Artificial Pancreas Device Systems

Policy Number: 1.01.30  Last Review: 1/2020
Origination: 1/2017  Next Review: 1/2021

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 automated insulin delivery system (artificial pancreas device system) with a low-glucose suspend feature may be considered medically necessary in patients with type 1 diabetes who meet all of the following criteria:

- Age 14 and older
- 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.

Use of a Food and Drug Administration–approved automated insulin delivery system (artificial pancreas device system) designated as hybrid closed-loop insulin delivery system (with low glucose suspend and suspend before low features) may be considered medically necessary in patients with type 1 diabetes who meet all of the following criteria:

- Age 7 and older
- Glycated hemoglobin level between 5.8% and 10.0%
- Used insulin pump therapy for more than 6 months
- At least 2 documented nocturnal hypoglycemic events in a 2-week period.

When Policy Topic is not covered

Use of an automated insulin delivery system (artificial pancreas device system) is considered investigational for individuals who do not meet the above criteria.

Use of an automated insulin delivery system (artificial pancreas device system) not approved by the Food and Drug Administration is investigational.
# Considerations

See the Codes table for details.

## Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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  With type 1 diabetes | **Interventions of interest are:**  
  - Artificial pancreas device system with a low-glucose suspend feature | **Comparators of interest are:**  
  - Nonintegrated continuous glucose monitoring plus insulin pump  
  - Self-monitoring blood glucose and multiple dose insulin injection therapy | **Relevant outcomes include:**  
  - Symptoms  
  - Change in disease status  
  - Morbid events  
  - Resource utilization  
  - Treatment-related morbidity |

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  - Morbid events  
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  - Treatment-related morbidity |

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

The following conclusions are based on a review of the evidence, including but not limited to, published evidence and clinical expert opinion, solicited via BCBSA’s Clinical Input Process.

For individuals who have type 1 diabetes (T1D) who receive an artificial pancreas device system with a low-glucose suspend feature, the evidence includes two 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, T1D, 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 six months of insulin pump use. Both RCTs reported significantly less hypoglycemia in the treatment group than in the control group. In both trials, primary outcomes were favorable for the group using an artificial pancreas system; however, findings from 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 (area under the curve for nocturnal hypoglycemic events). The area under the curve is not used for assessment in clinical practice but the current technology does allow user and provider review of similar trend data with continuous glucose monitoring. Results from the ASPIRE study suggested that there were increased risks of hyperglycemia and potential diabetic ketoacidosis in subjects using the threshold suspend feature. This finding may be related to whether or not actions are taken by the user to assess glycemic status, etiology of the low glucose (activity, diet or medication) and to resume insulin infusion. Both retrospective and prospective observational studies have reported reductions in rates and severity of hypoglycemic episodes in automated insulin delivery system users. The evidence is sufficient that the magnitude of reduction for hypoglycemic events in the T1D population 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. Evidence reported through clinical input supports that the outcome of hypoglycemia prevention provides a clinically meaningful improvement in net health outcome, and this use is consistent with generally accepted medical practice. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have T1D who receive an artificial pancreas device system with a hybrid closed-loop insulin delivery system, the evidence includes multicenter pivotal trials using devices cleared by the Food and Drug Administration, supplemental data and analysis for expanded indications and more recent studies focused on children and adolescents. Three crossover RCTs using a similar first-generation device approved outside the United States have been reported. Relevant outcomes are symptoms, change in disease status, morbid events, resource utilization, and treatment-related morbidity. Of the three 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 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). For the U.S. regulatory registration pivotal trial, the primary outcomes were safety and not efficacy. Additional evidence from device performance studies and clinical studies all demonstrate reductions in time spent in various levels of hypoglycemia, improved time in range (70-180mg/dl), rare diabetic ketoacidosis and few device-related adverse events. The evidence is sufficient that the
magnitude of reduction for hypoglycemic events in the T1D population is likely to be clinically significant. The variations in the definition of primary and secondary outcomes in the study design and conduct of the published evidence are limitations that preclude determining the effects of the technology on net health outcomes. Evidence reported through clinical input supports that the use of hybrid closed loop APDS systems provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. Reduction in the experience of hypoglycemia and inappropriate awareness of hypoglycemia and glycemic excursions were identified as important acute clinical outcomes in children, adolescents, and adults and are related to the future risk for end-organ complications. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Background
Diabetes and Glycemic Control
Tight glucose control in patients with diabetes has been associated with improved health outcomes. The American Diabetes Association has recommended a glycated hemoglobin level below 7% for most patients. However, hypoglycemia, may place a limit on the ability to achieve tighter glycemic control. Hypoglycemic events in adults range from mild to severe based on a number of factors including the glucose nadir, the presence of symptoms, and whether the episode can be self-treated or requires help for recovery. Children and adolescents represent a population of type 1 diabetics who have challenges in controlling hyperglycemia and avoiding hypoglycemia. Hypoglycemia is the most common acute complication of type 1 diabetes (T1D).

Table 1 is a summary of selected clinical outcomes in T1D clinical management and research.

Table 1. Outcome Measures for Type 1 Diabetes

<table>
<thead>
<tr>
<th>Measure</th>
<th>Definition</th>
<th>Guideline type</th>
<th>Organization</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>Stakeholder survey, expert opinion with evidence review</td>
<td>Type 1 Diabetes Outcome Program&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2017</td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>Glucose &lt;70mg/dl but ≥ 54 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 2</td>
<td>Glucose &lt;54 mg/dl</td>
<td></td>
<td></td>
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<tr>
<td>Level 3</td>
<td>Event characterized by altered mental/physical status requiring assistance</td>
<td>Professional Practice Committee with systematic literature review</td>
<td>ADA</td>
<td>2019</td>
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<td>---</td>
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<td>---</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>Same as Type 1 Diabetes Outcome Program⁹</td>
<td></td>
<td>ADA²</td>
<td>2019</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>Glucose &lt;70 mg/dL</td>
<td>Clinical Practice Consensus</td>
<td>ISPAD³</td>
<td>2018</td>
</tr>
<tr>
<td>Clinical alert for evaluation and/or treatment</td>
<td>Glucose &lt;54 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically important or serious</td>
<td>Severe cognitive impairment requiring external assistance by another person to take corrective action</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Hyperglycemia** | Glucose >180 mg/dL and ≤250 mg/dL | Type 1 Diabetes Outcome Program¹¹ |  | 2017 |
| Level 1 |  |  |  |  |
| Level 2 | Glucose >250 mg/dL |  |  |  |

| **Time in Range**<sup>b</sup> | Percentage of glucose readings in the range of 70–180 mg/dL per unit of time | Type 1 Diabetes Outcome Program⁹ |  | 2017 |
| Diabetic ketoacidosis (DKA) | Elevated serum or urine ketones > ULN Serum bicarbonate <15 mEq/L Blood pH <7.3 | Type 1 Diabetes Outcome Program¹³ |  | 2017 |

ADA: American Diabetes Association, ISPAD: International Society for Pediatric and Adolescent Diabetes; ULN: upper limit of normal.

*Steering Committee: representatives from American Association of Clinical Endocrinologists (AACE), American Association Diabetes Educators, the American Diabetes Association (ADA), the
Treatment

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

The use of the continuous glucose monitoring (CGM) component of diabetes self-management is specifically addressed in separate policy.

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

Regulatory Status

The Food and Drug Administration (FDA) describes the basic design of an artificial pancreas device system (APDS) as a CGM linked to an insulin pump with the capability to automatically stop, reduce, or increase insulin infusion based on specified thresholds of measured interstitial glucose.

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 tries to maintain these levels at all times. This system is fully automated and requires no interaction from the user (except for calibration of the CGM). There are two subtypes of control-to-target systems: insulin-only and bihormonal (eg, 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 in order for the insulin pump to determine the bolus meal dose of insulin. A hybrid system option with the patient administration of a premeal or partial premeal insulin bolus can be used in either control-to-range or control-to-target systems.

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

Table 2 summarizes the FDA-approved automated insulin delivery systems.
Table 2. FDA-Approved Automated Insulin Delivery Systems (Artificial Pancreas Device Systems)

<table>
<thead>
<tr>
<th>Device</th>
<th>Age Indication</th>
<th>Manufacturer</th>
<th>Date Approved</th>
<th>PMA No./Device Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>MiniMed 530G System&lt;sup&gt;a&lt;/sup&gt; (open-loop, LGS)</td>
<td>≥16 y</td>
<td>Medtronic</td>
<td>Jul 2013</td>
<td>P120010/OZO</td>
</tr>
<tr>
<td>MiniMed 630G System with SmartGuard&lt;sup&gt;b&lt;/sup&gt; (open-loop, LGS)</td>
<td>≥16 y, ≥14 y</td>
<td>Medtronic</td>
<td>Aug 2016</td>
<td>P150001/OZO, P150001/S008</td>
</tr>
<tr>
<td>MiniMed 670G System&lt;sup&gt;c&lt;/sup&gt; (hybrid closed-loop, LGS or PLGM)</td>
<td>≥14 y, ≥7-13 y</td>
<td>Medtronic</td>
<td>Sep 2016</td>
<td>P160017/OZP, P160017/S031</td>
</tr>
</tbody>
</table>


<sup>a</sup> 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).

<sup>b</sup> 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).

<sup>c</sup> MiniMed 670G System consists of the following devices: MiniMed 670G Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), One-Press Serter, and the Contour NEXT Link 2.4 Glucose Meter (at time of approval).

The MiniMed® 530G System includes a threshold suspend or LGS feature.<sup>5</sup> 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.<sup>6</sup> 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.
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. 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 most recent supplemental approval for the MiniMed® 670G System in July 2018 followed the granting a designation of breakthrough device status.

On June 21, 2018, the FDA approved the t:slim X2 Insulin Pump with Basal-IQ Technology (PMA P180008) for individuals who are 6 years of age and older. 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.

**Rationale**

This evidence review was created in January 2015 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through March 25, 2019.

The following conclusions are based on a review of the evidence, including but not limited to, published evidence and clinical expert opinion, solicited via BCBSA’s Clinical Input Process.

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

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

This review was informed by a TEC Assessment (2013) on artificial pancreas device systems (APDS). This evidence review addresses artificial pancreas devices that have been approved by the U.S. Food and Drug Administration.

**Low-Glucose Suspend Devices**

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

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

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is individuals with type 1 diabetes. Persons with T1D are especially prone to develop hypoglycemia. Alterations in the counterregulatory hormonal responses inherent in the disease, variable patient adherence and iatrogenic hypoglycemia caused by aggressive prevention of hyperglycemia are responsible for this propensity. Hypoglycemia affects many aspects of cognitive function, including attention, memory, and psychomotor and spatial ability. Severe hypoglycemia can cause serious morbidity affecting the central nervous system (eg, coma, seizure, transient ischemic attack, stroke), heart (eg, cardiac arrhythmia, myocardial ischemia, infarction), eye (eg, vitreous hemorrhage, worsening of retinopathy), as well as cause hypothermia and accidents that may lead to injury. Fear of hypoglycemia symptoms can also cause decreased motivation to adhere strictly to intensive insulin treatment regimens.
Interventions
The therapy being considered is an APDS that integrates a continuous glucose monitor and insulin pump and includes an LGS feature that can automatically and temporarily suspend insulin delivery when glucose levels fall below a prespecified level. The device alarms and the user must take an action to assess glycemic level and resume insulin infusion.

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

Outcomes
The general outcomes of interest are glycated hemoglobin (HbA1c) levels, time in range or target of glucose levels, and rates of hypoglycemia and hyperglycemia. Other outcomes of interest include quality of life and changes in health care utilization (eg, hospitalizations).

Timing
APDS are used by persons with type 1 diabetes when they have experienced hypoglycemic and/or hyperglycemic episodes that cannot be managed with intermittent self-monitoring of glucose and self-administration of insulin. Assessment of effect on the outcomes of interest can be made in 3-6 months. Duration of follow-up is life-long.

Setting
APDS are used by persons with type 1 diabetes in “free living” and home settings, with monitoring by primary care clinicians, diabetologists, and endocrinologists.

Systematic Reviews
A TEC Assessment (2013) reviewed studies that reported on the use of APDSs in patients with type 1 or type 2 diabetes taking insulin who were 16 years and older. It included studies that compared an APDS 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. Reviewers concluded that there was insufficient evidence to draw conclusions about the impact of an APDS, with an LGS feature, on health outcomes.

Randomized Controlled Trials
The single trial assessed in the TEC Assessment was the in-home arm of the Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial, reported by Bergenstal et al (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 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 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 HbA\textsubscript{1c} levels.

The primary endpoint, 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, the ASPIRE researchers (Garg et al [2012]) published data from the in-clinic arm of the study.\textsuperscript{10} 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 trial by Ly et al (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 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 trialists conducted a sensitivity analysis in patients younger than 12 years (15 patients in each treatment group). The high baseline hypoglycemia rates could be
explained in part by 2 outliers (children ages 9 and 10 years). When both children were excluded from the analysis, the primary outcome was no longer statistically significant. The incidence rate ratio for moderate and severe events excluding the 2 children was 1.7 (95% CI, 0.7 to 4.3). Mean \( \text{HbA}_{1c} \) levels (a secondary outcome) did not differ between groups at baseline or at 6 months. Change in \( \text{HbA}_{1c} \) levels during the treatment period was -0.06% (95% CI, -0.2% to 0.09%) in the pump-only group and -0.1% (95% CI, -0.3% to 0.03%) in the LGS group; the difference between groups was not statistically significant.

**Retrospective Studies**
Agrawal et al (2015) retrospectively analyzed use of the threshold suspend feature associated with the Paradigm Veo System in 20,973 patients, most of whom were treated outside of the United States.\(^{12}\) 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 14673 (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.

**Prospective Observational Studies**
Gómez et al (2017) published the results of a cohort of 111 type 1 diabetic individuals with documented hypoglycemia and hypoglycemia unawareness who received a sensor-augmented insulin pump with LGS therapy.\(^{13}\) 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). \( \text{HbA}_{1c} \) levels were reduced from a baseline value of 8.8% (SD=1.9%) to 7.5% (SD=1.0%) at 5 months (mean difference, -1.3%; 95% CI, -1.09% to -1.50%; p<0.001) and 7.1% (SD=0.8%; mean difference, -1.7%; 95% CI, -1.59% to -1.90%; p<0.001). At baseline, 80% of subjects had had at least 1 episode of hypoglycemic awareness compared with 10.8% at last follow-up (p<0.001). Episodes of severe hypoglycemia decreased from 66.6% to 2.7% (p<0.001).

**Section Summary: LGS Devices**
For individuals who have type 1 diabetes (T1D) who receive an artificial pancreas device system with a low-glucose suspend feature, the evidence
includes two 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, T1D, 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 six months of insulin pump use. Both RCTs reported significantly less hypoglycemia in the treatment group than in the control group. In both trials, primary outcomes were favorable for the group using an artificial pancreas system; however, findings from 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 (area under the curve for nocturnal hypoglycemic events). The area under the curve is not used for assessment in clinical practice but the current technology does allow user and provider review of similar trend data with continuous glucose monitoring.

Results from the ASPIRE study suggested that there were increased risks of hyperglycemia and potential diabetic ketoacidosis in subjects using the threshold suspend feature. This finding may be related to whether or not actions are taken by the user to assess glycemic status, etiology of the low glucose (activity, diet or medication) and to resume insulin infusion.

Both retrospective and prospective observational studies have reported reductions in rates and severity of hypoglycemic episodes in automated insulin delivery system users. The evidence is sufficient that the magnitude of reduction for hypoglycemic events in the T1D population 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.

Evidence reported through clinical input supports that the outcome of hypoglycemia prevention provides a clinically meaningful improvement in net health outcome, and this use is consistent with generally accepted medical practice. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Patient selection criteria considering FDA label and inclusion criteria in the evidence include: age 14 and older; glycated hemoglobin level between 5.8% and 10.0%; used insulin pump therapy for more than 6 months; and at least 2 documented nocturnal hypoglycemic events in a 2-week period.

**HYBRID CLOSED-LOOP INSULIN DELIVERY SYSTEMS**
Clinical Context and Therapy Purpose
The purpose of a hybrid closed-loop insulin delivery system in patients who have type 1 diabetes is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of a hybrid closed-loop insulin delivery system improve the net health outcome for individuals with type 1 diabetes?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with type 1 diabetes. Persons with T1D are especially prone to develop hypoglycemia. Alterations in the counterregulatory hormonal responses inherent in the disease, variable patient adherence and iatrogenic hypoglycemia caused by aggressive prevention of hyperglycemia are responsible for this propensity. Hypoglycemia affects many aspects of cognitive function, including attention, memory, and psychomotor and spatial ability. Severe hypoglycemia can cause serious morbidity affecting the central nervous system (eg, coma, seizure, transient ischemic attack, stroke), heart (eg, cardiac arrhythmia, myocardial ischemia, infarction), eye (eg, vitreous hemorrhage, worsening of retinopathy), as well as cause hypothermia and accidents that may lead to injury. Fear of hypoglycemia symptoms can also cause decreased motivation to adhere strictly to intensive insulin treatment regimens.

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

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

Outcomes
The general outcomes of interest are HbA1c levels, time in range or target of glucose levels, and rates of hypoglycemia and hyperglycemia. Other outcomes of interest include quality of life and changes in health care utilization (eg, hospitalizations).

Timing
APDS are used by persons with Type1 diabetes when they have experienced hypoglycemic and/or hyperglycemic episodes that cannot be managed with intermittent self-monitoring of glucose and self-administration of insulin.
Assessment of effect on the outcomes of interest can be made in 3-6 months. Duration of follow-up is life-long.

**Setting**

APDS are used by persons with type 1 diabetes in “free living” and home settings, with monitoring by primary care clinicians, diabetologists, and endocrinologists.

**Prospective Studies**

Bergenstal et al (2016) published a prospective single-arm study on the safety of the hybrid closed-loop system in patients with type 1 diabetes.\(^1\) 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 the closed-loop mode for a median of 97% of the study period. Mean (SD) HbA\(_1c\) levels were 7.4% (0.9%) at baseline and 6.9% (0.6%) at the end of the study, and the percentage of sensor glucose values within the target range was 66.7% at baseline and 72.2% at the end of the study. A related study in children is ongoing (NCT02660827).

A multicenter pivotal trial published by Garg et al (2017) evaluated the safety of Medtronic’s hybrid closed-loop system, using methods similar to those of Bergenstal et al (2016), (NCT02463097) and employing the same device (MiniMed 670G).\(^1\) Of 129 subjects, 124 completed the trial; 30 were adolescents (age range, 14-21 years) and 94 were adults (age range, 22-75 years), all of whom had type 1 diabetes for at least 2 years before the study, and used insulin pump therapy for 6 months or more. As with Bergenstal et al (2016), a 3-month study period was preceded by a run-in period for subjects to be more familiar with the equipment, and the sensor glucose values were confirmed by an extended hotel stay (6-day/5-night with daily exercise). In both the adolescent and adult cohorts, the trial found improvements during the study phase over the run-in phase, with an increased percentage of glucose values in the favorable range (for adults, a mean improvement of 68.8% to 73.8%; for adolescents, a mean improvement of 60.4% to 67.2%; p<0.001 for both cohorts). Similarly, the authors reported a decrease in the percentage of values outside of the target range (<70 mg/dL or >180 mg/dL): for adults, time spent below the target range decreased from 6.4% to 3.4% (p<0.001); time above the range decreased from 24.9% to 22.8%
For both cohorts, HbA1c levels showed a significant reduction between baseline and the end of the study: for adults, the mean decreased from 7.3% to 6.8% (p<0.001), while for adolescents, the mean decreased from 7.7% to 7.1% (p<0.001). Secondary outcomes, which included a reduction of nocturnal hyperglycemia and hypoglycemia, increase in mean overall body weight, and a reduction of basal insulin, were favorable for the study phase, compared with the run-in phase; measurements from the hotel stay verified the in-home glucose values. However, there were several limitations in the trial, including its nonrandomized design, the exclusion of individuals who had recently experienced diabetic ketoacidosis or severe hypoglycemia, and the interaction between subjects and site personnel. Additionally, most of the adult cohort were already using 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 et al (2017) published a randomized controlled crossover trial comparing the efficacy of a zone model predictive control algorithm with that of sensor-augmented pump therapy; 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 six-week, in-home study was divided into 2-week blocks, with 2 randomized groups alternating treatment between an artificial pancreas system (DiAs web monitoring) or sensor-augmented pump therapy (Dexcom Share); subjects in both arms reported glucose values and, if applicable, sensor failure. For several primary endpoints, which included percentage of time in the target glucose range (70-180 mg/dL) and reduction in hypoglycemia (<70 mg/dL), the algorithm-controlled artificial pancreas system was found to be superior to the sensor-augmented pump therapy (71.6 vs 65.2%, p=0.008; 1.3 vs 2%, p= 0.001, respectively); however, while the mean glucose value was lower in the artificial pancreas system than in the control group, the difference between them was not significant (p=0.059). Measurements of nocturnal hypoglycemia were consistent with day-to-day findings. For the secondary endpoint (safety of both systems after extended wear), the study found that the mean glucose did not change between the first and seventh day of wear. A limitation of the trial was its use of remote monitoring of subjects; also, the trialists noted that, given the marked difference in outcomes between responders and nonresponders, an error might have occurred in setting basal rates.

The remainder of the review is focused on additional studies that recently evaluated hybrid closed-loop (HCL) systems in children and adolescents with T1D. These studies are summarized in Tables 3 and 4.

The RCT by Tauschman, et al (2018) evaluated individuals with uncontrolled T1D as reflected in mean Hb1c >8 %. 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 a decrease in time spent with glucose <70mg/dl.

Abraham et al (2018) reported the results of a 6-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. At 6 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 6 months in either group.

Forlenza et al (2019) reported the data and analysis of the supplemental information filed with the FDA to support the expanded indication for the MiniMed 670G system to children 7-13 years of age. The nonrandomized, single-arm multicenter study reported the day and night use of the automated insulin delivery and PLGM for 3 months in the home setting. There were no serious adverse events and use of the system was associated with reduction in HbA1c and increased time in target glucose range.

Wood et al (2018) reported an in-clinic evaluation of a 7-13-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. The suspend before low prevention capability was confirmed in 97.5% of patients experiencing a sensor glucose of ≤ 55mg/dl.

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

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

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Intervention Study Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N Age Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Country(s)</td>
<td>Duration</td>
<td>Start/End</td>
<td>Deviations</td>
<td>Intervention Description</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------</td>
<td>----------</td>
<td>-----------</td>
<td>------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Tauschman (2018)</td>
<td>UK, US</td>
<td>6</td>
<td>05/12/2016-11/17/2017</td>
<td>86 years [6-12 years; n=23] [13-21 years; n=19]</td>
<td>SAPT with PLGM (n=46) Screening</td>
</tr>
<tr>
<td>Abraham (2018)</td>
<td>Australia</td>
<td>5</td>
<td>8/2014-NR</td>
<td>154 years 8-20 years 13.2 (2.8)</td>
<td>SAPT with PLGM (n=80)</td>
</tr>
<tr>
<td>Forlenza (2019)</td>
<td>US, Israel</td>
<td>9</td>
<td>4/18/2016-10/09/2017</td>
<td>105 years 7-13 years 10.8 (1.8)</td>
<td>SAPT with PLGM (n=80)</td>
</tr>
<tr>
<td>Wood (2018)</td>
<td>US, Israel</td>
<td>9</td>
<td>4/18/2016-10/09/2017</td>
<td>105 years 7-13 years 10.8 (1.8)</td>
<td>SAPT with PLGM (n=74)</td>
</tr>
<tr>
<td>Messer (2018)</td>
<td>US</td>
<td>3</td>
<td>2015-2018</td>
<td>31 years 14-26 17.8 (3.9)</td>
<td>SAPT with PLGM (n=74)</td>
</tr>
</tbody>
</table>

HCL: hybrid closed loop; FDA: Food and Drug Administration; PLGM: predictive low glucose suspend (suspend before low); PMA: premarket approval; RCT: randomized controlled trial; SAPT: sensor-augmented pump therapy; SD: standard deviation; NR: not reported; T1D: type 1 diabetes.

1 Data as submitted for FDA PMA Supplement P160017/S031.
2 MiniMed 640G is hybrid closed loop device approved for use outside of US.
3 MiniMed 670G is hybrid closed loop device approved for use in US.
Activity/exercise induced hypoglycemia protocol (walking, biking, playing Wii games, or other aerobic activities) intended to activate the “suspend before low” feature followed by evaluation up to 6 hours and at least 4 hours after insulin resumption.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Outcome</th>
<th>Secondary Outcome</th>
<th>Safety Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tauschman (2018)</strong></td>
<td>Group difference in time proportion in target glucose range (70-180mg/dL) at 12 weeks Mean (SD)</td>
<td>HbA1c % (SD) At 12 weeks 7.4 (0.6)</td>
<td>Hypoglycemia A. &lt;63mg/dl B. &lt;50mg/dl Percent time in given range (SD)</td>
</tr>
<tr>
<td>SAPT with PLGM</td>
<td>68% (8)</td>
<td>10.8 [8.2, 13.5] &lt;0.0001</td>
<td>-0.83 [-1.4, -0.16] 0.0130</td>
</tr>
<tr>
<td>SAPT alone</td>
<td>54% (9)</td>
<td></td>
<td>2.0 (0.9, 3.0)</td>
</tr>
<tr>
<td>Difference [95% CI] P</td>
<td>10.8 [8.2, 13.5] &lt;0.0001</td>
<td>-0.36 [-0.53, -0.19] &lt;0.0001</td>
<td>B. 0.3 (0.2, 0.6) 0.5 (0.2, 0.9)</td>
</tr>
<tr>
<td>SAPT with PLGM</td>
<td></td>
<td></td>
<td>-0.09 [-0.24, 0.01] 0.08</td>
</tr>
<tr>
<td>SAPT alone</td>
<td></td>
<td></td>
<td>B. 0.3 (0.2, 0.6) 0.5 (0.2, 0.9)</td>
</tr>
<tr>
<td>Study</td>
<td>Effect</td>
<td>HbA1c Mean % (SD)</td>
<td>Change in average percent time in hypoglycemia (SG &lt;63 mg/dl) at 6 months</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Abraham (2018)</strong>&lt;sup&gt;18&lt;/sup&gt;</td>
<td>SAPT with PLGM</td>
<td>n=76 2.8% Δ 1.4%</td>
<td>n=76 1.3% Δ 0.6%</td>
</tr>
<tr>
<td></td>
<td>SAPT alone</td>
<td>n=70 3% Δ 2.6%</td>
<td>n=70 1.4% Δ 1.2%</td>
</tr>
<tr>
<td></td>
<td>Difference in LS means [95% CI]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Forlenza (2019)</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Baseline Run-in phase (n=106)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-month study phase (n=105)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline Run-in phase (n=106)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>3-month study phase (n=105)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Run-in phase (n=106)</td>
<td>3-month study phase (n=105)</td>
<td>p</td>
<td>B. ≤54 mg/dl</td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.3 (1.5)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>0.8 (0.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Wood** (2018)¹ (NCT0266087)²⁰.

<table>
<thead>
<tr>
<th>Reference range³</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤55 mg/dl</td>
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<tr>
<td>≤60 mg/dl</td>
</tr>
<tr>
<td>≤65 mg/dl</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rate of “Suspend before Low” (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>77 (97.5)</td>
</tr>
<tr>
<td>71 (89.9)</td>
</tr>
<tr>
<td>63 (79.7)</td>
</tr>
</tbody>
</table>

**Messer** (2018)¹ (NCT02463097)²¹.

<table>
<thead>
<tr>
<th>Days 1-7</th>
<th>Days 22-28</th>
<th>Days 50-56</th>
<th>Days 78-84</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean percentage time in range (70-180 mg/dl) using HCL mode⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean % (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>69.7 (10.6)</td>
<td>69.5 (8.5)</td>
<td>71.9 (8.1)</td>
<td>71.5 (10.3)</td>
</tr>
</tbody>
</table>

CI: confidence interval; HCL: hybrid closed loop; IAH: impaired awareness of hypoglycemia; LS: least squares; PLGM: predictive low glucose suspend (suspend before low); SD: standard deviation; SAPT: sensor-augmented pump therapy; SG: sensor glucose; ∆: delta meaning change in status; T1D: type 1 diabetes.

¹ Data as submitted for FDA PMA Supplement P160017/S031.
² Clarke score: uses 8 questions to characterize an individual’s exposure to episodes of moderate and severe hypoglycemia to assess the glycemic threshold for and symptomatic response to hypoglycemia. A value ≥ 4 indicates IAH.
³ Simultaneous testing with either intravenous sampling or self-monitoring blood glucometer.
Open loop manual mode was used in a run-in phase to develop personalized parameters for HCL/Auto Mode phase.

**Section Summary: Hybrid Closed-Loop Insulin Delivery Systems**

For individuals who have T1D who receive an artificial pancreas device system with a hybrid closed-loop insulin delivery system, the evidence includes multicenter pivotal trials using devices cleared by the Food and Drug Administration, supplemental data and analysis for expanded indications and more recent studies focused on children and adolescents. Three crossover RCTs using a similar first-generation device approved outside the United States have been reported. Relevant outcomes are symptoms, change in disease status, morbid events, resource utilization, and treatment-related morbidity. Of the three 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 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). For the U.S. regulatory registration pivotal trial, the primary outcomes were safety and not efficacy. Additional evidence from device performance studies and clinical studies all demonstrate reductions in time spent in various levels of hypoglycemia, improved time in range (70-180mg/dl), rare diabetic ketoacidosis and few device-related adverse events. The evidence is sufficient that the magnitude of reduction for hypoglycemic events in the T1D population is likely to be clinically significant. The variations in the definition of primary and secondary outcomes in the study design and conduct of the published evidence are limitations that preclude determining the effects of the technology on net health outcomes. Evidence reported through clinical input supports that the use of hybrid closed loop APDS systems provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. Reduction in the experience of hypoglycemia and inappropriate awareness of hypoglycemia and glycemic excursions were identified as important acute clinical outcomes in children, adolescents, and adults and are related to the future risk for end-organ complications. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Patient selection criteria considering the FDA label and inclusion criteria in the evidence include: age seven and older; glycated hemoglobin level between 5.8% and 10.0%; used insulin pump therapy for more than six months, and at least two documented nocturnal hypoglycemic events in a two-week period.

**Summary of Evidence**

The following conclusions are based on a review of the evidence, including but not limited to, published evidence and clinical expert opinion, solicited via BCBSA’s Clinical Input Process.

For individuals who have type 1 diabetes (T1D) who receive an artificial pancreas device system with a low-glucose suspend feature, the evidence includes two 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, T1D, 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 six months of insulin pump use. Both RCTs reported significantly less hypoglycemia in the treatment group than in the control group. In both trials, primary outcomes were favorable for the group using an artificial pancreas system; however, findings from 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 (area under the curve for nocturnal hypoglycemic events). The area under the curve is not used for assessment in clinical practice but the current technology does allow user and provider review of similar trend data with continuous glucose monitoring. Results from the ASPIRE study suggested that there were increased risks of hyperglycemia and potential diabetic ketoacidosis in subjects using the threshold suspend feature. This finding may be related to whether or not actions are taken by the user to assess glycemic status, etiology of the low glucose (activity, diet or medication) and to resume insulin infusion. Both retrospective and prospective observational studies have reported reductions in rates and severity of hypoglycemic episodes in automated insulin delivery system users. The evidence is sufficient that the magnitude of reduction for hypoglycemic events in the T1D population 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. Evidence reported through clinical input supports that the outcome of hypoglycemia prevention provides a clinically meaningful improvement in net health outcome, and this use is consistent with generally accepted medical practice. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have T1D who receive an artificial pancreas device system with a hybrid closed-loop insulin delivery system, the evidence includes multicenter pivotal trials using devices cleared by the Food and Drug Administration, supplemental data and analysis for expanded indications and more recent studies focused on children and adolescents. Three crossover RCTs using a similar first-generation device approved outside the United States have been reported. Relevant outcomes are symptoms, change in disease status, morbid events, resource utilization, and treatment-related morbidity. Of the three 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 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). For the U.S. regulatory registration pivotal trial, the primary outcomes were safety and not efficacy. Additional evidence from device performance studies
and clinical studies all demonstrate reductions in time spent in various levels of hypoglycemia, improved time in range (70-180mg/dl), rare diabetic ketoacidosis and few device-related adverse events. The evidence is sufficient that the magnitude of reduction for hypoglycemic events in the T1D population is likely to be clinically significant. The variations in the definition of primary and secondary outcomes in the study design and conduct of the published evidence are limitations that preclude determining the effects of the technology on net health outcomes. Evidence reported through clinical input supports that the use of hybrid closed loop APDS systems provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. Reduction in the experience of hypoglycemia and inappropriate awareness of hypoglycemia and glycemic excursions were identified as important acute clinical outcomes in children, adolescents, and adults and are related to the future risk for end-organ complications. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**CLINICAL INPUT**

**Objective**
In 2019, clinical input was sought to help determine whether the use of an artificial pancreas device system with a hybrid closed-loop insulin delivery system for individuals with type 1 diabetes would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice.

**Respondents**
Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- Chaitanya Mamillapalli, MD, MRCP, FAPCR, Endocrinology, Springfield Clinic, identified by American Association of Clinical Endocrinologists (AACE)
- Javier Morales, MD, FACP, FACE, Diabetology, Advanced Internal Medicine Group, PC, identified by American Association of Clinical Endocrinologists (AACE)
- Vijay Shivaswamy, MBBS, Endocrinology, The University of Nebraska Medical Center and Omaha VA Medical Center, identified by American Association of Clinical Endocrinologists (AACE)
- Anonymous, MD, Pediatric Endocrine, identified by the American Academy of Pediatrics (AAP)**

* Indicates that no response was provided regarding conflicts of interest related to the topic where clinical input is being sought.

** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated
by a specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide a review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a specialty society and/or physician member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA or any Blue Plan.

**Clinical Input Responses**

### Clinical Indication

<table>
<thead>
<tr>
<th>Clinical Indication</th>
<th>Respondent</th>
<th>Identified by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals with type 1 diabetes who are treated with an artificial pancreas device system with a hybrid closed-loop insulin delivery system</td>
<td>Dr. Mamidipallal</td>
<td>AACE</td>
</tr>
<tr>
<td></td>
<td>Dr. Morales</td>
<td>AACE</td>
</tr>
<tr>
<td></td>
<td>Dr. Shivashwary</td>
<td>AACE</td>
</tr>
<tr>
<td></td>
<td>Anonymous††</td>
<td>AAP</td>
</tr>
</tbody>
</table>

* Indicates that no response was provided regarding conflicts of interest related to the topic where clinical input is being sought.

** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

### Additional comments:

- “Part of the challenges managing diabetics with full physiologic replacement, such as those with type 1 diabetes, includes trying to manage glycemic excursions and minimizing significant hypoglycemia from occurring. From a physiologic standpoint, in patients who have experienced hypoglycemia, hygolycemia unawareness continues to exist further propagating additional hypoglycemic events. Such events could lead to sudden catastrophe and cardiac death on the basis of electrolyte shifts that have been noted in several different studies. In addition, glycemic swings could also account for microvascular complications and progression of the such.” (Dr. Morales, identified by AACE)

See Appendix for additional responses.

**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.

**2019**
In response to requests, while this topic was under review in 2019, clinical input on the use of an artificial pancreas device system with a hybrid closed-loop insulin delivery system for individuals with type 1 diabetes was received from 4 respondents, including 4 physician-level responses identified through 2 specialty societies including physicians with academic medical center affiliations. Evidence from clinical input is integrated within the Rationale section summaries and the Summary of Evidence.

**2015**
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**
The American Diabetes Association has released multiple publications on controlling type 1 diabetes (see Table 5).

**Table 5. Recommendations on Diabetes**

<table>
<thead>
<tr>
<th>Date</th>
<th>Title</th>
<th>Publication Type</th>
<th>Recommendation</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>Type 1 Diabetes in Children and Adolescents</td>
<td>Position statement</td>
<td>Automated insulin delivery systems appear to improve glycemic control and reduce hypoglycemia in children and should be considered in pediatric patients with type 1 diabetes</td>
<td>B</td>
</tr>
<tr>
<td>2019</td>
<td>Standards of Medical Care in Diabetes</td>
<td>Guideline standard</td>
<td>Automated insulin delivery systems improve glycemic control and reduce hypoglycemia in adolescents and should be considered in adolescents with type 1 diabetes</td>
<td>B</td>
</tr>
<tr>
<td>2017</td>
<td>Standardizing Clinically Meaningful Outcome</td>
<td>Consensus report</td>
<td>Developed definitions for hypoglycemia, hyperglycemia, time in range, and diabetic ketoacidosis in type 1 diabetes</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Measures Beyond HbA1c for Type 1 Diabetes

LOE: Level of Evidence.

* Jointly published with American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange.

**American Association of Clinical Endocrinologists et al**
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. The statement emphasized the use of continuous glucose monitoring and insulin pump therapy for type 1 diabetes patients who are not in glycemic target ranges despite intensive attempts at self-blood glucose monitoring and multiple insulin injection therapy.

**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 6.

**Table 6. 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>Unpublished</td>
<td></td>
<td></td>
<td></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>0</td>
<td>Nov 2018 (withdrawn)</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>Mar 2018 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.
REFERENCES


Billing Coding/Physician Documentation Information

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>95250</td>
<td>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</td>
</tr>
<tr>
<td>95251</td>
<td>Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; interpretation and report</td>
</tr>
<tr>
<td>S1034</td>
<td>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</td>
</tr>
<tr>
<td>S1035</td>
<td>Sensor; invasive (e.g., subcutaneous), disposable, for use with artificial pancreas device system</td>
</tr>
<tr>
<td>S1036</td>
<td>Transmitter; external, for use with artificial pancreas device system</td>
</tr>
<tr>
<td>S1037</td>
<td>Receiver (monitor); external, for use with artificial pancreas device system</td>
</tr>
</tbody>
</table>

ICD-10 Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E10.10-</td>
<td>Diabetes mellitus code range</td>
</tr>
<tr>
<td>E13.9</td>
<td></td>
</tr>
</tbody>
</table>

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”.

1/1/2020  Investigational policy statement for use of hybrid closed loop insulin delivery system removed. Policy statements changed: The age criterion changed in the first medically necessary statement; medically necessary statement added on FDA-approved automated insulin delivery system (artificial pancreas device system) designated as hybrid closed loop insulin delivery system in patients with type 1 diabetes who meet specified criteria; and investigational statement added on use of an automated insulin delivery system (artificial pancreas device system) for individuals who have not met specified criteria.

### Appendix: Clinical Input

#### Respondent Profile

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Degree</th>
<th>Institutional Affiliation</th>
<th>Clinical Specialty</th>
<th>Board Certification and Fellowship Training</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chaitanya Mamillapalli</td>
<td>MD, MRCP, FAPCR</td>
<td>Springfield Clinic</td>
<td>Endocrinology</td>
<td>Board certified in Internal medicine and Endocrinology</td>
</tr>
<tr>
<td>2</td>
<td>Javier Morales</td>
<td>MD, FACP, FACE</td>
<td>Advanced Internal Medicine Group, P</td>
<td>Diabetology</td>
<td>Internal Medicine</td>
</tr>
<tr>
<td>3</td>
<td>Vijay Shivaswamy</td>
<td>MBBS</td>
<td>The University of Nebraska Medical Center and</td>
<td>Endocrinology</td>
<td>Endocrinology</td>
</tr>
</tbody>
</table>

Identified by American Association of Clinical Endocrinologists (AACE)
<table>
<thead>
<tr>
<th>#</th>
<th>YES/NO</th>
<th>Explanation</th>
<th>YES/NO</th>
<th>Explanation</th>
<th>YES/NO</th>
<th>Explanation</th>
<th>YES/NO</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
<td>No</td>
<td>I have served as consultant for Eli Lilly, Novo Nordisk-2 companies producing insulin, as well as GLP-1 receptor agonists and other diabetes-related products however, I do not serve as a consultant for insulin pump companies</td>
</tr>
</tbody>
</table>
### Clinical Input Responses

**Objective**
Clinical input is sought to help determine whether the use of an artificial pancreas device system with a hybrid closed-loop insulin delivery system for individuals with type 1 diabetes would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice.

The following PICO applies to this indication.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Individuals: With type 1 diabetes | Interventions of interest are:  
· Artificial pancreas device system with a hybrid closed-loop insulin delivery system | Comparators of interest are:  
· Artificial pancreas device system with low-glucose suspend feature | Relevant outcomes include:  
· Symptoms  
· Change in disease status  
· Morbid events |
Responses
1. We are seeking your opinion on whether using the interventions for the above indication provide a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience. Please address these points in your response:

- Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
- Specific outcomes that are clinically meaningful;
- Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication; and
- Supporting evidence from the authoritative scientific literature (please include PMID).

<table>
<thead>
<tr>
<th>#</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Relevant clinical scenarios where closed loop system can be useful:</td>
</tr>
<tr>
<td></td>
<td>T1 Diabetes patients:</td>
</tr>
<tr>
<td></td>
<td>• Long duration of diabetes</td>
</tr>
<tr>
<td></td>
<td>• Frequent hypoglycemia episodes</td>
</tr>
<tr>
<td></td>
<td>• Severe hypoglycemia episodes</td>
</tr>
<tr>
<td></td>
<td>• Significant variability in Glucose levels</td>
</tr>
<tr>
<td></td>
<td>• Patient who are willing to check blood glucose levels 4 times/day.</td>
</tr>
<tr>
<td></td>
<td>• Patient should be able to count carbohydrates</td>
</tr>
<tr>
<td></td>
<td>• History of severe hypoglycemia episodes</td>
</tr>
<tr>
<td></td>
<td>• T1 diabetes patients who spend significant amount of driving</td>
</tr>
<tr>
<td></td>
<td>• T1 Diabetes patients with commercial vehicle driving license</td>
</tr>
<tr>
<td></td>
<td>• T1 Diabetes patients working with heavy machinery</td>
</tr>
<tr>
<td></td>
<td>• T1 Diabetes patients within certain jobs (Police, military, athletes)</td>
</tr>
</tbody>
</table>

Specific outcomes that are clinically meaningful:

Improvement in average blood glucose levels.
Increase in the time spent in the euglycemic range.
Reduction in the number and duration of hypoglycemia episodes.
Use Predictive low glucose suspend system (PLGS) insulin delivery system which is a part of closed loop system has been shown to reduce the episodes of hypoglycemia significantly.

- PLGS reduced prolonged hypoglycemia (< 60 mg/dl, >120 minutes) episodes by 80%

- About 81% of the low suspend events, did not have low glucose values less than 51% (Choudhary P, Olsen BS, Conget I, Welsh JB, Vorrink L, Shin JJ. Hypoglycemia Prevention and User Acceptance of an Insulin Pump System with Predictive Low Glucose Management. Diabetes Technol Ther. 2016;18(5):288-
NOT SUITABLE FOR THE FOLLOWING GROUPS OF PATIENTS

• Target blood glucose is fixed in Automode to 120, and 670 G pump may not be suitable in patients who have are being targeted for much tighter control
• Pregnant patients who require much tighter glucose control
• Patients who cannot carbohydrate account
• Patients who have acute illness and have fluctuating insulin dosing requirements
• Patients who are on tapering dose of steroids regimen
• Patients who are noncompliant and have psychiatric issues

SUPPORTING EVIDENCE FROM THE AUTHORITATIVE SCIENTIFIC LITERATURE

Clinical studies demonstrate safety and glycemic benefit, but more data is required to determine long-term clinical effectiveness and will require improvements in performance and accuracy of the systems to be more widely adopted.


Bekiari performed a systemic review of 40 studies of both single hormone and dual hormone artificial pancreatic system.

• Use of artificial pancreas is associated with additional 140 minutes/day in near normoglycemia compared with control treatment
• Results were consistent across various settings and living conditions without remote monitoring
• There was a HbA1c reduction of about 0.3% noted in clinical trials with eight weeks intervention


Tauschmann M et al conducted an open-label single-period, parallel randomized controlled trial, in from 4 clinics in UK and 2 clinics in USA.

• 114 individuals were screened, and 86 eligible patients were randomly assigned to receive hybrid closed-loop therapy (n=46) or sensor-augmented pump therapy (n=40; control group) (with no low suspend feature)
• In the Artificial pancreas group, HbA1c improved from 8.3% (SD 0.6) to 8.0% (SD 0.6) after the 4-week run-in, and to 7.4% (SD 0.6) after the 12-week intervention period.
• In the control group, the HbA1c values were 8.2% (SD 0.5) at screening, 7.8% (SD 0.6) after run-in, and 7.7% (SD 0.5) after intervention; reductions in HbA1c percentages were significantly greater in the artificial pancreas group compared with the control group (mean difference in change 0.36%, 95% CI 0.19 to 0.53; p<0.0001)


• In the real-world experience of 26 T1 diabetes patients on 670G average sensor glucose readings dropped from a mean 169.46 mg/dL at baseline to 157.08 mg/dL at the end of the 3-month study period (P =.05).
• Also, the time spent with blood glucose levels greater than 180 mg/dL fell from 26.5% to 20% (P = .007), while
  the amount of time with glucose readings between 70 and 180 mg/dL increased from 61.7% to 71.1% (P = .02).

2 The management of diabetes has become complex over the years but the fundamental still remains that
  is that with lack of abundant beta cells, insufficient insulin production occurs. Part of the challenges
  managing diabetics with full physiologic replacement, such as those with type 1 diabetes, includes trying to manage
glycemic excursions and minimizing significant hypoglycemia from occurring. From a physiologic standpoint,
in patients who have experienced hypoglycemia, hypoglycemia unawareness continues to exist further
propagating additional hypoglycemic events. Such events could lead to sudden catastrophe and cardiac
death on the basis of electrolyte shifts that have been noted in several different studies. In addition, glycemic
swings could also account for microvascular complications and progression of the such.
To more specifically address the questions asked:
1. Relevant clinical scenarios (e.g., a chain of evidence where the technology is expected to provide
   a clinically meaningful improvement in net health outcome): These patients would include those with
   hypoglycemia unawareness and prone to nocturnal hypoglycemia where the auto shut off will circumvent such an event
   from occurring. This can also be useful for patients that already may have certain microvascular complications
   or other diabetes-related complications in hopes of reducing progression of the such
2. Specific outcomes that are clinically meaningful: Specifically, hypoglycemia especially nocturnal
   hypoglycemia. As we all are aware, these complications often times lead to additional unnecessary
   expenses, such as emergency department visits and limited hospitalizations
3. Any relevant patient inclusion/exclusion criteria or clinical context important to consider in
   identifying individuals for this indication: I think that this would be welcomed by all, particularly the older
   population who will have lower hypoglycemia response time. The limitation, unfortunately, may be
   dexterity, as well as unfamiliarity with technology.
4. Supporting evidence from the authoritative scientific literature:
   https://www.sciencedirect.com/science/article/abs/pii/S1521690X15000196?via%3Dihub or

3 Apart from the pivotal trial of the HCL (PMID 27629148, PMID 28134564) referenced in the draft
  evidence, the following trials shed more light into enhancement of outcomes by the use of HCL
  1) Hybrid closed-loop insulin delivery improves glucose control while reducing the risk of hypoglycemia
     across a wide age range in patients with sub-optimally controlled type 1 diabetes (a multicenter, 12-week
     randomized trial) (PMID: 30292578). This multinational, multicenter study is the largest randomized study
     of closed-loop use in outpatient settings so far. It is also the longest randomized outpatient study of 24 h
     per day, 7 days per week, closed-loop use in children as young as 6 years and older. Authors showed
     that compared with sensor-augmented insulin pump therapy, day-and-night hybrid closed-loop insulin
     delivery significantly improved the percentage of time spent within the glucose target range (3.9–10.0
     mmol/L) and mean glucose concentrations, and led to a significant decrease in HbA1c while reducing
     hyperglycemia and hypoglycemia in a mixed population with sub-optimally controlled type 1 diabetes.
     These improvements were seen irrespective of age.
a. Improved time in range  
b. Reduced A1c  
c. Reduced risk of hypoglycemia  
2) The OmniPod personalized MPC algorithm performed well and was safe during day and night use in adult, adolescent, and pediatric patients with type 1 diabetes. PMID: 29431513  
3) In-home use of MiniMed 670G system Auto Mode for 3 months by children with T1D, similar to MiniMed 670G system use by adolescents and adults with T1D, was safe and associated with reduced HbA1c levels and increased time in target glucose range, compared with baseline. PMID: 30585770

4

I have reviewed this document with mostly outdated references regarding the clinically meaningful improvements in outcomes in studies that compare the hybrid closed loop delivery and continuous glucose monitoring impact for low glucose suspend and I am baffled at the conclusion that “the evidence is insufficient to determine the effects of the technology on health outcomes”??

The DCCT clearly showed the challenges of managing type 1 diabetes in youth with higher rates of hypoglycemia and glucose variability. The data on page 4-7 regarding the veo from 2013 found a decrease in hypoglycemia, decrease in hypoglycemia during exercise and higher rates of moderate to severe hypoglycemia prior to using the Veo. The page 8 retrospective study again showed a 2.1->.64 % change with low glucose suspend. The prospective Medtronic study again showed a marked decrease in low blood sugars. These events can be fatal! This is our goal for treating our patients and yet your conclusions are that this is not adequate evidence.

Even your document cites the Position statements on page 13-14 and the current key trials which emphasize the use of continuous glucose monitoring impact on safety of use with insulin pumps. I disagree with your conclusions and feel that the evidence and professional society statements support the use of both LGS and hybrid closed loop delivery systems for type 1 diabetes patients.

NR = not reported

2. Based on the evidence and your clinical experience for each of the clinical indications described in Question 1:

a. Respond YES or NO for each clinical indication whether the intervention would be expected to provide a clinically meaningful improvement in net health outcome; AND

b. Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

<table>
<thead>
<tr>
<th>#</th>
<th>Indications</th>
<th>YES / NO</th>
<th>Low Confidence</th>
<th>Intermediate Confidence</th>
<th>High Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Individuals with type 1 diabetes who are treated with an artificial pancreas device system with a hybrid closed-loop insulin delivery system</td>
<td>Yes</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Individuals with type 1 diabetes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3. Based on the evidence and your clinical experience for each of the clinical indications described in Question 1:
   a. Respond YES or NO for each clinical indication whether this intervention is consistent with generally accepted medical practice; AND
   b. Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

<table>
<thead>
<tr>
<th>#</th>
<th>Indications</th>
<th>YES / NO</th>
<th>Low Confidence</th>
<th>Intermediate Confidence</th>
<th>High Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Individuals with type 1 diabetes who are treated with an artificial pancreas device system with a hybrid closed-loop insulin delivery system</td>
<td>Yes</td>
<td>1</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>Individuals with type 1 diabetes who are treated with an artificial pancreas device system with a hybrid closed-loop insulin delivery system</td>
<td>Yes</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>3</td>
<td>Individuals with type 1 diabetes who are treated with an artificial pancreas device system with a hybrid closed-loop insulin delivery system</td>
<td>Yes</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Individuals with type 1 diabetes who are treated with an artificial pancreas device system with a hybrid closed-loop insulin delivery system: Yes

NR = not reported

4. Additional comments about the clinical context or specific clinical pathways for this topic and/or any relevant scientific citations (including the PMID) with evidence that demonstrates health outcomes you would like to highlight.

<table>
<thead>
<tr>
<th>#</th>
<th>Additional Comments</th>
</tr>
</thead>
</table>
| 1 | The draft document describes Low Glucose suspend (LGS), but does not comment about Predictive low glucose suspend system (PLGS) insulin delivery system which is devised to decrease insulin delivery when patterns in continuous glucose monitoring (CGM) glucose levels predict future hypoglycemia. Insulin pumps equipped with PLGS technology include Medtronic 640G and 670G (Smartguard) and Tandem T:Slim X2 (Basal-IQ Technology): There is strong data to demonstrate the safety and efficacy of the PLGS systems which are an integral part of the closed loop systems. PLGS efficacy studies: 
   In this small study of 19 patients with T1 diabetes, there was a reduction in nocturnal hypoglycemia by almost 50% with use of PLGS system. 
   • The study consisted of patients aged 4 to 45 years old with an A1C ≤8.5%, Nocturnal hypoglycemia with at least 30 minutes of CGM values below 60 mg/dl occurred in 20% control nights versus 12%) intervention nights (odds ratio 1.91 [99% CI 1.57-2.32]; P-value <.001) with reduction in nocturnal hypoglycemia by almost 50%. 
   • In the 13-21 years subgroup, hypoglycemia was reduced from 22% to 14% and in the 22-45 years subgroup, reduction happened from 21% to 12% 
   • MiniMed Paradigm REAL-Time Veo System and Enlite glucose sensor (Medtronic Diabetes, Northridge, CA). 
   • Type 1 diabetes and a glycated hemoglobin level ≤8.0% who demonstrated at least a minimum amount of nocturnal hypoglycemia during a run-in phase. 
   • Use of a nocturnal low-glucose suspend system can substantially reduce overnight hypoglycemia without an increase in morning ketosis. 
   • Significant reduction in the duration of hypoglycemia (defined as <60 mg/dl) 
   a. Hypo>30 minutes (42% reduction) 
   b. Hypo>60 minutes (54% reduction) 
   c. Hypo>90 minutes (74% reduction) 
   d. Hypo>120 minutes (80% reduction). 
   Percentage of nights with hypoglycemia reduced 33%-021 
• Reductions in hypoglycemia – Use of the t:slim X2 Pump with Basal-IQ Technology in the
PROLOG study reduced the number of sensor glucose readings below 70 mg/dL by 31 percent compared to the control period without automated insulin suspension. Median time of glucose levels < 70 mg/dL was reduced from 3.6% at baseline to 2.6% during the 3-week period in the PLGS arm compared with 3.2% in the sensor augment pump therapy arm (SAP) (difference [PLGS – SAP] = −0.8%, 95% CI −1.1 to −0.5, P < 0.001).
- Participants with higher hypoglycemia entering the study saw the largest improvement.
- A significant hypoglycemia reduction was seen with Basal-IQ Technology in all groups, irrespective of age, baseline HbA1c, or baseline hypoglycemia rates.

Retrospective analysis:
- MiniMed 640G pump system,
- Choudhary et al retrospectively evaluated downloaded pump and sensor data. There were 2,322 suspend before low events (2.1 per subject-day).
  - The mean (± SD) duration of pump suspension events was 56.4 ± 9.6 min, and the mean subsequent sensor glucose (SG) nadir was 71.8 ± 5.2 mg/dL.
  - SG values following 1,930 (83.1%) of the predictive suspensions did not reach the preset low limit.
  - Nadir SG values of ≤50 and ≤60 mg/dL were seen in 207 (8.9%) and 356 (15.3%) of the predictive suspensions, respectively.
  - Blood glucose (BG) and SG values before and during the study were comparable (P > 0.05).
  - About 81% of the low suspend events, did not have low glucose values less than 51%
  - MiniMed 640G system can help patients avoid hypoglycemia, without significantly increasing hyperglycemia.

- The duration of nocturnal hypoglycemia was reduced by *50% with use of the MiniMed Paradigm Veo and MiniMed 530G “suspend on low” features, and was reduced by *75% with use of the MiniMed 640G “suspend before low” feature.

2 Diabetes is already an expensive disease. Monitoring it better with increased safety measures reduce hypoglycemic events, which have lead to exhausting additional costs on most health systems, both in the short term and long term. Furthermore, greater glycemic control by maintaining greater time in range may curtail macrovascular and microvascular complications associated with diabetes which can have significant long-term complications on the part of the patient as well as the health system caring for these patients.
While using an insulin infusion pump has certainly demonstrated significant in hypoglycemic events and improved control, there still is a learning curve required with appropriate bolus doses being provided for anticipated glycemic excursion based on carbohydrate load consumed. This can sometimes be challenging and intimidating for some patients. That being said, simplification by using a closed-loop system may further create confidence by the patient in addition to ensuring the tight glycemic control needed. This becomes increasingly important in certain areas where the luxury of a certified diabetes educator is lacking.

3 NR

Biest, Torben, et al. "DREAM5: An open-label, randomized, cross-over study to evaluate the safety and efficacy of day and night closed-loop control by comparing the MD-Logic automated insulin delivery system to sensor augmented pump therapy in patients with type 1 diabetes at home." Diabetes, Obesity and Metabolism (2018).

NR = not reported

5. Is there any evidence missing from the attached draft review of evidence that demonstrates clinically meaningful improvement in net health outcome?

<table>
<thead>
<tr>
<th>#</th>
<th>YES / NO</th>
<th>Citations of Missing Evidence</th>
</tr>
</thead>
</table>
|    |          | PROLOG trail:
| 2  | No       |                                  |
| 3  | Yes      | As stated above                  |
| 4  | Yes      | See above                       |

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in
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