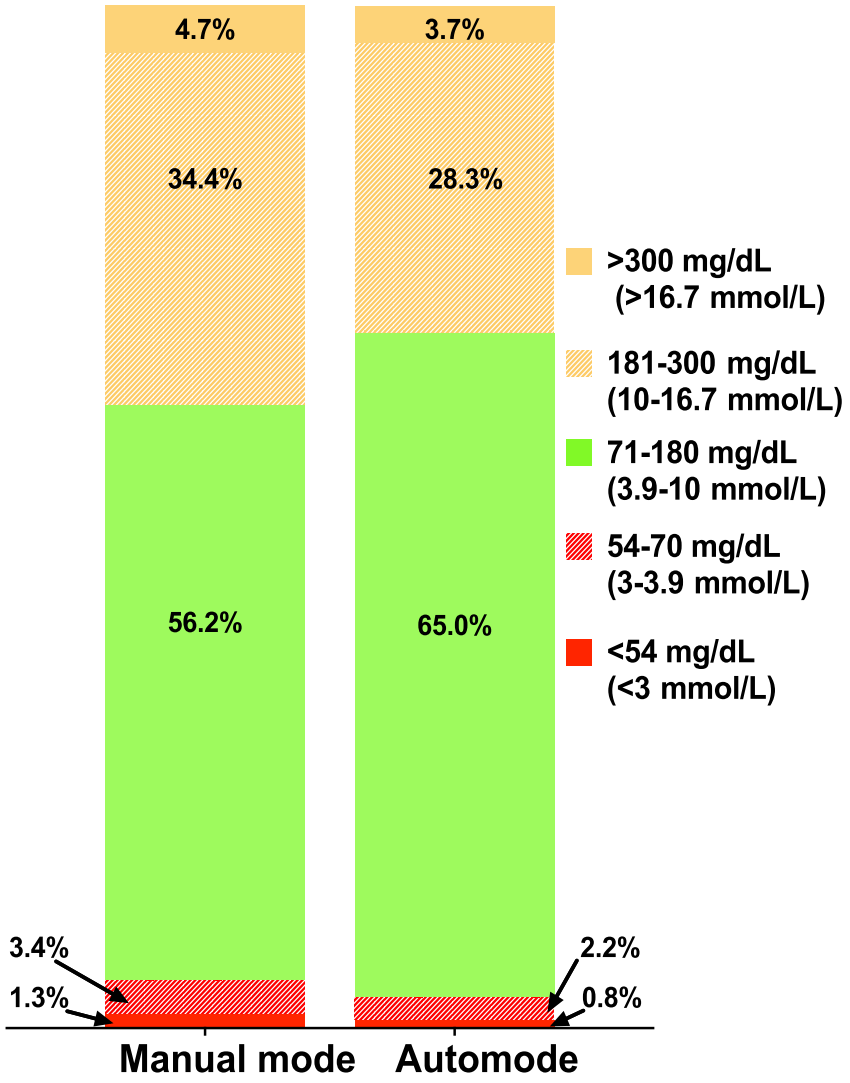


**Figure 2**—Comparison of time in target ranges during the 2-week run-in phase using open-loop pump settings to data from the 3-month HCL period for pediatric participants (aged 7–13 years old) in the 670G trial (30).

variability. Elleri et al. (34) reported that use of diluted insulin during overnight closed-loop control in 3- to 6-year-olds reduced rates of hypoglycemia and tended toward reduced glycemic variability as compared with standard insulin strength. Additionally, analysis of the data from that study demonstrated reduced interindividual variability in time to peak insulin action with diluted insulin (35). The reduced interindividual variability could be attributed to a reduction of mechanical delivery errors and more consistent absorption due to the larger volume of the subcutaneous deposit (35). Hvorka and colleagues are conducting an open-label, randomized crossover assessment of diluted insulin as compared with commercially available insulin preparations in children aged 1–7 years (NCT03101865).

In the midst of the era of personalized medicine, allowing for customization of these systems will also assist with their adoption. While the first commercially available closed-loop system alters basal insulin delivery to achieve a prefixed target of 120 mg/dL (6.7 mmol/L), with correction boluses targeting a glucose of 150 mg/dL (8.3 mmol/L), systems currently in development provide the option to alter this parameter. For pediatric patients, having alerts that are customizable is critical; for some, distinct auditory tones are desired, while others want to make sure alarms are discreet. As alerts may be missed overnight while asleep, determining strategies to amplify alerts or send the signal to other devices may improve reaction to system alarms. Simplifying meal announcement strategies will also reduce burden; some systems in development have adopted the approach of meal size rather than discrete carbohydrate content entry to address this. Finally, strategies to help manage glucose during exercise will be critical, as physical activity is a cornerstone of care. While closed-loop insulin delivery has been shown to reduce overnight hypoglycemia (36), automated insulin delivery without an exercise adaptation is not sufficient to mitigate hypoglycemia during physical activity. The first commercially available HCL system has a temporary target that increases the system set point from 120 mg/dL (6.7 mmol/L) to 150 mg/dL (8.3 mmol/L) in half-hour increments to a maximum duration of 12 h, and it is recommended that patients initialize this higher target 1–2 h prior to commencing exercise. Yet, some may find that this does not suffice to prevent hypoglycemia, and spontaneous exercise may make alteration of insulin delivery less feasible. Consensus guidelines to assist with glucose management in those with T1D have been developed based on starting glycemia and type of exercise (37), and feasibility studies have shown that consumption of supplemental carbohydrates during HCL insulin delivery may help mitigate hypoglycemia that may occur during physical activity (38). Various strategies to announce exercise are being explored for future iterations of HCL systems and will be fundamental to providing our youth the ability to participate fully in sports programs.

While first-generation systems will require a hybrid approach and meal announcement, it is anticipated that future generations of closed-loop artificial pancreas systems will be able to automatically deliver the full amount of insulin required for carbohydrate intake. Dual-hormone systems are also being explored, whether it be through the addition of glucagon in hopes of more closely approximating normal physiological function by infusing glucagon when sensor glucose levels trend low or through the addition of other adjunctive therapies, such as pramlintide or liraglutide (26,39,40).

## CONCLUSIONS

The approval of the first HCL device for T1D has opened the door for other systems that are potentially beneficial for youth of all ages, and ensuring that our youth are not left behind in this technological revolution will be critical. It is

**Table 1—Studies from ClinicalTrials.gov of closed-loop insulin delivery in youth with T1D**

| Study title | Age for inclusion | Environment* | ClinicalTrials.gov identifier | Device | Duration of closed-loop treatment |
|---|---|---|---|---|---|
| Safety Evaluation of the Hybrid Closed Loop (HCL) System in Pediatric Subjects With Type 1 Diabetes | 2–13 years | Free living | NCT02660827 | Medtronic 670G | Single-arm, nonrandomized 2-week run-in with usual pump settings, then 3-month HCL use |
| Comparison of Two Closed-Loop Strategies for Glucose Control in Type 1 Diabetes: The DREMED Trial-2 | 12–25 years | Segment 1: inpatient; segments 2 and 3: transitional (camp) | NCT02776696 | HCL vs. advanced HCL system | Segment 1: two 36-h inpatient admissions; segment 2: RCT with 2 days on each treatment; segment 3: randomized parallel design for 12 days on one of four HCL systems |
| Glycemic Control and the Brain in Children With Type 1 Diabetes | 14–17 years | Free living | NCT03428932 | Medtronic 670G | 6-month RCT of usual care vs. HCL |
| Cross-over Study to Evaluate the Safety and Efficacy of Night Closed-loop Control Using the MD-Logic Automated Insulin Delivery System Compared to Sensor Augmented Pump Therapy in Poorly Controlled Patients With Type 1 Diabetes | 10–18 years | Free living, nighttime closed-loop control | NCT02733211 | MD-Logic Automated Insulin Delivery System | 4-week crossover study of closed-loop insulin delivery overnight vs. SAP |
| The Artificial Pancreas in Very Young Children With T1D - Pilot (KidsAP01) | 1–7 years | Free living | NCT03101865 | FlorenceM closed-loop system | 3-week comparison of HCL using standard concentration insulin vs. diluted insulin |
| Closed Loop From Onset in Type 1 Diabetes (CLOuD) | 10–18 years | Free living | NCT02871089 | FlorenceM closed-loop system | 2-year RCT of HCL vs. usual care (injection therapy) |
| Adolescence and Diabetes: Can an Automated Closed Loop System Improve Control? (SPIDIMAN2) | 12–18 years | Free living | NCT03300934 | FD2 closed-loop system | 28-day two-period crossover study of HCL vs. pump therapy |
| Fuzzy Logic Automated Insulin Regulation (FLAIR) | 14–30 years | Free living | NCT03040414 | Medtronic 670G vs. advanced HCL system (PID + Fuzzy Logic) | 3-month RCT with crossover between the two study conditions |
| Closed-loop Control of Glucose Levels (Artificial Pancreas) for 15 Weeks in Adolescents and Adults With Type 1 Diabetes | ≥12 years | Free living | NCT02846857 | Dual-hormone vs. single-hormone closed-loop system | 15-week RCT of SAP vs. single-hormone closed-loop vs. dual-hormone closed-loop |
| Multi-center Trial in Adult and Pediatric Patients With Type 1 Diabetes Using Hybrid Closed Loop System at Home | 2–80 years | Free living | NCT02748018 | Medtronic 670G | 6-month RCT of HCL vs. usual care followed by 6-month continuation phase |
| Day and Night Closed-loop in Young People With Type 1 Diabetes (DAN05) | 6–18 years | Free living | NCT02925299 | FlorenceM | 6-month RCT of HCL vs. usual care |
| The International Diabetes Closed Loop (iDCL) Trial: Protocol 1 | ≥14 years | Free living | NCT02985866 | Artificial Pancreas with inControl Diabetes Management Platform | 3-month RCT of HCL vs. SAP therapy |

*Continued on p. 1577*

**Table 1—Continued**

| Study title | Age for inclusion | Environment* | ClinicalTrials.gov identifier | Device | Duration of closed-loop treatment |
|---|---|---|---|---|---|
| Safety and Efficacy of Artificial Pancreas With and Without a Meal Detection Module on Glycemic Control in Adolescents With Type 1 Diabetes After a Missed Bolus | 12–18 years | Inpatient | NCT02909829 | Closed-loop insulin delivery with a meal-detection mode | 9 h of HCL on three visits |
| International Diabetes Closed Loop (iDCL) Trial: Research Site Training Protocol | 14–74 years | Free living | NCT02844517 | inControl Diabetes Management Platform | 2 weeks of HCL use |
| Clinical Startup of the 670G Closed Loop Insulin Delivery System (670Gstartup) | ≥7 years | Free living | NCT03017482 | Medtronic 670G | Observational up to 1 year post–HCL initiation |
| Home Testing of Day and Night Closed Loop With Pump Suspend Feature (APCam11) | ≥6 years | Free living | NCT02523131 | FlorenceM | 3-month RCT of HCL vs. pump suspend feature vs. insulin pump therapy |
| Insulet Artificial Pancreas Free-Living IDE3 | 2–65 years | Transitional | NCT03216460 | Insulet automated glucose control system | 5-day/4-night HCL |

PID, proportional integral derivative; RCT, randomized controlled trial; SAP, sensor-augmented pump. *Defined as inpatient, research unit–based, transitional environment in hotels and camps, or free-living outpatient studies.

essential to recognize the unique factors that must be considered in the development of closed-loop systems for youth while also conducting studies and seeking regulatory approval for these systems in the pediatric population. As childhood is a time of both physical and mental development, a system that can adjust insulin delivery in real time based on sensor glucose readings will more closely mimic normal physiology than what can be achieved with quarterly health care visits. Furthermore, as described by participants in HCL studies, waking with fasting glucose levels close to target range may allow for better sleep and an improved start to the day (20), a finding that has been corroborated by youth and their parents (19). As Sir William Osler said, "The good physician treats the disease, the great physician treats the patient who has the disease." When caring for our youth with T1D, it is critical to remember first and foremost that our patients are kids. Closed-loop insulin delivery holds the promise to improve glycemic control while reducing the burden of this chronic medical condition, allowing pediatric patients with T1D to just be kids.

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