Medical Policy

BlueCross BlueShield Kansas
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Title: Automated Insulin Delivery Systems

Related Policy:	*Continuous Glucose Monitoring*

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Populations	Interventions	Comparators	Outcomes
Individuals: • With type 1 diabetes	Interventions of interest are: • Automated insulin delivery system with a low-glucose suspend feature	Comparators of interest are: • Non-integrated continuous glucose monitoring plus insulin pump • Self-monitoring blood glucose and multiple dose insulin injection therapy	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Resource utilization • Treatment-related morbidity
Individuals: • With type 1 diabetes	Interventions of interest are:	Comparators of interest are:	Relevant outcomes include: • Symptoms

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Individuals: • With type 2 diabetes	Interventions of interest are: • Automated insulin delivery system with a hybrid closed-loop insulin delivery system	Comparators of interest are: • Lifestyle changes • Medications • Long-term glucose monitoring • Weight management • Education and Support	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Resource utilization Treatment-related morbidity

DESCRIPTION

Automated insulin delivery systems, also known as artificial pancreas device systems, link a glucose monitor to an insulin infusion pump that automatically takes action (e.g., suspends or adjusts insulin infusion) based on the glucose monitor reading. These devices are proposed to improve glycemic control in patients with insulin-dependent diabetes, in particular, reduction of nocturnal hypoglycemia.

OBJECTIVE

The objective of this evidence review is to determine whether automated insulin delivery (AID) systems improve the net health outcome in nonpregnant individuals with diabetes compared with standard glucose monitoring, either continuous glucose monitoring or self-monitoring of blood glucose, plus an insulin pump or multiple insulin injection therapy.

BACKGROUND

Diabetes and Glycemic Control

Tight glucose control in patients with diabetes has been associated with improved health outcomes. The American Diabetes Association has recommended a glycated hemoglobin level below 7% for most patients. However, hypoglycemia may place a limit on the ability to achieve tighter glycemic control. Hypoglycemic events in adults range from mild to severe based on a number of factors including the glucose nadir, the presence of symptoms, and whether the episode can be self-treated or requires help for recovery. Children and adolescents represent a population of individuals with type 1 diabetes who have challenges in controlling hyperglycemia and avoiding hypoglycemia. Hypoglycemia is the most common acute complication of type 1 diabetes.

Table 1 is a summary of selected clinical outcomes in type 1 diabetes clinical management and research.

Table 1. Outcome Measures for Type 1 Diabetes

Measure	Definition	Guideline type	Organization	Date
Hypoglycemia		Stakeholder survey, expert opinion with evidence review	Type 1 Diabetes Outcome Program[a1,]	2017
Level 1 Level 2 Level 3	Glucose <70 mg/ dL but ≥54 mg/ dL Glucose <54 mg/ dL Event characterized by altered mental/physical status requiring assistance			
Hypoglycemia	Same as Type 1 Diabetes Outcome Program[a]	Professional Practice Committee with systematic literature review	ADA[2,]	2019
Hypoglycemia Clinical alert for evaluation and/or	 Glucose <70 mg/ dL Glucose <54 mg/ dL	Clinical Practice Consensus	ISPAD[3,]	2018

Measure	Definition	Guideline type	Organization	Date
treatment Clinically important or serious Severe hypoglycemia	Severe cognitive impairment requiring external assistance by another person to take corrective action			
Hyperglycemia Level 1 Level 2	 Glucose >180 mg/dL and ≤250 mg/dL Glucose >250 mg/dL		Type 1 Diabetes Outcome Program[a4,]	2017
Time in Range[b]	Percentage of glucose readings in the range of 70 to 180 mg/dL per unit of time		Type 1 Diabetes Outcome Program[a]	2017
Diabetic ketoacidosis (DKA)	Elevated serum or urine ketones >ULN Serum bicarbonate <15 mEq/L Blood pH <7.3		Type 1 Diabetes Outcome Program[a2,]	2017

ADA: American Diabetes Association, ISPAD: International Society for Pediatric and Adolescent Diabetes; ULN: upper limit of normal.
[a]Steering Committee: representatives from American Association of Clinical Endocrinologists (AACE), American Association Diabetes Educators, the American Diabetes Association (ADA), the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, type 1 diabetes Exchange.
[b]Time in range: has also been adopted by researchers evaluating the precision and effectiveness of emerging glucose monitoring and automated insulin delivery technologies.

Outcome measures for type 2 diabetes have been published, including those used for clinical trials focused on non-surgical treatments addressing hyperglycemia in adults with type 2 diabetes.[5,]

Treatment

Type 1 diabetes is caused by the destruction of the pancreatic beta cells which produce insulin, and the necessary mainstay of treatment is insulin injections. Multiple studies have shown that intensive insulin treatment, aimed at tightly controlling blood glucose, reduces the risk of long-term complications of diabetes, such as retinopathy and renal disease. Optimal glycemic control, as assessed by glycated hemoglobin, and avoidance of hyper- and hypoglycemic excursions have been shown to prevent diabetes-related complications. Currently, insulin treatment strategies include either multiple daily insulin injections or continuous subcutaneous insulin infusion with an insulin pump.

Advancements in diabetes technology have significantly improved the management of type 2 diabetes, particularly through the use of continuous glucose monitoring (CGM). CGM has been linked to better glycemic control, despite ongoing challenges for those on insulin therapy to meet their targets. Automated insulin delivery (AID) systems, which have shown benefits in type 1 diabetes, are being explored for type 2 diabetes to address dynamic insulin needs and improve outcomes. AID has the potential to enhance patient satisfaction and ease the complexity of intensive insulin regimens, though clinical data for type 2 diabetes is still limited.

Restoration of pancreatic function is potentially available through islet cell or allogeneic pancreas transplantation.

REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) describes the basic design of an automated insulin delivery (AID) system as a continuous glucose monitoring linked to an insulin pump with the capability to automatically stop, reduce, or increase insulin infusion based on specified thresholds of measured interstitial glucose.[6,]

The AID system components are designed to communicate with each other to automate the process of maintaining blood glucose concentrations at or near a specified range or target and to minimize the incidence and severity of hypoglycemic and hyperglycemic events. An AID system control algorithm is embedded in software in an external processor or controller that receives information from the continuous glucose monitoring and performs a series of mathematical calculations. Based on these calculations, the controller sends dosing instructions to the infusion pump.

Different AID system types are currently available for clinical use. Sensor augmented pump therapy with low glucose suspend (suspend on low) may reduce the likelihood or severity of a hypoglycemic event by suspending insulin delivery temporarily when the sensor value reaches (reactive) a predetermined lower threshold of measured interstitial glucose. Low glucose suspension automatically suspends basal insulin delivery for up to 2 hours in response to sensor-detected hypoglycemia.

A sensor augmented pump therapy with predictive low glucose management (suspend before low) suspends basal insulin infusion with the prediction of hypoglycemia. Basal insulin infusion is suspended when sensor glucose is at or within 70 mg/dL above the patient-set low limit and is predicted to be 20 mg/dL above this low limit in 30 minutes. In the absence of a patient response, the insulin infusion resumes after a maximum suspend period of 2 hours. In certain circumstances, auto-resumption parameters may be used.

When a sensor value is above or predicted to remain above the threshold, the infusion pump will not take any action based on continuous glucose monitoring readings. Patients using this system still need to monitor their blood glucose concentration, set appropriate basal rates for their insulin pump, and give premeal bolus insulin to control their glucose levels.

A control-to-range system reduces the likelihood or severity of a hypoglycemic or hyperglycemic event by adjusting insulin dosing only if a person's glucose levels reach or approach predetermined higher and lower thresholds. When a patient's glucose concentration is within the specified range, the infusion pump will not take any action based upon continuous glucose monitoring readings. Patients using this system still need to monitor their blood glucose concentration, set appropriate basal rates for their insulin pump, and give premeal bolus insulin to control their glucose levels.

A control-to-target system sets target glucose levels and tries to maintain these levels at all times. This system is fully automated and requires no interaction from the user (except for calibration of the continuous glucose monitoring). There are 2 subtypes of control-to-target

systems: insulin-only and bihormonal (eg, glucagon). There are no systems administering glucagon marketed in the United States.

A hybrid closed-loop system also uses automated insulin delivery with continuous basal insulin delivery adjustments. However, at mealtime, the patient enters the number of carbohydrates they are eating in order for the insulin pump to determine the bolus meal dose of insulin. A hybrid system option with the patient administration of a premeal or partial premeal insulin bolus can be used in either control-to-range or control-to-target systems.

An AID system may also be referred to as a "closed-loop" system. A closed-loop system has AID and continuous glucose sensing and insulin delivery without patient intervention. The systems utilize a control algorithm that autonomously and continually increases and decreases the subcutaneous insulin delivery based on real-time sensor glucose levels.

Table 2 summarizes the FDA cleared or approved automated insulin delivery systems.

Table 2. U.S. Food and Drug Administration-Approved Automated Insulin Delivery Systems

Device	Age Indication	Manufacturer	Date Approved	PMA No./Device Code
MiniMed 530G System[a](open-loop, LGS)	≥16 y	Medtronic	Jul 2013	P120010/OZO
MiniMed 630G System with SmartGuard™[b](open-loop, LGS)	≥16 y ≥14 y	Medtronic	Aug 2016 Jun 2017	P150001/OZO P150001/S008
MiniMed 670G System[c] (HCL, LGS or PLGM)	≥14 y ≥7 to 13 y	Medtronic	Sep 2016 Jul 2018	P160017/OZP P160017/S031
MiniMed 770G System[d] (HCL)	≥2 y	Medtronic	Aug 2020	P160017/S076
MiniMed 780G System[e] (HCL)	>7 y	Medtronic	May 2023	P160017/S091
t:slim X2 Insulin Pump with Basal-IQ Technology (LGS) [f]	>6 y	Tandem	Jun 2018	P180008/OZO, PQF
t:slim X2 Insulin Pump with Control-IQ Technology (HCL)	>6 y	Tandem	Dec 2019	DEN180058/QFG
Omnipod 5 (HCL)	>6 y	Insulet	Jan 2022	K203774
Omnipod 5 (HCL)	>2y	Insulet	Aug 2022	K220394
iLet Bionic Pancreas (CL)	>6 y	Beta Bionics	May 2023	K220916 K223846
t:slim X2 Insulin Pump with Control-IQ Technology (HCL)	≥2 y	Tandem	Nov 2023	K232382
Omnipod 5[g] (HCL)	>18y	Insulet	Aug 2024	K241777
t:slim X2 Insulin Pump with Control-IQ Technology (HCL)[h]	>18y	Tandem	Feb 2025	K243823

Device	Age Indication	Manufacturer	Date Approved	PMA No./Device Code
Alternate Controller Enabled Infusion Pump (twiist AID System)[i]	>6 y	Deka Research & Development (Sequel Med Tech)	Apr 2025	K250930
MiniMed 780G System (HCL)[j]	>18y	Medtronic	Aug 2025	P160017/S124

CL: closed-loop; HCL: hybrid closed-loop; LGS: low glucose suspend; OZO: Artificial Pancreas Device System, threshold suspend; OZP: Automated Insulin Dosing Device System, Single Hormonal Control; PMA: premarket approval; PLGM: predictive low glucose management.
[a]MiniMed 530G System consists of the following devices that can be used in combination or individually: MiniMed 530G Insulin Pump, Enlite™ Sensor, Enlite™Serter, the MiniLink Real-Time System,
the Bayer Contour NextLink glucose meter, CareLink® Professional Therapy Management Software for Diabetes, and CareLink® Personal Therapy Management Software for Diabetes (at time of approval).
[b]MiniMed 630G System with SmartGuard™ consists of the following devices: MiniMed 630G Insulin Pump, Enlite® Sensor, One-Press Serter, Guardian® Link Transmitter System,
CareLink® USB, Bayer's CONTOUR ® NEXT LINK 2.4 Wireless Meter, and Bayer's CONTOUR® NEXT Test Strips (at time of approval).
[c]MiniMed 670G System consists of the following devices: MiniMed 670G Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), One-Press Serter, and the Contour NEXT Link 2.4 Glucose Meter (at time of approval).
[d]MiniMed 770G System consists of the following devices: MiniMed 770G Insulin Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), One-Press Serter, the Accu-Chek Guide™ Link blood glucose meter, and the Accu-Chek Guide™ Test Strips.
[e]MiniMed 780G System consists of the following devices: MiniMed 780G Insulin Pump, the Guardian 4 Transmitter, the Guardian 4 Sensor (3), One-Press Serter, the Accu-Chek Guide™ Link blood glucose meter, and the Accu-Chek Guide™ Test Strips.
[f]Basal-IQ technology was discontinued as of December 2023. The manufacturer (Tandem) continues to maintain service for supply refills and/or technical support.
[g]Omnipod 5 System consists of a tubeless, wearable Pod that adjusts insulin delivery based on CGM readings, controlled via Bluetooth through a handheld device like a smartphone or provided controller. It can function in open loop (Manual Mode) or closed loop (Automated Mode with SmartAdjust™ algorithm enabled), where insulin delivery is managed by the algorithm installed on the Pod. In August 2024, the FDA extended the Omnipod 5 system's approval for adults with type 2 diabetes, following its 2022 clearance for children and adults with type 1 diabetes.
[h]Control-IQ+ technology is intended for use with compatible integrated CGM (iCGM) and ACE pumps to automatically increase, decrease, and suspend delivery of basal insulin based on iCGM readings and predicted glucose values. It can also deliver correction boluses when the glucose value is predicted to exceed a predefined threshold. In February 2025, the FDA extended the Control-IQ+ technology approval for adults with type 2 diabetes.
[i]The twiist AID System is indicated for type 1 diabetes and features Tidepool Loop technology, which allows for automatic adjustments in insulin delivery based on CGM readings and predicted glucose levels. The system integrates data from a CGM device, a control algorithm, and an insulin pump to help patients manage their blood sugar levels more effectively.
[j]The PMA supplement for the MiniMed 780G System is for expanding the indications for use to include type 2 diabetes mellitus in individuals 18 years of age and older requiring insulin.

The MiniMed 530G System includes a threshold suspend or low glucose suspend feature.[7,] The threshold suspend tool temporarily suspends insulin delivery when the sensor glucose level is at or below a preset threshold within the 60 to 90 mg/dL range. When the glucose value reaches this threshold, an alarm sounds. If patients respond to the alarm, they can choose to continue or cancel the insulin suspend feature. If patients fail to respond, the pump automatically suspends action for 2 hours, and then insulin therapy resumes.

The MiniMed® 630G System with SmartGuard™, which is similar to the 530G, includes updates to the system components including waterproofing.[8,] The threshold suspend feature can be

programmed to temporarily suspend delivery of insulin for up to 2 hours when the sensor glucose value falls below a predefined threshold value. The MiniMed 630G System with SmartGuard™ is not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a finger stick may be required. All therapy adjustments should be based on measurements obtained using a home glucose monitor and not on the values provided by the MiniMed 630G system. The device is not intended to be used directly for preventing or treating hypoglycemia but to suspend insulin delivery when the user is unable to respond to the SmartGuard™ Suspend on Low alarm to take measures to prevent or treat hypoglycemia themselves.

The MiniMed® 670G System is a hybrid closed-loop insulin delivery system consisting of an insulin pump, a glucose meter, and a transmitter, linked by a proprietary algorithm and the SmartGuard Hybrid closed-loop[9,]. The system includes a low glucose suspend feature that suspends insulin delivery; this feature either suspends delivery on low-glucose levels or suspends delivery before low-glucose levels, and has an optional alarm (manual mode). Additionally, the system allows semiautomatic basal insulin-level adjustment (decrease or increase) to preset targets (automatic mode). As a hybrid system, basal insulin levels are automatically adjusted, but the patient needs to administer premeal insulin boluses. The continuous glucose monitoring component of the MiniMed 670G System is not intended to be used directly for making manual insulin therapy adjustments; rather it is to provide an indication of when a glucose measurement should be taken. The MiniMed 670G System was originally approved for marketing in the United States on September 28, 2016 (P160017), and received approval for marketing with a pediatric indication (ages 7 to 13 years) on June 21, 2018 (P160017/S031).

The MiniMed 770G System is an iteration of the MiniMed 670G System. In July 2020, the device was approved for use in children ages 2 to 6 years. In addition to the clinical studies that established the safety and effectiveness of the MiniMed 670G System in users ages 7 years and older, the sponsor performed clinical studies of the 670G System in pediatric subjects ages 2 to 6 years. The FDA concluded that these studies establish a reasonable assurance of the safety and effectiveness of the MiniMed 770G System because the underlying therapy in the 670G system, and the associated Guardian Sensor (3), are identical to that of the 770G System.[10,]The FDA subsequently approved the MiniMed 780G System in May 2023.

On June 21, 2018, the FDA approved the t:slim X2 Insulin Pump with Basal-IQ Technology (PMA P180008) for individuals who are 6 years of age and older.[11,]This system was discontinued as of December 2023. The manufacturer (Tandem) will continue to maintain service for supply refills and/or technical support.

In December 2019, the FDA approved the t:slim X2 Insulin Pump with Control-IQ Technology through the De Novo process.[12,] The device uses the same pump hardware as the insulin pump component of the systems approved in t:slim X2 Insulin Pump with Basal-IQ Technology (P180008) and P140015. A custom disposable cartridge is motor-driven to deliver patient programmed basal rates and boluses through an infusion set into subcutaneous tissue.

In January 2022, the FDA approved the Omnipod 5 system for individuals who are 6 years of age and older with type 1 diabetes. The system uses SmartAdjust™ technology for use with compatible integrated CGMs and ACE pumps to automatically increase, decrease, and pause

delivery of insulin based on current and predicted glucose values. In August 2022, the FDA expanded the age indication to individuals who are 2 years and older with type 1 diabetes.[13,]

In May 2023, the FDA approved the first closed-loop system (iLet Bionic Pancreas) through the 510(k) premarket clearance pathway.[14,]

In August 2024, the FDA extended approval of the Omnipod 5 system for use by individuals who are 18 years of age and older with type 2 diabetes.[15,]

In February 2025, the FDA extended approval of the t:slim X2 Insulin Pump with Control-IQ+ technology for use by individuals who are 18 years of age and older for type 2 diabetes[16,]

In August 2025, the FDA extended approval of the MiniMed 780G System for use by individuals who are 18 years of age and older for type 2 diabetes requiring insulin.[17,]

POLICY

A. Use of an FDA cleared or approved automated insulin delivery system may be considered **medically necessary** when **ALL** of the following criteria is met:

    1. In individuals with type 1 diabetes who meet age requirement allowed by the FDA for the specific device prescribed (see Regulatory Status) **AND**

    2. Individual or caregiver must have completed a comprehensive education program within the past 12 months if they are a first time user of insulin pump therapy.

B. Use of an FDA cleared or approved automated insulin delivery system designated as a hybrid closed-loop insulin delivery system (with low glucose suspend and suspend before low features) may be considered **medically necessary** in individuals with type 2 diabetes who meet **ALL** the following criteria (see Policy Guidelines):

    1. Age 18 years and older **AND**
        a. Diagnosed with type 2 diabetes for at least 12 months;
        b. On multiple daily injections (insulin administration > 3x/day or use of insulin infusion pump) for at least 3 months;
        c. Glycated hemoglobin level ≥ 7% or experience significant hypoglycemia.

C. Use of an automated insulin delivery system not cleared or approved by the FDA is considered **experimental / investigational**.

D. All other indications for the use of an automated insulin delivery system is **experimental / investigational.**

POLICY GUIDELINES

A. Diabetes mellitus (DM) encompasses various distinct types, all of which are characterized by abnormal carbohydrate metabolism manifesting as hyperglycemia and may require insulin therapy. The current body of evidence supporting the use of automated insulin delivery (AID) systems for each type of DM is variable, and the initiation of additional clinical trials is unlikely. Consequently, Plans will need to consider the use of such technology, recognizing the potential for similar therapeutic benefits across the different forms of DM. Individuals with DM should understand the technology, be motivated to use the device correctly and consistently, adhere to a comprehensive treatment plan supervised by a qualified provider, and be capable of recognizing alerts and alarms from the device.

B. The U.S. Food and Drug Administration (FDA) has approved two hybrid closed-loop insulin delivery systems for type 2 diabetes management: the Omnipod 5 AID system (Insulet Corporation) and t:slim X2 insulin pump equipped with Control-IQ+ technology (Tandem Diabetes Care).
    1. The Omnipod 5 AID system was approved following a pivotal clinical trial by Pasquel et al in 2025 (SECURE-T2D; NCT05815342). Trial participants aged 18 to 75 years, who had been on a stable insulin regimen for at least three months prior to screening (as per the above policy criteria), were selected. Additionally, they could be on other

antihyperglycemic and weight loss drugs, provided there were no dose changes for at least 4 weeks before the trial commenced. However, those who experienced more than one severe hypoglycemic event or episode of diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome within 6 months before screening were excluded.

2. The t:slim X2 insulin pump equipped with Control-IQ+ technology was approved following a pivotal randomized controlled trial by Kudva et al in 2025 (2IQP; NCT05785832). Trial participants were aged 19 to 87 years and had type 2 diabetes for at least 6 months, according to clinical history and available laboratory data. All participants were receiving multiple daily injections of insulin with at least one injection containing rapid-acting insulin per day or were using an insulin pump for at least 3 months before enrollment. Mixed insulin use with a rapid-acting component was allowed. Concurrent treatment with noninsulin glucose-lowering medications or weight-reduction medications was permitted, provided the dose had been stable for the previous 3 months; during the trial, these medications were continued in both treatment groups.

C. This medical policy does not address use of automated insulin delivery systems in pregnancy.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review was created using searches of the PubMed database. The most recent literature update was performed through February 12, 2026.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

This evidence review addresses automated insulin delivery systems that have been approved by the U.S. Food and Drug Administration (FDA).

TYPE 1 DIABETES

LOW-GLUCOSE SUSPEND DEVICES

Clinical Context and Therapy Purpose

The purpose of automated insulin delivery (AID) systems with a low-glucose suspend feature in individuals who have type 1 diabetes is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with type 1 diabetes. Persons with type 1 diabetes are especially prone to develop hypoglycemia. Alterations in the counterregulatory hormonal responses inherent in the disease, variable patient adherence, and iatrogenic hypoglycemia caused by aggressive prevention of hyperglycemia are responsible for this propensity. Hypoglycemia affects many aspects of cognitive function, including attention, memory, and psychomotor and spatial ability. Severe hypoglycemia can cause serious morbidity affecting the central nervous system (eg, coma, seizure, transient ischemic attack, stroke), heart (eg, cardiac arrhythmia, myocardial ischemia, infarction), eye (eg, vitreous hemorrhage, worsening of retinopathy), as well as cause hypothermia and accidents that may lead to injury. Fear of hypoglycemia symptoms can also cause decreased motivation to adhere strictly to intensive insulin treatment regimens.

Interventions

The therapy being considered is an AID system that integrates a continuous glucose monitor and insulin pump and includes a low glucose suspend feature that can automatically and temporarily suspend insulin delivery when glucose levels fall below a prespecified level. The device alarms and the user must take an action to assess glycemic level and resume insulin infusion.

AID systems are used by persons with type 1 diabetes when they have experienced hyperglycemic and/or hypoglycemic episodes that cannot be managed with intermittent self-monitoring of glucose and self-administration of insulin.

Comparators

The following therapies are currently being used to treat type 1 diabetes: nonintegrated continuous glucose monitoring plus insulin pump (open-loop) or self-monitoring blood glucose and multiple dose insulin therapy.

Outcomes

The general outcomes of interest are glycated hemoglobin A_{1c} (HbA_{1c}) levels, time in range or target of glucose levels, and rates of hypoglycemia and hyperglycemia. Other outcomes of interest include quality of life and changes in health care utilization (eg, hospitalizations). The duration of follow-up is life-long.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Randomized Controlled Trials

The in-home arm of the Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial was reported by Bergenstal et al (2013).[18,]This industry-sponsored trial used the Paradigm Veo insulin pump. A total of 247 patients were randomized to an experimental group, in which a continuous glucose monitor with the low glucose suspend feature was used (n=121), or a control group, which used the continuous glucose monitor but not the low glucose suspend feature (n=126). Key eligibility criteria were 16 to 70 years of age, type 1 diabetes, and HbA1c levels between 5.8% and 10.0%. In addition, patients had to have more than 6 months of experience with insulin pump therapy and at least 2 nocturnal hypoglycemic events (≤65 mg/dL) lasting more than 20 minutes during a 2-week run-in phase. The randomized intervention phase lasted 3 months. Patients in the low glucose suspend group were required to use the feature at least between 10 PM and 8 AM. The threshold value was initially set at 70 mg/dL and could be adjusted to between 70 mg/dL and 90 mg/dL. Seven patients withdrew early from the trial; all 247 were included in the intention-to-treat analysis. The primary efficacy outcome was the area under the curve (AUC) for nocturnal hypoglycemia events. This was calculated by multiplying the magnitude (in milligrams per deciliter) and duration (in minutes) of each qualified hypoglycemic event. The primary safety outcome was change in HbA1c levels.

The primary endpoint, mean (standard deviation [SD]) AUC for nocturnal hypoglycemic events, was 980 (1200) mg/dL/min in the low glucose suspend group and 1568 (1995) mg/dL/min in the control group. The difference between groups was statistically significant (p<.001), favoring the intervention group. Similarly, the mean AUC for combined daytime and nighttime hypoglycemic events (a secondary outcome) significantly favored the intervention group (p<.001). Mean (SD) AUC values were 798 (965) mg/dL/min in the intervention group and 1164 (1590) mg/dL/min in the control group. Moreover, the intervention group experienced fewer hypoglycemic episodes (mean, 3.3 per patient-week; SD, 2.0) than the control group (mean, 4.7 per patient-week; SD, 2.7; p<.001). For patients in the low glucose suspend group, the mean number of times the feature was triggered per patient was 2.08 per 24-hour period and 0.77 each night (10 PM-8 AM). The median duration of nighttime threshold suspend events was 11.9 minutes; 43% of events lasted for less than 5 minutes, and 19.6% lasted more than 2 hours. In both groups, the mean sensor glucose value at the beginning of nocturnal events was 62.6 mg/dL. After 4 hours, the mean value was 162.3 mg/dL in the low glucose suspend group and 140.0 mg/dL in the control group.

Regarding safety outcomes and adverse events, change in HbA_{1c} level was minimal, and there was no statistically significant difference between groups. Mean HbA_{1c} levels decreased from 7.26

to 7.24 mg/dL in the low glucose suspend group and from 7.21 to 7.14 mg/dL in the control group. During the study period, there were no severe hypoglycemic events in the low glucose suspend group and 4 events in the control group (range of nadir glucose sensor values in these events, 40-76 mg/dL). There were no deaths or serious device-related adverse events.

A second RCT evaluated the in-home use of the Paradigm Veo System.[19,] The trial included 95 patients with type 1 diabetes between 4 and 50 years of age (mean age, 18.6 years; >30% of sample <18 years old) who had used an insulin pump for at least 6 months. In addition, participants had to have an HbA_{1c} level of 8.5% or less and have impaired awareness of hypoglycemia (defined as a score of at least 4 on the modified Clarke questionnaire). Patients were randomized to 6 months of in-home use of the Paradigm Veo System with automated insulin suspension when the glucose sensor reached a preset threshold of 60 mg/dL or to continued use of an insulin pump without the low glucose suspend feature. The primary study outcome was the combined incidence of severe hypoglycemic events (defined as hypoglycemic seizure or coma) and moderate hypoglycemic events (defined as an event requiring assistance from another person). As noted, findings were not reported separately for children and adults.

The baseline rate of severe and moderate hypoglycemia was significantly higher in the low glucose suspend group (129.6 events per 100 patient-months) than in the pump-only group (20.7 events per 100 patient-months). After 6 months of treatment, and controlling for the baseline hypoglycemia rate, the incidence rate per 100 patient-months was 34.2 (95% confidence interval [CI], 22.0 to 53.3) in the pump-only group and 9.6 (95% CI, 5.2 to 17.4) in the low glucose suspend group. The incidence rate ratio was 3.6 (95% CI, 1.7 to 7.5), which was statistically significant favoring the low glucose suspend group. Although results were not reported separately for children and adults, the trialists conducted a sensitivity analysis in patients younger than 12 years (15 patients in each treatment group). The high baseline hypoglycemia rates could be explained in part by 2 outliers (children ages 9 and 10 years). When both children were excluded from the analysis, the primary outcome was no longer statistically significant. The incidence rate ratio for moderate and severe events excluding the 2 children was 1.7 (95% CI, 0.7 to 4.3). Mean HbA_{1c} levels (a secondary outcome) did not differ between groups at baseline or at 6 months. Change in HbA_{1c} levels during the treatment period was -0.06% (95% CI, -0.2% to 0.09%) in the pump-only group and -0.1% (95% CI,-0.3% to 0.03%) in the low glucose suspend group; the difference between groups was not statistically significant.

The Predictive Low-Glucose Suspend for Reduction Of LOw Glucose (PROLOG) Trial was a 6-week crossover RCT of the t:slim X2 pump with Control-IQ Technology integrated with a Dexcom G5 sensor and a predictive low glucose suspend algorithm compared to sensor-augmented pump therapy.[20,] Participants (N=103) were ages 6 to 72 years; 58% were less than 18 years old, 16% were 6 to 11 years old, 43% were 12 to 17 years old, and 42% were 18 years or older. The primary outcome was CGM measured percentage of time <70 mg/dL in each 3-week period. Median time <70 mg/dL was reduced from 3.6% at baseline to 2.6% during the 3-week period in the predictive low glucose suspend system arm compared with 3.2% in the sensor augmented pump arm (difference [predictive low glucose suspend – sensor augmented pump], -0.8%; 95% CI, -1.1 to −0.5; p<.001). There was 1 severe hypoglycemic event in the sensor augmented pump arm and none in the predictive low glucose suspend arm.

Nonrandomized Studies

Agrawal et al (2015) retrospectively analyzed use of the threshold suspend feature associated with the Paradigm Veo System in 20,973 patients, most of whom were treated outside of the United States.[21,]This noncontrolled descriptive analysis provided information on the safety of the device when used in a practice setting. The threshold suspend feature was enabled for 100% of the time by 14,673 (70%) patients, 0% of the time by 2249 (11%) patients, and the remainder used it intermittently. The mean (SD) setting used to trigger suspension of insulin was a sensor glucose level of 62.8 (5.8) mg/dL. On days when the threshold suspend feature was enabled, there was a mean of 0.82 suspend events per patient-day. Of these, 56% lasted for 0 to 5 minutes, and 10% lasted the full 2 hours. Data on the length of the other 34% of events were not reported. On days when the threshold suspend feature was on, sensor glucose values were 50 mg/dL or less 0.64% of the time compared with 2.1% of sensor glucose values 50 mg/dL or less on days when the feature was off. Reduction in hypoglycemia was greatest at night. Sensor glucose percentages equivalent to 17 minutes per night occurred when the threshold suspend feature was off versus glucose percentages equivalent to 5 minutes per night when the threshold suspend feature was on. Data on the use of the device has suggested fewer and shorter hypoglycemic episodes. The length and severity of hypoglycemic episodes were not fully discussed in this article.

Gómez et al (2017) published the results of a cohort of 111 individuals with type 1 diabetes with documented hypoglycemia and hypoglycemia unawareness who received a sensor-augmented insulin pump with low glucose suspend therapy.[22,]Participants used a combination system with the Medtronic Paradigm 722 or Paradigm Veo pump connected to the MiniMed continuous glucose monitoring device. At a mean follow-up of 47 months (SD, 22.7), total daily insulin dose was reduced (mean difference, -0.22 U/kg; 95% CI, -0.18 to -0.26 U/kg; p<.001). Hemoglobin A_{1c} levels were reduced from a baseline value of 8.8% (SD, 1.9%) to 7.5% (SD, 1.0%) at 5 months (mean difference, -1.3%; 95% CI, -1.09% to -1.50%; p<.001) and 7.1% (SD, 0.8%; mean difference, -1.7%; 95% CI, -1.59% to -1.90%; p<.001). At baseline, 80% of subjects had had at least 1 episode of hypoglycemic awareness compared with 10.8% at last follow-up (p<.001). Episodes of severe hypoglycemia decreased from 66.6% to 2.7% (p<.001).

Section Summary: Low-Glucose Suspend Devices

The evidence includes 3 RCTs conducted in home settings. Primary eligibility criteria of the key RCT, the ASPIRE trial, were ages 16 to 70 years, type 1 diabetes, glycated hemoglobin levels between 5.8% and 10.0%, and at least 2 nocturnal hypoglycemic events (≤65 mg/dL) lasting more than 20 minutes during a 2-week run-in phase. Both trials required at least 6 months of insulin pump use. Both RCTs reported significantly less hypoglycemia in the treatment group than in the control group. In both trials, primary outcomes were favorable for the group using an artificial pancreas system; however, findings from 1 trial were limited by nonstandard reporting of hypoglycemic episodes, and findings from the other trial were no longer statistically significant when 2 outliers (children) were excluded from analysis. The RCT limited to adults showed an improvement in the primary outcome (AUC for nocturnal hypoglycemic events). The AUC is not used for assessment in clinical practice, but the current technology does allow user and provider review of similar trend data with continuous glucose monitoring.

Results from the ASPIRE study suggested that there were increased risks of hyperglycemia and potential diabetic ketoacidosis in subjects using the threshold suspend feature. This finding may

be related to whether or not actions are taken by the user to assess glycemic status, etiology of the low glucose (activity, diet or medication), and to resume insulin infusion.

Both retrospective and prospective observational studies have reported reductions in rates and severity of hypoglycemic episodes in AID system users. The evidence suggests that the magnitude of reduction for hypoglycemic events in the type 1 diabetes population is likely to be clinically significant.

HYBRID CLOSED-LOOP INSULIN DELIVERY SYSTEMS

Clinical Context and Therapy Purpose

The purpose of a hybrid closed-loop insulin delivery system in individuals who have type 1 diabetes is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with type 1 diabetes. Persons with type 1 diabetes are especially prone to develop hypoglycemia. Alterations in the counterregulatory hormonal responses inherent in the disease, variable patient adherence, and iatrogenic hypoglycemia caused by aggressive prevention of hyperglycemia are responsible for this propensity. Hypoglycemia affects many aspects of cognitive function, including attention, memory, and psychomotor and spatial ability. Severe hypoglycemia can cause serious morbidity affecting the central nervous system (eg, coma, seizure, transient ischemic attack, stroke), heart (eg, cardiac arrhythmia, myocardial ischemia, infarction), eye (eg, vitreous hemorrhage, worsening of retinopathy), as well as cause hypothermia and accidents that may lead to injury. Fear of hypoglycemia symptoms can also cause decreased motivation to adhere strictly to intensive insulin treatment regimens.

Interventions

The therapy being considered is a hybrid closed-loop insulin delivery system. A hybrid closed-loop system continuously adjusts insulin delivery. However, at mealtime, the patient enters the number of carbohydrates being consumed in order for the insulin pump to determine the bolus meal dose of insulin.

Comparators

The following therapies are currently being used to treat type 1 diabetes: an AID system with low glucose suspend feature, nonintegrated continuous glucose monitoring plus insulin pump (open-loop), or self-monitoring blood glucose and multiple dose insulin therapy.

Outcomes

The general outcomes of interest are HbA_{1c} levels, time in range or target of glucose levels, and rates of hypoglycemia and hyperglycemia. Other outcomes of interest include quality of life and changes in health care utilization (eg, hospitalizations). The duration of follow-up is life-long.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Randomized Controlled Trials

Jendle et al. (2025) conducted a 6-month, multicenter RCT across 32 international centers in the U.S., Europe, Canada, and New Zealand.[23,] The study involved individuals with type 1 diabetes aged 2–80 years, randomized 1:1 to the AID intervention (MiniMed™ 670G or 770G system) or multiple daily injections (MDI) with or without CGM. Participants were stratified into Group 1 (baseline HbA1c >8.0%) and Group 2 (baseline HbA1c ≤8.0%). Primary endpoints were change in mean HbA1c for Group 1, and percentage of time below 70 mg/dL (% time below range, TBR <70 mg/dL) for Group 2. A total of 252 participants were randomized: 129 to the AID intervention and 123 to the MDI control arm (Table 3).

In Group 1, mean HbA1c decreased significantly more in the AID arm than in the MDI arm (mean difference of -0.7% [95% CI -1.1% to -0.3%]; p =.0002) (Table 4). For the co-primary endpoint, there was a significant mean difference in %TBR <70 mg/dL favoring AID in Group 2 (−4.8% [-6.4% to -3.1%]; p <.0001) (Table 4). Time in range (TIR) (70-180 mg/dL) increased by 16.6% for Group 1 and 11.9% for Group 2 in the AID arm relative to MDI. Time above 180 mg/dL and above 250 mg/dL were also significantly reduced in the AID arms for both groups. In terms of safety, device-related serious adverse events were infrequent, with no significant differences between groups in rates of severe hypoglycemia or diabetic ketoacidosis. Study limitations included a predominantly white population (over 80%), the open-label trial design, and a wide age range (2-80 years) that may limit generalizability to specific age subgroups.

Renard et al. (2024) conducted a 13-week, multicenter RCT across 10 sites in the U.S. and 4 in France.[24,] The study involved adults aged 18-70 years with type 1 diabetes and HbA1c levels between 7-11% (53-97 mmol/mol). Participants were randomly assigned in a 2:1 ratio to either the intervention group, using the Omnipod 5 AID System, or the control group, using pump therapy with CGM, following a 2-week standard therapy period. The primary outcome measured was the TIR of glucose levels (70-180 mg/dL) during the trial. Out of the 194 participants, 132 were in the intervention group and 62 in the control group. The intervention group showed a significant improvement in TIR, with an average of 4.2 hours per day higher than the control group (mean difference of 17.5% [95% CI 14.0% to 21.1%]; p <.0001). Additionally, the intervention group experienced a greater reduction in HbA1c levels from baseline compared to the control group (mean ± SD 21.24 ± 0.75% [213.6 ± 8.2 mmol/mol] vs. 20.68 ± 0.93% [27.4 ± 10.2 mmol/mol], respectively; p <.0001).

Although there was no significant difference between the two groups in the mean difference between treatment groups during the 13-week trial period in percentage of time <54 mg/dL, the time spent above 180 mg/dL was significantly lower in the intervention group (37.6 ± 11.4% vs. 54.5 ± 15.4%; p <.0001). In terms of serious adverse events, there were no instances of

diabetes-related ketoacidosis or severe hypoglycemia in the intervention group. Study limitations included a lack of diversity in its population (84% of participants were white) and a high percentage of prior device use among participants (97% had used CGM before, and 87% were using an earlier Omnipod system as their insulin pump therapy).

Table 3. Summary of Key RCT Study Characteristics

Study; Trial	Countries	Sites	Dates	Inclusion Criteria	Participant Characteristics	Interventions	
						Active	**Control**
Jendle et al (2025)[23]; NCT02748018	US, Europe, Canada, New Zealand	32	2021 – 2024	• Age 2–80 years with type 1 diabetes for ≥1 year. • HbA1c ≥7.0% (≥53 mmol/mol) with or without CGM use. • On MDI therapy for ≥6 months; participants aged ≥15 years required to have used CGM or BGM for ≥3 months	• N=252 • Group 1 (HbA1c >8%): mean age 36.5 ± 20.6 yrs (AID) and 35.4 ± 20.5 yrs (MDI); Group 2 (HbA1c ≤8%): mean age 35.1 ± 21.0 yrs (AID) and 36.4 ± 20.5 yrs (MDI) • Majority white (Group 1: 82% AID, 80% MDI; Group 2: 82% AID, 88% MDI) • Baseline HbA1c: Group 1 mean 9.1% ± 0.9% (AID) and 8.9% ± 1.1% (MDI); Group 2 mean 7.5% ± 0.4% (AID) and 7.5% ± 0.4% (MDI)	n=129 MiniMed 670G or 770G AID system (automated basal insulin delivery with Guardian Sensor 4 CGM)	n=123 MDI with or without continuous glucose monitoring
Renard et al (2024)[24]; NCT05409131	US France	14	2022-2024	• Age 18–70 years and had type 1 diabetes for ≥1 year.	• N=194 • 60% female, mean ± SD age 36 ± 14 years	n=132 Omnipod 5 System with Dexcom G6	n=62 Participant's current insulin pump with Dexcom

Study; Trial	Countries	Sites	Dates	Inclusion Criteria	Participant Characteristics	Interventions	
				• HbA1c 7.0–11.0% (53-97 mmol/mol). At least 80% of participants to have a screening HbA1c ≥8.0% (64 mmol/mol). • On pump therapy for at least 3 months, with a requirement that at least 50% were using an Omnipod pump (Omnipod or Omnipod DASH Insulin Management System) at the time of enrollment	• US participants accounted for 61% of those randomized. • 87% were Omnipod pump users, and 94% had previous or current CGM use • Baseline point-of-care HbA1c was mean ± SD (range) 8.5 ± 0.8% (7.0-10.5%) [69 ± 8.7 (53–91) mmol/mol] in the intervention group and 8.6 ± 0.9% (7.0–10.9%) [70 ± 9.8 (53–96) mmol/mol] in the control group. • At screening, the point-of-care HbA1c measurement was ≥8.0% (64 mmol/mol) for 80% and 82% of participants in the intervention and control groups, respectively	continuous glucose monitoring system	G6 continuous glucose monitoring system

MDI: multiple daily injections; RCT: randomized controlled trial.

Table 4. RCT Study Results

Study; Trial	Primary Efficacy Outcomes	Key Secondary Efficacy Outcomes	Safety Outcomes	
Jendle et al (2025)[23]; NCT02748018	• Change in mean HbA1c with a baseline HbA1c >8.0% (Group 1) • Percentage of time *spent below 70 mg/dL (%TBR <70 mg/dL [<3.9 mmol/L]) for participants with baseline HbA1c ≤8.0% (Group 2)*	• Percentage of TBR<70 mg/dL (Group 1) • Percentage *of HbA1c (Group 2)*	• Rates of severe hypoglycemia • Rates *of diabetic ketoacidosis (DKA)*	• *Difference in diabetes treatment satisfaction score at 6 months*
N analyzed	AID Intervention • *n=56 (Group 1)* • *n=73 (Group* 2) MDI control • *n=54 (Group 1)* • *n*=69 (Group 2)	AID Intervention • *n=56 (Group 1)* • *n*=73 (Group 2) MDI control • *n=54 (Group 1)* • *n*=69 (Group 2)	AID Intervention • n=129 MDI Control • n=123	AID Intervention • n=37 (Group 1) • n=45 (Group 2) MDI Control • n=34 (Group 1) • n=57 (Group 2)
MiniMed™ 670G or 770G AID system	• Change: -1.4 ± 1.1 (Group 1) • Change: NA (Group 2)	• Change: NA (Group 1) • Change: 0.0 ± 0.6 (Group 2)	Severe hypoglycemia • NA (Group 1 and Group 2) DKA • 1 event (Group 1) (1.82 per 100 patient-years) • NA (Group 2)	• 29.2 ± 6.4 (Group 1) • 26.4 ± 7.1 (Group 2)
Multiple daily injections (MDI) with or without continuous glucose monitoring	• Change: -0.6 ± 0.9 (Group 1) • Change: NA (Group 2)	• Change: NA (Group 1) • Change: -0.1 ± 0.5 (Group 2)	Severe hypoglycemia: • NA (Group 1) • 2 events (Group 2) (3.52 per 100 patient-years) DKA: NA	• 23.9 ± 6.4 (Group 1) • 25.8 ± 6.6 (Group 2)
Adjusted Difference (95% Confidence Interval)	• -0.7% (-1.1, -0.3) (Group 1) • -4.8% (-6.4, -3.1) (Group 2)	• -3.6 (-5.4, -1.9) (Group 1) • 0.1 (-0.1, 0.3) (Group 2)	NA	• 4.8 (1.0, 8.6)(Group 1) • 0.2 (-2.9, 3.4) (Group 2)
p-value	• .0002a (Group 1) • <.0001b (Group 2)	• <.0001a (Group 1) • .001b (Group 2)	NA	• .015 (Group 1) • .883 (Group 2)
Renard et al (2024[24]); NCT05409131	• *Percentage of time in the glucose target range (TIR) (70–180 mg/dL) during the*	• *Mean percentage of time <54 mg/dL at 13 weeks*	• *Participants experiencing an event of severe hypoglycemia*	• *Participants experiencing other serious adverse events*

Study; Trial	Primary Efficacy Outcomes	Key Secondary Efficacy Outcomes	Safety Outcomes	
	13-week trial period as measured with the study CGM.	• *Mean percentage of time >180 mg/dL at 13 weeks*	*(requiring the assistance of another person due to altered consciousness and requiring another person to actively administer carbohydrate, glucagon, or other resuscitative actions)*	
N analyzed	n=131 Intervention n=62 Control	n=131 Intervention n=62 Control	n=132 Intervention n=62 Control	
Omnipod 5 System with Dexcom G6 continuous glucose monitoring system	*61.2 ± 11.2, 62.3 [55.2–68.8][c]*	• *0.23 ± 0.23, 0.17 [0.07–0.28]c* • *37.6 ± 11.4, 36.3 [29.8–43.9][c]*	*0*	1 (an unrelated tibia fracture)
Participant's insulin pump with Dexcom G6 continuous glucose monitoring system	*43.8 ± 14.5, 45.1 [34.3–53.6][c]*	• *0.37 ± 0.53, 0.16 [0.06–0.45]c* • *54.5 ± 15.4, 54.0 [42.3–64.4][c]*	*1 (1.6%)*	0
Adjusted Difference (95% Confidence Interval)	*17.5 (14.0, 21.1)*	• *-0.05 (-0.11, 0.00)* • *-16.8 (-20.8, -12.8)*	*NA*	
p-value	*<.0001*	• *.0501* • *<.0001*	*NA*	

NA: not applicable

a Comparison of change in HBA1c between AID intervention and MDI control.

b Comparison of end-of-study %TBR <70 mg/dL (<3.9 mmol/L) between AID intervention and MDI control.

[c] Data are Mean ± Standard Deviation and Median Interquartile Range.

Prospective Studies

Bergenstal et al (2016) published a prospective single-arm study on the safety of the hybrid closed-loop system in patients with type 1 diabetes.[25,]The study included 124 patients ages 14 to 75 years of age who had type 1 diabetes for at least 2 years, HbA_{1c} levels less than 10.0%, and who had used an insulin pump for at least 6 months. There was an initial run-in period at

baseline for patients to learn how to use the device followed by a 3-month period of device use. The study period included a 6-day hotel stay with a 1-day period of frequent sampling of venous blood glucose levels to verify device accuracy. The primary safety end points were the incidence of severe hypoglycemia and diabetic ketoacidosis and the incidence of device-related and serious adverse events.

There were no episodes of severe hypoglycemia or ketoacidosis during the study. A total of 28 device-related adverse events occurred, all of which could be resolved at home. There were 4 serious adverse events, 1 case each of appendicitis, bacterial arthritis, worsening rheumatoid arthritis, and *Clostridioides difficile* diarrhea. There were also a number of predefined descriptive end points (but no statistically powered efficacy end points). The device was in the closed-loop mode for a median of 97% of the study period. Mean (SD) HbA_{1c} levels were 7.4% (0.9%) at baseline and 6.9% (0.6%) at the end of the study, and the percentage of sensor glucose values within the target range was 66.7% at baseline and 72.2% at the end of the study. A related study in children has been completed (NCT02660827).

A multicenter pivotal trial published by Garg et al (2017) evaluated the safety of Medtronic's hybrid closed-loop system, using methods similar to those of Bergenstal et al (2016)(NCT02463097) and employing the same device (MiniMed 670G).[26,] Of 129 subjects, 124 completed the trial; 30 were adolescents (age range, 14 to 21 years) and 94 were adults (age range, 22 to 75 years), all of whom had type 1 diabetes for at least 2 years before the study, and used insulin pump therapy for 6 months or more. As with Bergenstal et al (2016), a 3-month study period was preceded by a run-in period for subjects to be more familiar with the equipment, and the sensor glucose values were confirmed by an extended hotel stay (6-day/5-night with daily exercise). In both the adolescent and adult cohorts, the trial found improvements during the study phase over the run-in phase, with an increased percentage of glucose values in the favorable range (for adults, a mean improvement of 68.8% to 73.8%; for adolescents, a mean improvement of 60.4% to 67.2%; $p<.001$ for both cohorts). Similarly, the authors reported a decrease in the percentage of values outside of the target range (<70 mg/dL or >180 mg/dL): for adults, time spent below the target range decreased from 6.4% to 3.4% ($p<.001$); time above the range decreased from 24.9% to 22.8% ($p=.01$). For both cohorts, HbA_{1c} levels showed a significant reduction between baseline and the end of the study: for adults, the mean decreased from 7.3% to 6.8% ($p<.001$), while for adolescents, the mean decreased from 7.7% to 7.1% ($p<.001$). Secondary outcomes, which included a reduction of nocturnal hyperglycemia and hypoglycemia, increase in mean overall body weight, and a reduction of basal insulin, were favorable for the study phase, compared with the run-in phase; measurements from the hotel stay verified the in-home glucose values. However, there were several limitations of the trial, including its nonrandomized design, the exclusion of individuals who had recently experienced diabetic ketoacidosis or severe hypoglycemia, and the interaction between subjects and site personnel. Additionally, most of the adult cohort were already using continuous glucose monitoring, and baseline HbA_{1c} levels were lower than average for both cohorts; both baseline characteristics potentially limit the generalizability of the results.

One type of hybrid insulin delivery system employs a predictive algorithm to keep the patient's glucose levels within a specific range or zone, only increasing or decreasing insulin levels if the device detects that glucose levels are going to fall outside the defined zone. Forlenza et al (2017) published a randomized controlled crossover trial comparing the efficacy of a zone model predictive control algorithm with that of sensor-augmented pump therapy.[27,] The trial included 20

subjects (19 completed), all with type 1 diabetes and having at least 3 months treatment with a subcutaneous insulin infusion pump. The 6-week, in-home study was divided into 2-week blocks, with 2 randomized groups alternating treatment between an artificial pancreas system (DiAs web monitoring) or sensor-augmented pump therapy (Dexcom Share); subjects in both arms reported glucose values and, if applicable, sensor failure. For several primary endpoints, which included percentage of time in the target glucose range (70 to 180 mg/dL) and reduction in hypoglycemia (<70 mg/dL), the algorithm-controlled artificial pancreas system was found to be superior to the sensor-augmented pump therapy (71.6 vs. 65.2%; p=.008; 1.3% vs. 2%; p=.001, respectively). However, while the mean glucose value was lower in the artificial pancreas system than in the control group, the difference between them was not significant (p=.059). Measurements of nocturnal hypoglycemia were consistent with day-to-day findings. For the secondary endpoint (safety of both systems after extended wear), the study found that the mean glucose did not change between the first and seventh day of wear. A limitation of the trial was its use of remote monitoring of subjects. Also, the trialists noted that given the marked difference in outcomes between responders and non-responders, an error might have occurred in setting basal rates. A randomized crossover trial reported by Pinsker et al (2022) evaluated sensor-augmented pump therapy compared to an adaptive zone model predictive control device. in 35 adults with type 1 diabetes.[28,] The adaptive device ran on a Google Pixel 3 smartphone and wirelessly paired with a Dexcom G6 sensor and a Tandem t:AP insulin pump. The primary outcome was sensor glucose time-in-range 70 to 180 mg/dL at 13 weeks. The automated adaptation settings did not significantly improve time-in-range (66% with sensor augmented pump vs 69% with automated insulin delivery; mean adjusted difference 2%; 95% CI -1% to +6%], p =.22). The investigators concluded that additional study and further refinement of the adaptation system are needed.

Brown et al. (2021) performed a single-arm, US multicenter, prospective study involving 241 participants to evaluate the Omnipod 5 AID System.[29,] The study began with a 2-week phase of standard therapy using the participants' usual insulin regimen, followed by three months of automated insulin delivery. The primary efficacy measures were changes in HbA1c levels and the percentage of time within the sensor glucose range of 70-180 mg/dL ("time in range"). Safety measures included the incidence of severe hypoglycemia and diabetic ketoacidosis. Out of the 241 enrolled participants, 235 (98%) completed the study, comprising 111 children (age 6–13.9 years) and 124 adults (age 14–70 years). The study revealed a significant reduction in HbA1c levels: in children, by 0.71% (7.8 mmol/mol) (mean ± SD: from 7.67 ± 0.95% to 6.99 ± 0.63% [60 ± 10.4 mmol/mol to 53 ± 6.9 mmol/mol], p <.0001), and in adults, by 0.38% (4.2 mmol/mol) (from 7.16 ± 0.86% to 6.78 ± 0.68% [55 ± 9.4 mmol/mol to 51 ± 7.4 mmol/mol], p <.0001). Time in range improved significantly from standard therapy by 15.6 ± 11.5% or 3.7 hours per day in children and by 9.3 ± 11.8% or 2.2 hours per day in adults (both p <.0001). Additionally, there was a decrease in hypoglycemia time (<70 mg/dL) among adults (median [interquartile range]: from 2.00% [0.63, 4.06] to 1.09% [0.46, 1.75], p <.0001), while this parameter remained unchanged in children. The study reported three severe hypoglycemia events unrelated to automated insulin delivery malfunction and one diabetic ketoacidosis event due to an infusion site failure. The primary limitations of this study were its noncomparative (single-arm) design without a control group to account for study participation effects, and the relatively well-controlled baseline glycemic metrics of participants, many of whom were already using insulin pumps and glucose sensors, which may limit generalizability.

Criego et al. (2024) presented findings from a long-term study on the Omnipod 5 AID System, an extension of Brown et al. (2021).[30,] HbA1c levels were monitored every 3 months for up to 15

months, and continuous glucose monitor metrics were tracked for up to 2 years. The study included 224 participants, who used the Omnipod system for a median of 22.3 months. HbA1c levels were maintained at 7.2% ± 0.7% for children and 6.9% ± 0.6% for adolescents/adults after 15 months (p <.0001 from baseline). Time in target range (70–180 mg/dL) was sustained at 65.9% ± 8.9% for children and 72.9% ± 11.3% for adolescents/adults during the extension phase (p <.0001 from baseline). There seven incidents of severe hypoglycemia and one incident of diabetic ketoacidosis during the extension period. Children and adolescents/adults spent a median of 96.1% and 96.3% of their time in Automated Mode, respectively.

The remainder of this review is focused on additional studies that recently evaluated hybrid closed-loop systems in children and adolescents with type 1 diabetes. These studies are summarized in Tables 5 and 6.

The RCT by Tauschman et al (2018) evaluated individuals with uncontrolled type 1 diabetes as reflected in mean HbA_{1c} >8%. Approximately, 50% of the subjects were between 6 to 21 years of age and 25% were age 6 to 12 years.[31,] Both groups achieved a reduction in HbA_{1c}, but the reduction was statistically greater in the hybrid closed-loop group compared to the control group. The investigators reported that the HbA_{1c} improvements were not different among children, adolescents, and adults (data not shown in tables). No severe hypoglycemic events were reported consistent with a decrease in time spent with glucose <70 mg/ dL.

Abraham et al (2018) reported the results of a 6-month, multicenter, RCT in children and adolescents with type 1 diabetes comparing use of an insulin pump with suspend before low or predictive low-glucose management with sensor-augmented insulin pump therapy alone.[32,] At 6 months, significant reductions were seen in day and night hypoglycemia and number of hypoglycemic events <63 mg/ dL lasting longer than 20 minutes. There were no differences in HbA_{1c} at 6 months in either group.

Forlenza et al (2019) reported the data and analysis of the supplemental information filed with the FDA to support the expanded indication for the MiniMed 670G system to children 7 to 13 years of age.[33,] The nonrandomized, single-arm, multicenter study reported the day and night use of the automated insulin delivery and predictive low glucose management for 3 months in the home setting. There were no serious adverse events and use of the system was associated with reduction in HbA_{1c} and increased time in target glucose range.

Wood et al (2018) reported an in-clinic evaluation of a 7 to 13-year-old cohort of the 670G pivotal trial that was designed to evaluate the performance characteristics of the device when activity induced hypoglycemic patterns were used to set individual device parameters for ongoing use by the study participant.[34,] The suspend before low prevention capability was confirmed in 97.5% of patients experiencing a sensor glucose of ≤55 mg/dL.

Messer et al (2018) reported on a subanalysis of the adolescent and young adult participants in the 670G pivotal trial to better characterize the carbohydrate input and insulin bolus determination features of the device over a 3-month period.[35,] Participants successfully utilized the device without significant changes in total daily dose of insulin but improved percentage time in range (70 to 180 mg/ dL).

Breton et al (2020) reported results of a 16-week, open-label RCT comparing the t:slim X2 insulin pump with Control-IQ Technology to sensor-augmented pump therapy in 101 children with type 1 diabetes age 6 to 13 years.[36,] The glucose level was in the target range for a greater percentage of time with the use of the hybrid closed-loop system than with the use of a sensor-augmented insulin pump. Improvements were sustained through 28 weeks in an uncontrolled extension study of 100 children who were enrolled in the RCT.[37,] Health-related quality of life and patient satisfaction measures from the RCT and the extension phase were reported by Cobry et al (2021).[38,] Neither children nor their parents in the hybrid closed-loop group reported statistically significant changes in these outcomes compared with the sensor-augmented pump therapy group. The authors concluded that children receiving the hybrid closed-loop system did not experience increased burden compared with those using sensor-augmented pump therapy.

Clinical study results for children ages 2 to 6 years are available in the FDA Summary of Safety and Effectiveness for the MiniMed 670G System (Tables 3 and 4).[10,] This was a descriptive study to evaluate the safe use of the device's auto mode and was not designed to determine the effectiveness of the device compared to alternative treatments. Based on the pivotal study and an additional performance study submitted for the evaluation, FDA concluded with a reasonable assurance of effectiveness that the MiniMed 770G System can automatically adjust basal insulin rates based on continuous glucose monitoring values.

Sherr et al. (2022) conducted a US multicenter, prospective outpatient clinical study of the Omnipod 5 AID System in very young children (N=80) aged 2.0-5.9 years.[39,] The study included a 14-day standard therapy phase where participants used their usual therapy to collect baseline continuous glucose monitoring (CGM) data, followed by a 13-week AID study phase. The primary glycemic endpoints were the HbA1c levels at the end of the AID phase compared to baseline and the TIR (70–180 mg/dL) during the AID phase compared to the standard therapy phase. The primary safety endpoints were the incidence rates of severe hypoglycemia and diabetic ketoacidosis. Results showed that HbA1c levels decreased by 0.55% (6.0 mmol/mol) ($p < .0001$), and the time with sensor glucose levels in the target range of 70-180 mg/dL increased by 10.9%, or 2.6 hours per day ($p < .0001$). Additionally, the time with glucose levels below 70 mg/dL decreased by a median of 0.27% ($p = .0204$). There were no episodes of severe hypoglycemia or diabetic ketoacidosis reported. The study's single-arm design, which involved interactions every two weeks, may have overestimated improvements in glycemic outcomes. Additionally, the study population's homogeneity (77.5% White non-Hispanic) and exclusion of participants with recent severe glycemic events limit the generalizability of the findings, necessitating further research with more diverse groups of young children.

DeSalvo et al (2024) evaluated the long-term safety and effectiveness of the Omnipod® 5 AID System in very young children with type 1 diabetes with up to 2 years of use.[40,] This was an extension trial of Sherr et al (2022). Participants (2-5.9 years of age at study enrollment) were provided the option to continue use of the AID system in an extension phase. HbA1c were monitored every 3 months for up to 15 months, and continuous glucose monitor metrics were tracked through 2 years. The study included 80 participants, who used the Omnipod system for a median of 18.2 months, inclusive of the 3-month pivotal trial. HbA1c levels were maintained at 7.0% ± 0.7% (53 ± 7.7 mmol/mol) after 15 months ($p < .0001$ from baseline). Time in target range (70-180 mg/dL) was sustained at 67.2% ± 9.3% during the extension phase ($p < .0001$ from standard therapy). Participants spent a median 97.1% of their time in Automated Mode, with one episode of severe hypoglycemia and one episode of diabetic ketoacidosis.

Forlenza et al. (2024) performed a retrospective analysis of US users (N=69,902) of the Omnipod 5 System with T1D, aged 2 years and older, who had sufficient data (≥90 days with ≥75% of days having ≥220 CGM readings/day) available in Insulet Corporation's device and person-reported datasets as of July 2023.[41,] The study summarized target glucose settings usage (i.e., 110-150 mg/dL in 10 mg/dL increments) and examined glycemic outcomes. Subgroup analyses included those using the lowest average glucose target (110 mg/dL) and stratification by baseline characteristics (e.g., age, prior therapy, health insurance coverage). Younger age groups more commonly used multiple and higher glucose targets. The median percentage of TIR (70-180 mg/dL) was 68.8% for users with an average glucose target of 110 mg/dL, 61.3% for 120 mg/dL, and 53.6% for 130-150 mg/dL, with minimal time spent <70 mg/dL (all medians <1.13%). Among those with an average glucose target of 110 mg/dL (n=37,640), the median TIR was 65.0% in children and adolescents (2-17 years) and 69.9% in adults (≥18 years). Subgroup analyses of users transitioning from Omnipod DASH (predicate device) or multiple daily injections, as well as Medicaid/Medicare users, demonstrated favorable glycemic outcomes. These findings from a large and diverse sample of nearly 70,000 children and adults show the effective use of the Omnipod 5 System under real-world conditions.

Table 5. Summary of Key Study Characteristics: Hybrid Closed-Loop in Children and Adolescents with Type 1 Diabetes

Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**		
				N Age Mean (SD)	**Intervention**	**Study Type**
Tauschmann et al (2018)[31,] NCT02523131	UK, US	6	05/12/2016-11/17/2017	• *86* • *>6 years* • *[6 to 12 years; n=23]* • *[13 to* 21 years; n=19]	• *MiniMed 640G2* • *HCL*	RCT Intervention: • *SAPT with PLGM (n=46)* • *Screening HbA1c %(SD)* • *8.*3 (0.6) Control: • *SAPT alone (n=40)* • *Screening HbA1c %(SD)* • *8.5* (0.5)
Abraham et al (2018)[32,]	Australia	5	8/2014 - NR	• *154* • *8 to 20 years* • *13.*2 (2.8)	• *MiniMed 640G2* • *HCL*	RCT Intervention: • *SAPT* with PLGM (n=80) Control: • SAPT alone (n=74)
Forlenza et al (2019)[42,] NCT02660827	US, Israel	9	4/18/2016-10/09/2017	• 105 • 7 to 13 years • 10.8 (1.8)	• MiniMed 670G3 • HCL	Noncomparative pivotal trial

Study; Trial	Countries	Sites	Dates	Participants		
Wood et al (2018)[34], NCT02660827	US, Israel	9	4/18/2016-10/09/2017	• 105 • 7 to 13 years • 10.8 (1.8)	• MiniMed 670G3 • HCL	12-hour clinic evaluation of PLGM performance in conjunction with exercise[4]
Messer et al (2018)[35], NCT02463097	US	3	2015-2018	• 31 • 14 to 26 years • 17.8 (3.9)	• MiniMed 670G3 • HCL	Sub-study of FDA pivotal trial for device: insulin delivery characteristics and time in range
FDA (2020)[10], Safety Evaluation of the Hybrid closed-loop (HCL) System in Pediatric Subjects with Type 1 Diabetes (G150247)	US	7	2017-2018	• 46 • 2 to 6 years	• MiniMed 670G3 • HCL	Noncomparative pivotal trial
Breton et al (2020)[36], NCT03844789	US	4	2019-2020	• 101 • 6 to 13 years	• t:slim X2 insulin pump with Control-IQ Technology4 • HCL	RCT, open label Intervention: • HCL (n=78) Control: • SAPT (n=23)
Brown et al (2021)[29], NCT04196140	US	17	2019-2020	• 241 (112 children ages 6 to 13.9 years, 128 adults age 14 to 70 years) • 6 to 70 years	• Omnipod 5 Automated Insulin Delivery System • HCL	Noncomparative pivotal trial
Sherr et al (2022)[39],	US	10	2020-2021	• 80 • [4.7 ± 1.0 (range, 2 to 6 years) • [2 to 4 years n=16; 20%)]	• Omnipod 5 Automated Insulin Delivery System	Single-arm, prospective outpatient study

FDA: U.S. Food and Drug Administration; HCL: hybrid closed-loop; NR: not reported; PLGM: predictive low glucose management; PMA: premarket approval; RCT: randomized controlled trial; SAPT: sensor-augmented pump therapy; SD: standard deviation; T1D: type 1 diabetes.
[2]MiniMed 640G is hybrid closed-loop device approved for use outside of US.
[3]MiniMed 670G is hybrid closed-loop device approved for use in US.

[4]t:slim X2 insulin pump with Control-IQ Technology is hybrid closed-loop device approved for use in US.
[5]Activity/exercise induced hypoglycemia protocol (walking, biking, playing Wii games, or other aerobic activities) intended to activate the "suspend before low" feature followed by evaluation up to 6 hours and at least 4 hours after insulin resumption.

Table 6. Summary of Key Study Results: Hybrid Closed-Loop in Children and Adolescents with Type 1 Diabetes

Study	Efficacy Outcomes			Safety Outcomes	
Tauschmann et al(2018)[31,]					
Outcome Measure	*Group difference in time proportion in target glucose range (70 to 180 mg/dL) at 12 weeks Mean (SD)*		*HbA_{1c} % (SD) At 12 weeks*	*Hypoglycemia* A. *<63 mg/ dL* B. *<50 mg/ dL* *Percent time in given range (SD)*	
• SAPT with PLGM • SAPT alone • Difference • [95% CI] • P • SAPT with PLGM • SAPT alone • Difference • [95% CI] • P	• 68% (8) • 54% (9) • 10.8 • [8.2,13.5] • <.0001	•	• 7.4 (0.6) • 7.7 (0.5) • -0.36 • [-0.53, -0.19] • <.0001	A. • 1.4 (0.9, 1.9) • 2.0 (0.9,3.0) • -0.83 • [-1.4,-0.16] • .0130 B. • 0.3 (0.2, 0.6) • 0.5 (0.2, 0.9) • -0.09 • [-0.24, 0.01] • .08	•
Abraham et al(2018)[32,]					
Outcome Measure	*Change in average percent time in hypoglycemia (SG <63 mg/ dL) at 6 months*	*Change in average percent time in hypoglycemia (SG <54 mg/ dL) at 6 months*	*HbA_{1c} Mean %(SD)*	*Hypoglycemic events (SG <63 mg/ dL for >20 minutes) Events per patient-year*	*IAH[2](%)* • Clarke score ≥4 • N=90 *(≥12 years)*
SAPT with PLGM	• n=76	• n=76	7.5(0.8) Δ 7.8(0.8)	139	4%

Study	Efficacy Outcomes			Safety Outcomes	
	• 2.8% Δ1.4%	• 1.3% Δ 0.6%			
SAPT alone	• n=70 • 3% Δ2.6%	• n =70 • 1.4% Δ1.2%	7.4(0.7) Δ 7.6(1.0)	227	13%
Difference in LS means [95% CI] p	• -0.95% • [-1.30, - 0.61] <.0001	• -0.44% • [-0.64, - 0.24] <.0001	• 0.09 • [-0.10, 0.27] .35	• [221,234 vs. 134,143] • <.001	• -0.04 • [- 0.52,0.4 3] .86
Forlenza et al(2019)[1] NCT02660827[4] [2],					
Outcome Measure	*HbA_{1c} Mean % (SD)*		*Time in Range(>70 to 180 mg/dL) Mean %(SD)*	*Hypogylcemia A. ≤70 mg/ dL B. ≤54 mg/ dL Mean %(SD)*	
Baseline Run-in phase (n=106) 3-month study phase (n=105) p	• 7.9 (0.8) • 7.5 (0.6) <.001	•	• 65 (7.7) <.001	A. ≤70 mg/ dL • 4.7 (3.8) • 3.0 (1.6) <.001 B. ≤54 mg/ dL • 1.3 (1.5) • 0.8 (0.7) <.001	•
Wood et al(2018)[1](NCT0266087)[3] [4],					
Outcome Measure	*N=79 participant activations of suspend before low Rate of "Suspend before Low" (%)*				
Reference range[3] • ≤55 mg/ dL • ≤60 mg/ dL	• 77 (97.5) • 71 (89.9)	•			

Study	Efficacy Outcomes			Safety Outcomes	
• ≤65 mg/ dL	• 63 (79.7)				
Messer et al(2018)[1](NCT02463097)[35,]					
Outcome measure	*Mean percentage time in range (70 to 180 mg/ dL) using HCL mode[4] Mean % (SD)*				
Days • Days 1-7 • Days 22-28 • Days 50-56 • Days 78-84	• 69.7 (10.6) • 69.5 (8.5) • 71.9 (8.1) • 71.5 (10.3)	•			
FDA (2020)[10,] Safety Evaluation of the Hybrid closed-loop (HCL) System in Pediatric Subjects with Type 1 Diabetes (G150247)					
Outcome measure	*Percent change from baseline in HbA_{1c} Mean (SD); 95% CI*	*Total Daily Dose of insulin at end of study Mean (SD)*	*Time in range during study period, % Mean (SD); 95% CI*	*Adverse events*	
	-0.5 (0.7); -0.7, -0.3	16.1 U (4.7)	<50 mg/dL: 0.5 (0.4); 0.4 to 0.6 <54 mg/dL: 0.8 (0.6); 0.6 to 1.0 <60 mg/dL: 1.5 (0.9);	• No reports of unanticipated serious adverse device effects, unanticipated non-serious adverse device/procedural effects	•

Study	Efficacy Outcomes			Safety Outcomes	
			1.2 to 1.8 <70 mg/dL: 3.5 (1.6); 3.0 to 3.971 <180 mg/dL: 63.6 (9.4); 60.8 to 66.4 >180 mg/dL: 33.0 (9.9); 0.4 to 0.6 >250 mg/dL: 10.7 (5.9); 8.9 to 12.4 >300 mg/dL: 3.7 (2.9); 2.9 to 4.6 >350 mg/dL: 1.2 (1.1); 0.8 to 1.5	• No reports of diabetic ketoacidosis events. • No reports of severe hypoglycemia events	
Breton et al (2020)[36,] Cobry et al (2021)[38,] NCT03844789					
Outcome measure	*HbA_{1c}* at 16 weeks		*Percent time in target range 70 to 180 mg/dL (Primary outcome)* *Mean (SD)*	*Adverse events*	

Study	Efficacy Outcomes			Safety Outcomes	
HCL	7.0 (0.8)		67 (10)	16 adverse events in 15 patients (19%) Median hypoglycemic events per week (IQR): 0.5 (0.1 to 0.8) Median hyperglycemic events per week (IQR): 3.0 (1.7 to 5.2) No severe hypoglycemia or diabetic ketoacidosis	
Control	7.6 (0.9)		55 (13)	3 adverse events in 2 patients (9%) Median hypoglycemic events per week (IQR): 0.6 (0.1 to 1.0) Median hyperglycemic events per week (IQR): 5.6 (3.4 to 8.1) No severe hypoglycemia or diabetic ketoacidosis	
Between-group difference	-0.4 (95% CI, -0.9 to 0.1; p=.08)		11% (7% to 14%); p<.001	Median hypoglycemic events per week: p=0.16	

Study	Efficacy Outcomes			Safety Outcomes	
				Median hyperglycemic events per week: p=.001	
Brown et al (2021)[29,]					
Outcome measure	*Mean reduction from baseline in HbA_{1c}*	*Time in range change from baseline (hours/day)*	*Reduction from baseline in time in hypoglycemia <70 mg/dL*	*Adverse events*	
Results	Children: 0.71% Adults: 0.38% both p<.0001 from baseline	Children: 3.7 Adults: 2.2 both p<.0001 from baseline	Children: no change Adults: 2.0% to 1.09%; p=.0001	3 severe hypoglycemia events not attributed to device malfunction, 1 diabetic ketoacidosis event from an infusion site failure	
Sherr et al (2022)[39,]					
Outcome measure	*Mean reduction from baseline in HbA_{1c}*	*Time in range change from baseline (hours/day)*	*Reduction from baseline in time in hypoglycemia <70 mg/dL*	*Adverse events*	
Results	Decrease by 0.55% (6.0 mmol/mol) (p<.0001)	Increase by 10.9%, or 2.6 h/day (p<.0001)	Declined by median 0.27% (p=.0204).	There were no episodes of severe hypoglycemia or diabetic ketoacidosis.	

Δ: delta meaning change in status; CI: confidence interval; HbA1c; hemoglobin A1c; HCL: hybrid closed-loop; IAH: impaired awareness of hypoglycemia; IQR: interquartile range; LS: least squares; PLGM: predictive low glucose management; SAPT: sensor-augmented pump therapy; SD: standard deviation; SG: sensor glucose; T1D: type 1 diabetes.

[1]Data as submitted for FDA PMA Supplement P160017/S031.

[2]Clarke score: uses 8 questions to characterize an individual's exposure to episodes of moderate and severe hypoglycemia to assess the glycemic threshold for and symptomatic response to hypoglycemia. A value ≥4 indicates

IAH.
[3]Simultaneous testing with either intravenous sampling or self-monitoring blood glucometer.
[4]Open loop manual mode was used in a run-in phase to develop personalized parameters for HCL/Auto Mode phase.

Section Summary: Hybrid Closed-Loop Insulin Delivery Systems
The evidence includes multicenter pivotal trials using devices cleared by the FDA, supplemental data and analysis for expanded indications, and more recent studies focused on children and adolescents. A 13-week multicenter RCT found that the first FDA-approved tubeless automated insulin delivery system (AID) significantly increased time in range by 4.2 hours per day and lowered HbA1c levels compared to continuous glucose monitoring (CGM) pump therapy. The automated insulin delivery system also resulted in fewer high glucose events and no serious adverse events. A second multi-center 6-month RCT comparing AID systems to multiple daily injections showed greater HbA1c reduction, improved time in range, and fewer high/low glucose events in the AID group with similar safety outcomes. Furthermore, 2 (of 3) crossover RCTs using a first-generation device, studied and approved outside the United States, found significantly better outcomes - such as reduced time in nocturnal hypoglycemia and increased time in the preferred glycemic range - compared to standard care. The third study yielded mixed results, showing significant improvement in nocturnal hypoglycemia but no significant change in time spent in the preferred glycemic range. Additional evidence from device performance and clinical studies demonstrates reductions in hypoglycemia, improved time within the range of 70 to 180 mg/dL, rare instances of diabetic ketoacidosis, and few device-related adverse events. The evidence suggests that the magnitude of reduction for hypoglycemic events in the type 1 diabetes population is likely to be clinically significant.

CLOSED-LOOP INSULIN DELIVERY SYSTEM

Clinical Context and Therapy Purpose
The purpose of a closed-loop insulin delivery system in individuals with type 1 diabetes is to improve glycemic control.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with type 1 diabetes.

Interventions
The therapy being considered is a closed-loop insulin delivery system.

Currently, the iLet Bionic Pancreas (Beta Bionics) is the only closed-loop insulin delivery system commercially available in the U.S. The system differs from hybrid closed-loop systems in that it is initialized only with a user's body weight and doses insulin autonomously without carbohydrate counting.[43,] Hybrid closed-loop systems require individualized insulin regimens and require the user to count the grams of carbohydrates to be eaten and then enter this number into their device's user interface. In contrast, the closed-loop insulin delivery system is initialized only based on body weight and requires only that the user make a qualitative estimate of carbohydrate content that is relative to what is usual for the user ("Usual For Me", "More", or "Less") compared to a typical meal of that type ("Breakfast", "Lunch", or "Dinner"). In response to qualitative meal announcements to the system by the user, the system delivers approximately 75% of the autonomously estimated insulin immediately and then autonomously adjusts insulin

dosing post-prandially as needed. Additionally, the device includes a feature which enables continued insulin delivery when CGM information is not available, based on a basal insulin profile autonomously determined and continually updated. Use of this feature, however, is intended to be temporary, with the goal to resume CGM-guided insulin dosing as soon as possible.

The system was developed as both an insulin-only system and a bihormonal system that administers both insulin and glucagon. Currently, only the insulin-only system has FDA clearance.

Comparators

The following therapies are currently being used to treat type 1 diabetes: an AID system with low glucose suspend feature, a hybrid closed-loop insulin delivery system, nonintegrated continuous glucose monitoring plus insulin pump (open-loop), or self-monitoring blood glucose and multiple dose insulin therapy.

Outcomes

The general outcomes of interest are glycated hemoglobin levels, time in range or target glucose levels, and rates of hypoglycemia and hyperglycemia. Other outcomes of interest include quality of life and changes in health care utilization (eg, hospitalizations). The duration of follow-up is life-long.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Randomized Controlled Trial

The iLet Bionic Pancreas System was compared to standard care in a multicenter RCT (NCT04200313) enrolling 219 individuals ages 6 to 79 years with type 1 diabetes (Table 5).[43,] Comparator group participants continued their pre-study subcutaneous insulin delivery (either multiple daily injections, an insulin pump without automation of insulin delivery, an insulin pump with predictive low glucose suspend feature, or an insulin pump as part of an HCL system) plus real-time CGM. The primary outcome was glycated hemoglobin level at 13 weeks and the key secondary outcome was the percent time A1c was below <54 mg/dL at 13 weeks.

Main results for the full group (N=326) were reported by Russell et al (2022) and are summarized in Table 6.[43,] Mean glycated hemoglobin decreased from 7.9% to 7.3% in the closed-loop insulin delivery system group while it did not change (7.7% at both time points) in the standard-care group (mean adjusted difference at 13 weeks, −0.5%; 95% CI −0.6% to −0.3%; p <.001). The rate of severe hypoglycemia was 17.7 events per 100 participant-years in the closed-loop insulin delivery system group and 10.8 events per 100 participant-years in the standard-care group (p=.39). No episodes of diabetic ketoacidosis occurred in either group.

The trial results for the subgroups of adults (ages 18 and older) and youth (ages 6 to 17 years) have additionally been reported and were similar to the main results for the full cohort (see Table 6). Kruger et al (2022) reported results for adults ages 18 and over (n=161).[44,] In this subgroup, mean glycated hemoglobin decreased from 7.6% (SD, 1.2%) at baseline to 7.1% (SD, 0.6%) at 13 weeks in the intervention group versus 7.6% (SD, 1.2%) to 7.5% (SD, 0.9%) with standard care (adjusted difference, -0.5%; 95% CI, -0.6% to -0.3%; p<.001). Time below 54 mg/dL was low at baseline (median 0.2%) and not significantly different between groups over 13 weeks (p=.24). The incidence of severe hypoglycemia did not differ between groups. Messer et al (2022) reported results for children and youth ages 6 to 17 years (n=165).[45,] Mean glycated hemoglobin decreased from 8.1% (SD, 1.2%) at baseline to 7.5% (SD, 0.7%) at 13 weeks in the intervention group versus 7.8% (SD, 1.1%) at both baseline and 13 weeks with standard care (adjusted difference, -0.5%; 95% CI, -0.7% to -0.2%).

Following the 13-week randomized portion of the trial, comparator group participants (n=90 of 107) crossed over and received the closed-loop insulin delivery system for 13 weeks.[46,] In this extension phase, improvement in glycemic control was of a similar magnitude to that observed during the randomized trial. Results were similar in the adult (n=42) and pediatric (n=48) cohorts.

Table 7. Closed-Loop Insulin Delivery System: Summary of Key Study Characteristics

Study	Countries	Sites	Dates	Inclusion Criteria	Participant Characteristics	Interventions	
						Active	Control
Russell et al (2022)[43,] NCT04200313	US	16	2020-2021	• Age 6 years or older, • clinical diagnosis of type 1 diabetes for at least 1 year, • used insulin for at least 1 year; • diabetes managed using the same regimen (either pump or multiple daily injections, with or without CGM) for 3 months or longer.	100 (31%) were using a hybrid closed-loop system, 14 (4%) a system with predictive low-glucose suspension, 102 (31%) an insulin pump without automation, and 110 (34%) multiple daily injections of insulin.	n=219 iLet Bionic Pancreas System	n=107 Standard Care: Insulin delivery method in use at the time of enrollment (could include hybrid closed-loop systems) and a real-time unblinded Dexcom G6 continuous glucose monitor provided by the trial.

RCT: randomized controlled trial.

Table 8. Closed-Loop Insulin Delivery System: Study Results

Study	Primary Efficacy Outcomes	Key Secondary Efficacy Outcome	Safety Outcomes		
Russell et al (2022)[43], Adult subgroup: Kruger et al (2022)[44], Youth subgroup: Messer et al (2022)[45], NCT04200313	*Mean glycated hemoglobin level at 13 weeks (SD)*	*Median percentage of time <54 mg/dL (IQR) at 13 weeks*	*Participants experiencing an event of severe hypoglycemia (defined as hypoglycemia with cognitive impairment requiring the assistance of a third party for treatment)*	*Participants experiencing diabetic ketoacidosis*	*Participants experiencing other serious adverse events*
N analyzed	219 intervention (112 youth), 107 Control (53 youth)	219 intervention (112 youth), 107 Control (53 youth)			
Closed-loop insulin delivery system	7.3 (0.7) Adults: 7.1 (0.6) Youth: 7.5 (0.7)	0.3 (0.2 to 0.6) Adults: 0.33 (0.14 to 0.52) Youth: 0.37 (0.16 to 0.66)	10/219 (5%) Adults: 7/107 (6.5%) Youth: 3/112 (2.7%)	0/219 Adults: 0 Youth: 0	3/219 (1%): 2 attempted suicide (age group not reported), 1 hypoglycemia
Standard Care	7.7 (1.0) Adults: 7.5 (0.9) Youth: 7.8 (1.1)	0.2 (0.1 to 0.6) Adults: 0.18 (0.08 to 0.58) Youth: 0.33 (0.18 to 0.63)	2/107 (2%) Adults: 2/54 (1.9%) Youth: 1/53 (1.9%)	0/107 Adults: 0 Youth:0	2/107 (2%): 1 spontaneous pneumothorax, 1 epiglottitis
Adjusted Difference (95% CI)	−0.5 (−0.6 to −0.3) Adults: −0.5%,(−0.6% to −0.3) Youth: −0.5 (−0.7 to −0.2)	0.0 (−0.1 to 0.04) Adults: 0.02 (−0.04 to 0.08) Youth: −0.04 (−0.13 to 0.03)	NA	NA	NA
p-value	<.001 Adults: <.001 Youth:.001	<.001 (noninferiority) Adults:.33 Youth:.24	.39	Not calculated	.77

IQR: interquartile range; SD: standard deviation.

Section Summary: Closed-Loop Insulin Delivery System
The evidence includes a 13-week multicenter RCT of the iLet Bionic Pancreas System compared to usual care in 219 individuals ages 6 to 79 years with type 1 diabetes. Comparator group participants continued their pre-study subcutaneous insulin delivery (either multiple daily injections, an insulin pump without automation of insulin delivery, an insulin pump with predictive low glucose suspend feature, or an insulin pump as part of an HCL system) plus real-time CGM. The glycated hemoglobin level decreased from 7.9% to 7.3% in the closed-loop insulin delivery system group and did not change (7.7% at both time points) in the standard-care group (mean adjusted difference at 13 weeks, −0.5%; 95%CI −0.6 to −0.3; p <0.001). The rate of severe hypoglycemia was 17.7 events per 100 participant-years in the closed-loop insulin delivery system group and 10.8 events per 100 participant-years in the standard-care group (p = 0.39). No episodes of diabetic ketoacidosis occurred in either group. The trial's results for the subgroups of adults (ages 18 and older) and youth (ages 6 to 17 years) have additionally been reported and were similar to the main results for the full cohort.

TYPE 2 DIABETES

HYBRID CLOSED-LOOP INSULIN DELIVERY SYSTEMS

Clinical Context and Therapy Purpose
The purpose of a hybrid closed-loop insulin delivery system in individuals who have type 2 diabetes is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with type 2 diabetes 18 years of age or older. Comprehensive management of type 2 diabetes involves addressing blood pressure, lipids, and glucose targets to reduce complication risks. Advances in glucose-lowering therapies have improved treatment options. However, many patients still require exogenous insulin therapy to achieve glycemic targets, but hesitancy and clinical inertia often lead to suboptimal outcomes.

Interventions
The therapy being considered is a FDA-approved hybrid closed-loop insulin delivery system. A hybrid closed-loop system continuously adjusts insulin delivery. However, at mealtime, the patient enters the number of carbohydrates being consumed in order for the insulin pump to determine the bolus meal dose of insulin. Two hybrid closed-loop insulin delivery systems have been approved by the FDA:

- On August 26, 2024, the FDA approved the Omnipod 5 System (Insulet Corporation, Acton, MA) for automated insulin dosing for individuals with type 2 diabetes in individuals aged 18 and older. Utilizing SmartAdjust™ technology, it works with compatible integrated CGMs and ACE pumps to automatically modify insulin delivery - whether increasing, decreasing, or pausing it - based on real-time and projected glucose levels. This technology is designed for single patient use and requires a prescription. The Omnipod 5 System comprises a wearable, tubeless on-body device known as the Pod,

which adjusts insulin delivery according to readings from a compatible CGM. Users interact with the system via a handheld device, such as a personal smartphone or the provided Controller, which connects through Bluetooth wireless technology. The system is a hybrid closed loop system and therefore can operate in either open loop (Manual Mode; SmartAdjust™ technology disabled) or closed loop (Automated Mode; SmartAdjust™ technology enabled). When Automated Mode is turned on, the SmartAdjust™ algorithm (installed on the Pod) controls insulin delivery based on recent CGM values.

- On February 24, 2025, the FDA approved the t:slim X2 Insulin Pump with Control-IQ Technology (Tandem Diabetes Care, San Diego, California) for individuals with type 2 diabetes in individuals aged 18 and older. Control-IQ+ technology is intended for use with compatible integrated CGMs and alternate controller enabled (ACE) pumps to automatically increase, decrease, and suspend delivery of basal insulin based on iCGM readings and predicted glucose values. It can also deliver correction boluses when the glucose value is predicted to exceed a predefined threshold.

Comparators
The following therapies are currently being used to treat type 2 diabetes: lifestyle changes, medications, long-term glucose monitoring, weight management, and education and support.

Outcomes
The general outcomes of interest are HbA_{1c} levels, time in range or target of glucose levels, and rates of hypoglycemia and hyperglycemia. Other outcomes of interest include quality of life and changes in health care utilization (eg, hospitalizations). The duration of follow-up is life-long.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

PROSPECTIVE STUDIES

Omnipod 5 Automated Insulin Delivery System
The efficacy and safety of the system has been demonstrated in individuals with type 2 diabetes in one pivotal multicenter clinical trial, and one single-arm feasibility and extension trial. Both studies were funded by Insulet Corporation. In August 2024, the FDA expanded the indications for the Omnipod 5 AID system, incorporating Insulet SmartAdjust technology, to include managing type 2 diabetes in individuals aged 18 years and older.

The FDA granted approval for the Omnipod 5 AID system based on the pivotal multicenter clinical trial by Pasquel et al (2025) (SECURE-T2D; NCT05815342).[47,] This single-arm prospective study

was performed at 21 US clinical centers and included individuals aged 18 to 75 years who had been using insulin for at least 3 months before screening, excluding those already using an AID system. The study began with a 14-day standard therapy phase, followed by 13 weeks of treatment with the Omnipod 5 device. The first participant was enrolled in April 2023, and the final follow-up visit for the last participant took place on February 2024. The primary efficacy outcome was the change in HbA1c level at 13 weeks, tested for noninferiority (0.3% margin) and superiority compared with baseline data. Among 305 participants (mean age, 57 years; 57% female; 24% Black, 22% Hispanic or Latino, and 50% White), 289 (95%) completed the trial. At baseline, the majority were using multiple daily injections (73%), basal insulin without bolus (21%), or an insulin pump (6%), and many were also using CGM (62%), GLP-1 receptor agonists (55%), or sodium-glucose transport protein 2 inhibitors (44%). Following AID use, HbA1c levels decreased from a mean (SD) of 8.2% (1.3) at baseline to 7.4% (0.9) at 13 weeks (mean difference, -0.8 [95% CI, -1.0 to -0.7] percentage points; p <.001 for noninferiority and superiority). Improvements were observed across various subgroups, including age, sex, race, ethnicity, and insurance status, and were notable regardless of the use of medications or pretrial mealtime insulin regimens. Time in the target glucose range (70-180 mg/dL) increased from a mean of 45% to 66% (mean difference, 20 percentage points; p <.001), while the percentage of time in hypoglycemic ranges (<54 mg/dL and <70 mg/dL) was noninferior compared with standard therapy. There was one episode of severe hypoglycemia reported, and no cases of diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome. This study has certain limitations, notably its single-arm design which lacked a concurrent control group. In summary, the initiation of AID usage led to reduced HbA1c levels in a varied group of adults with type 2 diabetes, indicating that AID could be a beneficial and safe option for insulin users.

Davis et al. (2023) evaluated the feasibility of the Omnipod 5 AID System in individuals with type 2 diabetes through a US-based multicenter outpatient trial.[48,] This study included participants who were either on basal-only insulin or basal-bolus insulin therapy, with or without CGM, and had an initial HbA1c of 8% or higher (≥64 mmol/mol). A total of 24 participants were involved, with an average age of 61 years (± 8 years), an initial HbA1c of 9.4% (± 0.9%) (79 ± 10 mmol/mol), and an average diabetes duration of 19 years (± 9 years). The participants initially underwent a two-week period of CGM sensor data collection, which was blinded for those not previously using CGM, while continuing their standard therapy (ST). Following this, they transitioned to using the Omnipod 5 AID system for an eight-week period. Those who were on basal-only insulin injections initially used the AID system in manual mode for two weeks before fully activating the device. The primary safety outcomes measured were the percentage of time with sensor glucose levels ≥250 mg/dL or <54 mg/dL during AID usage. Secondary outcomes included changes in HbA1c and TIR for glucose levels between 70-180 mg/dL. The findings demonstrated a significant reduction in the percentage of time with sensor glucose levels ≥250 mg/dL by 16.9% (± 16.2%) (p <.0001), while the percentage of time with glucose levels <54 mg/dL remained low during both ST and AID device use (median [interquartile range] 0.0% [0.00%, 0.06%] vs. 0.00% [0.00%, 0.03%]; p =.45). Furthermore, the participants' HbA1c levels decreased by 1.3% (± 0.7%) (14 ± 8 mmol/mol; p <.0001) and their TIR increased by 21.9% (± 15.2%) (p <.0001).

In a 6-month extension phase by Davis et al (2025),[49,] study participants (n=22) achieved a further decrease in percentage of time ≥ 250 mg/dL to 9.7% (± 9.2%) (p =.0002 vs. standard therapy). In addition, percentage of time <54 mg/dL remained low from standard therapy through extension (median [interquartile range] 0.02% [0.00%, 0.05%], p >.05). HbA1c

decreased by 1.6% (± 1.2%) (15.5 ± 13.1 mmol/mol, p <.0001) and TIR increased by 22.4% (± 19.2%) (p <.0001) from standard therapy through extension with no significant change in body mass index and without an observed increase in total daily insulin requirements. The primary limitations of the feasibility study (and extension phase) include its single-arm design, which did not include a control group for comparison, and potential biases from patient selection and clinical site interactions, which may affect the generalizability of the findings.

T:Slim X2 Insulin Pump with Control-IQ+ technology

The efficacy and safety of the system has been demonstrated in individuals with type 2 diabetes in one pivotal multicenter RCT, funded by Tandem Diabetes Care. In February 2025, the FDA expanded the indications for the t:slim X2 insulin pump with Control-IQ+ technology to include managing type 2 diabetes in individuals aged 18 years and older. The FDA granted approval for the t:slim X2 insulin pump with Control-IQ+ technology based on the pivotal multicenter RCT by Kudva et al (2025) (2IQP; NCT05785832).[50,]This was a multicenter RCT performed at 21 US and Canadian centers and included individuals aged 19 to 87 years who had type 2 diabetes for at least 6 months based on clinical and lab data. All individuals were on multiple daily insulin injections with at least one rapid-acting insulin dose per day or had been using an insulin pump for at least 3 months before the study began. The study comprised 319 patients, enrolled from June 2023, to June 2024, who were randomly assigned in a 2:1 ratio to either use of AID with the t:slim system or continue their existing insulin-delivery method (control group), with both groups using CGM. Among 319 participants (mean age, 58 years; 48% female; 22% Black, 11% Hispanic or Latino, and 70% White), 311 (97%) completed the trial. At baseline, the majority were using multiple daily injections (96%) or an insulin pump (4%), and many were also using CGM (71%), GLP-1 receptor agonists (46%), or sodium-glucose transport protein 2 inhibitors (37%). The primary outcome was glycated hemoglobin levels at 13 weeks. Results showed a reduction of 0.9 percentage points in the AID group (from 8.2±1.4% at baseline to 7.3±0.9% at 13 weeks) compared to a 0.3 percentage point decrease in the control group (from 8.1±1.2% to 7.7±1.1%), with a mean adjusted difference of -0.6 percentage points (95% CI, -0.8 to -0.4; p <.001). Additionally, the mean percentage of time patients maintained their glucose within the target range of 70 to 180 mg/dl increased from 48±24% to 64±16% in the AID group, while the control group saw a marginal increase from 51±21% to 52±21% (mean difference, 14 percentage points; 95% CI, 11 to 17; p <.001). All other CGM outcomes related to hyperglycemia showed significant improvement in the AID group compared to the control group. The frequency of CGM-measured hypoglycemia was low in both groups, with a severe hypoglycemia event occurring in one patient in the AID group. These results appeared to be robust across a range of per-protocol and sensitivity analyses.

Section Summary: Hybrid Closed-Loop Insulin Delivery Systems for Type 2 Diabetes

The evidence includes multicenter pivotal trials and feasibility studies using devices cleared by the FDA. A US multicenter clinical trial of 305 adults using the Omnipod 5 AID system showed a significant average reduction in HbA1c levels from 8.2% to 7.4% over 13 weeks (treatment effect: -0.8%, 95% CI, -1.0 to -0.7, p<.001). The greatest improvements were noted in individuals with higher initial HbA1c levels. An 8-week study followed by a 6-month extension with Omnipod demonstrated significant reductions in high sensor glucose levels and HbA1c, increased time in the target range by 22%, and no significant changes in BMI or insulin requirements. A second US and Canadian multicenter RCT reported on 319 adults, randomly assigned to either the AID group using the t:slim X2 insulin pump equipped with Control-IQ+ technology or their existing insulin method, both utilizing CGM. The AID group showed a notable

reduction of 0.9 percentage points in HbA1c (from 8.2±1.4% at baseline to 7.3±0.9% at 13 weeks), compared to a modest 0.3 percentage point decrease in the control group (from 8.1±1.2% to 7.7±1.1%). The mean adjusted difference was -0.6 percentage points (95% CI, -0.8 to -0.4; p<.001). Individuals in the AID group showed an increased percentage of time maintaining glucose within the target range, with low hypoglycemia frequency and consistent results across various sensitivity analyses. These studies demonstrate favorable glycemic outcomes in type 2 diabetes patients using hybrid closed-loop insulin delivery systems, similar to the benefit observed in trials involving adults with type 1 diabetes.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2019 Input

Clinical input supported that the outcome of hypoglycemia prevention provides a clinically meaningful improvement in net health outcome, and this use is consistent with generally accepted medical practice. Clinical input also supported that the use of hybrid closed-loop AID systems provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. Reduction in the experience of hypoglycemia and inappropriate awareness of hypoglycemia and glycemic excursions were identified as important acute clinical outcomes in children, adolescents, and adults and are related to the future risk for end-organ complications.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Association of Clinical Endocrinology

In 2021, the American Association of Clinical Endocrinology (AACE) published a clinical practice guideline for the use of advanced technology in the management of individuals with diabetes.[51,] The guideline included the following statements:

"Low-glucose suspend (LGS) is strongly recommended for all persons with T1D to reduce the severity and duration of hypoglycemia, whereas predictive low glucose suspend (PLGS) is strongly recommended for all persons with T1D to mitigate hypoglycemia. Both systems do not lead to a rise in mean glucose, and lead to increased confidence and trust in the technology, more flexibility around mealtimes, and reduced diabetes distress for both persons with diabetes and caregivers. Therefore, anyone with frequent hypoglycemia, impaired hypoglycemia

awareness, and those who fear hypoglycemia leading to permissive hyperglycemia should be considered for this method of insulin delivery. "Grade A; High Strength of Evidence

"AID systems are strongly recommended for all persons with T1D, since their use has been shown to increase TIR, especially in the overnight period, without causing an increased risk of hypoglycemia. Given the improvement in TIR and the reduction in hyperglycemia with AID, this method of insulin delivery is preferred above other modalities. For persons with diabetes with suboptimal glycemia, significant glycemic variability, impaired hypoglycemia awareness, or who allow for permissive hyperglycemia due to the fear of hypoglycemia, such AID systems should be considered." Grade A; High Strength of Evidence

In 2022, AACE published a clinical practice guideline update on developing a diabetes mellitus comprehensive care plan.[52,]The guideline included the following recommendations associated with AID systems:

"Automated insulin delivery (AID) systems, which include an insulin pump, an integrated CGM, and computer software algorithm, aim to better emulate physiological insulin replacement and achieve glycemic targets. This technology is recommended for many persons with T1D since its use has been shown to increase TIR while often reducing hypoglycemia or at least without causing increased hypoglycemia. Grade A; BEL [best evidence level] 1"

American Diabetes Association
The American Diabetes Association has issued recommendations regarding the use of AID systems in the 2026 Standards of Care in Diabetes, offering guidance for the management of both type 1 and type 2 diabetes (Table 9).[53,]

Table 9. American Diabetes Association Recommendations on Controlling Type 1 and Type 2 Diabetes

Date	Title	Publication Type	Recommendation (Level of Evidence)
2026	Diabetes Technology: Standards of Care in Diabetes - 2026	Guideline standard	• 7.25a AID [automated insulin delivery] systems are the preferred insulin delivery method over MDI [multiple daily injections], CSII [continuous subcutaneous insulin infusion], and sensor-augmented pumps in people with type 1 diabetes, (A) adults with type 2 diabetes, (A) children and adolescents with type 2 diabetes, (E) and those with other forms of insulin deficient diabetes. (B, C, D, E) Choice of an AID system should be made based on the individual's circumstances, preferences, and needs. (E) • 7.25b Consider AID systems for select people with type 2 diabetes treated with basal insulin not achieving individualized glycemic goals. (B) Choice of an AID system should be made

Date	Title	Publication Type	Recommendation (Level of Evidence)
			based on the individual's circumstances, preferences, and needs. (E) • 7.26 Individuals with diabetes who have been using CSII and/or AID should • have continued access across third party payors. (E)

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 10.

Table 10. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT07401901[a]	Evaluation of the Safety and Effectiveness of the Novel Medtronic Experimental Automated Insulin Delivery System (NMX8) in Adults Living With Type 1 Diabetes	230	Feb 2028
NCT07287943[a]	Efficacy and Safety of Medtronic 780G Automated Insulin Delivery System in Adults With Type 1 Diabetes and Gastroparesis	34	Dec 2026

NCT: national clinical trial.
[a]Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
A4226	Supplies for maintenance of insulin infusion pump with dosage rate adjustment using therapeutic continuous glucose sensing, per week
A9274	External ambulatory insulin delivery system, disposable, each, includes all supplies and accessories
E0784	External ambulatory infusion pump, insulin
E0787	External ambulatory infusion pump, insulin, dosage rate adjustment using therapeutic continuous glucose sensing
S1034	Artificial pancreas device system (e.g., low glucose suspend [LGS] feature) including continuous glucose monitor, blood glucose device, insulin pump and computer algorithm that communicates with all of the devices
S1035	Sensor; invasive (e.g., subcutaneous), disposable, for use with artificial pancreas device system
S1036	Transmitter; external, for use with artificial pancreas device system
S1037	Receiver (monitor); external, for use with artificial pancreas device system

REVISIONS	
03-06-2015	Policy added to the bcbsks.com web site.
02-03-2016	Updated Description section.
	Updated Rationale section.
	Updated References section.
10-01-2016	In Coding section: ▪ Added ICD-10 codes effective 10-01-2016: E13.37X1, E13.37X2, E13.37X3
01-18-2017	Updated Description section.
	Updated Rationale section.
	Updated References section.
01-01-2018	In Coding section: ▪ Added CPT code: 95249. ▪ Revised nomenclature to CPT codes: 95250, 95251. ▪ Removed ICD-9 codes.
03-01-2018	In Policy section: ▪ Added new Item C, "Use of hybrid closed loop insulin delivery system (including the Food and Drug Administration-approved device for age 14 and older) as an artificial pancreas device system is considered experimental / investigational."

REVISIONS	
	NOTE: The above revision was published to the bcbsks.com website on 01-30-2018; however, the revision was removed prior to medical policy implementation.
03-01-2018	Updated Description section.
	In Policy section: ▪ Removed previous Item A 2, "Type 1 diabetes" ▪ Removed previous Item A 4, "Used insulin pump therapy for more than 6 months" ▪ In current Item A 3 (previously Item A 5), removed "At least 2 documented nocturnal hypoglycemic events (see Policy Guidelines) in a 2 week period" and added "Hypoglycemic unawareness OR multiple documented episodes of nocturnal hypoglycemia (see Policy Guidelines)" ▪ Updated Policy Guidelines.
	Updated Rationale section.
	Updated References section.
11-07-2018	In Policy language: ▪ In Item A 1, "Age 16 and older" revised to read "Meets age requirement allowed by the FDA for the specific device prescribed (see Regulatory Status)."
	Updated References section.
01-04-2019	Updated Description section.
	Updated Rationale section.
	Remainder of policy reviewed; no revisions made.
05-21-2019	Updated Description section.
	In Policy section: ▪ In Item A, added "automated insulin delivery system" to read, "Use of an FDA-approved automated insulin delivery system (artificial pancreas device system) with a low glucose suspend feature may be considered medically necessary in patients with type 1 diabetes who meet ALL of the following criteria:" ▪ In Item B, added "automated insulin delivery system" and "individuals who do not meet the above criteria" and removed "all other situations" to read, "Use of an automated insulin delivery system (artificial pancreas device system) is considered experimental / investigational in individuals who do not meet the above criteria." ▪ Added new Item C, "Use of an automated insulin deliver system (artificial pancreas device system) not approved by the FDA is considered experimental / investigational."
	Updated Rationale section.
	Updated References section.
05-22-2020	Updated Description section.
	In Coding section: ▪ Added HCPCS Codes: A4226, E0787 (Eff 01-01-2020)
	Updated Rationale section.
	Updated Reference section.
06-03-2021	Updated Description section.
	In Policy section: In Item A: ▪ Removed "Difference approved 03-01-18" from A.1. ▪ Replaced "Glycated hemoglobin value between 5.8% and 10.1%" with "level < 10.0%" in Item A.2. ▪ Removed "Hypoglycemic unawareness OR multiple documented episodes of nocturnal hypoglycemia (see Policy Guidelines)." ▪ Added A.3 and A.4 Item B added to the policy Policy Guidelines removed from the policy

REVISIONS	
	Updated Rationale section.
	Updated Reference section.
06-01-2022	Updated Policy Section: ▪ Policy criteria changed to the following: A. Use of an FDA-approved automated insulin delivery system (artificial pancreas device system) with a low glucose suspend feature may be considered medically necessary when ALL of the following criteria is met: 1. In patients with type 1 diabetes who meet age requirement allowed by the FDA for the specific device prescribed (see Regulatory Status) AND 2. Individual or caregiver must have completed a comprehensive education program within the past 12 months if they are a first time user of insulin pump therapy B. Use of an automated insulin delivery system (artificial pancreas device system) not approved by the FDA is considered experimental / investigational. C. All other indications for automated insulin delivery system (artificial pancreas device system) considered not medically necessary
	Updated Coding Section ▪ Converted ICD-10 codes to range
08-22-2023	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Codes ▪ Removed 95249, 95250, and 95251
	Updated References Section
08-27-2024	Updated Description Section
	Updated Rationale Section
	Updated References Section
06-10-2025	Updated Title ▪ Title changed from "Artificial Pancreas Device Systems" to "Automated Insulin Delivery Systems"
	Updated Description Section
	Updated Policy Section ▪ Section A: Added: "cleared or" Removed "(artificial pancreas device system) with a low glucose suspend feature" ▪ Added Section B: B. Use of an FDA cleared or approved automated insulin delivery system designated as a hybrid closed-loop insulin delivery system (with low glucose suspend and suspend before low features) may be considered medically necessary in individuals with type 2 diabetes who meet ALL the following criteria: 1. Age 18 years and older AND a. Diagnosed with type 2 diabetes for at least 12 months; b. On multiple daily injections (insulin administration > 3x/day or use of insulin infusion pump) for at least 3 months; c. Glycated hemoglobin level ≥ 7% or experience significant hypoglycemia. ▪ Section C and D: Removed "(artificial pancreas device system)"
	Updated Policy Guidelines ▪ Added Policy Guidelines

REVISIONS	
	A. Diabetes mellitus (DM) encompasses various distinct types, all of which are characterized by abnormal carbohydrate metabolism manifesting as hyperglycemia and may require insulin therapy. The current body of evidence supporting the use of automated insulin delivery (AID) systems for each type of DM is variable, and the initiation of additional clinical trials is unlikely. Consequently, Plans will need to consider the use of such technology, recognizing the potential for similar therapeutic benefits across the different forms of DM. Individuals with DM should understand the technology, be motivated to use the device correctly and consistently, adhere to a comprehensive treatment plan supervised by a qualified provider, and be capable of recognizing alerts and alarms from the device. B. The U.S. Food and Drug Administration (FDA) has approved two hybrid closed-loop insulin delivery systems for type 2 diabetes management: the Omnipod 5 AID system (Insulet Corporation) and t:slim X2 insulin pump equipped with Control-IQ+ technology (Tandem Diabetes Care). 1. The Omnipod 5 AID system was approved following a pivotal clinical trial by Pasquel et al in 2025 (SECURE-T2D; NCT05815342). Trial participants aged 18 to 75 years, who had been on a stable insulin regimen for at least three months prior to screening (as per the above policy criteria), were selected. Additionally, they could be on other antihyperglycemic and weight loss drugs, provided there were no dose changes for at least 4 weeks before the trial commenced. However, those who experienced more than one severe hypoglycemic event or episode of diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome within 6 months before screening were excluded. 2. The t:slim X2 insulin pump equipped with Control-IQ+ technology was approved following a pivotal randomized controlled trial by Kudva et al in 2025 (2IQP; NCT05785832). Trial participants were aged 19 to 87 years and had type 2 diabetes for at least 6 months, according to clinical history and available laboratory data. All participants were receiving multiple daily injections of insulin with at least one injection containing rapid-acting insulin per day or were using an insulin pump for at least 3 months before enrollment. Mixed insulin use with a rapid-acting component was allowed. Concurrent treatment with noninsulin glucose-lowering medications or weight-reduction medications was permitted, provided the dose had been stable for the previous 3 months; during the trial, these medications were continued in both treatment groups. C. This medical policy does not address use of automated insulin delivery systems in pregnancy.
	Updated Rationale Section
	Updated Coding Section ▪ Added A9274 and E0784
	Updated References Section
Posted: 05-14-2026 Effective: 06-15-2026	Updated Description Section
	Updated Policy Section ▪ Change statement D from not medically necessary to experimental / investigational
	Updated Rationale Section
	Updated Reference Section

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