Insulin Infusion Pumps, Automated Insulin Delivery and Artificial Pancreas Device Systems

Effective: February 1, 2025

Next Review: October 2025
Last Review: December 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

An external insulin infusion pump is typically used to deliver insulin into patients with diabetes mellitus. Automated insulin delivery systems (including but not limited to artificial pancreas devices) monitor glucose levels and automatically adjust the delivery of insulin to help achieve tight glucose control.

MEDICAL POLICY CRITERIA

Note: This policy is does not address stand-alone continuous glucose monitors (CGM) which may be considered medically necessary.

I. An *automated insulin delivery system* (including artificial pancreas devices) may be considered **medically necessary** for diabetes mellitus when either of the following Criteria are met:

A. The patient has type 1 diabetes mellitus and all of the following Criteria (1. – 3.) are met:

1. The device is approved by the Food and Drug Administration (FDA) and the patient meets the FDA approved age requirements for the device (see Policy

Guidelines); and

2. Glycated hemoglobin level (Hemoglobin A1c or HbA1c) between 5.8% and 10.0%; and
3. Used insulin pump therapy for more than 3 months.

B. The patient has gestational diabetes or preconception/pregnancy related suboptimal glycemic control (e.g., erratic blood sugars, ketoacidosis, or symptomatic hypoglycemia).

II. An *external insulin infusion pump* may be considered **medically necessary** when either of the following Criteria are met:

A. The patient has diabetes mellitus; or

B. The patient has gestational diabetes or preconception/pregnancy related suboptimal glycemic control (e.g., erratic blood sugars, ketoacidosis, or symptomatic hypoglycemia).

III. A replacement for all or part of the *external insulin pump* or FDA-approved *automated insulin delivery system* (including artificial pancreas device systems) may be considered **medically necessary** when both of the following Criteria (A. and B.) are met:

A. The pump is no longer able to perform its basic function due to one or more of the following:

1. Device is out of the warranty period; or
2. Damage or wear; or
3. The device can no longer meet the patient's medical needs due to a significant change in the patient's medical condition (e.g., larger insulin reservoir needed).

B. The current device cannot be repaired or adapted adequately to meet the patient's medical needs.

IV. The use of an *external insulin infusion pump* is considered **not medically necessary** when Criterion II. is not met.

V. A replacement for all or part of the *external insulin pump* or FDA-approved *automated insulin delivery system* (including artificial pancreas device systems) that does not meet Criterion III. is considered **not medically necessary**.

VI. The use of an *automated insulin delivery system* (including artificial pancreas device systems) is considered **investigational** when Criterion I. is not met including but not limited to a device that is not approved by the FDA.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

FDA-Approved Automated Insulin Delivery Systems (Artificial Pancreas Device Systems)

Device	Age Indication	Manufacturer
MiniMed™ 530G System[a] (open-loop, LGS)	≥16 years	Medtronic
MiniMed™ 630G System with SmartGuard™[b] (open-loop, LGS): o MiniMed™ 630G with Guardian™ Sensor 3 o MiniMed™ 630G with Enlite™ Sensor	 ≥14 years ≥16 years	Medtronic
MiniMed™ 670G System[c] (hybrid closed-loop, LGS or PLGM)	≥7 years	Medtronic
MiniMed™ 770G System[d] (hybrid closed-loop, LGS or PLGM)	≥2 years[e]	Medtronic
MiniMed 780G System (hybrid closed-loop)[f]	≥7 years	Medtronic
t:slim X2 Insulin Pump with Basal-IQ Technology (LGS) t:slim X2 Insulin Pump with Control-IQ Technology (HCL)	≥6 years	Tandem
Omnipod 5 (hybrid closed-loop)	≥2 years	Insulet
iLet Bionic Pancreas (closed loop)	≥6 years	Beta Bionics

[a] MiniMed 530G System consists of the following devices that can be used in combination or individually: MiniMed 530G Insulin Pump, Enlite™ Sensor, Enlite™ Serter, the MiniLink Real-Time System, the Bayer Contour NextLink glucose meter, CareLink® Professional Therapy Management Software for Diabetes, and CareLink® Personal Therapy Management Software for Diabetes (at time of approval).
[b] MiniMed 630G System with SmartGuard™ consists of the following devices: MiniMed 630G Insulin Pump, Enlite® Sensor, One-Press Serter, Guardian® Link Transmitter System, CareLink® USB, Bayer's CONTOUR ® NEXT LINK 2.4 Wireless Meter, and Bayer's CONTOUR® NEXT Test Strips (at time of approval).
[c] MiniMed 670G System consists of the following devices: MiniMed 670G Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), One-Press Serter, and the Contour NEXT Link 2.4 Glucose Meter (at time of approval).
[d] MiniMed 770G System consists of the following devices: MiniMed 770G Insulin Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), one-press serter, the Accu-Chek Guide Link blood glucose meter, and the Accu-Chek Guide Test Strips. The system requires a prescription.
[e] The 770G System may not be safe for use in patients who require less than a total daily insulin dose of 8 units per day because the device requires a minimum of 8 units per day to operate safely.
[f] MiniMed 780G System consists of the following devices: MiniMed 780G Insulin Pump, the Guardian 4 Transmitter, the Guardian 4 Sensor (3), One-Press Serter, the Accu-Chek Guide™ Link blood glucose meter, and the Accu-Chek Guide™ Test Strips

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- Automated insulin delivery system (artificial pancreas device system)
  - History and physical
  - Age of patient
  - Name and type of device requested
  - Documented use of insulin pump for more than 3 months
  - When applicable, documentation of gestational diabetes or preconception/pregnancy related suboptimal glycemic control (e.g., erratic blood sugars, ketoacidosis, or symptomatic hypoglycemia)
- External insulin infusion pumps
  - Clinical documentation of diabetes mellitus
  - When applicable, documentation of gestational diabetes or preconception/pregnancy related suboptimal glycemic control (e.g., erratic blood sugars, ketoacidosis, or symptomatic hypoglycemia)

- Replacement and upgrades
    - History and physical
    - Name and type of device requested
    - Documentation of specifically why pump is no longer able to perform its basic function
    - Documentation that the current device cannot be repaired or adapted adequately to meet the patient's needs

CROSS REFERENCES

1. Digital Health Products, Medicine, Policy No. 175
2. Medication Policy Manual, Note: Click the link for the appropriate Medication Policy. Once the medication policy site is open, do a find (Ctrl+F) and enter drug name in the find bar to locate the appropriate policy.

BACKGROUND

Maintenance of a target blood glucose and target glycated hemoglobin (HgA1c < 7%), a marker which is used as a proxy for average blood glucose, is now considered standard of care for patients with diabetes. Also known as tight diabetes control, this strategy is intended to prevent severe hypoglycemic events and lower the risk of cardiovascular disease mortality associated with uncontrolled glycemia.[1] In order to achieve tight glucose control, several devices may be used individually or in combination which includes but is not limited to continuous glucose monitors, insulin pumps, and more recently artificial pancreas device systems. The Food and Drug Administration (FDA) describes the basic design of an artificial pancreas device system (APDS) as a continuous glucose monitor (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. 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) a predetermined lower threshold of measured interstitial glucose. Low glucose suspension (LGS) automatically suspends basal insulin delivery for up to two 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 two 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 always tries to maintain these levels. This system is fully automated and requires no interaction from the user (except for calibration of the CGM). There are two subtypes of control-to-target systems: insulin-only and bihormonal (e.g., glucagon). There are no systems administering glucagon marketed in the United States.

An APDS 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. There are no completely closed-loop insulin delivery systems marketed in the United States.

A hybrid closed-loop system also uses automated insulin delivery with continuous basal insulin delivery adjustments. However, at mealtime, the patient enters the number of carbohydrates they are eating 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.

REGULATORY STATUS

There are several APDS devices approved by the Food and Drug Administration (FDA). These systems are regulated by the FDA as class III device systems.

The MiniMed® 530G System includes a threshold suspend or LGS feature.[2] 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 two 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.[3] The threshold suspend feature can be programmed to temporarily suspend delivery of insulin for up to two 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.[4] 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 670G System was originally approved for marketing in the United States on September 28, 2016 (P160017) and received approval for marketing with a pediatric indication (ages 7-13 years) on June 21, 2018 (P160017/S031).

On August 31, 2020, the MiniMed® 770G System received Premarket Approval from the FDA. The 770G System was approved as a supplement to the previously approved MiniMed 670G System.[5] Approval of the MiniMed 770G System expanded the indications for use to users down to two years old and updated the pump communication protocol to Bluetooth. The 770G System is a hybrid closed loop system that measures glucose levels and automatically adjusts insulin delivery by either administering or withholding insulin. The 770G System consists of the MiniMed 770G Insulin Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), one-press serter, the Accu-Chek Guide Link blood glucose meter, and the Accu-Chek Guide Test Strips. The system requires a prescription. The 770G System was approved for the following indications:

> The MiniMed 770G system is intended for continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) for the management of type 1 diabetes mellitus in persons two years of age and older requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin. The MiniMed 770G System includes SmartGuard technology, which can be programmed to automatically adjust delivery of basal insulin based on continuous glucose monitoring (CGM) sensor glucose values and can suspend delivery of insulin when the sensor glucose value falls below or is predicted to fall below predefined threshold values.
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> The Medtronic MiniMed 770G System consists of the following devices: MiniMed 770G Insulin Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), one-press serter, the Accu-Chek Guide™ Link blood glucose meter, and the Accu-Chek Guide™ Test Strips. The system requires a prescription.
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> The Guardian Sensor (3) has not been evaluated and is not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a fingerstick may be required. All therapy adjustments should be based on measurements obtained using a blood glucose meter and not on values provided by the Guardian Sensor (3).

Per the FDA approval, a prominent boxed warning is included in the labeling regarding use of the 770G System in users with a total daily insulin dose of less than 8 units, “Medtronic performed an evaluation of the 770G closed loop system and determined that it may not be safe for use in patients who require less than a total daily insulin dose of 8 units per day because the device requires a minimum of 8 units per day to operate safely.”

On June 21, 2018, the FDA approved the t:slim X2 Insulin Pump with Basal-IQ Technology (PMA P180008) for individuals who are six years of age and older.[6] 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, the FDA approved the t:slim X2 Insulin Pump with Control-IQ Technology through the De Novo process.[7] The device uses the same pump hardware as the insulin pump component of the systems approved in t:slim X2 Insulin Pump with Basal-IQ Technology (P180008) and P140015. A custom disposable cartridge is motor-driven to deliver patient programmed basal rates and boluses through an infusion set into subcutaneous tissue.

In 2022, the 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. In January, approval for the SmartAdjust™ technology was granted for ages six and up, and in September approval was expanded to allow for use in people ages two and older.[8, 9] 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, the FDA approved the first closed-loop system (iLet Bionic Pancreas) through the 510(k) premarket clearance pathway.[10] The iLet pump is an alternate controller enabled (ACE) pump intended to deliver insulin under the skin based on input from an integrated continuous glucose monitor (iCGM) and an interoperable automated glycemic controller (iAGC), in people 6 years of age or older with diabetes mellitus. The iLet ACE Pump is intended for single-person use; it is not to be shared.[11]

There are many insulin pumps on the market that are approved by the FDA. FDA 510(k) Product Code: LZG.

EVIDENCE SUMMARY

EXTERNAL INSULIN INFUSION PUMP

Randomized controlled trials (RCTs) have evaluated insulin pumps with various functionalities including a low glucose suspend (LGS) feature.[12-17] Results of these studies have demonstrated that insulin infusion pumps may, in carefully selected patient populations, control blood glucose to near-normal levels.

ARTIFICIAL PANCREAS DEVICE SYSTEMS

The key clinical outcomes regarding the clinical utility of artificial pancreas device systems (APDSs) relate to their ability to improve morbidity and mortality associated with clinically significant, severe, and acute hypoglycemia or hyperglycemic events.

Low Glucose Suspend Devices

Systematic Review and Technology Assessments

Alotaibi (2020) published the results of a systematic review (SR) with meta-analysis on the efficacy and safety of insulin pump therapy with predictive low glucose suspend (PLGS) features in children and adolescents with type 1 diabetes (T1D).[18] RCTs evaluating sensor augmented pump (SAP) with a PLGS feature compared to SAP or insulin pump therapy without SAP in decreasing hypoglycemia in children and adolescents with type 1 diabetes were considered. Although all RCTs with patients aged 2 to 18 years with at least two weeks follow-up were evaluated, only five RCTs with total sample size of 493 children aged 6 to 18 years met inclusion criteria. The risk of bias within studies was low for allocation concealment and random sequence generation was low for most studies. Blinding was not always feasible given the nature of the intervention; three of the studies were open-label, whereas in two of the studies, participants were blinded to the intervention, and in one study the outcome assessors also were blinded to the intervention. Risk of publication bias could not be assessed due to the small number of studies evaluated. Intention-to-treat analysis was used in all studies to account for loss of follow-up. Results indicate there is high quality evidence that PLGS is superior to SAP in decreasing percent of time spent in hypoglycemia (sensor glucose [SG] <3.9 mmol/L [<70 mg/dL]/24 h) and nocturnal hypoglycemia (SG <3.9 mmol [<70 mg/dL]/L/night) with an absolute mean difference of 17.4 min/d (95% CI -19.2, -15.5) and 26.3 min/night (95% CI: -35.5, -16.7), respectively. Percent time spent in hyperglycemia or episodes of diabetic ketoacidosis were not found to be different between groups. The only study with a duration long enough to assess health related quality of life showed no significant difference from baseline to study completion. The authors concluded that among children and adolescents with type 1 diabetes treated with insulin pump therapy, the utilization of PLGS is superior to SAP in decreasing mild to moderate daytime and nocturnal hypoglycemia without increasing the risk of hyperglycemia, but note that future studies evaluating long-term safety and cost-effectiveness are warranted.

Randomized Controlled Trials

Boucsein (2024) published a open-label RCT evaluating the efficacy and safety of an automated insulin delivery for children and youth with type 1 diabetes and elevated glycated hemoglobin.[19] Participants (n = 80; age 7 to 25 years of age) were randomized to use an automated insulin delivery system (MiniMed 780G) or to receive usual diabetes care of multiple daily injections or non--automated pump therapy (control). At 13 weeks, the mean (±SD) glycated hemoglobin decreased from 10.5±1.9% to 8.1±1.8% in the automated insulin delivery group but remained relatively consistent in the control group, changing from 10.4±1.6% to 10.6±1.8% (baseline-adjusted between-group difference, -2.5 percentage points; 95% confidence interval [CI], -3.1 to -1.8; P<0.001). Patients in the automated insulin delivery group spent on average 8.4 hours more in the target glucose range of 70 to 180 mg/dl than those in the control group. One severe hypoglycemia event and two diabetic ketoacidosis events occurred in the control group, with no such events in the automated insulin delivery group.

Collyns (2021) published the results of a randomized crossover study conducted at two sites comparing the MiniMed Advanced Hybrid Closed-Loop (AHCL) 670G system to sensor-augmented pump therapy with predictive low glucose management (SAP + PLGM) in patients with T1D.[20] Of the 60 patients enrolled, 59 completed the study. Patients were naive to automated insulin delivery ranged in age from seven to 80 years (mean age 23.3 ± 14.4 years), The treatment intervention sequence was randomly assigned 1:1 stratified by

participants' age. Each study phase was four weeks, preceded by a two- to four-week run-in and separated by a 2-week washout. Time in target range (TIR, 3.9-10 mmol/L) was higher in the AHCL compared to the SAP + PLGM group (70.4 ± 8.1% vs. 57.9 ± 11.7%, p < 0.001). Mean sensor glucose (SG) at run-in was 9.3 ± 0.9 mmol/L and improved with AHCL (8.5 ± 0.7 mmol/L, p < 0.001) and deteriorated during PLGM (9.5 ± 1.1 mmol/L, p < 0.001). There was one episode of mild diabetic ketoacidosis, which occurred during the SAP + PLGM arm, attributed to an infusion set failure in combination with an intercurrent illness.

Beardsall (2020) published the results of a randomized, open-label, parallel controlled trial in 20 pre-term infants receiving CGM alone supported by a paper algorithm compared to CGM with an additional intervention period of closed-loop CGM. The closed-loop system was comprised of (i) an Enlite CGM sensor, (ii) a laptop computer running a model predictive control algorithm and (iii) two Alaris syringe pumps. All 20 babies remained in the study throughout the intervention period from 48 to 72 hours and the mean (SD) length of glucose data collected in each study arm was 137 (16.4) hours and 136 (8.7) hours for CGM and CGM plus closed loop, respectively. During the intervention period, the median (IQR) time spent in the target range (sensor glucose [SG] 4.0–8.0 mmol/L) was significantly higher in babies in the closed-loop group 91% (78, 99) compared with controls 26% (6-64); p<0.001. In addition, the time spent in the wider target range of 2.6–10.0 mmol/L was higher in the closed-loop group: median 100% compared with control group, median 84%. Lower SG was observed in the closed-loop group median (IQR) 6.2 (6.1-7.1) mmol/L compared with the control group 8.6 (7.4-11.1) mmol/L (p=0.002). Time spent with SG levels <2.6 mmol/L and glucose variability as measured by the SD of SG were similar between groups. In the postintervention period (post-72 hours), there was qualitatively increased time in both glucose target ranges (4.0–8.0 and 2.6–10.0 mmol/L) in the closed-loop group compared with the control group, but these differences did not reach statistical significance. In the closed-loop study group, two babies had documented episodes of hypoglycemia with blood glucose (BG) <2.6 mmol/L, both associated with a change of maintenance fluids. In the control study group, no babies had a documented BG value <2.6 mmol/L. One baby in the control group had an episode lasting 205 min when the SG fell to <2.6 mmol/L (BG was not checked at this time). Limitations to this study include small sample size, lack of blinding, and short study duration. While Medtronic provided the continuous glucose monitoring systems and sensors, the company had no role in study design, data acquisition, preparation of the manuscript, or decision to publish the study.

Breton (2020) published the results of a multi-site RCT comparing a closed-loop system of insulin delivery (closed-loop group, n=78) and a sensor-augmented insulin pump (control group, n=23) in children 6 to 13 years of age who had type 1 diabetes.[21] The primary outcome was the percentage of time that glucose levels were in the target range of 70 to 180 mg per deciliter, as measured by CGM. The mean (±SD) percentage of time that the glucose level was in the target range over the 16 weeks of treatment increased from 53±17% at baseline to 67±10% in the closed-loop group and from 51±16% to 55±13% in the control group (mean adjusted difference, 11 percentage points [equivalent to 2.6 hours per day]; 95% confidence interval, 7 to 14; p<0.001). The median percentage of time that the system was in the closed-loop mode was 93% (interquartile range, 91 to 95) for patients in the closed-loop group. No episodes of diabetic ketoacidosis or severe hypoglycemia were noted in either study group. Improvements were sustained through 28 weeks in an uncontrolled extension study of 100 children who were enrolled in the RCT (Kanapka 2021).[22] Health-related quality of life and patient satisfaction measures from the RCT and the extension phase were reported by Cobry (2021).[23] Neither children nor their parents in the closed-loop system group reported statistically significant changes in these outcomes compared with the sensor-augmented

insulin pump group. The authors concluded that children receiving the closed-loop system did not experience increased burden compared with those using sensor-augmented insulin pump.

Outcomes of the Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial were reported by Bergenstal (2013).[16] This industry-sponsored trial used the Paradigm Veo insulin pump. A total of 247 patients were randomized to an experimental group, in which a continuous glucose monitor with the LGS feature was used (n=121), or a control group, which used the continuous glucose monitor but not the LGS feature (n=126). Key eligibility criteria were 16-to-70 years old, T1D, and HbA1c levels between 5.8% and 10.0%. In addition, patients had to have more than six months of experience with insulin pump therapy and at least two nocturnal hypoglycemic events (≤65 mg/dL) lasting more than 20 minutes during a two-week run-in phase. The randomized intervention phase lasted three months. Patients in the LGS group were required to use the feature at least between 10 PM and 8 AM. The threshold value was initially set at 70 mg/dL and could be adjusted to between 70 mg/dL and 90 mg/dL. Seven patients withdrew early from the trial; all 247 were included in the intention-to-treat analysis. The primary efficacy outcome was the area under the curve (AUC) for nocturnal hypoglycemia events. This was calculated by multiplying the magnitude (in milligrams per deciliter) and duration (in minutes) of each qualified hypoglycemic event. The primary safety outcome was change in HbA1c levels.

The primary end point, mean (standard deviation [SD]) AUC for nocturnal hypoglycemic events, was 980 (1200) mg/dL/min in the LGS group and 1568 (1995) mg/dL/min 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 (SD) AUC values were 798 (965) mg/dL/min in the intervention group and 1164 (1590) mg/dL/min in the control group. Moreover, the intervention group experienced fewer hypoglycemic episodes (mean, 3.3 per patient-week; SD=2.0) than the control group (mean, 4.7 per patient-week; SD=2.7; $p<0.001$). 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 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 five minutes, and 19.6% lasted more than two hours. In both groups, the mean sensor glucose value at the beginning of nocturnal events was 62.6 mg/dL. After four hours, the mean value was 162.3 mg/dL in the LGS group and 140.0 mg/dL in the control group.

Regarding safety outcomes and adverse events, change in HbA1c level was minimal, and there was no statistically significant difference between groups. Mean HbA1c levels decreased from 7.26 to 7.24 mg/dL in the LGS group and from 7.21 to 7.14 mg/dL in the control group. During the study period, there were no severe hypoglycemic events in the LGS group and four events in the control group (range of nadir glucose sensor values in these events, 40-76 mg/dL). There were no deaths or serious device-related adverse events.

Before reporting on in-home findings, the ASPIRE researchers (Garg [2012]) published data from the in-clinic arm of the study.[24] This randomized crossover trial included 50 patients with type 1 diabetes who had at least three months of experience with an insulin pump system. After a two-week run-in period to verify and optimize basal rates, patients underwent two in-clinic exercise sessions to induce hypoglycemia. The LGS feature on the insulin pump was

turned on in one session and off in the other session, in random order. When on, the LGS feature was set to suspend insulin delivery for two hours when levels reached 70 mg/dL or less. The goal of the study was to evaluate whether the severity and duration of hypoglycemia were reduced when the LGS feature was used. The study protocol called for patients to start exercise with glucose levels between 100 mg/dL and 140 mg/dL and to use a treadmill or stationary bicycle until their plasma glucose levels were 85 mg/dL or less. The study outcome (duration of hypoglycemia) was defined as the period of time glucose values were lower than 70 mg/dL and above 50 mg/dL, and hypoglycemia severity was defined as the lowest observed glucose value. A successful session was defined as an observation period of 3 to 4 hours and with glucose levels above 50 mg/dL. Patients who did not attain success could repeat the experiment up to three times.

The 50 patients attempted 134 exercise sessions; 98 of them were successful. Duration of hypoglycemia was significantly shorter during the LGS-on sessions (mean, 138.5 minutes; SD=68) than the LGS-off sessions (mean, 170.7 minutes; SD=91; p=0.006). Hypoglycemia severity was significantly reduced in the LGS-on group. The mean (SD) lowest glucose level was 59.5 (72) mg/dL in the LGS-on group and 57.6 (5.7) mg/dL in the LGS-off group (p=0.015). Potential limitations of the Garg study included evaluation of the LGS feature in a research setting and short assessment period.

A second RCT evaluated the in-home use of the Paradigm Veo System.[12] The trial by Ly (2013) in Australia was excluded from the 2013 TEC Assessment due to the inclusion of children and adults and lack of analyses stratified by age group (the artificial pancreas system approved in the United States at the time of the review was only intended for individuals ≥16 years). The Ly trial included 95 patients with T1D between 4 and 50 years of age (mean age, 18.6 years; >30% of sample <18 years old) who had used an insulin pump for at least 6 months. In addition, participants had to have an HbA1c level of 8.5% or less and have impaired awareness of hypoglycemia (defined as a score of at least four on the modified Clarke questionnaire). Patients were randomized to six months of in-home use of the Paradigm Veo System with automated insulin suspension when the glucose sensor reached a preset threshold of 60 mg/dL or to continued use of an insulin pump without the LGS feature. The primary study outcome was the combined incidence of severe hypoglycemic events (defined as hypoglycemic seizure or coma) and moderate hypoglycemic events (defined as an event requiring assistance from another person). As noted, findings were not reported separately for children and adults.

The baseline rate of severe and moderate hypoglycemia was significantly higher in the LGS group (129.6 events per 100 patient-months) than in the pump-only group (20.7 events per 100 patient-months). After six months of treatment, and controlling for the baseline hypoglycemia rate, the incidence rate per 100 patient-months was 34.2 (95% confidence interval [CI], 22.0 to 53.3) in the pump-only group and 9.6 (95% CI, 5.2 to 17.4) in the 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 trialists conducted a sensitivity analysis in patients younger than 12 years (15 patients in each treatment group). The high baseline hypoglycemia rates could be explained in part by two outliers (children ages nine and 10 years). When both children were excluded from the analysis, the primary outcome was no longer statistically significant. The incidence rate ratio for moderate and severe events excluding the two children was 1.7 (95% CI, 0.7 to 4.3). Mean HbA1c levels (a secondary outcome) did not differ between groups at baseline or at 6 months. Change in HbA1c levels during the treatment period was - 0.06% (95% CI, -0.2% to 0.09%) in

the pump-only group and -0.1% (95% CI, -0.3% to 0.03%) in the LGS group; the difference between groups was not statistically significant.

Prospective Studies

Gómez (2017) published the results of a cohort (n = 111) individuals with T1D with documented hypoglycemia and hypoglycemia unawareness who received a sensor-augmented insulin pump with LGS therapy.[25] 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). HbA1c levels were reduced from a baseline value of 8.8% (SD=1.9%) to 7.5% (SD=1.0%) at five 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 one 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).

Retrospective Studies

Agrawal (2015) retrospectively analyzed use of the threshold suspend feature associated with the Paradigm Veo System in 20,973 patients, most of whom were treated outside of the United States.[26] This noncontrolled descriptive analysis provided information on the safety of the device when used in a practice setting. The threshold suspend feature was enabled for 100% of the time by 14,673 (70%) patients, 0% of the time by 2249 (11%) patients, and the remainder used it intermittently. The mean (SD) setting used to trigger suspension of insulin was a sensor glucose level of 62.8 (5.8) mg/dL. On days when the threshold suspend feature was enabled, there was a mean of 0.82 suspend events per patient day. Of these, 56% lasted for 0 to 5 minutes, and 10% lasted the full two hours. (Data on the length of the other 34% of events were not reported.) On days when the threshold suspend feature was on, sensor glucose values were 50 mg/dL or less 0.64% of the time compared with 2.1% of sensor glucose values 50 mg/dL or less on days when the feature was off. Reduction in hypoglycemia was greatest at night. Sensor glucose percentages equivalent to 17 minutes per night occurred when the threshold suspend feature was off vs glucose percentages equivalent to five minutes per night when the threshold suspend feature was on. Data on the use of the device has suggested fewer and shorter hypoglycemic episodes. The length and severity of hypoglycemic episodes were not fully discussed in this article.

Section Summary

For individuals who have T1D who receive an artificial pancreas device system with a low glucose suspend feature, the evidence includes three RCTs conducted in patients six years and older. Relevant outcomes are symptoms, change in disease status, morbid events, resource utilization, and treatment-related morbidity. All of these RCTs reported primary outcomes were favorable for the group using an artificial pancreas system; however, findings from one trial were limited by nonstandard reporting of hypoglycemic episodes, and findings from the other trial were no longer statistically significant when two outliers (children) were excluded from analysis. The RCT limited to adults showed an improvement in the primary outcome (AUC for nocturnal hypoglycemic events). AUC is not used for assessment in clinical practice, but the current technology does allow user and provider review of similar trend data with a CGM.

Results from the ASPIRE study suggested that there were increased risks of hyperglycemia and potential DKA 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.

In addition, one small study reported favorable outcomes for closed-loop systems in pre-term infants, however, this study is limited by very small sample size, lack of blinding, and short study duration.

The evidence is sufficient that the magnitude of reduction for hypoglycemic events in the population with T1D is likely to be clinically significant. Limitations of the published evidence preclude determining the effects of the technology on overall glycemic control as assessed by HbA1c and other parameters and thus, net health outcomes.

Hybrid Closed-loop Insulin Delivery Systems

Systematic Review

Di Molfetta (2024) published a network meta-analysis study comparing the efficacy and safety of different hybrid closed-loop (HCL) systems in people with diabetes.[27] The study included 28 randomized clinical trials (RCTs) with a total of 3,444 participants with type 1 diabetes. The results showed that HCL systems significantly increased time in target range (TIR) compared to subcutaneous insulin therapy without continuous glucose monitoring (SIT). The Minimed 780G achieved the highest TIR, followed by the Control-IQ, Minimed 670G, CamAPS Fx, and DBLG1, with mean differences ranging from 5.1% to 10.69% compared to SIT. Additionally, all HCL systems decreased time below target range, with the largest reductions seen with DBLG1 (-3.69%), Minimed 670G (-2.9%), and Minimed 780G (-2.79%). The study found no significant difference in the risk of severe hypoglycemia and diabetic ketoacidosis between HCL systems and other types of insulin therapy, providing support for clinical decision-making.

Michou (2023) published a SR and meta-analysis to evaluate the efficacy of automatic insulin delivery (AID) systems in children and adolescents with T1D.[28] A total of 26 RCTs (n = 915) were included in the meta-analysis. AID systems revealed statistically significant differences in the main outcomes, such as the proportion of time in the target glucose range (3.9-10 mmol/L) ($p < 0.00001$), in hypoglycemia (<3.9 mmol/L) ($p = 0.003$) and mean proportion of HbA1C ($p = 0.0007$) compared to control group. The authors conclude that AID systems are superior to insulin pump therapy, sensor-augmented pumps and multiple daily insulin injections. Most of the included studies have a high risk of bias because of allocation, blinding of patients and blinding of assessment. Sensitivity analyses showed that patients < 21 years of age with T1D can use AID systems, after proper education, following their daily activities.

Peacock (2023) published a systematic review of reported trials and real-world studies for commercial hybrid closed-loop (HCL) automated insulin delivery (AID) systems.[29] Fifty-nine studies were included in the SR (19 for 670G; eight for 780G; 11 for Control-IQ; 14 for CamAPS FX; four for Diabeloop; and three for Omnipod-5). Twenty were real-world studies, and 39 were trials or sub-analyses. These studies highlighted that HCL systems improve time in range (TIR) and arouse minimal concerns around severe hypoglycemia. A meta-analysis was not conducted, and statistical tests were not used due to broad inclusion criteria and heterogeneity of the included papers. Many of the participants in the studies included had

optimal baseline TIR and HbA1c and may have been of high socioeconomic status. Furthermore, most of the studies were conducted in the USA. Due to the differences in study designs and trial populations between the various AID systems, it was not possible to conclusively determine differences between them. The authors conclude that HCL systems are an effective and safe option for improving diabetes care. Real-world comparisons between systems and their effects on psychological outcomes require further study.

Karageorgiou (2019) published a systematic review and network meta-analysis evaluating the efficacy of closed-loop systems in glycemic control for non-adults with type 1 diabetes mellitus.[30] The meta-analysis included 25 studies (n = 504). The closed-loop system group spent a significantly higher percentage of time in a target glycemic range and the mean glucose was also decreased in the closed-loop system group (MD: 3.01%, 95% CI 1.68 to 4.34%). Overall, the closed-loop system showed better outcomes compared to standard insulin pumps for non-adults.

Prospective Studies

Van den Heuvel (2024) published a prospective, multicenter, exploratory, open-label, randomized controlled trial comparing the efficacy of an advanced hybrid closed-loop (AHCL) system with multiple daily injections of insulin (MDI) plus real-time continuous glucose monitoring (RT-CGM) in adults with type 1 diabetes (T1D) and suboptimal glucose control.[31] This analysis represents a predefined exploratory cohort (cohort B) from the ADAPT (ADvanced Hybrid Closed Loop Study in Adult Population with Type 1 Diabetes) study. The study included 13 participants with HbA1c ≥8.0%, who were randomly allocated to either switch to AHCL (n = 8) or continue with MDI + RT-CGM (n = 5) for six months. The results showed that the mean HbA1c level decreased by 1.70 percentage points in the AHCL group, compared to a 0.60 percentage point decrease in the MDI + RT-CGM group, with a model-based treatment effect of -1.08 percentage points (95% CI = -2.17 to 0.00 percentage points; p = 0.0508) in favor of AHCL. Additionally, the percentage of time spent with sensor glucose levels between 70 and 180 mg/dL was significantly higher in the AHCL group (73.6%) compared to the MDI + RT-CGM group (46.4%), with a model-based between-group difference of 28.8 percentage points (95% CI = 12.3 to 45.3 percentage points; p = 0.0035). No severe adverse events, including diabetic ketoacidosis or severe hypoglycemia, occurred in either group. Most of the authors receive financial compensation from the device company.

Quirós (2024) published a multicenter prospective cohort study comparing glycemic control and maternal-fetal outcomes in pregnant women with type 1 diabetes (T1D) using hybrid closed loop (HCL) versus multiple daily insulin injections (MDI) plus continuous glucose monitoring.[32] The study included 112 women, with 59 using HCL and 53 using MDI. The results showed that there was no significant difference in HbA1c levels between the two groups in any trimester, although MDI users had a greater decrease in HbA1c in the second trimester (-6.12 ± 9.06 vs. -2.16 ± 7.42 mmol/mol, P = 0.031). Additionally, there was no difference in time spent within the target glucose range (TIR) and time above range (TAR) between the two groups. However, HCL users had a higher total insulin dose in the second trimester (+0.13 IU/kg·day) and gained more weight during pregnancy (βadjusted = 3.20 kg, 95% CI 0.90-5.50). Furthermore, newborns of HCL users were more likely to have higher birthweight (βadjusted = 279.0 g, 95% CI 39.5-518.5) and macrosomia (ORadjusted = 3.18, 95% CI 1.05-9.67) compared to MDI users, although these associations disappeared when maternal weight gain or third trimester HbA1c was included in the models.

Edd (2023) published a prospective, multicentre, open-label, RCT in people (n = 75) with T1D, with an HbA1c of at least 8.0% (64 mmol/mol), on MDI+isCGM therapy.[33] To reassess the 6-month efficacy and to assess the 12-month sustained efficacy of the MiniMed™ 780G advanced hybrid closed-loop automated insulin delivery (AID) system compared to multiple daily injections plus intermittently scanned glucose monitoring (MDI+isCGM) in people with type 1 diabetes not meeting glucose targets. After a 6-month study phase, participants randomized at baseline to MDI+isCGM switched to AID (SWITCH) while the others continued AID therapy (SUSTAIN) for an additional 6 months. The primary endpoint of this continuation phase was the within-group change in mean HbA1c between six and 12 months, with superiority in the SWITCH group and noninferiority in the SUSTAIN group (ClinicalTrials.gov: NCT04235504). A total of 39 SWITCH and 36 SUSTAIN participants entered the continuation phase. In the SWITCH group, HbA1c was significantly decreased by -1.4% (95% confidence interval [CI] -1.7% to -1.1%; $p < 0.001$) from a mean ± SD of 8.9% ± 0.8% (73.9 ± 8.6 mmol/mol) at six months to 7.5% ± 0.6% (58.5 ± 6.9 mmol/mol) at 12 months. Mean HbA1c increased by 0.1% (95% CI -0.05% to +0.25%), from 7.3% ± 0.6% (56.5 ± 6.7 mmol/mol) to 7.4% ± 0.8% (57.7 ± 9.1 mmol/mol) in the SUSTAIN group, meeting noninferiority criteria. Three severe hypoglycemia events occurred in two SWITCH participants during the continuation phase. The authors concluded that ADAPT study phase glycemic improvements were reproduced and sustained in the continuation phase, supporting the early adoption of AID therapy in people with T1D not meeting glucose targets on MDI therapy.

Brown (2021) reported results of the noncomparative pivotal trial of the Omnipod 5 Automated Insulin Delivery System.[34] The study included 241 participants (112 children ages 6 to 13.9 years and 128 adults ages 14 to 70 years). The mean reduction from baseline in HbA1c was 0.71% for children and 0.38% for adults (both $p<0.0001$ from baseline). Change in time in range compared to baseline (hours/day) was 3.7 for children and 2.2 for adults (both $p<0.0001$). Reduction from baseline in time in hypoglycemia <70 mg/dL was 2.0% to 1.09% for adults while no change was reported for children. The adverse events reported were three severe hypoglycemia events not attributed to device malfunction and one diabetic ketoacidosis event from an infusion site failure.

Sherr (2022) reported outcomes in children ages 2 to 5.9 using the Omnipod 5 Automated Insulin Delivery System at 10 U.S. sites.[35] Eighty children were evaluated following use of the device for 13 weeks following 14 days of baseline data collection on their usual therapy. From baseline, HbA1c decreased by 0.55% (6.0 mmol/mol) ($p< 0.0001$), time with sensor glucose levels in target range (70 to 180 mg/dL) increased by 10.9%, or 2.6 h/day ($p< 0.0001$), and time with levels <70 mg/dL declined by median 0.27% ($p=0.0204$).

Bergenstal (2016) published a prospective single-arm study on the safety of the hybrid closed-loop system in patients with type 1 diabetes.[36] It included 124 patients ages 14-to-75 years old who had type 1 diabetes for at least two years, had HbA1c levels less than 10.0%, and who had used an insulin pump for at least six months. There was an initial run-in period at baseline for patients to learn how to use the device followed by a three-month period of device use. The study period included a 6-day hotel stay with a one-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

four serious adverse events, one 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 multicenter pivotal trial published by Garg (2017) evaluated the safety of Medtronic's hybrid closed-loop system, using methods similar to those of Bergenstal (NCT02463097) and employing the same device (MiniMed 670G).[37] 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 two years before the study, and used insulin pump therapy for six months or more. A three-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 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 CGM, 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 (2017) published a randomized controlled crossover trial comparing the efficacy of a zone model predictive control algorithm with that of sensor-augmented pump therapy; the trial included 20 subjects (19 completed), all with type 1 diabetes and having at least three months treatment with a subcutaneous insulin infusion pump.[38] The six week, in-home study was divided into 2-week blocks, with two 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 end points, 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 end point (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.

Pinsker (2022) published the results of a randomized crossover trial comparing sensor-augmented pump therapy to an adaptive zone model predictive control device in 35 adults with T1D.[39] 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 RCT by Tauschman (2018) evaluated individuals with uncontrolled type 1 diabetes as reflected in mean Hb1c <8 %.[40] Approximately, 50% of the subjects were between 6-21 years of age and 25% are 6-12 years old. Both groups achieved a reduction in HbA1c but were statistically greater in the HCL 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 decrease in time spent with glucose <70mg/dl.

Abraham (2018) reported the results of a six month, multicenter, RCT in children and adolescents with T1D comparing use of an insulin pump with suspend before low or predictive low-glucose management (PLGM) with sensor-augmented insulin pump therapy (SAPT) alone.[41] At six months, significant reductions were seen in day and night hypoglycemia and number of hypoglycemic events <63mg/dl lasting longer than 20 minutes. There were no differences in HbA1c at six months in either group. A follow-up analysis in 140 participants evaluated the effect of percentage time of sensor use on glycemic control in individuals on SAPT with and without PLGM.[42] The mean ± SD age of the cohort was 13.4 ± 2.8 years, duration of diabetes was 7.1 ± 3.7 years and HbA1c was 7.5 ± 0.8%. The sensor use was calculated as a percentage; the number of sensor glucose recordings was compared to the number of expected total recordings, which was then categorized into four groups <40%, 40 to <60%, 60 to <80% and ≥80%. The frequency of sensor use was 7.86% (n = 11) in <40%, 24.29% (n = 34) in 40 to <60%, 36.43% (n = 51) in 60 to <80% and 31.43% (n = 44) in ≥80%. With every 10% increase in sensor use in participants in the SAPT group, mean reduction of HbA1c was −0.14% [−0.25 to −0.04] (p = 0.007) while in the PLGM group, the mean reduction was −0.04% [−0.15 to 0.06] (p = 0.361). These results indicate that improvement in glycemic control is dependent on frequency of sensor use, with higher sensor uptake corresponding to improved glycemic outcomes.

Forlenza (2019) reported the data and analysis of the supplemental information filed with the FDA to support the expanded indication for the MiniMed 670G system to children 7 to 13 years of age.[43] The nonrandomized, single arm multicenter study reported the day and night use of the automated insulin delivery and PLGM for three 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 (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.[44] The suspend before low prevention capability was confirmed in 97.5% of patients experiencing a sensor glucose of ≤ 55mg/dl.

Messer (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 three-month period.[45] Participants successfully utilized the device without significant changes in total daily dose of insulin but improved percentage time in range (70 to 180 mg/dl).

Section Summary

For individuals who have T1D who receive an artificial pancreas device system with a hybrid closed-loop insulin delivery system, the evidence includes a multicenter pivotal trial 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 studied and 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 three crossover RCTs two found significantly better outcomes (ie, time spent in nocturnal hypoglycemia and time spent in preferred glycemic range) with the device than with standard care. The third study 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 to 180mg/dl), rare diabetic ketoacidosis and few device-related adverse events. The evidence suggests that the magnitude of reduction for hypoglycemic events in the population with T1D population is likely to be clinically significant. The variation in the definition of primary and secondary outcomes in the study design and conduct of the published evidence limit the ability to determine the effects of the technology on net health outcomes. 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.

Closed-Loop Insulin Delivery System

Systematic Reviews

Teixeira (2024) published a meta-analysis and trial sequential analysis of RCTs to evaluate the efficacy of automated insulin delivery (AID) devices in pregnant women with type 1 diabetes (T1DM).[46] Five RCTs with a total of 236 pregnant women, of whom 117 (50.6%) received AID were included in the analysis. There was a significant increase in nocturnal time in range (TIR; mean difference [MD] 12.69%; 95% CI 8.74-16.64; $p < 0.01$; $I2 = 0\%$) and a decrease in glucose variability (standard deviation of glucose; MD -2.91; 95% CI -5.13 to -0.69; $p = 0.01$; $I2 = 0\%$). No significant differences were observed for TIR, high blood glucose index (HBGI), low blood glucose index (LBGI), mean glucose and time spent in hyperglycemia and hypoglycemia. The statistical significance obtained in nocturnal TIR was conclusive and with minimal risk of a type I error. The authors conclude that AID systems can significantly improve nocturnal glycemic control and potentially reduce glycemic variability in pregnant women with

T1DM, with no effect in the risk of hypoglycemia and hyperglycemia compared with current insulin treatments.

Oktavian (2023) published a SR evaluating the use of use of a bionic pancreas in patients with type 1 diabetes (T1D). Nine studies were included in this review. The data from these studies suggested that the use of a bionic pancreas could reduce the HbA1c (mean difference [MD] = −0.40% [95% confidence interval [CI] = −0.59 to −0.21], I2 = 0%, p < 0.0001) and mean glucose levels (MD = −21.06 [95% CI = −24.66 to −17.46], I2 = 45%, p < 0.00001) and improve the time in range (TIR) (MD = 14.41% [95% CI = 10.99 to 17.83], I2 = 60%, p < 0.00001). The most common adverse events reported were nausea and vomiting. Limitations included small sample sizes, lack of long-term follow-up, and heterogeneity of study methods. The authors conclude that the use of a bionic pancreas shows potential in preventing complications of T1D by improving the TIR and decreasing the HbA1c and mean glucose levels. Furthermore, serious adverse events with the use of a bionic pancreas and standard of care show insignificant results, suggesting a good safety profile.

Randomized Controlled Trials

Kim (2024) published the results of a multicentre, parallel-group, comparing the efficacy and safety of a tubeless, on-body automated insulin delivery (AID) system with a tubeless, on-body sensor-augmented pump (SAP) in adults with type 1 diabetes (T1DM).[47] The 12-week randomized controlled trial, which included 104 participants (53 in the AID group and 51 in the SAP group), found that the AID system significantly improved glycemic profiles, with a mean increase in time in range (TIR) from 62.1% to 71.5% (±10.7%), compared to the SAP group's increase from 64.7% to 66.9% (±15.0%), resulting in a 6.5% (95% CI 3.6%, 9.4%) difference between the adjusted means (p<0.001). Additionally, the AID system showed reduced time below range, time above range, and coefficient of variation (CV), as well as lower mean glucose levels. HbA1c levels decreased from 50.9 mmol/mol (6.8%) to 45.9 mmol/mol (6.4%) in the AID group and from 48.7 mmol/mol (6.6%) to 45.7 mmol/mol (6.3%) in the SAP group, but the difference between the groups was not significant (-0.7 mmol/mol, 95% CI -2.0, 0.8 mmol/mol, p=0.366). No diabetic ketoacidosis or severe hypoglycaemia events occurred in either group.

Castellanos (2023) evaluated the performance of the iLet bionic pancreas (BP) in non-Hispanic White individuals (here referred to as "Whites") and in Black, Hispanic, and other individuals (here collectively referred to as "Minorities").[48] This multicenter, RCT evaluated glycemic management with the BP versus standard of care (SC) in 161 adult and 165 pediatric participants with T1D over 13 weeks. In Whites (n = 240), the mean baseline-adjusted difference in 13-week HbA1c between the BP and SC groups was -0.45% (95% CI -0.61 to -0.29 [-4.9 mmol/mol; -6.6 to -3.1]; P < 0.001), while this difference among Minorities (n = 84) was -0.53% (-0.83 to -0.24 [-6.0 mmol/mol; -9.2 to -2.8]; p < 0.001). In Whites, the mean baseline-adjusted difference in time in range between the BP and SC groups was 10% (95% CI 7-12; p < 0.001) and in Minorities was 14% (10-18; p < 0.001). The authors conclude that the BP improves glycemic control in both Whites and Minorities and offers promise in decreasing health care disparities.

Ekhlaspour (2023) published the results of a six-month, multicenter RCT evaluating the benefits of automated insulin delivery (AID) among individuals with T1D in sub-populations of baseline device use determined by continuous glucose monitor (CGM) use status and insulin delivery via multiple daily injections (MDI) or insulin pump.[49] Participants (n = 168) were

assigned to closed-loop control (CLC, Control-IQ, Tandem Diabetes Care), or sensor-augmented pump (SAP) therapy. The trial included a two- to eight-week run-in phase to train participants on study devices. The participants were stratified into four subgroups: insulin pump and CGM (pump+CGM), pump-only, MDI and CGM (MDI+CGM), and MDI users without CGM (MDI-only) users. We compared glycemic outcomes among four subgroups. At baseline, 61% were pump+CGM users, 18% pump-only users, 10% MDI+CGM users, and 11% MDI-only users. Mean time in range 70-180 mg/dL (TIR) improved from baseline in the four subgroups using CLC: pump+CGM, 62% to 73%; pump-only, 61% to 70%; MDI+CGM, 54% to 68%; and MDI-only, 61% to 69%. The reduction in time below 70 mg/dL from baseline was comparable among the four subgroups. No interaction effect was detected with baseline device use for TIR (P = .67) or time below (p = 0.77). On the System Usability Questionnaire, scores were high at 26 weeks for all subgroups: pump+CGM: 87.2 ± 12.1, pump-only: 89.4 ± 8.2, MDI+CGM 87.2 ± 9.3, MDI: 78.1 ± 15. The authors conclude that there was a consistent benefit in patients with T1D when using CLC, regardless of baseline insulin delivery modality or CGM use. Suggesting that this CLC system can be considered across a wide range of patients.

Mauras (2023) published the results of a RCT evaluating the bionic pancreas (BP) generated backup insulin dose for injection for pump users (including long-acting insulin dose, a four period basal insulin profile, short acting meal doses and a glucose correction factor) provided in case of device malfunction.[50] Following a 13-week trial in T1D, participants using the BP (6-83 years) completed 2-4 days, in which they were randomly assigned to their prestudy insulin regimen (n = 147) or to follow BP-provided guidance (n = 148). Glycemic outcomes with BP guidance were similar to those reinstituting their prestudy insulin regimen, with both groups having higher mean glucose and lower time-in-range than while using the BP during the 13-week trial. In conclusion, a backup insulin regimen automatically generated by the BP can be safely implemented if need arises to discontinue use of the BP. Clinical Trial Registry: clinicaltrials.gov; NCT04200313.

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.[51] 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.

The main results for the full group (n = 326) were reported by Russell (2022).[51] 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 (2022) reported results for adults ages 18 and over (n= 161).[52] In this subgroup, mean glycated hemoglobin decreased from 7.6% (± 1.2%) at baseline to 7.1% (± 0.6%) at 13 weeks in the intervention group versus 7.6% (± 1.2%) to 7.5% (± 0.9%) with

standard care (adjusted difference -0.5%, 95% confidence interval [CI] -0.6% - -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 (2022) reported results for children and youth ages 6 to 17 years (n = 165).[53] Mean glycated hemoglobin decreased from 8.1% (± 1.2%) at baseline to 7.5% (± 0.7%) at 13 weeks in the intervention group versus 7.8% (± 1.1%) at both baseline and 13 weeks with standard care (adjusted difference -0.5%; 95% CI -0.7% - -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.[54] 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) cohort.

Section Summary: Closed-Loop Insulin Delivery System

The evidence includes a SR (nine studies), including 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. The evidence supports the bionic pancreas may improve health outcomes by preventing complications of T1D by improving the TIR and decreasing the HbA1c and mean glucose levels. Furthermore, serious adverse events with the use of a bionic pancreas and standard of care show insignificant results, suggesting a good safety profile.

PRACTICE GUIDELINE SUMMARY

AMERICAN DIABETES ASSOCIATION

The 2024 American Diabetes Association Standards of Medical Care in Diabetes provides the following recommendations on controlling diabetes:[55]

> 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 (Level of Evidence 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 (Level of Evidence A) or other types of insulin-deficient diabetes (Level of

Evidence 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. (Level of Evidence A)

Individuals with diabetes may be using systems not approved by the U.S. Food and Drug Administration, such as do-it yourself closed-loop systems and others; health care professionals cannot prescribe these systems but should assist in diabetes management to ensure the safety of people with diabetes. (Level of Evidence E)

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND THE AMERICAN COLLEGE OF ENDOCRINOLOGY

The American Association of Clinical Endocrinologists published a 2022 update of their Clinical Practice Guideline: Developing a Diabetes Mellitus (DM)Comprehensive Care Plan.[56] The guideline includes the following recommendations:

Insulin pump therapy (CSII) provides constant/continuous infusion of fast-acting insulin driven by mechanical force and delivered via a cannula inserted under the skin. CSII can improve (or enhance) glycemic control and should be an option for insulin delivery for appropriate persons with DM. Ideally, these individuals should also use CGM. (Grade B, Best Evidence Level 1)

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

The American Association of Clinical Endocrinologists and American College of Endocrinology (2018) published a joint position statement on the integration of insulin pumps and continuous glucose monitoring in patients with diabetes.**[57]** The statement emphasized the use of continuous glucose monitoring and insulin pump therapy for T1D patients who are not in glycemic target ranges despite intensive attempts at self-blood glucose monitoring and multiple insulin injection therapy.

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS

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.[58] 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

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

SUMMARY

There is enough research to show that the use of an external insulin infusion pump or FDA-approved automated insulin delivery system (artificial pancreas device) improves health outcomes for select patients with diabetes mellitus or preconception/pregnancy related suboptimal glycemic control. Clinical practice guidelines based on research recommend these devices in certain populations and clinical scenarios. Therefore, the use of an external insulin infusion pump or an FDA-approved automated insulin delivery system (artificial pancreas device) may be considered medically necessary when policy criteria are met.

There is not enough research to show that an insulin pump or FDA-approved automated insulin delivery system (artificial pancreas device) improve health outcomes in all other situations. No clinical practice guidelines based on research recommend these devices for patients not addressed in the policy criteria. Therefore, the use of an external insulin infusion pump or FDA-approved automated insulin delivery system (artificial pancreas device) is investigational when the policy criteria are not met.

All or part of an insulin pump or automated insulin delivery system (artificial pancreas device) may warrant replacement or upgrade when the current device is no longer able to perform its basic function and cannot be repaired or adapted adequately to meet the patient's medical needs. Therefore, a replacement or upgrade may be considered medically necessary when policy criteria are met. A replacement or upgrade is considered not medically necessary when the device is adequately functioning and can meet the patient's medical needs.

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CODES

Codes	Number	Description
CPT	None	
HCPCS	A4226	Supplies for maintenance of insulin infusion pump with dosage rate adjustment using therapeutic continuous glucose sensing, per week
	A9999	Miscellaneous DME supply or accessory, not otherwise specified
	E0784	External ambulatory infusion pump, insulin
	E0787	External ambulatory infusion pump, insulin, dosage rate adjustment using therapeutic continuous glucose sensing
	E1399	Durable medical equipment, miscellaneous
	S1034	Artificial pancreas device system (e.g., low glucose suspend [LGS] feature) including continuous glucose monitor, blood glucose device, insulin pump and computer algorithm that communicates with all of the devices
	S1035	Sensor; invasive (e.g., subcutaneous), disposable, for use with artificial pancreas device system
	S1036	Transmitter; external, for use with artificial pancreas device system
	S1037	Receiver (monitor); external, for use with artificial pancreas device system

Date of Origin: *September 2000*