Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Artificial Pancreas Device Systems

Description/Background

Diabetes and Glycemic Control

Tight glucose control in patients with diabetes has been associated with improved outcomes. The American Diabetes Association (ADA) recommends a glycated hemoglobin (HbA1c) level below 7% for most patients. However, hypoglycemia, defined as plasma glucose below 70 mg/dL, 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 Type 1 diabetics who have challenges in controlling hyperglycemia and avoiding hypoglycemia. Hypoglycemia is the most common acute complication of Type 1 diabetes (T1D).

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 treatment clinically important or serious severe hypoglycemia	Glucose <70 mg/dl Glucose <54 mg/dl Severe cognitive impairment requiring external assistance by another person to take corrective action	Clinical Practice Consensus	ISPAD[3]	2018
Hyperglycemia Level 1 Level 2	Glucose >180 mg/dl and ≤250 mg/dl Glucose >250 mg/dl		Type 1 Diabetes Outcome Program[a1]	2017
Time in Range[b]	Percentage of glucose readings in the range of 70-180 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[a3]	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, T1D 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.

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.

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

Type 2 Diabetes

Patients with type 2 diabetes who cannot achieve optimal glucose control on oral agents alone may benefit from insulin therapy.

Recently, the Hygieia d-Nav® insulin guidance system was developed to provide personalized insulin dosing recommendations to patients with Type 2 Diabetes. The Hygieia's d-Nav® system allows patients to enhance their insulin regimen by providing dose-by-dose guidance, while performing titration in the background, ultimately stabilizing blood glucose levels. Patients are provided a software application that connects to the cloud and uses a patented algorithm to identify blood glucose patterns to recommend personalized doses with minimal health care provider (HCP) intervention. Individuals using this application experience ongoing support through Hygieia, including insulin guidance, and frequent virtual visits. The individual's health

care provider can access patient information via a provider-facing software to track and manage the insulin regimen as needed.

Regulatory Status

The Food and Drug Administration (FDA) describes the basic design of an artificial pancreas device system (APDS) as a CGM linked to an insulin pump with the capability to automatically stop, reduce, or increase insulin infusion based on specified thresholds of measured interstitial glucose.[4] The APDS 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 APDS control algorithm is embedded in software in an external processor or controller that receives information from the CGM and performs a series of mathematical calculations. Based on these calculations, the controller sends dosing instructions to the infusion pump.

Different APDS types are currently available for clinical use. Sensor augmented pump therapy (SAPT) with low glucose suspend (LGS) (suspend on low) may reduce the likelihood or severity of a hypoglycemic event by suspending insulin delivery temporarily when the sensor value reaches (reactive) predetermined lower threshold of measured interstitial glucose. Low glucose suspension (LGS) 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 (PLGM) (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 CGM 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 CGM 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 CGM). There are 2 subtypes of control-to-target systems: insulin-only and bi-hormonal (e.g., glucagon). There are no systems administering glucagon marketed in the United States.

An artificial pancreas device system may also be referred to as a “closed-loop” system. A closed-loop system has automated insulin delivery 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.

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.

These systems are regulated by FDA as class III device systems.

Table 2 summarizes the FDA-approved automated insulin delivery systems.

Table 2. FDA-Approved Automated Insulin Delivery Systems (Artificial Pancreas Device 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] (hybrid closed-loop, LGS or PLGM	>14 y ≥7-13 y	Medtronic	Sep 2016 Jul 2018	P160017/OZP P160017/S031
t:slim X2 Insulin Pump with Basal-IQ Technology (LGS)[6]	>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
MiniMed™ 770G System	>2 y	Medtronic	Sep 2020	P160017/QZP
MiniMed 780G System	≥7y	Medtronic	May 2023	P160017/S091
Omnipod 5	≥6 y	Insulet	Jan 2022	K203768K203772
iLet Bionic Pancreas	≥6 y	Beta Bionics	May 2023	K220916 K223846

FDA: Food and Drug Administration; LGS: low glucose suspend; OZO: Artificial Pancreas Device System, threshold suspend; OZP: Automated Insulin Dosing Device System, Single Hormonal Control; PMA: premarket approval.
[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).

The MiniMed® 530G System includes a threshold suspend or LGS 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 an LGS 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 CGM 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 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. 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.

The most recent supplemental approval for the MiniMed® 670G System in July 2018 followed the granting a designation of breakthrough device status.[5]

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.[10] The System consists of the t:slim X2 Insulin Pump paired with the Dexcom G5 Mobile CGM (Continuous Glucose Monitor), as well as the Basal-IQ Technology. The t:slim X2 Insulin Pump is intended for the subcutaneous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. The t:slim X2 Insulin Pump can be used solely for continuous insulin delivery and as part of the System as the receiver for a therapeutic CGM. The t:slim X2 Insulin Pump running the Basal-IQ Technology can be used to suspend insulin delivery based on CGM sensor readings. Introduction into clinical care is planned for summer 2019.

In December 2019, FDA approved the t:slim X2 Insulin Pump with Control-IQ Technology through the De Novo process.11 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.

The Hygieia d-Nav® system received 510k clearance through FDA in February 2019 for intended for use by adults with Type 2 diabetes as an aid in optimizing insulin management. The system requires a physician prescription and can be billed using existing CPT III codes in combination with appropriate proxy codes submitted by physicians. The Hygieia d-Nav® insulin guidance system provides personalized insulin dosing recommendations to patients with Type 2 Diabetes. It is the equivalent of an artificial pancreas (i.e., A closed loop system or Automated Insulin Delivery), for the millions of diabetes patients that inject their insulin rather than using a pump.

In September 2020, FDA approved the MiniMed™ 770G System for type 1 diabetics ages 2 years and up. The hybrid closed loop diabetes management device is a bluetooth-enabled version of the previously discussed MiniMed® 670G System.

In April 2022, FDA approved the MiniMed™ Extended Reservoir for the subcutaneous infusion of medication, including insulin from compatible Medtroinc insulin pumps and infusion sets. This extended reservoir can be used up to 7 days as compared to the predicate which is used up to 3 days.

In 2022, FDA approved the Omnipod 5 ACE Pump for the subcutaneous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. The Omnipod 5 ACE Pump is able to reliably and securely communicate with compatible, digitally connected devices, including automated insulin dosing software, to receive, execute, and confirm commands from these devices.

In May 2023, FDA approved the first closed-loop system through the 510(k) premarket clearance pathway.[9.]

Medical Policy Statement

The safety and effectiveness of an FDA-approved artificial pancreas device systems with a low glucose suspend feature and hybrid closed loop systems may be considered established in patients with insulin-requiring diabetes who meet specified patient selection criteria. It is a useful therapeutic option for selected patients.

The safety and effectiveness of an FDA approved closed loop insulin delivery system (e.g., iLet bionic pancreas) may be considered established in individuals with Type 1 diabetes who meet specified patient selection criteria. It is a useful therapeutic option for selected patients.

The safety and effectiveness of an FDA approved insulin guidance system (e.g., D-Nav) as an aid in optimizing glycemic control may be considered established for individuals with insulin dependent Type 2 diabetes. It is a useful therapeutic option.

Inclusionary and Exclusionary Guidelines

Inclusions:

Use of a U.S. Food and Drug Administration–cleared or approved artificial pancreas device systems with a **low-glucose suspend feature** may be considered established in patients with insulin-requiring diabetes who meet the following criteria:
Type I Diabetes:

- Age 6 or older

Type II Diabetes:

- Age 6 or older **AND**A history of one level 3 (glucose < 54 mg/dl [3.0mmol/L]) hypoglycemic event characterized by altered mental and/or physical state requiring third party assistance for treatment of hypoglycemia (i.e., hypoglycemia unawareness); **OR**
- Recurrent level 2 (glucose < 54 mg/dl [3.0mmol/L]) hypoglycemic events despite multiple attempts to adjust medications (s) and/or modify the diabetes treatment plan (e.g., nocturnal hypoglycemia)

Use of a Food and Drug Administration–cleared or approved automated insulin delivery system (artificial pancreas device system) designated as **hybrid closed loop insulin delivery system** (with low glucose suspend and suspend before low features) is considered established in patients with insulin requiring diabetes who meet the following criteria:
Type I Diabetes:

- Age 6 and older, **OR**
- Age 2 to <6 years **AND**
    - Clinical diagnosis of type 1 diabetes for 3 months or more
    - Glycated hemoglobin level <10.0%
    - Minimum daily insulin requirement (Total Daily Dose) of greater than or equal to 8 units

Type II Diabetes:

- Age 6 and older **AND**A history of one level 3 (glucose < 54 mg/dl [3.0mmol/L]) hypoglycemic event characterized by altered mental and/or physical state requiring third party assistance for treatment of hypoglycemia (i.e., hypoglycemia unawareness; **OR**
- Recurrent level 2 (glucose < 54 mg/dl [3.0mmol/L]) hypoglycemic events despite multiple attempts to adjust medications and/or modify the diabetes treatment plan (e.g., nocturnal hypoglycemia)

OR

Use of a FDA cleared or approved automated insulin delivery system (artificial pancreas device system) designated as a **closed-loop insulin delivery system** may be considered established in individuals with type 1 diabetes who meet all of the following criteria:

- Age 6 years and older **AND**
    - Clinical diagnosis of type 1 diabetes for 12 months or more;
    - Using insulin for at least 12 months;
    - Diabetes managed using the same regimen (either pump or multiple daily injections, with or without continuous glucose monitoring) for 3 months or longer.

Exclusions:

- Use of an artificial pancreas device systems is considered experimental/investigational in all other situations.
- Use of an artificial pancreas device system not cleared or approved by the FDA is experimental/investigational.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

A4225	A4230	A4232	A4224	A4226	A9274	S1034
S1035	S1036	S1037	E0784	E0787	0740T	
0741T						

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

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 one 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. RCTs 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations."

LOW-GLUCOSE SUSPEND DEVICES

Clinical Context and Therapy Purpose

The purpose of APDS with a low-glucose suspend (LGS) feature in individuals who have type 1 diabetes (T1D) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of an APDS with an LGS feature improve the net health outcome for individuals with type 1 diabetes?

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant population of interest is individuals with type 1 diabetes. Persons with T1D 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 (e.g., coma, seizure, transient ischemic attack, stroke), heart (e.g., cardiac arrhythmia, myocardial ischemia, infarction), eye (e.g., 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 APDS that integrates a continuous glucose monitor and insulin pump and includes an LGS 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.

APDS are used by persons with type1 diabetes when they have experienced hypoglycemic and/or hypoglycemic episodes that cannot be managed with intermittent self-monitoring of glucose and self-administration of insulin. APDS are used by persons with type1 diabetes in “free-living” and home settings, with monitoring by primary care clinicians, diabetologists, and endocrinologists.

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

Outcomes
The general outcomes of interest are glycated hemoglobin (HbA1c) 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 (e.g., hospitalizations). The duration of follow-up is life-long.

Review of Evidence

Randomized Controlled Trials

The in-home arm of the Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial, published by Bergenstal et al in 2013.[15] This was an industry-sponsored trial using the Medtronic Paradigm Veo insulin pump. A total of 247 patients were randomly assigned to an experimental group, in which a CGM with the low glucose suspend feature was used (n=121), or a control group that used the CGM but not the LGS feature (n=126). Key eligibility criteria were 16- to 70-years old, type 1 diabetes, and an HbA_{1c} level between 5.8% and 10.0%. In addition, patients needed to have 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 a value between 70 to 90 mg/dL. Seven patients withdrew early from the study; all 247 were included in the ITT analysis. The primary efficacy outcome was the area under the curve (AUC) for nocturnal hypoglycemia events. This was calculated by multiplying the magnitude (in mg per deciliter) and duration (in minutes) of each qualified hypoglycemic event. The primary safety outcome was change in HbA_{1c} levels.

The primary end point, mean AUC for nocturnal hypoglycemic events, was 980 (standard deviation [SD]:1200) in the low glucose suspend group and 1568 (SD:1995) in the control group. The difference between groups was statistically significant ($p<0.001$), favoring the intervention group.

Similarly, the mean AUC for combined daytime and nighttime hypoglycemic events, a secondary outcome, significantly favored the intervention group ($p<0.001$). Mean AUC values were 798 (SD: 965) in the intervention group and 1164 (SD: 1590) in the control group. Moreover, the intervention group experienced fewer hypoglycemic episodes than the control group, a mean of 3.3 (SD=2.0) per patient-week versus a mean of 4.7 (SD=2.7) per patient-week ($p<0.001$). For patients in the LGS group, the mean number of times the feature was triggered per patient was 2.08 per 24 hour period and 0.77 per 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 LGS group compared with 140.0 mg/dL in the control group.

Regarding safety outcomes and adverse events, change in glycated hemoglobin level was minimal and there was not a statistically significant difference between groups. Mean HbA_{1c} decreased from 7.26 to 7.24 in the low glucose suspend group and from 7.21 to 7.14 in the control group. During the study period, there were no severe hypoglycemic events in the LGS group, and there were 4 events in the control group (nadir glucose sensor values in these events ranged from 40 mg/dL to 76 mg/dL). There were no deaths or serious device-related adverse events.

A second RCT evaluated in-home use of the evaluating the Medtronic Paradigm Veo System.[16] The trial included 95 patients with type 1 diabetes who used an insulin pump and were between the ages of 4 to 50 years (mean age, 18.6 years). Patients were randomized to 6 months of in-home use of the Paradigm Veo system with automated insulin suspension when the sensor glucose reached a preset glucose threshold of 60 mg/dL or to continued use of an insulin pump without the LGS feature. The primary study outcome was 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). Findings were not reported separately for children and adults.

The baseline rate of severe and moderate hyperglycemia was significantly higher in the LGS group than the pump-only group (129.6 vs. 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% CI, 22.0 to 53.3) in the pump-only group and 9.6 (95% CI, 5.2 to 17.4) in the LGS group. The incidence rate ratio was 3.6 (95% CI, 1.7 to 7.5), which was statistically significant favoring the LGS group. Although results were not reported separately for children and adults, the authors conducted a sensitivity analysis in patients younger than 12 years (15 patients in each treatment group). The high baseline hypoglycemia rates can be explained in part by 2 outliers; these were children (ages 9 and 10 years). When these 2 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 glycated hemoglobin level (%), a secondary outcome, did not differ between groups at baseline or at 6 months. Change in HbA_{1c} 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 Basal-IQ integrated with a Dexcom G5 sensor and a predictive low glucose suspend algorithm compared to sensor-augmented pump therapy.[17] Participants (N=103) were ages 6-72 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 continuous glucose monitoring 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 (PLGS) arm compared with 3.2% in the sensor augmented pump arm (difference [PLGS − sensor augmented pump] = −0.8%, 95% CI −1.1 to −0.5, $P < 0.001$). There was one severe hypoglycemic event in the sensor augmented pump arm and none in the predictive low glucose suspend arm.

Nonrandomized Studies

In 2015, Agrawal et al published a retrospective analysis on use of the threshold suspend feature associated with the Medtronic Paradigm Veo System in 20,973 patients, most of whom were treated outside of the United States.[18] This noncontrolled descriptive analysis can provide 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 patients (70%), 0% of the time by 2249 (11%) patients, and the remainder used it intermittently. The mean setting used to trigger suspension of insulin was a sensor glucose level of 62.8 mg/dL (SD=5.8). 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 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. Use of the device appears to be associated with fewer and shorter hypoglycemic episodes. The length and severity of hypoglycemic episodes was not fully discussed in this article.

Gómez et al (2017) published the results of a cohort of 111 type 1 diabetic individuals with documented hypoglycemia and hypoglycemia unawareness who received a sensor-augmented insulin pump with LGS therapy.[19] Participants used a combination system with the Medtronic Paradigm 722 or Paradigm Veo pump connected to the MiniMed CGM 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<0.001). HbA_{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<0.001) and 7.1% (SD=0.8%; mean difference, -1.7%; 95% CI, -1.59% to -1.90%; p<0.001). At baseline, 80% of subjects had had at least 1 episode of hypoglycemic awareness compared with 10.8% at last follow-up (p<0.001). Episodes of severe hypoglycemia decreased from 66.6% to 2.7% (p<0.001).

Section Summary: Low-Glucose Suspend Devices
For individuals who have type 1 diabetes who receive an artificial pancreas device system with a low-glucose suspend feature, the evidence includes 23 RCTs conducted in home settings. Relevant outcomes are symptoms, change in disease status, morbid events, resource utilization, and treatment-related morbidity. Primary eligibility criteria of the key RCT, the ASPIRE trial, were ages 16-to-70 years old, 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 automated insulin delivery system users. The evidence is sufficient 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 **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest is individuals with type 1 diabetes. Persons with T1D 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 (e.g., coma, seizure, transient ischemic attack, stroke), heart (e.g., cardiac arrhythmia, myocardial ischemia, infarction), eye (e.g., 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 automated insulin delivery system with LGS feature, nonintegrated CGM 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 (e.g., hospitalizations). The duration of follow-up is life-long.

Review of Evidence

Prospective Studies
Bergenstalet al (2016) published a prospective single-arm study on the safety of the hybrid closed-loop system in patients with type 1 diabetes.[20] It included 124 patients ages 14-to-75 years old who had type 1 diabetes for at least 2 years, HbA1c 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 Clostridium 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) HbA1c 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 is ongoing (NCT02660827).

A multicenter pivotal trial published by Garget 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).[21] Of 129 subjects, 124 completed the trial; 30 were adolescents (age range, 14-21 years) and 94 were adults (age range, 22-75 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<0.001 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<0.001); time above the range decreased from 24.9% to 22.8% (p=0.01). For both cohorts, HbA1c 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<0.001), while for adolescents, the mean decreased from 7.7% to 7.1% (p<0.001). 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 in 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 HbA1c 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.[22] 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.[12] 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 (70-180 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=0.008; 1.3 vs 2%, p= 0.001, 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=0.059). 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 nonresponders, 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.[23.] 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.

The remainder of the 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 3 and 4.

The RCT by Tauschman, et al (2018) evaluated individuals with uncontrolled type 1 diabetes as reflected in mean Hb1c >8%. Approximately, 50% of the subjects were between 6-21 years of age and 25% were 6-12 years old.[24] Both groups achieved a reduction in HbA1c but the reduction was statistically greater in the hybrid closed loop group compared to the control group. The investigators reported that the HbA1c 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.[25] 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 HbA1c 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 7-13 years of age.[8] 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 HbA1c 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.[26] 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. Participants successfully utilized the device without significant changes in total daily dose of insulin but improved percentage time in range (70-180 mg/dl).[28]

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 ages 6 to 13 years.[27] 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.[28] Health-related quality of life and patient satisfaction measures from the RCT and the extension phase were reported by Cobry et al (2021).[29] 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.

No studies of a hybrid closed loop system in children under age 6 years have been published, but clinical study results for children ages 2-6 years are available in the FDA Summary of Safety and Effectiveness for the MiniMed 670G System (Tables 3 and 4).[6] 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.

Table 3. Summary of Key Study Characteristics: HCL in T1D Children and Adolescents

Study; Trial	Countries	Sites	Dates	Participants	Intervention	Study Type
Tauschmann (2018)	UK, US	6	2016-2017	86 >6 years [6-12 years; n=23] [13-21 years; n=19]	MiniMed 640G[2] HCL	RCT Intervention: SAPT with PLGM (n=46) Screening HbA_{1c} % (SD) 8.3 (0.6)
Abraham (2018)	Australia	5	2014-NR	154 8-20 years 13.2 (2.8)	MiniMed 640G[2] HCL	RCT Intervention: SAPT with PLGM (n=80) Control: SAPT alone (n=74)
Forlenza (2019) NCT02660827	US, Israel	9	2016-2017	105 7-13 years 10.8 (1.8)	MiniMed 670G[3] HCL	Noncomparative pivotal trial
Wood (2018) NCT02660827	US, Israel	9	2016-2017	105 7-13 years 10.8 (1.8)	MiniMed 670G[3] HCL	12 hour clinic evaluation of PLGM performance in conjunction with exercise[4]
Messer (2018) NCT02463097	US	3	2015-2018	31 14-26 17.8 (3.9)	MiniMed 670G[3] HCL	Sub-study of FDA pivotal trial for device: insulin delivery characteristics and time in range
FDA (2020) Safety Evaluation of the Hybrid Closed Loop (HCL) System in Pediatric Subjects with	US	7	2017-2018	46 2-6 years	MiniMed 670G[3] HCL	Noncomparative pivotal trial

Type 1 Diabetes (G150247)						
Breton et l (2020)	US	4	2019-2020	101 6-13 years	t:slim X2 insulin pump with Control-IQ Technology[4] HCL	RCT, open label Intervention: HCL (n=78) Control: SAPT (n=23)
Brown et al (2021)	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

HCL: hybrid closed loop; FDA: Food and Drug Administration; PLGM: predictive low glucose suspend (suspend before low); PMA: premarket approval; RCT: randomized controlled trial; SAPT: sensor-augmented pump therapy; SD: standard deviation
[1] Data as submitted for FDA PMA Supplement P160017/S031
[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] 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.
[4]t:slim X2 insulin pump with Control-IQ Technology is hybrid closed loop device approved for use in US.

Table 4. Summary of Key Study Results: HCL in T1D Children and Adolescents

Study	Primary Outcome	Primary Outcome	Secondary Outcome	Safety Outcome	Safety Outcome
Tauschmann (2018)	Group difference in time proportion in target glucose range (70-180 md/dl) at 12 weeks Mean (SD)			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] <0.0001		HbA_{1c} % (SD) At 12 weeks 7.4 (0.6) 7.7 (0.5) -0.36 [-0.53, -0.19] <0.0001	A. 1.4 (0.9, 1.9) 2.0 (0.9, 3.0) -0.83 [-1.4, -0.16] 0.0130 B.0.3 (0.2, 0.6) 0.5 (0.2, 0.9) -0.09 [-0.24, 0.01] 0.08	
Abraham (2018)	Change in average	Change in average	HbA_{1c} Mean % (SD)	Hypoglycemic events (SG <63	IAH[2]

	percent time in hypoglycemia (SG <63 mg/dl) at 6 months	percent time in hypoglycemia (SG <54 mg/dl) at 6 months		mg/dl for >20 minutes Events per patient-year	(%) Clarke score ≥4 N=90 (≥ 12 years)
SAPT with PLGM SAPT alone Difference in LS means [95% CI] p	N=76 2.8% Δ 1.4% N=70 3% Δ 2.6% -0.95% [-1.30, -0.61] <0.0001	N=76 1.3% Δ 0.6% N=70 1.4% Δ 1.2% -0.44% [-0.64, -0.24] <0.0001	7.5 (0.8) Δ 7.8 (0.8) 7.4 (0.7) Δ 7.6 (1.0) 0.09 [-0.10, 0.27] =0.35	139 227 [221, 234 vs. 134, 143] <0.001	4% 13% -.04 [-0.52, 0.43] 0.86
Forlenza (2019) NCT02660827 Baseline Run-in phase (n=105) 3 month Study phase (n=105) P Baseline Run-in phase (n=106) 3 month study phase (n=105) P Baseline Run-in phase (n=105) 3 month study phase (105) p	HbA_{1c} Mean % (SD) 7.9 (0.8) 7.6 (0.6) <0.001		Time in Range (>70-180) Mean % (SD) 56.2 (11.4) 65 (7.7) <0.001	Hypoglycemia A.≤70 mg/dl B.≤54 mg/dl (Mean 5 [SD]) A.<70 mg/dl 4.7 (3.8) 3.0 (1.6) <0.001 B.≤54 mg/dl 1.3 (1.5) 0.8 (0.7) <0.001	
Wood (2018) NCT0266087 Reference range[3] ≤55 mg/dl ≤60 mg/dl	N=79 Participant activations of suspend before low Rate of "suspend before low" (%) 77 (97.5) 71 (89.9)				

≤65 mg/dl	63 (79.7)				
Messer (2018) NCT02463097 Days 1-7 Days 22-28 Days 50-56 Days 78-84	Mean percentage time in range (70-180 mg/dl using HCL mode[4] Mean % (SD) 69.7 (10.6) 69.5 (8.5) 71.9 (8.1) 71.5 (10.3)				
FDA (2020) Safety Evaluation of the Hybrid Closed Loop (HCL) System in Pediatric Subjects with Type 1 Diabetes (G150247)	Percent change from baseline in HbA1c 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); 1.2 to 1.8 ≤70 mg/dL: 3.5 (1.6); 3.0 to 3.9 71 to ≤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 unanticipated serious adverse device effects, unanticipated non-serious adverse device/procedural effects No reports of diabetic ketoacidosis events. No reports of severe hypoglycemia events	
Breton et l (2020) Cobry et al (2021)	Glycated hemoglobin level at 16 weeks		Percent time in target range 70 to 180 mg/dL (Primary outcome)	Adverse events	

			Mean (SD)		
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=0.08)		11% (7% to 14%); P <.001	Median hypoglycemic events per week: P =.16 Median hyperglycemic events per week: P =.001	
Brown et al (2021)					
Outcome measure	Mean reduction from baseline in HbA1c	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%	3 severe hypoglycemia events not attributed to device	

			to 1.09%; P.0001	malfunction, 1 diabetic ketoacidosis event from an infusion site failure	

CI: confidence interval; HCL: hybrid closed loop; IAH: impaired awareness of hypoglycemia; LS: least squares; PLGM: predictive low glucose suspend (suspend before low); RCT: randomized controlled trial; RR: relative risk; SAPT: sensor-augmented pump therapy; SG: sensor glucose; Δ: delta meaning change in status.
[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
For individuals who have type 1 diabetes who receive an artificial pancreas device system with a hybrid closed-loop insulin delivery system, the evidence includes multicenter pivotal trials using devices cleared by the Food and Drug Administration, supplemental data and analysis for expanded indications and more recent studies focused on children and adolescents. Three crossover RCTs using a similar first- generation device approved outside the United States have been reported. Relevant outcomes are symptoms, change in disease status, morbid events, resource utilization, and treatment-related morbidity. Of the 3 crossover RCTs assessing a related device conducted outside the United States, 2 found significantly better outcomes (i.e., time spent in nocturnal hypoglycemia and time spent in preferred glycemic range) with the device than with standard care and the other had mixed findings (significant difference in time spent in nocturnal hypoglycemia and no significant difference in time spent in preferred glycemic range). Additional evidence from device performance studies and clinical studies all demonstrate reductions in time spent in various levels of hypoglycemia, improved time in range (70-180 mg/dl), rare diabetic ketoacidosis, and few device-related adverse events. The evidence is sufficient that the magnitude of reduction for hypoglycemic events in the type 1 diabetes population is likely to be clinically significant.

Hygieia d-Nav® Insulin Guidance System
Donnelly et al (2015) conducted a service evaluation of the effectiveness of using d-Nav (a handheld device that automates the process of insulin dosage titration using the Diabetes Insulin Guidance System [DIGS] software) in achieving glycaemic control in patients with type 2 diabetes.[32] The study comprised an exploratory single-centre pilot evaluation of the use of d-Nav in patients with type 2 diabetes aged ≥21 years with an HbA1c level ≥53mmol/mol (≥7.0%) who were receiving insulin therapy for at least one year. Patients were asked to use d-Nav to monitor their blood glucose level before every insulin injection and, when they suspected the occurrence of hypoglycemia, to allow d-Nav to adjust their insulin dosage. At scheduled three-monthly clinic visits, HbA1c was measured and information on episodes of hypoglycaemia collected from d-Nav and by patient reporting. Patients were followed for a minimum of six months. A total of 94 patients completed the evaluation as active users. The mean (± standard deviation) HbA1c for active users decreased from 77±15mmol/mol (9.2±1.4%) at baseline to 62±13mmol/mol (7.8±1.2%) at the three- to five-month clinic visit and to 59±13mmol/mol (7.5±1.2%) at the six- to 12-month clinic visit. In patients for whom paired data were available, the decreases were statistically significant at both post-baseline visits (both p<0.001). The frequency of minor hypoglycaemia (blood glucose ≤3.6mmol/L) was low.

According to Thompson et al (2018), in patients with type 2 diabetes mellitus, insulin may be used to augment therapy with oral glycemic medications or as insulin replacement therapy.[33] The American Diabetes Association suggests the use of long-acting (basal) insulin to augment

therapy with one or two oral agents or one oral agent plus a glucagon-like peptide 1 receptor agonist when the A1C level is 9% or more, especially if the patient has symptoms of hyperglycemia or catabolism. Insulin regimens should be adjusted every three or four days until targets of self-monitored blood glucose levels are reached. A fasting and premeal blood glucose goal of 80 to 130 mg per dL and a two-hour postprandial goal of less than 180 mg per dL are recommended. Insulin use is associated with hypoglycemia and weight gain. Insulin analogues are as effective as human insulin at lowering A1C levels with lower risk of hypoglycemia, but they have significantly higher cost. Patients with one or more episodes of severe hypoglycemia (i.e., requiring assistance from others for treatment) may benefit from a short-term relaxation of glycemic targets. Several new insulin formulations have been approved recently that are associated with less risk of hypoglycemia compared with older formulations. The goals of therapy should be individualized based on many factors, including age, life expectancy, comorbid conditions, duration of diabetes, risk of hypoglycemia, cost, patient motivation, and quality of life.

In a multicenter randomized controlled study, Bergenstal et al (2019), tested whether the combination of the d-Nav insulin guidance system and the health care professional (HCP) support (d-Nav + HCP-S) is superior to HCP support alone (HCP-S).[34] One hundred eighty one subjects using insulin with sub-optimally controlled type 2 diabetes were randomized 1:1 to either d-Nav+HCP-S or HCP-S alone. Both groups were contacted 7 times during a 6-month follow-up. The primary outcome was to compare average change in HbA1c during the study while the secondary outcome was to compare the percent of participants who achieve HbA1c <7% (<53mmol/mol), <8% (<64mmol/mol), and >9·0% (>75mmol/mol) at study end. Safety was assessed by the frequency of hypoglycaemia. The Student's t-test was used to assess the primary outcome for statistical significance. At baseline, HbA1c was 8·7%±0·8% (72±8·8mmol/mol) in the d-Nav+HCP-S group and 8·5%±0.8% (69mmol/mol±8·8mmol/mol) in the HCP-S (p=0·2). The mean decrease of HbA1c from baseline to 6 months was 1·0%±1·0% (11±11mmol/mol) in the d-Nav+HCP-S group, and 0·3%±0·9% (3·3mmol/mol±9·9mmol/mol) in the HCP-S group (p<0·0001). For the d-Nav+HCP-S group, reduction in HbA1c was achieved by 1·1±0·2 automated insulin titrations per week. The frequency of hypoglycaemia (<54 mg/dL or <3·0mmol/l) was similar between the groups at 0.3 hypoglycemic readings per month (p>0·9).

For patients using basal-bolus insulin therapy, it is widespread clinical practice to aim for a 50-50 ratio between basal and total daily bolus. However, this practice was based on a small study of individuals without diabetes. To assess the rule in real-world practice, Harper et al (2023) retrospectively analyzed patients on basal-bolus therapy that was adjusted at least weekly by an artificial intelligence-driven titration within the d-Nav® Insulin Management Technology.[35] The authors obtained de-identified data from the Diabetes Centre of Ulster Hospital for patients with four inclusion criteria: type 2 Diabetes (T2D), on d-Nav >6 months, on basal-bolus insulin therapy >80% of the time (based on insulin analogs), and no gap in data >3 months. A cohort of 306 patients was assembled, followed by the d-Nav service for 3.4 ± 1.8 years (mean ± SD), corresponding to about 180 autonomous insulin dose titrations and about 5000 autonomous individual dose recommendations per patient. After an initial run-in period, mean glycated hemoglobin (HbA1c) values in the cohort were maintained close to 7%. Surprisingly, in just over threequarters of the cohort, the average basal insulin fraction was <50%; in half of the cohort average basal insulin fraction <41.2%; and in one-quarter the basal insulin fraction was <33.6%. Further, the basal insulin fraction did not remain static over time. In half of the patients, the basal insulin fraction varied by ≥1.9×; and, in 25% of the patients, ≥2.5×.

Schneider et al (2018) examined the use of insulin management services to enable patients to optimize insulin dosing to achieve HbA1c targets and subsequently reduce health care costs.[36] Two hundred seventeen insulin-reliant patients were enrolled in the d-Nav® Insulin Guidance Service through a participating insurance group. A prospective cost analysis was conducted using data from enrolled patients who completed the first 90 days of follow up. Of the 192 patients who completed the 90-day study period, 54 (28.13%) were prescribed one or more expensive medications at baseline, but 45 (83.33%) of those patients were eligible for medication discontinuation after 90 days. At baseline, the annual cost of expensive medications per patient was $7564 (CI: $5191-$9938) and $1483 (CI: -$1463-$4429) at 90 days (p<0.001). Direct savings from medication elimination was estimated to be $145 per patient per month (PPPM) or $1736 per patient per year (PPPY) for all patients and $514 PPPM/$6172 PPPY for the target group. Patients that completed the 90-day period reduced HbA1c levels from 9.37% (CI:7.72%-11.03%) at baseline to 7.71% (CI: 6.70%-8.73%) (p<0.001).

Section Summary: d-Nav Insulin Guidance System
The evidence for the d-Nav Insulin Guidance System includes a single center pilot evaluation, a multicenter randomized clinical study and retrospective case analysis. With the use of the d-Nav system $HbA1_C$ decreased.

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.[33,] 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 automated insulin delivery 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 (e.g., 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).[38] 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.[38] 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 <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 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).[39] 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 = 0.24). 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).[35.] 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.[40] 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 5. 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) 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 6. Closed-Loop Insulin Delivery System: Study Results

Study	Primary Efficacy Outcomes	Key Secondary Efficacy Outcome	Safety Outcomes		
Russell et al (2022) Adult subgroup: Kruger et al (2022) Youth subgroup: Messer et al (2022)	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)	N/A	N/A	N/A
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.

SUMMARY OF EVIDENCE

For individuals who have insulin dependent diabetes who receive an artificial pancreas device system with a low-glucose suspend feature, the evidence includes 2 randomized controlled trials (RCTs) conducted in home settings. Relevant outcomes are symptoms, change in disease status, morbid events, resource utilization, and treatment-related morbidity. Primary eligibility criteria of the key RCT, the Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial, were ages 16-to-70 years old, 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 (area under the curve for nocturnal hypoglycemic events). The area under the curve 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 automated insulin delivery system users. The evidence is sufficient that the magnitude of reduction for hypoglycemic events in the type 1 diabetes population is likely to be clinically significant. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have insulin dependent diabetes who receive an artificial pancreas device system with a hybrid closed-loop insulin delivery system, the evidence includes multicenter pivotal trials using devices cleared by the U.S. Food and Drug Administration, supplemental data and analysis for expanded indications, and more recent studies focused on children and adolescents. Three crossover RCTs using a similar first- generation device approved outside the United States have been reported. Relevant outcomes are symptoms, change in disease status, morbid events, resource utilization, and treatment-related morbidity. Of the 3 crossover RCTs assessing a related device conducted outside the United States, 2 found significantly better outcomes (i.e., time spent in nocturnal hypoglycemia and time spent in preferred glycemic range) with the device than with standard care and the other had mixed findings (significant difference in time spent in nocturnal hypoglycemia and no significant difference in time spent in preferred glycemic range). Additional evidence from device performance studies and clinical studies all demonstrate reductions in time spent in various levels of hypoglycemia, improved time in range (70-180 mg/dl), rare diabetic ketoacidosis, and few device-related adverse events. The evidence is sufficient that the magnitude of reduction for hypoglycemic events in the type 1 diabetes population is likely to be clinically significant. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have type 2 diabetes who enroll in the Hygieia d-Nav® insulin guidance system, the evidence includes one randomized control trial, a single center pilot evaluation and one cost effectiveness study. The d-Nav® system does provide clinically relevant information in the management of diabetes compared to conventional management alone. Therefore, the evidence is sufficient to determine that the technology results in an improvement in net health outcomes.

For individuals who have insulin dependent diabetes who receive an iLet Bionic Pancreas 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. The evidence is sufficient that the use of a bionic pancreas was associated with a greater reduction than standard care in the glycated hemoglobin level. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

2019

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 artificial pancreas device 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

American Diabetes Association[31]

The American Diabetes Association has released multiple publications on controlling type 1 diabetes (see Table 5).

Table 5. Recommendations on Diabetes

Date	Title	Publication Type	Recommendation	LOE
2023	Diabetes Technology: Standards of Care in Diabetes—2023	Guideline Standard	Automated insulin delivery systems should be offered for diabetes management to youth and adults with type 1 diabetes(A) and other types of insulin deficient diabetes (E) who are capable of using the device safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs Insulin pump therapy alone with or without sensor-augmented pump low glucose suspend feature and/or automated insulin delivery systems should be offered for diabetes management to youth and adults on multiple daily injections with type 1 diabetes (A) or other types of insulin-deficient diabetes(E) who are capable of using the device safely (either by themselves or with a caregiver) and are not able to use or do not choose an automated insulin delivery system. The choice of device should be made based on the individual's circumstances, preferences, and needs. (A)	
2017	Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes	Consensus report[25a]	Developed definitions for hypoglycemia, hyperglycemia, time in range, and diabetic ketoacidosis in type 1 diabetes	N/A

HbA1c: hemoglobin A1c;LOE: Level of Evidence.
[a]Jointly published with the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange.

American Association of Clinical Endocrinologists et al[30]

In 2021, the American Association of Clinical Endocrinologists published a clinical practice guideline for the use of advanced technology in the management of individuals with diabetes. 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 [Automated insulin delivery] 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

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02748018	Multi-center, Randomized, Parallel, Adaptive, Controlled Trial in Adult and Pediatric Patients With Type 1 Diabetes Using Hybrid Closed Loop System and Control (CSII, MDI, and SAP) at Home	280	Jan 2024
NCT03739099	Assessment of the Efficacy of Closed-loop Insulin Therapy (**Artificial Pancreas**) on the Control of Type 1 Diabetes in Prepubertal Child in Free-life: Comparison Between Nocturnal and 24-hour Use on 18 Weeks, Followed by an Extension on 18 Weeks	122	May 2023
Unpublished			
NCT03774186	Pregnancy Intervention With a Closed-Loop System (PICLS) Study	47	June 2022
NCT03784027	An Open-label, Multi-centre, Multi-national, Randomised, 2-period Crossover Study to Assess the Efficacy, Safety and Utility of Closed Loop Insulin Delivery in Comparison With Sensor Augmented Pump Therapy Over 4 Months in Children With Type 1 Diabetes Aged 1 to 7 Years in the Home Setting With Extension to Evaluate the Efficacy of Home Use of Closed Loop Insulin Delivery.	81	Dec 2021
NCT04269668[a]	An Open-label, Two-center, Randomized, Cross-over Study to Evaluate the Safety and Efficacy of Glycemic Control Using Hybrid-closed Loop vs. Advanced Hybrid Closed-loop in Young Subjects With Type 1 Diabetes	28	Mar 2021

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

Government Regulations

National:

There is no national coverage determination (NCD) specifically addressing the artificial pancreas device systems (insulin pump with insulin suspend systems). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Local:

LCD: L33822, Glucose Monitors, effective for services on or after 01/01/24.

CONTINUOUS GLUCOSE MONITORS (CGM)

CGM devices covered by Medicare under the DME benefit are defined in CMS Ruling 1682R as therapeutic CGMs. Refer to the Non-Medical Necessity Coverage and Payment Rules in the LCD-related Policy Article for additional information.

Therapeutic CGMs and related supplies are covered by Medicare when all of the following coverage criteria (1-5) are met:

1. The beneficiary has diabetes mellitus (Reference ICD-10 Codes that Support Medical Necessity section for applicable diagnoses); and,

2. The beneficiary is insulin-treated with multiple (three or more) daily injections of insulin or a Medicare-covered continuous subcutaneous insulin infusion (CSII) pump; and,

3. The beneficiary's treating practitioner has concluded that the beneficiary (or beneficiary's caregiver) has sufficient training using the CGM prescribed as evidenced by providing a prescription; and,
4. The CGM is prescribed in accordance with its FDA indications for use; and,
5. The beneficiary for whom a CGM is being prescribed, to improve glycemic control, meets at least one of the criteria below:

    A. The beneficiary is insulin-treated; or,
    B. The beneficiary has a history of problematic hypoglycemia with documentation of at least one of the following (see the POLICY SPECIFIC DOCUMENTATION REQUIREMENTS section of the LCD-related Policy Article (A52464)):
        - Recurrent (more than one) level 2 hypoglycemic events (glucose <54mg/dL (3.0mmol/L)) that persist despite multiple (more than one) attempts to adjust medication(s) and/or modify the diabetes treatment plan; or,
        - A history of one level 3 hypoglycemic event (glucose <54mg/dL (3.0mmol/L)) characterized by altered mental and/or physical state requiring third-party assistance for treatment of hypoglycemia
5. Within six (6) months prior to ordering the CGM, the treating practitioner has an in-person or Medicare-approved telehealth visit with the beneficiary to evaluate their diabetes control and determined that criteria (1)-(4) above are met.

When a therapeutic CGM (code K0554) is covered, the related supply allowance (code K0553) is also covered.

If any of coverage criteria (1-6) are not met, the CGM and related supply allowance will be

denied as not reasonable and necessary.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Chronic Intermittent Intravenous Insulin Therapy (CIIIT)
- Continuous Subcutaneous Insulin Infusion (CSII) (Insulin Pumps) and Transdermal Insulin Delivery Systems
- Intermittent (72 Hours or Greater) or Continuous Invasive Glucose Monitoring

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References

1. American Diabetes Association. 6. Glycemic Targets. Diabetes Care. Jan 2017; 40(Suppl 1): S48-S56. PMID 27979893
2. American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2019. Diabetes Care. Jan 2019; 42(Suppl 1): S61-S70. PMID 30559232
3. Abraham MB, Jones TW, Naranjo D, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatr Diabetes. Oct 2018; 19 Suppl 27: 178-192. PMID 29869358
4. Agiostratidou G, Anhalt H, Ball D, et al. Standardizing Clinically Meaningful Outcome Measures Beyond HbA 1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care. Dec 2017; 40(12): 1622-1630. PMID 29162582
5. Food and Drug Administration (FDA). Guidance for Industry and Food and Drug Administration Staff: The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems [draft]. 2012; https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259305.pdf. Accessed July 3, 2022
6. Food & Drug Administration. MiniMed 770G System. Summary of Safety and Effectiveness Data. 2020. https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160017S076B.pdf. July 3, 2022.
7. Forlenza GP, Li Z, Buckingham BA, et al. Predictive Low-Glucose Suspend Reduces Hypoglycemia in Adults, Adolescents, and Children With Type 1 Diabetes in an At-Home Randomized Crossover Study: Results of the PROLOG Trial. Diabetes Care. Oct 2018; 41(10): 2155-2161. PMID 30089663
8. Food and Drug Administration (FDA). Premarket Approval (PMA): MiniMed 530G System. 2013; https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P120010. Accessed July 3, 2022

9. Food & Drug Administration. 2023. FDA Clears New Insulin Pump and Algorithm-Based Software to Support Enhanced Automatic Insulin Delivery. https://www.fda.gov/news-events/press-announcements/fda-clears-new-insulin-pump-and-algorithm-based-software-support-enhanced-automatic-insulin-delivery. Accessed June 2023.
10. Food and Drug Administration (FDA). Premarket Approval (PMA): MiniMed 630G System with Smartguard. 2016; https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?ID=320606. Accessed July 3, 2022
11. Food and Drug Administration (FDA). Premarket Approval (PMA): MiniMed 670G System. 2016; https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160017. Accessed July 3, 2022.
12. Food and Drug Administration (FDA). t:slim X2 Insulin Pump with Basal-IQ Technology Premarket Approval (2018). https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180008A.pdf. Accessed July 3, 2022.
13. Faulds ER, Zappe J, Dungan KM. REAL-WORLD IMPLICATIONS OF HYBRID CLOSE LOOP (HCL) INSULIN DELIVERY SYSTEM. Endocr Pract. May 2019; 25(5): 477-484. PMID 30865545
14. Blue Cross and Blue Shield Technology Evaluation Center (TEC). Artificial Pancreas Device Systems. TEC Assessments. 2013;Volume 28:Tab 14
15. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a Hybrid Closed-Loop Insulin Delivery System in Patients With Type 1 Diabetes. JAMA. Oct 04 2016; 316(13): 1407-1408. PMID 27629148
16. Ly TT, Nicholas JA, Retterath A, et al. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. JAMA. Sep 25 2013; 310(12): 1240-7. PMID 24065010
17. Forlenza GP, Ekhlaspour L, Breton M, et al. Successful At-Home Use of the Tandem Control-IQ Artificial Pancreas System in Young Children During a Randomized Controlled Trial. Diabetes Technol Ther. Apr 2019; 21(4): 159-169. PMID 30888835
18. American Diabetes Association. 7. Diabetes Technology: Standards of Medical Care in Diabetes-2021. Diabetes Care. Jan 2021; 44(Suppl 1): S85-S99. PMID 33298418
19. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose Outcomes with the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults with Type 1 Diabetes. Diabetes Technol Ther. Mar 2017; 19(3): 155-163. PMID 28134564
20. Beato-Vibora PI, Gallego-Gamero F, Lazaro-Martin L, et al. Prospective Analysis of the Impact of Commercialized Hybrid Closed-Loop System on Glycemic Control, Glycemic Variability, and Patient-Related Outcomes in Children and Adults: A Focus on Superiority Over Predictive Low-Glucose Suspend Technology. Diabetes Technol Ther. Dec 2020; 22(12): 912-919. PMID 31855446
21. Garg S, Brazg RL, Bailey TS, et al. Reduction in duration of hypoglycemia by automatic suspension of insulin delivery: the in-clinic ASPIRE study. Diabetes Technol Ther. Mar 2012; 14(3): 205-9. PMID 22316089
22. Tauschmann M, Thabit H, Bally L, et al. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. Lancet. Oct 13 2018; 392(10155): 1321-1329. PMID 30292578
23. Wood MA, Shulman DI, Forlenza GP, et al. In-Clinic Evaluation of the MiniMed 670G System "Suspend Before Low" Feature in Children with Type 1 Diabetes. Diabetes Technol Ther. Nov 2018; 20(11): 731-737. PMID 30299976

24. Breton MD, Kanapka LG, Beck RW, et al. A Randomized Trial of Closed-Loop Control in Children with Type 1 Diabetes. N Engl J Med. Aug 27 2020; 383(9): 836-845. PMID 32846062
25. Kanapka LG, Wadwa RP, Breton MD, et al. Extended Use of the Control-IQ Closed-Loop Control System in Children With Type 1 Diabetes. Diabetes Care. Feb 2021; 44(2): 473-478. PMID 33355258
26. Cobry EC, Kanapka LG, Cengiz E, et al. Health-Related Quality of Life and Treatment Satisfaction in Parents and Children with Type 1 Diabetes Using Closed-Loop Control. Diabetes Technol Ther. Jun 2021; 23(6): 401-409. PMID 33404325
27. Abraham MB, Nicholas JA, Smith GJ, et al. Reduction in Hypoglycemia With the Predictive Low-Glucose Management System: A Long-term Randomized Controlled Trial in Adolescents With Type 1 Diabetes. Diabetes Care. Feb 2018; 41(2): 303-310. PMID 29191844
28. Forlenza GP, Pinhas-Hamiel O, Liljenquist DR, et al. Safety Evaluation of the MiniMed 670G System in Children 7-13 Years of Age with Type 1 Diabetes. Diabetes Technol Ther. Jan 2019; 21(1): 11-19. PMID 30585770
29. Messer LH, Forlenza GP, Sherr JL, et al. Optimizing Hybrid Closed-Loop Therapy in Adolescents and Emerging Adults Using the MiniMed 670G System. Diabetes Care. Apr 2018; 41(4): 789-796. PMID 29444895
30. Brown SA, Forlenza GP, Bode BW, et al. Multicenter Trial of a Tubeless, On-Body Automated Insulin Delivery System With Customizable Glycemic Targets in Pediatric and Adult Participants With Type 1 Diabetes. Diabetes Care. Jul 2021; 44(7): 1630-1640. PMID 34099518
31. Gomez AM, Marin Carrillo LF, Munoz Velandia OM, et al. Long-Term Efficacy and Safety of Sensor Augmented Insulin Pump Therapy with Low-Glucose Suspend Feature in Patients with Type 1 Diabetes. Diabetes Technol Ther. Feb 2017; 19(2): 109-114. PMID 28001445
32. Brown SA, Kovatchev BP, Raghinaru D, et al. Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes. N Engl J Med. Oct 31 2019; 381(18): 1707-1717. PMID 31618560
33. Donnelly R, Carr S, and Harper R. Diabetes insulin guidance system: a real-world evaluation of new technology (d-Nav) to achieve glycaemic control in insulin-treated type 2 diabetes. Practical Diabetes. 2015; 32(7):247-252.
34. Thompson A, Khan M, Jones M and George C. Type 2 diabetes mellitus: outpatient insulin management. Am Fam Physician. 2018; 97(1):29-37.
35. Bergenstal R, Johnson M, Passi R, et al. Automated insulin dosing guidance to optimize insulin management in patients with type 2 diabetes; a multi-center randomized controlled trial. Lancet. Mar 2019; 393(10176):1138-1148.
36. Harper R, Bashan E, Williams KJ, et al. Challenging the 50-50 rule for the basal bolus insulin ratio in patients with type 2 diabetes who maintain stable glycaemic control. Diabetes Obes Metab. 2023; 25:581-585.
37. Schneider JE, Parikh A, Stojanovic I. Impact of a novel insulin management service on non-insulin pharmaceutical expenses. JHEOR. 2018; 6(1):53-62.
38. Russell SJ, Beck RW, Damiano ER, et al. Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes. N Engl J Med. Sep 29 2022; 387(13): 1161-1172. PMID 36170500
39. Kruger D, Kass A, Lonier J, et al. A Multicenter Randomized Trial Evaluating the Insulin-Only Configuration of the Bionic Pancreas in Adults with Type 1 Diabetes. Diabetes Technol Ther. Oct 2022; 24(10): 697-711. PMID 36173236

40. Messer LH, Buckingham BA, Cogen F, et al. Positive Impact of the Bionic Pancreas on Diabetes Control in Youth 6-17 Years Old with Type 1 Diabetes: A Multicenter Randomized Trial. Diabetes Technol Ther. Oct 2022; 24(10): 712-725. PMID 36173237
41. Blue Cross Blue Shield Association. Artificial Pancreas Devices Systems. Medical Policy Reference Manual. MPRM 1.01.30. Issue: 11:2017. Updated Aug 2023.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through March 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/17	3/8/17	2/28/17	Joint policy established
5/1/18	2/20/18	2/20/18	Medical policy statement changes: Insulin requiring diabetes added, at least 2 documented nocturnal hypoglycemic events to which member has not responded. Hybrid closed loop insulin delivery system, age 14 and older added to exclusions.
5/1/19	2/19/19		Routine policy maintenance. Removed Medicaid section.
7/1/19	4/16/19		Rational updated references 2, 17-21, and 23 added. Policy statements changed: The age criterion changed; statement added on FDA-approved automated insulin delivery system (artificial pancreas device system) designated as hybrid closed loop insulin delivery system in patients with insulin requiring diabetes who meet specified criteria. Third bullet under inclusions now reads "Individuals with demonstrated hypoglycemia unawareness." Removed 6 month requirement.
7/1/20	4/14/20		Routine policy maintenance. Added code E0787 as established, no change in policy status.
7/1/21	4/20/21		MPS revised to lower age cuttoff to 6 years. Added criteria for age 2-6. Table 2 and 5 edited.
7/1/22	4/19/22		Updated ADA guidelines and CT section. No changes in policy status.
7/1/23	4/18/23		Routine policy maintenance, added reference 29. No change in policy status. (ds)
9/1/23	8/23/23		Added Hygieia d-Nav insulin guidance system to policy as established, added literature on d-Nav. Added iLet bionic pancreas. References added. Added codes

			0740T and 0741T as established. Added codes A4225, A4230, A4232, A4226, A4224 and E0784 as established. Added statements to Inclusion section on hypoglycemia unawareness. Vendor managed: J & B—BCN/BCNA; Northwood—PPO. (ds)
7/1/24	4/16/24		Inclusion/Exclusion section language revised for clarification. Type I & Type II diabetes language added. Vendor managed: Northwood (ds)

Next Review Date: 2nd Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: ARTIFICIAL PANCREAS DEVICE SYSTEMS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.