Medical Policy

Advanced Diabetes Management Technology

MEDICAL POLICY NUMBER: 27

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INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance, and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☐ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

Notice to Medicaid Policy Readers: For comprehensive rules and guidelines pertaining to this policy, readers are advised to consult the Oregon Health Authority. It is essential to ensure full understanding and compliance with the state's regulations and directives. Please refer to OHA's OARs and prioritized list for the following coverage guidelines:

Continuous Blood Glucose Monitors: Guideline Note 108

Self-Monitoring of Blood Glucose in Diabetes: Guideline Note A2, OAR 410-12-0520

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

Note:

- The following advanced diabetes management technologies are **not addressed by this medical policy,** but are **reviewed by Providence Health Plan's Pharmacy Department**. If approved, these devices will be made available at the member's pharmacy at applicable durable medical equipment cost-share.

Insulin Pump	Continuous Glucose Monitors
• Omnipod • V-Go	• Freestyle Libre • Dexcom

Advanced Diabetes Management Technology

I. The following advanced diabetes management technology
   - Disposable external insulin infusion pump
   - Non-disposable external insulin infusion pump
   - Continuous glucose monitoring systems

- Integrated insulin infusion and glucose monitoring system

May be considered **medically necessary** for the treatment of insulin-dependent diabetes when both of the following criteria are met (A.-B.):

A. The requested device is FDA-approved and is being used in accordance with the approved indications of use (see Table 1 for list of devices and indications); **and**
B. The patient is currently treated with multiple daily injections of insulin (i.e., at least 2 injections per day) that includes a rapid-acting insulin (such as Humalog®) or regular insulin (such as Humulin R®).**)**

II. Advanced diabetes management technology (disposable and non-disposable external insulin infusion pump and integrated insulin infusion and glucose monitoring system) is considered **not medically necessary** when criterion I. above is not met.

Replacement of Advanced Diabetes Management Technology

III. Upgrade or replacement of existing advanced diabetes management technology may be considered **medically necessary** when there is documentation that one or more of the device components meet all of the following criteria (A.-C.):

A. Are no longer functional; **and**
B. Are not under warranty (see Table 1 for list of devices); **and**
C. Cannot be repaired**.**

IV. Upgrade or replacement of existing advanced diabetes management technology is considered **not medically necessary and not covered** when criterion III. above is not met.

Removal of Advanced Diabetes Management Technology

V. Removal of any advanced diabetes management technology may be considered **medically necessary** if it has been thoroughly evaluated and found to be no longer functional and was appropriately placed for medical necessity.

Not Covered

VI. Implantable insulin infusion pumps are considered **not medically necessary** for any indication, including the treatment of insulin-dependent diabetes.

VII. Enhancements or optional accessories for existing advanced diabetes management technology via smartphones, tablets, wrist-watches and computers are considered convenience items and therefore are **not medically necessary**, including, but not limited to (A.-D.):

A. Mobile Apps (e.g., t: connect®, Glooko, Dexcom Share2 App, Dexcom Follow, Dexcom CLARITY® Reports App, MiniMed Connect)

B. Diabetes management software (e.g., Dexcom CLARITY®, FreeStyle CoPilot Health Management System, Medtronic CareLink® system)
C. Remote glucose monitoring devices (e.g., mySentry)
D. Hypoglycemic wristband alarm (e.g., Diabetes Sentry™).

Link to Evidence Summary

POLICY CROSS REFERENCES

- Diabetes: Blood Glucose Monitors and Supplies, MP239

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

BACKGROUND

Diabetes Mellitus

Patients with poorly controlled diabetes mellitus (DM; or simply referred to as diabetes) are at risk for numerous acute and chronic complications. Common long-term complications due to elevated blood glucose include cardiovascular disease, kidney damage, eye disease, and nerve damage. Pregnant women with poorly controlled diabetes are at higher risk for maternal and neonatal complications. Extremely elevated blood glucose levels may lead to diabetic ketoacidosis and other potentially life-threatening conditions. Conversely, overly aggressive treatment of diabetes may lead to life-threatening hypoglycemia, especially among patients with comorbidities who are unaware of the signs and symptoms of hypoglycemia.[1]

Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) systems are devices that measure glucose levels in interstitial fluid at frequent predetermined intervals. CGM systems are designed to obtain information regarding daily patterns in glucose levels that, when evaluated in real time or reviewed retrospectively, can guide adjustments to therapy, with the goal of improving overall glycemic control.[1] Devices which are used for short periods (3-14 days) where data is sent to the physician, are referred to as professional devices. CGMs designed for individual use and monitoring for longer period are referred to as long-term CGMs.

Glucose measurements provided during continuous monitoring by traditional "nontherapeutic" devices are not intended to replace standard self-monitoring of blood glucose (SMBG) obtained using fingerstick blood samples. However, CGMs are considered an adjunct to SMBG, alerting the patient to the need for self-monitoring. Newer generation CGM devices, that are intended to replace SMBG, defined by the centers for Medicare & Medicaid as "therapeutic" devices, are currently being developed. To date, two "therapeutic" devices have been approved by the U.S. Food & Drug Administration.

CGM devices typically consist of a disposable sensor, a transmitter, and a monitor. The subcutaneous insertion of the glucose sensor (usually in the abdomen) allows the measurement of interstitial fluid

glucose as it diffuses from capillaries to cells, using either enzymatic (glucose oxidase reaction) or microdialysis technology. Interstitial glucose levels generally have good agreement with arterial glucose levels, although there can be significant variation for a small number of individuals. Each sensor can continuously measure glucose for up to seven days, providing real-time data every 1 to 10 minutes. Currently available CGM devices provide either historic (retrospective) data or real-time data. CGM systems also have out-of-range alarms and "trend alarms" that are designed to warn the patient of impending hypo- or hyperglycemia.[1]
There are three types of CGM devices currently on the market, which are described below:

Professional/Short Term CGMs:
Professional CGMs are purchased by healthcare providers and are prescribed to an individual to use over a short period of time (between 3-14 days depending on the device) to record and store glucose data for diagnostic purposes. The individual returns to the physician's office where the data can be analyzed and used to prescribe an appropriate insulin regimen. These devices may be indicated for use either as an adjunctive device to complement standard home blood glucose monitoring devices, or device which replaces the need to standard home blood glucose monitoring devices.

Personal/Long-term CGMs:
Personal CGMs are purchased by individuals and provide retrospective or real-time glucose values that allow users to track patterns and possibly identify episodes of low and high blood glucose levels. The data can be downloaded to personal computers or mobile phones using custom software and stored for historical analysis. The devices may alert the user if a glucose level falls below or rises above a preset/default values. These devices may be indicated for use either as an adjunctive device to complement standard home blood glucose monitoring devices, or device which replaces the need to standard home blood glucose monitoring devices.

Implantable glucose sensors:

These new devices are intended for long term use (90 days) and include a sensor which is implanted subcutaneously in the upper arm to measure glucose. The measurement is then relayed to a transmitter. The data can be downloaded to personal computers or mobile phones using custom software. These devices are indicated for use as an adjunctive device to complement, not replace, information obtained from standard home blood glucose monitoring devices.

Insulin Pumps

Insulin pumps are devices used to deliver insulin in a programmed and controlled manner to diabetic individuals by way of continuous subcutaneous insulin infusion (CSII). These devices work with a separate glucometer through manual or remote functions. The goals of insulin pump therapy are to achieve near-normal control of blood glucose levels. They are proposed as an alternative to administering insulin via multiple daily injections (MDI) and are thought to improve metabolic control in people with diabetes. Insulin pumps are categorized as follows:

1. External insulin pumps are devices which deliver insulin via subcutaneous or intraperitoneal routes. These devices are traditionally worn on a belt or kept in a pocket with tubing connecting the pump to the infusion set. Newer devices contain components with varying degrees of wireless connectivity, some of which may be worn directly on the skin. In addition, external insulin pumps

may be either disposable or have disposable components, but both types are programmable. However, separate from pumps, patch devices deliver preset dosages of insulin transdermally and lack programmability.
The following are examples of FDA cleared external insulin delivery systems:

Conventional:

- t:flex (Tandem Diabetes Care, Inc.)

Disposable:

- OmniPod System (Insulet) (wireless and programmable, but has disposable components)
- V-Go™ Disposable Insulin Delivery Device (Valeritas, Inc.) (non-programmable patch)
- Finesse™ Personal Insulin Delivery Patch (Calibra Medical, Inc.) (non-programmable patch)

2. Implantable insulin pumps deliver insulin via intraperitoneal or intravenous routes. Currently, there are no implantable insulin infusion pumps that are approved by the FDA. However, some devices have been granted Investigational Device status.

Combination Integrated Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitoring (CGM) Systems

This is the general term for a system that allows for communication between two devices:

1. an insulin pump that administers continuous subcutaneous insulin infusion (CSII), and
2. a continuous glucose monitor (CGM)

These systems are also known as CSII-CGM systems, or combination systems. There are several types of integrated systems, all with varying levels of automation. These systems may or may not include software for tracking and trending glucose readings. Some systems connect the insulin pump to the CGM using wired technology while others are wireless. These CSII-CGM systems include sensor-augmented systems and artificial pancreas device systems, and are described in detail below. Please see Table.1 below for a list of FDA-approved integrated CSII-CGM devices.

Sensor-Augmented Systems

In these systems, the CGM sensor communicates glucose readings to the pump via a transmitter. This transmitter allows patients to view real-time glucose values, and will not use the continuous glucose monitoring (CGM) data to calculate insulin doses. Patients are still required to perform self-monitoring of blood glucose by way of a finger stick to generate the information needed to adjust insulin levels. These systems typically require manual adjustment of insulin administration rates as well as manual calculation and administration of pre-meal insulin bolus doses.

Artificial Pancreas Device System (APDS)

According to the U.S. Food & Drug Administration (FDA):[2]

> "The Artificial Pancreas Device System is a system of devices that closely mimics the glucose regulating function of a healthy pancreas. Sometimes an artificial pancreas device system is referred

to as a "closed-loop" system, an 'automated insulin delivery' system, or an 'autonomous system for glycemic control.'

Most Artificial Pancreas Device Systems consists of three types of devices already familiar to many people with diabetes:

1. **Continuous Glucose Monitor (CGM).** A sensor placed under the patient's skin (subcutaneously) measures the glucose in the fluid around the cells (interstitial fluid) which is associated with blood glucose levels. A small transmitter sends information to a receiver.
    - **Blood Glucose Device (BGD).** Currently, to get the most accurate estimates of blood glucose possible from a CGM, the patient needs to periodically calibrate the CGM using a blood glucose measurement from a BGD.
2. **Control algorithm**. A control algorithm is software embedded in an external processor (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. The control algorithm can be run on any number of devices including an insulin pump, computer or cellular phone. The FDA does not require the control algorithm to reside on the insulin pump.
3. **Insulin pump.** Based on the instructions sent by the controller, an infusion pump adjusts the insulin delivery to the tissue under the skin.

An Artificial Pancreas Device System not only monitors glucose levels in the body but also automatically adjusts the delivery of insulin to reduce high blood glucose levels (hyperglycemia) and minimize the incidence of low blood glucose (hypoglycemia) with little or no input from the patient."[2]

Types of Artificial Pancreas Device Systems (APDS)

According to the FDA:[2]

> "Researchers and manufacturers are developing three main categories of Artificial Pancreas Delivery Systems. They differ in how the insulin pump acts on readings from the continuous glucose monitoring system.

- Threshold Suspend Device System

  The goal of a threshold suspend device system is to help reverse a dangerous drop in blood glucose level (hypoglycemia) or reduce its severity by temporarily suspending insulin delivery when the glucose level falls to or approaches a low glucose threshold. These are sometimes referred to as "low glucose suspend systems."

  This kind of system serves as a potential back-up when a patient is unable to respond to a low blood sugar (hypoglycemic) event. Patients using this system will still need to be active in managing their blood glucose levels by periodically checking their blood glucose levels and by administering insulin or eating.

- Insulin-Only System

An insulin-only system achieves a target glucose level by automatically increasing or decreasing the amount of insulin infused based on the CGM values. These systems may be hybrid systems that automatically adjust basal insulin with the user manually delivering bolus insulin to cover meals, or could be fully closed loop systems, where the system automatically adjusts basal insulin and provide insulin for meals.

- Bi-Hormonal Control System

  A bi-hormonal control system achieves a target glucose level by using two algorithms to instruct an infusion pump to deliver two different hormones – one hormone (insulin) to lower glucose levels and another (such as glucagon) to increase blood glucose levels. The bi-hormonal system mimics the glucose-regulating function of a healthy pancreas more closely than an insulin-only system."[2]

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

Table 1. Examples of FDA-Approved Advanced Diabetes Management Technologies

Note:

The FDA frequently approves diabetic devices. Please consult the FDA premarket approval (PMA) and 510(k) premarket notification databases for new devices not listed below.

Professional Short-term CGM Devices				
Device	**Manufacturer**	**Age Restriction**	**Indications**	**Contraindications**
FreeStyle Libre Pro Flash [3]	Abbott Warranty: 1 year	18 years and older	• Diabetes mellitus (type 1 or type 2) • Requires a prescription. • Sensors can be worn up to 14 days. • Does not require user calibration with blood glucose values. • Detection of episodes of hyperglycemia and hypoglycemia.	• Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, or diathermy treatment. • Has NOT been approved for pregnant individuals.
FreeStyle Libre 2 System[4]	Abbott Warranty: 1 year	4 years or older	• Intended to replace blood glucose testing for diabetes treatment decisions, unless otherwise indicated.	• Automated Insulin Delivery: The System must not be used with

			• The System also detects trends and tracks patterns and aids in the detection of episodes of hyperglycemia and hypoglycemia, • The System is also intended to autonomously communicate with digitally connected devices. • The System can be used alone or in conjunction with these digitally connected devices where the user manually controls actions for therapy decisions.	automated insulin dosing (AID) systems, including closed loop and insulin suspend systems. • The System must be removed prior to Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, or high-frequency electrical heat (diathermy) treatment.
iPro®2 [5] (to be used with either the Enlite sensor or Sof-Sensor)	Medtronic, MiniMed Warranty: 1 year	18 years and older	• Diabetes mellitus (type 1 or type 2) • Requires a prescription. • Prevents data viewing by patients in real time. • Enlite sensors can be worn up to 6 days. Sof-sensors may be worn up to 3 days. • An adjunctive device to complement, not replace, information obtained from standard home glucose monitoring devices.	• None known.
Personal Long-term CGM Devices				
Device	**Manufacturer**	**Age Restriction**	**Indications**	**Contraindications**
DexCom G6 System[6] (therapeutic) *If approved, this device will be made available at the member's pharmacy at applicable durable medical equipment cost-share.	DexCom Warranty: 3 months for transmitter; 1 year for receiver	2 years of age and older	Same indications as G5 predecessor, with one additional indication: • Intended to autonomously communicate with digitally connected devices, including automated insulin dosing (AID) systems. • Compatible with t:slim Insulin Pump.	Same contraindications as G5 predecessor
DexCom G7 CGM System *If approved, this device will be made available at the	DexCom	2 years of age and older	The Dexcom G7 Continuous Glucose Monitoring System (Dexcom G7 CGM System or	

member's pharmacy at applicable durable medical equipment cost-share.			G7) is a real time, continuous glucose monitoring device indicated for the management of diabetes in persons 2 years and older. The Dexcom G7 CGM System is intended to replace fingerstick BG testing for diabetes treatment decisions. Interpretation of the Dexcom G7 CGM System results should be based on the glucose trends and several sequential sensor readings over time. The Dexcom G7 CGM System also aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments. The Dexcom G7 CGM System is also intended to autonomously communicate with digitally connected devices, including automated insulin dosing (AID) systems. The Dexcom G7 CGM System can be used alone or in conjunction with these digitally connected medical devices for the purpose of managing diabetes.	
FreeStyle Libre Flash* (therapeutic) *If approved, this device will be made available at the member's pharmacy at applicable durable medical equipment cost-share.	Abbott Warranty: 1 year	18 years and older	• Diabetes mellitus (type 1 or type 2) • Requires a prescription. • Sensors can be worn up to 10 days. • Replaces fingerstick blood glucose testing for diabetes treatment decisions.	• MRI, (CT) scan, or diathermy treatment. • Has NOT been approved for pregnant individuals or persons on dialysis. • Not recommended for critically-ill population.
Guardian Connect [7] (Not therapeutic)	Medtronic MiniMed Warranty: 1 year	14 to 75 years of age	• Diabetes mellitus (type 1 or type 2) • Requires a prescription. • For continuous or periodic monitoring of glucose levels	• People who are unwilling or unable to perform a minimum of two meter blood glucose tests per day

			• Provides real-time glucose values and trends through a Guardian Connect app installed on a compatible consumer electronic mobile device.	• People who are unable or unwilling to maintain contact with their healthcare professional. • Patients with insufficient vision or hearing to allow recognition of the alerts generated by the Guardian Connect app.

Integrated Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitoring (CGM) Systems		
Device	**Indications/Contraindications**	**Age**
MiniMed Paradigm® REAL-Time Revel™ System By Medtronic Warranty: 4 years	• Indicated for the continuous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. • Use of insulin pumps with the optional sensor and transmitter components is indicated for continuous or periodic monitoring of glucose levels in the fluid under the skin, and possible low and high blood glucose episodes in adults (ages 18 and older).	≥ 18 years
t:slim G4™ By Tandem® Diabetes Care Warranty: 4 years	• 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 G4 Insulin Pump can be used solely for continuous insulin delivery and as part of the t:slim G4 System to receive and display continuous glucose measurements from the Dexcom G4 Platinum Sensor and Transmitter. • The t:slim G4 System also includes continuous glucose monitoring (CGM) indicated for detecting trends and tracking patterns in persons with diabetes for use as an adjunctive device to complement, not replace, information obtained from standard home glucose monitoring devices. • The t:slim G4 System is indicated for use in individuals 12 years of age and greater • The t:slim G4 System is intended for single patient use and requires a prescription	≥ 12 years
t:slim X2™ Insulin Pump with Dexcom G5 Mobile CGM By Tandem® Diabetes Care Warranty: 3 months for transmitter; 4 years for receiver	• 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 t:slim X2 System to receive and display continuous glucose measurements from the Dexcom G5 Mobile Sensor and Transmitter. • The t:slim X2 System also includes continuous glucose monitoring (CGM) indicated for the management of diabetes. The Dexcom G5 Mobile CGM is designed to replace fingerstick blood glucose testing for diabetes treatment decisions. • The t:slim X2 System is indicated for use in individuals 6 years of age and greater. • The t:slim X2 System is intended for single patient use and requires a prescription. The device is indicated for use with NovoLog or Humalog U-100 insulin.	≥ 6 years

t:slim X2™ Insulin Pump with Control-IQ By Tandem® Diabetes Care Warranty: 4 years	• Intended for single patient, home use and requires a prescription. The pump is indicated for use with NovoLog or Humalog U-100 insulin. • Control-IQ technology is intended for use with a compatible integrated continuous glucose monitor (iCGM, sold separately) and ACE pump to automatically increase, decrease, and suspend delivery of basal insulin based on CGM readings and predicted glucose values. It can also deliver correction boluses when the glucose value is predicted to exceed a predefined threshold. • Control-IQ technology is intended for the management of Type 1 diabetes mellitus in persons 6 years of age and greater. Control-IQ technology is intended for single patient use. Control-IQ technology is indicated for use with NovoLog or Humalog U-100 insulin. • Control-IQ technology should not be used by anyone under the age of six years old. It should also not be used in patients who require less than 10 units of insulin per day or who weigh less than 55 pounds. • Control-IQ technology is not indicated for use in pregnant women, persons on dialysis, or critically ill patients. • The pump is not intended for anyone unable or unwilling to: ○ Use the pump, CGM, and all other system components in accordance with their respective instructions for use ○ Test BG levels as recommended by a healthcare provider ○ Demonstrate adequate carbohydrate-counting skills ○ Maintain sufficient diabetes selfcare skills ○ See a healthcare provider(s) regularly	≥ 6 years
t:slim X2 Insulin Pump with Basal-IQ Technology By Tandem® Diabetes Care Warranty: 4 years	• The t:slim X2 Insulin Pump with Basal-IQ Technology (the System) consists of the t:slim X2 Insulin Pump which contains the Basal-IQ technology, and a continuous glucose monitor (CGM). Compatible CGMs include the Dexcom G5 Mobile CGM and integrated continuous glucose monitors (iCGMs) that are listed in the labeling for this device. • 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 t:slim X2 Insulin Pump with Basal-IQ Technology System. • When the System is used with the Dexcom G5 Mobile CGM or a compatible iCGM, the Basal-IQ Technology can be used to suspend insulin delivery based on CGM sensor readings.	≥ 6 years
MiniMed 530G By Medtronic Warranty: 4 years	• Intended for continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) for the management of diabetes in persons…requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin…can be programmed to automatically suspend delivery of insulin when the sensor glucose value falls below a predefined threshold value. • 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 values provided by the MiniMed 530G System • Not intended to be used directly for preventing or treating hypoglycemia but to suspend insulin delivery when the user is unable to respond to the Threshold Suspend alarm to take measures to prevent or treat hypoglycemia themselves.	≥ 16 years

MiniMed 630G By Medtronic Warranty: 4 years	• Intended for continuous delivery of basal insulin (at user selected rates) and administration of insulin boluses in for the management of diabetes mellitus in persons fourteen years of age and older requiring insulin, as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin. The MiniMed 630G system includes SmartGuard, which 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. • 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 values provided by the MiniMed 630G system. • Not intended to be used directly for preventing or treaing hypoglycemia but to suspend insulin delivery when the user is unable to…take measure to prevent or treat hypoglycemia themselves.	≥ 14 years
MiniMed 670G By Medtronic Warranty: 4 years	• Intended for continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) for the management of Type 1 diabetes mellitus in persons, seven years of age and older, requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin. • Not indended for use in children under the age of 7. • Not intended for use in patients who require less than a total daily insulin dose of 8 units per day. • The reservoir is contraindicated for the infusion of blood or blood products. • Infusion sets are indicated for subcutaneous use only and not for intravenous (IV) infusion or the infusion of blood or blood products.	≥ 7 years
MiniMed 770G By Medtronic Warranty: 4 years	• Intended for continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) for the management of Type 1 diabetes mellitus in persons, two years of age and older, requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin. • Not indended for use in children under the age of 2. • Not intended for use in patients who require less than 8 units or greater than 250 units of total daily insulin dose per day. • The reservoir is contraindicated for the infusion of blood or blood products. • Infusion sets are indicated for subcutaneous use only and not for intravenous (IV) infusion or the infusion of blood or blood products.	≥ 2 years
Guardian Connect By Medtronic Warranty: 1 year	• Indicated for continuous or periodic monitoring of glucose levels in the interstitial fluid under the skin, in patients (14 to 75 years of age) with diabetes mellitus. • Provides real-time glucose values and trends through a Guardian Connect app installed on a compatible consumer electronic mobile device. It allows users to detect trends and track patterns in glucose concentrations. The Guardian Connect app alerts if a Guardian Sensor (3) glucose level reaches, falls below, rises above, or is predicted to surpass set values. • 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 values provided by the Guardian Sensor (3). • The Guardian Connect system is comprised of the following devices: Guardian Connect app, Guardian Sensor (3), and the Guardian Connect transmitter.	14-75 years

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of advanced diabetes management technology. Below is a summary of the available evidence identified through February 2024.

Continuous Glucose Monitors

Adults with Type 1 Diabetes

Systematic Reviews

- In 2020, Pease and colleagues conducted a systematic review assessing the efficacy of technology in Type 1 diabetes.[8] Investigators systematically searched the literature through April 2019, identified eligible studies, assessed study quality and estimated mean difference for quality of life in network meta-analysis with random effects. In total, 52 eligible studies comparing 12 diabetes management technologies (n=3,975) were included for review. Integrated insulin pump and continuous glucose monitoring (CGM) systems with low-glucose suspend or hybrid closed-loop algorithms resulted in A1c levels 0.96% lower than multiple daily injections with either flash glucose monitoring or capillary glucose testing, respectively. In addition, integrated systems had the best ranking for A1c reduction utilizing the surface under the cumulative ranking curve (SUCRA-96.4). While treatment effects were nonsignificant for many technology comparisons regarding severe hypoglycemia and quality of life, simultaneous evaluation of outcomes in cluster analyses as well as narrative synthesis appeared to favor integrated insulin pump and continuous glucose monitors. Overall risk of bias was moderate-high. Investigators concluded that integrated insulin pump and CGM systems with low-glucose suspend or hybrid closed-loop capability appeared best for A1c reduction, composite ranking for A1c and severe hypoglycemia, and possibly quality of life, but noted that certainty of evidence was very low due to the limitations of studies included for review.

- In 2017, Benkhadra et al. published a systematic review that evaluated real-time (rt) CGM in type 1 diabetics, including 11 RCTs with moderate- to low-risk of bias published through January of 2015.[9] Primary outcomes assessed were HbA1c, time spent in hypoglycemia and number of hypoglycemic episodes. Meta-analysis results found that in adult patients (>15 years of age) the use of rt-CGM was associated with a statistically significant reduction in HbA1c (-0·276; 95% CI: -0·465 to -0·087, p<0.001). There was no statistically significant difference in time spent in hypoglycemia or the number of hypoglycemic episodes in any age group.

- In 2019, Hayes published a review of continuous glucose monitoring systems for various patient populations including adults with type 1 diabetes, which included 23 RCTS published through July 2018.[1] Six of the included RCTs evaluated CGM as an adjunct to SMBG versus SMBG alone in adults with type 1 diabetes, with three studies that included only adults and three studies that enrolled both adult and pediatric patients but reported separate analyses for adult patients. Two RCTs found that constant use of CGM for six months was associated with statistically significant improvements in HbA1c levels. However, two RCTs found that constant use of CGM for three or six months did not

significantly improvement HbA1c. Despite somewhat inconsistent findings, the review rated the use of CGM in adults with type 1 diabetes as "A", for the use of CGM in patients who have not achieved adequate glycemic control despite frequent SMBG. The review concluded that between the highly consistent findings that CGM was beneficial in studies in which data for children and adults were combined, and some positive findings concerning the benefits of CGM in studies of only adult patients with type 1 diabetes, that CGM use in this population has some proven benefit.

- In 2012, Langendam et al. published a Cochrane review that compared CGM with conventional SMBG in patients of all ages with type 1 diabetes, including 22 RCTs published through May 2011.[10] The primary objective outcomes assessed were changes in HbA1c, number of episodes of severe hypoglycemia, number of episodes with mild hypoglycemia and number of ketoacidotic events. The meta-analyses showed that, across all age groups, CGM provided a benefit for patients who started on CGM plus continuous subcutaneous insulin infusion (CSII) via pump compared with patients using multiple daily injections (MDI) and SMBG. However, this analysis analyzed pediatric and adults patients together and had very high heterogeneity between studies (I^2 =84%), limiting its applicability to only the adult population. In the adults only analyses, after 3 months, four of the five RCTs reported significantly greater decrease in HbA1c level for patients using CGM compared with SMBG. Of the RCTS with 6-12 month follow-up, three of the four RCTs also reported significantly greater decrease in HbA1c level for patients using CGM compared with SMBG. Five RCTS reported hypoglycemic measures as outcomes, but only one found a significant decrease in hypoglycemic measures in the CGM group compared to the SMBG group (-16.60% time; 95% CI: -25.06, -8.14). Three RCTS reported hyperglycemic events and three reported ketoacidotic events, but none of these studies found significant differences in either outcome between groups.

Randomized Controlled Trials (RCTs)

Since the publication of the systematic reviews described above, there have been several RCTs published that assessed the use of CGM in type 1 diabetic adults. These RCTs are described below.

- In 2015, New et al. published a 100-day, prospective, multicenter trial including adults (>18 years of age) with type 1 or type 2 diabetes on MDI or CSII (> 6 months) with HbA1c values of 7–11%, who performed SMBG an average of 2–7 times per day.[11] Overall, 126 type one diabetics were split between three groups (n=42 patients per group): CGM with alarms, CGM without alarms and SMBG. Approximately one third of the patients were using CSII for insulin administration and two thirds were using MDI. The only outcome where type 1 diabetic patients were analyzed separately from type 2 patients was the time spent outside a glucose target. Type 1 diabetics using CGM with alarm spent significantly less time outside of their targeted glucose range than those using SMBG (-1.3 hrs/day difference; 95% CI: -2.52 to -0.28; p=0.0149) but the difference between the CGM with no alarm and the SMBG group was not significant. Separate analyses for type 1 and type 2 diabetics regarding the use if CSII versus MDI were not performed.

- In 2017, Beck et al. published the results of a multicenter RCT that included 158 adults with type 1 diabetes who were using MDI and had hemoglobin A1c (HbA1c) levels of 7.5% to 9.9% who were randomly assigned 2:1 to CGM (n = 105) or SMBG (n = 53).[12] The primary outcome measure was the difference in change in HbA1c level from baseline to 24 weeks and secondary measures included hypoglycemia at less than 70 mg/dL. Mean HbA1c reduction from baseline was significantly improved in the CGM group (1.1% at 12 weeks and 1.0% at 24 weeks) compared to the SMBG group

(0.5% and 0.4%) (p <0 .001). At 24 weeks, the adjusted treatment-group difference in mean change in HbA1c level from baseline was -0.6% (95% CI, -0.8% to -0.3%; p < 0.001). Median duration of hypoglycemia at less than <70 mg/dL was 43 min/d (IQR, 27-69) in the CGM group versus 80 min/d (IQR, 36-111) in the control group (p = 0.002).

- In 2017, Lind et al. published a multicenter open-label crossover RCT that included 161 individuals with type 1 diabetes and HbA1c of at least 7.5% treated with MDI. Participants were randomized to receive treatment for 26 weeks, separated by a washout period of 17 weeks and the difference in HbA1c between weeks 26 and 69 was analyzed. A total of 142 participants were analyzed at follow-up and mean HbA1c was 7.92% during CGM use and 8.35% during SMBG (mean difference, -0.43% [95% CI, -0.57% to -0.29%]; p < 0.001).

Section Summary

As demonstrated by the review of the systematic reviews and randomized trials noted above, the use of CGM devices for adults with type 1 diabetes, lack of glycemic control, and other specific indications has been established as standard of care. Therefore, the remaining evidence review will focus on the potentially experimental and investigational uses of CGMS.

Pregnant Women

Systematic Reviews

- In 2013, Voormolen et al. published a systematic review that evaluated the efficacy of CGM compared with SMBG in pregnant women with type 1 or type 2 diabetes or gestational diabetes (GDM) in studies identified up to February 2013.[13] Two moderately-sized RCTs were included that employed retrospective CGM (n=46 T1D and 25 T2D, and n=73 GDM) and two RCTS which employed real-time CGM (n=123 T1D and 31 T2D, and n=25 T1D). Due to heterogeneity between studies, meta-analyses were not possible. One small RCT on retrospective CGM showed a significant reduction in third-trimester HbA1c compared with SMBG (mean 5.8% versus 6.4%; p=0.007) and a significant reduction in neonatal macrosomia (35% versus 60%; odds ratio [OR], 0.36; 95% CI, 0.13 to 0.98; p=0.05). A second RCT on real-time CGM reported that the use of CGM did not significantly improve any of the outcomes measured, including glycemic control (reported as HbA1c or severe hypoglycemia), neonatal macrosomia, preeclampsia, cesarean delivery, and neonatal hypoglycemia.

- In 2015 (updated 2018), Hayes published a systematic review which included a review of the evidence for the use of CGM in pregnant women.[1] This review included three RCTs that evaluated CGM as an adjunct to SMBG versus SMBG. However, all three studies addressed different clinical situations. One large RCT enrolled 154 women with pre-pregnancy type 1 diabetes and found that CGM was not associated with significant improvement in glycemic control, decreased pregnancy complication rates, or any of the neonatal outcomes assessed. A second RCT enrolled 73 women diagnosed with gestational diabetes (GDM) and found that CGM improved identification of women who required insulin and/or metformin (31% monitored with CGM versus 8% monitored by SMBG, p=0.0149) but the use of CGM was not associated with better maternal or neonatal outcomes. The third RCT enrolled 71 women who had pre-pregnancy type 1 or type 2 diabetes and found that use of CGM was associated with statistically significant decrease in mean HbA1c (5.8% in the CGM group versus 6.4% in the SMBG group, p=0.007), and marginally significant decreases in mean birth weight

(effect size 0.7 SD, 95% confidence interval 0.0 to 1.3; p=0.05), and risk of macrosomia (OR 0.36; 95% CI: 0.13 to 0.98, p=0.05).[14] All three of the included studies were limited by lack of blinding and post-partum follow-up and small sample numbers for some of the outcomes assessed. The review concluded that additional well-designed studies of CGM are needed to determine the efficacy and clinical utility of CGM in pregnant women who have gestational, type 1, or type 2 diabetes.

- In 2017, Moy et al. published an update to their 2014 Cochrane review comparing several techniques of blood glucose monitoring and their impact on maternal and infant outcomes among pregnant women with pre-existing type I or type 2 diabetes, including two RCTS comparing CGM versus standard monitoring (N=225 women).[15] All of the RCTs included in this review had been included in the previous Hayes review, described above. The review reported no statistical differences in pre-eclampsia (RR 1.37, 95% CI 0.52 to 3.59), caesarean section (average RR 1.00, 95% CI 0.65 to 1.54) and large-for-gestational age (average RR 0.89, 95% CI 0.41 to 1.92) outcomes between groups. In the 2008 Murphy RCT (n=71), mean maternal HbA1c (as the measure of glycemic control) was lower for women in the CGM group (mean difference of -0.60 %, 95% CI -0.91 to -0.29).[14] The review reported that there was insufficient evidence to assess perinatal mortality and there were no significant differences for preterm birth (< 37 weeks' gestation). One RCT was determined to be of low quality and the other RCT was deemed very low quality and had a very high degree of statistical heterogeneity for a number of outcomes due to large CI's crossing the line of no effect and small sample sizes for a number of outcomes. The review concluded that there is no glucose monitoring technique that is superior to any other technique among pregnant women with pre-existing type 1 or type 2 diabetes, and additional large well-designed RCTs are required to inform choices of glucose monitoring techniques.

Randomized Controlled Trials (RCTs)

Since the systematic reviews described above, only one RCT was identified that evaluated the use of CGM in pregnant women. This RCT is described below.

- In 2016, Wei et al. published an RCT that investigated the effects of CGM on maternal and neonatal outcomes in 106 women with gestational diabetes mellitus (GDM).[16] Women were randomly allocated to the antenatal care plus CGM group or the self-monitoring blood glucose (SMBG) group. There were no significant differences in prenatal or obstetric outcomes (e.g., caesarean delivery rate, Apgar score, macrosomia or neonatal hypoglycemia) between the CGM and SMBG groups. The lack of difference between groups was attributed to small sample size. HbA1C levels were not significantly different between groups. Only two maternal outcomes were found to be significantly different between groups: the proportion of GDM women with excessive gestational weight gain was lower in the CGM group than in the SMBG group (33.3% vs. 56.4%, p = 0.039), and women who initiated CGMs earlier gained less weight (p = 0.017). Limitations of the trial included missing clinical data throughout the trial as well as at 6-weeks post-partum, small sample size. The investigators stated that larger follow-up studies were needed to determine if CGM improves maternal and neonatal outcomes in patients with GDM.

Section Summary

The evidence regarding the use of CGMs in pregnant women with pre-gestational diabetes has limitations. Studies have recruited different patient populations, assessing a combination of type 1

and/or type 2 diabetic women. Only one of the two RCTs involving pre-gestational type 1 and type 2 diabetics found that use of CGM was associated with statistically significant improvements in maternal glycemia and some neonatal outcomes. Despite these limitations, there is a relatively high risk of adverse maternal and neonatal outcomes associated with poorly controlled overt diabetes. According to the CDC,[17] blood sugar that is not well controlled in a pregnant woman with type 1 or type 2 diabetes may increase comorbidity risks, including but not limited to: birth defects, large-for-gestational-age babies, Cesarean section, preeclampsia, preterm birth, and miscarriage.

There is a paucity of evidence regarding the use of CGMs in pregnant women who develop gestational diabetes mellitus (GDM). Studies have addressed different clinical situations. One RCT reported that CGM use in women with GDM was better able to predict women who would require antidiabetic therapies but did not find any improvement in maternal and neonatal outcomes. The second RCT assessed a large number of maternal and neonatal outcomes and the only significant outcome reported was a reduction in excessive maternal weight gain in the CGM group. In addition, according to the CDC, GDM has a short duration, as it usually develops during the middle of pregnancy, and can often be controlled through eating healthy foods and regular exercise.[18] At this time, the efficacy of CGM use for women who develop GDM has not been established.

Type-1 Diabetes in Children and Adolescents

Systematic Reviews

- In 2012, Yeh et al. published a systematic review evaluating, in part, the comparative effectiveness of self-monitoring of blood glucose (SMBG) and real-time CGM (rt-CGM), including five RCTs which reported data separately for younger age groups (N=434 children <18 years).[19] Although one small cross-over trial reported that use of CGM was associated with a statistically significant improvement in mean HbA1c (mean difference −0.46% ; 95% CI −0.26% to −0.66%; p < 0.001) in 72 pediatric patients,[20] the remaining four moderately-sized RCTs did not find a significant decrease in HbA1c levels with the use of rt-CGMs. In the pooled analysis, there were significant differences in change from baseline HbA1c level whether SMBG or rt-CGM was used.

- In 2013, Poolsup et al. published a meta-analysis to assess the effect of CGM on glycemic control in type 1 diabetic children in RCTs identified up to May 2013 that were ≥ 8 weeks in duration, and that reported HbA1c outcomes.[21] Ten RCTs (N= 817, children ≤ 18 years old with type 1 diabetes). Of the 10 studies included, seven were of high quality, and three of low quality. Among the pediatric type 1 diabetics, CGM did not reduce HbA1c to a greater degree than SMBG (mean difference, −0.13%; 95% CI, −0.38% to 0.11%; p=0.27). The reviewers found significant heterogeneity among the included studies (I2=71%) likely due to several factors including: heterogeneity in study sample size (range, 11 to 156 patients), differences in frequency and duration of CGM use, differences in the intervention period, and the intervention used.

- In 2014, Matsuda and Brennan published a systematic review that evaluated the efficacy of CGM for adolescents (aged 12 to 18 years) with type 1 diabetes compared to SBMG alone, including RCTs from 2002 through 2012 that reported the number of hypoglycemic episodes (blood glucose <70 mg/dL) and HbA1c levels.[22] Only two moderately-sized multicenter RCTs (n= 40, 45) were included. Although no heterogeneity between studies was detected, there were differences in the length of diagnosis of subjects at baseline, which can impact HbA1c values. Reduction in HbA1c from baseline

to 26 weeks in both studies was not significantly different between groups (mean difference = −0.11; 95% CI, −0.61 to 0.39; p=0.674). Therefore, CGM was not significantly more effective than SMBG in adolescent patients for controlling HbA1c. The review concluded that more evaluation is needed of the efficacy of CGM in the adolescent population.

- In 2019, Hayes published a systematic review which included a review of the evidence for the use of CGM in pediatric patients with type 1 diabetes.[1] This review included six RCTs that evaluated CGM as an adjunct to SMBG versus SMBG alone, all of which had been included in the previous review, described above. Three of the included studies enrolled only pediatric patients and three studies enrolled pediatric and adult patients but reported results separately for pediatric patients. Overall, results of these studies suggest that the use of CGM does not improve glycemic control or provides only limited improvement. Five of the six included studies were RCTs, which found that constant or nearly constant use of CGM as an adjunct to SMBG did not significantly improve mean HbA1c levels compared with use of SMBG alone. The sixth included study was a small cross-over trial by Battelino, described above. Although one of the RCTs reported that use of CGM was associated with statistically significant reductions in severe hypoglycemia in pediatric patients, this finding was not replicated in the three other RCTs which reported hypoglycemia as an outcome. The review concluded that additional well-designed studies of CGM were needed to determine the efficacy of CGM in pediatric patients who have type 1 diabetes, giving the use of this device a "C" rating due to inconsistent findings in this population.

Section Summary

The evidence for the use of CGM in children with type 1 diabetes is conflicting. Trials that have recruited mixed diabetic populations (adults and children), report improved glycemia control in children when analyzed separately form adults. However, trials that have focused solely on children and adolescents report that the use of CGM does not improve glycemic control in children and adolescent diabetic patients despite constant or near-constant use. In addition, the impact of CGM use by compliant children and adolescents on long-term health outcomes is lacking. Despite conflicting results and limited evidence of improved health outcomes, poorly controlled diabetes in children can lead to numerous adverse outcomes in this population. According to the American Diabetes Association, children are less able or unable to recognize or articulate their hypoglycemia, and lack of glycemic control in children can have adverse effects on brain development and function.[23] In addition to neurological vulnerability, poor management of glycemic control in children can impact their growth and sexual maturity.

Type-2 Diabetes in Children, Adolescents, and Adults

Systematic Reviews

- In the 2013, Poolsup et al. meta-analysis described above, the reviewers also assessed the effect of CGM on glycemic control in type 2 diabetic adults in RCTs identified up to May 2013 that were ≥ 8 weeks in duration, and that reported HbA1c outcomes.[21] Four RCTs (N=161 adults ≥ 18 years of age with type 2 diabetes) were included, two of which were of high quality and two of low quality. In a pooled analysis of retrospective and real-time (rt) CGMs, CGM was significantly more efficacious than SMBG in terms of HbA1c reduction (mean difference, −0.31%; 95% CI, −0.6% to −0.02%; p=0.04). However, sub-group analyses identified that retrospective CGM was not superior to SMBG.

Studies sizes were of moderate size, ranging from 25 to 100 patients). The only benefit was from rt-CGM. There was no heterogeneity (I2=0%) between the included studies, although there were variations in terms of study quality, frequency and duration of CGM use, and interventions.

- In 2019, Hayes published a systematic review which included a review of the evidence for the use of CGM in adult patients with type 2 diabetes.[1] This review included five RCTs that evaluated CGM as an adjunct to SMBG versus SMBG. In the three RCTS in which the CGM was used constantly, one study (n=100) reported significant improvement in mean HbA1c with the use of CGM (p<0.001) in an adjusted analysis, but the other two RCTs (n=50 and 92) did not find significant improvements in HbA1c with the use of the device. Limitations of these RCTS included: significant differences in baseline characteristics between groups, no blinding reported and short-term (<1 year) follow-up. However, the two included small RCTs (n=52 and 65) in which CGM was used intermittently (two or three 3-day sessions over 2 - 3 months) both reported that CGM was associated with statistically significant improvements in mean HbA1c. All included studies suffered from small sample size, limited follow-up, and some degree of industry support. The review concluded that additional studies were needed to determine whether CGM is beneficial in this diabetic population, giving the use of this device in type 2 diabetic adults a "C" rating due to inconsistent findings and a rating of "D2" for type 2 diabetic children due to a paucity of evidence concerning use of CGM in this population.

- The systematic review conducted to formulate the 2022 National Institute for Health and Care Excellence (NICE) guidelines on management of type 2 diabetes in adults (aged 18 and over), included two small RCTs (N=165) of insulin-dependent patients with mean baseline HbA1c levels between 8.3% - 8.9%.[24] The studies had very different follow-up periods (12 weeks and 52 weeks) and were deemed to be of low and very low quality. The meta-analysis showed an overall significant and clinically important reduction in HbA1c levels in people on insulin in the CGM group compared to those on SMBG alone up to 12 months. However, between the two trials there were conflicting results reported for this outcome. The review concluded there was still uncertainty regarding the effectiveness of CGM in this population.

Randomized Controlled Trials (RCTs)

- In 2016, Sato et al. published a small RCT which assessed the effect of treatment guidance based on data from a CGM device on glycemic control in 34 patients with insulin-dependent type 2 diabetes.[25] The intervention group received treatment guidance based on the CGM data, while the control group received advice based on SMBG and glycosylated hemoglobin (HbA1c) levels. At eight months, there was no significant difference in the change from baseline of HbA1c between the two groups. There was also no significant difference in the change from baseline in the Diabetes Treatment Satisfaction Questionnaire score between the two groups. The authors concluded that treatment guidance using retrospective CGM data was not effective for improving glycemic control and therapeutic satisfaction in Japanese patients with type 2 diabetes, but further studies that include larger populations are needed to confirm the present findings.

Section Summary

The evidence for the use of CGM in patients with type 2 diabetes consists of several small- to medium-sized RCTS and three systematic reviews of these RCTs. The RCTs of CGM in adults with type 2 diabetes

have published conflicting results. The published RCTs are heterogeneous in terms of sample size, frequency and duration of CGM use, the intervention period, intervention used, and quality. There is a paucity of evidence on the use of CGM in children and adolescents with type 2 diabetes. At this time, the efficacy of CGM use for type 2 diabetics, of any age, has not been established. In addition, evidence is needed to determine if CGM improves long-term health outcomes, such as avoidance of long-term diabetic complications, in this patient population.

Implantable Long-term CGMs

Systematic Reviews

- In 2023 Hayes conducted a health technology assessment of the accuracy and utility of the Eversense Continuous Glucose Monitor for maintaining glycemic control in adults with diabetes mellitus.[26] Searching the literature, investigators identified 10 studies (reported in 11 publications) that compared Eversense with venous blood glucose (VBG) or self-monitored blood glucose (SMBG) using finger stick blood sampling and a glucometer. The assessment included prospective single-arm cohort studies, randomized controlled trial, and a randomized crossover trial. Outcomes of interest included Eversense's clinical validity, clinical utility and safety.

  Overall, evidence suggested that Everesense device is highly correlated with rerference standards (VBG or SMBG). While results suggested moderate accuracy, with a high proportion of readings falling outside of 20% of the reference standard (7%-16%), a lack of consensus regarding what is considered accurate in assessments of interstitial glucose compared with blood glucose limits definitive conclusions. Hayes ultimately assigned a "C" rating (potential but unproven benefit), concluding that "low quality" evidence suggested that Eversense was highly correlated with and moderately accurate in the measurement of glucose levels compared with VBG or SMBG as reference standards. Limitations included small sample sizes, lack of long-term data, lack of power analysis, lack of reporting of patient characteristics, lack of reporting details of study procuedures, and a lack of reporting of patient recruitment methods.

Nonrandomized Studies

- In 2015, Dehennis et al. published a small multicenter study which assessed the accuracy of glucose measurement by the Senseonics' Eversense® CGM system compared to measurements obtained by venous blood, including 24 adults (between the ages of 18 and 65) with insulin-dependent type 1 or type 2 diabetes.[27] Twenty two of the twenty four (92%) sensors reported glucose continuously for 90 days, and the mean absolute relative difference (MARD) for all 24 sensors was 11.4 ± 2.7% compared to venous reference glucose values. There was no significant difference in glucose values detected by the CGM compared to standard blood glucose monitoring throughout the 90-day study, nor was there a significant difference between the two methods at low (<70mg/dL) or high >180mg/dL glucose levels. No serious adverse events were noted. The authors concluded that the study showed successful in-clinic and home use of the Senseonics CGM system over 90 days in subjects with diabetes mellitus.

- In 2017, Kropff et al. published the results of an uncontrolled multicenter observational trial which assessed the accuracy and longevity of the implantable Eversense CGM in the PRECISE study, including 71 adults (18 years and older) with type 1 and type 2 diabetes. The participants were

followed for 180 days to test the accuracy of the implanted CGM.[28] The mean absolute relative difference (MARD) for venous reference glucose values >4.2 mmol/L over the study duration was 11.1% (95% CI 10.5, 11.7). However, device performance in the hypoglycemic range (≤75 mg/dL) significantly less than the overall performance (21.7 vs. 11.6% MARD; p< 0.001). A Kaplan-Meier analysis for sensor survival estimated that 100, 82, and 40% of sensors were functional through day 45, day 90, and day 180, respectively. The authors noted that participants with type 2 diabetes and participants of non-Caucasian descent were underrepresented in this study; limiting the applicability of the results to a wider population.

Insulin Pumps

Type 2 Diabetes Patients

Systematic Reviews

- In 2021, Hayes published a systematic review evaluating the safety and efficacy of the V-Go disposable insulin delivery device for the management of type 1 or type 2 diabetes mellitus.[29] Searching the literature through September 2018, investigators identified 2 poor-quality retrospective cohort study assessing V-Go in the treatment of 116 patients with type 2 diabetes. In the larger study, patients on basal insulin injections with baseline HbA1c levels of 7% to 14% were switched to either V-Go or basal-bolus insulin injections. While both groups experienced significant improvements from baseline at 7-month follow-up, V-Go patients experienced significantly greater reductions in HbA1c values (– 0.64; 95% CI, -1.17 to -0.10; $p = 0.02$). Limitations included the study's small sample size, retrospective design, variable follow-up durations and author conflicts of interest with the device manufacturer. A smaller study assessing 23 patients reported similar results at 12-week follow-up.

  Given the very-low quality of evidence, authors concluded that evidence did not allow for conclusions to be drawn regarding the safety or efficacy of the V-Go system. While early results indicate that V-Go may improve patients' glycemic control as measured by reductions in hemoglobin A1c levels, substantial uncertainty remains given the limited number of studies conducted to date, lack of long-term follow-up, unclear patient selection criteria and small sample sizes. Investigators concluded that V-Go "may be a good option for patients with poorly controlled type 2 diabetes," but ultimately assigned the system a "D2" rating (insufficient evidence).

- In 2012, the Agency for Healthcare and Research Quality published a comparative effectiveness review of methods of insulin delivery which focused, in part, on type 2 diabetics.[30] The review included three RCTs of 6-12 months duration and one crossover trial published prior to July 2011, with no significant heterogeneity found between studies. Studies reported no difference in the effect of continuous subcutaneous insulin infusion (CSII) and multiple daily insulin injections (MDI) on HbA1c (moderate strength of evidence [SOE]), severe hypoglycemia (low SOE) or hyperglycemia (low SOE) for adults with type 2 diabetes. The evidence was insufficient to make definitive conclusions about the relative effects of these therapies on hyperglycemia and weight. In general, the existing studies were small and of fair to poor quality. The review concluded that both CSII and MDI have similar effectiveness on glycemic control and severe

hypoglycemia in type 2 diabetics and therefore the approach to intensive insulin therapy could be individualized to patient preference that would maximize their quality of life.

- A second systematic review was published by Yeh et al. that also included the same four trials and arrived at similar conclusions.[19]

Randomized Controlled Trials (RCTs)

- In 2014, Reznik et al. published results from the industry-sponsored open-label OpT2mise RCT which compared CSII with MDI for treatment of type 2 diabetes.[31] Patients with type 2 diabetes who had poor glycemic control despite MDI with insulin analogues were enrolled into a 2-month dose-optimization run-in period. After the run-in period, patients with HbA1c of 8.0-12.0% were randomly assigned (1:1) to pump treatment or to continue with multiple daily injections. Neither patients nor investigators were masked to treatment allocation. In the intent to treat population, 495/590 screened patients entered the run-in phase and 331 were randomized (168 to CSII, 163 to MDI). At six months post-randomization, mean HbA1c had decreased by 1.1% (SD 1.2%) in the CSII group and 0.4% (SD 1.1%) in the MDI, resulting in a significant between-group difference of -0.7% (95% CI -0.9 to -0.4%; p<0.0001). In addition, the mean total daily insulin dose was 97 units (SD 56) in the CSII group versus 122 units (SD 68) for MDI (p<0.0001), with no significant difference in bodyweight change between the two groups. There was no significant difference between groups in the number diabetes-related serious adverse events. Limitations of this RCT included lack of blinding of patients and investigators, exclusion of patients with high daily insulin doses, actual dose of insulin could not be assessed, and the finding that patients in the MDI group showed a decrease in their daily frequency of self-monitoring during the treatment phase, which may have impacted insulin dosing.

- In 2016, Aronson et al.[32] published results at 12-month follow-up of the OpT2mise RCT discussed above.[31,32] During the six months randomization phase of the OpT2mise trial the MDI group was switched to CSII. The pump therapy group maintained their HbA1c improvement at 12 months while the MDI group, which was switched to pump therapy, showed a 0.8% reduction, with the final HbA1c level being identical in both arms. Total daily insulin dose (TDD) in the pump group remained stable at 12 months. The MDI-pump group showed a 19% decline in TDD, such that by 12 months TDD was equivalent in both groups. The investigators concluded that the pump therapy has a sustained durable effect on glycemic control in type 2 diabetes.

Summary

There is insufficient evidence regarding the use of CSII in type 2 diabetic patients is as effective in controlling glycemia as MDI. The majority of RCTs published to date have reported no difference in the effect of CSII and MDI on HbA1c, severe hypoglycemia or hyperglycemia for adults with type 2 diabetes. While this could indicate that the two methods of insulin administration may be equal, these RCTs were small in number, moderate quality and typically reported on small sample sizes. At this time definitive conclusions about the effectiveness of CSII compared to MDI in type 2 diabetic patients cannot be drawn.

Integrated Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitor (CGM) (CSII-CGM) Systems

Artificial Pancreas Device Systems

Three recent systematic reviews evaluated the efficacy of artificial pancreas device systems relative to conventional pump therapy and other types of insulin-based treatment.[33-35] Reviews reported improvements in patients' time spent in the hypoglycemic phase, proportion of time with sensor glucose level above 10 mmol/L and patients' daily insulin requirements. Each study concluded that artificial pancreas systems are safe and efficacious approaches for the treatment of type 1 diabetes, despite the need for additional studies to further establish validity.

Sensor-Augmented CSII-CGM Systems

Systematic Reviews and Technology Assessments

In 2016, the United Kingdom-based National Institute for Health Research (NHS) published a systematic review and technology assessment integrated sensor-augmented pump therapy systems [the MiniMed® Paradigm Veo system and the Animas Vibe and G4® PLATINUM CGM (continuous glucose monitoring) system] for managing blood glucose levels in type 1 diabetes.[36] This technology assessment informed the 2016 guidelines published by the National Institute for Health and Care Excellence (NICE) on these devices (see Clinical Practice Guidelines section below). The review of the evidence was performed prior to March 2015. In the evaluation of the clinical effectiveness of the integrated continuous subcutaneous insulin infusion (CSII)-CGM system (Animas Vibe pump with Decom G4 CGM), seven comparative studies were included. Three of the included studies compared CSII-CGM to CSII-SMBG (self-monitoring of blood glucose), and four studies compared CSII-CGM to multiple daily injections (MDI)-SMBG. While most of these studies included small sample sizes (n=16 to 76), the large RCTs included in the review are described in detail below.[37,38] Although the review reported that the integrated CSII-CGM system significantly improved HbA1c levels and quality of life compared to MDI-SMBG, the evidence base was poor and the quality of the included studies deemed as low.

Randomized Controlled Trials

In 2008, Hirsch et al. published six-month results of a multicenter RCT designed to evaluate the effectiveness and safety of the Paradigm CSII-CGM system compared with a Paradigm CSII pump used with SMBG (CSII-SMBG), including 146 subjects (ages of 12 to 72 years) with type 1 diabetes and baseline HbA1c levels of greater than or equal to 7.5%. At six months, change in HbA1c from baseline was significant for both groups ($p<0.001$), however; the between-group differences were not significant (CSII-CGM group = -0.71% [+/-0.71%] and by -0.56 [+/-0.72%] in the CSII-SMBG group). In addition, the percentage of subjects that achieved 7% HbA1c was not significantly different between groups. CSII-CGM subjects showed no change in mean hypoglycemia area under the curve (AUC), whereas CSII-SMBG subjects showed an increase ($p=0.001$) in hypoglycemia AUC during the blinded periods of the study. The between-group difference in hypoglycemia area under the curve (AUC) was significant ($p<0.0002$). Fourteen severe hypoglycemic events occurred (11 in the CSII-CGM group and three in the CSII-SMBG group, $p=0.04$). One limitation of this study was the enrollment of subjects who were not actively engaged in their diabetes self-management prior to the study.

In 2010, Bergenstal et al. published one-year results from a multicenter RCT evaluating the effectiveness of sensor-augmented insulin pump therapy in type 1 diabetes. Efficacy of Paradigm REAL-Time sensor-

augmented pump therapy (CSII-CGM) was compared with that of a regimen of MDI-SMBG in 485 patients (329 adults and 156 children) with inadequately controlled type 1 diabetes. At one year, the baseline mean HbA1c had decreased from 8.3% to 7.5% in the CSII-CGM group, compared to the MDI-SMBG group, where the decrease was from 8.3% to 8.1%. The difference in decrease in HbA1c was significantly different between the two groups (p<0.001). The proportion of patients who reached the glycated hemoglobin target (<7%) was greater in the CSII-CGM group than in the MDI-SMBG group. The rate of severe hypoglycemia in the CSII-CGM group (13.31 cases per 100 person-years) did not differ significantly from that in the MDI-SMBG group (13.48 per 100 person-years, p=0.58). Limitations of this trial include lack a blinding of patients, investigators, and caregivers with regards to the intervention used; limited generalizability of results due to narrow range of HbA1c used as inclusion criteria; and patients in the CSII-CGM group received more contact with clinical staff members than did patients in the MDI-SMBG group during the first 5 weeks of the study.

In 2012, Battelino et al. published findings of a European multicenter crossover trial that included 153 children and adults with type 1 diabetes.[39] The study used the MiniMed Paradigm REAL-Time system, which integrates a CGM device and an insulin pump system. Patients were randomized to use of the system for 6 months with the sensor on and 6 months with the sensor off, in random order, with a washout period of 4 months between interventions. Baseline HbA1c ranged from 7.5% to 9.5%. After treatment, mean HbA1c was 8.04% in the sensor on arm and 8.47% in the sensor off arm. The mean difference in HbA1c between groups was -0.43% (95% CI, -0.32% to -0.55%; p<0.001). Neither of the above trials were blinded, and neither compared continuous with intermittent use of the CGM.

Nonrandomized Studies

In 2013, Nørgaard et al. reported on the largest and longest multicenter prospective observational study of continuous glucose monitoring with insulin infusion pumps, so called sensor-augmented pump therapy.[40] The investigators reported on a 12-month observational study in patients with type 1 diabetes treated with continuous subcutaneous insulin infusion (CSII), upon the introduction of continuous glucose monitoring (CGM). The study was conducted in 15 countries to document the real-life use of sensor-augmented pump therapy and assess which variables are associated with improvement in type 1 diabetes management. Data from 263 patients (38% male; mean age, 28.0±15.7 years [range, 1-69 years]; body mass index, 23.3±4.9 kg/m(2); diabetes duration, 13.9±10.7 years; CSII duration, 2.6±3 years) were collected. Baseline mean HbA1c was 8.1±1.4%; 82% had suboptimal HbA1c (≥7%). The investigators found that the average sensor use for 12 months was only 30% (range, 0-94%), and that sensor use decreased with time (first 3 months, 37%; last 3 months, 27%). The investigators found that there were significantly more patients with an HbA1c value of < 7.5% after 3 months of sensor-augmented pump therapy than at baseline (baseline, 29%; 3 months, 37%) However, the percentage of patients with an HbA1c value of < 7.5% decreased over the 12-month observation period, such that the percentage of patients with an HbA1c value of < 7.5% after 12 months was not statistically significantly higher than at baseline.

<u>APD Systems with Threshold Suspend</u>

Systematic Reviews and Technology Assessments

In 2016, the ECRI Institute published an updated emerging technology report on threshold suspend systems for managing hypoglycemia in patients with type 1 diabetes.[41] This report included two RCTs

(described below), one small prospective pre-post study in 21 children, and one retrospective analysis (described below).[42-44] All four studies reported on the number of moderate and/or severe hypoglycemia events. Although studies reported this measure in different ways, study patients using the MiniMed Veo or 530G with the threshold suspend/LGS feature activated had improvement in this outcome compared with study patients using sensor-augmented pump therapy, the MiniMed Veo or 530G with the threshold-suspend/LGS feature turned off, or patients using a standard insulin pump alone. The report concluded that compared with sensor-augmented systems therapy alone, sensor-augmented integrated systems with threshold suspend resulted in fewer severe hypoglycemic episodes (requiring assistance for treatment or resulting in seizure or coma), including nocturnal episodes. The assessment deemed the strength of evidence for this outcome as moderate. However, conclusions could not be reached regarding the following outcomes due to low or very low strength of evidence: whether threshold suspend devices were more effective than standard pump therapy alone for any outcomes reported, including severe hypoglycemic episodes, HbA1c and ketoacidosis. In addition, although the report indicated that the threshold suspend systems did not appear to be more effective than sensor-augmented systems, or standard pumps, this was based on low level evidence (only two RCTs).

In the 2016 NHS systematic review of integrated sensor-augmented pump therapy systems described above, the reviewers reported that the Veo system reduced the number of hypoglycemic events compared to other treatments, but did not improve other outcomes, including HbA1c levels.[36] This analysis was based on two RCTs, one of which compared Veo with an integrated CSII-CGM system and the other study compared Veo with a CSII-SMBG system in a mixed population. These two RCTs are described in detail below.[43,44] The reviewers deemed the evidence base as poor for all treatments, including the Veo, with the quality of the included studies being generally low.

Randomized Controlled Trials (RCTs)

In 2012, Garg et al. published data from the in-clinic arm of the ASPIRE randomized crossover trial that included 50 patients with type 1 diabetes who had at least 3 months' experience with an insulin pump system.[45] The goal of the study was to evaluate whether the severity and duration of hypoglycemia was reduced when the LGS feature was used. After a 2-week run-in period, patients underwent two in-clinic exercise sessions to induce hypoglycemia. The LGS feature on the insulin pump was turned on in one session and off in the other session, in random order. The study protocol called for patients to start exercise with a glucose level of 100 to 140 mg/dL, and to use a treadmill or stationary bicycle until their plasma glucose level was 85 mg/dL or less. The mean duration of hypoglycemia was significantly less during the LGS-on sessions (138.5 minutes; SD=68 minutes) than the LGS-off sessions (170.7 minutes; SD=91 minutes; p=0.006). In addition, hypoglycemia severity was significantly lower in the LGS-on group, with the mean lowest glucose level being 59.5 mg/dL in the LGS-on group and 57.6 mg/dL (p=0.015) in the LGS-off group.

In 2013, Bergenstal et al. published the results of the ASPIRE RCT that evaluated the efficacy and safety of sensor-augmented insulin-pump therapy with and without the threshold suspend feature in patients with nocturnal hypoglycemia, using the European-approved version of the MiniMed 530G, called the Paradigm Veo System.[43] Patients with type 1 diabetes and documented nocturnal hypoglycemia were randomly assigned to receive sensor-augmented insulin-pump therapy with or without the threshold suspend feature for three months. Of a total of 247 patients, 127 patients were randomly assigned to receive sensor-augmented insulin-pump therapy with the threshold suspend and 126 patients served as controls, receiving standard sensor-augmented insulin-pump therapy. The changes in HbA1c values

were similar in the two groups. However, the mean AUC for nocturnal hypoglycemic events that was 37.5% lower in the threshold suspend group than in the control group (980 ± 1200 mg per deciliter x minutes versus 1568 ± 1995 mg per deciliter × minutes; p<0.001). Thus, hypoglycemic events occurred 31.8% less frequently in the threshold suspend group than in the control group (1.5 ± 1.0 vs. 2.2 ± 1.3 per patient-week, p<0.001). The authors concluded that over a three month period, the use of sensor-augmented insulin-pump therapy with the threshold suspend feature reduced nocturnal hypoglycemia without increasing glycated hemoglobin values.

In 2013, Ly et al. also published results from an RCT that included 95 subjects randomized to six months of treatment with either Medtronic Paradigm Veo System (n=46) or to insulin pump treatment alone (n=49).[44] Subjects were aged 4 to 50 years old with type 1 diabetes, had used an insulin pump for at least 6 months, had an HbA1c level of 8.5% or less, and had impaired awareness of hypoglycemia. The authors noted that the baseline rate of severe hypoglycemic events (defined as hypoglycemic seizure or coma) and moderate hypoglycemic events (defined as an event requiring assistance from another person) was significantly higher in the Veo group (129.6 vs 20.7 events per 100 subject-months). After six months, the frequency of moderate to severe hypoglycemic events per 100 subject-months was 34.2 in the control group vs. 9.6 in the Veo group. The authors reported the incidence rate ratio was 3.6 (p<0.001), indicating greater improvement in the LGS group compared with the pump-only group. The incidence rate ratio for moderate and severe events excluding the two children was 1.7 (p=0.08). Mean HbA1c level, a secondary outcome, did not differ between groups at baseline or at six months. Change in HbA1c levels during the treatment period was -0.06% in the control group and -0.1% in the experimental group.

Nonrandomized Studies

In 2015, Agrawal et al. published a retrospective study of the Medtronic Paradigm Veo System, including 20,973 subjects who were allowed to adjust the threshold suspend feature manually and upload their pump and sensor data for a period of 40 weeks.[42] The authors compared data from 758,382 subject-days when the suspend feature was activated to the 166,791 subject-days when it was not. Overall 70% of subjects (n=14,673) had the suspend feature activated 100% of the time, while 11% (n=2249) did not use that feature at all. The remaining 19% of subjects used the feature some unspecified portion of the time. On days when the threshold suspend feature was on, overall, there was an average of 0.82 suspend events per subject-day. In addition, glucose values were reported to be 50 mg/dL or less 0.64% of the time when the feature was on versus 2.1% of the time when the feature was off. The reduction in hypoglycemia was greatest at night. The authors concluded that the use of an automated insulin delivery device with threshold suspend appeared to be associated with fewer and shorter hypoglycemic episodes. However, the length and severity of hypoglycemic episodes was not fully described.

<u>Insulin-Only APD Systems</u>

Randomized Controlled Trials

In 2016, Ly et al. published the results of a small RCT which evaluated the experimental predecessor to the MiniMed 670G insulin-only system, including 21 children and adolescents with type 1 diabetes at diabetes camp.[46] During the camp study, 21 subjects completed 50 overnight closed-loop (OCL) nights and 52 control nights with only sensor-augmented therapy. The median time spent in range (70 to

150 mg/dL) was significantly greater during OCL at 66.4% (n = 55) versus 50.6% (n = 52) during the control period (p = 0.004). In addition, the investigators reported that less time was spent in the hypoglycemic ranges <60 mg/dL and <70 mg/dL during OCL compared with the control period (p = 0.003 and p < 0.001, respectively), indicating that the hybrid closed loop system is effective in improving time spent in range as well as reducing nocturnal hypoglycemia during the overnight period in children and adolescents with type 1 diabetes in a diabetes camp setting.

Nonrandomized Studies

Prior to the FDA approval of the MiniMed 670G, in 2016, Ly et al. published a small case series evaluating the hybrid system in nine adults and 15 adolescents in supervised hotel-based studies over four to five days.[47] The overall mean percentage of time in range (70–180 mg/dL, 3.9–10 mmol/L) during hybrid closed-loop was 71.8% in the adult cohort and 69.8% in the adolescent cohort. The overall percentage of time spent under 70 mg/dL (3.9 mmol/L) was 2.0% in the adult cohort and 2.5% in the adolescent cohort. Mean glucose values were 152 mg/dL (8.4 mmol/L) in the adult cohort and 153 mg/dL (8.5 mmol/L) in the adolescent cohort.

In 2016, Bergenstal et al. published the results of an investigational device exemption (IDE) study designed to assess the safety of the MiniMed 670G, including adolescents (n = 30, ages 14-21 years) and adults (n = 94, ages 22-75 years) who had type 1 diabetes mellitus for at least 2 years, HbA1c less than 10.0%, and prior insulin pump therapy for a minimum of 6 months.[48] All subjects wore the 670G system for approximately 3.5 months. All subjects underwent a two week in-home run-in phase using the 670G in Manual mode (sensor-augmented pump) followed by a 3 month phase when the system was used in auto "hybrid" mode to automatically adjust basal insulin levels. During the auto phase, all subjects underwent a 6 day/5 night supervised hotel stay that included a 24-hour blood sampling period to compare glucose sensor measurements to lab-based venous blood glucose measurements. The purpose of the hotel phase was to stress the subjects with sustained daily exercise and unrestricted eating to monitor the device's response to significant physiological variations. The authors reported that no episodes of severe hypoglycemia or ketoacidosis were noted during the study period. There were 20 device-related adverse events reported during the study period, including skin irritation or rash (n=2), hyperglycemia (n=6), and severe hyperglycemia (defined as greater than 300 mg/dL, n=12). All events were resolved at home. The closed-loop auto function was used for a median of 87.2% of the study period. The authors reported that their study demonstrated that hybrid closed-loop automated insulin delivery was associated with few serious or device-related adverse events in individuals with type 1 diabetes. Limitations, as reported by the authors, included a lack of a control group or randomization, relatively short study duration and an imbalance between the lengths of the three study periods. They concluded that longer-term randomized studies were needed to further evaluate the safety and efficacy of the 670G system.

In 2017, Garg et al. published additional results from the same study cohort used by Bergenstal et al., described above.[49] In this publication, the authors reported that during the auto phase, the mean in-target glucose sensor reading in the adolescent group increased from 60.4% to 67.2% between the run-in to the auto phase (p<0.001). For the adult group, the mean in-target glucose sensor reading went from 68.8% to 73.8% (p<0.001). Similarly, time with glucose sensor readings of > 180 mg/dL decreased from 35.3% to 30.0% in the adolescent group (p<0.001) and 24.9% to 22.8% in the adult group (p<0.01). The mean time with sensor glucose readings < 70 mg/dL decreased from 4.3% to 2.8% in the adolescent group (p<0.0009) and 6.4% to 3.4% (p<0.001) in the adult group. Mean HbA1c concentrations

decreased from 7.7% at baseline to 7.1% (p<0.001) at the end of the 3-month auto phase in the adolescent group and from 7.3% to 6.8% (p<0.001) in the adult group during the same time frame. The percent nighttime sensor glucose readings > 180 mg/dL decreased from 30.3% to 25.6% (p<0.001) in the adolescent group and 25.8% to 20.4% (p<0.001) in the adult group. Similarly, mean nighttime sensor glucose readings < 50 mg/dL decreased from 1.3% to 0.6% in the adolescent group (p<0.001) and 1.1 to 0.7% (p<0.001) in the adult group. Additional limitations not described above include restriction to relatively healthy and well-controlled patients and low baseline HbA1c, which limits the generalizability of the results. Regardless, the investigators concluded that the 670G, when operating in auto "hybrid" mode provided significantly better blood glucose control over the use of the device while in manual sensor-augmented therapy mode.

Bi-Hormonal APD Systems

Randomized Controlled Trials

In 2015, Haidar et al. published results from a Canadian open-label randomized controlled crossover trial that compared dual-hormone artificial pancreas, single-hormone artificial pancreas, and conventional insulin pump therapy (plus self-monitoring of blood glucose) for glycemic control in patients aged 12 years or older with type 1 diabetes. Of the 40 patients recruited and randomized, only 30 patients (20 adults and 10 adolescents) completed the study and were included in the analysis. The mean proportion of time spent in the plasma glucose target range (4.0-10.0 mmol/L for 2-hours post-prandially and 4.0-8.0 mmol/L otherwise) over 24 hours was 62% (SD 18%), 63% (SD 18%), and 51% (SD 19%) with single-hormone artificial pancreas, dual-hormone artificial pancreas, and conventional insulin pump therapy, respectively.[50] The mean difference in time spent in the target range between single-hormone artificial pancreas and conventional insulin pump therapy was 11% (p=0.002) and between dual-hormone artificial pancreas and conventional insulin pump therapy was 12% (p=0.0001), indicating that both the single- and dual-hormone systems were more effective than conventional CSII at maintaining glucose levels within a healthy target range. There was no difference in the proportion of time spent in the target range between the single-hormone and dual-hormone artificial pancreas systems. In addition, the percentage of patients in each group with at least one hypoglycemic event between single-hormone artificial pancreas and conventional insulin pump therapy was 17% and 83%, respectively (p<0.0001) and between dual-hormone artificial pancreas and conventional insulin pump therapy was 21% and 83%, respectively (p=0.0001), indicating that both the single- and dual-hormone systems were more effective than conventional CSII at reducing hypoglycemic events. This was true for both the total number of events as well as nocturnal and exercise-induced events. There was no difference in hypoglycemic events between the single-hormone and dual-hormone artificial pancreas systems. Limitations of this study include: small sample size, high drop-out rate, and the fact that the study was performed strictly in an inpatient setting and only for the duration of one day.

CLINICAL PRACTICE GUIDELINES

Continuos Glucose Monitors

Adult Patients

Advanced Technologies & Treatments for Diabetes (AATD) Congress

In 2019, the AATD Congress published recommendations addressing clinical targets for continuous monitoring data Interpretation on the basis of expert consensus.[51] The consensus report was endorsed by the American Diabetes Association, American Association of Clinical Endocrinologists, American Association of Diabetes Educators, European Association for the Study of Diabetes, Foundation of European Nurses in Diabetes, International Society for Pediatric and Adolescent Diabetes, JDRF, and Pediatric Endocrine Society. Please refer to the following link to view data tables of outlining each recommendation.

American Diabetes Association (ADA)

The 2020, the ADA "Standards of Medical Care in Diabetes" evidence-based guidelines recommended the following regarding the use of CGMs, insulin pumps and integrated systems for people with diabetes mellitus:[52]

- When prescribing continuous glucose monitoring (CGM) devices, robust diabetes education, training, and support are required for optimal CGM device implementation and ongoing use. People using CGM devices need to have the ability to perform self-monitoring of blood glucose in order to calibrate their monitor and/or verify readings if discordant from their symptoms. **Grade of Evidence: E**
- When used properly, real-time continuous glucose monitors in conjunction with insulin therapy are a useful tool to lower A1C levels and/or reduce hypoglycemia in adults with type 1 diabetes who are not meeting glycemic targets, have hypoglycemia unawareness, and/or have episodes of hypoglycemia. **Grade of Evidence: A**
- When used properly, intermittently scanned continuous glucose monitors in conjunction with insulin therapy are useful tools to lower A1C levels and/or reduce hypoglycemia in adults with type 1 diabetes who are not meeting glycemic targets, have hypoglycemia unawareness, and/or have episodes of hypoglycemia. **Grade of Evidence: C**
- When used properly, real-time and intermittently scanned continuous glucose monitors in conjunction with insulin therapy are useful tools to lower A1C and/or reduce hypoglycemia in adults with type 2 diabetes who are not meeting glycemic targets. **Grade of Evidence: B**
- Continuous glucose monitoring (CGM) should be considered in all children and adolescents with type 1 diabetes, whether using injections or continuous subcutaneous insulin infusion, as an additional tool to help improve glucose control. Benefits of CGM correlate with adherence to ongoing use of the device. **Grade of Evidence: B**
- Real-time continuous glucose monitoring (CGM) devices should be used as close to daily as possible for maximal benefit. Intermittently scanned CGM devices should be scanned frequently, at a minimum once every 8 hours. **Grade of Evidence: A**
- Real-time continuous glucose monitors may be used effectively to improve A1C levels, time in range, and neonatal outcomes in pregnant women with type 1 diabetes. **Grade of Evidence: B**
- Blinded continuous glucose monitor data, when coupled with diabetes self-management education and medication dose adjustment, can be helpful in identifying and correcting patterns of hyper- and hypoglycemia in people with type 1 diabetes and type 2 diabetes. **Grade of Evidence: E**
- People who have been using continuous glucose monitors should have continued access across third-party payers. **Grade of Evidence: E**
- Insulin pump therapy may be considered as an option for all adults, children, and adolescents with type 1 diabetes who are able to safely manage the device. **Grade of Evidence: A**

- Individuals with diabetes who have been successfully using continuous subcutaneous insulin infusion should have continued access across third-party payers. **Grade of Evidence: E**
- Sensor-augmented pump therapy with automatic low glucose suspend may be considered for adults and children with type 1 diabetes to prevent/mitigate episodes of hypoglycemia. **Grade of Evidence: B**
- Automated insulin delivery systems may be considered in children B and adults with type 1 diabetes to improve glycemic control. **Grade of Evidence: A**
- Individual patients may be using systems not approved by the U.S. Food and Drug Administration such as do-it-yourself closed loop systems and others; providers cannot prescribe these systems but can provide safety information/troubleshooting/backup advice for the individual devices to enhance patient safety. **Grade of Evidence: E**
- Sensor-augmented pump therapy with automatic low glucose suspend may be considered for adults and children with type 1 diabetes to prevent/mitigate episodes of hypoglycemia. **Grade of Evidence: B**
- Automated insulin delivery systems should be considered in adults with type 1 diabetes who have the skills to use them in order to improve time in range, reduce HbA1C and hypoglycemia. **Grade of Evidence: B**
    - These systems may also be useful to improve glycemia in children. **Grade of Evidence: B**
- Individual patients may be using systems not approved by the U.S. Food and Drug Administration such as do-it-yourself closed loop systems and others; providers cannot prescribe these systems but can provide safety information/troubleshooting/backup advice for the individual devices to enhance patient safety. **Grade of Evidence: E**

Oregon Health Evidence Review Commission (HERC)

In 2017, HERC issued a coverage guidance addressing CGM for the treatment of diabetes.[53] Investigators made the following recommendations:

- Real-time CGM is recommended for coverage (*weak recommendation*) in adults with type 1 diabetes mellitus:
    - Who have received or will receive diabetes education specific to the use of CGM and who have used the device for at least 50% of the time at their first follow-up visit and
    - Who have baseline HbA1c levels greater than or equal to 8.0%, frequent or severe hypoglycemia, or impaired awareness of hypoglycemia (including presence of these conditions prior to initiation of CGM).
- Real-time CGM (including the CGM-enabled insulin pump) is recommended for coverage (*weak recommendation*) in adults with type 1 diabetes on insulin pump management who have received or will receive diabetes education specific to the use of CGM and who have used the device for at least 50% of the time at their first follow-up visit.
- Real-time CGM is not recommended for coverage in adults with type 2 diabetes (*weak recommendation*).
- Retrospective CGM is not recommended for coverage in patients of any age with type 1 or type 2 diabetes (*strong recommendation*).

Endocrine Society

The 2016 Endocrine Society evidence-based clinical practice guideline on "Continuous Subcutaneous Insulin Infusion Therapy and Continuous Glucose Monitoring in Adults"[54] recommended the following regarding the use of CGMs for people with diabetes mellitus:

- Real-time CGM is recommended for adults with well-controlled DM1 and for adults with DM1 who have HbA1c levels above target. Patients should be willing and able to use a CGM device on a nearly daily basis.
- Short-term use of real time CGM is suggested for adult patients with DM2 who have HbA1c levels greater or equal to 7% and are both willing and able to use a CGM device.
- Education, training, and ongoing support to help achieve and maintain individualized glycemic goals are suggested for adults with diabetes using CGM.

National Institute for Health and Care Excellence (NICE)

The 2022 NICE guideline "Type 1 Diabetes in Adults: Diagnosis and Management"[55] was based on a systematic review of the evidence and recommended the following regarding the use of CGMs for people with type 1 diabetes:

- Routine use of real time (rt) CGM in adults with type 1 diabetes is not recommended.
- Consider rt- CGM for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and calibrate it as needed, and who have at least one of the following (despite optimized use of insulin therapy and conventional blood glucose monitoring): more than one episode a year of severe hypoglycemia that has no obviously preventable cause; complete hypoglycemia unawareness; frequent asymptomatic hypoglycemia that interferes with daily activities; extreme fear of hypoglycemia; or hyperglycemia that persists despite frequent testing (but only continue CGM if HbA1c can be sustained at 7% or below, or if there has been a fall in HbA1c of 2.5% or more).
- For adults with type 1 diabetes using CGM, insulin therapy should be applied with either multiple daily injections of insulin or continuous subcutaneous insulin infusion therapy.

The 2022 NICE guideline "Type 2 Diabetes in Adults: Management" did not recommend the use of CGMs for people with type 2 diabetes due to a lack of high quality RCTs and conflicting evidence. The panel stated that there is still uncertainty regarding the effectiveness of continuous glucose monitoring.[24]

American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE)

In 2016, the AACE and ACE published a joint consensus statement on "Outpatient Glucose Monitoring"[56] recommended the following regarding the use of CGMs for people with diabetes mellitus:

- CGM is recommended for adults and children with type 1 diabetes, particularly for individuals with a history of severe hypoglycemia and hypoglycemia unawareness, and to assist in correcting hyperglycemia in patients not within target range for blood glucose level.
- Before CGM use, patients should have knowledge of the basics of sensor insertion, calibration, and real-time data interpretation. More in-depth training and more frequent follow-up is recommended for CGM users who are children.
- Current evidence is limited for CGM use for patients with type 2 diabetes who are receiving insulin or sulfonylureas; trials assessing the use of CGM for these patients are ongoing.
- No recommendation was provided regarding the use of CGM for persons with type 2 diabetes who have a low risk of hypoglycemia.

- The benefits of CGM in pregnant individuals with preexisting diabetes are unclear; and additional studies are needed. CGM should primarily be considered a teaching tool when used during pregnancy, and should be used to evaluate peak postprandial blood glucose, fine-tune insulin dosing, and identify foods associated with blood glucose fluctuations.
- Additionally, CGM can be used as a supplement to blood glucose monitoring during pregnancy, in particular for monitoring nocturnal hypoglycemia or hyperglycemia and postprandial hyperglycemia.

Children and Adolescent Patients

American Diabetes Association

The 2019, the ADA "Standards of Medical Care in Diabetes"[57] evidence-based guidelines recommended the following regarding the use of CGMs for people with diabetes mellitus:

- Real-time CGM should be considered in children and adolescents with type 1 diabetes, whether using multiple daily injections or continuous subcutaneous insulin infusion, as an additional tool to help improve glucose control and reduce the risk of hypoglycemia. Benefits of CGM correlate with adherence to ongoing use of the device. Level of Evidence = A (Clear evidence from well-conducted adequately powered RCTs)
- Sensor-augmented pump therapy may be considered for children, adolescents and adults to improve glycemic control without an increase in hypoglycemia or severe hypoglycemia. Benefits correlate with adherence to ongoing use of the device. Level of Evidence = A (Clear evidence from well-conducted adequately powered RCTs)
- When prescribing continuous glucose monitoring, robust diabetes education, training and support are required for optimal continuous glucose monitor implementation and ongoing use.
- When used properly, CGM in conjunction with intensive insulin regimens (defined as multiple-dose insulin **or** insulin pump therapy) is a useful tool to lower A1C in selected adults (aged 25 years) with type 1 diabetes. Level of Evidence = A (Clear evidence from well-conducted adequately powered RCTs)
- Real-time CGM may be a useful tool in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. Level of Evidence = B (Supportive evidence from well-conducted cohort studies and case series)
- Real-time CGM should be used as close to daily as possible for maximal benefit. Level of Evidence = A (Clear evidence from well-conducted adequately powered RCTs)
- Sensor-augmented pump therapy with automatic low-glucose suspend may be considered for adults with type 1 diabetes at high risk of hypoglycemia to prevent episodes of hypoglycemia and reduce their severity. Level of Evidence = B (Supportive evidence from well-conducted cohort studies and case series)

Oregon Health Evidence Review Commission (HERC)

In 2017, HERC issued a coverage guidance addressing CGM for the treatment of diabetes.[53] Investigators made the following recommendations:

- Real-time CGM is recommended for coverage (*weak recommendation*) in children and adolescents under age 21 with type 1 diabetes who have received or will receive diabetes

education specific to the use of CGM and who have used the device for at least 50% of the time at their first follow-up visit.
- Retrospective CGM is not recommended for coverage in patients of any age with type 1 or type 2 diabetes (*strong recommendation*).

International Society for Pediatric and Adolescent Diabetes (ISPAD)

The 2014 ISPAD evidence –based clinical practice consensus guideline, "Assessment and Monitoring of Glycemic Control in Children and Adolescents with Diabetes"[58] recommended the following regarding the use of CGMs for children with diabetes mellitus:

- CGM may particularly benefit individuals with hypoglycemic unawareness because CGM devices can be set to alert patients when glucose is below a specified range or when glucose falls at a rapid rate. However, it is currently recommended that CGM values are confirmed by SMBG for real-time adjustments of insulin dosing.

National Institute for Health and Care Excellence (NICE)

The 2023 NICE guideline, "Diabetes (Type 1 and Type 2) in Children and Young People: Diagnosis and Management"[59] recommended the following regarding the use of CGMs for children with diabetes mellitus:

- Offer ongoing real-time (rt)-CGM monitoring with alarms to children and young people with type 1 diabetes who have at least one of the following: frequent severe hypoglycemia, impaired awareness of hypoglycemia associated with adverse consequences (e.g., seizures or anxiety), or inability to recognize or communicate about symptoms of hypoglycemia.
- Consider ongoing rt-CGM for neonates, infants, and preschool children; children and young people who undertake high levels of physical activity; and children and young people who have comorbidities (i.e., anorexia nervosa) or who are receiving treatment (e.g., corticosteroids) that impedes control of blood glucose levels.
- Consider intermittent CGM to improve blood glucose control in children and young people who have hyperglycemia that persists despite insulin adjustment and additional support.

<u>Pregnant Women</u>

American Diabetes Association (ADA)

The 2019, the ADA "Standards of Medical Care in Diabetes"[57] evidence-based guidelines recommended the following regarding the use of CGMs for people with diabetes mellitus:

- Real-time CGM may be used effectively to improve A1C levels and neonatal outcomes in pregnant women with type 1 diabetes. Level of Evidence = B (Supportive evidence from well-conducted cohort studies and case series)

In 2017, HERC issued a coverage guidance addressing CGM for the treatment of diabetes.[53] Investigators made the following recommendations:

- CGM is not recommended for coverage during pregnancy for type 2 diabetes or gestational diabetes (*weak recommendation*).

- CGM is recommended for coverage for women with type 1 diabetes who are pregnant or who plan to become pregnant within six months without regard to HbA1c levels (*weak recommendation*).

National Institute for Health and Care Excellence (NICE)

The NICE 2020 guideline, "Diabetes in Pregnancy: Management from Preconception to the Postnatal Period"[60] recommended the following regarding the use of CGMs for pregnant individuals with diabetes:

- CGM should not be offered routinely to pregnant women with diabetes.
- Consider CGM for pregnant women on insulin therapy who either have severe hypoglycemia or unstable blood glucose levels, or to gain information about changes in blood glucose levels.

Endocrine Society

The 2013 Endocrine Society evidence-based clinical practice guideline on "Diabetes and Pregnancy"[61] suggested that CGM be used during pregnancy for women with overt or gestational diabetes when SMBG is not sufficient to assess glycemic control. The society deemed this a weak recommendation due to low quality evidence. The society stated that "although there is a paucity of literature on continuous glucose monitoring use during pregnancy, there is evidence that in gestational diabetes, it will detect clinically meaningful hypoglycemia and postprandial hyperglycemia that may go unrecognized by self-monitoring of blood glucose".

Insulin Pumps

Type 2 Diabetes Patients

Endocrine Society

In 2016, the Endocrine Society conducted a systematic review in support of their clinical practice guidelines addressing the use of continuous subcutaneous insulin infusion (CSII) for the treatment of diabetes.[54] Authors recommended CSII with good adherence to monitoring and dosing patients with type 2 diabetes mellitus who have poor glycemic control despite intensive insulin therapy, oral agents, other injectable therapy and lifestyle modifications.

National Institute for Health and Care Excellence (NICE)

The 2015 NICE guideline, "Type 2 Diabetes in Adults: Management"[60] , did not address the use of an insulin pump as a treatment option for type 2 diabetic adults. However, the 2008 Tech Appraisal Guidance [TA151]: Continuous subcutaneous insulin infusion (CSII) for the treatment of diabetes mellitus, [62] recommended against the use of insulin pumps for treatment of type 2 diabetic patients of any age.

American Association of Clinical Endocrinologists/American College of Endocrinology

In 2014, the AACE/ACE published a clinical practice guideline addressing insulin pump use for the treatment of diabetes.[63] The guideline included a recommendation for the use of continuous

subcutaneous insulin infusion, stating that ideal CSII candidates include intensively managed insulin-dependent type 2 diabetics who meet the following criteria:

- Currently performing ≥ 4 insulin injections and ≥ 4 self-monitored blood glucose measurements daily
- Motivated to achieve optimal blood glucose control
- Willing and able to carry out the tasks that are required to use this complex and time consuming therapy safely and effectively
- Willing to maintain frequent contact with their health care team

Pediatric Patients

International Society for Pediatric and Adolescent Diabetes (ISPAD)

The 2014 ISPAD evidence –based clinical practice consensus guideline: Assessment and Monitoring of Glycemic Control in Children and Adolescents with Diabetes[64] stated that, "improvements in glycemic control, particularly when provided by intensive insulin treatment with multiple daily injections (MDI) or pump therapy with dose adjustments, reduces the risks of vascular complications." This statement was based on a combination of high quality evidence from well-conducted RCTs and expert consensus.

In the guideline, the ISPAD also stated that, "insulin pump therapy is at present the best way to imitate the physiological insulin profile" and that, "CSII has been proven to be safe in all ages and allows exact and flexible insulin dosing in small increments, multiple bolus dosing without need for injections, different prandial bolus options, and hourly adaptation of basal insulin."

National Institute for Health and Care Excellence (NICE)

The 2023 NICE guideline, "Diabetes (Type 1 and Type 2) in Children and Young People: Diagnosis and Management",[59] regarding children under the age of 18, recommended criteria based on the 2008 Tech Appraisal Guidance [TA151].[62] The NICE recommendations for CSII therapy were as follows:

- "Continuous subcutaneous insulin infusion (CSII or 'insulin pump') therapy is recommended as a treatment option for adults and children 12 years and older with type 1 diabetes mellitus provided that:
    - Attempts to achieve target HbA1c levels with MDIs result in the person experiencing disabling hypoglycaemia. (disabling hypoglycaemia is defined as the repeated and unpredictable occurrence of hypoglycaemia that results in persistent anxiety about recurrence and is associated with a significant adverse effect on quality of life); or
    - HbA1c levels have remained high (8.5% or above) on MDI therapy (including, if appropriate, the use of long-acting insulin analogues) despite a high level of care.
- For children younger than 12 years with type 1 diabetes mellitus CSII therapy is recommended as a treatment option when MDI therapy is considered to be impractical or inappropriate.
- For children between the ages of 12 and 18 years the same criteria for adults for CSII apply, but these children are also expected to undergo a trial of MDI therapy prior to CSII.
- It is recommended that CSII therapy be initiated only by a trained specialist team, which should normally comprise a physician with a specialist interest in insulin pump therapy, a diabetes

specialist nurse and a dietitian. Specialist teams should provide structured education programmes and advice on diet, lifestyle and exercise appropriate for people using CSII.
- Following initiation in adults and children 12 years and older, CSII therapy should only be continued if it results in a sustained improvement in glycaemic control, evidenced by a fall in HbA1c levels, or a sustained decrease in the rate of hypoglycaemic episodes. Appropriate targets for such improvements should be set by the responsible physician, in discussion with the person receiving the treatment or their carer.
- CSII therapy is not recommended for the treatment of people (children or adults) with type 2 diabetes mellitus."

Pregnant Women

American Diabetes Association (ADA)

In 2019, the ADA published a clinical practice guideline addressing the management of diabetes during pregnancy.[65] Authors stated "both multiple daily insulin injections and continuous subcutaneous insulin infusion are reasonable delivery strategies" with neither having been proven superior during pregnancy.

National Institute for Health and Care Excellence (NICE)

The NICE 2020 guideline, Diabetes in Pregnancy: Management from Preconception to the Postnatal Period[60] recommended the following:

> "Offer women with insulin-treated diabetes continuous subcutaneous insulin infusion (CSII; also known as insulin pump therapy) during pregnancy if adequate blood glucose control is not obtained by MDI without significant disabling hypoglycaemia. Disabling hypoglycaemia means the repeated and unpredicted occurrence of hypoglycaemia requiring third-party assistance that results in continuing anxiety about recurrence and is associated with significant adverse effect on quality of life."

The NICE guideline further states that:

> "Compared with MDI, CSII used during pregnancy in women with overt diabetes provides comparable or better glycemic control and pregnancy outcomes with no greater risk or possibly lower risk of maternal hypoglycemia. Additionally, compared with MDI, CSII provides greater lifestyle flexibility, easier blood glucose management, less blood glucose variability, and facilitates managing glucose control in the peri-delivery setting."

Endocrine Society

The 2013 Endocrine Society evidence-based clinical practice guideline on diabetes and pregnancy[61] recommended the, "ongoing use of CSII during pregnancy in women with diabetes when this has been initiated before pregnancy (strong recommendation, moderate quality evidence), but suggest that CSII not be initiated during pregnancy unless other insulin strategies including multiple daily doses of insulin have first been tried and proven unsuccessful." This was a weak recommendation based on low quality evidence. The guideline states that this refers to both type 1 and type 2 diabetic patients.

Combination Integrated Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitoring (CGM) Systems

American Diabetes Association (ADA)

In 2019, the ADA "Standards of Medical Care in Diabetes" evidence-based guidelines made the following recommendations for insulin pumps:[66]

- "Most adults, children and adolescents with type 1 diabetes should be treated with intensive insulin therapy with either multiple daily injections or an insulin pump."
- "Insulin pump therapy may be considered as an option for all children and adolescents, especially in children under 7 years of age."
- Automated insulin delivery systems may be considered in children more than 7 years of age and adults with type 1 diabetes to improve glycemic control.

ADA recommendations for continuous glucose monitoring include:

- "Sensor-augmented pump therapy may be considered for children, adolescents, and adults to improve glycemic control without an increase in hypoglycemia or severe hypoglycemia."
- "Sensor-augmented pump therapy with automatic low-glucose suspend may be considered for adults with type 1 diabetes at high risk at hypoglycemia to prevent episodes of hypoglycemia and reduce their severity."

The ADA stated that automated insulin delivery systems may lower the risk of exercise-related hypoglycemia and may confer psychosocial benefits.

National Institute for Health and Care Excellence (NICE)

In 2016, the National Institute for Health and Care Excellence (NICE) published an evidence-based guideline on use of the MiniMed Paradigm Veo system (the European equivalent of the MiniMed 530G).[67] Recommendations were as follows:

- "The MiniMed Paradigm Veo system is recommended as an option for managing blood glucose levels in people with type 1 diabetes only if:
    - They have episodes of disabling hypoglycaemia (defined as the repeated and unpredictable occurrence of hypoglycaemia that results in persistent anxiety about recurrence and is associated with a significant adverse effect on quality of life); despite optimal management with continuous subcutaneous insulin infusion, and
- The MiniMed Paradigm Veo system should be used under the supervision of a trained multidisciplinary team who are experienced in continuous subcutaneous insulin infusion and continuous glucose monitoring for managing type 1 diabetes only if the person or their carer:
    - Agrees to use the sensors for at least 70% of the time
    - Understands how to use it and is physically able to use the system, and
    - Agrees to use the system while having a structured education programme on diet and lifestyle, and counselling.
- People who start to use the MiniMed Paradigm Veo system should only continue to use it if they have a decrease in the number of hypoglycaemic episodes that is sustained. Appropriate targets for such improvements should be set."

American Diabetes Association (ADA)

The 2023 ADA "Diabetes Technology: Standards of Care in Diabetes" evidence-based guidelines do not included artificial pancreas devices in their recommendations.[68] However, they state the following:

- " The type(s) and selection of devices should be individualized based on a person's specific needs, preferences, and skill level. In the setting of an individual whose diabetes is partially or wholly managed by someone else (e.g., a young child or a person with cognitive impairment or dexterity, psychosocial, and/or physical limitations), the caregiver's skills and preferences are integral to the decision-making process".
- " Initiation of continuous glucose monitoring, continuous subcutaneous insulin infusion, and/or automated insulin delivery early in the treatment of diabetes can be beneficial depending on a person's/caregiver's needs and preferences"

American Association of Clinical Endocrinologists / American College of Endocrinology (AACE/ACE)

In 2015, the AACE/ACE published a joint clinical practice guideline for developing a diabetes mellitus comprehensive care plan.[69] This guideline is primarily based in evidence.

The panel recommended that sensor-augmented CSII, including those with a threshold-suspend function, should be considered for patients who are at risk of hypoglycemia. This was a strong recommendation, based on strong evidence.

- In 2018, the AACE/ACE published a joint clinical practice guideline on the integration of insulin pumps and continuous glucose monitoring in patients with diabetes mellitus.[70] This guideline is primarily based in evidence.

The panel recommended that integration of CHM and CSII may be considered in patients already on CSII or appropriate for initiating CSII. Investigators noted that the ideal approach of integrating CSII and CGM is still under investigation.

EVIDENCE SUMMARY

Insulin pumps that have the ability to read and display data from continuous glucose monitors (CGM) are commonly called integrated continuous subcutaneous insulin infusion (CSII) – CGM system. Integrated systems that have no automation are referred to as sensor-augmented systems, and have been shown to improve various measures of glycemic control. The evidence regarding the efficacy of sensor-augmented systems consists of several randomized controlled trials with moderately-sized study cohorts, as well as large case series. These studies indicated that patients using sensor-augmented systems have significantly lower HbA1c levels and fewer hypoglycemic episodes than patients using CSII and self-monitoring of blood glucose (SMBG), and patients using multiple daily insulin injections and SMBG.

Integrated systems that have various levels of automation are referred to as the FDA as artificial pancreas device systems (APDS). APDSs that have a threshold suspend (or low-glucose suspend) mode, including the MiniMed 530G and 630G systems, have been studied in several medium- to large-sized randomized controlled trials and one very large retrospective analysis (over 20, 000 patients). Studies

evaluating the first insulin-only APDS, referred to as the hybrid MiniMed670G system, consists of one small RCT and several small but compelling trials. There is consistent evidence that both threshold suspend and insulin-only APDSs reduce the number and duration of total and nocturnal hypoglycemic events in children, adolescents and adults compared to sensor-augmented systems.

Lastly, studies on experimental bi-hormonal APDS, referred to as "true" closed-loop, fully automated APDS are emerging. There are no bi-hormonal APDSs that have been approved by the FDA at this time, and the evidence currently consists of small in-patient "proof-of-concept" studies.

BILLING GUIDELINES AND CODING

HCPCS codes S1030 and S1031 are not recognized as valid codes for claim submission as indicated in the relevant Company Coding Policy (*HCPCS S-Codes and H-Codes*, 22.0). Providers need to use alternate available CPT or HCPCS codes to report for this service. If no specific CPT or HCPCS code is available, then an unlisted code may be used. Note that unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. Thus, if an unlisted code is billed related to a non-covered service addressed in this policy, it will be denied as not covered.

- Based on CPT code descriptions, limits have been placed on the following codes:
  - A cumulative total of 365 disposable, invasive sensors (HCPCS: A9276) are eligible for reimbursement per calendar year.
  - A cumulative total of 12 requests for supply allowance for therapeutic CGMs (HCPCS: A4238 or A4239) are eligible for reimbursement per calendar year.

- Code A4224 will not be reimbursed more than 52 times per calendar year.

CODES*		
CPT	0446T	Creation of subcutaneous pocket with insertion of implantable interstitial glucose sensor, including system activation and patient training
	0447T	Removal of implantable interstitial glucose sensor from subcutaneous pocket via Incision
	0448T	Removal of implantable interstitial glucose sensor with creation of subcutaneous pocket at different anatomic site and insertion of new implantable sensor, including system activation
	95249	Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; patient-provided equipment, sensor placement, hook-up, calibration of monitor, patient training, and printout of recording
	95250	Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; physician or other qualified health care professional (office) provided equipment, sensor placement, hook-up, calibration of monitor, patient training, removal of sensor, and printout of recording
	95251	Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; analysis, interpretation and report

HCPCS	A4224	Supplies for maintenance of insulin infusion catheter, per week
	A4225	Supplies for external insulin infusion pump, syringe type cartridge, sterile, each
	A4226	Supplies for maintenance of insulin infusion pump with dosage rate adjustment using therapeutic continuous glucose sensing, per week
	A4230	Infusion set for external insulin pump, non needle cannula type
	A4231	Infusion set for external insulin pump, needle type
	A4232	Syringe with needle for external insulin pump, sterile, 3 cc
	A4238	Supply allowance for adjunctive continuous glucose monitor (CGM), includes all supplies and accessories, 1 month supply = 1 unit of service
	A4239	Supply allowance for non-adjunctive, non-implanted continuous glucose monitor (cgm), includes all supplies and accessories, 1 month supply = 1 unit of service
	A9274	External ambulatory insulin delivery system, disposable, each, includes all supplies and accessories
	A9276	Sensor; invasive (e.g., subcutaneous), disposable, for use with non-durable medical equipment interstitial continuous glucose monitoring system, one unit = 1 day supply
	A9277	Transmitter; external, for use with non-durable medical equipment interstitial continuous glucose monitoring system
	A9278	Receiver (monitor); external, for use with non-durable medical equipment interstitial continuous glucose monitoring system
	E0782	Infusion pump, implantable, non-programmable (includes all components, e.g., pump, catheter, connectors, etc.)
	E0783	Infusion pump system, implantable, programmable (includes all components, e.g., pump, catheter, connectors, etc.)
	E0784	External ambulatory infusion pump, insulin
	E0786	Implantable programmable infusion pump, replacement (excludes implantable intraspinal catheter)
	E0787	External ambulatory infusion pump, insulin, dosage rate adjustment using therapeutic continuous glucose sensing
	E1399	Durable medical equipment, miscellaneous
	E2102	Adjunctive non-implanted continuous glucose monitor or receiver
	E2103	Non-adjunctive, non-implanted continuous glucose monitor or receiver
	~~G0308~~	**Termed 12/31/2022** ~~Creation of subcutaneous pocket with insertion of 180 day implantable interstitial glucose sensor, including system activation and patient training~~
	~~G0309~~	**Termed 12/31/2022** ~~Removal of implantable interstitial glucose sensor with creation of subcutaneous pocket at different anatomic site and insertion of new 180 day implantable sensor, including system activation~~
	J1811	Insulin (Fiasp) for administration through DME (i.e., insulin pump) per 50 units
	J1813	Insulin (Lyumjev) for administration through DME (i.e., insulin pump) per 50 units
	J1817	Insulin for administration through DME (i.e., insulin pump) per 50 units
	~~K0553~~	**TERMED 12/31/2022** ~~Supply allowance for therapeutic continuous glucose monitor (CGM), includes all supplies and accessories, 1 unit of service = 1 month's supply~~
	~~K0554~~	**TERMED 12/31/2022**

		~~Receiver (monitor), dedicated, for use with therapeutic continuous glucose monitor system~~
	K0601	Replacement battery for external infusion pump owned by patient, silver oxide, 1.5 volt, each
	K0602	Replacement battery for external infusion pump owned by patient, silver oxide, 3 volt, each
	K0603	Replacement battery for external infusion pump owned by patient, alkaline, 1.5 volt, each
	K0604	Replacement battery for external infusion pump owned by patient, lithium, 3.6 volt, each
	K0605	Replacement battery for external infusion pump owned by patient, lithium, 4.5 volt, each
	S1030	Continuous noninvasive glucose monitoring device, purchase (for physician interpretation of data, use cpt code)
	S1031	Continuous noninvasive glucose monitoring device, rental, including sensor, sensor replacement, and download to monitor (for physician interpretation of data, use cpt code)

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
6/2023	Interim update. Added criteria regarding device removal. Removal of S1030 & S1031.
7/2023	Interim update and code set update for Q3 codes. Add a cumulative limit of 12 per calendar year for A4238 and A4239
6/2024	Annual update. No changes to criteria.