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Glucose Monitoring and Insulin Delivery Devices for Managing Diabetes

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

EXCEPTION: For HCSC members residing in the state of Arkansas, § 23-79-603 relating to diabetes treatment, requires coverage for medically necessary equipment, supplies and services to the treatment of Type 1, Type II, and gestational diabetes, when prescribed by a physician. This includes: blood glucose monitors, which include all commercially available blood glucose monitors designed for patient use and for persons who have been diagnosed with diabetes; blood glucose monitors for the legally blind, which include all commercially available blood glucose monitors designed for patient use with adaptive devices and for persons who are legally blind and have been diagnosed with diabetes; insulin pumps as prescribed by the physician and appurtenances thereto, which include insulin infusion pumps and

supplies such as skin preparations, adhesive supplies, infusion sets, cartridges, batteries and other disposable supplies needed to maintain insulin pump therapy, including durable and disposable devices used to assist in the injection of insulin; podiatric appliances for prevention of complications associated with diabetes, which include therapeutic molded or depth-inlay shoes, replacement inserts, preventive devices, and shoe modifications for prevention and treatment. This applies to the following: Fully Insured Group, Student, Small Group, Mid-Market, Large Group, HMO, EPO, PPO, POS. Unless indicated by the group, this mandate or coverage will not apply to ASO groups.

Coverage

NOTE 1: Please see the Regulatory Status section for additional information on devices. The Regulatory Status section is not an all-inclusive list of devices commercially available.

Glucose Monitoring Devices
Blood glucose monitors (BGMs) designed for home use self-monitoring of blood glucose levels **may be considered medically necessary** for the following individuals with**:**

- Type 1 diabetes,
- Type 2 diabetes, OR
- Gestational diabetes.

Professional (intermittent 72 hour) monitoring of glucose levels in interstitial fluid **may be considered medically necessary** for individuals who are capable of using the device safely, and meet either of the following criteria:

- Individuals with Type 1 or Type 2 insulin dependent diabetes prior to insulin pump initiation to determine basal insulin levels; OR
- Individuals with Type 1 or Type 2 diabetes whose diabetes is poorly controlled (see **NOTE 2** below) on their current therapy regimen.

NOTE 2: Poorly controlled diabetes includes but is not limited to the following clinical situations:

- Unexplained hypoglycemic episodes;
- Hypoglycemic unawareness;
- Suspected postprandial hyperglycemia;
- Persistent hyperglycemia and hemoglobin level (HbA1c) levels above target; OR
- Recurrent diabetic ketoacidosis.

Long-term continuous glucose monitoring (CGM) of glucose levels in interstitial fluid **may be considered medically necessary** in individuals with diabetes (Type 1 or Type 2 DM) who:

- Are willing and able to use the device;
- Have adequate medical supervision; AND
- Who experience significant hypoglycemia OR are treated with insulin therapy.

Other uses of continuous monitoring of glucose levels in interstitial fluid, including real-time monitoring, as a technique of diabetic monitoring, not meeting above noted criteria **is considered not medically necessary.**

Continuous glucose monitoring using an implantable glucose sensor (i.e., Eversense™ CGM system/Eversense E3 CGM system) used in accordance with the U.S. Food and Drug Administration (FDA) labeling, **may be considered medically necessary** when **ALL** the following criteria are met:

- Individuals with Type 1 or individuals with Type 2 diabetes requiring insulin;
- Are willing and able to use the device;
- Have adequate medical supervision; AND
- Who have poor control over their blood glucose levels (see **NOTE 2**).

NOTE 3: No additional documentation is required for continuation of a continuous glucose monitoring device or supplies needed for a patient with diabetes mellitus who is currently using a continuous monitoring device.

External Insulin Infusion Pumps

An external insulin infusion pump, including non-disposable and programmable disposable devices, with or without wireless communication capability used in accordance with the U.S. FDA labeling, **may be considered medically necessary** for the indications of**:**

- Documented management of individuals with type 1 diabetes who are willing and able to use the device and have completed a comprehensive diabetic education program; **OR**

- Documented management of individuals with type 2 diabetes who are:
    - Willing and able to use the device; and
    - Have completed a comprehensive diabetic education program; and
    - Have adequate medical supervision; and
    - Who are inadequately controlled with their current insulin regimen; and
    - Documentation of <u>any</u> of the following while on a regimen of insulin adjustments:
        1. Glycosylated hemoglobin level (HbA1c) >7.0 percent; OR
        2. Severely unstable blood glucose levels (brittle diabetes mellitus) with recurrent episodes of diabetic ketoacidosis, hypoglycemia, or both, resulting in recurrent and/or prolonged hospitalization; OR
        3. History of recurring hypoglycemia or severe glycemic excursions; OR
        4. Wide fluctuations in blood glucose before mealtime; OR
        5. Fasting blood glucose levels are much higher on awakening in the morning ("dawn phenomenon") with fasting blood sugars frequently exceeding 200 mg/dL.

NOTE 4: No additional documentation is required for continuation of an external insulin pump or supplies needed for the insulin pump for a patient with diabetes mellitus who is currently using an external insulin pump.

Disposable (mechanical) insulin delivery devices, including but not limited to V-Go™ and CeQur Simplicity™, **are considered experimental, investigational and/or unproven.**

ARTIFICIAL PANCREAS DEVICES SYSTEMS

Use of an artificial pancreas device system used in accordance with the U.S. FDA labeling **may be considered medically necessary** in patients who meet the following criteria for both:

- External insulin infusion pumps (noted below); AND
- Long-term Continuous Glucose Monitoring (CGM) (noted below).

Long-term continuous glucose monitoring (CGM) of glucose levels in interstitial fluid used in accordance with the U.S. FDA labeling, **may be considered medically necessary** in individuals with diabetes (Type 1 or Type 2 DM) who:

- Are willing and able to use the device;
- Have adequate medical supervision; AND
- Who experience significant hypoglycemia OR are treated with insulin therapy.

External Insulin Infusion Pumps

An external insulin infusion pump, including non-disposable and programmable disposable devices, with or without wireless communication capability used in accordance with the U.S. FDA labeling, **may be considered medically necessary** for the indications of**:**

- Documented management of individuals with type 1 diabetes who are willing and able to use the device and have completed a comprehensive diabetic education program; **OR**

- Documented management of individuals with type 2 diabetes who are:
    - Willing and able to use the device; and
    - Have completed a comprehensive diabetic education program; and
    - Have adequate medical supervision; and
    - Who are inadequately controlled with their current insulin regimen; and
    - Documentation of any of the following while on a regimen of insulin adjustments:
        1. Glycosylated hemoglobin level (HbA1c) >7.0 percent; OR
        2. Severely unstable blood glucose levels (brittle diabetes mellitus) with recurrent episodes of diabetic ketoacidosis, hypoglycemia, or both, resulting in recurrent and/or prolonged hospitalization; OR
        3. History of recurring hypoglycemia or severe glycemic excursions; OR
        4. Wide fluctuations in blood glucose before mealtime; OR
        5. Fasting blood glucose levels are much higher on awakening in the morning ("dawn phenomenon") with fasting blood sugars frequently exceeding 200 mg/dL.

Use of an automated insulin delivery system (artificial pancreas device system) **is experimental, investigational and/or unproven** for individuals who do not meet the above criteria.

Use of an automated insulin delivery system (artificial pancreas device system) not approved by the U.S. Food and Drug Administration **is experimental, investigational and/or unproven.**

Replacement of a continuous glucose monitoring device, an external insulin pump or an artificial pancreas device system **may be considered medically necessary** when the patient meets **ALL** of the following:

- The patient has been on a continuous glucose monitoring device, an external insulin infusion pump or an artificial pancreas device system; AND
- The device is already owned by the patient; AND
- The device cannot be repaired, is not under warranty, and replacement is necessary because the device is no longer functional for the purpose for which it was intended.

Additional software or hardware required for downloading data to a device such as personal computer, smart phone, or tablet to aid in self-management of diabetes mellitus, to include remote glucose monitoring device (i.e., mySentry) **are considered a convenience item and therefore not medically necessary.**

The use of an insulin titration guidance system with support from health-care professionals (e.g., d-Nav® System **is considered experimental, investigational and/or unproven**.

Policy Guidelines

None.

Description

Diabetes mellitus (DM) is a disease of abnormal glucose metabolism caused by either a deficiency of insulin or resistance to insulin, resulting in elevated blood glucose levels. The American Diabetes Association Standards of Medical Care in Diabetes (2023) notes diabetes can be classified into general categories: Type 1 (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood), Type 2 diabetes (due to a non-autoimmune progressive loss of adequate β-cell insulin secretion frequently on the background of insulin resistance and metabolic syndrome), gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation) and specific types of diabetes due to other causes e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation). They also note the traditional paradigms of Type 2 diabetes occurring only in adults and Type 1 diabetes (T1D) only in children are no longer accurate, as both diseases occur in both age-groups. (1)

Blood Glucose Control

The advent of blood glucose monitors for use by patients in the home revolutionized the management of diabetes. Using fingersticks, patients can monitor their blood glucose levels both to determine the adequacy of hyperglycemia control and to evaluate hypoglycemic episodes. Tight glucose control, defined as a strategy involving frequent glucose checks and a target hemoglobin A1c (HbA1c) level in the range of 7%, is now considered standard of care for diabetic patients. Randomized controlled trials (RCTs) assessing tight control have demonstrated benefits for patients with Type 1 diabetes in decreasing microvascular complications. The impact of tight control on Type 1 diabetes and macrovascular complications such as stroke or myocardial infarction is less certain. The Diabetes Control and Complications Trial (2002) demonstrated that a relative HbA1c level reduction of 10% is clinically meaningful and corresponds to approximately a 40% decrease in risk for progression of diabetic retinopathy and 25% decrease in risk for progression of renal disease. (2)

Due to an increase in turnover of red blood cells during pregnancy, HbA1c levels are slightly lower in women with a normal pregnancy compared with nonpregnant women. The target HbA1c in women with diabetes is also lower in pregnancy. The American Diabetes Association recommends that, if achievable without significant hypoglycemia, the HbA1c levels should range between 6.0 to 6.5%; an HbA1c level less than 6% may be optimal as the pregnancy progresses. (3)

Tight glucose control requires multiple daily measurements of blood glucose (i.e., before meals and at bedtime), a commitment that some patients may find difficult to meet. The goal of tight glucose control has to be balanced with an associated risk of hypoglycemia. Hypoglycemia is known to be a risk in patients with Type 1 diabetes. While patients with insulin-treated Type 2 diabetes may also experience severe hypoglycemic episodes, there is a lower relative likelihood of severe hypoglycemia compared with patients who had Type 1 diabetes. (4) An additional limitation of periodic self-measurements of blood glucose is that glucose levels are seen in isolation, and trends in glucose levels are undetected. For example, while a diabetic patient's fasting blood glucose level might be within normal values, hyperglycemia might be undetected postprandially, leading to elevated HbA1c levels.

Management

Measurements of glucose in the interstitial fluid have been developed as a technique to measure glucose values automatically throughout the day, producing data that show the trends in glucose levels. Although devices measure glucose in the interstitial fluid on a periodic rather than a continuous basis, this type of monitoring is referred to as continuous glucose monitoring (CGM).

Currently, CGM devices are of two designs; real-time CGM (rtCGM) provides real-time data on glucose level, glucose trends, direction, and rate of change and, intermittently viewed (iCGM) devices that show continuous glucose measurements retrospectively. These devices are also known as flash-glucose monitors (FGM).

Approved devices now include devices indicated for pediatric use and those with more advanced software, more frequent measurements of glucose levels, or more sophisticated alarm systems. Devices initially measured interstitial glucose every 5 to 10 minutes and stored data for download and retrospective evaluation by a clinician. With currently available devices, the intervals at which interstitial glucose is measured ranges from every 1 to 2 minutes to 5 minutes, and most provide measurements in real-time directly to patients. While CGM potentially eliminates or decreases the number of required daily fingersticks, it should be noted that, according to the U.S. Food and Drug Administration (FDA) labeling, some monitors are not intended as an alternative to traditional self-monitoring of blood glucose levels but rather as adjuncts to monitoring, supplying additional information on glucose trends not available from self-monitoring while other devices are factory calibrated and do not require fingerstick blood glucose calibration. Devices may be used intermittently (i.e., for periods of 72 hours) or continuously (i.e., on a long-term basis).

Supplemental Devices

Many additional tools are available to help with diabetic management including the mySentry™ device which offers remote glucose monitoring and provides CGM and insulin pump information to users. The device allows users to monitor from up to 50 feet away. (5)

Insulin Infusion Pumps

Continuous insulin infusion can be delivered by use of an external insulin pump. An external insulin infusion pump is a portable, programmable, battery-operated device with a drug reservoir, attached to a subcutaneous needle or catheter that provides continuous subcutaneous insulin infusion (CSII) in patients with DM. The aim of CSII is to try to approximate the insulin delivery more closely to the behavior of the normal pancreas, by providing continuously infused, low volume basal insulin for fasting periods and the delivery of increased rate boluses to cover meals. (6)

Artificial Pancreas Device Systems (APDS)

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

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

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

Table 1. Outcome Measures for Type 1 Diabetes

Measure	Definition	Guideline Type	Organization	Date
Hypoglycemia		Stakeholder survey, expert opinion with evidence review	Type 1 Diabetes Outcome Program[a] (7)	2017
Level 1 Level 2 Level 3	Glucose < 70 mg/dl but ≥ 54 mg/dl Glucose < 54 mg/dl Event characterized by altered mental/ physical status requiring assistance			
Hypoglycemia	Same as Type 1 Diabetes Outcome Program[a]	Professional Practice Committee with systematic literature review	ADA (8)	2019
Hypoglycemia Clinical alert for evaluation and/or treatment Clinically important or Serious Severe hypoglycemia	Glucose < 70 mg/dl Glucose < 54 mg/dl Severe cognitive impairment requiring external assistance by another person to take corrective action	Clinical Practice Consensus	ISPAD (9)	2018
Hyperglycemia Level 1 Level 2	Glucose > 180 mg/dL and ≤250 mg/dL Glucose > 250 mg/dL		Type 1 Diabetes Outcome Program[a] (10)	2017
Time in Range[b]	Percentage of glucose readings in the range of 70–180 mg/dL per unit of time		Type 1 Diabetes Outcome Program[a]	2017
Diabetic ketoacidosis (DKA)	Elevated serum or urine ketones >		Type 1 Diabetes Outcome Program[a] (8)	2017

	ULN Serum bicarbonate <15 mEq/L Blood pH <7.3			

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

[a] Steering Committee: representatives from American Association of Clinical Endocrinologists (AACE), American Association Diabetes Educators, the American Diabetes Association (ADA), the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, Type 1 diabetes Exchange.

[b] Time in range: has also been adopted by researchers evaluating the precision and effectiveness of emerging glucose monitoring and automated insulin delivery technologies.

Treatment

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

Restoration of pancreatic function is potentially available through islet cell or allogeneic pancreas transplantation. (See medical policy SUR703.013 and SUR703.057 for information on pancreas and related organ tissue transplantation.)

Regulatory Status

Continuous Glucose Monitoring Systems

Multiple CGM systems have been approved or cleared by the FDA (see Table 2). FDA product codes: [PMA] QCD, MDS, PQF; [510(k)] QBJ, QLG. Please note, this list is not all inclusive; refer to the FDA website for the most up to date listing of approved devices.

CGM devices labeled as “Pro” for specific professional use with customized software and transmission to health care professionals are not enumerated in this list.

The Flash glucose monitors (e.g., FreeStyle Libre, Abbott) use intermittent scanning. The current version of the FreeStyle Libre device includes real-time alerts, in contrast to earlier versions without this feature.

Table 2. CGM Systems Approved by the U.S. Food and Drug Administration

Device	Manufacturer	Approval or Clearance	Indications

Continuous Glucose Monitoring System (CGMS®)	MiniMed	1999	3-day use in physician's office.
GlucoWatch G2® Biographer		2001	Not available since 2008.
Guardian®-RT (Real-Time) CGMS	MiniMed (now Medtronic)	2005	
Dexcom® STS CGMS system	Dexcom	2006	
Paradigm® REAL-Time System (second generation called Paradigm Revel System)	MiniMed (now Medtronic)	2006	Integrates a CGM with a Paradigm insulin pump.
FreeStyle Navigator® CGM System	Abbott	2008	
Dexcom® G4 Platinum	Dexcom	2012	Adults ≥18 y; can be worn for up to 7 days.
		2014	Expanded to include patients with diabetes 2-17 y.
Dexcom® G5 Mobile CGM	Dexcom	2016[a]	Replacement for fingerstick blood glucose testing in patients ≥2 y. System requires at least 2 daily fingerstick tests for calibration purposes, but additional fingersticks are not necessary because treatment decisions can be made based on device readings. (11)
Dexcom® G6 Continuous Glucose Monitoring System	Dexcom	2018	Children, adolescents, and adults ≥ 2 y; indicated for the management of diabetes in persons age ≥2 y. Intended to replace fingerstick blood glucose testing for diabetes treatment decisions. Intended to autonomously communicate with digitally connected devices, including automated insulin dosing (AID) systems. with 10-day wear.
Freestyle Libre® Flash Glucose Monitoring System	Abbott	2017	Adults ≥18 y. Indicated for the management of diabetes and can be worn up to 10 days It is designed to replace

			blood glucose testing for diabetes treatment decisions.
Freestyle Libre® Flash Glucose Monitoring System	Abbott	2018	Adults ≥18 y. Extended duration of use to 14 days.
Freestyle Libre® 2 Flash Glucose Monitoring System	Abbott	2020	Children, adolescents, and adults ≥ 4 y.
Guardian Connect	Medtronic MiniMed	2018	Adolescents and adults (14-75 y) Continuous or periodic monitoring of interstitial glucose levels. Provides real-time glucose values, trends, and alerts through a Guardian Connect app installed on a compatible consumer electronic mobile device.
Eversense Continuous Glucose Monitoring System	Senseonics	2018/2019	Adults ≥18 y. Continually measuring glucose levels up to 90 days. Use as an adjunctive device to complement, not replace, information obtained from standard home blood glucose monitoring devices. Adults ≥18 y. Continually measuring glucose levels up to 90 days. Indicated for use to replace fingerstick blood glucose measurements for diabetes treatment decisions. Historical data from the system can be interpreted to aid in providing therapy adjustments.
Eversense E3 Continuous Glucose Monitoring System	Senseonics	2022	Adults ≥18 y. Continually measuring glucose levels up to 180 days. The system is indicated for use to replace fingerstick blood glucose measurements for diabetes treatment decisions. The

			system is intended to provide real-time glucose readings, provide glucose trend information, and provide alerts for the detection and prediction of episodes of low blood glucose (hypoglycemia) and high blood glucose (hyperglycemia). The system is a prescription device. Historical data from the system can be interpreted to aid in providing therapy adjustments. These adjustments should be based on patterns and trends seen over time.
FreeStyle Libre 3 CGM System	Abbott	2022	Children, adolescents, and adults ≥ 4y.
Dexcom® G7 Continuous Glucose Monitoring System	Dexcom	2022	Children, adolescents, and adults ≥ 2 y.

CGM: continuous glucose monitoring; y: years.
[a] As a supplement to the G4 premarketing approval

Insulin Pumps

Disposable (mechanical) Insulin Delivery Devices

A type of delivery system has been approved by the FDA as a Class II, 510(k) external insulin infusion pump, the V-Go™ (Valeritas, Inc., Bridgewater, NJ). V-Go is a mechanical (no electronics), single-use (for one 24-hour time period) disposable insulin infusion device. The device has an integrated stainless-steel subcutaneous needle. The V-Go delivers a continuous infusion of insulin at a fixed rate as well as allows the user to initiate bolus injections. (12)

The CeQur Simplicity is a disposable 3-day wearable insulin patch device that adheres to the skin and mechanically delivers on-demand subcutaneous mealtime insulin bolus doses. CeQur Simplicity provides bolus-only delivery of insulin and could be an alternative to other insulin injection devices (e.g., syringe or pen).

Artificial Pancreas Device Systems

The U.S. FDA describes the basic design of an artificial pancreas device system as a continuous glucose monitoring linked to an insulin pump with the capability to automatically stop, reduce, or increase insulin infusion based on specified thresholds of measured interstitial glucose. (13)

The artificial pancreas device system components are designed to communicate with each other to automate the process of maintaining blood glucose concentrations at or near a

specified range or target and to minimize the incidence and severity of hypoglycemic and hyperglycemic events. An artificial pancreas device system control algorithm is embedded in software in an external processor or controller that receives information from the continuous glucose monitoring and performs a series of mathematical calculations. Based on these calculations, the controller sends dosing instructions to the infusion pump.

Different artificial pancreas device system types are currently available for clinical use. Sensor augmented pump therapy with low glucose suspend (suspend on low) may reduce the likelihood or severity of a hypoglycemic event by suspending insulin delivery temporarily when the sensor value reaches (reactive) a predetermined lower threshold of measured interstitial glucose. Low glucose suspension automatically suspends basal insulin delivery for up to 2 hours in response to sensor-detected hypoglycemia.

A sensor augmented pump therapy with predictive low glucose management (suspend before low) suspends basal insulin infusion with the prediction of hypoglycemia. Basal insulin infusion is suspended when sensor glucose is at or within 70 mg/dL above the patient-set low limit and is predicted to be 20 mg/dL above this low limit in 30 minutes. In the absence of a patient response, the insulin infusion resumes after a maximum suspend period of 2 hours. In certain circumstances, auto-resumption parameters may be used.

When a sensor value is above or predicted to remain above the threshold, the infusion pump will not take any action based on continuous glucose monitoring readings. Patients using this system still need to monitor their blood glucose concentration, set appropriate basal rates for their insulin pump, and give premeal bolus insulin to control their glucose levels.

A control-to-range system reduces the likelihood or severity of a hypoglycemic or hyperglycemic event by adjusting insulin dosing only if a person's glucose levels reach or approach predetermined higher and lower thresholds. When a patient's glucose concentration is within the specified range, the infusion pump will not take any action based upon CGM readings. Patients using this system still need to monitor their blood glucose concentration, set appropriate basal rates for their insulin pump, and give premeal bolus insulin to control their glucose levels.

A control-to-target system sets target glucose levels and tries to maintain these levels at all times. This system is fully automated and requires no interaction from the user (except for calibration of the continuous glucose monitoring). There are 2 subtypes of control-to-target systems: insulin-only and bihormonal (e.g., glucagon). There are no systems administering glucagon marketed in the United States.

A hybrid closed-loop system also uses automated insulin delivery with continuous basal insulin delivery adjustments. However, at mealtime, the patient enters the number of carbohydrates they are eating in order for the insulin pump to determine the bolus meal dose of insulin. A hybrid system option with the patient administration of a premeal or partial premeal insulin bolus can be used in either control-to-range or control-to-target systems.

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

Table 3 summarizes the FDA cleared or approved automated insulin delivery systems. Please note, this list is not all inclusive; refer to the FDA website for the most up to date listing of approved devices.

Table 3. U.S. FDA-Approved Automated Insulin Delivery Systems (Artificial Pancreas Device Systems)

Device	Age Indication	Manufacturer	Date Approved	PMA Number/ Device Code
MiniMed 530G System[a] (open-loop, LGS)	≥16 y	Medtronic	Jul 2013	P120010/OZO
MiniMed 630G System with SmartGuard™ [b] (open-loop, LGS)	≥16 y ≥14 y	Medtronic	Aug 2016 Jun 2017	P150001/OZO P150001/S008
MiniMed 670GSystem[c] (hybrid closed-loop, LGS or PLGM)	≥14 y ≥7-13 y	Medtronic	Sep 2016 Jul 2018	P160017/OZP P160017/S031
MiniMed 770G System[d] (hybrid closed-loop) (14)	≥2 y	Medtronic	Aug 2020	P160017/S076
MiniMed 780G System[e] (hybrid closed-loop) (15)	≥7 y	Medtronic	May 2023	P160017/S091
t:slim X2 Insulin Pump with Basal-IQ Technology (LGS) (16)	≥6 y	Tandem	Jun 2018	P180008/OZO, PQF
t:slim X2 Insulin Pump with Control-IQ Technology (HCL)	≥6 y	Tandem	Dec 2019	DEN180058/QFG

HCL: hybrid closed-loop; FDA: Food and Drug Administration; LGS: low glucose suspend; OZO: Artificial Pancreas Device System, threshold suspend; OZP: Automated Insulin Dosing Device System, Single Hormonal Control; PMA: premarket approval; PLGM: predictive low glucose management; y: year(s).
[a]MiniMed 530G System consists of the following devices that can be used in combination or individually: MiniMed 530G Insulin Pump, Enlite™ Sensor, Enlite™ Serter, the MiniLink Real-Time System, the Bayer Contour NextLink glucose meter, CareLink® Professional Therapy Management Software for Diabetes, and CareLink® Personal Therapy Management Software for Diabetes (at time of approval).
[b]MiniMed 630G System with SmartGuard™ consists of the following devices: MiniMed 630G Insulin Pump, Enlite® Sensor, One-Press Serter, Guardian® Link Transmitter System, CareLink® USB, Bayer's CONTOUR ® NEXT LINK 2.4 Wireless Meter, and Bayer's CONTOUR® NEXT Test Strips (at time of approval).
[c]MiniMed 670G System consists of the following devices: MiniMed 670G Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), One-Press Serter, and the Contour NEXT Link 2.4 Glucose Meter (at time of approval).
[d]MiniMed 770G System consists of the following devices: MiniMed 770G Insulin Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), one-press serter, the Accu-Chek Guide™ Link blood glucose meter, and the Accu-Chek Guide™ Test Strips.

[e]MiniMed 780G System consists of the following devices: MiniMed 780G Insulin Pump, the Guardian 4 Transmitter, the Guardian 4 Sensor (3), One-Press Serter, the Accu-Chek Guide™ Link blood glucose meter, and the Accu-Chek Guide™ Test Strips.

The MiniMed® 530G System includes a threshold suspend or low glucose suspend feature. (17) The threshold suspend tool temporarily suspends insulin delivery when the sensor glucose level is at or below a preset threshold within the 60- to 90-mg/dL range. When the glucose value reaches this threshold, an alarm sounds. If patients respond to the alarm, they can choose to continue or cancel the insulin suspend feature. If patients fail to respond, the pump automatically suspends action for two hours, and then insulin therapy resumes.

The MiniMed® 630G System with SmartGuard™, which is similar to the 530G, includes updates to the system components including waterproofing. (18) The threshold suspend feature can be programmed to temporarily suspend delivery of insulin for up to two hours when the sensor glucose value falls below a predefined threshold value. The MiniMed 630G System with SmartGuard™ is not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a fingerstick may be required. All therapy adjustments should be based on measurements obtained using a home glucose monitor and not on the values provided by the MiniMed 630G system. The device is not intended to be used directly for preventing or treating hypoglycemia but to suspend insulin delivery when the user is unable to respond to the SmartGuard™ Suspend on Low alarm to take measures to prevent or treat hypoglycemia themselves.

The MiniMed® 670G System is a hybrid closed-loop insulin delivery system consisting of an insulin pump, a glucose meter, and a transmitter, linked by a proprietary algorithm and the SmartGuard Hybrid Closed Loop. (19) The system includes a low glucose suspend feature that suspends insulin delivery; this feature either suspends delivery on low-glucose levels or suspends delivery before low-glucose levels and has an optional alarm (manual mode). Additionally, the system allows semiautomatic basal insulin-level adjustment (decrease or increase) to preset targets (automatic mode). As a hybrid system; basal insulin levels are automatically adjusted, but the patient needs to administer premeal insulin boluses. The CGM component of the MiniMed 670G System is not intended to be used directly for making manual insulin therapy adjustments; rather it is to provide an indication of when a glucose measurement should be taken. The MiniMed 670G System was originally approved for marketing in the United States on September 28, 2016 (P160017) and received approval for marketing with a pediatric indication (ages 7-13 years) on June 21, 2018 (P160017/S031).

The MiniMed 770G System is an iteration of the MiniMed 670G System. In July 2020, the device was approved for use in children ages 2 to 6 years. In addition to the clinical studies that established the safety and effectiveness of the MiniMed 670G System in users ages 7 years and older, the sponsor performed clinical studies of the 670G System in pediatric subjects ages 2 to 6 years. FDA concluded that these studies establish a reasonable assurance of the safety and effectiveness of the MiniMed 770G System because the underlying therapy in the 670G system, and the associated Guardian Sensor 3, are identical to that of the 770G System. (14)

On June 21, 2018, the FDA approved the t:slim X2 Insulin Pump with Basal-IQ Technology (PMA P180008) for individuals who are 6 years of age and older. (16) The System consists of the t:slim X2 Insulin Pump paired with the Dexcom G5 Mobile CGM (Continuous Glucose Monitor), as well as the Basal-IQ Technology. The t:slim X2 Insulin Pump is intended for the subcutaneous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. The t:slim X2 Insulin Pump can be used solely for continuous insulin delivery and as part of the System as the receiver for a therapeutic continuous glucose monitoring. The t:slim X2 Insulin Pump running the Basal-IQ Technology can be used to suspend insulin delivery based on continuous glucose monitoring sensor readings.

In December 2019, FDA approved the t:slim X2 Insulin Pump with Control-IQ Technology through the De Novo process. (20) The device uses the same pump hardware as the insulin pump component of the systems approved in t:slim X2 Insulin Pump with Basal-IQ Technology (P180008) and P140015. A custom disposable cartridge is motor-driven to deliver patient programmed basal rates and boluses through an infusion set into subcutaneous tissue. A new type of glycemic controller, the Control-IQ Technology controller, when used as a system with compatible iCGMs (integrated continuous glucose monitors) and ACE pumps (alternate controller-enabled insulin pumps) can be used by individuals with type 1 diabetes to automatically increase, decrease and suspend delivery of basal insulin to the patient based on insulin delivery history, iCGM readings and predicted glucose values. The controller can also automatically deliver a specific amount of insulin when the glucose value is predicted to exceed a predefined amount. (103)

Software-based Insulin Dose Management

In 2019, the FDA provided 510(k) clearance for the d-Nav® System. The d-Nav® System (Hygieia, Inc.) is a software-based, prescription-only product designed to provide the next insulin dose recommendation as an aid for personal insulin management for individuals with type 2 diabetes. The product integrates the health care provider (HCP) prescribed starting insulin dose instructions with automated dosing guidance to the patient based on comparing regularly measured blood glucose data trends to a device specified target range. The d-Nav System contains two user interactive software elements; the d-Nav phone app and the d-Nav website. (21)

Rationale

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

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

CONTINUOUS GLUCOSE MONITORING DEVICES

This section of the medical policy focuses on the clinical utility of continuous glucose monitoring (CGM) systems. That is, their ability to provide additional information on glucose levels leads to improved glucose control, or to reduce the morbidity and mortality associated with clinically significant severe and acute hypoglycemic or hyperglycemic events. Because diabetic control encompasses numerous variables, including the diabetic regimen and patient self-management, RCTs are important to isolate the contribution of interstitial glucose measurements to overall diabetes management.

For the evaluation of the clinical utility of CGM, studies would need to use the test as either an adjunct or a replacement to current disease status measures to manage treatment decisions in patients with diabetes. Outcomes would include measures of glucose control, QOL and measures of disease progression. HbA1c has commonly been accepted as a marker of glucose control; more recent studies have also reported time in hyperglycemia, time in hypoglycemia, and time in range as intermediate outcome measures.

Continuous Glucose Monitoring Devices for Long-Term Use in Type 1 Diabetes

In some parts of the analysis of Type 1 diabetes, there is a combined discussion of real-time and intermittently scanned glucose monitoring because several systematic reviews provided information relevant to both types of devices.

Clinical Context and Therapy Purpose

The purpose of long-term continuous glucose monitoring devices is to provide a testing option that is an alternative to or an improvement on existing testing used in the management of individuals with Type 1 diabetes.

The question addressed in this medical policy is: Does long-term use of a CGM device improve the net health outcome for individuals with Type 1 diabetes?

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with Type 1 diabetes. All individuals with Type 1 diabetes require engagement in a comprehensive self-management and clinical assessment program that includes assessment of blood glucose control.

Interventions
The test being considered is the use of a CGM device to assess blood glucose levels as part of optimal diabetes management. Long-term use is generally used for more than 72 hours.

Currently, CGM devices are of 2 designs; real-time CGM (rtCGM) provides real-time data on glucose level, glucose trends, direction, and rate of change, and intermittently scanned (iCGM) devices that show continuous glucose measurements retrospectively. These latter devices are also known as flash-glucose monitors.

Comparators
The following practice is currently being used to measure glucose levels: capillary blood sampling (finger stick) for self-monitoring of blood glucose (SMBG). Standard treatment for patients with Type 1 diabetes includes injection of long-acting basal insulin plus multiple daily injections (MDI) of rapid-acting insulin boluses as required for meal intake. Activity level may require patients need to modify the timing and dose of insulin administration. Individuals with Type 1 diabetes may also use an insulin pump either for initial treatment or convert to pump use after a period of MDI. Individuals are required to check their blood glucose before making preprandial insulin calculations, in response to symptoms of hypoglycemia or related to activity-related insulin adjustments.

Outcomes
The general outcomes of interest are change in hemoglobin A1c (HbA1c) levels, time spent in hypoglycemia and hyperglycemia, time in range (generally glucose of 70-180 mg/dl), the incidence of hypoglycemic events, complications of hypoglycemia, and QOL. To assess short-term outcomes such as HbA1c levels, a minimum follow-up of 8 to 12 weeks is appropriate.

Study Selection
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
A number of systematic reviews and meta-analyses have assessed RCTs evaluating CGM for long-term, daily use in treating Type 1 diabetes (T1D). (22-27) These systematic reviews have

focused on slightly different populations, and some did not separate long-term CGM from intermittent glucose monitoring. (25)

The only analysis to use individual patient data was published by Benkhadra et al. (2017). (28) The meta-analysis evaluated data from 11 RCTs that enrolled patients with Type 1 diabetes and compared real-time CGM with a control intervention. Studies in which patients used insulin pumps or received multiple daily insulin injections were included. Reviewers contacted corresponding study authors requesting individual patient data; data were not obtained for 1 trial. Mean baseline HbA1c levels were 8.2% in adults and 8.3% in children and adolescents. The overall risk of bias in the studies was judged to be moderate. In pooled analyses, there was a statistically significantly greater decrease in HbA1c levels with real-time CGM vs control conditions. Overall, the degree of difference between groups was 0.26%. In subgroup analyses by age, there was a significantly greater change in HbA1c levels among individuals 15 years and older, but not among the younger age groups. There were no significant differences between groups in the time spent in hypoglycemia or the incidence of hypoglycemic events. Key findings are shown in Table 4.

Table 4. Individual Patient Data Meta-Analytic Outcomes for Real-Time CGM in Type I Diabetes

Number of Trials	N	Group	Point Estimate	95% Confidence Intervals	p
Change in HbA1c Levels, %					
8	1371	Overall	-0.258	0.464 to -0.052	0.014
7	902	Age >15 y	-0.356	0.551 to -0.160	<0.001
7	178	Age 13-15 y	-0.039	-0.320 to 0.242	0.787
7	291	Age ≤ 12 y	-0.047	0.217 to 0.124	0.592
Time spent in hypoglycemia <60 mg/dL, min					
4	706	Overall	-8.549	-31.083 to 13 985	0.457
4	467	Age >15 y	-8.095	-32.615 to 16.425	0.518
3	109	Age 13-15 y	-13.966	31.782 to 3.852	0.124
3	130	Age ≤ 12 y	-9.366	19.898 to 1.167	0.081
Incidence of hypoglycemic events <70 mg/dL, mean no. events					
3	351	Overall	0.051	-0.314 to 0.416	0.785
3	277	Age >15 y	-0.074	-0.517 to 0.368	0.742
2	47	Age 13-15 y	0.536	0.243 to 1.316	0.177
2	27	Age ≤ 12 y	0.392	0.070 to 0.854	0.097

Adapted from Benkhadra et al. (2017). (28)
CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; y: years.

Randomized Controlled Trials

Recent RCTs are described next and in Tables 5 and 6. HbA1c, blood glucose, event rates, and patient reported outcomes were assessed at 6 months. None of the studies were blinded. The

studies had a large number of pre-specified secondary endpoints, and analyses took into consideration the statistical impact of multiple comparisons.

Two, 2017 RCTs evaluated long-term, real-time CGM in patients with Type 1 diabetes treated with multiple daily insulin injections. Both trials used the Dexcom G4 CGM device. Lind et al. (2017) reported on a crossover study with 142 adults ages 18 and older who had baseline HbA1c levels of 7.5% or higher (mean baseline HbA1c level, >8.5%). (29) Enrolled patients underwent 26-week treatment periods with a CGM device and conventional therapy using SMBG, in random order. There was a 17-week washout period between intervention phases. The primary endpoint was the difference in HbA1c levels at the end of each treatment period. Mean HbA1c levels were 7.9% during CGM use and 8.4% during conventional therapy (MD = -0.4%; p<0.01). Treatment satisfaction (measured by the Diabetes Treatment Satisfaction Questionnaire) was significantly higher in the CGM phase than in the conventional treatment phase (p<0.001). There was 1 (0.7%) severe hypoglycemic event during the CGM phase and 5 (3.5%) events during conventional therapy. The percentage of time with hypoglycemia (<70 mmol/L) was 2.8% during CGM treatment and 4.8% during conventional therapy.

In the second study, Beck et al. (2017) randomized 158 patients on a 2:1 basis to 24 weeks of CGM (n=105) or usual care (n=53). (30) The primary outcome (change in HbA1c levels at 24 weeks) was 1.0% in the CGM group and 0.4% in the usual care group (p<0.001), with a between-group difference of 0.6%. Prespecified secondary outcomes on the proportion of patients below a glycemic threshold at 24 weeks also favored the CGM group. The proportion of patients with HbA1c levels less than 7.0% was 18 (18%) in the CGM group and 2 (4%) in the control group (p=0.01). Prespecified secondary outcomes related to hypoglycemia also differed significantly between groups, favoring the CGM group. Comparable numbers for time spent at less than 50 mg/dL were 6 minutes per day in the CGM group and 20 minutes per day in the usual care group (p=0.001). The median change in the rate per 24 hours of hypoglycemia events lasting at least 20 minutes at less than 3.0 mmol/L (54 mg/dL) fell by 30% from 0.23 at baseline to 0.16 during follow-up in the CGM group but was practically unchanged (0.31 at baseline and 0.30 at follow-up) in the usual care group (p=0.03). (31) QOL measures assessing overall well-being (World Health Organization Well-Being Index), health status (EQ-5D-5L), diabetes distress (Diabetes Distress Scale), hypoglycemic fear (worry subscale of the Hypoglycemia Fear Survey), and hypoglycemic confidence (Hypoglycemic Confidence Scale) have also been reported. (32) There were no significant differences between CGM and usual care in changes in well-being, health status, or hypoglycemic fear. The CGM group demonstrated a greater increase in hypoglycemic confidence (p=0.01) and a greater decrease in diabetes distress (p=0.01) than the usual care group.

Two RCTs were published in 2020 that assessed CGM with a Dexcom G5 in adolescents and young adults (Laffel et al., 2020) (33) and in older adults (Pratley et al., 2020) (34) Both studies found modest but statistically significant differences in HbA1c between patients who used the CGM devices compared to the control arm at follow-up. Secondary measures of HbA1c and blood glucose were mostly better in the CGM arm. Patient-reported outcome measures were not significantly different between the groups, except that glucose monitoring satisfaction was

higher in the adolescents and young adults who used CGM. With the newer technology, patients were able to use a smartphone app to monitor glucose levels.

Two RCTs have evaluated long-term use of intermittently-scanned CGM. Leelarathna et al. (2022) reported results of the FLASH-UK (NCT03815006) multicenter RCT including individuals age 16 years and older in the United Kingdom with type 1 diabetes and HbA1c levels between 7.5% and 11.0% who were receiving either continuous subcutaneous insulin infusion or multiple daily injections of insulin. (35) The trial was conducted from 2019 to 2021 and compared intermittently-scanned CGM (FreeStyle Libre 2; n=78) worn on the arm for 14 days versus usual care with fingerstick testing (n=78). The primary outcome was the HbA1c at 24 weeks. The difference in decrease in HbA1c level at 24 weeks was −0.5% (95% CI, −0.7 to −0.3; p<.001) favoring CGM. The difference in time per day that the glucose level was in target range was 9.0% (95% CI, 4.7 to 13.3) higher or 130 minutes (95% CI, 68 to 192) longer in the CGM group compared to usual care. No participants in the CGM group versus 2 participants in the usual care group had an episode of severe hypoglycemia.

Yan et al. (2023) reported results of a multicenter RCT (NCT03522870) conducted in China from 2019 to 2022 comparing intermittently-scanned CGM (FreeStyle Libre; n=54) to capillary blood glucose monitoring (n=50) in adults with sub-optimally controlled type 1 diabetes. (36) Participants had HbA1c between 7% and 10%. The primary outcome was change in HbA1c at 24 weeks. The mean reduction in the primary outcome in the CGM group was 0.7% versus 0.3% in the control group (difference, 0.3%; 95% CI, 0.0 to 0.6; p=.04). The mean time-in-range increased to 63% at 24 weeks in CGM versus 58% in control (difference, 6% [1.4 hours / day];95% CI, -11 to -1; p=.02). No participants in the CGM group versus 4 participants in the control group experienced an event of diabetic ketoacidosis. No participants in either group experienced severe hypoglycemia.

Table 5. Summary of Key RCT Characteristics in Patients with Type 1 Diabetes

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					CGM	SMBG
Beck et al. (2017) (30) DIAMOND				Adults aged 25 or older with baseline HbA1c levels between 7.5% and 10%	Dexcom G4 real-time CGM (n=105)	Usual care (n=53)
Laffel et al. (2020) (33)	U.S.	14	2018-2019	Adolescents and young adults age 14 to 24 years with HbA1c 7.5% to 10.9% with multiple daily insulin injections	Dexcom G5 real-time CGM with training on use and a smartphone app and 2 calibration BG per day (n=74)	Fingerstick blood glucose meter checks at least 4 times daily (n=79)

				or an insulin pump		
Pratley et al. (2020) (34) (WISDM)	U.S.	22	1993-2012	Older adults ≥60 years of age with HbA1c < 10.0% with multiple daily insulin injections or an insulin pump	Dexcom G5 real-time CGM with training on use and 2 calibration BG checks per day (n=103)	Fingerstick blood glucose meter checks at least 4 times daily (n=100)
Leelarathna et al. (2022) (35)	U.K.	8	2019-2021	Ages 16 and older with type 1 diabetes and HbA1c levels between 7.5% and 11.0% who were receiving either continuous subcutaneous insulin infusion or multiple daily injections of insulin; mean age, 44 years; mean HbA1c, 8.6%	FreeStyle Libre 2 intermittently-scanned CGM worn on the arm for 14 days (n=78)	Usual care with finger stick testing (n=78)
Yan et al. (2023) (36)	China	3	2018-2022	Ages 18 and older with type 1 diabetes and HbA1c between 7% and 10% with stable insulin regimen; 64% female; mean age, 34 years; mean HbA1c, 8.1%	FreeStyle Libre intermittently scanned CGM (n=54)	Fingerstick blood glucose meter checks (n=50)

BG: blood glucose; CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; RCT: randomized controlled trial; SMBG: self-monitored blood glucose; WISDM: Wireless Innovation for Seniors With Diabetes Mellitus.

Table 6. Summary of Key RCT Results in Patients with Type 1 Diabetes

Study	HbA1c	HbA1c	Blood Glucose (SD) mg/dL	Hypo-glycemic Episodes	Patient Reported Outcomes	Patient Reported Outcomes
Beck et al. (2017) (30) DIAMOND	*Change from Baseline*	*Proportion <7.0%*		*Minutes per day <70 mg/dL*		
CGM	1.0%	18 (18%)		43		
SMBG	0.4%	2 (4%)		80		
Diff (95% CI)	0.6%					
P	<.001	.01		0.002		
Laffel et al. (2020) (33)	*Change from Baseline*	*Percent with Reduction of 0.5%*	*Mean (SD)*	*Per Week*	*PAD-PS Survey*	*Glucose Monitoring Satisfaction*
CGM	-0.4 (1.0)	44%	199 (36)	1.4 (0.4 to 2.6)		
SMBG	0.1 (0.8)	21%	217 (35)	1.7 (1.0 to 3.1)		
Diff (95% CI)	-0.37 (-0.66 to -0.08)	23% (7% to 37%)	-14.3 (-23.6 to -5.1)	-0.3 (-0.7 to 0.1)	-0.1 (-3.0, 4.0)	0.27 (0.06, 0.54)
P	.01	.005	.003	.11	.73	.003
Pratley et al. (2020) (34) (WISDM)	*At follow-up*	*Percentage of time glucose values <70 mg/dL*		*Per week*	*Quality of life*	*Hypoglycemia Awareness*
CGM	7.2 (0.9)	2.7%	162 (23)	0.8 (0.3-2.2)		
SMBG	7.4 (0.9)	4.9%	171 (30)	1.8 (0.7-4.0)		
Diff (95% CI)	-0.3 (-0.4 to -0.1)	-1.9% (-2,8 to -1.1)	−7.7 (−13.1 to −2.4)	−0.9 (−1.3 to −0.5)		
P		<.001	.005	<.001	NS	NS
Leelarathna et al. (2022) (35)	*Change from baseline, mean (SD)*	*Proportion ≤7.0%, n (%)*	*At 24 weeks follow-up*	*Severe hypoglycemia, n (%)*	*NR*	*NR*
CGM	-0.8 (0.8)	11 (15)	178 (32)	0 (0)		
SMBG	-0.2 (0.6)	5 (7)	185 (40)	2 (3)		
Diff (95% CI)	-0.5 (-0.7 to -0.3)	OR=2.4 (0.8 to 7.8)	-11 (-20 to 0)	NR		
P	<.001	NR	NR	NR		
Yan et al. (2023) (36)	*Change from baseline, mean (SD)*				*NR*	*NR*

CGM	0.7%		153 (26)	0		
SMBG	0.3%		166 (29)	0		
Diff (95% CI)	0.3% (0.0 to 0.6)		11 (1 to 21)			
P	.04		0.03			

CGM: continuous glucose monitor; CI: confidence interval; HbA1c: hemoglobin A1c; NR: not reported; NS: not significant; PAD-PS; Problem Areas in Diabetes-Pediatric Survey; RCT: randomized controlled trial; SD: standard deviation; SMBG: self-monitored blood glucose; WISDM: Wireless Innovation for Seniors With Diabetes Mellitus

Observational Studies

Because several RCTs exist, observational studies will be summarized briefly below only if they capture longer periods of follow-up- (>6 months), larger populations, or particular subgroups of interest.

Long-term follow-up

Observational studies with follow-up of more than 6 months including adults with type 1 diabetes have shown that reductions in acute diabetes events, including severe hypoglycemia and diabetic ketoacidosis are maintained for 1 to 2 years. (37, 38)

Pregnant People

One trial of real-time CGM in pregnant women with Type 1 diabetes has been reported. Study characteristics results and gaps are summarized here and in Tables 7 to 10. Feig et al. (2017) reported results of 2 multicenter RCTs in women ages 18 to 40 with Type 1 diabetes who were receiving intensive insulin therapy and who were either pregnant (≤13 weeks and 6 days of gestation) or planning a pregnancy. (39) The trial enrolling pregnant women is reviewed here. Women were eligible if they had a singleton pregnancy and HbA1c levels between 6.5% and 10.0%. The trial was conducted at 31 hospitals in North America and Europe. Women were randomized to CGM (Guardian REAL-Time or MiniMed Minilink system) plus capillary glucose monitoring or capillary glucose monitoring alone. Women in the CGM group were instructed to use the devices daily. Women in the control group continued their usual method of capillary glucose monitoring. The target glucose range was 3.5 to 7.8 millimole/L and target HbA1c levels were 6.5% or less in both groups. The primary outcome was the difference in change in HbA1c levels from randomization to 34 weeks of gestation. The proportion of completed scheduled study visits was high in both groups; however, participants using CGM had more unscheduled contacts, which were attributed both to sensor issues and to sensor-related diabetes management issues. The median frequency of CGM use was 6.1 days per week (interquartile range, 4.0-6.8 d/wk) and 70% of pregnant participants used CGM for more than 75% of the time. The between-group difference in the change in HbA1c levels from baseline to 34 weeks of gestation was statistically significant favoring CGM (MD, -0.19%; 95% CI, -0.34 to -0.03; p=0.02). Women in the CGM group spent an increased percentage of time in the recommended glucose control target range at 34 weeks of gestation (68% vs 61%, p=0.003). There were no between-group differences in maternal hypoglycemia, gestational weight gain, or total daily insulin dose. A smaller proportion of infants of mothers in the CGM group were large-for-gestational age

(odds ratio [OR], 0.51; 95% CI, 0.28 to 0.90; p=0.02). In addition, for infants of mothers in the CGM group, there were fewer neonatal intensive care admissions lasting more than 24 hours (OR=0.48; 95% CI, 0.26 to 0.86; p=0.02), fewer incidences of neonatal hypoglycemia requiring treatment with intravenous dextrose (OR=0.45, 0.22 to 0.89; p=0.025), and reduced total length of hospital stay (3.1 days vs 4.0 days; p=0.0091). Skin reactions occurred in 49 (48%) of 103 CGM participants and 8 (8%) of 104 control participants.

Table 7. RCT Characteristics for Real-Time CGM in Pregnant People With Type 1 Diabetes

Study; Registration	Countries	Sites	Dates	Participants	Interventions	
					Active	Com-parator
Feig et al. (2017) (39); NCT01788527	Canada, England, Scotland, Spain, Italy, Ireland, U.S.	31	2013-2016	Pregnant women (<14 wk gestation) with Type 1 diabetes receiving intensive insulin therapy with HbA1c levels between 6.5% and 10.0% (mean, 6.9%); mean age, 31 y.	CGM (real-time) (n=108)	SMBG (n=107)

CGM: continuous glucose monitoring: HbA1c: hemoglobin A1c; NCT: national clinical trial; RCT: randomized controlled trial; SMBG: self-monitored blood glucose; wk: week; y: years.

Table 8. RCT Outcomes for Real-Time CGM in Pregnant People With Type 1 Diabetes

	Infant				Maternal	
Study	Large for Gestational Age	Gestational Age at Delivery, wk	Severe Hypoglycemia	Caesarean Section	HbA1c Levels: Change from Baseline to 34 wk of Gestation	Severe Hypo-glycemia
Feig et al. (2017) (39)						
N	211	201	200	202	173	214
CGM	53 (53%)	Median, 37.4	15 (15%)	63 (63%)	-0.54	11 (11%)
Control	69 (69%)	Median, 37.3	28 (28%)	74 (73%)	-0.35	12 (12%)
TE (95% CI)	OR=0.51 (0.28 to 0.90)	NR	OR=0.45 (0.22 to 0.89)	NR	-0.19% (-0.34% to -0.03%)	NR
p	0.02	0.50	0.025	0.18	0.02	1.0

Values are n or n (%) or as otherwise indicated.
CI: confidence interval; CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; TE: treatment effect; wk: week.

The purpose of the limitations tables (see Tables 9 and 10) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 9. Study Relevance Limitations of RCTs for Real-Time CGM in Pregnant People With Type 1 Diabetes

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Feig et al. (2017) (39)	4. Run-in period requirement may have biased selection to highly compliant participants.	3. More unscheduled contacts in CGM group.	3. More unscheduled contacts in CGM group.		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CGM: continuous glucose monitoring; RCT: randomized controlled trial.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use. 5. Enrolled study populations do not reflect relevant diversity.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 10. Study Design and Conduct Limitations of RCTs for Real-Time CGM in Pregnant People With Type 1 Diabetes

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Feig et al. (2017) (39)		1. Not blinded; chance of bias in clinical				3, 4. Treatment effects and confidence

		management				intervals not calculated for some outcomes

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CGM: continuous glucose monitoring; RCT: randomized controlled trial.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Continuous Glucose Monitoring Devices for Long-Term Use in Type 1 Diabetes

Numerous RCTs and several systematic reviews of RCTs have evaluated CGM in patients with Type 1 diabetes. RCTs have evaluated both real-time and intermittently scanned CGM devices. Two recent RCTs in patients who used multiple daily insulin injections and were highly compliant with CGM devices during run-in phases found that CGM was associated with a larger reduction in HbA1c levels than previous studies. Reductions were 0.4% and 0.6%, respectively, compared with approximately 0.2% to 0.3% in previous analyses. One of the 2 RCTs prespecified hypoglycemia-related outcomes and time spent in hypoglycemia was significantly lower in the CGM group.

One RCT in pregnant women with Type 1 diabetes (n=215) has compared CGM with SMBG. Adherence was high in the CGM group. The difference in the change in HbA1c levels from baseline to 34 weeks of gestation was statistically significant favoring CGM, and women in the CGM group spent an increased percentage of time in the recommended glucose control target range at 34 weeks of gestation. There were no between-group differences in maternal hypoglycemia, gestational weight gain, or total daily insulin dose. A smaller proportion of infants of mothers in the CGM group were large for gestational age, had neonatal intensive care admissions lasting more than 24 hours, and had neonatal hypoglycemia requiring treatment. The total length of hospital stay was shorter by almost 1 day in the CGM group.

Continuous Glucose Monitoring Devices for Short-Term Use in Type 1 Diabetes

Clinical Context and Therapy Purpose

The purpose of the short-term use of CGM devices is to provide a testing option that is an alternative to or an improvement on existing testing used in the management of individuals with Type 1 diabetes.

The question addressed in this medical policy is: Does the short-term use of a CGM device improve the net health outcome for individuals with Type 1 diabetes?

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with Type 1 diabetes. All individuals with Type 1 diabetes require engagement in a comprehensive self-management and clinical assessment program that includes assessment of blood glucose control. Individuals with Type 1 diabetes may have poorly controlled diabetes, despite current use of best practices, including situations such as unexplained hypoglycemic episodes, hypoglycemic unawareness, suspected postprandial hyperglycemia, and recurrent diabetic ketoacidosis. In addition, individuals with Type 1 diabetes may need to determine basal insulin levels prior to insulin pump initiation.

Interventions

The testing being considered is the short-term use of a CGM device to assess blood glucose levels as part of optimal diabetes management. Short-term use is generally for 72 hours. However, reports of use range from 3-30 days.

Comparators

The following practice is currently being used to measure glucose levels: capillary blood sampling (finger stick) for SMBG. Standard treatment for patients with Type 1 diabetes includes injection of long-acting basal insulin plus MDI of rapid-acting insulin boluses as required for meal intake. Activity level may require patients need to modify the timing and dose of insulin administration. Individuals with Type 1 diabetes may also use an insulin pump either for initial treatment or convert to pump use after a period of MDI. Individuals are required to check their blood glucose before making preprandial insulin calculations, in response to symptoms of hypoglycemia or related to activity-related insulin adjustments.

Outcomes

For short-term use of CGM, the general outcomes of interest include time in range (generally glucose of 70-180 mg/dl), frequency and time spent in hypoglycemia and, frequency and time spent in hyperglycemia for the duration of the monitoring. Repeat CGM may be necessary to assess the impact of changes in management.

Study Selection

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Meta-analyses of glucose monitoring devices for Type 1 diabetes tend to combine studies of short-term glucose monitoring with studies of long-term CGM. For this body of evidence, there is variability in the definitions of short-term monitoring and the specific monitoring protocols used. Also, many of the trials of short-term monitoring have included additional interventions to optimize glucose control (e.g., education, lifestyle modifications).

Two meta-analyses were identified that reported separate subgroup analyses for short-term, intermittent monitoring. In a Cochrane review by Langendam et al. (2012), 4 studies (n=216) compared real-time short-term glucose monitoring systems with SMBG, and the pooled effect estimate for change in HbA1c levels at 3 months was not statistically significant (MD change, -0.18; 95% CI, -0.42 to 0.05). (24) The meta-analysis by Wojciechowski et al. (2011) of RCTs on CGM (described previously) also included a separate analysis of 8 RCTs of short-term intermittent monitoring. (26) On pooled analysis, there was a statistically significant reduction in HbA1c levels with short-term intermittent glucose monitoring compared with SMBG (WMD = -0.26; 95% CI, -0.45 to -0.06).

Randomized Controlled Trials

The largest RCT was the Management of Insulin-Treated Diabetes Mellitus (MITRE) trial, published by Newman et al. (2009); it evaluated whether the use of the additional information provided by minimally invasive glucose monitors improved glucose control in patients with poorly controlled insulin-requiring diabetes. (40) This 4-arm RCT was conducted at secondary care diabetes clinics in 4 hospitals in England. This trial enrolled 404 people over the age of 18 years, with insulin-treated diabetes (Types 1 or 2) for at least 6 months, who were receiving 2 or more injections of insulin daily. Most (57%) participants had Type 1 diabetes (41% had Type 2 diabetes, 2% were classified as “other”). Participants had to have 2 HbA1c values of at least 7.5% in the 15 months before trial entry and were randomized to 1 of 4 groups. Two groups received minimally invasive glucose monitoring devices (GlucoWatch Biographer or MiniMed Continuous Glucose Monitoring System [CGMS]). Short-term glucose monitoring was used (i.e., monitoring was performed over several days at various points in the trial). These groups were compared with an attention control group (standard treatment with nurse feedback sessions at the same frequency as those in the device groups) and a standard control group (reflecting common practice in the clinical management of diabetes). Changes in HbA1c levels from baseline to 3, 6, 12, and 18 months were the primary indicator of short- to long-term efficacy. At 18 months, all groups demonstrated a decline in HbA1c levels from baseline. Mean percentage changes in HbA1c levels were -1.4% for the GlucoWatch group, - 4.2% for the CGMS group, -5.1% for the attention control group, and -4.9% for the standard care control group. In the intention-to-treat analysis, no significant differences were found between any groups at

any assessment times. There was no evidence that the additional information provided by the devices changed the number or nature of treatment recommendations offered by the nurses. Use and acceptability indicated a decline for both devices, which was most marked in the GlucoWatch group by 18 months (20% still using GlucoWatch vs 57% still using the CGMS). In this trial of unselected patients, glucose monitoring (CGMS on an intermittent basis) did not lead to improved clinical outcomes.

Pregnant People

Systemic Reviews

Voormolen et al. (2013) published a systematic review of the literature on CGM during pregnancy. (41) They identified 11 relevant studies (n=534). Two were RCTs, one of which was the largest of the studies (n=154). Seven studies used CGMs that do not have data available in real-time; the remaining 4 studies used real-time CGM. Reviewers did not pool study findings; they concluded that the evidence was limited on the efficacy of CGM during pregnancy. The published RCTs are described next.

Randomized Controlled Trials

Three RCTs of short-term glucose monitoring in pregnant women with Type 1 or Type 2 diabetes are summarized in Tables 11 to 14 and the following paragraphs. While both trials included a mix of women with Type 1 and Type 2 diabetes, most women had Type 1 diabetes in both trials, so the trials are reviewed in this section.

Voormolen et al. (2018) reported results of the GlucoMOMS trial, a multicenter, open-label RCT conducted between 2011 and 2015 in the Netherlands including pregnant women age 18 years and over with either diabetes mellitus type 1 (n=109), type 2 (n=82), or gestational (n=109) diabetes requiring insulin therapy before 30 weeks of gestation. The trial compared blinded CGM (n=147) to standard treatment (n=153). (42) Glycemic control was measured by CGM for 5 to 7 days every 6 weeks in the CGM group and SMBC was used in both groups. The primary outcome was macrosomia (birth weight above the 90th percentile). The incidence of large-for-gestational-age was 31% in the CGM group and 28% in the standard treatment group (RR=1.1; 95% CI, 0.8 to 1.4). HbA1c levels were similar between treatment groups.

Secher et al. (2013) randomized 154 women with Type 1 (n=123) and Type 2 (n=31) diabetes to real-time CGM in addition to routine pregnancy care (n=79) or routine pregnancy care alone (n=75). (43) Patients in the CGM group were instructed to use the CGM device for 6 days before each of 5 study visits and were encouraged to use the devices continuously; 64% of participants used the devices per-protocol. Participants in both groups were instructed to perform 8 daily self-monitored plasma glucose measurements for 6 days before each visit. Baseline mean HbA1c levels were 6.6% in the CGM group and 6.8% in the routine care group. The 154 pregnancies resulted in 149 live births and 5 miscarriages. The prevalence of large-for-gestational age infants (at least 90th percentile), the primary study outcome, was 45% in the CGM group and 34% in the routine care group. The difference between groups was not statistically significant (p=0.19). Also, no statistically significant differences were found between groups for secondary outcomes, including the prevalence of preterm delivery and the

prevalence of severe neonatal hypoglycemia. Women in this trial had low baseline HbA1c levels, which might explain the lack of impact of CGM on outcomes. Other factors potentially contributing to the negative findings included the intensive SMBG routine in both groups and the relatively low compliance rate in the CGM group.

Murphy et al. (2008) in the United Kingdom randomized 71 pregnant women with Type 1 (n=46) and Type 2 (n=25) diabetes to CGM or usual care. (44) The intervention consisted of up to 7 days of CGM at intervals of 4 to 6 weeks between 8 weeks and 32 weeks of gestation. Neither participants nor physicians had access to the measurements during sensor use; data were reviewed at study visits. In addition to CGM, the women were advised to measure blood glucose levels at least 7 times a day. Baseline HbA1c levels were 7.2% in the CGM group and 7.4% in the usual care group. The primary study outcome was maternal glycemic control during the second and third trimesters. Eighty percent of women in the CGM group wore the monitor at least once per trimester. Mean HbA1c levels were consistently lower in the intervention arm, but differences between groups were statistically significant only at week 36. For example, between 28 weeks and 32 weeks of gestation, mean HbA1c levels were 6.1% in the CGM group and 6.4% in the usual care group (p=0.10). The prevalence of large-for-gestational age infants (at least 90th percentile) was a secondary outcome. Thirteen (35%) of 37 infants in the CGM group were large-for-gestational age compared with 18 (60%) of 30 in the usual care group. The odds for reduced risk of a large-for-gestational age infant with CGM was 0.36 (95% CI, 0.13 to 0.98; p=0.05).

Table 11. RCT Characteristics for Short-Term CGM in Pregnant People With Type 1 Diabetes

Study; Registration	Countries	Sites	Dates	Participants	Interventions	
					Active	Com-parator
Voormolen et al. (2018) (42)	Netherlands and Belgium	23	2011-2015	Pregnant women with type 1 (n=109) or type 2 (n=82) diabetes who were undergoing insulin therapy at gestational age <16 weeks, or women who were undergoing insulin treatment for gestational diabetes (n=109) at gestational age <30 weeks; mean age, 32 y; mean HbA1c, 52 mmol/mol.	CGM (for 5-7 days every 6 weeks) plus SOC (n=147)	SOC (n=153)

Secher et al. (2013) (43); NCT00994357	Denmark	1	2009-2011	Pregnant women with Type 1 (80%) or Type 2 (20%) diabetes; mean gestational age, <14 wk); median HbA1c level, 6.7%; median age, 32 y.	CGM (for 6 d before each study visits; encouraged to used continuously) plus SOC (n=79).	SOC (n=75)
Murphy et al. (2008) (44); ISRCTN84461581	U.K.	2	2003-2006	Pregnant women with Type 1 (65%) and Type 2 (35%) diabetes; mean gestational age, 9.2 wk; mean HbA1c level, 7.3%; mean age, 31 y.	CGM (up to 7 d of CGM at intervals of 4-6 wk) plus SOC (n=38).	SOC (n=33)

CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; NCT: national clinical trial; RCT: randomized controlled trial; SOC: standard of care; wk: week; y:years.

Table 12. RCT Results for Short-Term CGM in Pregnant People With Type 1 Diabetes

Study	**Infant**				**Maternal**	
	Large-for-Gestational Age	Gestational Age at Delivery	Severe Hypo-glycemia	Caesarean Section	HbA1c levels; at 36 weeks' Gestation [a]	Severe Hypo-glycemia
Voormolen et al. (2018) (42)						
n	290	290	290	290		NR
CGM	(31)	266	25 (18%)	23 (21%)		
Control	(28)	266	25 (17%)	26 (23%)		
TE (95% CI)	RR=1.1 (0.8 to 1.4)	1.1 (0.9 to 1.4)	1.0 (0.6 to 1.7)	NR	'No difference'	
p						
Secher et al. (2013) (43)						
n	154	154	145	154	NR	154
CGM	34 (45%)	Median, 263	9 (13%)	28 (37%)	Median, 6.0%	16%
Control	25 (34%)	Median, 264	10 (14%)	33 (45%)	Median, 6.1%	16%
TE (95% CI)	NR	NR	NR	NR	NR	NR
p	0.19	0.14	0.88	0.30	0.63	0.91
		Weeks				
Murphy et al. (2008) (44)						

n	71	71	68	69	71	NR
CGM	13 (35%)	Mean, 37.6	3 (8%)	27 (71%)	Mean, 5.8%	
Control	18 (60%)	Mean, 37.5	5 (17%)	21 (61%)	Mean, 6.4%	
TE (95%CI)	OR=0.36 (0.13 to 0.98)	NR	NR	NR	0.6% (CI NR)	
p	0.05	0.80	0.50	0.40	0.007	

Values are n or n (%) or as otherwise indicated.
CGM: continuous glucose monitoring; CI: confidence interval; HbA1c: hemoglobin A1c; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; TE: treatment effect.
[a] N inconsistently reported for HbA1c outcome.

Tables 13 and 14 display notable limitations identified in each study.

Table 13. Study Relevance Limitations of RCTs of Intermittent CGM in Pregnant People With Type 1 Diabetes

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
Voormolen et al. (2018) (42)		4. Only 66% of the participants used devices per protocol			
Secher et al. (2013) (43)	4. Study population had relatively low HbA1c levels.	4. Only 64% of the participants used devices per protocol.			
Murphy et al. (2008) (44)					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; RCT: randomized controlled trial.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use; 5. Enrolled study populations do not reflect relevant diversity.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 14. Study Design and Conduct Limitations of RCTs of Short-Term Glucose Monitoring in Pregnant People With Type 1 Diabetes

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Complete-ness[d]	Power[e]	Statistical[f]
Voormolen et al. (2018) (42)		1. Not blinded; chance of bias in clinical management				
Secher et al. (2013) (43)		1. Not blinded; chance of bias in clinical management				3, 4. Treatment effects and confidence intervals not calculated
Murphy et al. (2008) (44)		1. Not blinded; chance of bias in clinical management				3, 4. Treatment effects and confidence intervals not calculated for some outcomes

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

RCT: randomized controlled trial.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Glucose Monitoring Devices for Short-Term Use in Type 1 Diabetes

For short-term monitoring of Type 1 diabetes, there are few RCTs and systematic reviews. The evidence for short-term monitoring on glycemic control is mixed, and there was no consistency in HbA1c levels. Some trials have reported improvements in glucose control for the intermittent monitoring group but limitations in this body of evidence preclude conclusions. The definitions of control with short-term CGM use, duration of use and the specific monitoring protocols varied. In some studies, short-term monitoring was part of a larger strategy aimed at optimizing glucose control, and the impact of monitoring cannot be separated from the impact of other interventions. Studies have not shown an advantage for intermittent glucose monitoring in reducing severe hypoglycemia events, but the number of events reported is generally small and effect estimates imprecise. The limited duration of use may preclude an assessment of any therapeutic effect. RCTs of short-term CGM use for monitoring in pregnancy included women with both Type 1 and 2 diabetes, with most having Type 1 diabetes. One trial reported a difference in HbA1c levels at 36 weeks; the proportion of infants that were large for gestational age (>90th percentile) favored CGM while the second trial did not. The differences in the proportions of infants born via cesarean section, gestational age at delivery, and infants with severe hypoglycemia were not statistically significant.

Continuous Glucose Monitoring Devices for Use in Individuals with Type 2 Diabetes Who Are Treated with Insulin Therapy

There is limited ability to distinguish between long-term and short-term glucose monitoring in the analysis of the data for Type 2 diabetes, consistent with the literature.

Clinical Context and Therapy Purpose

The purpose of long-term and short-term CGM devices is to provide a treatment option that is an alternative to or an improvement on existing therapies such as SMBG.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with Type 2 diabetes who are treated with insulin therapy and who experience poor diabetes control despite current use of best practices. Poor control includes situations such as unexplained hypoglycemic episodes, hypoglycemic unawareness, and persistent hyperglycemia and A1C levels above target.

In addition, some individuals with type 2 diabetes may need to determine basal insulin levels prior to insulin pump initiation.

All individuals with type 2 diabetes require engagement in a comprehensive self-management and clinical assessment program that includes assessment of blood glucose control.

Interventions

The testing being considered is the use of long-term or short-term CGM devices to assess blood glucose levels as part of optimal diabetes management.

Comparators
Blood glucose monitoring is an essential component of type 2 diabetes management in order to monitor for and prevent hypoglycemia and hyperglycemia. For these individuals, guidelines recommend blood glucose monitoring prior to meals and snacks, at bedtime, occasionally postprandially, prior to exercise, when low blood glucose is suspected, after treating low blood glucose, and prior to and while performing critical tasks such as driving. The following practice is currently being used to measure glucose levels: SMBG (capillary blood sampling (finger stick) using blood glucose meters) and periodic measurement of HbA1c.

Outcomes
The general outcomes of interest are change in HbA1c levels, frequency of and time spent in hypoglycemia, frequency and time spent in hyperglycemia, complications of hypoglycemia and hyperglycemia, and QOL. To assess short-term outcomes such as HbA1c levels, a minimum follow-up of 8 to 12 weeks is appropriate. To assess long-term outcomes such as time spent in hypoglycemia, the incidence of hypoglycemic events, complications of hypoglycemia, and QOL, follow-up of 6 months to 1 year would be appropriate.

Study Selection
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials
Three RCTs evaluated CGM in individuals with type 2 diabetes using multiple daily insulin injections or an insulin pump (Tables 15 and 16). (45, 46, 47) One evaluated real-time CGM using the Dexcom device and 2 evaluated intermittently scanned CGM using the Freestyle Libre system.

Beck et al. (2017) reported on the DIAMOND RCT. (45) DIAMOND compared CGM with the Dexcom device to SMBG in 158 participants at 25 endocrinology practices in North America (22 in the U.S., 3 in Canada). Participants who were adherent during a run-in period were eligible for randomization. Change in HbA1c level from baseline to 24 weeks was the primary outcome. Analyses were adjusted for baseline HbA1c levels and were performed using intention-to-treat analysis with missing data handling by multiple imputations. Week 24 follow-up was completed by 97% of the CGM group and 95% of the control group. Mean CGM use was greater than 6 days/week at 1 month, 3 months, and 6 months. The adjusted difference in mean change in

HbA1c level from baseline to 24 weeks was -0.3% (95% CI, -0.5% to 0.0%; p=.022) favoring CGM. The adjusted difference in the proportion of patients with a relative reduction in HbA1c level of 10% or more was 22% (95% CI, 0% to 42%; p=.028) favoring CGM. There were no events of severe hypoglycemia or diabetic ketoacidosis in either group. The treatment groups did not differ in any of the QOL measures.

Haak et al. (2017) compared intermittently scanned CGM with the Freestyle Libre device in 224 individuals at 26 European centers. (46) At 6 months, there was no difference between groups in the primary outcome of change in HbA1c (p=.8222). However, results for secondary outcomes including time in hypoglycemia and treatment satisfaction favored the CGM group. No serious adverse events or severe hypoglycemic events were reported related to device use.

Yaron et al. (2019) reported higher treatment satisfaction (the primary outcome) in 101 individuals using a flash glucose monitor compared to SMBG. (47) On secondary glycemic control measures, HbA1c was reduced by 0.82% compared to 0.33% in the control group (p=.005) without an increase in the frequency of hypoglycemic events.

One RCT evaluated CGM in patients treated with basal insulin. Martens et al. (2021) reported results of a RCT comparing real-time CGM with SMBG in 176 patients with poorly controlled type 2 diabetes (HbA1c levels 7.8% to 11.5%) treated with basal insulin without prandial insulin. (48) At 8 months, there was a statistically significantly greater decrease in mean HbA1c in the CGM group (adjusted difference, -0.4%; 95% CI -0.8% to -0.1%; p=.02), with 1 hypoglycemic event in each group. Aleppo et al. (2021) reported a 6-month follow-up study of 163 patients who had been randomized in this same trial (93.1%). (49) Patients originally randomized to SMBG continued to use SMBG for another 6 months, and the CGM group was randomly reassigned either to continue CGM or discontinue CGM and resume SMBG. In the group that discontinued CGM, mean HbA1c increased from 7.9% at 8 months to 8.2% at 14 months, whereas in the group that continued CGM, mean HbA1c decreased from 8.2% to 8.1%.

Table 15. Key RCT Characteristics for Continuous Glucose Monitoring in Individuals with Type 2 Diabetes on Insulin

Study Registration	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Beck et al. (2017) (DIAMOND) (45) NCT02282397	U.S., Canada	25	2014-2016	Adults with T2D using multiple daily injections of insulin with HbA1c levels 7.5%-10.0% (baseline mean, 8.5%); mean age, 60 y.	Real-time CGM, (n=79).	SMBG (n=79)

Haak et al. (2017) (46) NCT02082184	Multiple European	26	2014-2015	Adults with type 2 diabetes treated with insulin for at least 6 months and on their current regimen for 3 months or more, HbA1c 7.5 to 12.0%.	Flash glucose monitoring with FreeStyle Libre device n = 149	SMBG n = 75
Yaron et al. (2019) (47) NCT02809365	Israel	2	2016-2017	Adults with type 2 diabetes on multiple daily insulin injections for at least 1 year.	Flash glucose monitoring with FreeStyle Libre device n = 53	SMBG n = 48
Martens et al. (2021) (48) Aleppo et al. (2021) (49)	U.S.	15	2018-2019	Adults with T2D treated with 1 to 2 daily injections of basal insulin without prandial insulin; HbA1c levels 7.8% to 11.5% (baseline mean, 9.1%); mean age, 57 y	Real-time CGM (n=116)	SMBG (n=59)

CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; NCT: national clinical trial; NR: not reported; RCT: randomized controlled trial; SMBG: self-monitored blood glucose; T2D: Type 2 diabetes; wk: week; y: years.

Table 16. Key RCT Outcomes for Continuous Glucose Monitoring in Individuals with Type 2 Diabetes on Insulin

Study	Reduction in HbA1c Levels (Mean Range); %	HbA1c Level <7.0%, n (%)	Relative Reduction in HbA1c Level ≥10%, n (%)	Hypoglycemic or Ketoacidosis Events	Diabetes Complications (retinopathy, nephropathy, neuropathy, diabetic foot)	Health-Related Quality of Life
	Baseline to 24 Wk	At 24 Wk	At 24 Wk			DTSQ Overall Mean Score at 24 WK

Beck et al. 2017) (45)						
N	158	158	158	158	NR	150
CGM	8.6 to 7.7	11 (14%)	40 (52%)	0		Baseline: 1.78 24 weeks: 1.61
Control	8.6 to 8.2	9 (12%)	24 (32%)	0		Baseline: 1.69 24 weeks: 1.78
TE (95% CI)	-0.3 (-0.5 to 0.0)	3% (-9% to 14%)	22% (0% to 42%)			0.22 (0.08 to 0.36)
p	0.022	0.88	0.028			0.009
Haak et al. (2017) (46) NCT02082184						
	HbA1c change from baseline to 6 months: -3.1 (SE 0.75) mmol/L (-0.29% ±0.07%) vs -3.4 (SE 1.04 [-0.31 ± 0.09%]) p=.8222			Time in hypoglycemia: <3.9 mmol/L: reduced by mean 0.47 (SE 0.13) hours/day; p=.0006 <3.1 mmol/L reduced by 0.22 ±0.07 hours/day; p=.0014		
Yaron et al. (2019) (47) NCT02809365						
	Change in HbA1c –0.82% (9 mmol/mol) –0.33% (3.6				NR	Treat-ment satisfac-tion (Primary outcome, DTSQc)

	mmol/ mol) p=.005					at 10 weeks: 2.47 (0.77) vs.2.18 (0.83); p=.053
Martens et al. (2021) (48) Aleppo et al. (2021) (49) NCT03566693						
N	156	156	156	175	NR	NR
CGM	9.1 to 8.0	20 (19%)	66 (63%)	1 hyopglycemic event, 1 ketoacidosis event		
Control	9.0 to 8.4	5 (10%)	21 (41%)	1 hypoglycemic event		
TE (95% CI)	-0.4 (-0.8 to-0.1)	11.8 (0.6 to 24.5)	22.4 (12.0 to 32.0)			
p	0.02	0.04	< 0.001			

CGM: continuous glucose monitoring; CI: confidence interval; DTSQ: Diabetes Treatment Satisfaction; HbA1c: hemoglobin A1c; N: number; NCT: national clinical trial; NR: not reported; RCT: randomized controlled trial; SE: standard error; TE: treatment effect; wk: week.

Observational Studies

Because several RCTs exist, observational studies will be summarized briefly below only if they capture longer periods of follow-up (>6 months), larger populations, or particular subgroups of interest.

Long-term follow-up

Observational studies with follow-up of more than 6 months including adults with type 2 diabetes, the majority of whom were on insulin, have shown that reduction in mean HbA1c is maintained for 12 months, (50) and reductions in acute diabetes events, including severe hypoglycemia and diabetic ketoacidosis are maintained for 1 to 2 years. (37, 51, 38)

Individuals with Significant Hypoglycemia

Twelve-month open-access, follow-up results for long-term CGM with the Freestyle Libre device in 108 individuals from the Haak et al. (2017) 6-month trial were reported in a second publication by Haak et al. (2017). (52) Hypoglycemia was analyzed using 3 different glucose level thresholds (<70 mg/dl, <55 mg/dl, and <45 mg/dl). At 12-month follow-up, hypoglycemic events were reduced by 40.8% to 61.7% with a greater relative reduction in the most severe thresholds of hypoglycemia. At all 3 glucose level thresholds, there were statistically significant reductions in time in hypoglycemia, frequency of hypoglycemic events, time in nocturnal hypoglycemia, and frequency of nocturnal hypoglycemia. Change for hypoglycemic events per

day at 12 months compared to baseline was also significant: -40.8% (glucose <70 mg/dl, p<.0001); -56.5% (glucose <55 mg/dl, p<.0001); -61.7% (glucose <45 mg/dl, p=.0001).

Pregnant People

Wilkie et al. (2023) reported results of a systematic review of CGM in type 2 diabetes in pregnancy. (53). The review includes the same 3 RCTs described below. The meta-analytic treatment effect estimate of large-for-gestational-age infants (CGM, n=56 vs. control, n=53) was OR, 0.8 (95% CI, 0.3 to 1.8). There was no difference in development of preeclampsia (OR, 1.6, 95% CI, 0.3 to 7.2).

As discussed in the section on CGM in pregnant women with type 1 diabetes, 3 RCTs have evaluated short-term glucose monitoring in pregnant women with type 1 and type 2 diabetes. Most women had type 1 diabetes in both trials. There were 25 (35%) women with type 2 diabetes in Murphy et al. (2008) (44) and 31 (20%) with type 2 diabetes in Secher et al. (2013) (43) and 82 (27%) women with type 2 diabetes in Voormolen (2018). (42). Results for women with type 2 diabetes were not reported in Murphy et al. (2008). Secher et al. (2013) reported that 5 (17%) women with type 2 diabetes experienced 15 severe hypoglycemic events, with no difference between groups; other analyses were not stratified by diabetes type.

Section Summary: CGM Devices for Use in Individuals with Type 2 Diabetes Who Are Treated with Insulin

Three RCTs have evaluated CGM compared to SMBG in individuals with type 2 diabetes on intensive insulin therapy, 1 using real-time CGM and 2 using an intermittently scanned device. One RCT evaluated CGM in patients treated with basal insulin using real-time CGM. All found either improved glycemic outcomes or no difference between groups with no increase in hypoglycemic events. In the DIAMOND trial, the adjusted difference in mean change in HbA1c level from baseline to 24 weeks was -0.3% (95% CI, -0.5% to 0.0%; p=.022) favoring CGM. The adjusted difference in the proportion of patients with a relative reduction in HbA1c level of 10% or more was 22% (95% CI, 0% to 42%; p=.028) favoring CGM. There were no events of severe hypoglycemia or diabetic ketoacidosis in either group. Yaron et al. (2019) reported higher treatment satisfaction with CGM compared to control (the primary outcome). At 12-month follow-up in one of the trials of the Freestyle Libre device, hypoglycemic events were reduced by 40.8% to 61.7% with a greater relative reduction in the most severe thresholds of hypoglycemia. In the Martens trial of individuals treated with basal insulin without prandial insulin, there was a statistically significantly greater decrease in mean HbA1c in the CGM group (adjusted difference, -0.4%; 95% CI -0.8% to -0.1%; p=.02), with 1 hypoglycemic event in each group.

Continuous Glucose Monitoring Devices for Use in Individuals with Type 2 Diabetes Who Are Not Treated with Insulin Therapy

Clinical Context and Therapy Purpose

The purpose of long-term and short-term CGM devices is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with type 2 diabetes.

The question addressed in this medical policy is: Does the use of long-term or short-term CGM devices improve the net health outcome for individuals with type 2 diabetes on less intensive therapy (i.e., who do not require multiple daily insulin injections or an insulin pump)?

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with type 2 diabetes who are not treated with insulin therapy.

All individuals with type 2 diabetes require engagement in a comprehensive self-management and clinical assessment program that includes assessment of blood glucose control.

Interventions
The testing being considered is the long-term or short-term use of CGM devices to assess blood glucose levels as part of optimal diabetes management.

Currently, CGM devices are of 2 designs; rtCGM provides real-time data on glucose level, glucose trends, direction, and rate of change, and iCGM devices that show continuous glucose measurements retrospectively. These devices are also known as flash-glucose monitors.

Comparators
SMBG (capillary blood sampling [finger stick]) using blood glucose meters and periodic measurement of HbA1c is used to measure glucose levels.

In contrast to recommendations in individuals on intensive insulin regimens, guidelines are less clear on when to prescribe blood glucose monitoring and how often monitoring is needed in individuals with type 2 diabetes who are not on insulin therapy. In individuals on oral antidiabetic agents only, routine glucose monitoring may be of limited additional clinical benefit. (54)

Outcomes
The general outcomes of interest are change in HbA1c levels, frequency of and time spent in hypoglycemia, frequency and time spent in hyperglycemia, complications of hypoglycemia and hyperglycemia, and QOL. To assess short-term outcomes such as HbA1c levels, a minimum follow-up of 8 to 12 weeks is appropriate. To assess long-term outcomes such as time spent in hypoglycemia, the incidence of hypoglycemic events, complications of hypoglycemia, and QOL, follow-up of 6 months to 1 year would be appropriate.

<u>Study Selection</u>
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

There is limited ability to distinguish between long-term and short-term glucose monitoring in the analysis of the data for type 2 diabetes, consistent with reporting in the literature. Therefore, this section includes both long-term and short-term uses.

Randomized Controlled Trials

Four RCTs evaluated CGM in individuals with Type 2 diabetes who are not treated with insulin therapy (Tables 17 and 18).

Ehrhardt et al. (2011) reported the results of a RCT evaluating the intermittent use of a CGM device over 12 weeks in adults with type 2 diabetes treated with diet/exercise and/or glycemia-lowering medications but not prandial insulin who had an initial HbA1c level of at least 7% but not more than 12%. (55) Twenty-nine of 100 participants (29.0%) were using basal insulin alone or in combination with oral agents. The trial compared real-time CGM with the Dexcom device used for 4 cycles (2 weeks on and 1 week off) with SMBG. Vigersky et al. (2012) reported follow up data through 52 weeks. (56) The primary efficacy outcome was a mean change in HbA1c levels. Mean HbA1c levels in the CGM group were 8.4% at baseline, 7.4% at 12 weeks, 7.3% at 24 weeks, and 7.7% at 52 weeks. In the SMBG group, these values were 8.2% at baseline, 7.7% at 12 weeks, 7.6% at 24 weeks, and 7.9% at 52 weeks. During the trial, the reduction in HbA1c levels was significantly greater in the CGM group than in the SMBG group ($p=.04$). After adjusting for potential confounders (e.g., age, sex, baseline therapy, whether the individual started taking insulin during the study), the difference between groups overtime remained statistically significant ($p<.001$). The investigators also evaluated SMBG results for both groups. The mean proportions of SMBG tests less than 70 mg/dL were 3.6% in the CGM group and 2.5% in the SMBG group ($p=.06$).

Price et al. (2021) reported results from the COntinuous Glucose Monitoring & Management In TypE 2 Diabetes (COMMITED; NCT03620357) RCT comparing rt-CGM (10 days a month for 3 months) to SMBG in adult patients with type 2 diabetes (HbA1c between 7.8% and 10.5%) who were receiving 2 or more oral antidiabetic drugs, but not insulin, in the U.S. and Canada between 2018 and 2020. (57) Participants were 47% female, 74% White, 14% Asian, 7% Black and 29% Hispanic. The mean age was 60 years. The change in HbA1c at week 12 was not statistically different (-0.5 (1.3) % vs -0.2 (1.1) % for the CGM and SMBG groups, respectively; $p=.74$). The reduction in HbA1c was not sustained at month 9 for either group (-0.2 (0.9) % vs 0.1 (1.3) %, respectively, for CGM versus SMBG groups ($p=.79$).

Wada et al. (2020) reported results of an open-label, multicenter RCT in Japan including participants with non-insulin-treated type 2 diabetes with HbA1c ≥7.5% and <8.5%. (58)

The trial compared flash glucose monitoring worn for 12 weeks (n=49) and conventional SMBG (n=51). The primary outcome was change in HbA1c level at 12 weeks. There was no significant between-group difference in the change from baseline in the 2 groups at 12 weeks (CMG, -0.43% vs. SMBG, -0.30%; difference=-0.13%; 95% CI, −0.35 to 0.09; p=.24) but there was a difference favoring CGM at 24 weeks (difference, −0.29%; 95% CI, −0.54 to −0.05; p=.02).

Aronson et al. (2023) reported results of the IMMEDIATE multicenter RCT (NCT04562714) conducted in Canada including adults with type 2 diabetes and HbA1c of 7.5% or higher who were using at least 1 non-insulin antihyperglycemic therapy. (59) The 2 treatment groups were the flash glucose monitor CGM group (FreeStyle Libre Pro; n=58) worn 14 days at baseline and again at week 14 plus diabetes self-management education versus diabetes self-management education alone (DSME; n=58). DSME included instruction to self-monitor blood glucose at least 4 times daily. The primary outcome was the difference in percentage mean Time In Range (TIR; glucose 70-180 mg/dl) at 16 weeks. At 16 weeks, the CGM group had significantly greater mean TIR (difference=9.9%; 2.4 hours; 95% CI, 17.3% to 2.5%; p<.01). The mean HbA1c at 16 weeks was 7.6% in the CGM group compared to 8.1% in the DSME group (adjusted mean difference, 0.3%; 95% CI, 0% to 0.7%; p=.05). The Glucose monitoring satisfaction score was higher in the CGM group compared with the DSME group but there were no differences in the other patient-reported outcomes (Diabetes Distress Score, Adherence to Refills and Medications Scale for Diabetes and Skills, Confidence & Preparedness Index).

Tables 19 and 20 display notable limitations identified in the studies. These include a lack of blinding and heterogeneity in the participant populations, lack of data on diabetic events and percent of patients meeting target goals and insufficient duration to determine effects on diabetic complications.

Table 17. Key RCT Characteristics for CGM in Individuals with Type 2 Diabetes not on Insulin Therapy

Study Registration	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Ehrhardt et al. (2011) (55) Vigersky et al. (2012) (56)	U.S.	1	NR	Adults with T2D using oral antidiabetic agents without prandial insulin; HbA1c levels 7.0%-12.0% (baseline mean, 8.3%), mean age, 58 y.	Real-time CGM for 4 cycles of 3 wk (n=50).	SMBG (n=50)

				29 of 100 (29%) were using basal insulin**.**		
Price et al. (2021) (57)	U.S. and Canada	8	2018-2020	Adults with T2D receiving 2+oral antidiabetic drugs, HbA1c between 7.8% and 10.5%, not receiving insulin; mean age, 60y, mean HbA1c, 8.4%	Real-time CGM (Dexcom G6) for 10 days a month for 3 months (n=46)	SMBG (n=24)
Wada et al. (2020) (58)	Japan	5	2017-2018	Ages 20 to 70 with non-insulin-treated type 2 diabetes with HbA1c ≥7.5% and <8.5%; mean age, 58 y; mean HbA1c, 7.8%	Flash glucose monitor (Freestyle Libre) for 12 weeks (n=49)	SMBG schedule not described (n=51)
Aronson et al. (2023) (59)	Canada	6	2020-2021	Adults with type 2 diabetes and HbA1c ≥7.5% who were using at least one non-insulin antihyperglycemic therapy; mean age, 58y; mean HbA1c, 8.6%	Flash glucose monitor (FreeStyle Libre Pro) for 14 days plus diabetes self-management education (n=58)	Diabetes self-management education alone (included SMBG) (n=58)

CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; NR: not reported; RCT: randomized controlled trial; SMBG: self-monitored blood glucose; T2D: Type 2 diabetes; wk: week.

Table 18. Key RCT Outcomes for CGM in Individuals with Type 2 Diabetes not on Insulin Therapy

Study	HbA1c Levels (Mean Range); %	HbA1c Level <7.0%, n (%)	Relative Reduction in HbA1c Level ≥10%, n (%)	Hypoglycemic or Ketoacidosis Events	Diabetes Complications (retinopathy, nephropathy, neuropathy, diabetic foot)	Patient Reported Outcomes
Ehrhardt et al. (2011) (55) **Vigersky et al. (2012)**						

(56)						
N	100	NR	NR	NR	NR	NR
CGM	8.4 to 7.4					
Control	8.2 to 7.7					
TE (95% CI)	NR					
p	0.006					
Price et al. (2021) (57)						
	At week 12	At week 12	NR			
N	67	67				
CGM	8.0 (1.1)	(18%)		0		
Control	8.1 (1.0)	(9%)		1		
TE (95% CI)	NR			NR		
p	0.74	0.26		NR		
Wada et al. (2020) (58)						
	Change from baseline to 12 weeks	NR	NR	Hypoglycemia, n		Diabetes Treatment Satisfaction Questionnaire (DTSQ) score, mean (SD)
N	93			93		90
CGM	-0.43			2		35 (5)
Control	-0.30			1		31 (7)
TE (95% CI)	-0.13 (-0.35 to 0.09)			NR		NR
p	0.24			NR		<.001
Aronson et al. (2023) (59)						
	At 16 weeks	NR	NR	At least one hypoglycemic event, n(%)	NR	Glucose monitoring satisfaction score (GMSS), mean (SD) at week 16
N	108					NR
CGM	7.6			30 (59%)		3.9 (0.5)
Control	8.1			24 (50%)		3.4 (0.5)

TE (95% CI)	0.3% (0.0 to 0.7) favoring CGM			NR		0.5 (0.7 to 0.3) favoring CGM
p	0.05			NR		<.01

CGM: continuous glucose monitoring; CI: confidence interval; DTSQ: Diabetes Treatment Satisfaction; HbA1c: hemoglobin A1c; N: number; NCT: national clinical trial; NR: not reported; RCT: randomized controlled trial; TE: treatment effect; wk: week.

Table 19. Study Relevance Limitations of RCTs of CGM in Individuals with Type 2 Diabetes Not on Insulin Therapy

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Ehrhardt et al. (2011) (55) Vigersky et al. (2012) (56)	1. study population a mix of participants using basal insulin or oral agents alone.			1. Focused on HbA1c; did not include outcomes on adverse events, quality of life, or diabetic complications. 6. No justification for clinically significant difference.	**1**. Follow-up not sufficient to determine effects on diabetic complications.
Price et al. (2021) (57)					1. Treatment and follow-up of 3 months
Wada et al. (2020) (58)	5. Study conducted in Japan			1. Did not report key outcomes on participants meeting target A1c levels	1. Treatment for 12 weeks with 12 additional weeks of follow-up
Aronson et al. (2023) (59)	5. Study conducted in Canada			1. Did not report key outcomes on participants meeting target A1c levels	1. Follow-up of 16 weeks

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; QOL: quality of life; NCT: national clinical trial; RCT: randomized controlled trial.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use; 5. Enrolled study populations do not reflect relevant diversity.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 20. Study Design and Conduct Limitations of RCTs of CGM in Individuals with Type 2 Diabetes Not on Insulin Therapy

Study; Trial	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Complete-ness[d]	Power[e]	Statistical[f]
Ehrhardt et al. (2011) (55) Vigersky et al. (2012) (56)		1. Not blinded; chance of bias in clinical management.				
Price et al. (2021) (57)		1. Not blinded			1, 2, 3: No information on power or sample size calculations	
Wada et al. (2020) (58)		1. Not blinded				
Aronson et al. (2023) (59)		1. Not blinded				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CGM: continuous glucose monitoring; RCT: randomized controlled trial.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Continuous Glucose Monitoring Devices for Use in Individuals with Type 2 Diabetes Who Are Not Treated with Insulin Therapy

The trials reported mixed results with respect to benefits of CGM regarding glycemic control. However, participant populations were heterogenous with regard to their diabetic treatment regimens, and participants might not have been receiving optimal therapy. In individuals on oral antidiabetic agents only, routine glucose monitoring may be of limited additional clinical benefit. Additional evidence would be needed to show what levels of improvements in HbA1c over the short-term in this population would be linked to meaningful improvements over the long-term in health outcomes such as diabetes-related morbidity and complications.

Continuous Glucose Monitoring Use in Pregnant People With Gestational Diabetes

Clinical Context and Therapy Purpose

The purpose of long-term CGM and short-term (intermittent) glucose monitoring devices is to provide a treatment option that is an alternative to or an improvement on existing therapies in persons with gestational diabetes.

The question addressed in this medical policy is: Do the use of long-term CGM and short-term (intermittent) glucose monitoring devices improve the net health outcome for persons with gestational diabetes?

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest are persons with gestational diabetes.

Interventions

The testing being considered are devices that provide continuous, long-term glucose levels to the patient to direct insulin regimens and intermittent (i.e., 72 hours), the results of short-term monitoring of glucose levels are used by the provider to optimize management.

Comparators
The following practice is currently being used to measure glucose levels: capillary blood sampling (finger stick) for blood glucose meters for self-monitoring.

Outcomes
The general outcomes of interest are a change in HbA1c levels, time spent in hypoglycemia, the incidence of hypoglycemic events, complications of hypoglycemia and QOL.

To assess short-term outcomes such as HbA1c levels, time spent in hypoglycemia, the incidence of hypoglycemic events and, complications of hypoglycemia, a minimum follow-up of 8 to 12 weeks is appropriate. To assess long-term outcomes such as QOL and maternal and infant outcomes, follow-up of 24 to 36 weeks would be appropriate.

Study Selection
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials
Two trials of glucose monitoring in women with gestational diabetes has been published. Trial characteristics, results, and limitations are shown in Tables 21 to 24 and briefly described below. In addition, the GlucoMOMS trial described in the previous section on pregnant women with type 1 diabetes also included 109 women with gestational diabetes. (42)

Lai et al. (2023) published results of an RCT comparing CGM plus SMGB (n=77) to SMGB (n=77) in pregnant people with gestational diabetes at 24 to 28 gestation with HbA1c <6% between 2019 and 2021 at a single center in China (NCT03955107). (60) Study visits occurred at 4 and 8 weeks. Participants in the CGM group were provided with a Medtronic CGM system that measured subcutaneous interstitial glucose for 3 consecutive days and were instructed to use CGM every 4 weeks (0, 4, and 8 weeks). The SMBG group was instructed to perform SMBG 4 times per day for 3 consecutive days every 4 weeks (0, 4 and 8 weeks). Participants in both groups continued their usual protocol of capillary glucose monitoring during their pregnancy and were asked to perform SMBG at least 7 times weekly. Most outcomes did not differ by treatment group with the exception of proportion of participants within recommended gestational weight gain (59.7% vs. 40.3%, p=.046).

In an RCT, Wei et al. (2016) evaluated the use of CGM in 120 women with gestational diabetes at 24 to 28 weeks. (61) Patients were randomized to prenatal care plus CGM (n=58) or SMBG (n=62). The CGM sensors were reportedly inserted for 48 to 72 hours on weekdays; it is not

clear whether the readings were available in real-time. The investigators assessed a number of end points and did not specify primary outcomes; a significance level of $p < 0.05$ was used for all outcomes. The groups did not differ significantly in a change in most outcomes, including a change in maternal HbA1c levels, rates of preterm delivery before the 35th gestational week, cesarean delivery rates, proportions of large-for-gestational age infants, or rates of neonatal hypoglycemia. Women in the CGM group gained significantly less weight than those in the SMBG group.

Table 21. Key RCT Characteristics for CGM in Pregnant People With Gestational Diabetes

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Lai et al. (2023) (60)	China	1	2019-2021	Pregnant people with gestational diabetes with HbA1c <6% at 24–28 gestational weeks; singleton pregnancy, preconception BMI ≥ 18kg/m^2; mean HbA1c level, 5.9%; mean age, 32 years	CGM + SMBG every four weeks until antepartum (n=77)	SMBG (n=77)
Wei et al. (2016) (61)	China	1	2011-2012	Pregnant women with gestational diabetes diagnosed between 24 and 28 wk of gestation; mean HbA1c level, 5.8%; mean age, 30 years.	CGM (48-721 on weekdays) (n=51)	SMBG (n=55)

BMI: Body mass index; CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; RCT: randomized controlled trial; SMBG: self-monitored blood glucose; wk: week.

Table 22. RCT Outcomes for CGM in Pregnant People With Gestational Diabetes

Study	Infant				Maternal	
	Large-for-Gestational Age, n (%)	Gestational Age at Delivery, wk	Severe Hypo-glycemia, n (%)	Caesarean Section, n (%)	HbA1c Levels Before Delivery[a]	Severe Hypo-glycemia
Lai et al. (2023) (60)						
N	124	NR	124	124	124	NR
CGM	5 (8)		1 (2)	34 (55)	Mean, 5.3%	
Control	5 (8)		1 (2)	36 (58)	Mean, 5.4%	
TE (95% CI)	1.00 (0.52 to 1.91)		RR=1.00 (0.25 to 4.04)	RR=0.94 (0.65 to 1.34)	NR	
p	1.0		1.0	0.71	0.60	
Wei et al. (2016) (61)						
N	106	106	106	106	NR	NR
CGM	18 (35)	Mean, 37.4	4 (8)	31 (60)	Mean, 5.5%	
Control	29 (53)	Mean, 37.5	7 (13)	38 (69)	Mean, 5.6%	
TE (95% CI)	NR	NR	NR	NR	NR	
p	0.07	0.92	0.41	0.37	0.09	

Values are n (%) or as otherwise indicated.
CGM: continuous glucose monitoring; CI: confidence interval; HbA1c: hemoglobin A1c; NR: not reported; RCT: randomized controlled trial; TE: treatment effect; wk: week.
[a] N inconsistently reported for HbA1c outcome.

Tables 23 and 24 display notable limitations identified in each study.

Table 23. Study Relevance Limitations of RCTs for CGM in Pregnant People With Gestational Diabetes

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Lai et al. (2023) (60)	4. Study population had relatively low HbA1c level 5. Study conducted entirely in China	4. Compliance with CGM not reported	4. Compliance with control not reported	**1**. Maternal hypoglycemia not reported	

Wei et al. (2016) (61)	4. Study population had relatively low HbA1c level. 5. Study conducted entirely in China	4.Compliance with CGM not reported.			

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; RCT: randomized controlled trial.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use; 5. Enrolled study populations do not reflect relevant diversity.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 24. Study Design and Conduct Limitations of RCTs for CGM in Pregnant People With Gestational Diabetes

Study	Allo-cation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Lai et al. (2023) (60)	3. Not reported	1. Not blinded	2. Hierarchy of outcomes unclear in publication	1, 2. 15 (19%) participants in each group discontinued study and were not accounted for in analysis	1. No power calculations reported; primary outcome not specified in publication but listed in registration	
Wei et al. (2016) (61)	3. Not reported.	1. Not blinded; chance of bias in clinical management.	1. Registra-tion not reported.	5. Exclusions not well justified.	1. No power calculations reported; primary	3, 4. Treatment effects and CIs

					outcome not specified.	not calculated.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CGM: continuous glucose monitoring; CI: confidence interval; RCT: randomized controlled trial.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Continuous Glucose Monitoring Use in Pregnant People With Gestational Diabetes

The 2 RCTs in women with gestational diabetes was conducted in China with the intervention starting in the second or third trimester and mean baseline HbA1c level less than 6.0%. The GlucoMOMS trial also included women with gestational diabetes. Trial reporting was incomplete; however, there were no differences between groups for most reported outcomes.

Continuous Glucose Monitoring Implanted Device

Clinical Context and Therapy Purpose

The purpose of an implantable CGM device is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with diabetes.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with type 1 or type 2 diabetes.

Interventions

One implantable CGM device (Eversense) is FDA cleared for use in the U.S. The Eversense Continuous Glucose Monitoring System is implanted in the subcutaneous skin layer and provides continuous glucose measurements over a 40-400 mg/dL range. The system provides real-time glucose values, glucose trends, and alerts for hypoglycemia and hyperglycemia and low glucose through a mobile application installed on a compatible mobile device platform. The Eversense CGM System is a prescription device indicated for use in adults (age 18 and older)

with diabetes for up to 180 days. The device was initially approved as an adjunctive glucose monitoring device to complement information obtained from standard home blood glucose monitoring devices. Prescribing providers are required to participate in insertion and removal training certification.

Comparators
The following practice is currently being used to measure glucose levels: capillary blood sampling (finger stick) with blood glucose meters for self-monitoring.

Outcomes
The general outcomes of interest are a change in HbA1c levels, time spent in hypoglycemia, the incidence of hypoglycemic events, complications of hypoglycemia and QOL.

To assess short-term outcomes such as HbA1c levels, time spent in hypoglycemia, the incidence of hypoglycemic events, and complications of hypoglycemia, a minimum follow-up of 8 to 12 weeks is appropriate. To assess long-term outcomes such as QOL and maternal and infant outcomes, follow-up of 24 to36 weeks would be appropriate.

Study Selection
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Studies
One trial of implantable CGM in people with diabetes has been published. Trial characteristics, results, and limitations for the RCTs are shown in Tables 25 to 28 and briefly described below.

Renard et al. (2022) reported results of the multicenter France Adoption Randomized Clinical Trial (NCT03445065) comparing implantable Eversense real-time CGM (n=159) versus self-monitoring of blood glucose or intermittently scanned CGM (n=80) in individuals with type 1 or type 2 diabetes. (62) Participants were adults, age 18 years and older, on multiple daily insulin injections or insulin pump. Participants were enrolled in 2 cohorts. Cohort 1 (n=149) included participants with type 1 or type 2 diabetes with HbA1c levels >8%. Cohort 2 (n=90) included participants with type 1 with time spent with glucose values below 70 mg/dL for more than 1.5 hours per day in the previous 28 days. The primary outcomes were changes in HbA1c at day 180 in cohort 1 and change in time spent with glucose below 54 mg/dL between days 90 and 120 in cohort 2. In cohort 1, there was no difference in HbA1c at day 180 (difference=-0.1; 95% CI, -0.4 to 0.1; p=.34) or in time in range (difference=-0.9; 95% CI, -6.7 to 4.8; p=.75). For cohort 2, the mean difference in time spent below 54mg/dL between days 90 and 120 was statistically

significant favoring implantable CGM (difference=-1.6% [23minutes]; 95% CI, -3.1 to -0.1; p=.04). Six out of 239 (3%) participants experienced skin irritation and/or redness from sensor insertion; 5 (2%) reported itching or pruritus and 5 (2%) reported at least one hematoma formation. Results for the patient-reported outcomes were not provided, but the text indicated that there were 'no significant changes'.

Table 25. Key RCT Characteristics for implantable CGM in People With Diabetes

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Renard et al. (2022) (62)	France	20	2018-2020	Adults, age ≥18 years, with type 1 or type 2 diabetes on multiple daily insulin injections or insulin pump. Cohort 1 (n=149) included participants with type 1 or type 2 diabetes with HbA1c levels >8% ;55% female; 87% type 1 diabetes; mean age, 43 y Cohort 2 (n=90) included participants with type 1 with time spent with glucose values <70mg/dL for >1.5 hours per day in the previous 28 days; 28% female; mean age, 46 y	' Enabled' Eversense sensor; Not allowed to use any other CGM Cohort 1 n=97 Cohort 2 n=62	Blinded Eversense sensor; Continued using SMBG or intermittently-scanned CGM Cohort 1 n=52 Cohort 2 n=28

Table 26. Summary of Key RCT Results for implantable CGM in People With Diabetes

Study	HbA1c	Blood Glucose (SD) mg/dL	Hypoglycemic Episodes	Patient Reported Outcomes
Renard et al. (2022) (62)				
Cohort 1 (type 1 or type2, high baseline HbA1c)	At day 180, primary outcome	Time below range (<54) between day 90 and 120		
N	149	149	149	NR
Implantable CGM	8.7 (1.1)	1.2 (2.0)	0	

Control	8.8 (1.0)	1.4 (1.8)	1	
Diff (95% CI)	-0.1 (-0.4 to 0.1)	-0.1 (-0.7 to 0.4)		'No difference'
p	0.34	0.68		
Cohort 2 (type 1, significant time with low glucose)	At day 180	Time below range (<54) between day 90 and 120; primary outcome		
N	90	90	90	NR
Implantable CGM	7.4 (0.9)	3.9 (3.1)	0	
Control	6.9 (1.0)	6.0 (5.3)	0	
Diff (95% CI)	0.1 (-0.2 to 0.4)	-1.6 (-3.1 to -0.1)		'No difference'
p	0.62	0.04		

Table 27. Study Relevance Limitations of RCTs for implantable CGM in People With Diabetes

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Renard et al. (2022) (62)	5. Study conducted entirely in France; racial characteristics not reported			1. Percent of participants meeting target HbA1c goals not reported	1, 2. Follow-up limited to 180 days

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; RCT: randomized controlled trial.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use; 5. Enrolled study populations do not reflect relevant diversity.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 28. Study Design and Conduct Limitations of RCTs for implantable CGM in People With Diabetes

Study	Allo-cation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]

Renard et al. (2022) (62)		1. Control arm described as 'blinded' but only participants in the implantable CGM arms were trained to use the system and were not allowed to use other CGM while participants in the control arm were allowed to use other CGM devices	2. Several outcomes reported as no change without numeric results	1. ITT analyses were reported. However, 50% of participants had primary outcome measurements taken outside of window in cohort 1. In cohort 2, 27% of participants had less than 70% of CGM data available for the primary outcome.	1. Assumptions for power calculations not given	3, 4. Numeric results not given for several outcome measures

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CGM: continuous glucose monitoring; RCT: randomized controlled trial.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized Studies

Data from 3 nonrandomized prospective studies (PRECISE, PRECISE II, AND PRECISION) were provided to the U.S. Food and Drug Administration (FDA) for the initial approval of Eversense as an adjunctive device. (63, 64) Expanded approval was granted in June 2019 and Eversense is now approved as a device to replace fingerstick blood glucose measurements for diabetes

treatment decisions. (65) Historical data from the system can be interpreted to aid in providing therapy adjustments. No new clinical studies were conducted to support the change in the indications for the device. The sponsor had previously performed clinical studies to establish the clinical measurement performance characteristics of the device, including accuracy across the claimed measuring range (40 to 400 mg/dL glucose), precision, claimed calibration frequency (every 12 hours), the wear period for the sensor (90 days), and performance of the alerts and notifications. This same clinical study information was used to support what the FDA considered a reasonable assurance of safety and effectiveness of the device for the replacement of fingerstick blood glucose monitoring for diabetes treatment decisions.

In 2022, Eversense was FDA approved for use up to 180 days. Approval was based on the PROMISE pivotal study, which was designed to assess the safety and accuracy of the 180-day device. (66) PROMISE was a prospective, multicenter, unblinded, nonrandomized study of 181 adults with Type 1 (69.6%) and type 2 (30.4%) diabetes conducted at 8 sites in the U.S. Participants had diabetes for at least 1 year. Participants were heterogenous with regard to diabetes treatment: 50.8% were using a continuous insulin infusion pump, 35.9% multiple daily injections of insulin, 8.8% oral diabetes medications only, and 4.4% basal insulin or only 1 injection per day (4.4%). Accuracy of the device was evaluated by comparing CGM to glucose analyzer values during 10 clinic visits. Sensors were removed after day 180.The safety endpoint was the rate of device-related or sensor insertion/removal procedure-related serious adverse events. For primary sensors, the percent CGM readings within 20% of glucose analyzer values was 92.9%; the overall mean absolute relative difference was 9.1%. There were no serious adverse events related to the device or insertion/removal procedures. There were no unanticipated adverse events and the most frequently reported adverse events were dermatological (e.g., skin irritation). All primary sensors were successfully removed on the first attempt.

Multiple post-marketing registry studies of the Eversense device have been published (Tables 29 and 30). Sanchez et al. (2019) reported glucometric and safety data on the first 205 patients in the U.S. to use the Eversense device for at least 90 days. (67) Of the 205 patients, 62.9% reported having T1D, 8.8% Type 2 diabetes (T2D), and 28.3% were unreported; results were not reported separately by diabetes type. Deiss et al. (2019) reported safety outcomes for 3023 patients from 534 sites in Europe and South Africa who had used the device for 6 months or longer. (68) There were no serious adverse events, and the most commonly reported adverse events were sensor site infection and skin irritation. Tweden et al. (2019) reported accuracy and safety data from 945 patients in Europe and South Africa who used either the 90-day or 180-day Eversense system for 4 insertion-removal cycles. (69) The percentage of patients using the 180-day system increased from cycle 1 to 4 as the device became more widely available (9%, 39%, 68% and 88% in cycles 1-4). There was no evidence of degradation of performance of the device over repeated insertion/removal cycles. Adverse events were not otherwise reported. Irace et al. (2020) reported results of an uncontrolled study of 100 adults with type 1 diabetes at 7 centers in Italy who had the Eversense 180-day device inserted for the first time. Forty-five percent of participants were previous CGM users. Overall, HbA1c declined from a mean of 7.4% at baseline to 6.9% at 180 days ($p<.0001$). The greatest mean reduction was in the subgroup of

participants that were CGM naive. No serious device-related adverse events occurred. There were 2 device-related adverse events: A mild incision site infection in one participant and inability to remove the device on the first attempt in a second participant. (70)

Limitations of the evidence base include lack of direct comparisons to SMBG, lack of differentiation in outcomes for type 1 diabetes versus type 2 diabetes, and variability in reporting of trends in secondary glycemic measures. As a condition of approval, the Eversense sponsor is required to conduct a post-approval-study to evaluate the safety and effectiveness of the system compared to self-monitoring of blood glucose using a blood glucose meter in participants with either Type 1 or Type 2 diabetes (NCT04836546). (65) The study is expected to be completed in March 2026.

Table 29. Postmarketing Studies of the Eversense Device- Characteristics

Study	Study Type	Country	Dates	Participants	Test/ Treatment	Follow-Up
Deiss et al. (2019) (68)	Prospective Single-arm	Europe and South Africa	2016-2018	Adults (≥ 18 years) with T1D or T2D (% not reported) Consecutive patients who reached 4 sensor insertion/ removal cycles Total N=3023; 6 months of use (N=969), 1 year of use (N=173)	Implanted CGM Single sensor (90-day or 180 days)	Up to 1 year
Sanchez et al. (2019) (67)	Prospective Single-arm	United States	2018-2019	Consecutive participants who reached a 90-day wear period of the device (62.9% T1D, 8.8% T2D, 28.3% unreported) N=205)	Implanted CGM	90 days
Tweden et al. (2019) (69)	Prospective Single-arm	Europe and South Africa	2016-2019	Adult patients with T1D or T2D (% not known) for whom the Eversense CGM	Implanted CGM 90 day system or 180 day system	4 Insertion-removal Cycles

				System was prescribed and inserted by their health care provider across approximately 1000 centers in Europe and South Africa (N=945)		
Irace et al. (2020) (70) NCT04160156	Prospective Single arm	Italy	2018-2019	Adults (≥ 18 years) with T1D; 56% used insulin pumps and 44% used multiple daily injections of insulin; 45% were previous CGM users. Mean HbA1c 7.4% (SD 0.92%)	Implanted CGM 180-day system	180 days

CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; SD: standard deviation; T1D: type 1 diabetes; T2D: type 2 diabetes.

Table 30. Postmarketing Studies of the Eversense Device-Results

Study **Efficacy Outcomes**	**Efficacy Results**	**Adverse Events**
Deiss et al. (2019) (68)		**N=3023**
	NR (safety only)	133 adverse events (85 procedure-related, 22 device related, 6 drug-related, 4 device/procedure related; 16 not related) No related serious adverse events through 4 insertion/ removal cycles. infection (n=29 patients); adhesive patch irritation (n=20 patients); unsuccessful first removal attempt (n=23 patients)
Sanchez et al. (2019) (67)	**N=205**	**N=205**
MARD (glucose range 40-400 mg/dl)	11.2% (SD 11.3%, median 8.2%).	

Mean SG (mg/dL)	161.8 Median 157.2 (IQR 138.4 to 178.9)	10 (5%) transient skin irritation, redness, and/or swelling. 4 (2%) mild infection, 3 (1.5%) hypoglycemia that was self-treated, 4 (2%) failure to remove the sensor on the first attempt, and 5 (2.5%) skin irritation due to the adhesive
% SG values in hypoglycemia (<54 mg/dL), 24-hour period	1.2% (18.0 minutes)	
% SG values in hypoglycemia (<54 mg/dL), nighttime	1.7%	
TIR, 24-hour period	62.3% (~15 hours)	
TIR, nighttime	61.8%	
Time in mild hyperglycemia, 24- hour period	21.9%	
Time in mild hyperglycemia, nighttime	21.5%	
Time in significant hyperglycemia, 24-hour period	11.6%	
Time in significant hyperglycemia, nighttime	12.1%	
Tweden et al. (2019) (69)		
MARD (glucose range 40-400 mg/dl)	Mean 11.5% to 11.9% during each sensor cycle	No evidence of degradation of performance from the repeated insertion and removal procedures occurring in approximately the same subcutaneous tissue of the body. Adverse events otherwise not reported.
Mean SG (mg/dL)	156.5 to 158.2 mg/dL across 4 sensor cycles	
% SG values in significant hypoglycemia (<54 mg/dL), 24-hour period	1.1% to 1.3% (16 to 19 minutes)	
% SG values in significant hypoglycemia (<70 mg/dL), 24-hour period	4.6% to 5.0% (66 to 72 minutes)	
TIR, 24-hour period	63.2% to 64.5% (910 to 929 minutes)	
Time in hyperglycemia (>180-250 mg/dL), 24-hour period	22.8% to 23.2% (328 to 334 minutes)	
Time in significant hyperglycemia (>250 mg/dL), 24-hour period	8.1% to 8.8% (117 to 127 minutes)	
Irace et al. (2020) (70)		
HbA1c change from baseline % (SD)	7.4 % (0.92) to 6.9 (0.76)	No serious device-related adverse events occurred. There were 2 device-related adverse events: A mild incision site infection in one
Mean change from baseline to 180 days, %(SD)	0.43 (0.69); p<.001	
Time in range change from baseline	63% to 69%	

Mean change from baseline to 18 days	6%; p<.0001	participant and inability to remove the device on the first attempt in a second participant.

CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; IQR: interquartile range; MARD: mean absolute relative difference; NR: not reported; SD: standard deviation; SG: sensor glucose; TIR: time in range.

Section Summary: Continuous Glucose Monitoring Implanted Device for Long-Term Use

One RCT compared implantable CGM with control (self-monitoring of blood glucose or intermittently scanned CGM). The RCT was conducted in France and enrolled participants in 2 cohorts; cohort 1 (n=149) included participants with type 1 or type 2 diabetes with HbA1c >8.0% while cohort 2 (n=90) included participants with type 1 diabetes with time spent with glucose values below 70 mg/dL for more than 1.5 hours per day in the previous 28 days. In cohort 1, there was no difference in mean HbA1c, time in range, or patient-reported outcomes at day 180. In cohort 2, the mean difference in time spent below 54 mg/dL between days 90 and 120 was statistically significant favoring implantable CGM (difference=-1.6% [23 minutes]; 95% CI, -3.1 to -0.1; p=.04). There were no differences in patient reported outcomes.

Nonrandomized prospective studies and postmarketing registry studies assessed the accuracy and safety of an implanted glucose monitoring system that provides CGM for up to 4 insertion/removal cycles as an adjunct to home glucose monitoring devices. Accuracy measures included the mean absolute relative difference between paired samples from the implanted device and a reference standard blood glucose measurement. The accuracy tended to be lower in hypoglycemic ranges. The initial approval of the device has been expanded to allow the device to be used for glucose management decision making. The same clinical study information was used to support what the FDA considered a reasonable assurance of safety and effectiveness of the device for the replacement of fingerstick blood glucose monitoring for diabetes treatment decisions. In February 2022, the FDA expanded approval of the device for use up to 180 days. Approval was based on the PROMISE pivotal clinical trial, which assessed accuracy and safety but not glycemic outcomes. Limitations of the evidence base include lack of direct comparisons to SMBG, lack of differentiation in outcomes for type 1 diabetes versus type 2 diabetes, and variability in reporting of trends in secondary glycemic measures.

Summary of Evidence: Glucose Monitoring Devices

Type 1 Diabetes

For individuals who have Type 1 diabetes who are willing and able to use the device, and have adequate medical supervision, who receive long-term continuous glucose monitoring (CGM), the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related morbidity. RCTs have evaluated both real-time and intermittently scanned CGMs. Long-term CGM resulted in significantly improved glycemic control for adults and children with type 1 diabetes, particularly highly compliant patients. Two RCTs in patients who used multiple daily insulin injections and were highly compliant with CGM devices during run-in phases found that CGM was associated

with a larger reduction in HbA1c levels than previous studies. One of the 2 RCTs prespecified hypoglycemia-related outcomes and reported that time spent in hypoglycemia was significantly less in the CGM group. One RCT in pregnant women with Type 1 diabetes, which compares real-time CGM with self-monitoring of blood glucose (SMBG), has also reported a difference in change in HbA1c levels, an increased percentage of time in the recommended glucose control target range, a smaller proportion of infants who were large for gestational age, a smaller proportion of infants who had neonatal intensive care admissions lasting more than 24 hours, a smaller proportion of infants who had neonatal hypoglycemia requiring treatment, and reduced total length of hospital stay all favoring CGM. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with type 1 diabetes who receive short-term continuous glucose monitoring, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, morbid events, quality of life (QOL), and treatment-related morbidity as well as intermediate outcomes related to measures of glucose control such as frequency and time in hypoglycemia and hyperglycemia. The evidence for short-term monitoring of glycemic control is mixed, and there was no consistency in HbA1c levels. Some trials have reported improvements in glucose control for the short-term monitoring group but limitations in this body of evidence preclude conclusions. The definitions of control with short-term CGM use, duration of use and the specific monitoring protocols varied. In some studies, short-term monitoring was part of a larger strategy aimed at optimizing glucose control, and the impact of monitoring cannot be separated from the impact of other interventions. Studies have not shown an advantage for intermittent glucose monitoring in reducing severe hypoglycemia events, but the number of events reported is generally small and effect estimates imprecise. The limited duration of use may preclude an assessment of any therapeutic effect. Two RCTs of short-term CGM use for monitoring in pregnancy included women with both Type 1 and 2 diabetes, with most having Type 1 diabetes. One trial reported a difference in HbA1c levels at 36 weeks; the proportion of infants that were large for gestational age (>90th percentile) favored CGM while the second trial did not. The differences in the proportions of infants born via cesarean section, gestational age at delivery, and infants with severe hypoglycemia were not statistically significant in either study. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Type 2 Diabetes

For individuals with type 2 diabetes who are treated with insulin therapy who receive long-term CGM, theevidence includes RCTs. Relevant outcomes are symptoms, morbid events, QOL, and treatment-related morbidity. RCTs have included individuals on intensive insulin therapy and individuals on basal insulin. Three RCTs have evaluated CGM compared to SMBG in individuals with type 2 diabetes on intensive insulin therapy; 1 using real-time CGM and 2 using an intermittently scanned device. One RCT evaluated CGM in patients treated with basal insulin. All found either improved glycemic outcomes or no difference between groups with no increase in hypoglycemic events. In the DIAMOND trial, the adjusted difference in mean change in HbA1c level from baseline to 24 weeks was -0.3% (95% CI, -0.5% to 0.0%; p=.022) favoring CGM. The adjusted difference in the proportion of patients with a relative reduction in HbA1c

level of 10% or more was 22% (95%CI, 0% to 42%; p=.028) favoring CGM. There were no events of severe hypoglycemia or diabetic ketoacidosis in either group. Yaron et al. (2019) reported higher treatment satisfaction with CGM compared to control (the primary outcome). At 12-month follow-up in one of the trials of the Freestyle Libre device, hypoglycemic events were reduced by 40.8% to 61.7% with a greater relative reduction in the most severe thresholds of hypoglycemia. In the Martens trial of individuals treated with basal insulin without prandial insulin, there was a statistically significantly greater decrease in mean HbA1c in the CGM group (adjusted difference, -0.4%; 95%CI -0.8% to -0.1%; p=.02), with 1 hypoglycemic event in each group. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with type 2 diabetes who are not treated with insulin therapy who receive long-term CGM, the evidence includes 4 RCTs. Relevant outcomes are symptoms, morbid events, QOL, and treatment-related morbidity. Results were mixed regarding benefits of CGM with respect to glycemic control. Participant populations were heterogenous with regard to their diabetic treatment regimens, and participants might not have been receiving optimal therapy. In individuals on oral antidiabetic agents only, routine glucose monitoring may be of limited additional clinical benefit. Additional evidence would be needed to show what levels of improvement in blood glucose excursions and HbA1c levels over the short-term in this population would be linked to meaningful improvement in long-term health outcomes such as diabetes-related morbidity and complications. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with type 2 diabetes who receive short-term continuous glucose monitoring, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, morbid events, QOL, and treatment-related morbidity as well as intermediate outcomes related to measures of glucose control such as frequency and time in hypoglycemia and hyperglycemia. The evidence for short-term monitoring of glycemic control is mixed, and there was no consistency in HbA1c levels. Some trials have reported improvements in glucose control for the short-term monitoring group but limitations in this body of evidence preclude conclusions. The definitions of control with short-term CGM use, duration of use and the specific monitoring protocols varied. In some studies, short-term monitoring was part of a larger strategy aimed at optimizing glucose control, and the impact of monitoring cannot be separated from the impact of other interventions. Studies have not shown an advantage for intermittent glucose monitoring in reducing severe hypoglycemia events but the number of events reported is generally small and effect estimates are imprecise. The limited duration of use may preclude an assessment of any therapeutic effect. Three RCTs of short-term CGM use for monitoring in pregnancy included women with both type 1 and 2 diabetes, with most having type 1 diabetes. One trial reported a difference in HbA1c levels at 36 weeks; the proportion of infants that were large for gestational age (>90th percentile) favored CGM while the other trials did not. The differences in the proportions of infants born via cesarean section, gestational age at delivery, and infants with severe hypoglycemia were not statistically significant in studies in which these outcomes were reported. Limitations of the published evidence preclude determining the

effects of the technology on net health outcome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Gestational Diabetes

For individuals who are pregnant with gestational diabetes who receive long-term CGM or short-term(intermittent) glucose monitoring, the evidence includes RCTs. Relevant outcomes are symptoms, morbid events, QOL, and treatment-related morbidity. In the RCTs, trial reporting was incomplete; however, there was no difference between the groups for most reported outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Devices

Although additional software or hardware required for downloading data to a device such as personal computer, smart phone, or tablet to aid in self-management of diabetes mellitus, or to remotely monitor glucose levels may offer convenience or ease in observation in tracking glucose levels, there is insufficient evidence to indicate a benefit from these additional tools to the overall health outcomes in diabetic management.

Continuous Glucose Monitoring with an Implantable Device (Eversense)

For individuals with type 1 or type 2 diabetes who receive continuous glucose monitoring with an implantable device, the evidence includes an RCT and nonrandomized studies. The RCT compared implantable CGM with control (self-monitoring of blood glucose or intermittently scanned CGM). The RCT was conducted in France and enrolled participants in 2 cohorts; cohort 1 (n=149) included participants with type 1 or type 2 diabetes with HbA1c >8.0% while cohort 2 (n=90) included participants with type 1 diabetes with time spent with glucose values below 70 mg/dL for more than 1.5 hours per day in the previous 28 days. In cohort 1, there was no difference in mean HbA1c, time in range, or patient-reported outcomes at day 180. In cohort 2, the mean difference in time spent below 54 mg/dL between days 90 and 120 was statistically significant favoring implantable CGM (difference=-1.6% [23 minutes]; 95% CI, -3.1 to -0.1; p=.04). There were no differences inpatient reported outcomes. Nonrandomized prospective studies and post-marketing registry studies assessed the accuracy and safety of an implanted glucose monitoring system. Accuracy measures included the mean absolute relative difference between paired samples from the implanted device and a reference standard blood glucose measurement. The accuracy tended to be lower in hypoglycemic ranges. The initial approval of the device has been expanded to allow the device to be used for glucose management decision making. The same clinical study information was used to support what the FDA considered a reasonable assurance of safety and effectiveness of the device for the replacement of fingerstick blood glucose monitoring for diabetes treatment decisions. In February 2022, the FDA expanded approval of the device for use up to 180 days. Approval was based on the PROMISE pivotal clinical trial, which assessed accuracy and safety but not glycemic outcomes.

Practice Guidelines and Position Statements

American Association of Clinical Endocrinologists

In 2022, the American Association of Clinical Endocrinology (AACE) published clinical practice guideline for developing diabetes care plans and made the following recommendations (level of evidence) on CGM: (71)

- "All persons who use insulin should use continuous glucose monitoring (CGM) or perform blood glucose monitoring (BGM) a minimum of twice daily and ideally before any insulin injection." (**Grade A; Best Evidence Level 1**)
- "Real-time continuous glucose monitoring (rtCGM) or intermittently scanned continuous glucose monitoring (isCGM) is recommended for all persons with T1D, regardless of insulin delivery system, to improve A1C levels and to reduce the risk for hypoglycemia and DKA." **(Grade A; Best Evidence Level 1)**
- "rtCGM or isCGM is recommended for persons with T2D who are treated with insulin therapy, or who have high risk for hypoglycemia and/or with hypoglycemia unawareness." **(Grade A; Best Evidence Level 1)**

In 2021, the American Association of Clinical Endocrinology (AACE) published recommendations on the use of advanced technology in the management of diabetes and made the following recommendations (level of evidence) on CGM: (72)

- CGM is strongly recommended for all persons with diabetes treated with intensive insulin therapy, defined as 3 or more injections of insulin per day or the use of an insulin pump. (**Grade A; High Strength of Evidence**)
- CGM is recommended for all individuals with problematic hypoglycemia (frequent/severe hypoglycemia, nocturnal hypoglycemia, hypoglycemia unawareness). (**Grade A; Intermediate-High Strength of Evidence**)
- CGM is recommended for children/adolescents with T1D. (**Grade A; Intermediate-High Strength of Evidence**)
- CGM is recommended for pregnant women with T1D and T2D treated with intensive insulin therapy. (**Grade A; Intermediate-High Strength of Evidence**)
- CGM is recommended for women with gestational diabetes mellitus (GDM) on insulin therapy. (**Grade A; Intermediate Strength of Evidence**)
- CGM may be recommended for women with GDM who are not on insulin therapy. (**Grade B; Intermediate Strength of Evidence**)
- CGM may be recommended for individuals with T2D who are treated with less intensive insulin therapy. (**Grade B; Intermediate Strength of Evidence**)

<u>American Diabetes Association</u>

The American Diabetes Association (2023) “Standards of Medical Care in Diabetes (73)
" made the following recommendations (**level of evidence**) on CGM devices:

- "Real-time CGM (**A**) or intermittently scanned continuous glucose monitoring (**B**) should be offered for diabetes management in adults with diabetes on multiple daily injections or continuous subcutaneous insulin infusion who are capable of using devices safely (either by

themselves or with a caregiver). The choice of device should be made based on patient circumstances, desires, and needs."

- Real-time CGM (**A**) or intermittently scanned continuous glucose monitoring (**C**) should be used for diabetes management in adults with diabetes on basal insulin who are capable of using devices safely (either by themselves or with a caregiver). The choice of device should be made based on patient circumstances, desires, and needs."
- Real-time CGM (**B**) or intermittently scanned continuous glucose monitoring (**E**) should be offered for diabetes management in youth with type 1 diabetes on multiple daily injections or continuous subcutaneous insulin infusion who are capable of using the device safely (either by themselves or with a caregiver). The choice of device should be made based on patient circumstances, desires, and needs."
- "Real-time continuous glucose monitoring or intermittently scanned continuous glucose monitoring should be offered for diabetes management in youth with type 2 diabetes on multiple daily injections or continuous subcutaneous insulin infusion who are capable of using the devices safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs." **(E)**
- When used as an adjunct to pre- and postprandial blood glucose monitoring, CGM can help to achieve A1c targets in diabetes and pregnancy (**B**)
- Periodic use of real-time or intermittently scanned cCGM or use of professional CGM can be helpful for diabetes management in circumstances where continuous use of CGM is not appropriate, desired, or available (**C**).

National Institute for Health and Care Excellence

In 2022, the National Institute for Health and Care Excellence (NICE) updated its guidance on management of type 1 (74) and type 2 (75) diabetes. The guidance included the following updated recommendations on CGM (refer to source documents for complete guidance):

Type 1 Diabetes

- "Offer adults with type 1 diabetes a choice of real-time continuous glucose monitoring (rtCGM) or intermittently scanned continuous glucose monitoring (isCGM, commonly referred to as 'flash'), based on their individual preferences, needs, characteristics, and the functionality of the devices available. "

"When choosing a (CGM) device:

- use shared decision making to identify the person's needs and preferences, and offer them an appropriate device
- if multiple devices meet their needs and preferences, offer the device with the lowest cost" (74)

Type 2 Diabetes

"Offer intermittently scanned continuous glucose monitoring (isCGM, commonly referred to as 'flash') to adults with type 2 diabetes on multiple daily insulin injections if any of the following apply:

- they have recurrent hypoglycaemia or severe hypoglycaemia
- they have impaired hypoglycaemia awareness
- they have a condition or disability (including a learning disability or cognitive impairment) that means they cannot self-monitor their blood glucose by capillary blood glucose monitoring but could use an isCGM device (or have it scanned for them)
- they would otherwise be advised to self-measure at least 8 times a day."

"Offer isCGM to adults with insulin-treated type 2 diabetes who would otherwise need help from a care worker or healthcare professional to monitor their blood glucose."

"Consider real-time continuous glucose monitoring (rtCGM) as an alternative to isCGM for adults with insulin-treated type 2 diabetes if it is available for the same or lower cost." (75)

The guidance and accompanying evidence review do not specifically mention implantable CGM devices.

Endocrine Society

The Endocrine Society (2022) published clinical practice guidelines of management of individuals at high risk of hypoglycemia and included the following recommendations on CGM: (76)

- We recommend CGM rather than self-monitoring of blood glucose (SMBG) by fingerstick for patients with type 1 diabetes (T1D) receiving multiple daily injections (MDIs).
- We suggest real-time continuous glucose monitoring CGM be used rather than no CGM for outpatients with type 2 diabetes (T2D) who take insulin and/or sulfonylureas (SUs) and are at risk for hypoglycemia.

In 2016, the Endocrine Society published clinical practice guidelines that included the following recommendations on CGM (77):

“6. Real-time continuous glucose monitors in adult outpatients:

6.1 We recommend real-time continuous glucose monitoring (RT-CGM) devices for adult patients with T1DM [type 1 diabetes mellitus] who have A1C levels above target and who are willing and able to use these devices on a nearly daily basis.

6.2 We recommend RT-CGM devices for adult patients with well-controlled T1DM who are willing and able to use these devices on a nearly daily basis.

Use of continuous glucose monitoring in adults with type 2 diabetes mellitus [T2DM]

6.3 We suggest short-term, intermittent RT-CGM use in adult patients with T2DM (not on prandial insulin) who have A1C levels ≥7% and are willing and able to use the device.”

Ongoing and Unpublished Clinical Trials: CGM

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 31.

Table 31. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03981328	The Effectiveness of Real Time Continuous Glucose Monitoring to Improve Glycemic Control and Pregnancy Outcome in Patients With Gestational Diabetes Mellitus	372	Dec 2023
NCT03908125[a]	A Post- Approval Study to Evaluate the Long-term Safety and Effectiveness of the Eversense® Continuous Glucose Monitoring (CGM) System.	273 (actual enrollment)	Mar 2023
NCT04836546	A Post Approval Study to Evaluate the Safety and Effectiveness of the Eversense® Continuous Glucose Monitoring (CGM) System Used Non-adjunctively	925	Mar 2026
NCT05131139	Enhance Study: A Prospective, Multicenter Evaluation of Accuracy and Safety of the Eversense CGM System With Enhanced Features	350	Sep 2025
Unpublished			
NCT04535830	The Effectiveness of Flash Glucose Monitoring System on Glycemic Control in Patients With New-onset Type 2 Diabetes A Randomized Controlled Trial	200	Sep 2021 (unknown status)
NCT03445065[a]	Benefits of a Long Term Implantable Continuous Glucose Monitoring System for Adults With Diabetes - France Randomized Clinical Trial	239	Aug 2020

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

EXTERNAL INSULIN INFUSION PUMPS

This section of the policy on external insulin infusion pumps was originally based on Centers for Medicare and Medicaid Services (CMS) policy.

Centers for Medicare and Medicaid Services (CMS) (6)

The CMS "Decision Memo for Insulin Infusion Pump" (CAG-00041N) provided an analysis of scientific data on continuous subcutaneous insulin infusion (CSII). The CMS analysis included the following information.

Within the past few years, "intensive therapy" for diabetes management has gained favor as it seems to offer the greatest hope of preventing diabetic complications. Intensive therapy refers to frequent delivery of exogenous insulin (usually by injection four times a day or alternatively by continuous infusion) to obtain tight control in the normal blood glucose range. The Diabetes

Control and Complications Trial (DCCT) offered compelling evidence that intensive treatment achieving tight glycemic control reduces the occurrence of microvascular and neuropathic complications in patients treated before the development of advanced disease. This trial involved 1,441 Type 1 diabetics at 29 medical centers. On average, patients were followed for an average of 6.5 years (range 3-9 years) before the study was terminated. The study's principal outcome measure was retinopathy, but it also included data regarding renal, neurologic, cardiovascular, and neuropsychological complications as well as adverse effects from treatment.

The DCCT examined two cohorts, a primary prevention cohort with complication-free disease duration of one to five years, and a secondary intervention cohort with a disease course of one to fifteen years, and the initial signs of diabetic complications. Subjects were randomly assigned to the experimental group receiving intensive therapy or the control group receiving conventional therapy. Subjects in the experimental groups followed an intensive therapy regimen aimed at achieving as close to normal blood glucose levels as possible. Intensive therapy subjects had a choice of two methods of delivery of exogenous insulin; either via three or more daily insulin injections or external pump. [By the end of the study, 42% of the experimental subjects were using insulin pumps]. Subjects assigned to conventional therapy took one or two subcutaneous insulin injections per day. The study's results showed members of the intensive therapy group to have statistically significantly less progression of diabetic complications than the conventional therapy group: reduction in nephropathy of 34% and 43% for the primary prevention and secondary intervention cohorts respectively; 76% and 54% reduction in retinopathy, 69% and 57% reduction in neuropathy. The study found no statistically significant differences in quality of life between members of the conventional and intensive therapy groups (based on a questionnaire). The study's results were so convincing of the benefits of intensive therapy that the independent data monitoring committee recommended early termination of the trial. As the evidence favoring intensive therapy accumulated, investigators could no longer legitimately encourage subjects to remain in the less effective conventional therapy group.

The DCCT demonstrated that intensive therapy offers numerous advantages over conventional therapy by decreasing the development of many long-term diabetic complications. However, in the short-term, the DCCT suggests that intensive therapy may pose some increased risks over conventional therapy. Subjects in the intensive therapy group experienced approximately triple the incidence of severe hypoglycemia (defined as hypoglycemia requiring assistance from another person) compared to the control group ($p<0.001$). There was, however, no statistically significant difference between intensive and conventional therapy groups for occurrence of diabetic ketoacidosis (DKA) or changes in neuropsychological functioning. The increased risk of hypoglycemia prompted the DCCT authors to recommend caution in starting intensive therapy for patients with a history of severe hypoglycemia or hypoglycemia unawareness. Additionally, the DCCT study population excluded prospective subjects who already had advanced diabetic complications. Given that implementing intensive therapy is not risk-free, the authors caution; "The risk-benefit ratio with intensive therapy may be less favorable...in patients with advanced complications."

Another area where CSII may offer additional benefit over multiple daily injections (MDI) is for those diabetics exhibiting "dawn phenomenon." Dawn phenomenon represents early morning hyperglycemia thought to result from insufficient nocturnal insulin. A study by Koivisto suggests that for diabetics using CSII, the dawn phenomenon may be prevented by programming the pump to increase the nocturnal rate of insulin infusion. Although little scientific data currently exists to prove the benefit of decreased early morning hyperglycemia, current beliefs regarding tight glycemic control suggest benefit of avoidance of hyperglycemia at any time.

In a study conducted by Bode et al. on patients who had been on MDI and experienced poor glycemic control including severe hypoglycemia, the authors found that when patients switched to CSII, there were statistically significantly fewer episodes of severe hypoglycemia, and no difference in events of DKA. Of note, HbA1c was not different between the groups, in contrast to other studies which have documented decreased HbA1c for patients on CSII.

In 1991, the Agency for Health Care Policy and Research (AHCPR) issued an assessment of insulin pump therapy. The AHCPR assessment stated that "the overall clinical evidence indicates that CSII is as effective as MDI in attaining normoglycemia in patients with insulin dependent diabetes mellitus who require intensive insulin therapy." In addition, the report noted: "Results from a number of controlled clinical trials have shown that CSII devices are effective in providing near-normo-glycemia and in improving metabolic control in patients with IDDM -- there is as yet no evidence to show that CSII is superior in clinical efficacy to MDI." AHCPR cautioned that "any form of intensive insulin therapy is also contraindicated for individuals with hypoglycemia unawareness and those with untreated preproliferative or proliferative retinopathy." Although the report noted that CSII poses risks of DKA, hypoglycemia, and skin infections, AHCPR suggested that these risks might be ameliorated as the technology improves.

In October 1994, ECRI Institute, a technology assessment firm based in Plymouth Meeting, Pennsylvania, completed an assessment of CSII pumps. ECRI concluded that:

- Insulin pump therapy produces greater metabolic control than conventional therapy; AND
- Insulin pump therapy may produce greater metabolic control than intensive injection therapy; AND
- The success of insulin pump therapy depends heavily upon proper patient selection, which in turn, depends heavily upon patient motivation.

Regarding risks of severe hypoglycemic events, ECRI suggested that CSII might offer a decreased risk compared to MDI but that this is unproven "even though it seems that fewer severe hypoglycemic episodes are observed during insulin pump therapy than during intensive injection therapy, it would seem clinically prudent to assume that the number of these episodes in these two treatment types is equal." Of note, ECRI recommended caution in starting pump therapy on elderly patients because they may have difficulty responding to the warning symptoms of hypoglycemia.

In a study conducted in Japan by Ohkubo et al. on insulin-requiring Type II diabetics, the authors found a difference in the incidence and progression of diabetic complications for those patients on intensive insulin treatment. However, the number of patients studied was small and no patients with advanced complications were included. In addition, no patients were on CSII. Of note, the authors state that "the benefit of intensive insulin therapy for Type II diabetics with advanced microvascular complications is not yet established."

Practice Guidelines and Position Statements: External Insulin Pumps

The 2021 Association of Diabetes Care and Education Specialists notes in their Practice Paper on “Continuous Subcutaneous Insulin Infusion (CSII) without and with Sensor Integration” that the assessment of people with diabetes (PWD) is important in ensuring success with pump therapy. Assessment includes:

- Clinical Indications for Insulin Pump use,
- Lifestyle indications, and
- Desired attributes of a pump Candidate (and/or parent(s) of pump candidate).

Also noted is that “Regular assessments should be done to evaluate changes in a PWD’s clinical condition, motivation, abilities, and life circumstances that may necessitate the need to reconsider appropriateness of pump therapy”. (78)

Both the 2021 American Diabetes Association (ADA) Standards of Medical Care in Diabetes (79) and the 2021 American Association of Clinical Endocrinologists Clinical Practice Guideline: The Use of Advanced Technology in the Management of Persons with Diabetes Mellitus (72) provide information and evidenced based guideline recommendations for professionals and other stakeholders for the use of advanced technologies for the management of people with diabetes mellitus. Several different topics are addressed regarding insulin delivery devices (e.g., smart pens, insulin pumps, conventional pumps, smartphone applications, and sensor-augmented pump therapy). While it continues to be true that patient selection is the key to appropriate utilization of any treatment, both documents address individuals/patient populations who may benefit from specific devices.

Disposable Insulin Delivery Device

Rosenfeld et al. reported on patient perceptions in a retrospective analysis of glycemic control in 23 patients. Following use of the V-Go, patients answered telephonic surveys about their perception of the device. Clinical data was retrospectively collected prior to V-Go initiation and following 12 weeks of use, at the completion of treatment and 12 weeks following discontinuation. The authors concluded glycemic control improved when patients were switched to the V-Go for insulin delivery and it deteriorated when the V-Go was discontinued. (80)

Kapitza et al. in a proof-of-concept study evaluated the clinical functionality, safety and pharmacodynamics of the V-Go. Six patients with Type 2 DM had the V-Go applied to the lower abdomen once daily for 7 days. (days 1-3 inpatient, days 4-7 outpatient). Capillary blood glucose concentrations were measured during inpatient as well as outpatient phases of the study. Overall glycemic control tended to improve. The authors concluded the V-Go is an

attractive alternative to subcutaneous insulin injection therapy because metabolic control appears to be maintained or even improved without increasing daily insulin doses. (81)

Lajara et al. (2015) conducted a retrospective analysis of electronic medical records to assess the outcomes of switching patients with sub-optimally controlled diabetes (defined as a glycated hemoglobin [HbA1c] greater than 7%), to the V-Go® disposable insulin delivery device. The analysis included 204 patients. Results reported by the authors included "Overall, there was a significant decrease in HbA1c after switching to V-Go at the 14- and 27-week follow-up visits. The least-squares mean (LSM) change in HbA1c (95% confidence interval) from baseline to 14 weeks was -1.53% (-1.69% to -1.37%; P<0.001), and from baseline to 27 weeks was -1.79% (-1.97% to -1.61%; P<0.001). Significant reductions in mean HbA1c were achieved at both visits in all patient subsets…" Hypoglycemic events were no more frequent on V-Go than on previous therapy. The conclusions reached by the authors included "V-Go is safe and effective in patients with sub-optimally controlled diabetes requiring insulin therapy. Glycemic control improved significantly, less insulin was required, and hypoglycemic events were similar after patients switched to insulin delivery by V-Go." (82)

Bergenstal et al. (2019) in a RCT compared bolus insulin delivery using an insulin patch versus an insulin pen. The multicenter RCT evaluated efficacy, safety and self-reported outcomes in adults with Type 2 diabetes who were inadequately controlled on basal insulin. Adults with type 2 diabetes (n = 278, age: 59.2 – 8.9 years), were randomized to patch (n = 139) versus pen (n = 139) for 48 weeks, with crossover at week 44. Baseline insulin was divided 1:1 basal: bolus. Using a pattern-control logbook, subjects adjusted basal and bolus insulin weekly using fasting and premeal glucose targets. The authors reported the following results: Glycated hemoglobin (HbA1c) change (least squares mean – standard error) from baseline to week 24 (primary endpoint) improved (P < 0.0001) in both arms, -1.7% – 0.1% and -1.6% – 0.1% for patch and pen (-18.6 – 1.1 and -17.5 – 1.1 mmol/mol), and was maintained at 44 weeks. The coefficient of variation of 7-point self-monitoring blood glucose decreased more (P = 0.02) from baseline to week 44 for patch versus pen. There were no differences in adverse events, including hypoglycemia (three severe episodes per arm), and changes in weight and insulin doses. Subject-reported treatment satisfaction, quality of life, experience ratings at week 24, and device preferences at week 48 significantly favored the patch. Most health care providers preferred patch for mealtime insulin. The authors noted Bolus insulin delivered by patch and pen using an algorithm-based weekly insulin dose titration significantly improved HbA1c in adults with type 2 diabetes, with improved subject and health care provider experience and preference for the patch. (83)

Summary of Evidence for Disposable Insulin Delivery Devices

One multicenter RCT evaluated efficacy, safety and self-reported outcomes in adults with Type 2 diabetes who were inadequately controlled on basal insulin. Both insulin delivery patch and pen improved HbA1c. Due to the limited study results available (retrospective studies, small studies and short-term studies), disposable insulin delivery devices are considered experimental, investigational and/or unproven.

Supplemental Devices
Although additional software or hardware required for downloading data to a device such as personal computer, smart phone, or tablet to aid in self-management of diabetes mellitus, or to remotely monitor glucose levels may offer convenience or ease in observation in tracking glucose levels there is insufficient evidence to indicate a benefit from these additional tools to the overall health outcomes in diabetic management.

ARTIFICIAL PANCREAS DEVICE SYSTEMS (APDS)
This section of the policy addresses artificial pancreas devices that have been approved by the U.S. FDA.

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

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

The following PICO was used to select literature to inform this policy.

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

Interventions
The therapy being considered is an APDS that integrates a continuous glucose monitor and insulin pump and includes an LGS feature that can automatically and temporarily suspend insulin delivery when glucose levels fall below a prespecified level. The device alarms and the user must take an action to assess glycemic level and resume insulin infusion.

APDS are used by persons with type 1 diabetes when they have experienced hyperglycemic and/or hypoglycemic episodes that cannot be managed with intermittent self-monitoring of glucose and self-administration of insulin.

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

Outcomes
The general outcomes of interest are glycated hemoglobin A1c (HbA1c) levels, time in range or target of glucose levels, and rates of hypoglycemia and hyperglycemia. Other outcomes of interest include quality of life and changes in health care utilization (e.g., hospitalizations). The duration of follow-up is life-long.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials
The in-home arm of the Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial, published by Bergenstal et al. in 2013. (84) This industry-sponsored trial used the Paradigm Veo insulin pump. A total of 247 patients were randomized to an experimental group, in which a continuous glucose monitor with the LGS feature was used (n=121), or a control group, which used the continuous glucose monitor but not the LGS feature (n=126). Key eligibility criteria were 16-to-70 years old, Type 1 diabetes, and HbA1c levels between 5.8% and 10.0%. In addition, patients had to have more than 6 months of experience with insulin pump therapy and at least 2 nocturnal hypoglycemic events (≤65 mg/dL) lasting more than 20 minutes during a 2-week run-in phase. The randomized intervention phase lasted 3 months. Patients in the LGS group were required to use the feature at least between 10 PM and 8 AM. The threshold value was initially set at 70 mg/dL and could be adjusted to between 70 mg/dL and 90 mg/dL. Seven patients withdrew early from the study; all 247 were included in the intention-to-treat analysis. The primary efficacy outcome was the area under the curve (AUC) for nocturnal hypoglycemia events. This was calculated by multiplying the magnitude (in milligrams per deciliter) and duration (in minutes) of each qualified hypoglycemic event. The primary safety outcome was change in HbA1c levels.

The primary endpoint, mean (standard deviation [SD]) AUC for nocturnal hypoglycemic events, was 980 (1200) mg/dL/min in the LGS group and 1568 (1995) mg/dL/min in the control group. The difference between groups was statistically significant ($p<0.001$), favoring the intervention group. Similarly, the mean AUC for combined daytime and nighttime hypoglycemic events (a

secondary outcome) significantly favored the intervention group (p<0.001). Mean (SD) AUC values were 798 (965) mg/dL/min in the intervention group and 1164 (1590) mg/dL/min in the control group. Moreover, the intervention group experienced fewer hypoglycemic episodes (mean, 3.3 per patient-week; SD=2.0) than the control group (mean, 4.7 per patient-week; SD=2.7; p<0.001). For patients in the LGS group, the mean number of times the feature was triggered per patient was 2.08 per 24-hour period and 0.77 each night (10 PM-8 AM). The median duration of nighttime threshold suspend events was 11.9 minutes; 43% of events lasted for less than 5 minutes, and 19.6% lasted more than 2 hours. In both groups, the mean sensor glucose value at the beginning of nocturnal events was 62.6 mg/dL. After 4 hours, the mean value was 162.3 mg/dL in the LGS group and 140.0 mg/dL in the control group.

Regarding safety outcomes and adverse events, change in HbA1c level was minimal, and there was no statistically significant difference between groups. Mean HbA1c levels decreased from 7.26 to 7.24 mg/dL in the LGS group and from 7.21 to 7.14 mg/dL in the control group. During the study period, there were no severe hypoglycemic events in the LGS group and 4 events in the control group (range of nadir glucose sensor values in these events, 40-76 mg/dL). There were no deaths or serious device-related adverse events.

A second RCT evaluated the in-home use of the Paradigm Veo System. (85) The trial included 95 patients with type 1diabetes between 4 and 50 years of age (mean age, 18.6 years; >30% of sample <18 years old) who had used an insulin pump for at least 6 months. In addition, participants had to have an HbA1c level of 8.5% or less and have impaired awareness of hypoglycemia (defined as a score of at least 4 on the modified Clarke questionnaire). Patients were randomized to 6 months of in-home use of the Paradigm Veo System with automated insulin suspension when the glucose sensor reached a preset threshold of 60 mg/dL or to continued use of an insulin pump without the low glucose suspend feature. The primary study outcome was the combined incidence of severe hypoglycemic events (defined as hypoglycemic seizure or coma) and moderate hypoglycemic events (defined as an event requiring assistance from another person). As noted, findings were not reported separately for children and adults.

The baseline rate of severe and moderate hypoglycemia was significantly higher in the LGS group (129.6 events per 100 patient-months) than in the pump-only group (20.7 events per 100 patient-months). After 6 months of treatment, and controlling for the baseline hypoglycemia rate, the incidence rate per 100 patient-months was 34.2 (95% confidence interval [CI], 22.0 to 53.3) in the pump-only group and 9.6 (95% CI, 5.2 to 17.4) in the LGS group. The incidence rate ratio was 3.6 (95% CI, 1.7 to 7.5), which was statistically significant favoring the LGS group. Although results were not reported separately for children and adults, the trialists conducted a sensitivity analysis in patients younger than 12 years (15 patients in each treatment group). The high baseline hypoglycemia rates could be explained in part by two outliers (children ages 9 and 10 years). When both children were excluded from the analysis, the primary outcome was no longer statistically significant. The incidence rate ratio for moderate and severe events excluding the 2 children was 1.7 (95% CI, 0.7 to 4.3). Mean HbA1c level (a secondary outcome) did not differ between groups at baseline or at 6 months. Change in HbA1c levels during the treatment period was - 0.06% (95% CI, -0.2% to 0.09%) in the pump-only group and -0.1% (95%

CI, -0.3% to 0.03%) in the LGS group; the difference between groups was not statistically significant.

The Predictive Low-Glucose Suspend for Reduction Of LOw Glucose (PROLOG) Trial was a 6-week crossover RCT of the t:slim X2 pump with Basal-IQ integrated with a Dexcom G5 sensor and a predictive low glucose suspend algorithm compared to sensor-augmented pump therapy. (86) Participants (N=103) were ages 6-72 years; 58% were less than 18 years old, 16% were 6 to 11 years old, 43% were 12 to 17 years old, and 42% were 18 years or older. The primary outcome was CGM measured percentage of time <70 mg/dL in each 3-week period. Median time <70 mg/dL was reduced from 3.6% at baseline to 2.6% during the 3-week period in the predictive low glucose suspend system arm compared with 3.2% in the sensor augmented pump arm (difference [predictive low glucose suspend − sensor augmented pump] = −0.8%, 95% CI −1.1 to −0.5, p<0.001). There was 1 severe hypoglycemic event in the sensor augmented pump arm and none in the predictive low glucose suspend arm.

Nonrandomized Studies

In 2015, Agrawal et al. retrospectively analyzed use of the threshold suspend feature associated with the Paradigm Veo System in 20,973 patients, most of whom were treated outside of the United States. (87) This noncontrolled descriptive analysis provides information on the safety of the device when used in a practice setting. The threshold suspend feature was enabled for 100% of the time by 14,673 (70%) patients, 0% of the time by 2249 (11%) patients, and the remainder used it intermittently. The mean (SD) setting used to trigger suspension of insulin was a sensor glucose level of 62.8 (5.8) mg/dL. On days when the threshold suspend feature was enabled, there was a mean of 0.82 suspend events per patient-day. Of these, 56% lasted for 0 to 5 minutes, and 10% lasted the full 2 hours. (Data on the length of the other 34% of events were not reported.) On days when the threshold suspend feature was on, sensor glucose values were 50 mg/dL or less 0.64% of the time compared with 2.1% of sensor glucose values 50 mg/dL or less on days when the feature was off. Reduction in hypoglycemia was greatest at night. Sensor glucose percentages equivalent to 17 minutes per night occurred when the threshold suspend feature was off vs glucose percentages equivalent to 5 minutes per night when the threshold suspend feature was on. Data on the use of the device has suggested fewer and shorter hypoglycemic episodes. The length and severity of hypoglycemic episodes were not fully discussed in this article.

Gómez et al. (2017) published the results of a cohort of 111 individuals with Type 1 diabetes documented hypoglycemia and hypoglycemia unawareness who received a sensor-augmented insulin pump with LGS therapy. (88) Participants used a combination system with the Medtronic Paradigm 722 or Paradigm Veo pump connected to the MiniMed CGM device. At a mean follow-up of 47 months (SD=22.7), total daily insulin dose was reduced (mean difference, -0.22 U/kg; 95% CI, -0.18 to -0.26 U/kg; p<0.001). HbA1c levels were reduced from a baseline value of 8.8% (SD=1.9%) to 7.5% (SD=1.0%) at 5 months (mean difference, -1.3%; 95% CI, -1.09% to -1.50%; p<0.001) and 7.1% (SD=0.8%; mean difference, -1.7%; 95% CI, -1.59% to -1.90%; p<0.001). At baseline, 80% of subjects had had at least 1 episode of hypoglycemic

awareness compared with 10.8% at last follow-up (p<0.001). Episodes of severe hypoglycemia decreased from 66.6% to 2.7% (p<0.001).

Section Summary: LGS Devices

For individuals who have type 1 diabetes who receive an artificial pancreas device system with a low-glucose suspend feature, the evidence includes three randomized controlled trials (RCTs) conducted in home settings. Relevant outcomes are symptoms, change in disease status, morbid events, resource utilization, and treatment-related morbidity. Primary eligibility criteria of the key RCT, the Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial, were ages 16-to-70 years old, Type 1 diabetes, glycated hemoglobin levels between 5.8% and 10.0%, and at least 2 nocturnal hypoglycemic events (≤65 mg/dL) lasting more than 20 minutes during a 2-week run-in phase. Both trials required at least six months of insulin pump use. Both RCTs reported significantly less hypoglycemia in the treatment group than in the control group. In both trials, primary outcomes were favorable for the group using an artificial pancreas system; however, findings from one trial were limited by nonstandard reporting of hypoglycemic episodes, and findings from the other trial were no longer statistically significant when two outliers (children) were excluded from analysis. The RCT limited to adults showed an improvement in the primary outcome (area under the curve for nocturnal hypoglycemic events). The area under the curve is not used for assessment in clinical practice but the current technology does allow user and provider review of similar trend data with CGM.

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

Both retrospective and prospective observational studies have reported reductions in rates and severity of hypoglycemic episodes in automated insulin delivery system users. The evidence is sufficient that the magnitude of reduction for hypoglycemic events in the type 1 diabetic population is likely to be clinically significant.

Hybrid Closed-Loop Insulin Delivery Systems

Clinical Context and Therapy Purpose

The purpose of a hybrid closed-loop insulin delivery system in individuals who have type 1 diabetes is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with type 1 diabetes. Persons with type 1 diabetes are especially prone to develop hypoglycemia. Alterations in the counterregulatory hormonal responses inherent in the disease, variable patient adherence and iatrogenic hypoglycemia caused by aggressive prevention of hyperglycemia are responsible for this

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

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

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

Outcomes
The general outcomes of interest are HbA1c levels, time in range or target of glucose levels, and rates of hypoglycemia and hyperglycemia. Other outcomes of interest include quality of life and changes in health care utilization (e.g., hospitalizations). The duration of follow-up is life-long.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Prospective Studies
In 2016, Bergenstal et al. published a prospective single-arm study on the safety of the hybrid closed-loop system in patients with type 1 diabetes. (89) It included 124 patients ages 14-to-75 years old who had type 1 diabetes for at least 2 years, had HbA1c levels less than 10.0%, and who had used an insulin pump for at least 6 months. There was an initial run-in period at baseline for patients to learn how to use the device followed by a 3-month period of device use. The study period included a 6-day hotel stay with a 1-day period of frequent sampling of venous blood glucose levels to verify device accuracy. The primary safety end points were the incidence of severe hypoglycemia and diabetic ketoacidosis and the incidence of device-related and serious adverse events.

There were no episodes of severe hypoglycemia or ketoacidosis during the study. A total of 28 device-related adverse events occurred, all of which could be resolved at home. There were 4 serious adverse events, 1 case each of appendicitis, bacterial arthritis, worsening rheumatoid arthritis, and *Clostridium difficile* diarrhea. There were also a number of predefined descriptive end points (but no statistically powered efficacy end points). The device was in closed-loop mode for a median of 97% of the study period. Mean (SD) HbA1c levels were 7.4% (0.9%) at baseline and 6.9% (0.6%) at the end of the study, and the percentage of sensor glucose values within the target range was 66.7% at baseline and 72.2% at the end of the study. A related study in children has been completed (NCT02660827).

A 2017 multicenter pivotal trial published by Garg et al. evaluated the safety of Medtronic's hybrid closed-loop system, using methods similar to those of Bergenstal et al. (2016), (NCT02463097) and employing the same device (MiniMed 670G). (90) Of 129 subjects, 124 completed the trial; 30 were adolescents (age range, 14-21 years) and 94 were adults (age range, 22-75 years), all of whom had Type 1 diabetes for at least 2 years before the study and used insulin pump therapy for 6 months or more. As with Bergenstal et al. (2016), a 3-month study period was preceded by a run-in period for subjects to be more familiar with the equipment, and the sensor glucose values were confirmed by an extended hotel stay (6-day/5-night with daily exercise). In both the adolescent and adult cohorts, the trial found improvements during the study phase over the run-in phase, with an increased percentage of glucose values in the favorable range (for adults, a mean improvement of 68.8% to 73.8%; for adolescents, a mean improvement of 60.4% to 67.2%; $p<0.001$ for both cohorts). Similarly, the authors reported a decrease in percentage of values outside of the target range (<70 mg/dL or >180 mg/dL): for adults, time spent below the target range decreased from 6.4% to 3.4% ($p<0.001$); time above the range decreased from 24.9% to 22.8% ($p=0.01$). For both cohorts, HbA1c levels showed a significant reduction between baseline and the end of study: for adults, the mean decreased from 7.3% to 6.8% ($p<0.001$), while for adolescents, the mean decreased from 7.7% to 7.1% ($p<0.001$). Secondary outcomes, which included a reduction of nocturnal hyperglycemia and hypoglycemia, increase in mean overall body weight, and a reduction of basal insulin, were favorable for the study phase, compared with the run-in phase; measurements from the hotel stay verified the in-home glucose values. However, there were several limitations in the trial, including its nonrandomized design, the exclusion of individuals who had recently experienced diabetic ketoacidosis or severe hypoglycemia, and the interaction between subjects and site personnel. Additionally, most of the adult cohort were already using CGM, and baseline HbA1c levels were lower than average for both cohorts; both baseline characteristics potentially limit the generalizability of the results.

One type of hybrid insulin delivery system employs a predictive algorithm to keep the patient's glucose levels within a specific range or zone, only increasing or decreasing insulin levels if the device detects that glucose levels are going to fall outside the defined zone. In 2017, Forlenza et al. published a randomized controlled crossover trial comparing the efficacy of a zone model predictive control algorithm with that of sensor-augmented pump therapy. (91) The trial included 20 subjects (19 completed), all with Type 1 diabetes and having at least 3 months

treatment with a subcutaneous insulin infusion pump. The 6-week, in-home study was divided into 2-week blocks, with 2 randomized groups alternating treatment between an artificial pancreas system (DiAs web monitoring) or sensor-augmented pump therapy (Dexcom Share); subjects in both arms reported glucose values and, if applicable, sensor failure. For several primary end points, which included percentage of time in the target glucose range (70-180 mg/dL) and reduction in hypoglycemia (<70 mg/dL), the algorithm-controlled artificial pancreas system was found to be superior to the sensor-augmented pump therapy (71.6 vs 65.2%, p=0.008; 1.3 vs 2%, p= 0.001, respectively); however, while the mean glucose value was lower in the artificial pancreas system than in the control group, the difference between them was not significant (p=0.059). Measurements of nocturnal hypoglycemia were consistent with day-to-day findings. For the secondary end point (safety of both systems after extended wear), the study found that the mean glucose did not change between the first and seventh day of wear. A limitation of the trial was its use of remote monitoring of subjects; also, the trialists noted that, given the marked difference in outcomes between responders and nonresponders, an error might have occurred in setting basal rates. A randomized crossover trial reported by Pinsker et al. (2022) evaluated sensor-augmented pump therapy compared to an adaptive zone model predictive control device. In 35 adults with type 1 diabetes. (92) The adaptive device ran on a Google Pixel 3 smartphone and wirelessly paired with a Dexcom G6 sensor and a Tandem t:AP insulin pump. The primary outcome was sensor glucose time-in-range 70 to 180 mg/dL at 13 weeks. The automated adaptation settings did not significantly improve time-in-range (66% with sensor augmented pump vs 69% with automated insulin delivery; mean adjusted difference 2%; 95% CI -1% to +6%], p =.22). The investigators concluded that additional study and further refinement of the adaptation system are needed.

The remainder of the review is focused on additional studies that recently evaluated hybrid closed-loop (HCL) systems in children and adolescents with T1D. These studies are summarized in Tables 32 and 33.

The RCT by Tauschmann, et al. (2018) evaluated individuals with uncontrolled T1D as reflected in mean Hb1c >8 %. (93) Approximately, 50% of the subjects were between 6-21 years of age and 25% are 6-12 years old. Both groups achieved a reduction in HbA1c but the reduction was statistically greater in the HCL group compared to the control group. The investigators reported that the HbA1c improvements were not different among children, adolescents, and adults (data not shown in tables). No severe hypoglycemic events were reported consistent with a decrease in time spent with glucose <70mg/dL.

Abraham et al. (2018) reported the results of a 6-month, multicenter, RCT in children and adolescents with T1D comparing use of an insulin pump with suspend before low or predictive low-glucose management (PLGM) with sensor-augmented insulin pump therapy (SAPT) alone. (94) At 6 months, significant reductions were seen in day and night hypoglycemia and number of hypoglycemic events <63mg/dL lasting longer than 20 minutes. There were no differences in HbA1c at 6 months in either group.

Forlenza et al. (2019) reported the data and analysis of the supplemental information filed with the FDA to support the expanded indication for the MiniMed 670G system to children 7-13 years of age. (95) The nonrandomized, single-arm multicenter study reported the day and night use of the automated insulin delivery and PLGM for 3 months in the home setting. There were no serious adverse events and use of the system was associated with reduction in HbA1c and increased time in target glucose range.

Wood et al. (2018) reported an in-clinic evaluation of a 7-13-year-old cohort of the 670G pivotal trial that was designed to evaluate the performance characteristics of the device when activity induced hypoglycemic patterns were used to set individual device parameters for ongoing use by the study participant. (96) The suspend before low prevention capability was confirmed in 97.5% of patients experiencing a sensor glucose of ≤ 55mg/dL.

Messer et al. (2018) reported on a sub analysis of the adolescent and young adult participants in the 670G pivotal trial to better characterize the carbohydrate input and insulin bolus determination features of the device over a 3-month period. (97) Participants successfully utilized the device without significant changes in total daily dose of insulin but improved percentage time in range (70-180 mg/dL).

Breton et al. (2020) reported results of a 16-week, open-label RCT comparing the t:slim X2 insulin pump with Control-IQ Technology to sensor-augmented pump therapy in 101 children with Type 1 diabetes ages 6 to 13 years. (98) The glucose level was in the target range for a greater percentage of time with the use of the hybrid closed loop system than with the use of a sensor-augmented insulin pump. Improvements were sustained through 28 weeks in an uncontrolled extension study of 100 children who were enrolled in the RCT. (99) Health-related quality of life and patient satisfaction measures from the RCT and the extension phase were reported by Cobry et al. (2021). (100) Neither children nor their parents in the hybrid closed loop group reported statistically significant changes in these outcomes compared with the sensor-augmented pump therapy group. The authors concluded that children receiving the hybrid closed loop system did not experience increased burden compared with those using sensor-augmented pump therapy.

No studies of a hybrid closed loop system in children under age 6 years have been published, but clinical study results for children ages 2-6 years are available in the FDA Summary of Safety and Effectiveness for the MiniMed 670G System (Tables 32 and 33). (14) This was a descriptive study to evaluate the safe use of the device's auto mode and was not designed to determine the effectiveness of the device compared to alternative treatments. Based on the pivotal study and an additional performance study submitted for the evaluation, FDA concluded with a reasonable assurance of effectiveness that the MiniMed 770G System can automatically adjust basal insulin rates based on CGM values.

Table 32. Summary of Key Study Characteristics: Hybrid Closed-Loop in Children and Adolescents with Type 1 Diabetes

Study; Trial	Countries	Sites	Dates	Participants	Intervention Study Type

				N **Age** **Mean (SD)**		
Tauschmann et al. (2018) (93) NCT02523131	UK, US	6	05/12/2016 - 11/17/2017	• 86 • >6 years • [6-12 years; n=23] • [13-21 years; n=19]	• Mini Med 640G[2] • HCL	RCT Intervention: • SAPT with PLGM (n=46) • Screening HbA1c %(SD) • 8.3 (0.6) Control: • SAPT alone (n=40) • Screening HbA1c % (SD) • 8.5 (0.5)
Abraham et al. (2018) (94)	Australia	5	8/2014-NR	• 154 • 8-20 years • 13.2(2.8)	• Mini Med 640G[2] • HCL	RCT Intervention: • SAPT with PLGM (n=80) Control: • SAPT alone (n=74)
Forlenza et al. (2019)	US, Israel	9	4/18/2016-10/09/2017	• 105 • 7-13 years	• Mini Med 670G[3]	Non-comparative pivotal trial

NCT02660827 (95)				• 10.8 (1.8)	• HCL	
Wood et al. (2018) **NCT02660827 (96)**	US, Israel	9	4/18/2016-10/09/2017	• 105 • 7-13 years • 10.8 (1.8)	• Mini Med 670G[3] • HCL	12-hour clinic evaluation of PLGM performance in con-junction with exercise[4]
Messer et al. (2018) **NCT02463097 (97)**	US	3	2015-2018	• 31 • 14-26 years • 17.8 (3.9)	• Mini Med 670G[3] • HCL	Sub-study of FDA pivotal trial for device: insulin delivery characteristics and time in range
FDA (2020) (14) Safety Evaluation of the Hybrid Closed Loop (HCL) System in Pediatric Subjects with Type 1 Diabetes (G150247)	US	7	2017-2018	• 46 • 2-6 years	• Mini Med 670G[3] • HCL	Non-comparative pivotal trial
Breton et al. (2020) (98) NCT03844789	US	4	2019-2020	• 101 • 6-13 years	• t:slim X2 insulin pump with Control-IQ Tech-nology[4] • HCL	RCT, open label Intervention: • HCL (n=78) Control: • SAPT (n=23)

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

[2]MiniMed 640G is hybrid closed loop device approved for use outside of US.
[3]MiniMed 670G is hybrid closed loop device approved for use in US.
[4]t:slim X2 insulin pump with Control-IQ Technology is hybrid closed loop device approved for use in US.
[5]Activity/exercise induced hypoglycemia protocol (walking, biking, playing Wii games, or other aerobic activities) intended to activate the "suspend before low" feature followed by evaluation up to 6 hours and at least 4 hours after insulin resumption.

Table 33. Summary of Key Study Results: Hybrid Closed-Loop in Children and Adolescents with Type 1 Diabetes

Study	Efficacy Outcomes			Safety Outcomes	
Tauschmann et al. (2018) (93)					
Outcome Measure	Group difference in time proportion in target glucose range (70-180 md/dL) at 12 weeks Mean (SD)		HbA1c % (SD) At 12 weeks	Hypo-glycemia A. <63mg/dL B. <50mg/dL Percent time in given range (SD)	
• SAPT with PLGM • SAPT alone • Difference • [95% CI] • P • SAPT with PLGM • SAPT alone • Difference • [95% CI] • P	• 68% (8) • 54% (9) • 10.8 • [8.2,13.5] • <0.0001		• 7.4(0.6) • 7.7(0.5) • -0.36 • [-0.53, -0.19] • <0.0001	**A**. • 1.4 (0.9, 1.9) • 2.0 (0.9, 3.0) • -0.83 • [-1.4, -0.16] • 0.0130 **B.** • 0.3 (0.2, 0.6) • 0.5 (0.2, 0.9) • -0.09 • [-0.24, 0.01] • 0.08	
Abraham et al. (2018) (94)					
Outcome Measure	*Change in average percent time in hypoglycemia (SG*	*Change in average percent time in hypoglycemia (SG <54mg/dL) at 6 months*	*HbA1c* *Mean %(SD)*	*Hypo-glycemic events* *(SG <63mg/dL for >20 minutes)*	*IAH[2](%)* • *Clarke score≥4*

	<63mg/dL) at 6 months			*Events per patient-year*	• *N=90 (≥12 years)*
SAPT with PLGM	• n=76 • 2.8% Δ 1.4%	• n=76 • 1.3% Δ 0.6%	7.5(0.8) Δ 7.8(0.8)	139	4%
SAPT alone	• n=70 • 3% Δ 2.6%	• n =70 • 1.4% Δ 1.2%	7.4(0.7) Δ 7.6(1.0)	227	13%
Difference in LS means [95% CI] p	• -0.95% • [-1.30, -0.61] <0.0001	• -0.44% • [-0.64, -0.24] <0.0001	• 0.09 • [-0.10, 0.27] 0.35	• [221, 234 vs 134, 143] • <0.001	• -.04 • [-0.52, 0.43] • 0.86
Forlenza et al. (2019)[1] NCT02660827 (95)					
Outcome Measure	*HbA1c Mean % (SD)*		*Time in Range (>70-180 mg/dL) Mean % (SD)*	*Hypogylcemia A. ≤70 mg/dL B.≤54 mg/dL Mean %(SD)*	
Baseline Run-in phase (n=106) 3-month study phase (n=105) P	• 7.9 (0.8) • 7.5 (0.6) <0.001		• 65 (7.7) <0.001	**A**.≤70 mg/dL • 4.7(3.8) • 3.0 (1.6) <0.001 **B**.≤54 mg/dL • 1.3 (1.5) • 0.8 (0.7) <0.001	
Wood et al. (2018)[1] NCT0266087 (96)					
Outcome Measure	*N=79 participant activations of suspend before low Rate of "Suspend before Low" (%)*				
Reference range[3] • ≤55 mg/dL • ≤60 mg/dL	• 77 (97.5) • 71 (89.9)				

• ≤65 mg/dL	• 63 (79.7)				
Messer et al. (2018)[1] (NCT02463097) (97)					
Outcome Measure	*Mean percentage time in range (70-180 mg/dL) using HCL mode[4] Mean % (SD)*				
Days • Days 1-7 • Days 22-28 • Days 50-56 • Days 78-84	 • 69.7 (10.6) • 69.5 (8.5) • 71.9 (8.1) • 71.5 (10.3)				
FDA (2020) (14) **Safety Evaluation of the Hybrid Closed Loop (HCL) System in Pediatric Subjects with Type 1 Diabetes (G150247)**					
Outcome Measure	*Percent change from baseline in HbA1c Mean (SD); 95% CI*	*Total Daily Dose of insulin at end of study Mean (SD)*	*Time in range during study period, % Mean SD); 95% CI*	*Adverse events*	
	-0.5 (0.7); -0.7, -0.3	16.1 U (4.7)	<50 mg/dL: 0.5 (0.4); 0.4 to 0.6 <54 mg/dL: 0.8 (0.6); 0.6 to 1.0 <60 mg/dL: 1.5 (0.9); 1.2 to 1.8 <70 mg/dL: 3.5 (1.6); 3.0 to 3.971	• No reports of unanticipated serious adverse device effects, unanticipated non-serious adverse device/ procedural effects • No reports of diabetic ketoacidosis events.	

			<180 mg/dL: 63.6 (9.4); 60.8 to 66.4 >180 mg/dL: 33.0 (9.9); 0.4 to 0.6 >250 mg/dL: 10.7 (5.9); 8.9 to 12.4 >300 mg/dL: 3.7 (2.9); 2.9 to 4.6 >350 mg/dL: 1.2 (1.1); 0.8 to 1.5	• No reports of severe hypoglycemia events	
Breton et al. (2020) (98) **Cobry et al. (2021) (100)** **NCT03844789**					
Outcome measure	*HbA1c at 16 weeks*		*Percent time in target range 70 to 180 mg/dL (Primary outcome)* *Mean (SD)*	*Adverse events*	
HCL	7.0 (0.8)		67 (10)	16 adverse events in 15 patients (19%) Median hypoglycemic events per week (IQR): 0.5 (0.1 to 0.8) Median hyperglycemic events per week (IQR): 3.0	

				(1.7 to 5.2) No severe hypoglycemia or diabetic ketoacidosis	
Control	7.6 (0.9)		55 (13)	3 adverse events in 2 patients (9%) Median hypoglycemic events per week (IQR): 0.6 (0.1 to 1.0) Median hyperglycemic events per week (IQR): 5.6 (3.4 to 8.1) No severe hypoglycemia or diabetic ketoacidosis	
Between-group difference	-0.4 (95% CI, -0.9 to 0.1; p=0.08)		11% (7% to 14%); p<0.001	Median hypoglycemic events per week: p= 0.16 Median hyperglycemic events per week: p=0.001	

Δ: delta meaning change in status; CI: confidence interval; HbA1c; hemoglobin A1c; HCL: hybrid closed loop; IAH: impaired awareness of hypoglycemia; IQR: interquartile range; LS: least squares; PLGM: predictive low glucose management; SAPT: sensor-augmented pump therapy; SD: standard deviation; SG: sensor glucose; T1D: type 1 diabetes.

[1]Data as submitted for FDA PMA Supplement P160017/S031.

[2]Clarke score: uses 8 questions to characterize an individual's exposure to episodes of moderate and severe hypoglycemia to assess the glycemic threshold for and symptomatic response to hypoglycemia. A value ≥ 4 indicates IAH.

[3]Simultaneous testing with either intravenous sampling or self-monitoring blood glucometer.

[4]Open loop manual mode was used in a run-in phase to develop personalized parameters for HCL/Auto Mode phase.

Section Summary: Hybrid Closed-Loop Insulin Delivery Systems

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

Summary of Evidence for Artificial Pancreas Device Systems

For individuals who have type 1 diabetes who receive an artificial pancreas device system with a low-glucose suspend feature, the evidence includes three randomized controlled trials (RCTs) conducted in home settings. Relevant outcomes are symptoms, change in disease status, morbid events, resource utilization, and treatment-related morbidity. Primary eligibility criteria of the key RCT, the Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial, were ages 16-to-70 years old, Type 1 diabetes, glycated hemoglobin levels between 5.8% and 10.0%, and at least 2 nocturnal hypoglycemic events (≤65 mg/dL) lasting more than 20 minutes during a 2-week run-in phase. Both trials required at least six months of insulin pump use. Both RCTs reported significantly less hypoglycemia in the treatment group than in the control group. In both trials, primary outcomes were favorable for the group using an artificial pancreas system; however, findings from one trial were limited by nonstandard reporting of hypoglycemic episodes, and findings from the other trial were no longer statistically significant when two outliers (children) were excluded from analysis. The RCT limited to adults showed an improvement in the primary outcome (area under the curve for nocturnal hypoglycemic events). The area under the curve is not used for assessment in clinical practice but the current technology does allow user and provider review of similar trend data with continuous glucose monitoring. Results from the ASPIRE study suggested that there were increased risks of hyperglycemia and potential diabetic ketoacidosis in subjects using the threshold suspend feature. This finding may be related to whether or not actions are taken by the user to assess glycemic status, etiology of the low glucose (activity, diet or medication) and to resume insulin infusion. Both retrospective and prospective observational studies have reported reductions in rates and severity of hypoglycemic episodes in automated insulin delivery system users. The

evidence is suggests that the magnitude of reduction for hypoglycemic events in the type 1 diabetic population is likely to be clinically significant. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

Practice Guidelines and Position Statements: Artificial Pancreas Device Systems

American Association of Clinical Endocrinologists et al.

In 2021, the American Association of Clinical Endocrinologists published a clinical practice guideline for the use of advanced technology in the management of individuals with diabetes. (72) The guideline included the following statements:

"Low-glucose suspend (LGS) is strongly recommended for all persons with T1D to reduce the severity and duration of hypoglycemia, whereas predictive low glucose suspend (PLGS) is strongly recommended for all persons with T1D to mitigate hypoglycemia. Both systems do not lead to a rise in mean glucose, and lead to increased confidence and trust in the technology, more flexibility around mealtimes, and reduced diabetes distress for both persons with diabetes and caregivers. Therefore, anyone with frequent hypoglycemia, impaired hypoglycemia awareness, and those who fear hypoglycemia leading to permissive hyperglycemia should be considered for this method of insulin delivery."
Grade A; High Strength of Evidence

"AID [Automated insulin delivery] systems are strongly recommended for all persons with T1D, since their use has been shown to increase TIR, especially in the overnight period, without causing an increased risk of hypoglycemia. Given the improvement in TIR and the reduction in hyperglycemia with AID, this method of insulin delivery is preferred above other modalities. For persons with diabetes with suboptimal glycemia, significant glycemic variability, impaired

hypoglycemia awareness, or who allow for permissive hyperglycemia due to the fear of hypoglycemia, such AID systems should be considered."
Grade A; High Strength of Evidence

American Diabetes Association

The American Diabetes Association has released multiple publications on controlling Type 1 diabetes (see Table 34).

Table 34. American Diabetes Association Recommendations on Controlling Type 1 Diabetes

Date	Title	Publication Type	Recommendation (Level of Evidence)
2023	Diabetes Technology: Standards of Care in Diabetes—2023	Guideline standard (101)	Automated insulin delivery systems should be offered for diabetes management to youth and adults with type 1 diabetes (A) and other types of insulin deficient diabetes (E) who are capable of using the device safely (either by themselves or with a caregiver). The choice of device should be made based on the individual's circumstances, preferences, and needs. Insulin pump therapy alone with or without sensor-augmented pump low glucose suspend feature and/or automated insulin delivery systems should be offered for diabetes management to youth and adults on multiple daily injections with type 1 diabetes (A) or other types of insulin-deficient diabetes (E) who are capable of using the device safely (either by themselves or with a caregiver) and are not able to use or do not choose an automated insulin delivery system. The choice of device should be made based on the individual's circumstances, preferences, and needs. (A)
2017	Standardizing Clinically Meaningful Outcome	Consensus report[a] (10)	Developed definitions for hypoglycemia, hyperglycemia, time in range, and diabetic ketoacidosis in Type 1 diabetes. (NA)

	Measures Beyond HbA1c for Type 1 Diabetes		

HbA1c: hemoglobin A1c; N/A: not applicable.

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

Ongoing and Unpublished Clinical Trials: Artificial Pancreas Device Systems

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 35.

Table 35. Summary of Key Trials

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

	and Efficacy of Glycemic Control Using Hybrid-closed Loop vs. Advanced Hybrid Closed-loop in Young Subjects With Type 1 Diabetes		

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

Software-Based Insulin Dose Management

In 2019, Bergenstal et al. reported on a multicenter (3 diabetes centers in the U.S.), randomized controlled study that evaluated whether the combination of the d-Nav device and health-care professional support was superior to health-care professional support alone. (102) Patients were eligible if they were aged 21-70 years, diagnosed with type 2 diabetes with a glycated haemoglobin (HbA1c) concentration of 7.5% or higher (≥58 mmol/mol) and 11% or lower (≤97 mmol/mol), and had been using the same insulin regimen for the previous 3 months. Exclusion criteria included body-mass index of 45 kg/m^2 or higher; severe cardiac, hepatic, or renal impairment; and more than two severe hypoglycaemic events in the past year. Both groups were contacted seven times (three face-to-face and four phone visits) during 6 months of follow-up. The primary objective was to compare average change in HbA1c from baseline to 6 months. Safety was assessed by the frequency of hypoglycaemic events. Between Feb 2, 2015, and March 17, 2017, 236 patients were screened for eligibility, of whom 181 (77%) were enrolled and randomly assigned to the intervention (n=93) and control (n=88) groups. At baseline, mean HbA1c was 8.7% (SD 0.8; 72 mmol/mol [SD 8.8]) in the intervention group and 8.5% (SD 0.8; 69 mmol/mol [SD 8.8]) in the control group. The mean decrease in HbA1c from baseline to 6 months was 1.0% (SD 1.0; 11 mmol/mol [SD 11]) in the intervention group, and 0.3% (SD 0.9; 3.3 mmol/mol [9.9]) in the control group (p<0·0001). The frequency of hypoglycaemic events per month was similar between the groups. The authors noted the combination of automated insulin titration guidance with support from health-care professionals offers superior glycaemic control compared with support from health-care professionals alone. Such a solution facilitated safe and effective insulin titration in a large group of patients with type 2 diabetes, and now needs to be evaluated across large health-care systems to confirm these findings and study cost-effectiveness.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	95249, 95250, 95251, 0446T, 0447T, 0448T, 0740T, 0741T

HCPCS Codes	A4224, A4225, A4226, A4230, A4231, A4232, A4233, A4234, A4235, A4236, A4238, A4239, A4253, A4271, A9274, A9275, A9276, A9277, A9278, E0607, E0784, E0787, E2100, E2101, E2102, E2103, E2104, G0308, G0309, K0553, K0554, S1030, S1031, S1034, S1035, S1036, S1037, S9145

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
02/15/2024	Document updated with literature review. The following changes were made to Coverage: 1) Criteria under the Glucose Monitoring Devices section have changed: professional (intermittent 72 hour) monitoring of glucose levels in interstitial fluid, long-term continuous glucose monitoring (CGM) of glucose levels in interstitial fluid and continuous glucose monitoring using an

	implantable glucose sensor; 2) Criteria under the following sections have changed: External Insulin Infusion Pumps and Artificial Pancreas Devices Systems; 3) NOTE 4 was removed and other notes were re-numbered. The following references were added: 15, 35-38, 42, 50-51, 53-54, 57-60, 62, 71, 76, 86, 92, 102 and 104; others updated, some removed.
01/01/2023	Document updated with literature review. The following change was made to Coverage: 1) Eversense E3 CGM system was added to the following statement: Continuous glucose monitoring using an implantable glucose sensor (i.e., Eversense™ CGM system/Eversense E3 CGM system) used in accordance with the U.S. Food and Drug Administration (FDA) labeling, may be considered medically necessary when criteria noted above under the long-term (continuous) CGM monitoring section is met; 2) Added the following: The use of an insulin titration guidance system with support from health-care professionals (e.g. d-Nav® System is considered experimental, investigational and/or unproven. References 1, 40, 45, 46, 51, 55, 57-59, 83, 86-88 were added; some references were updated and others removed.
09/15/2021	Document updated with literature review. The following changes were made to Coverage: 1) Clarified the second bullet under Professional (intermittent 72 hour) monitoring of glucose levels; 2) Added to NOTE 2-Persistent hyperglycemia and hemoglobin level (HbA1c) levels above target as an indicator of poorly controlled diabetes; 3) Added CeQur Simplicity™ and removed Finesse insulin delivery patch as an example of disposable (mechanical) insulin delivery device; 4) Removed the ALERT addressing Animas devices. References added: 17-18, 21-25, 30, 35, 40, 46, 48, 54, 56-57, 62-63, 68, 78-80, 83, 85-86, 90-91.
07/15/2020	Document updated with literature review. The following changes were made in Coverage: 1) Long-term Continuous Glucose Monitoring (CGM) criteria has changed; 2) Artificial Pancreas Device Systems criteria has changed; 3) Replacement criteria has been changed and clarified to include continuous glucose monitoring devices; 4) NOTE 3 and 5 have been added; 5) Numbers referring to NOTEs have been renumbered. The following reference numbers were added: 72-90.
10/15/2019	Document updated with literature review. The following changes were made to the Coverage section: 1) Changed the following statement from being considered experimental, investigational and/or unproven to being considered not medically necessary: Other uses of continuous monitoring of glucose levels in interstitial fluid, including real-time monitoring, as a technique of diabetic monitoring, not meeting above noted criteria is considered not medically necessary, 2) Clarified the Coverage statement for implantable glucose sensors 3) Added the word “mechanical” for clarification, to the following statement: Disposable (mechanical) insulin delivery devices, including but not limited to V-Go™ and Finesse insulin delivery patch, are considered experimental, investigational and/or unproven, 4) Added the following note for clarification Note 1 addresses the

	Regulatory Status section, 5) Removed the following bullet from NOTE 5 in the Coverage section: Patient is otherwise treatable only by conventional infusion pump in an institutional setting, or compliance difficulties make intermittent injection ineffective, 6) Added NOTE 3: Documentation for initial benefit determination should include a 30 day glucose log or pump download within the most recent 90 day period. Continuation of continuous monitoring previously supplied for a member with Type 1 Diabetes new to the plan is not considered an initial benefit determination for the purposes of this policy; 7) Changed hypoglycemic criteria from below 50 mg/dl to a value of ≤ 70 mg/dl. 8) Clarified statement on long term personal CGM for patients with Type 1 insulin dependent diabetes who are pregnant. 9) Changed Coverage concerning implantable interstitial glucose sensors for CGM To: Continuous glucose monitoring using an implantable glucose sensor (i.e., Eversense™ CGM system) used in accordance with the FDA labelling, may be considered medically necessary when criteria noted above under the personal continuous glucose (long-term) monitoring (CGM) section is met. The following references were added: 2, 13-20, 25-27, 31, 35-37, 41-43, 47-48, 64, and 69.
05/09/2019	Coverage clarified for external insulin infusion pumps: Added the wording "including non-disposable and programmable disposable (e.g., Omnipod) devices," to the following statement: An external insulin infusion pump, including non-disposable and programmable disposable (e.g., Omnipod) devices, with or without wireless communication capability, may be considered medically necessary when ALL of the following criteria are met.
04/01/2018	Document updated with literature review. 1) Coverage for Continuous or Intermittent Monitoring of Glucose in Interstitial Fluid is unchanged. 2) Coverage for Insulin Infusion Pumps had the word external added to the coverage statement, for clarification. Insulin Infusion Pumps were previously addressed on DME101.048. 3) Coverage has changed for Artificial Pancreas Device Systems. Hybrid closed-loop insulin delivery system devices have been added to the coverage statements and may be considered medically necessary when stated criteria are met. Use of an artificial pancreas device system is considered experimental, investigational and/or unproven in all other situations when criteria noted are not met. Replacement coverage has changed to include artificial pancreas device systems, when stated criteria are met. The following statement was added to the coverage: Replacement of insulin pumps or artificial pancreas device systems that are functional and are currently under warranty, for the sole purpose of obtaining the most recent technology (e.g., an upgrade) is considered not medically necessary. Title changed from: Continuous or Intermittent Monitoring of Glucose in Interstitial Fluid.
01/01/2017	Coverage for Artificial Pancreas Device Systems has changed, "for persons 16 years and older" was removed from the criteria and the following information was added to the coverage statement: Artificial pancreas device

	systems are medical devices that link a glucose monitor to an insulin infusion pump that automatically takes action based on the glucose monitor reading. These devices are proposed to improve glycemic control in patients with insulin-dependent diabetes, in particular, control of nocturnal hypoglycemia. The following coverage statement was added: Medical devices that are not U. S. Food and Drug Administration (FDA) approved, including but not limited to the implantable interstitial glucose sensor from Senseonics are considered experimental investigational and/or unproven.
02/15/2015	Document updated with literature review. The following was added to the coverage section: Additional software or hardware required for downloading data to a device such as personal computer, smart phone, or tablet to aid in self-management of diabetes mellitus, to include remote glucose monitoring device (i.e., mySentry) are considered a convenience item and therefore not medically necessary.
08/01/2014	The coverage specific to artificial pancreas systems was changed to include the following: Use of an artificial pancreas system, with low-glucose suspend (LGS) features when performed according to FDA-approved indications for persons 16 years and older, may be considered medically necessary when: Patient meets criteria for insulin infusion pump (see separate policy DME101.048 Insulin Infusion Pump) and Patient meets criteria for personal continuous glucose (long-term) monitoring noted above and Patient has one of the following: Hypoglycemic unawareness or Multiple documented episodes of nocturnal hypoglycemia, (less than 50mg/dL).
07/01/2014	Document updated with literature review. The following was added to Coverage: Use of an artificial pancreas system, including but not limited to closed-loop monitoring devices with low-glucose suspend (LGS) features are considered experimental, investigational and/or unproven. CPT/HCPCS code(s) updated.
06/01/2012	Document updated with literature review. The following changes were made to the Personal CGM coverage: 1) Removed conditional criteria for patients with Type I insulin dependent diabetes who are pregnant. 2) “Hypoglycemic unawareness or frequent hypoglycemia” is a new option added under the requirement for “And have not achieved adequate metabolic control as evidenced by at least one of the following:” 3) Removed requirement for previous professional (intermittent 72 hour) glucose monitoring.
01/01/2011	Document updated with literature review. The following was changed: “in patients age 26 years or older” was removed from the criteria for personal (continuous long-term) monitoring.
10/15/2009	Policy updated without literature review. No change in coverage.
04/15/2009	Policy updated with literature, change in coverage. Change in coverage to conditionally allow Professional (intermittent 72 hour) monitoring of glucose levels in interstitial fluid for patients with Type I or Type II insulin dependent diabetes. Change in coverage to conditionally allow Personal (continuous

	long term) monitoring of glucose levels in interstitial fluid, including real-time monitoring, as a technique of diabetic monitoring, in patients age 25 years or older with Type I insulin dependent diabetes.
01/01/2008	Codes Revised/Added/Deleted
09/15/2007	Revised/updated entire document
05/01/2006	Revised/updated entire document
10/24/2003	Revised/updated entire document
01/01/2000	Revised/updated entire document
11/01/1997	Revised/updated entire document
12/01/1996	Revised/updated entire document
05/01/1996	Revised/updated entire document
05/01/1990	New medical document