# Artificial Pancreas Device Systems

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## Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Artificial Pancreas Device Systems when it is determined to be medically necessary because the criteria shown below are met.

### When Policy Topic is covered

Use of a U.S. Food and Drug Administration–approved artificial pancreas device system with a low-glucose suspend feature may be considered medically necessary in patients with type 1 diabetes who meet all of the following criteria:

- Age 16 and older
- Type 1 diabetes
- Glycated hemoglobin value between 5.8% and 10.0%
- Used insulin pump therapy for more than 6 months
- At least 2 documented nocturnal hypoglycemic events (see Considerations section) in a 2-week period.

### When Policy Topic is not covered

Use of an artificial pancreas device system is considered investigational in all other situations.

Use of hybrid closed loop insulin delivery system system (including the Food and Drug Administration–approved device for age 14 and older) as an artificial pancreas device system is considered investigational.

## Considerations

The definition of a hypoglycemic episode is not standardized. In the pivotal ASPIRE randomized controlled trial, a hypoglycemic episode was defined as a sensor glucose value of 65 mg/dL or less between 10 p.m. and 8 a.m. for more than 20 consecutive minutes in the absence of a pump interaction within 20 minutes.

## Description of Procedure or Service

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<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
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| Individuals:  
  - With type 1 diabetes | Interventions of interest are:  
  - Artificial pancreas device system | Comparators of interest are:  
  - Standard glucose monitoring plus | Relevant outcomes include:  
  - Symptoms  
  - Change in disease |
Artificial pancreas device systems link a glucose monitor to an insulin infusion pump that automatically takes action (e.g., suspends or adjusts insulin) based on the glucose monitor reading. These devices are proposed to improve glycemic control in patients with insulin-dependent diabetes, in particular control of nocturnal hypoglycemia.

For individuals who have type 1 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, 1 trial was limited by its nonstandard reporting of hypoglycemic episodes, and the other trial was no longer statistically significant when 2 outliers were excluded from analysis. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have type 1 diabetes who receive a hybrid closed-loop insulin delivery system, the evidence includes a single-arm study and a multicenter pivotal trial using a device cleared by the Food and Drug Administration and 3 crossover RCTs using a similar device approved outside the United States. Relevant outcomes are symptoms, change in disease status, morbid events, resource utilization, and treatment-related morbidity. The single-arm study analysis is part of an ongoing study; it was not designed to evaluate the impact of the device on glycemic control and did not include a comparison intervention. The pivotal trial, submitted with other materials for device approval, evaluated the safety of the device and was not designed to address efficacy. Published data are needed on the efficacy of the semiautomatic insulin adjustment feature of the new device compared with current standard care. Of the 3 crossover RCTs assessing a
related device conducted outside the United States, two found significantly better outcomes (ie, time spent in nocturnal hypoglycemia and time spent in preferred glycemic range) with the new 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). The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**

**Diabetes and Glycemic Control**

Tight glucose control in patients with diabetes has been associated with improved health outcomes. The American Diabetes Association has recommended a glycated hemoglobin level below 7% for most patients. However, hypoglycemia, 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, presence of symptoms, and whether the episode can be self-treated or requires help for recovery.

**Hypoglycemia**

Hypoglycemia affects many aspects of cognitive function, including attention, memory, and psychomotor and spatial ability. Severe hypoglycemia can cause serious morbidity affecting the central nervous system (eg, coma, seizure, transient ischemic attack, stroke), heart (eg, cardiac arrhythmia, myocardial ischemia, infarction), eye (eg, vitreous hemorrhage, worsening of retinopathy), as well as cause hypothermia and accidents that may lead to injury. Fear of hypoglycemia symptoms can also cause decreased motivation to adhere strictly to intensive insulin treatment regimens.

The definition of a hypoglycemic episode is not standardized. In the pivotal Automation to Simulate Pancreatic Insulin Response randomized controlled trial, a hypoglycemic episode was defined as a sensor glucose value of 65 mg/dL or less between 10 pm and 8 am for more than 20 consecutive minutes in the absence of a pump interaction within 20 minutes. In 2017, the American Diabetes Association provided definitions; serious, clinically significant hypoglycemia (glucose levels <54 mg/dL) and glucose alert value (glucose ≤70 mg/dL). These definitions were based on recommendations from the International Hypoglycaemia Study Group.¹

**Treatment**

According to the U.S. Food and Drug Administration (FDA), an artificial pancreas is a medical device that links a glucose monitor to an insulin infusion pump, and the pump automatically reduces and increases subcutaneous insulin delivery according to measured subcutaneous glucose levels using a control algorithm. Because control algorithms can vary significantly, there are a variety of artificial pancreas device systems currently under development. These systems span a wide range of designs from a low-glucose suspend (LGS) device systems to the more complex bihormonal control-to-target systems.

FDA has described 3 main categories of artificial pancreas device systems: threshold suspend device, control-to-range, and control-to-target systems. With
threshold suspend device systems, also called LGS systems, the delivery of insulin is suspended for a set time when 2 glucose levels are below a specified low level indicating hypoglycemia. With control-to-range systems, the patient sets his or her own insulin dosing within a specified range, but the artificial pancreas device system takes over if glucose levels outside that range (higher or lower). Patients using this type of system still need to check blood glucose levels and administer insulin as needed. With control-to-target systems, the device aims to maintain glucose levels near a target level (eg, 100 mg/dL). Control-to-target systems are automated and do not require user participation except to calibrate the continuous glucose monitoring system. Several device subtypes are being developed: those that deliver insulin-only, bihormonal systems, and hybrid systems.

**Regulatory Status**
In 2013, the MiniMed® 530G System (Medtronic) was approved by FDA through the premarket approval process (P120010). This system integrates an insulin pump and glucose meter and includes an LGS feature. 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 device is approved only for use in patients 16 years and older.

In 2016, the MiniMed® 630G System with SmartGuard™ (Medtronic) was approved through the premarket approval process (P150001). It is also for use in patients 16 years and older. The system is similar to the 530G but offers updates to the system components including waterproofing. The threshold suspend feature is the same as in the 530G. FDA product code: OZO.

In 2016, the MiniMed® 670G System (Medtronic), a hybrid closed-loop insulin delivery system, was approved by FDA through the premarket approval process (P160017). It consists of an insulin pump, a glucose meter, and a transmitter, linked by a proprietary algorithm and, the SmartGuard Hybrid Closed Loop. The system includes an LGS feature that suspends insulin delivery; either suspend on low or suspend before low and have an optional alarm. Additionally, the system involves semiautomatic insulin-level adjustment to preset targets. As a hybrid system; basal insulin levels are automatically adjusted, but the patient needs to administer premeal insulin boluses. The system is approved for patients with type 1 diabetes who are at least 14 years old. It is contraindicated for children under age 7 and patients who require less than a total daily insulin dose of 8 units. The 670G system is expected to be available commercially in 2017 through a priority access program, which will be offered to patients already using the Medtronic 630G system.
**Rationale**

This evidence review was created in January 2015 and has been updated regularly with searches of the MEDLINE database. The most recent literature updated review was performed through October 15, 2017. This review was initially informed by a 2013 TEC Assessment on artificial pancreas device systems. This evidence review addresses artificial pancreas devices that have been approved or cleared by the U.S. Food and Drug Administration (FDA).

Assessment of efficacy for therapeutic intervention involves a determination whether the intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition. The following is a summary of the key literature.

**Low-Glucose Suspend Devices**

The first device (MiniMed 530G) categorized by FDA as an artificial pancreas device system (subcategory: threshold suspend device system) was approved in September 2013. The system integrates a continuous glucose monitor and insulin pump and includes a low-glucose suspend (LGS) feature that can automatically and temporarily suspend insulin delivery when glucose levels fall below a prespecified level. A similar device, the Medtronic Paradigm Veo system, has been used outside of the United States and assessed in published studies.

A 2013 TEC Assessment reviewed studies that reported on the use of artificial pancreas device systems in patients with type 1 or type 2 diabetes taking insulin who were 16 years and older. It included studies that compared an artificial pancreas device system containing an LGS feature with the best alternative treatment in the above population, had at least 15 patients per arm, and reported on hypoglycemic episodes. A single trial met the inclusion criteria, and the TEC Assessment indicated that, although the trial results were generally favorable, the study was flawed and further research was needed. The TEC Assessment concluded that there was insufficient evidence to draw conclusions about the impact of an artificial pancreas device system, with an LGS feature, on health outcomes.

The single trial in the TEC Assessment was the in-home arm of the Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial, published by Bergenstal et al in 2013. 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, type 1 diabetes, and...
glycated hemoglobin (HbA\textsubscript{1c}) levels between 5.8\% and 10.0\%. In addition, patients had to have more than 6 months of experience with insulin pump therapy and at least 2 nocturnal hypoglycemic events (≤65 mg/dL) lasting more than 20 minutes during a 2-week run-in phase. The randomized intervention phase lasted 3 months. Patients in the 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 study; 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 HbA\textsubscript{1c} 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 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 and 140.0 mg/dL in the control group.

Regarding safety outcomes and adverse events, change in HbA\textsubscript{1c} level was minimal, and there was no statistically significant difference between groups. Mean HbA\textsubscript{1c} 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 4 events in the control group (range of nadir glucose sensor values in these events, 40-76 mg/dL). There were no deaths or serious device-related adverse events.

Before reporting on in-home findings, in 2012 the ASPIRE researchers (Garg et al) published data from the in-clinic arm of the study.\textsuperscript{5} This randomized crossover trial included 50 patients with type 1 diabetes who had at least 3 months of experience with an insulin pump system. After a 2-week run-in period to verify and optimize basal rates, patients underwent 2 in-clinic exercise sessions to induce hypoglycemia. The LGS feature on the insulin pump was turned on in 1 session and off in the other session, in random order. When on, the LGS feature was set to suspend insulin delivery for 2 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 3 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. The 2013 trial, by Ly et al 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 is only intended for individuals ≥16 years). The Ly trial included 95 patients with type 1 diabetes between 4 and 50 years of age (mean age, 18.6 years; >30% of sample <18 years old) who had used an insulin pump for at least 6 months. In addition, participants had to have an HbA1c level of 8.5% or less and have impaired awareness of hypoglycemia (defined as a score of at least 4 on the modified Clarke questionnaire). Patients were randomized to 6 months of in-home use of the Paradigm Veo System with automated insulin suspension when the glucose sensor reached a preset threshold of 60 mg/dL or to continued use of an insulin pump without the 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 6 months of treatment, and controlling for the baseline hypoglycemia rate, the incidence rate per 100 patient-months was 34.2 (95% confidence interval [CI], 22.0 to 53.3) in the pump-only group and 9.6 (95% CI, 5.2 to 17.4) in the 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 could be
explained in part by two outliers (children ages 9 and 10 years). When both children were excluded from the analysis, the primary outcome was no longer statistically significant. The incidence rate ratio for moderate and severe events excluding the 2 children was 1.7 (95% CI, 0.7 to 4.3). Mean HbA1c level (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.

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

Section Summary: Low-Glucose Suspend Devices
Several RCTs have evaluated the first FDA-approved artificial pancreas device, which includes an LGS feature, or a similar device used outside of the United States. Two RCTs were conducted in-home settings. 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. However, the magnitude of reduction for hypoglycemic events in this population, which was a secondary outcome, is likely to be clinically significant.

The other RCT included adults and children. Data were not stratified by age group, and when all data were included, the primary outcome (moderate and severe hypoglycemia events) was significantly decreased in a group assigned to a device with an LGS feature compared with a pump-only group. However, when 2 children with outlying data were excluded, the difference between groups was no longer statistically significant. Thus there is uncertainty whether the LGS feature improves clinical outcomes in the adult population.
HYBRID CLOSED-LOOP INSULIN DELIVERY SYSTEMS

The MiniMed 670G, which uses a combination of control-to-range and control-to-target strategies, was approved by FDA in September 2016. In 2016, Bergenstal et al published a prospective single-arm study on the safety of the system in patients with type 1 diabetes. It included 124 patients ages 14-to-75 years old who had type 1 diabetes for at least 2 years, had HbA$_1c$ levels less than 10.0%, and who had used an insulin pump for at least 6 months. There was an initial run-in period at baseline for patients to learn how to use the device followed by a 3-month period of device use. The study period included a 6-day hotel stay with a 1-day period of frequent sampling of venous blood glucose levels to verify device accuracy. The primary safety end points were the incidence of severe hypoglycemia and diabetic ketoacidosis and the incidence of device-related and serious adverse events.

There were no episodes of severe hypoglycemia or ketoacidosis during the study. A total of 28 device-related adverse events occurred, all of which could be resolved at home. There were 4 serious adverse events, 1 case each of appendicitis, bacterial arthritis, worsening rheumatoid arthritis, and Clostridium difficile diarrhea. There were also a number of predefined descriptive end points (but no statistically powered efficacy end points). The device was in closed-loop mode for a median of 97% of the study period. Mean (SD) HbA$_1c$ levels were 7.4% (0.9%) at baseline and 6.9% (0.6%) at the end of the study, and the percentage of sensor glucose values within the target range was 66.7% at baseline and 72.2% at the end of the study. This trial and a related study in children are ongoing (NCT02463097, NCT02660827; see the Ongoing and Unpublished Clinical Trials section).

A 2017 multicenter pivotal trial published by Garg et al evaluated the safety of Medtronic’s hybrid closed-loop system, using methods similar to those of Bergenstal and employing the same device (MiniMed 670G). 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, 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 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, HbA$_1c$ 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 continuous glucose monitoring, and baseline HbA$_1c$ levels were lower than average for both cohorts; both baseline characteristics potentially limit the generalizability of the results.

Previously, a device similar to the MiniMed 670G, in that both systems can control-to-range or control-to-target, was evaluated in other countries where it is called the MD-Logic artificial pancreas system. Initial studies were conducted in controlled settings (ie, children’s camp or inpatient)\textsuperscript{10,11} and, in 2014, Nimri et al published findings of an in-home randomized crossover trial with 24 patients.\textsuperscript{12} In this crossover trial, eligible patients were between the ages of 12 and 65, had type 1 diabetes diagnosed at least 1 year previously, used an insulin pump for at least 3 months, and HbA$_1c$ levels between at least 6.5% and less than 10.0%. Patients were excluded if they had a history of diabetic ketoacidosis or severe hypoglycemia within the past month. In random order, patients used the MD-Logic system for 6 weeks and standard continuous subcutaneous glucose infusion for 6 weeks, with a 5-week washout period between study arms. Before the intervention period, patients had a 1-month run-in period with the MD-Logic device. Sensor thresholds on the device were initially set to sound a 20-minute alarm at 350 mg/dL (high glucose) and 75 mg/dL (low glucose), but patients were permitted to modify or shut off these settings.

Twenty-one patients completed the study; 19 had valid data from at least 12 nights and were included in the main analyses. In the intention-to-treat analysis, the primary outcome (time spent with glucose level <70 mg/dL; was significantly lower in the MD-Logic group (median, 2.53%) than in the control group (5.16%; p=0.020). Time spent between 70 mg/dL and 140 mg/dL (a secondary outcome) was significantly higher in the closed-loop group (47.4%) than in the control group (36.26%; p=0.003). There was no statistically significant between-group difference in the time spent below 50 mg/dL, but this was low in both groups. During the study, severe hypoglycemia occurred in 1 participant in the control arm and none in the intervention arm.

Also in 2014, Nimri et al analyzed data from 15 patients at a single center participating in a multinational 2-arm crossover study.\textsuperscript{13} Study eligibility criteria included age 10 to 65 years, type 1 diabetes diagnosed at least 1 year previously, use of an insulin pump for at least 3 months, and HbA$_1c$ levels between at least 7.0% and less than 10.0%. As in the other Nimri study, patients were excluded if they had a history of diabetic ketoacidosis or severe hypoglycemia within the past month. The intervention consisted of 4 consecutive nights of home use of the MD-Logic device and an open-loop glucose monitor and insulin pump system, in random order. The primary end points were the overall time spent in nocturnal hypoglycemia (defined as glucose levels <70 mg/dL) and the percentage of nights...
when mean overnight glucose levels were between 90 mg/dL and 140 mg/dL in each patient. One of the primary outcomes (time spent <70 mg/dL) was significantly lower in the MD-Logic group (p=0.003), and there was no significant between-group difference in the other primary outcome.

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. In 2017, Forlenza et al 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 3 months treatment with a subcutaneous insulin infusion pump. The 6-week, in-home study was divided into 2-week blocks, with 2 randomized groups alternating treatment between an artificial pancreas system (DiAs web monitoring) or sensor-augmented pump therapy (Dexcom Share); subjects in both arms reported glucose values and, if applicable, sensor failure. For several primary 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 authors noted that, given the marked difference in outcomes between responders and nonresponders, an error might have occurred in setting basal rates.

Section Summary: Hybrid Closed-Loop Insulin Delivery Systems

Several studies have been published on a hybrid closed-loop insulin delivery system, but only 2 uncontrolled studies used a device approved in the United States. The single-arm study using the FDA-approved device focused on safety outcomes. There were no episodes of severe hypoglycemia, diabetic ketoacidosis during the study, and no device-related severe adverse events. The analysis was not designed to evaluate the impact of the device on glycemic control and did not include a comparison intervention; this study is ongoing. A 2017 pivotal trial of the same device likewise evaluated its safety, rather than comparing it with another intervention. Among studies on a similar device used outside of the United States, 2 crossover RCTs found significantly better outcomes (ie, more time spent in the glycemic range and less time spent <70 mg/dL) in the artificial pancreas group than in the control group. Another crossover RCT had mixed outcomes (ie, time spent <70 mg/dL) was significantly lower in the artificial pancreas device group than in the control group but no significant between-group difference in the time spent in nocturnal hypoglycemia. Two of the crossover RCTs included some patients younger than the FDA lower limit of 14 years. Published data are needed.
on the efficacy of the semiautomatic insulin adjustment feature in the new FDA-approved device, specifically studies comparing glycemic control outcomes using the new device to glycemic control with currently used systems.

**Summary of Evidence**

For individuals who have type 1 diabetes who receive an artificial pancreas device system with a low-glucose suspend feature, the evidence includes 2 RCTs conducted in-home settings. Relevant outcomes are symptoms, change in disease status, morbidity 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, 1 trial was limited by its nonstandard reporting of hypoglycemic episodes, and the other trial was no longer statistically significant when 2 outliers were excluded from analysis. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have type 1 diabetes who receive a hybrid closed-loop insulin delivery system, the evidence includes a single-arm study and a multicenter pivotal trial using a device cleared by the Food and Drug Administration and 3 crossover RCTs using a similar device approved outside the United States. Relevant outcomes are symptoms, change in disease status, morbidity events, resource utilization, and treatment-related morbidity. The single-arm study analysis is part of an ongoing study; it was not designed to evaluate the impact of the device on glycemic control and did not include a comparison intervention. The pivotal trial, submitted with other materials for device approval, evaluated the safety of the device and was not designed to address efficacy. Published data are needed on the efficacy of the semiautomatic insulin adjustment feature of the new device compared with current standard care. Of the 3 crossover RCTs assessing a related device conducted outside the United States, two found significantly better outcomes (ie, time spent in nocturnal hypoglycemia and time spent in preferred glycemic range) with the new 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). The evidence is insufficient to determine the effects of the technology on health outcomes.

**Supplemental Information**

**Clinical Input From Physician Specialty Societies and Academic Medical Centers**

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

In response to requests, input on artificial pancreas device systems was received from 2 physician specialty societies and 4 academic medical centers when the policy was under review in 2015. Input was mixed on whether artificial pancreas systems, including closed-loop monitoring devices with a low-glucose suspend threshold feature, are considered medically necessary. Most reviewers thought there are sufficient supportive data on devices with a low-glucose suspend feature in patients at high risk of hypoglycemia, but some thought the data insufficient.

**Practice Guidelines and Position Statements**

**American Diabetes Association**
In 2017, the American Diabetes Association (ADA) confirmed its previous recommendation of sensor-augmented insulin pump therapy with a low-glucose suspend feature for patients with type 1 diabetes and nocturnal hypoglycemia. Additionally, ADA referenced several trials of artificial pancreas devices, determining that “this technology may be particularly useful in insulin-treated patients with hypoglycemia unawareness and/or frequent hypoglycemic episodes.” The ADA’s 2017 standards in diabetes acknowledged that, while more long-term studies of continuous glucose monitoring are needed, the evidence indicates the safety of hybrid closed-loop systems.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Medicare National Coverage**
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02523131</td>
<td>Home Testing of Day and Night Closed Loop With Pump Suspend Feature (APCam11)</td>
<td>84</td>
<td>Oct 2017 (ongoing)</td>
</tr>
<tr>
<td>NCT02463097a</td>
<td>Hybrid Closed Loop Pivotal Trial in Type 1 Diabetes</td>
<td>127</td>
<td>May 2018</td>
</tr>
<tr>
<td>NCT02660827a</td>
<td>Safety Evaluation of the Hybrid Closed Loop (HCL) System in Pediatric Subjects With Type 1 Diabetes</td>
<td>200</td>
<td>Apr 2018</td>
</tr>
<tr>
<td>NCT02488616</td>
<td>Closed-loop Control of Glucose Levels (Artificial Pancreas) for 5 Days in Adults With Type 1 Diabetes</td>
<td>40</td>
<td>Nov 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.
References


Billing Coding/Physician Documentation Information

95250  Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; sensor placement, hook-up, calibration of monitor, patient training, removal of sensor, and printout of recording
95251  Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; interpretation and report
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
Sensor; invasive (e.g., subcutaneous), disposable, for use with artificial pancreas device system

Transmitter; external, for use with artificial pancreas device system

Receiver (monitor); external, for use with artificial pancreas device system

**ICD-10 Codes**

**E10.10- E13.9**

Diabetes mellitus code range

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

1/1/2017 New Policy. Artificial pancreas device system with low glucose suspend feature may be considered medically necessary for patients with type 1 diabetes who meet criteria; otherwise artificial pancreas device systems are considered investigational.

1/1/2018 Added Investigational statement: Use of hybrid closed loop insulin delivery system as an artificial pancreas device system is considered investigational.

1/1/2019 Investigational policy statement for use of hybrid closed loop insulin delivery system amended to “(including the Food and Drug Administration–approved device for age 14 and older)”. Added “Age 16 and older” to medically necessary statement rather than “Age consistent with the FDA Approval for the device requested”.

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