Clinical UM Guideline

Subject:	Continuous Glucose Monitoring Devices and External Insulin Infusion Pumps		
Guideline #:	CG-DME-42	**Publish Date:**	06/28/2023
Status:	Revised	**Last Review Date:**	05/11/2023

Description

This document addresses the use of continuous glucose monitoring devices (CGMs, also referred to as continuous *interstitial* glucose monitoring devices), automated insulin delivery systems, and non-implanted insulin pump devices for the management of diabetes mellitus.

External insulin infusion pumps are programmable, battery-powered mechanical syringe/reservoir devices controlled by a micro-computer to provide continuous subcutaneous insulin infusion (CSII) in individuals with diabetes mellitus.

CGM devices are used for the continuous monitoring of interstitial glucose concentrations. These devices have been shown to assist in the management of some individuals with diabetes mellitus.

External insulin infusion pumps and CGMs maybe be combined to form automated insulin delivery systems. Some of these systems require the intervention of the individual being treated to manage major aspects of their insulin administration, such as basal rate and prandial bolus insulin dosing. These devices are referred to as "open-loop" systems. Other automated delivery systems, referred to as "hybrid closed-loop", require minimal intervention, and include automated control of basal insulin infusion rates and low glucose suspend features. "Hybrid closed-loop" systems still require patient-directed prandial insulin dosing. Finally, some advanced systems under development, referred to as "closed-loop" systems, require no intervention by the treated individual when under normal operating conditions.

Note: Some insulin pump devices come equipped with the capacity to be combined with CGM devices to create automated insulin delivery systems. Such devices can be used as stand-alone insulin pumps or as combined systems, depending upon an individual's need.

Note: This document does not address supplies related to the use of automated insulin delivery devices.

Note: For additional information regarding diabetes care, please see:

- CG-SURG-79 Implantable Infusion Pumps

Note: This document contains three sections addressing different types of devices:

I. External Insulin Infusion Pumps: Addresses stand-alone external insulin infusion pumps.
II. Continuous Interstitial Glucose Monitoring Devices: Addresses stand-alone CGM devices.
III. Automated Insulin Delivery Systems: Addresses devices that combine the functions of both external insulin pumps and CGMs.

Clinical Indications

I. EXTERNAL INSULIN INFUSION PUMPS

Medically Necessary:

External insulin pumps (both disposable and durable) with wireless communication capability are considered **medically necessary** in any of the following groups (A, B, **or** C):

A. Individuals with documented diabetes mellitus (any type) meeting *all* the following criteria (1 through 5):
   1. Completed a comprehensive diabetes education program within the past 2 years; **and**
   2. Follows a program of multiple daily injections of insulin; **and**
   3. Has frequent self-adjustments of insulin doses for the past 6 months; **and**
   4. Requires multiple blood glucose tests daily or is using a continuous glucose monitor; **and**
   5. Has documentation of *any* of the following while on a multiple daily injection regimen:
      a. Glycosylated hemoglobin level (HbA1c) greater than 7.0 percent; **or**
      b. Diabetic ketoacidosis; **or**
      c. Hospitalization as a result of diabetes; **or**
      d. History of recurring hypoglycemia or severe glycemic excursions; **or**
      e. Wide fluctuations in blood glucose before mealtime; **or**
      f. "Dawn phenomenon" with fasting blood sugars frequently exceeding 200 mg/dl; **or**
      g. Microvascular or macrovascular complications (for example, diabetic retinopathy or cardiovascular disease); **or**
B. Individuals with documented diabetes mellitus (any type) and are pre-conception or currently pregnant, to reduce the incidence of fetal mortality or anomaly; **or**
C. Individuals with diabetes mellitus (any type) successfully using a continuous insulin infusion pump prior to enrollment and requiring multiple blood glucose tests daily during the month prior to enrollment.

Refills for medically necessary disposable external insulin pumps are considered **medically necessary.**

Continued use of an external insulin pump is considered **medically necessary** when there is documentation that both criteria A and B below are met:

A. Individual has used the device as intended; **and**

B. Device has resulted in desired clinical benefit (for example, improved HbA1c control or fewer episodes of symptomatic hypoglycemia or hyperglycemia).

Replacement pumps:

The replacement of external insulin pumps is considered **medically necessary** when the following criteria have been met:

A. The device is out of warranty, **and**
B. The device is malfunctioning, **and**
C. The device cannot be refurbished.

Note: The medical necessity of the replacement of an external insulin pump for pediatric individuals (under 18 years of age) who require a larger insulin reservoir will be considered on a case-by-case basis. The following information is required when submitting requests:

A. Current insulin pump reservoir volume; **and**
B. Current insulin needs; **and**
C. Current insulin change out frequency required to meet individual needs.

Not Medically Necessary:

The use of external insulin pumps for any indication other than those listed above is considered **not medically necessary.**

Use of a disposable external insulin pump with **no** wireless communication capability (for example, V-Go®, CeQur® Simplicity™) is considered **not medically necessary** under all circumstances.

Continued use of an external insulin pump is considered **not medically necessary** when continued use criteria above have not been met.

Replacement of currently functional and warranted external insulin pumps is considered **not medically necessary** when the replacement of external insulin pumps medically necessary criteria (A, B, and C) above have not been met**.**

II. CONTINUOUS INTERSTITIAL GLUCOSE MONITORING DEVICES

Medically Necessary:

Continuous Glucose Monitoring Devices and External Insulin Infusion Pumps

Professional, intermittent, short-term use of continuous interstitial glucose monitoring devices as an adjunct to standard care is considered **medically necessary** when **all** of the following criteria are met:

A. Individual is diagnosed with diabetes mellitus (any type); **and**
B. Inadequate glycemic control despite compliance with self-monitoring, including fasting hyperglycemia or recurring episodes of hypoglycemia. This poor control is in spite of compliance with multiple alterations in self-monitoring and insulin administration regimens to optimize care; **and**
C. Insulin injections are required multiple times daily or an insulin pump is used for maintenance of blood sugar control; **and**
D. Multiple blood glucose tests are required daily; **and**
E. Monitoring and interpretation are under the supervision of a physician; **and**
F. The device is only used for a maximum of 14 consecutive days on an appropriate, periodic basis.

Personal long-term use of continuous interstitial glucose monitoring devices as an adjunct to standard care is considered **medically necessary** for *any* of the following:

A. Individuals greater than or equal to 14 years old with diabetes mellitus (any type) who meet the following criteria:
    1. Inadequate glycemic control, demonstrated by HbA1c measurements 7.0% or greater, despite multiple alterations in self-monitoring and insulin administration regimens to optimize care; **and**
    2. Insulin injections are required multiple times daily or a medically necessary insulin pump is used for maintenance of blood sugar control; **or**
B. Individuals, *regardless of age*, with diabetes mellitus (any type) who meet the following criteria:
    1. Recurring episodes of hypoglycemia; **and**
    2. Inadequate glycemic control despite multiple alterations in self-monitoring and insulin administration regimens to optimize care; **and**
    3. Insulin injections are required multiple times daily or a medically necessary insulin pump is used for maintenance of blood sugar control; **or**
C. Individuals with type 1 diabetes who are pregnant, during the course of the pregnancy, who meet the following criteria:
    1. Inadequate glycemic control, including fasting hyperglycemia or with recurring episodes of hypoglycemia in spite of compliance with multiple alterations in self-monitoring and insulin administration regimens to optimize care; **and**
    2. Insulin injections are required multiple times daily or a medically necessary insulin pump is used for maintenance of blood sugar control; **and**
    3. Multiple blood glucose tests are required daily.

Continued use of a continuous interstitial glucose monitoring device is considered **medically necessary** when there is documentation that both criteria A and B below are met:

A. Individual has used the device as intended; **and**
B. Device has resulted in desired clinical benefit (for example, improved HbA1c control or fewer episodes of symptomatic hypoglycemia or hyperglycemia).

The replacement of non-implanted continuous interstitial glucose monitoring devices is considered **medically necessary** when the following criteria have been met:

A. The device is out of warranty; **and**
B. The device is malfunctioning; **and**
C. The device cannot be refurbished.

Use of implantable interstitial glucose sensors is considered **medically necessary** for individuals when the criteria below have been met:

A. The individual is 18 years of age or older; **and**
B. The individual meets the medical necessity criteria above for personal long-term use of continuous interstitial glucose monitoring devices (A, B, or C).

The replacement of an implantable interstitial glucose sensor is considered **medically necessary** in accordance with FDA approved indications for use.

Not Medically Necessary:

Use of continuous interstitial glucose monitoring devices is considered **not medically necessary** for all other indications, including but not limited to when the criteria above have not been met.

Continued use of a continuous interstitial glucose monitoring device is considered **not medically necessary** when continued use criteria above have not been met.

Replacement of currently functional and warranted continuous interstitial glucose monitoring devices is considered **not medically necessary** when the replacement of continuous interstitial glucose monitoring devices medically necessary criteria (A, B, and C) above have not been met**.**

III. AUTOMATED INSULIN DELIVERY SYSTEMS

Medically Necessary:

Use of an open-loop or hybrid closed-loop automated insulin delivery system with a low glucose suspend feature is considered **medically necessary** for individuals who meet the following criteria:

A. Type 1 diabetes mellitus; **and**
B. Age 2 or older; **and**
C. HbA1c value of 5.8% to 10%.

Continued use of an open-loop or hybrid closed-loop automated insulin delivery system is considered **medically necessary** when there is documentation that both criteria A and B below are met:

A. Individual has used the device as intended; **and**
B. Device has resulted in desired clinical benefit (for example, improved HbA1c control or fewer episodes of symptomatic hypoglycemia or hyperglycemia).

Replacement of a previously approved open-loop or hybrid closed-loop automated insulin delivery system is considered **medically necessary** when the medically necessary criteria above have previously been met *and* all of the criteria below have been met:

A. The device is out of warranty; **and**
B. The device is malfunctioning; **and**
C. The device cannot be refurbished.

Not Medically Necessary:

Continued use of an open-loop or hybrid closed-loop automated insulin delivery system is considered **not medically necessary** when continued use criteria above have not been met.

Replacement of currently functional and warranted open-loop or hybrid closed-loop automated insulin delivery system is considered **not medically necessary** when the replacement of open-loop or hybrid closed-loop automated insulin delivery system medically necessary criteria (A, B, and C) above have not been met**.**

Use of an open-loop or hybrid closed-loop automated insulin delivery system, including those with a low glucose suspend feature, is considered **not medically necessary** for individuals who have not met the criteria above.

Use of non-hybrid closed-loop or non-FDA-approved hybrid closed-loop automated insulin delivery system is considered **not medically necessary** under all circumstances.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Infusion pumps and automated insulin delivery systems
When services may be Medically Necessary when criteria are met:

HCPCS	
A9274	External ambulatory insulin delivery system, disposable, each, includes all supplies and accessories [when specified as a disposable system with wireless communication capability]
E0784	External ambulatory infusion pump, insulin [for automated insulin delivery systems when specified as an open-loop or hybrid closed-loop system]
E0787	External ambulatory infusion pump, insulin, dosage rate adjustment using therapeutic continuous glucose sensing
S1034	Artificial pancreas device system (e.g., low glucose suspend [LGS] feature) including continuous glucose monitor, blood glucose device, insulin pump and computer algorithm that communicates with all of the devices [when specified as an open-loop or hybrid closed-loop system]

ICD-10 Diagnosis	
E08.00-E13.9	Diabetes mellitus
O24.011-O24.93	Diabetes mellitus in pregnancy, childbirth and the puerperium
P70.2	Neonatal diabetes mellitus

When services are Not Medically Necessary:
For the procedure codes listed above when criteria are not met or for all other diagnoses not listed; or when the code describes a procedure, device or situation designated in the Clinical Indications section as not medically necessary.

When services are also Not Medically Necessary:

HCPCS	
A9274	External ambulatory insulin delivery system, disposable, each, includes all supplies and accessories [when specified as a system with **no** wireless communication capability, such as the V-Go and the CeQur Simplicity disposable external insulin delivery devices]
E0784	External ambulatory infusion pump, insulin [when specified as other than an open-loop or hybrid closed-loop system (for example, closed-loop system)]
S1034	Artificial pancreas device system (e.g., low glucose suspend [LGS] feature) including continuous glucose monitor, blood glucose device, insulin pump and computer algorithm that communicates with all of the devices [when specified as other than an open-loop or hybrid closed-loop system (for example, closed-loop system)]

ICD-10 Diagnosis

All diagnoses

Continuous interstitial glucose monitoring devices
When services may be Medically Necessary when criteria are met:

CPT

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

HCPCS

A4238	Supply allowance for adjunctive non-implanted continuous glucose monitor (CGM), includes all supplies and accessories, 1 month supply = 1 unit of service
A4239	Supply allowance for non-adjunctive, non-implanted continuous glucose monitor (CGM), includes all supplies and accessories, 1 month supply = 1 unit of service
A9276	Sensor; invasive (e.g., subcutaneous), disposable, for use with non-durable medical equipment interstitial continuous glucose monitoring system, 1 unit = 1 day supply
A9277	Transmitter; external, for use with non-durable medical equipment interstitial continuous glucose monitoring system
A9278	Receiver (monitor); external, for use with non-durable medical equipment interstitial continuous glucose monitoring system
A9279	Monitoring feature/device, stand-alone or integrated, any type, includes all accessories, components and electronics, not otherwise classified
E2102	Adjunctive, non-implanted continuous glucose monitor or receiver
E2103	Non-adjunctive, non-implanted continuous glucose monitor or receiver [that is, a device that does not require a finger stick, e.g., Dexcom G5]
G0308	Creation of subcutaneous pocket with insertion of 180 day implantable interstitial glucose sensor, including system activation and patient training

G0309	Removal of implantable interstitial glucose sensor with creation of subcutaneous pocket at different anatomic site and insertion of new 180 day implantable sensor, including system activation
S1030	Continuous noninvasive glucose monitoring device, purchase
S1031	Continuous noninvasive glucose monitoring device, rental, including sensor, sensor replacement, and download to monitor

ICD-10 Diagnosis

E08.00-E13.9	Diabetes mellitus
O24.011-O24.93	Diabetes mellitus in pregnancy, childbirth and the puerperium
P70.2	Neonatal diabetes mellitus

When services are Not Medically Necessary:
For the procedure codes listed above when criteria are not met or for all other diagnoses not listed; or when the code describes a procedure, device or situation designated in the Clinical Indications section as not medically necessary.

Discussion/General Information

According to the American Diabetes Association (ADA), diabetes is one of the most common chronic diseases in the United States (U.S.), with approximately 30 million Americans with diagnosed disease. Another 8 million are believed to have undiagnosed disease. Diabetes mellitus, the fourth leading cause of death in the U.S., is a chronic condition, marked by impaired metabolism of carbohydrate, protein and fat, affecting nearly 21 million Americans. The underlying problem in diabetes is in the production or utilization of insulin, the hormone secreted by the pancreas that controls the level of blood sugar by regulating the transfer of glucose from the blood into the cells. Diabetes mellitus, if poorly controlled, can cause cardiovascular disease, retinal damage that could lead to blindness, damage to the peripheral nerves, and injury to the kidneys. Management of diabetes mellitus involves normalization of blood sugar without potentially dangerous hypoglycemia, or low blood sugar. Type 1 diabetes can occur at any age, but is most commonly diagnosed from infancy to late 30s. In type 1 the pancreas produces little to no insulin, and the body's immune system destroys the insulin-producing cells in the pancreas. Type 2 diabetes typically develops after age 40, but has recently begun to appear with more frequency in children. If a person is diagnosed with type 2 diabetes, the pancreas still produces insulin, but the body does not produce enough or is not able to use it effectively.

For some individuals with diabetes, the use of multiple daily insulin injection therapy is insufficient to provide adequate control of blood sugar levels. In such cases, an external insulin pump may be recommended. These devices are worn externally and are attached to a temporary subcutaneous insulin catheter placed into the skin of the abdomen. The pump involves the use of a computer-controlled mechanism that can be set to administer the insulin at a set (basal) rate or provide injections (bolus) as needed. The pump typically has a syringe reservoir that

has a 2- to 3-day insulin capacity. The purpose of the insulin pump is to provide an accurate, continuous, controlled delivery of insulin which can be regulated by the user to achieve intensive glucose control.

Whether an individual with diabetes uses injection therapy or an insulin pump, the individual needs to check blood glucose concentrations multiple times a day to make sure they are staying within normal blood glucose range. As with injection therapy, sometimes self-monitoring blood glucose management is also insufficient. In such circumstances, the use of a CGM may be warranted. These devices measure glucose concentrations in the fluid in between the body's cells, also known as interstitial fluid. They are designed to provide real-time glucose measurements, which have been found to accurately reflect blood glucose levels.

External Insulin Infusion Pumps

Insulin administration may be done in several ways. The most common method is multiple daily injections (MDI) via a syringe and subcutaneous injection. Dosing of these injections is timed by the individual to coincide with expected changes in blood sugar concentrations such as occur following meals. Another common method is via external insulin infusion pump. These devices are worn externally and are attached to a temporary subcutaneous insulin catheter placed into the skin of the abdomen. The pump is controlled by a computer-controlled pump mechanism that can be set to administer the insulin at a set rate or provide bolus injections as needed. The pump typically has a syringe reservoir that has a 2- to 3-day insulin capacity. The purpose of the insulin pump is to provide an accurate, continuous, controlled delivery of insulin which can be regulated by the user to achieve intensive glucose control objectives and to prevent the metabolic complications of hypoglycemia, hyperglycemia and diabetic ketoacidosis. Other more recently developed devices are not battery powered and rely on mechanical instillation of programmed basal and bolus insulin.

Since the publication of the Diabetes Control and Complication Trial (1993), there has been a growing body of evidence to suggest that improved blood glucose control in diabetics leads to improved clinical outcomes, especially with regard to long-term diabetic complications. This has led to an approach of intensive diabetic management to maintain blood glucose to as near normal as possible over all hours of the day and over the life span of the individual. Implementation of this approach requires the individual to be capable of, and committed to, a day-to-day medical program of some complexity. It requires ongoing compliance with multiple daily glucose measurements and insulin injections accompanied by appropriate adjustments in insulin dose. Additionally, successful intensive diabetic management requires response to a variety of external factors including changes in diet, exercise and the presence of infection. Despite this complexity, many motivated individuals can, with adequate training and support, achieve significant improvements in glucose control using this approach. Both multiple daily insulin injections and continuous subcutaneous insulin infusion via an external pump are effective means of providing intensive diabetic management (DCCT Research Group, 1993). Controlled trials comparing these insulin delivery methods show that in most individuals overall blood glucose control is the same or slightly improved with insulin pump treatment. However, in diabetics treated with insulin pumps, hypoglycemia is less frequent and nocturnal glucose control is improved.

The evidence supports the efficacy of the external insulin infusion pump for properly trained diabetics who are not well controlled on intensive, multi-dose insulin therapy. Benefits are seen in long-term control as shown by lowered glycosylated HbA1c levels. In addition, stability of blood glucose self-measurement values as well as surveyed functional status and quality of life outcomes have been shown to improve in individuals using continuous insulin pump therapy.

The use of external insulin infusion pumps requires careful selection of individuals, meticulous monitoring, and thorough education and long-term ongoing follow-up. This care is generally provided by a multidisciplinary team of health professionals with specific expertise and experience in the management of individuals on insulin pump treatment.

Definitive, agreed upon selection criteria for continuous insulin infusion have not been established. Intensive insulin therapy has been shown to reduce complications and improve outcome in pregnant women with type 1 diabetes, and external insulin pump therapy is considered an appropriate alternative to MDI for this group (Kitzmiller, 1991). There is also evidence to support the use of external insulin pump therapy for type 1 diabetics who have not achieved adequate glucose control despite MDI. There is evidence to suggest that insulin pumps may benefit individuals with various types of glycemic excursions such as the "dawn phenomenon" (early morning rise in blood glucose), nocturnal hypoglycemic episodes, hypoglycemic unawareness, and severe hypoglycemia (Hirsch, 1990; Pickup, 2002; Selam, 1990).

In 2014, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) published a consensus statement addressing insulin pump use (Grunberger, 2014). This document provided proposed clinical characteristics of individuals with both type 1 and type 2 diabetes who may be suitable insulin pump candidates. Among the proposed characteristics were labile diabetes, frequent hypoglycemia, significant 'dawn phenomenon,' and microvascular and macrovascular complications. Additionally, candidates should be undergoing self-testing for blood glucose ≥ 4 per day, ≥ 4 insulin injections daily, and have elevated HbA1c. Recommendations are also provided for the treatment of diabetes during pregnancy. Finally, they specify special characteristics for individuals who are not good candidates for insulin pump therapy, including those who are unable or unwilling to perform MDI, self-monitoring of blood glucose levels, and carbohydrate counting; those who are not motivated to achieve better blood glucose control, and individuals with serious psychological or psychiatric conditions.

The benefit of insulin pump use for individuals with type 2 diabetes was established by the results of the OpT2mise Study (Aronson, 2016; Conget, 2016; Reznik, 2014). This well designed and conducted randomized controlled trial (RCT) concluded that for individuals with poorly controlled type 2 diabetes despite MDI, use of an insulin pump can be a valuable treatment option.

A newer type of mechanical disposable insulin pump (V-Go) has been proposed as an alternative to standard pump therapy. The existing evidence addressing this device is mainly in the form of short-term, retrospective studies, most involving case series methodologies with small populations (Boonin, 2017; Johns, 2014; Lajara, 2016b; Meade, 2021; Rosenfeld, 2012; Sutton, 2016; Winter, 2015). One large case series study involved 116 subjects and

reported significant reductions in mean HbA1c in subjects with both type 2 and type 1 diabetes (-1.17%, p=0.02), as well as significant decreases in volume of required insulin (35 units/day vs. 47 units/day at 27 weeks, p<0.001) (Lajara, 2016a). A comparative trial reported by Lajara (2015) involved 204 subjects using the V-Go device vs. MDI. As with the above-described study, significant improvements in HbA1c concentration and decreases in required insulin volume were reported (-1.58% at 27 weeks and, p<0.001 for both).

Raval and colleagues (2019) reported the results of a retrospective cohort study involving data derived from the HealthCore Integrated Research Database. The study looked at 118 matched pairs of individuals with type 2 diabetes undergoing treatment with either the V-Go wearable insulin pump or MDI with 12 months of data available. At the end of 12 months of treatment both cohorts were reported to have improvements in percent HbA1c ≤ 9%, but no differences between groups were noted (p<0.001 for V-Go group and p=0.046 for the MDI group; p=0.263 between groups). Insulin prescription fills were reported to be lower in the V-Go group (mean change: -0.8 vs. +1.8 fills, p<0.001). A decrease in insulin total daily dose during the last 6 months of follow-up was also reported in the V-Go group (mean change in insulin units per day: -29.2 vs. +5.8, p<0.001).

Grunberger (2020) reported the results of a prospective open label case series study initially involving 188 subjects with type 2 diabetes and suboptimal glycemic control (HbA1c ≥ 7%) treated with the V-Go device. At 12 months, 112 subjects (60%) remained in the study, with 66 still on V-Go device. The authors reported a mean decrease in HbA1c from baseline of - 0.64%; (p=0.003) and total daily dose of insulin of 12 units/day (p<0.0001) at 12 months. However, due to the high dropout rate and lack of blinding, the value of this data is uncertain.

At this time, there is no clinical trial data comparing the V-Go device to a standard battery-operated pump device. The clinical utility of the V-Go device remains uncertain at this time.

The CeQur Simplicity is a mechanical, disposable patch device that adheres to the skin and delivers on-demand subcutaneous mealtime insulin bolus doses for up to 3 days. Unlike other "pump" devices, the CeQur does not provide a constant infusion of insulin and is intended to be an alternative to mealtime bolus injections via syringe or pen. At this time there are a limited number of studies published addressing the safety and efficacy of this device. The first was a small RCT involving 38 subjects with either type 1 (n=26) or type 2 (n=12) diabetes assigned to treatment with either the bolus patch or standard injection therapy (n=19 each; Bohannon, 2011). The mean daily seven-point blood glucose (MDBG) was not significantly different between groups (8.61 ± 0.28 vs. 9.02 ± 0.26 mmol/L, p=0.098). However, the standard deviation of MDBG was lower using bolus patch (3.18 ± 0.18 vs. 3.63 ± 0.17 mmol/L; p=0.004) as was the coefficient of variation (p=0.046). No severe hypoglycemia episodes or serious adverse events were reported. This small study was suggestive of equivalency with standard injection therapy, but due the small sample size and other issue, generalizability is limited.

In 2019 Bergenstal reported the results of a larger RCT involving 278 subjects with type 2 diabetes assigned to treatment with the bolus patch (n=139) or injection pen (n=139). Subjects were followed for 48 weeks with crossover at week 44. As with the Bohannon study, MDBG was not significantly different between groups (1.5 ± 4.5, p=0.73). However, the coefficient of variation of MDBG was lower using bolus patch (-1.54 ± 1.1, p=0.02). No

differences between groups were reported with regard to occurrences of HbA1c, severe hypoglycemia episodes, serious adverse events, changes in weight, or insulin doses.

Overall, based on this limited evidence, it would appear that the use of the CeQur device is similar to standard injection therapy. However, additional studies would be helpful to understand the benefits of this device over standard care, and its role within the treatment continuum.

Back-up Insulin Infusion Pumps

Modern external infusion pumps appear safe and reliable, and studies reviewed did not indicate a need for a "back-up" pump. If an insulin pump fails, an individual can and should revert to daily multiple injections until the pump is repaired or replaced.

Insulin Infusion Pump Reservoir Issues

Some pediatric individuals experience increased insulin requirements which exceed the capabilities of the insulin reservoir of their current external insulin pump. In such cases, it may be reasonable to replace their existing pump with a model that has a reservoir that meets their insulin requirements. Requests for this type of equipment upgrade would be reviewed individually taking into account the unique needs of the individual and capacity of existing equipment.

Insulin Infusion Pumps During Pregnancy

In 2018, Feig and others published the results of a large well-designed RCT involving 248 pregnant subjects who routinely used insulin pump therapy. Subjects were assigned to treatment with MDI or pump therapy throughout their gestation. Interestingly, the results indicated that subjects in the MDI group had a greater decrease in HbA1c at 34 weeks (p=0.001). Additionally, at 24 and 34 weeks, MDI users were more likely to achieve target HbA1c (72.1% vs. 63.1%; p=0.009 and 65.1% vs. 52.0%; p=0.001, respectively). Pump group subjects experienced more hypertensive disorders (30.6% vs. 15.5%; p=0.011), increased gestational hypertension (14.4 vs. 5.2%; p=0.025), more incidences of neonatal hypoglycemia (31.8 vs. 19.1%, p=0.05), and had more neonatal intensive care unit (NICU) admissions > 24 h (44.5 vs. 29.6%; p=0.02). The authors concluded that, "MDI users were more likely to have better glycemic outcomes and less likely to have gestational hypertension, neonatal hypoglycemia, and NICU admissions than pump users. These data suggest that implementation of insulin pump therapy is potentially suboptimal during pregnancy." In light of these findings, further investigation into the use of pump therapy in pregnant individuals is warranted.

Continuous Interstitial Glucose Monitoring Devices

Devices are available that continuously monitor glucose concentrations in the fluid in between the body's cells, also known as interstitial fluid. Such devices have been proposed as an adjunct to routine blood-based glucose

measurements in individuals with trouble maintaining appropriate blood glucose levels despite frequent blood-based monitoring or those with frequent undetected hypoglycemic events.

Such devices are referred to as continuous interstitial glucose monitoring (CGM) devices and are designed to provide real-time interstitial glucose measurements, which have been found to accurately reflect blood glucose levels. Furthermore, such devices have special features such as low and high glucose concentration alarms and data storage for later analysis. The stored data has been shown to be useful in identifying ways to improve individual care by altering diet, exercise, medication types, and timing of insulin administration.

There are a wide variety of interstitial glucose monitoring devices available. These devices can be divided into those intended for professional or personal use. Professional use involves periodic monitoring with retrospective review of the data by a medical provider and personal use involves longer-term real-time use by the individual. There are several devices on the market that allow for 6-, 7-, and 14-day monitoring intervals. Additionally, most CGMs are intended to be used as an adjunct to traditional monitoring of capillary blood glucose monitors. The U.S Food and Drug Administration (FDA) has approved devices for use without the need for blood glucose testing for diabetes treatment decisions, including the FreeStyle Libre Flash Glucose Monitoring System, Freestyle Libre 2, Freestyle Libre 3 (Abbott Diabetes Care Inc., Alameda, CA) as well as the Dexcom G6 and Dexcom G7 CGM systems (Dexcom, Inc. San Diego, CA). The Freestyle Libre Flash Glucose Monitoring System was the first CGM system approved by the FDA that did not require calibration by the user. The Freestyle Libre 2 and Freestyle Libre 3 devices which received FDA approval in November 2022 and April 2023, respectively, are comparable to the predicate Freestyle Libre Flash but have additional features. Similarly, the Dexcom G7 which received FDA approval in September 2022, has some additional features that are not found in the predicate Dexcom G6 CGM system.

As noted above, short-term use devices are intended to be used periodically, and are usually dispensed by the treating provider who then collects, analyzes and interprets the resultant data in a retrospective manner.

Personal CGM devices involve long-term use, are usually purchased by or for the individual for whom it has been prescribed and are intended to be used continuously in real-time to help guide daily care. Periodic data downloading and analysis by the individuals and/or provider may also occur and provide additional data to guide care.

The FDA approved the Eversense implantable continuous interstitial glucose monitoring system on June 21, 2018, for continually measuring glucose levels in adults 18 years and older with diabetes for up to 90 days. Additional approval for use up to 180 days was granted on September 30, 2020. This device is implanted in the physician's office into the skin of the upper arm through a small incision. It is then removed when it expires and may be replaced with another sensor at a site on the contralateral arm to allow continued monitoring.

Meta-Analyses Data

The use of CGMs for the monitoring and treatment of type 1 diabetes has been the topic of many studies. These studies have investigated the use of these devices in several different populations, including children, individuals with difficulty with controlling their conditions, and pregnant women with diabetes. These studies have subsequently been subject to additional meta-analyses demonstrating significant benefits to (Benkhadra, 2017; Floyd, 2012; Gandhi, 2011; Langendam, 2012; Poolsup, 2013; Yeh, 2012).

With regard to individuals with type 2 diabetes specifically, the Gandhi study mentioned above included three RCTs that included subjects with type 2 diabetes. These studies involved heterogeneity with regard to inclusion of subjects who did and did not require insulin therapy. Their meta-analysis of the three trials indicated statistically significant reductions in HbA1c with CGM vs. self-monitoring blood glucose (SMBG). Likewise, the study by Poolsup previously described involved a meta-analysis of four trials including adults with type 2 diabetes. In their analysis, CGM appeared to result in improved HbA1c reductions compared to SMBG, with a pooled mean difference of -0.31% (p=0.04). These studies reported the use of different types of devices (for example, retrospective CGM vs. real-time CGM) and significant variability in frequency of CGM use.

Representative RCTs Addressing CGM for Type 1 Diabetes

Since the publication of the seminal article by the Juvenile Diabetes Research Foundation (JDRF) Continuous Glucose Monitoring Study Group (Tamborlane, 2008), a large number of studies have provided evidence demonstrating significant benefits to individuals with type 1 diabetes when treated with CGM. This study reported that when compared to the control group, the CGM group in this age group had significantly better results compared to the standard care group in regard to almost all measures of glycemic control, including: overall HbA1c change from baseline to 26 weeks (−0.71 to −0.35, p<0.001) improved, relative reduction in HbA1c of 10% or more (13% vs. 2%, p=0.003), number of subjects achieving target HbA1c goals less than 7.0% with no severe hypoglycemic events (15% vs. 3%, p=0.006), and higher percentage of time within normal blood glucose range (p<0.001). The data for the 8- to14-year-old age group demonstrated a significantly greater relative reduction in HbA1c of 10% or more (p=0.04) and a higher percentage of subjects achieving an HbA1c less than 7.0% (p=0.01). The 15- to 24-year-old group had no significant differences noted. The findings of this study suggest that CGM may provide benefit for adults over age 24 and, to a lesser degree, children, and adolescents under age 15. The authors note that the rate of sensor use between age groups may be related to the differences in clinical outcomes. The group with the least reported benefits, the 15-24 years-old, had only a 30% sensor use frequency. The group with the most benefit, those 25 years of age and older had the highest use of sensor frequency at 83%. The group with intermediate results, 8-14 years-old, had an intermediate frequency of use of 50%. The rate of parental supervision and support for CGM was greater for the 8-14 years age group than for the 15- to 24-year-old group, which may explain the higher rate of utilization and the significantly better results in younger children. The findings of this study suggest that significant benefits may be gained with CGM when a high level of compliance with therapy is achieved. It should be noted that this study population was composed of highly motivated individuals who measured their blood glucose levels 5 times a day or more and had a beginning HbA1c of 10% or less.

In an extension study of the study reported by Tamborlane, 214 of 219 (98%) control group subjects were followed for an additional 6 months and asked to use CGM daily (JDRF, 2010). This included 80 subjects who were at least 25 years old, 73 who were 15-24 years old, and 61 who were 8-14 years old. Among the 154 subjects with baseline HbA1c at least 7%, there was a significant decrease in HbA1c at 6 months after CGM use in the older age group (mean change in HbA1c, -0.4% ± 0.5%, p=0.003). There was a significant treatment group difference favoring the CGM group in mean HbA1c at 26 weeks adjusted for baseline values. The authors concluded that the weight of evidence suggests that CGM is beneficial for individuals with type 1 diabetes who have already achieved excellent control with HbA1c of less than 7.0% with SMBG.

Several studies have specifically focused on the use of CGM in pediatric populations. The results of the Diabetes Research in Children Network (DirecNet) Study Group RCT were published by Mauras in 2011. This study evaluated the use of CGM in the management of young children aged 4 to younger than 10 years with type 1 diabetes. In this study, 146 children were assigned to either CGM or usual care. At baseline, 30 children (42%) had an HbA1c of at least 8%. The primary outcome was reduction in HbA1c by at least 0.5% without the occurrence of severe hypoglycemia at 26 weeks. The authors reported that 19% in the CGM group and 28% in the usual care group (p=0.17) met this endpoint. Mean change in HbA1c, a secondary outcome, did not differ significantly between groups (-0.1 in each group, p=0.79).

An RCT published by Battelino (2011) involving 120 children and adults on intensive therapy for type 1 diabetes HbA1c < 7.5% were assigned to either SMBG with a masked CGM every second week for 5 days (n=58) or real-time CGM (n=62). The authors reported that the time per day spent in hypoglycemia was significantly shorter in the CGM group vs. the control group (mean ± standard deviation [SD] 0.48 ± 0.57 and 0.97 ± 1.55 h/day, respectively, p=0.03). HbA1c at 26 weeks was lower in the CGM group than in the control group (p=0.008). The time spent in the 70 to 180 mg/dL normoglycemia range was significantly longer in the CGM group vs. the control group (mean hours per day, 17.6 vs. 16.0, p=0.009). The authors concluded that CGM was associated with reduced time spent in hypoglycemia and a concomitant decrease in HbA1c in children and adults with type 1 diabetes.

Another RCT published by this group involved 153 children and adults with type 1 diabetes receiving regular care with an insulin pump and who had HbA1c between 7.5-9.5% (Battelino, 2012). Subjects were assigned to receive care with their insulin pump with a connected CGM device with the sensor either on or off for 6 months. Following the initial 6 months, participants underwent a 4 month-long washout period and then were crossed over to the other treatment arm for 6 months. The initial assignments included 77 subjects in the sensor-on group and 76 to the sensor-off group. At the end of the trial period, the mean difference in HbA1c was -0.43% in favor of the sensor-on arm (p<0.001). Following cessation of glucose sensing, HbA1c reverted to baseline levels. The authors reported that less time was spent with sensor glucose < 3.9 mmol/l during the sensor-on period than in the sensor-off period (19 vs. 31 min/day, p=0.009). The mean number of daily boluses increased in the sensor-on group (6.8 vs. 5.8, p<0.0001), together with the frequency of use of the temporary basal rate (0.75 vs. 0.26, p<0.0001) and manual insulin suspend (0.91 vs. 0.70, p<0.018) functions. No differences between groups were reported with regard to severe hypoglycemic events (p=0.40). The authors concluded that CGM was associated with decreased HbA1c levels and time spent in hypoglycemia in individuals with type 1 diabetes using insulin pump therapy. More frequent self-adjustments of insulin therapy may have contributed to these effects.

More recently, several studies have addressed the use of CGM in adult populations. Beck and colleagues (2017a) reported on the results of the DIAMOND RCT. This study included 158 adults with type 1 diabetes using multiple daily insulin injections and with HbA1c levels of 7.5% to 9.9%. All subjects were randomized in a 2:1 fashion to receive treatment with either CGM (n=105) or standard care (n=53). HbA1c level, the primary outcome measure, was measured in a centralized lab from baseline to 24 weeks. A total of 155 (98%) of subjects completed the study (n=102 for the CGM group [97%], n=53 for the control group [100%]). Median CGM use in the experimental group was 7 days a week at a 4, 12, and 24 weeks, with only 2 subjects discontinuing CGM use prior to 24 weeks. In the CGM group, mean HbA1c was reduced 1.1% at 12 weeks and 1.0% at 24 weeks. In the control group mean HbA1c reduction 0.5% and 0.4%, respectively (between group difference at 24 weeks, p<0.001). The adjusted difference in mean change in HbA1c level from baseline to 24 weeks in the CGM group was -0.6% (p<0.001). The median duration of hypoglycemia at a blood glucose concentration of < 70 mg/dL was 43 min/day in the CGM group vs. 80 min/day in the control group (p=0.002). Additional significant differences between groups at 24 months in favor of the CGM group were noted for glucose variability (coefficient of variation 36 vs. 42, p<0.001), minutes per day with blood glucose concentration within range (736 minutes vs. 650, p=0.005), and median duration of hypoglycemia at blood glucose concentration less than >180 mg/dL (638 minutes vs. 740, p=0.03). The occurrence of severe hypoglycemia events did not differ between groups, with two events reported in each group. The authors concluded that, "Among adults with type 1 diabetes who used multiple daily insulin injections, the use of CGM compared with usual care resulted in a greater decrease in HbA1c level during 24 weeks." They further commented that, "Further research is needed to assess longer-term effectiveness, as well as clinical outcomes and adverse effects."

Also in 2017, Lind and colleagues published the results of the GOLD trial. This RCT involved an open-label crossover randomized study design. The study involved 161 subjects with type 1 diabetes and HbA1c (HbA1c) of greater than or equal to 7.5% who were treated with multiple daily insulin injections. All subjects were assigned to receive their initial treatment with a CGM or standard care for a period of 26 weeks followed by a washout period of 17 weeks and then another 26 weeks with the alternate treatment. Complete data for analysis was available for a total of 142 subjects (88/2%). Mean HbA1c was 7.92% during the CGM phase and 8.35% during the control treatment phase (p<0.001). Overall mean use time during the CGM phase was 87.8% (range 86.5-91.9%). In subjects using the CGM greater than 70% if the time, HbA1c was reduced by 0.46% compared to no reduction in those using CGM less than 70% of the time. Mean self-measurement of blood glucose was performed 2.75 times a day in the CGM group vs. 3.66 times per day in the control group. The mean percentage of time in a hypoglycemic state (< 70 mg/dL) was 2.97% in the CGM phase vs. 4.79% in the control phase. A second lower hypoglycemic threshold for blood glucose concentration of < 54 mg/dL also reported, with the mean percentage of time below that threshold reported as 0.79% for the GICM phase vs. 1.89% for the control phase. Severe hypoglycemic events were reported in 1 subject in the CGM phase vs. 5 subjects in the control phase (p=ns). There were no significant differences between groups with regard to the rate of serious adverse events. The 19 subjects without full data available were younger, had significantly higher HbA1c and had a history of hypoglycemic events. The authors made similar conclusions those of the DIAMOND study:

> Among patients with inadequately controlled type 1 diabetes treated with multiple daily insulin injections, the use of continuous glucose monitoring compared with conventional treatment for 26 weeks resulted in lower HbA1c. Further research is needed to assess clinical outcomes and longer-term adverse effects.

The results from the DIAMOND and GOLD trials are supportive of the use of CGM in individuals with type 1 diabetes. However, it should be noted that the benefits were modest, with mean HbA1c reductions between 0.4 and 0.6% and showed no significant difference between CGM and standard care with regard to the incidence of severe hypoglycemic events. Additionally, it must be noted that these study results involved highly motivated and monitored subjects under the care of endocrinologists in the framework of a clinical trial.

Battelino (2017) reported the results of an unblinded, randomized, parallel, controlled trial involving children 8 to 18 years of age with type 1 diabetes being treated with insulin pump therapy. Subjects were assigned in a 1:1 fashion to treatment with the Medtronic 640G system with the predictive low glucose management (PLGM) either on (n=47) or off (n=49). The trial period was 2 weeks in duration. A significant difference between groups was noted with regard to the number of hypoglycemic events (glucose concentrations ≤ 65 mg/dL; ≥ 20 minutes long) with the PLGM ON group experiencing 4.4 episodes vs. 7.4 for the PLGM OFF group (p=0.008). Similar findings were reported when the data were stratified by day (2.9 vs. 4.6, respectively, p=0.022) and night (1.5 vs. 2.8, respectively, p=0.025). However, the number of hypoglycemic events below 50 mg/dL was not significantly different. The time spent below 65 mg/dL, 60 mg/dL, and 50 mg/dL was less in the PLGM ON group (p=0.0106, p=0.089, and p=0.0203, respectively). The time spent above 140 mg/dL was significantly higher in the PLGM ON group (p=0.0165), but time spent above 180 mg/dL and 250 mg/dL was not (p-value not provided). The time spent within range, 70-140 mg/dL was significantly shorter in the PLGM ON group (p=0.0387), but time spent within the 70-180 mg/dL range was not. Mean and median sensor glucose measurements, sensor glucose measurements at 7:00 AM, mean and median blood glucose measurements, blood glucose measurements at 7:00 AM, and morning ketones were not significantly different between groups. No device-related serious adverse events were reported. However, the device was replaced on three occasions, and multiple sensor-related problem were reported, mostly due to lost connectivity.

Abraham (2018) described an RCT involving pediatric subjects aged 8 to 20 years old with type 1 diabetes assigned to treatment with either standard sensor-augmented therapy or the MiniMed 640G system with predictive low glucose suspend (PLGS) feature. The low glucose threshold was set for 61 mg/mL for the duration of the study. Subjects were selected on the basis of having at least one hypoglycemic event (serum glucose < 3.5 mmol/L) or three episodes of being at risk of hypoglycemia (4.4 mmol/L) during a 2-week assessment period. All subjects were required to use their assigned device for a minimum 80% of the time and followed for 6 months following randomization. At the end of the study the low threshold group 18 subjects (21%) lost to follow-up and the 640G group had 6 subjects (7%) lost to follow-up. The intent-to-treat population included 154 subjects, 74 in the sensor-augmented therapy group and 80 in the 640G group. Both groups demonstrated significant reductions in time spent in hypoglycemia (sensor-augmented therapy group, 3% to 2.6%, p=0.03 vs. 640G group 2.8% to 1.4%, p<0.0001, respectively). The 640G group results were more significant vs. the sensor-augmented therapy group (p<0.0001). The low threshold suspend group did not have any significant reductions in time spent in daytime hypoglycemia

(2.5% vs. 2.3%, p=0.07), but did have significant nocturnal reductions (p=0.04). The 640G group had significant reductions in both day and nighttime hypoglycemia (day 2.4% vs. 1.3, p<0.001 and night 3.4% vs. 1.6%, p<0.0001, respectively). Compared to the sensor-augmented therapy group, the 640G group had significantly fewer hypoglycemic events (227 vs. 139, p<0.001). Interestingly, a significant increase in time with > 270 mg/dL was reported in both groups (p<0.0001 for both). No significant changes in HbA1c were noted in either group. The authors concluded that use of the 640G device with PLGS d feature reduced hypoglycemia without deterioration in glycemic control.

In 2018, Little and colleagues reported the results of the HypoCOMPaSS study, a 2 x 2 RCT comparing the following treatment methods: 1) MDI with self-monitoring of blood glucose, 2) MDI with self-monitoring of blood glucose and real-time CGM, 3) continuous insulin infusion with self-monitoring of blood glucose, and 4) continuous insulin infusion with self-monitoring of blood glucose and real-time CGM. Subjects all had type 1 diabetes and were aged 18 -74. The intervention period consisted of 24 weeks where subjects were treated per assignment, followed by reversion to routine care with additional data collection and visits at 12, 18 and 24 months. During the follow-up period, subjects were given the option to change their insulin delivery method and the CGM group was allowed continued use of the device while the self-monitoring of blood glucose group continued with that methodology. A total of 96 subjects were randomized and 76 (79%) completed the 24-month study period. The MDI group contained 50 subjects, with 39 (78%) completing the study period. Only 26% were still using this treatment method at end of the study. The insulin pump group began with 48 subjects, with 39 (81%) completing the study. A total of 68% were still using their pump at the end of the study. The CGM group involved 48 subjects, with 37 (77%) completing the study, and 30% were still using the devices at the end of the study. The self-monitoring of blood glucose group began with 48 subjects. It was not clear how many of these subjects completed the study from the study publication. No significant differences were noted between the daily injection and pump groups with regard to hypoglycemia awareness over the 24-month study period. Likewise, no differences were reported between the self-monitoring of blood glucose group and the CGM group with regard to hypoglycemia awareness, severe hypoglycemia or any secondary outcomes. Only 30% of CGM subjects continued to use their devices for the full 24 months. In the overall population, there was improvement in hypoglycemia awareness, sustained throughout the study period (Gold score 5.1 vs. 3.7, p<0.0001). Similar results were reported for the severe hypoglycemia rate (8.9 episodes/person-year vs. 0.4, (p<0.0001) and HbA1c (8.2 vs. 7.7; p=0.003). This study found no differences between the use of CGMs and serial monitoring of blood glucose, which warrants closer investigation.

Heinemann (2018) reported the results if a RCT evaluating the use of real-time CGM in subjects undergoing MDI therapy. This 6-month open label study involved 149 subjects who wore a masked CGM system for 28 days and were then assigned to 26 weeks of unmasked treatment with either a CGM (n=75) or continued self-monitoring (n=74). The latter group wore a masked CGM system during weeks 22-26. The mean number of hypoglycemic events per 28 days in the CGM group was reduced (10.8 to 3.5) but reductions among the self-monitoring groups were negligible (14.4 to 13.7) (p<0.0001). The incidence of hypoglycemic events decreased by 72% in the CGM group (incidence rate ratio, 0.28, p<0.0001).

As prospective cohort study involving 515 adult subjects with type 1 diabetes undergoing treatment with CGM and insulin pumps was published by Charleer (2018). The types of pumps and CGMs used were determined by the treating physician and involved most brands available on the European market at the time of the trial. Subjects were followed for 12 months and 417 (81%) of subjects used the CGM for the full study period. The authors reported that HbA1c decreased significantly from 7.7% to 7.4% at 12 months ($p<0.0001$). They also noted that subjects who started CGM therapy due to insufficient glycemic control had a greater decrease in HbA1c vs. subjects who had indications of hypoglycemia or pregnancy.

Laffel and others (2020) reported on the results of an RCT involving 153 subjects aged 14 to 24 years with type 1 diabetes assigned to treatment with a CGM (Dexcom G5, n=74) vs. serial blood glucose monitoring (n=79) for 26 weeks. Use of the CGM device fell from 82% to 68% of subjects using it at least 5 times a week, with 10 subjects (14%) not using it at all, including 3 dropouts. The control group wore a blinded CMG for 1 week prior to the 13-week visit and then again 2 weeks prior to the 26-week visit. In the CGM group, mean HbA1c concentrations changed from 8.9% at baseline to 8.5% at 26 weeks. For the control group mean HbA1c was 8.9% at baseline and 26 weeks (between-group comparison at 26 weeks $p=0.01$). Time in range (70-180 mg/dL) was significantly better in the CGM group vs. controls (37% to 43% vs. 36% to 35%, respectively, $p<0.001$). Time in hypoglycemia (< 70 and < 54 mg/dL) was also reported to be significantly improved in the CGM group ($p=0.2$ and $p=0.002$, respectively). Similarly, time in hyperglycemia (< 180, < 250< and < 300 mg/dL) was also significantly improved ($p=0.007$, $p<0.001$, and $p<0.001$ respectively). No significant differences were reported with regard to adverse events. The results of this study demonstrate good outcomes for adolescents using CGMs vs. manual blood glucose monitoring over the short term. However, the significant rate of non-use of the CGM is concerning, and in line with prior reports involving this age population.

Overall, the available RCT evidence addressing the use of CGM devices in individuals with type 1 diabetes is mixed but skewed to beneficial outcomes with the use of CGM devices. Data from meta-analyses supports this conclusion and indicates that the use of CGM results in improved glycemic control for adults with type 1 diabetes and for children with type 1 diabetes who used real-time CGM devices.

Use of CGMs for individuals with type 2 diabetes is less well studied but has been widely accepted as being standard of care for certain populations of individuals. One of the few well-conducted studies on this issue was reported on by Martens (2021). This RCT involved 175 subjects with type 2 diabetes with basal insulin assigned to management with either CGM (n=116) or standard blood glucose monitoring (n=59). The authors reported that at 8 months follow-up the mean HbA1c concentrations decreased significantly in the CGM group when compared to the blood monitoring group (9.1% to 8.0% in the CGM group vs. 9.0% to 8.4% in the blood monitoring group, $p=0.02$). Additionally, the mean percentage of time in the target glucose range (70 to 180 mg/dL) was 59% in the CGM group vs. 43% in the blood monitoring group ($p<0.001$). The mean percentage of time at greater than 250 mg/dL was also significantly improved in the CGM group (11% vs 27%, respectively; $p<0.001$).

Implantable Interstitial Glucose Monitors

Multiple well-designed trials have demonstrated the accuracy of implantable CGMs when compared to both blood glucose measurements and non-implantable CGMs (Aronson, 2019; Boscari, 2021a and 2021b; Christiansen, 2018 and 2019; Jafri, 2020; Sanchez, 2019). Additional studies have demonstrated significant impact of the Eversense device on HbA1c concentrations and the effectiveness of alerts for hypoglycemia (Irace , 2020; Kropff, 2017; Tweden, 2020). The rate of adverse events and durability of the sensors have also been investigated and shown to be within acceptable range (Deiss, 2019). A study by Renard (2021) demonstrated a significant decrease in time below range (< 55 mg/dL) as a result of Eversense use when compared to self-monitoring or non-implantable CGM use.

The results of these trials demonstrate reasonable accuracy relative to laboratory blood glucose measures, with results being within accepted standards. Additionally, the available data demonstrate acceptable long-term performance out to 180 days for the Eversense device. Use of this device has been accepted as equivalent to non-implantable devices in the most recent version of the ADA Standards of Care in Diabetes (2022).

Real-time CGM use in Individuals with Type 2 Diabetes

Real-time CGM devices utilize an interstitial glucose sensor device attached to the skin, which is linked to a monitoring device which constantly provides up-to-date glucose concentration data which can be read and utilized by the treated individual or their caregiver. Such devices also store data for analysis at a later date to evaluate trends.

In 2008, Yoo published the results of a prospective, open-label RCT involving 57 subjects with poorly controlled type 2 diabetes. Subjects were assigned to treatment with SMBG (n=28) vs. real-time CGM (rt-CGM) with the Guardian RT device (n=29). The CGM group underwent a 3-day period of real-time CGM once a month for a total of 3 months. Alarm thresholds were set for > 300 mg/dL for hyperglycemia and < 60 mg/dL for hypoglycemia, and subjects were instructed on what actions to take in the event of an alarm occurring. Following each completed rt-CGM period the CGM data was analyzed to clarify problem with the subject's diet and exercise habits. Based on that information, subjects received diet and lifestyle counseling from diabetes nurse educators. Control SMBG subjects also received monthly lifestyle counseling based on blood glucose values. Adjustments in oral hypoglycemic agents or insulin dosage were not permitted in either group during the study period. At the end of the study, the authors reported that only the CGM group had a significant improvement in body mass index (BMI; 25.0 ± 3.0 kg/m^2 to 24.3 ± 3.5 kg/m^2, p<0.008), but neither group had significant changes in waist circumference or lipid profiles. Both groups were reported to have had significant improvements in HbA1c concentrations (9.1% vs. 8.0%, p<0.001 in the CGM group, 8.7% vs. 8.3%, p=0.01 in the control group), with the CGM group having significantly greater improvement (p=0.004). The proportion of time with blood glucose concentrations > 250 mg/dL decreased from 17.8% to 8.98% in the CGM group over the study period (p=0.01). However, time spent between 80 and 250 mg/mL and < 60 mg/dL did not significantly change in this group (p=0.7 and p=0.1, respectively). The mean amplitude of glycemic excursions (MAGE) was reported to have decreased significantly in the CGM group (208.48 mg/dL vs. 163.32 mg/dL, p=0.004). Data for the control group regarding time with blood glucose concentrations > 250 mg/dL, time spent between 80 and 250 mg/mL, and < 60 mg/dL was not reported. Total exercise time per week was significantly increased in the CGM group vs. controls (188.2 min/week to 346.6 min/week vs. 191.5 min/week

to 235.0 min/week, respectively, p=0.02). No serious adverse events were reported for either group. The authors concluded that the use of rt-CGM successfully modified the subject's diet and exercise habits and helped improve glycemic control compared to SMBG.

Blackberry and others (2014) reported the results of a randomized controlled study involving 92 insulin-naive subjects with type 2 diabetes, assigned to either self-monitoring of blood glucose (SMBG; n=42) or SMBG plus short-term CGM (n=47). Subjects were prescribed glulisine for subjects with the high post-prandial hyperglycemia excursions. The authors reported no significant differences between groups with relation to the incidence of major hypoglycemia (2/89 vs. 0/82, p=0.17) or improvements in HbA1c (-2.7 vs. -2.4, p=0.31). However, they did report that more CGM subjects than SMBG subjects commenced use of glulisine (26/48 vs. 7/44; p<0.001), indicating increased recognition of post-prandial hyperglycemia.

A subsequent re-review of this report was conducted and published in a surveillance report in 2016. The conclusions found no grounds to alter the conclusions regarding CGM made in the 2012 report.

Sierra (2017) published a study involving claims data from 2816 subjects in a large U.S.-based health insurance database to evaluate the impact of professional continuous glucose monitoring in a population with type 2 diabetes. While the majority of their study focused on economic issues, they did report finding a significant difference-in-difference benefit to the use of professional CGM on HbA1c concentrations (-0.44%, p<0.001). However, while this change was statistically significant, its clinical value is unclear. Furthermore, the description of the results related to this finding were limited, and there were significant methodological flaws detailed in the study, including the retrospective nature of the study and uncertainty regarding the time proximity of the HbA1c measurements in relation to the relevant clinical time points.

Beck (2017b) conducted a prospective RCT involving 159 subjects with well-controlled type 2 diabetes assigned to routine care augmented by use of a personal CGM device vs. standard care (n=79 per group). The control group wore a blinded CGM throughout the 24-week study period. They reported that mean HbA1c levels at 12 weeks decreased significantly in both groups, but more so in the CGM group (-1% vs. 0.6%, p=0.005). Between 12 and 24 weeks, mean HbA1c level increased slightly in both groups, with no differences reported. At 24 weeks, the adjusted difference between groups in mean HbA1c change from baseline to 24 weeks was 0.3% (p=0.022). No differences were reported with regard to the prespecified secondary outcomes, including the proportions of participants with HbA1c levels below 7.0%, HbA1c levels below 7.5%, and relative reduction of at least 10%. The median CGM-measured time in the range of 70 to 180 mg/dL increased more in the CGM group than in the control group, from 802 minutes per day at baseline to 882 minutes per day at 24 weeks in the CGM group and from 794 to 836 minutes per day in the control group. No p-values were provided for this difference. No differences were reported between groups with regard to change in insulin dose or the incidence of severe hypoglycemia or ketoacidosis. The results of this study demonstrate that the use of CGM devices for individuals with type 2 diabetes may result in lower HbA1c concentrations.

Furler (2020) published a report of an open-label RCT involving 299 subjects with type 2 diabetes assigned to care with a flash CGM set to professional mode (n=149) vs. standard care (n=150). Subjects in the professional CGM

group were not able to view the CGM data and were asked to wear the device for 5-14 days every 3 months over a 12-month period to capture data. At the end of each recording period the data was downloaded by their healthcare professional and discussed with the subject. Control subjects wore the professional CGM device at baseline and 12 months only and the results were not discussed with them. There were no significant differences reported between groups with regard to the primary outcome measure, mean HbA1c at 12 months (-0.3% vs -0.5%, p=0.59). However, at 6 months there was a significant difference reported (8.1% vs. 8.6%, p=0.001). The mean percentage time in target range was significantly better in the CGM group (54.8% vs. 46.9%, p=0.0043). The authors reported this difference was more pronounced between 6 a.m. and midnight, with the CGM group having a 9.2% higher mean percent time within target range (p=0.0021). No differences between groups was reported for this measure for midnight to 6 a.m. (p=0.06). From baseline to 9 months CGM use fell to 78%. Mean between-group difference in HbA1c results did not change when device non-users were removed from the analysis. No significant changes in median number of non-insulin drugs used, subjects using insulin, or median total insulin dose were reported. The authors concluded that professional CGM use in individuals with type 2 diabetes did not improve HbA1c concentrations over 12 months. However, it did improve time in range at 12 months and HbA1c at 6 months. While the results suggest a potential benefit of professional CGM use in individuals with type 2 diabetes, the authors note that the time in range outcome at 12 months findings were "exploratory and need to be interpreted with caution, particularly in the context of an open label trial in which the primary outcome was negative".

Overall, the existing evidence addressing the use of CGM individuals with type 2 diabetes is weaker than that for individuals with type 1 diabetes. The available meta-analyses report significant variability in the literature with regard to the types of interventions investigated, the frequency of use, and populations involved. Although the meta-analyses available to date have found a statistically significant benefit of CGM in terms of glycemic control, the small number of RCTs and the variability among interventions makes it difficult to identify an optimal approach to CGM use or subgroup of individuals with type 2 diabetes who might benefit. Nonetheless, the data does indicate significant benefits for individuals with type 2 diabetes with regard to short-term HbA1c concentrations, time in range, lowered BMI, and recognition of post-prandial hypoglycemia. On the basis of these findings the use of CGMs in this population has become an accepted practice and is currently recommended by the American Diabetes Association (2022), and for all insulin-using individuals, regardless of diabetes type, by the American Association of Clinical Endocrinologists and American College of Endocrinology (Grunberger, 2018).

Flash-CGM use in Individuals with Type 2 Diabetes

Flash CGM devices (for example, FreeStyle Libre Flash Glucose Monitoring System, Abbott Laboratories, Abbott Park, Ill) utilize an interstitial glucose sensor device attached to the skin for up to 14 days. This sensor takes measurements every 15 minutes, which may be accessed in real-time by triggering a separate reader/scanner unit, which wirelessly links to the sensor. Such devices also store data for analysis at a later date to evaluate trends.

Vigersky (2012) and Ehrhardt (2011) reported the results of an RCT involving 100 subjects with type 2 diabetes not using prandial insulin. Subjects were assigned to 6 months of treatment with either intermittent use of a flash CGM device (FreeStyle Libre glucose monitoring system) for four 2-week cycles (2 weeks on/1 week off, n=50) vs. with SMBG (n=50). The reported mean decline from baseline in HbA1c in the CGM vs. the SMBG group was 1.0% vs.

0.5% at 12 weeks post-treatment initiation, 1.2% vs. 0.5% at 24 weeks, 0.8% vs. 0.5% at 38 weeks, and 0.8% vs. 0.2% at 1 year, respectively. Over the course of the study, the reduction in HbA1c was significantly greater than the SMBG group (p=0.04). After adjusting for potential confounding variables including age, sex, baseline therapy, and whether the individual started taking insulin during the study, the difference between groups over time remained statistically significant (p<0.001). It was noted that improvements in the CGM group occurred without a need for intensification of medical therapy, which was needed in the control group.

Bolinder (2016) described the results of a prospective unblinded RCT involving 241 subjects with type 1 diabetes who were assigned to treatment with either flash CGM (n=120) or SMBG (n=121) for 6 months. Mean time in hypoglycemia in the flash group decreased from 3.38 h/day at baseline to 2.03 h/day and from 3.44 h/day to 3.27 h/day in the control group (p<0.0001). The authors noted that this was a 38% reduction in time in hypoglycemia in the flash group. At 6 months, HbA1c concentrations in the flash group were essentially unchanged compared with the control group, and no device-related hypoglycemia or safety issues were reported.

Haak and others (2017a) reported the results of a prospective 6-month unblinded RCT involving 224 subjects with type 2 diabetes assigned to either SMBG (n=75) or treatment with flash glucose monitoring (n=149). Control SMBG subjects followed their routine care procedures and wore a blinded CGM device for the final 2 weeks of the study period. The flash CGM group used their device to manage their care in lieu of SMBG. A total of 139 CGM group subjects (93.2%) and 62 control subjects (82.7%) completed the study (89.7% overall). At 6 months, no differences between groups was reported with regard to HbA1c concentrations (p=0.82). In a pre-specified analysis, a significant difference in HbA1c concentrations was noted in subjects less than 65 years of age (p=0.03). In contrast, in subjects over 65, the opposite effect was reported, with the control group have a significantly lower HbA1c (p=0.008). Time spent in hypoglycemia, < 70 mg/dL, < 55 mg/dL and < 45mg/dL, were significantly shorter in the CGM group, with 43%, 53%, and 64% reduction reported, respectfully (p=0.0006, p=0.004, and p=0.0013 respectfully). Likewise nocturnal hypoglycemia decreased by 54% (p=0.0001) and daytime hypoglycemia decreased by 31% (p=0.0374). Frequency of events with blood glucose < 70 mg/dL, < 55 mg/dL, and < 45mg/dL reduced by 28%, 44%, and, 49% in the CGM group vs. controls, respectively (p=0.0164, p=0.0017, and p=0.0098, respectively). SMBG frequency reduced significantly in the CGM group, from a mean of 3.8 tests per day to 0.4 test per day. No change in SMGB frequency was reported in the control group. Average sensor scanning frequency, a measure of how frequently a subject checked their glucose concentration, was 8.4 times per day, twice the number of times the control group did SMBG measurements. However, there was no correlation between scanning frequency and reduced time in hypoglycemia of change in HbA1c. No differences were reported between groups with regard to total daily, basal, or bolus insulin doses. No serious adverse events related to the study device were reported. Adverse events were reported in 6 CGM group subjects related to sensor adhesive reactions, which were treated topically and resolved by the end of the study. The authors concluded that "Flash glucose-sensing technology use in type 2 diabetes with intensive insulin therapy results in no difference in HbA1c change and reduced hypoglycemia, thus offering a safe, effective replacement for SMBG."

An additional 6-month open-label extension study involving all 139 CGM group subjects from this study was published later in 2017 (Haak, 2017b). At the completion of the trial, time in hypoglycemia was reported to have decreased by 50% vs. baseline measurement 12 months prior (-0.7 hours, p=0.0002). Nocturnal hypoglycemia (<70

mg/dL) was reduced by 52% vs. baseline (2300 to 0600 hours, p=0.0002). No changes to time in range (70-180 md/dL) were reported. SMBG continued to decrease, with the final data reporting 0.2 tests per day and a scanning frequency of 7.1 times per day. No serious adverse events related to the study device were reported, but 9 subjects reported 16 sensor-related adverse events, which were treated topically and resolved by the end of the study. The authors concluded that the use of flash CGM in individuals with type 2 diabetes treated by intensive insulin therapy over 12 months was associated with a sustained reduction in hypoglycemia and safely and effectively replaced SMBG.

Al Hayek (2017) reported the results of a case series study on 47 adolescents (age 13-19) with type 1 diabetes who were treated with flash CGM for 3 months. The authors reported that compared to baseline measurements, significant improvement in HbA1c level (8.5% to 7.84%, p=0.008) and hypoglycemia (1.05 to 0.08, p=0.023) were seen at 3 months. In subjects undergoing MDI (n=29), significant improvement was noted for HbA1c level (p=0.014) and hypoglycemia (p=0.001). Similarly, in the subjects undergoing insulin pump treatment (n=18), no change was noted for HbA1c, but incidence of hypoglycemia deceased significantly (p=0.001).

In 2018 Saboo and others reported the results of a case series study involving 108 subjects with type 2 diabetes treated with flash CGM and followed for 14 days. As a result of flash CGM use, 98 subjects had therapy changes, and the remainder underwent diet and lifestyle modifications. Mean HbA1c decreased from 7.96% to 7.03% by the end of 15 days (no p-value provided). They reported that glycemic variability curves derived from the flash CGM devices helped in recognizing and treating masked or asymptomatic hypoglycemic events in this population.as well as graphically showed intervals of optimal and sub-optimal glycemia.

Dunn described a study using data from a registry of subjects using the Freestyle Libre device (2018). The analysis set involved 63.8 million sensor scans from 85,831 devices. The Freestyle Libre device allows the user to scan for glucose concentrations on demand, and the study investigated the association between scan rate and HbA1c, with estimated HbA1c concentrations being calculated based on mean glucose readings. They reported that the estimated HbA1c declined from 8.0% to 6.7%, as scan frequency increased (p<0.001). Time below 70.2 mg/dL, 55.8 mg/dL, and 45 mg/dL decreased by 15%, 40% and 49%, respectively (all p<0.001). Time above 180 mg/dL decreased from 10.4 to 5.7 h/day (p<0.001) while time in range increased from 12.0 to 16.8 h/day (p<0.001).

In 2020 Yaron and colleagues reported the results of an unblinded RCT involving 101 subjects with type 2 diabetes to 10 weeks of treatment with a flash glucose device (n=53) or standard care (n=48). Flash group subjects were asked to use the flash scanner every 8 hours and the data was downloaded every 2-4 weeks. During inpatient visits, data from the flash device (Flash group) and the standard blood glucose monitor (Control Group) was used to counsel subjects in self-care. In the ITT analysis the mean (SD) change in HbA1c was demonstrated to have decreased -0.82% in the Flash group vs. -0.33 in the control group (p=0.005). HbA1c reduction, with adjustment for HbA1c values at baseline, was -0.85% in the Flash group vs. -0.32% in the control group (p<0.0001). The frequency of hypoglycemic episodes was not significantly different between groups and no severe hypoglycemic or serious adverse events were reported.

Overall, the data regarding the impact of flash CGM devices for individuals with type 2 diabetes is indicative of significant benefits with regard to decreased HbA1c concentrations and decreased overall and nocturnal time in the hypoglycemic range.

CGM use by Pregnant Individuals with Diabetes

In 2013, Voormolen and others published a systematic review of the literature on CGM during pregnancy. The review involved 11 studies that met inclusion criteria involving a total of 534 subjects. Only 2 of the studies were RCTs. No meta-analysis was conducted, but they concluded that evidence is limited on the efficacy of CGM during pregnancy.

The largest RCT published to date investigating the use of CGM during pregnancy was published by Secher in 2013. This study involved 154 subjects assigned to either real-time CGM in addition to routine pregnancy care (n=79) or routine care (n=75). There were 123 women with type 1 diabetes and 31 with type 2 diabetes included. The CGM group used the CGM device for the 6 days prior to each of 5 study visits and were encouraged to use the devices continuously. Subjects in each group were instructed to perform 8 SMBG daily for 6 days before each study visit. Only 64% of participants in the CGM group were reported to have complied with the per-protocol use. No significant differences between groups were noted with regard to HbA1c, SMBG values, insulin dose, and hyper- and hypoglycemic events. Subjects with type 1 diabetes experienced a significantly greater number of hypoglycemic events vs. type 2 subjects, irrespective of treatment group. The authors reported 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 control group, with no difference between groups noted (p=0.19). No significant differences were reported between groups for the secondary outcome measures, which included prevalence of preterm delivery and the prevalence of severe neonatal hypoglycemia. Similar findings were reported for type 1 subjects, regardless of treatment group. The authors noted that the subjects had well-controlled diabetes at baseline, which might help explain the lack of impact of CGM on outcomes. Other factors potentially contributing to the negative findings include the intensive SMBG routine in both groups and the relatively low compliance rate (64%) in the CGM group with the instruction of use the CGM devices for 6 days before each of 5 study visits.

Murphy (2008) reported the results of an RCT involving 71 pregnant subjects with type 1 (n=46) or type 2 (n=25) diabetes assigned to treatment with either CGM (n=38) or usual care (n=33). CGM group subjects underwent 7 days of CGM at intervals of 4 to 6 weeks between 8 and 32 weeks of gestation and were advised to measure blood glucose levels at least 7 times a day. While mean HbA1c levels were lower in the CGIM group at all time points, these differences were not found to be statistically significant for most measurements. For the 32- to 36-week period, the CGM group had significantly better HbA1c levels vs. controls (p<0.007). No significant differences were reported between groups with regard to neonatal morbidity or mortality. Significant differences were noted in favor of the CGM group with regard to the mean birth weight (Standard deviation [SD] 0.9 vs. 1.6, p=0.5) and microsomia (SD 35 vs. 60, p=0.05). The authors reported that 13/37 (35%) of infants in the CGM group were large for gestational age vs. 18 of 30 (60%) in the control group. The OR 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).

In 2017, Feig and others reported the results of two unblinded RCT studies involving 325 women, 215 who were pregnant and 110 who were planning pregnancy, assigned to treatment with CGM with standard care or standard care alone. In the study involving pregnant subjects 108 were assigned to the CGM group and 107 to the control group. In the study with non-pregnant subjects, 53 were assigned to the CGM group and 75 to the control group. Pregnant subjects were followed through 34 weeks gestation and non-pregnant subjects were followed to 24 weeks or conception, whichever occurred first. The authors reported a small but significant benefit to CGM use in the pregnant subjects with regard to HbA1c concentrations (mean difference -0.19%, p=0.0207). No differences in HbA1c concentrations were noted in the non-pregnant cohort (p=0.20). In the pregnant cohort, those in the CGM group had significantly more time within target glycemic range (68% vs. 61%, p=0.0034) and reduced time above target range (27% vs. 32%, p=0.0279). No differences were reported with regard to episodes of severe hypoglycemic, hyperglycemic, or ketoacidosis events. The CGM group subjects did have fewer episodes of neonatal ICU visits > 24 hrs (0.48; 0.26 vs. 0.86, p=0.0157), fewer episodes of neonatal hypoglycemia requiring IV treatment (0.22 vs. 0.89, p=0.025), and total reduced hospital length of stay (3.1 vs. 4.0, p=0.0091). No significant differences between groups were reported with regard to serious adverse events in either cohort.

Voormolen (2018) reported a large RCT involving 300 women with type 1 diabetes (n=109), type 2 diabetes (n=82) or gestational diabetes (n=109) assigned to treatment with either retrospective CGM (n=147) or standard treatment (n=153). A retrospective CGM, iPro2 (Medtronic, Northridge, California) was used, which does not provide real-time access to CGM data during use. Readings are uploaded to a web-based program (Carelink iPro Therapy Management Software for Diabetes) and are presented graphically for analysis by a provider. Subjects allocated to the CGM were instructed to use the device for 5-7 days every 6 weeks and thereafter used to guide nutritional regimens and insulin therapy. After significant dropouts in the CGM group, 95 (66%) women from the CGM group and 144 (98%) women from the control group were included in the per-protocol analyses. Macrosomia occurred in 44 (31.0%) of the births in the CGM group and in 42 (28.4%) of the births in the control group (relative risk [RR], 1.09). The incidence of pregnancy-induced hypertension was noted in 19 (13.3%) subjects in the CGM group and 27 (18.4%) subjects in the control group (RR, 0.72; p=0.24). A statistically significant lower incidence of pre-eclampsia was reported in the CGM group, occurring in 5 (3.5%) subjects in the CGM group vs. 27 (18.4%) subjects in the control group (RR, 0.30). HELLP syndrome did not occur in the CGM group but occurred in 4 subjects in the control group (RR, 0.11). No significant differences between groups was reported with regard to onset of labor, route of delivery, mean birthweight, or infants large for gestational age or small for gestational age, or mean HbA1c concentrations. Subgroup analyses by type of diabetes did not reveal an association between CGM use and change in HbA1c levels. Subgroup analyses for type of diabetes showed no significant difference in rate of macrosomia for type 1, type 2, and gestational diabetes. Results of the per-protocol analysis for macrosomia were 32.6% vs. 28.5% (RR, 1.15). The authors concluded that intermittent use of retrospective CGM did not reduce the risk of macrosomia in women with type 1, type 2, and gestational diabetes requiring insulin therapy.

While neither of these studies found a statistically significant difference in their primary outcome, and the strength of evidence for the use of CGM for pregnant individuals is currently weak, such use of CGM has become the standard of care for this population.

Continuous Glucose Monitoring Devices and External Insulin Infusion Pumps

Automated Insulin Delivery Devices

The combined use of an insulin pump and CGM, either with separate devices or using a device that incorporates both functions, has become more prevalent in clinical practice for individuals with difficult to control diabetes. An evolution of this combination therapy has led to the development of "closed-loop" or "automated insulin delivery device" systems. Such devices combine the use of both an insulin pump and a CGM device, but are designed to work automatically without the involvement of the individual to monitor glucose concentrations and the administration of insulin.

The FDA has developed a guide to the three different types of automated insulin delivery devices, including:

- Open-loop systems
- Hybrid closed-loop systems
- Closed-loop systems

Many different types of automated insulin delivery devices are currently available or under development. Descriptions of each are provided in the beginning of the Rationale section above.

At this time, several automated insulin delivery systems have been approved by the FDA. The Medtronic MiniMed 530G and 630G are open-loop devices with a threshold suspend feature. The 630G may also be used as a stand-alone insulin pump device when not paired with CGM sensor and transmitter devices. The MiniMed 670G system is a hybrid closed-loop system that received FDA approval in September 2016. The MiniMed 770G system, another hybrid closed-loop system and evolution of the 670G, received FDA approval in November 2019. The MiniMed 780G system, a hybrid closed-loop system built upon the MiniMed 770G, received FDA approval in April 2023 and is indicated for use with the Guardian Sensor (3)/Guardian Link (3) Transmitter, or with the Guardian 4 sensor/Guardian 4 transmitter. The Tandem t:slim X2 insulin pump with Control-IQ technology, which when paired to the Dexcom G6 also functions as a hybrid closed-loop system, received FDA clearance in May 2020.

Automated insulin delivery systems integrate an external insulin pump and CGM device to potentially provide tighter glucose control than is possible with these two devices alone, or together but not integrated. Open-loop devices require manual adjustment of insulin administration rates based on CGM data as well as manual calculation and administration of pre-meal insulin bolus doses. Most such devices still require self-monitoring of blood glucose concentrations as well. Open-loop devices may include a low glucose suspend feature that suspends insulin delivery for a set period of time when the CGM device detects that glucose concentrations have reached a pre-set lower threshold. Some open-loop devices may go a step further and involve a "predictive" low glucose suspend feature. This feature uses a predictive algorithm to determine when glucose concentrations are headed towards a pre-set lower threshold and then decrease or suspend insulin delivery before the threshold is reached. Hybrid closed-loop devices eliminate the requirement of routine manual adjustment of pump administration rates, with the insulin pump and CGM devices working together to predict and calculate insulin dose requirements. However, these types of devices still require the manual calculation and administration of pre-meal insulin bolus doses, hence the

"hybrid" moniker. Finally, closed-loop systems are fully automated and require little intervention or involvement of the individual beyond routine system calibration.

Open-loop Threshold Suspend Devices

There are currently several well-designed and conducted studies addressing the use of the threshold suspend-type device. The first was reported by Bergenstal and others in 2013. This industry-sponsored trial involved 247 subjects who were randomly assigned to treatment with a combined insulin pump-continuous interstitial glucose monitor (CGM) system with or without a threshold suspend function (experimental group, n=121; controls n=126, respectively). Enrolled subjects were between 16 and 70 years old, had type 1 diabetes with glycated hemoglobin (HbA1c) levels between 5.8% and 10.0%, had been using an insulin pump for at least 6 months and experienced at least two nocturnal hypoglycemic events (≤ 65 mg/dL) lasting more than 20 minutes during a 2-week run-in phase. Subjects in the experimental group were required to use the suspend feature at a minimum between 10 PM and 8 AM daily for the duration of the 3-month long trial period. In this group, the threshold value was initially set at 70 mg/dL and could be adjusted to a value between 70 to 90 mg/dL.

The authors selected area under the curve (AUC) for nocturnal hypoglycemia events as the primary efficacy outcome measure. They calculated this by multiplying the magnitude (in milligrams per deciliter) and duration (in minutes) of each qualified hypoglycemic event. The primary safety outcome was the change in HbA1c levels at the end of the trial period. The mean AUC for nocturnal hypoglycemic events was 980 in the experimental group and 1568 in the control group, indicating a 37% reduction in nocturnal hypoglycemia events in the experimental group vs. controls (1.5 ± 1.0 vs. 2.2 ± 1.3 per patient week, $p<0.0001$). Combined daytime and nighttime hypoglycemic events were a secondary outcome measure, and the results likewise indicated a significant decrease in the intervention group (798 ± 965 mg per deciliter × minutes vs. 1164 ± 1590 mg per deciliter × minutes, $p<0.001$). In terms of overall event data, the intervention group experienced a mean of 3.3 hypoglycemic episodes per subject-week vs. 4.7 per subject-week in the control group ($p<0.001$). The mean number of times the suspend feature was activated in the experimental group per subject was 2.08 per 24-hour period and 0.77 each nocturnal measuring period. The mean sensor glucose value at the beginning of nocturnal events was the same for each group, 62.6 mg/dL. However, after 4 hours, the mean sensor glucose value was 162.3 mg/dL in the experimental group and 140.0 mg/dL in the control group. The authors reported that there was no statistically significant difference between groups with regard to change in HbA1c levels. No severe hypoglycemic events were reported in the experimental group vs. four in the control group. There were no deaths or serious device-related adverse events. It should be noted that this study involved the use of the Medtronic Paradigm Veo System which was commercialized in Europe in 2010 after receiving a CE mark.

The second randomized controlled trial (RCT), published by Ly in 2013, also used the Medtronic Paradigm Veo System. This study involved 95 subjects randomized to 6 months of treatment with either Veo system (n=46) or to insulin pump treatment alone (n=49). Subjects were aged 4 to 50 years old with type 1 diabetes, had used an insulin pump for at least 6 months, had an HbA1c level of 8.5% or less, and had impaired awareness of hypoglycemia. Impaired awareness of hypoglycemia was defined as a score of at least 4 on the modified Clarke questionnaire. The automated insulin suspension threshold was 60 mg/dL. The primary study outcome was 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). The authors noted that the baseline rate of severe and moderate hypoglycemia was significantly higher in the experimental group (129.6 vs 20.7 events per 100 subject-months). After 6 months, the frequency of moderate to severe hypoglycemic events per 100 subject-months was 34.2 in the control group vs. 9.6 in the experimental group. The authors reported the incidence rate ratio was 3.6 ($p<0.001$). No episodes of ketoacidosis or hyperglycemia with ketosis were reported in either group. The authors conducted a sensitivity analysis in subjects younger than 12 years (n=15 per group). They noted that the high baseline hypoglycemia rates could be explained in part by 2 outliers, and when those subjects 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 ($p=0.08$). 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% in the control group and -0.1% in the experimental group (p=not significant).

A retrospective analysis of the threshold suspend feature was reported by Agrawal (2015). This cohort study involved 20,973 subjects using the Medtronic Paradigm Veo System. Subjects were able to adjust the threshold suspend feature at their discretion and uploaded their pump and sensor data during a 40-week period. The authors compared data from 758,382 subject-days when the suspend feature was activated to the 166,791 subject-days when it was not. Overall, 70% of subjects (n=14,673) had the suspend feature activated 100% of the time. Conversely, 11% (n=2249) did not use that feature at all. The remaining subjects used the feature some unspecified portion of the time. The mean sensor threshold for the suspension feature was a glucose level of 62.8 mg/dL. According to the authors, there was a mean of 0.82 suspend events per subject-day on days when the feature was active. On days when the threshold suspend feature was on, sensor glucose values were reported to be 50 mg/dL or less 0.64% of the time vs. 2.1% of sensor glucose values 50 mg/dL or less on days when the feature was off. The reduction in hypoglycemia was greatest at night. They concluded that the use of an automated insulin delivery device with threshold suspend appeared to be associated with fewer and shorter hypoglycemic episodes. However, data describing the length and severity of hypoglycemic episodes was not fully discussed in this article.

In 2017, Gómez (2017) published the results of a cohort study evaluating the safety and efficacy of sensor-augmented pumps (SAPs) with low-threshold suspend feature in 11 subjects with hypoglycemia unawareness. All subjects used a combination system involving the Medtronic Paradigm 722 or Paradigm Veo pump connected to the MiniMed CGM device. The mean follow-up time was 47 ± 22.7 months; the authors reported that the total daily dose of insulin improved from 0.89 ± 0.39 U/kg to 0.67 ± 0.25 U/kg at the last visit ($p<0.001$). The mean number of basal doses increased from 4.7 ± 1.7 to 5.1 ± 1.4 at the last visit, and the number of boluses decreased from 5.1 ± 2.1 to 4.7 ± 1.5. Sensor use over the course of the study did not change significantly ($p=0.105$). The mean HbA1c concentrations improved from 8.1 ± 1.9% at baseline to 7.1 ± 0.8% at last follow-up ($p<0.001$). At baseline, only 17% of subjects had achieved HbA1c ≤ 7.0%, whereas at last follow-up 43% of subjects had achieved HbA1c ≤ 7.0% ($p<0.001$). Furthermore, at baseline 80% of subjects had had at least one episode of hypoglycemic awareness compared to 10.8% at last follow-up ($p<0.001$). Similarly, episodes of severe hypoglycemia decreased from 66.6% to 2.7% ($p<0.001$). This study demonstrated significant benefits to SAP therapy with a low glucose suspend threshold.

In 2019, Forlenza and colleagues reported the results of a prospective cohort study involving 105 subjects aged 7-13 years with type 1 diabetes treated with the MiniMed™ 670G system with SmartGuard™ technology in auto mode for 3 months. The reported that sensor glucose decreased 6.9 ± 17.2 mg/dL ($p<0.001$). They also reported significant benefits with regard to decreases in HbA1c ($p<0.001$), percentage of time in target glucose range ($p<0.001$), sensor glucose coefficient of variation ($p=0.009$). No episodes of severe hypoglycemia or diabetic ketoacidosis were reported.

The studies described above demonstrate a significant benefit to individuals who utilized threshold suspend-type devices, with significant reduction in severe hypoglycemic events.

Hybrid Closed-Loop Devices

Hybrid closed-loop systems are able to increase, decrease or stop insulin delivery automatically beyond pre-set infusion rates in response glucose concentration measurements by a paired CGM device. Most available devices have two modes, Manual and Automatic. In Manual mode, the device operates in a similar fashion to a low glucose suspend threshold device, stopping insulin delivery in response to low glucose measurements by the CGM. In Automatic mode, the device can automatically adjust basal insulin infusion rates to increase, decrease, or suspend delivery based on CGM data. In either mode, the user must manually deliver insulin during meals. This combination of an automatic basal insulin delivery mode combined with manual bolus insulin delivery prior to meals is referred to as a "hybrid closed-loop" system. The critical difference between threshold suspend-type devices and the hybrid closed-loop system is the ability to automatically vary basal insulin infusion rates based on CGM data. Such automated closed-loop control of insulin administration is a new tool in the treatment of diabetes.

A small observational case series (de Bock, 2016) involved 8 subjects with type 1 diabetes and was designed to evaluate a hybrid closed-loop algorithm. During the study, the investigators challenged the hybrid closed-loop system (MiniMed™ 670G) with hypoglycemic stimuli including exercise and an over-calibrated sensor set to read glucose concentrations as higher than actually present. The authors reported no overnight or exercise-induced hypoglycemia during use of the device. They noted that all recorded daytime hypoglycemia events were attributable to bolused post-prandial insulin in participants with aggressive carbohydrate factors. They concluded that algorithm refinement was needed in preparation for long-term outpatient trials.

Bergenstal et al. (2016) published the results of a pivotal safety study of the MiniMed 670G system in a research letter in the Journal of the American Medical Association. The study involved 123 subjects aged 14-75 years old who had type 1 diabetes mellitus for at least 2 years, HbA1c less than 10, and insulin pump therapy for a minimum of 6 months. All subjects wore the 670G system for approximately 3.5 months. The study involved three phases, including a 2-week run-in period, a 3-month at-home use period, and a 5-day/6-night hotel study. The run-in period involved familiarization of the participants to the device. The home-use period involved a 6-day period where the device was used in the non-auto mode, to allow for collection of insulin use and glucose sensor levels. During the home study phase, subjects were required to have a companion with them during the night to respond to sensor alarms as needed. Following that period, the participants were instructed to use the device in the closed-loop auto mode for the duration of the home phase. During this phase, the high sensor glucose alert was set at 300 mg/dL and

the low sensor glucose alert was set at 70 mg/dL. The target glucose was 120 mg/dL, although a temporary target of 150 mg/dL could be used in certain scenarios (for example, exercise). The hotel phase of the study occurred during the 3-month home study period, with at least 20 subjects participating in this phase each month. The purpose of this portion of the study was to stress the subjects with sustained daily exercise and unrestricted eating to monitor the device's response to significant physiological variations. The authors reported that no episodes of severe hypoglycemia or ketoacidosis were noted during the study period. There were 20 device-related adverse events reported during the study period, including skin irritation or rash (n=2), hyperglycemia (n=6), and severe hyperglycemia (defined as greater than 300 mg/dL, n=12). All events were resolved at home. The closed-loop auto function was used for a median of 87.2% of the study period. HbA1c levels improved from 7.4% at baseline to 6.9% at the completion of the study period. The daily dose of insulin changed from 47.5 U/d to 50.9 U/d, and mean weight changed from 76.9 kg to 77.6 kg. The percentage of sensor glucose values within the target range changed from 66.7% at baseline to 72.2% at study end. No statistical analysis was provided on these results. The authors reported that their study demonstrated that hybrid closed-loop automated insulin delivery was associated with few serious or device-related adverse events in individuals with type 1 diabetes. They noted, however, that their study had several limitations, including a lack of a control group, restriction to relatively healthy and well-controlled subjects, and a relatively short follow-up. The authors caution that this study's design was descriptive, and its purpose was limited to the evaluation of the safe use of the 670G AutoMode function. This study (IDE G140167) was not designed to determine the effectiveness of the device compared to conventional methods such as manual daily insulin injections or non-automated insulin pump therapy.

Garg and colleagues (2017) published the results of an open-label safety study of the MiniMed 670G system involving 124 subjects (30 adolescents aged 14-21 years old and 94 adults). All subjects underwent a 2-week in-home run-in phase using the 670G in open-loop mode followed by a 3-month hybrid closed-loop phase. During the hybrid closed-loop phase, all subjects underwent a 6 day/5-night supervised hotel stay that included a 24-hour blood sampling period to compare glucose sensor measurements to lab-based venous blood glucose measurements. The authors reported that sensor glucose readings during the hybrid closed-loop phase indicated that use of the 670G appeared to mitigate hyper- and hypoglycemia events in both the adolescent and adult groups. The mean in-target glucose sensor reading in the adolescent group increased from 60.4% to 67.2% between the run-in to the hybrid closed-loop phase ($p<0.001$). For the adult group, the mean in-target glucose sensor reading went from 68.8% to 73.8% ($p<0.001$). Similarly, time with glucose sensor readings of > 180 mg/dL decreased from 35.3% to 30.0% in the adolescent group ($p<0.001$) and 24.9% to 22.8% in the adult group ($p<0.01045$). The mean time with sensor glucose readings <70 mg/dL decreased from 4.3% to 2.8% in the adolescent group ($p<0.000928$) and 6.4% to 3.4% ($p<0.001$) in the adult group. HbA1c concentrations decreased from a mean of 7.7% at baseline to 7.1% ($p<0.001$) at the end of the 3-month hybrid closed-loop phase in the adolescent group and from 7.3% to 6.8% ($p<0.001$) in the adult group during the same time frame. The percent nighttime sensor glucose readings > 180 mg/dL decreased from 30.3% to 25.6% ($p<0.001$) in the adolescent group and 25.8% to 20.4% ($p<0.001$) in the adult group. Similarly, mean nighttime sensor glucose readings < 50 mg/dL decreased from 1.3% to 0.6% in the adolescent group ($p<0.001$) and 1.1 to 0.7% ($p<0.001$) in the adult group. These results demonstrated that within the study population, the hybrid closed-loop system was both safe and provided significantly better blood glucose control over treatment with an open-loop device.

A subset analysis of the Garg 2017 study involving 31 adolescent and young adult subjects aged 14-26 years old was reported by Messer in 2018. The results included a significant improvement in HbA1c (0.75 ± 0.69%, p<0.0001). Total daily dose of insulin did not change significantly (58.6 units/day vs. 60.3, p=0.49). The carbohydrate to insulin (C:I) ratio were more aggressive for all meals with 670G compared with baseline open loop treatment, and decreased from 8.9 at baseline to 7.6 at 3 months (p<0.001). Overall time spent in therapeutic range (70-190 mg/dL) significantly increased with 670G use (55.3% to 69% at 3 months, p<0.001). When comparing time in range between the 670G in auto mode vs. manual mode, the time spent in range was reported to be significantly improved while in auto mode (71.5% vs. 57.4% at 3 months, p<0.005). However, use of auto mode decreased over time, with 87% use in the first 7 days to 71.8% at the end of 3 months. Linear regression analysis demonstrated a correlation with auto mode and time in range (r^2=0.19, p<0.0001).

The FDA's summary of safety and effectiveness data (SSED) for the MiniMed 670G system includes a description of the pivotal study described above (G140167), as well as a smaller Guardian CGM sensor performance study (G140053). The latter study was intended to determine the accuracy and precision of the Guardian sensor CGM component of the 670G device in 93 subjects with type I or type II diabetes mellitus between the ages of 14-75 years. Of this subject pool, 82 completed the study. This prospective, single-sample correlational study did not involve a control group. All subjects wore the Guardian sensor for a 7-day training period followed by a 7-day study period. Subjects were randomized to one of two groups that determined when they participated in the in-clinic frequent sample testing; a day cohort (hours 1-12) and an evening cohort (hours 12-24). There were five adverse events reported during the study, all which resolved without residual sequelae, including gastroenteritis, worsening of benign prostatic hypertrophy, rash at the IV site, upper respiratory symptoms, and a skin blister from skin tac used under tape. No data were presented regarding the impact of the use of the Guardian sensor on diabetes-related health outcomes.

Nimri (2017) published the results of a small single-blind randomized controlled crossover trial involving 75 subjects with type 1 diabetes (25 adults and 50 children and adolescents). Subjects were assigned to a 4-night monitoring period with either the MD-Logic Artificial Pancreas hybrid closed-loop device or control therapy with an SAP. The MD-Logic System is composed of a MiniMed® Veo™ (the marketing name for the 670G in Europe) combined insulin pump and CGM device, Enlite® glucose sensors, CONTOUR® LINK blood glucose meter, and a PC-based control algorithm. Following a training period, subjects underwent a 4-day period of nocturnal testing with their assigned device. After a 10-day washout period, the subjects underwent a second 4-day nocturnal testing period with the alternate device. The authors reported that the intent-to-treat analysis demonstrated that percentage of time spent with sensor glucose < 70 mg/dL was significantly lower in the hybrid closed-loop group vs. the SAP group (2.07% vs. 2.6%, p=0.004). Likewise, the percentage of time spent within normal range (90-140 mg/dL) was significantly greater in the hybrid closed-loop group vs. controls (75% vs. 50%, p=0.008). The per-protocol analysis showed that the percentage of time spent with sensor glucose < 70 mg/dL in the hybrid closed-loop group was approximately half of controls (0.67% vs. 1.43%, p=0.005). The authors concluded that this study demonstrated the safety and efficacy of the MD-Logic system for overnight use in children and adults. However, additional investigation with larger populations is warranted to further understand the benefits of this system.

A randomized open-label crossover trial investigating the use of CGMs in adult subjects with type 1 diabetes with impaired awareness of hypoglycemia (Gold score ≥ 4) was published by van Beers in 2017. In this study, 52 CGM-naive subjects were assigned to 16 weeks of treatment with CGM with the MiniMed Veo followed by 12 weeks of washout and then 16 weeks of self-monitoring of blood glucose as a control, or to the same treatments in reverse order (n=26 in each group). A masked CGM was worn by subjects during the control period. The authors reported that the percent time spent in a normoglycemic state was greater in the CGM trial period vs. the control period (65% vs. 55.4%, respectively, p<0.0001). The number of severe hypoglycemic events was significantly lower in the CGM trial period vs. the control period (14 vs. 33, respectively, p=0.033). No differences were noted with regard to the number of subjects in each trial experiencing severe hypoglycemic events resulting in seizure or coma (n=4). The number of subjects experiencing one of more severe hypoglycemic events was 10 in the CGM trials vs. 18 in the control trials (odds ratio [OR], 0.45, p=0.018). No significant differences between trial groups were noted with regard to mean HbA1c change, self-reported hypoglycemia awareness scores, or QOL measures. No serious adverse events related to the study intervention were reported.

Forlenza (2018) reported on a randomized, cross-over controlled study involving 103 subjects with type 1 diabetes assigned to treatment with a Control-IQ System, a hybrid closed-loop system comprised of the Tandem Diabetes Care t:slimx2 insulin pump (Tandem Diabetes Care, San Diego, CA) with the Basal-IQ PLGS function and the Dexcom G5 CGM device (Dexcom, San Diego, CA). The first group had the PLGS function activated (PLGS group) and the second group had the PLGS deactivated ('SAP' group). In the latter group, the system activated the suspend feature once a preset low threshold was passed, as opposed to having the system calculate and predict when that would occur and intervene sooner. Subjects spent 3 weeks in each group of the trial for a total of 6 weeks. The median time < 70 mg/dL was significantly reduced in the PLGS group, from 3.6% to 2.6% vs. 3.6% to 3.2% in the SAP arm. This represented a 31% reduction in time < 70 mg/dL (p<0.001). Similar results were reported for time < 60 mg/dL (p<0.001), time < 54 mg/dL (p<0.001), and time < 50 mg/dL (p=0.02). The frequency of CGM-defined hypoglycemic events was also significantly lower in the PLGS group (p<0.001). During hypoglycemic events, mean time < 54 mg/dL was 41.0 min in the PLGS group vs. 47.6 min in the SAP group. Mean time in range 70–180 mg/dL increased in the PLGS group vs. the SAP group (64% at baseline, 65% with PLGS, and 63% with SAP; p<0.001). The percent time > 180 mg/dL was not significantly different between groups (p=0.12) but was significant for > 250 m/dL (p=0.008). No significant differences between groups was noted with regard to adverse events. The authors concluded that the hybrid closed-loop system composed of the Tandem t:slim X2 with Basal-IQ and the Dexcom G5 CGM significantly reduced hypoglycemia without rebound hyperglycemia.

Brown and colleagues published another RCT in 2019 involving 168 subjects treated in the community setting for 6 months with either the Control-IQ System (n=112) or control therapy with an SAP (n=56), which varied by subject depending upon whether or not they had existing devices. The mean percentage of time within the target glucose range increased in the hybrid closed-loop group vs. the control (61 ± 17% at baseline to 71 ± 12% at 6 months, and 59 ± 14% at baseline and unchanged at 6 months respectively, p<0.001). Percentage of time with glucose level > 180 mg per deciliter (36% to 27% for the hybrid closed-loop group vs. unchanged for controls), mean glucose level (166 mg/dL to 156 mg/dL vs. 169 mg/dL to 170 mg/dL, respectively), HbA1c (7.4% to 7.06% vs. 7.4% to 7.39%, respectively), and percentage of time that the glucose level < 70 mg per deciliter (3.58% to 1.58% vs. 2.84% to 2.25%, respectively) or < 54 mg per deciliter (0.9% to 0.29% vs. 0.56% to 0.35%, respectively) were all

significantly improved in the hybrid closed-loop group vs. controls (p<0.001, p=0.001, p<0.001, and p=0.02, respectively). The mean adjusted difference in glycated hemoglobin level after 6 months was -0.33 percentage points (p=0.001). The median percentage of time that the system was in closed-loop mode was 90% over 6 months. The authors reported no serious hypoglycemic events occurred in either group; but one episode of diabetic ketoacidosis occurred in the closed-loop group.

Isganaitis (2021) published a prespecified subanalysis of 63 subjects aged 14-24 years old who participated in the trial published by Brown described above. In this population, the time in range increased by 13% with the Control-IQ device vs. decreased by 1% with control treatment (p<0.001). This largely was due to a significant reduction in time spent > 180 mg/dL (p<0.001). Time spent < 70 mg/dL was significantly decreased in the hybrid closed-loop group vs. the control group (1.6% vs. 0.3%, p=0.002). Average use of the Control-IQ device was 89% over the 6-month trial period. Mean adjusted difference in HbA1c at the completion of the trial was 0.30% in the hybrid closed-loop group vs. controls (p=0.13). There was one adverse event in the form of diabetic ketoacidosis reported in the hybrid closed-loop group.

A continuation study of the same trial reported on 109 subjects from the hybrid closed-loop group randomly assigned to either continued management for 3 months with either the Control-IQ System (n=54) or management with a CGM with predictive low-glucose suspend function (n=55) (Brown, 2021). Mean time in range (70-180 mg/dL) at the completion of the initial trial was 71.1%. At the completion of the 13-week extension study the hybrid closed-loop group time in range was 67.6 % vs. 70.0% in the control group (p<0.001). Mean HbA1c was 7.05% at the start of this study and 7.18% at 13 weeks in the hybrid closed-loop group and 7.35% in the control group (p<0.0035). Time spent > 180 mg/dL was lower in the hybrid closed-loop group compared to the control group (p<0.001). Time spent < 54 mg/dL was similar between groups (p=0.41). HbA1c concentrations at 13 weeks was lower for the hybrid closed-loop group vs. the control group (7.2% vs. 7.5%, p=0.0035). There were no severe hypoglycemia or diabetic ketoacidosis events in either group.

The same group published the results of an open-label RCT involving 101 subjects aged 6 to 13 years randomized in a 3:1 fashion to treatment with the Control-IQ System (n=78) or open loop system, with or without low glucose suspend feature (n=23) (Breton, 2020). The trial lasted for 16 weeks. In the control group, 15/23 subjects used the Tandem t:slim X2 insulin pump without Control-IQ Technology and the Dexcom G6 CGM. It is not clear what devices the remainder of the control subjects utilized. Hybrid-closed-loop subjects had more unscheduled visits vs. control subjects (9 vs. 1, no p-value provided). Device problems were encountered 29 times in the hybrid closed-loop group. No data were reported on device problems in the control group. Mean percentage of time within the target range (70-180 mg/dL) increased from 57 ± 17% at baseline to 67 ± 13% at 16 weeks in the hybrid closed-loop group and 51 ± 16% to 55 ± 13% in the control group (p<0.001 for between group difference). Mean percentage time within target range during daytime hours (6 a.m. to midnight) was 63% in the hybrid group vs. 56% in the control group. During night hours (midnight to 6 a.m.) mean percentage time within target range was 80% vs. 54%, respectively. The change in percent time < 70 mg/dL from baseline was -0.11 ± 1.07% and 0.56 ± 1.05%, respectively. No p-values were provided for either result. Change in HbA1c from baseline was -0.59 ± 0.69 and -0.31 ±. 057, respectively (p=0.08). The target of HbA1c < 7 was achieved in 51% of hybrid closed-loop subjects vs. 18% in control subjects at 16 weeks (no p-values provided). No significant differences between groups

were reported with regard to daily insulin use per kilogram of body weight. Similarly, no significant differences between groups were reported with regard to adverse events, with 15 (19%) of subjects in the control group experiencing adverse events vs. 2 (9%) of control subjects (p=0.5). No instances of severe hypoglycemia or diabetic ketoacidosis were reported. The median number of hyperglycemic events was significantly lower in the hybrid closed-loop group vs. control group (3.0 vs. 5.6, p=0.001). The authors concluded that use of a hybrid closed-loop system improved time within range when compared to sensor augmented pump therapy in children with type 1 diabetes. This conclusion appears to be accurate.

Kanapka (2021) published the results of a 12-week extension study involving the subjects from the Breton study in which all subjects were treated with the Control-IQ device. In the group who were originally controls in the Breton study, the mean percentage of time in range (70-180 mg/dL) with the Control-IQ device increased from 55% to 65% (p<0.001). Time spent > 70% was achieved by 36% of the original control subjects. Time spent <5 4 mg/dL was reported to be < 1% in the extension phase vs. 14% when receiving the control treatment in the original study (p=0.03). In the subjects who continued to use the Control-IQ device, mean time in range increased from 53% at their original study baseline to 66% through the 12 weeks of the extension period. No episodes of diabetic ketoacidosis or severe hypoglycemia occurred in either cohort.

Sherr (2020) reported on the results of a cohort study of 36 subjects using a hybrid closed-loop system (Omnipod Horizon™ Automated Glucose Control System) in an experimental residential setting for 96 hours following a week of standard therapy. Subjects had HbA1c < 10.0% and were using insulin pump therapy or multiple daily injections. The study included children (age 8-11, n=14), adolescents (age 12-16, n=10) and adults (age 19-48, n=10). Percentage time ≥ 250 mg/dL while in the closed-loop phase reduced 1.6-, 3.4-, and 2.0-fold per respective age group vs. the standard care period (p= 0.1, p=0.02, and p=0.03, respectively). The percentage of time < 70 mg/dL during closed-loop phase was 1.9%, 2.5%, and 2.2%, which was reported to be a statistically significant decrease in the adult subgroup vs. standard care (p=0.005, p=0.3, and p=0.3). The percentage time between 70-180 mg/dL increased during the closed-loop phase vs. standard care and reached significance for adolescents and children (79.0% vs. 60.6%, p=0.01; 69.2% vs. 54.9%, p=0.003, respectively). The authors concluded that the Omnipod hybrid closed-loop device was safe and performed well over 5 days and 4 nights.

Ekhlaspour and colleagues (2019) reported the results of an RCT involving 48 children with type 1 diabetes aged 6 to 18 years who were attending a ski camp for children with diabetes. All subjects were randomly assigned to treatment with a standard open-loop sensor-augmented system with the predictive low glucose suspend feature turned off (n=24) vs. treatment with a hybrid closed-loop system (Tandem t:slim X2 insulin pump without Control-IQ Technology/Dexcom G6 CGM hybrid closed-loop, n=24). The study was conducted in two sequential phases, the first involving adolescents aged 13-18 years (n=24), and the second children ages 6-12 years (n=24). Subjects in each phase were stratified into treatment with the open- and hybrid closed-loop devices on a 1:1 basis. All subjects were also required to wear a Dexcom 5G CGM device and Fitbit Charge activity tracker which were tracked in real-time by study investigators. Subjects were followed for 2 days of the camp during which they were managed with their assigned device. Subjects in the open-loop control group used their usual system which involved a variety of devices. Subjects with a recent history of hypoglycemia were excluded. No significant adverse events were reported in either phase of the trial. Use of the hybrid closed-loop system was associated with a significant

increase in percent time-in-range (70–180 mg/dL) vs. the control group over the entire camp duration (12%, or ~3 hours, 66.4 ± 16.4 vs. 53.9 ± 24.8%, p=0.010). The authors reported that this difference was more evident during nighttime (28%, 78.6 ± 20.3 vs. 50.9 ± 34.2%, p=0.001). The hybrid closed-loop group had significantly lower mean glucose concentrations (161 ± 30 vs. 177 ± 37 mg/dL, p=0.023) and the reduction in average nighttime glucose was even more significant (143 ± 36 vs. 175 ± 53 mg/dL, p=0.005). No difference between groups was reported for the average time in hypoglycemia (< 70 mg/dL, 2% [0.5–3.8] vs 0.8% [0–3.7], respectively, p=ns). Use of the hybrid closed-loop system was associated with a 15% reduction in time spent with hyperglycemia (> 180 mg/dL, 31.4 ± 17.6% vs. 43 ± 24.5%, p=0.015), which was more than doubled during nighttime monitoring (18.2 ± 21.4% vs. 44.5 ± 36.9%, p=0.001). The incidence of significant hyperglycemia (> 250 mg/dL) was not significantly different between groups, nor was the mean total daily amount of insulin. The authors concluded that the use of the Control-IQ system improved glycemic control and safely reduced exposure to hyperglycemia relative to sensor augmented pumps in pediatric patients with T1D during prolonged intensive winter sports. While these findings may be true in this study population, whether or not similar findings in larger, less-well controlled subjects, especially those with recent hypoglycemic events and subjects doing different types of activities is unclear.

McAuley (2020) reported the results of an RCT involving 120 subjects with type 1 diabetes receiving treatment with MDI or insulin pump without CGM who were assigned to undergo 26 weeks of treatment with the MiniMed 670G (n=61) vs. their usual care (n=59). Time in range (70-180 mg/dL) for the 670G group increased from 55% to 70%, vs. the control group which remained unchanged (p<0.0001). HbA1c was lower in the 670G group vs. controls at study completion (7% vs. 7.4%, respectively; p<0.0001). Total daily insulin dose did not change over the course of the study in either group, and no between-group differences were reported. Seventeen (9 device-related) serious adverse events were reported in the 670G group vs. 13 in the control group.

Collyns (2021) reported the results of a randomized, open-label, two-sequence crossover study involving 59 subjects aged 7-80 years with type 1 diabetes and assigned to treatment with the MiniMed 670G in automatic mode vs. 670G in manual mode (sensor-augmented pump therapy with predictive low glucose function). Each phase was 4 weeks in duration, preceded by a 2- to 4-week run-in and separated by a 2-week washout. The authors reported time in target range (70-180 mg/dL) was significantly better in the automatic vs. manual group (70.41% vs. 57.9%, p<0.001). This improvement was noted to be greater overnight (18.8%, p<0.001). All age-groups demonstrated improvement, with adolescents (14-21 years) having the largest improvement (14.4%). Mean sensor glucose improved significantly in the automatic group (9.3 mmol/L to 8.5 mmol/L, p<0.001). However, mean sensor glucose was worse in the manual group (9.3 mmol/L to 9.5 mmol/L, p<0.001). Time in range was reported to be optimal when the algorithm set point was 5.6 mmol/L vs. 6.7 mmol/L (72.0% vs. 64.6%, respectively). During the trial period, the 670G's automatic mode was active 96.4% of the time and the percentage of hypoglycemia (< 3.9 mmol/L) improved to 2.1% (p=0.034) in the automatic group. The total number of adverse events was similar between the 670G group and controls (19 vs. 18), with five adverse events deemed to be possibly or probably related to the device.

Breton (2021) reported the results of a retrospective analysis of 9451 subjects ≥ 6 years of age who had used the Control-IQ System for at least 12 months in addition to a minimum of 2 weeks of ≥ 75% CGM data prior to use of the Control-IQ. The population included 83% of subjects with type 1 diabetes, 4% with type 2 and 14% type not

reported. The median percent time using the Control-IQ system in automated mode was 94.2%, with no significant changes over the trial period. A total of 9010 subjects (96.8%) had ≥ 75% of their CGM data available for comparison to the Control-IQ data. The authors reported that median percent time in range (70-180 mg/dL) was 63.6 at baseline vs. 73.6% at 12 months (p<0.001). The median percent time < 70 mg/dL remained consistent at ~1%. However, median percent time < 54 mg/dL statistically increased from 0.1% to 0.15%. The authors reported that most of these improvements for type 1 subjects were driven by significant increases in time in range at night, with a median > 90% between 4 and 7 AM. In the type 2 subjects, the improvements over baseline were similar throughout the day, with a peak > 90% by 4 AM.

Messer (2021) reported the results of a prospective case series study involving 191 subjects 6-17 years of age treated with the Control-IQ System. The percent time in range (70-180 mg/dL) improved from 57% to 66% at 6 months (p<0.001), and the proportion of subjects reaching the time in range target (> 70%) doubled from 23.5% to 46.7% at 6 months (p<0.001). Use of the Sleep Activity feature, which narrows the algorithm target range to 112.5-120 mg/dL, increased throughout the first 6 months, indicating that it was used for more hours per night, on average, across time (p<0.001). The authors reported that subjects with higher baseline HbA1c experienced the most substantial improvements in glycemic control. Percent of time using the Control-IQ feature was 86.4% at 6 months, and < 4% of the cohort discontinued use.

Several additional studies involving other hybrid closed-loop devices have been published (Abraham, 2016; Anderson, 2016; Bally, 2017; Benhamou, 2018; Brown, 2015; Carlson, 2022; DeBoer, 2017; Del Favero, 2015; Kovatchev, 2014, 2017; Leelaranthna, 2014; Ly, 2014; Nimri, 2014a, 2014b; Pinsker, 2016; Sharifi, 2016; Stewart, 2016; Tauschmann, 2016a, 2016b, 2016c, 2018). As with the studies described above, these studies also demonstrate improved control of glucose concentrations with fewer hypoglycemic events with a hybrid closed-loop delivery system.

At this time, the data demonstrates an incremental benefit of automated hybrid closed-loop control of insulin administration compared to other treatment methods. Additionally, expert clinical opinion supports the use of these devices in light of the potential significant benefits available to the most at-risk individuals with type 1 diabetes.

Closed-Loop Devices

At this time, there are no fully closed-loop devices with FDA approval available on the market in the U.S., although several are under investigation. Forlenza (2016) published the results of a small RCT involving 14 subjects randomized to treatment with either closed-loop treatment with the Medtronic ePID (external physiological insulin delivery) 2.0 controller vs. MDI therapy with blinded CGM (n=7 in each group) for a 72-hour period. The results indicated that mean serum glucose values were significantly lower in the closed-loop group vs. the controls (111 mg/dL vs. 130 mg/dL, p=0.003). This was achieved without increased risk of hypoglycemia, as demonstrated by the percentage of time < 70 mg/dL being lower in the closed-loop group vs. controls (1.9% vs. 4.8%, p=0.46). While the authors concluded that their results suggest that closed-loop therapy is superior to conventional therapy in maintaining euglycemia without increased hypoglycemia, additional investigation is warranted in larger studies.

Another small RCT published by Thabit (2017) involved 40 adult subjects with type 2 diabetes assigned to a 72-hour treatment period with either closed-loop treatment with the Florence D2W-T2 automated system (using a model-predictive control algorithm to direct subcutaneous delivery of rapid-acting insulin analogue without meal-time insulin boluses) or standard of care with subcutaneous insulin therapy. The Florence D2W-T2 is composed of a tablet computer-based control algorithm linked to an Abbott Freestyle Navigator II CGM and a Sooil DANA R Diabecare insulin pump. In this study, the proportion of time spent in target sensor glucose range was significantly higher in the closed-loop group vs. the control group (59.8% vs. 38.1%, p=0.004). The proportion of time spent with glucose concentrations >10.0 mmol/L was significantly lower in the closed-loop group vs. controls (30.1 vs. 49.1, p=0.011). No significant differences between groups were reported for mean sensor glucose concentrations or time spent with glucose concentrations lower than the target range. Glucose variability was significantly reduced compared to controls (coefficient of variation [CV], 27.9 vs. 33.4, p=0.042), and nocturnal time spent within target range was significantly greater in the closed-loop group as well (68.9% vs. 48.8%, p=0.007). No episodes of severe hypo- or hyperglycemia with ketonemia occurred in either group. As with the previously described study, these results are promising, but additional investigation involving larger studies is needed.

A meta-analysis published by Weisman and others (2017) evaluated the existing data addressing the efficacy of closed loop "artificial pancreas" devices compared to care with a conventional insulin pump. A total of 24 studies were included, with 19 involving single hormone devices and 5 involving dual hormone systems. Two studies involved both types of devices. A total of 585 subjects were included in the analysis. The authors reported a high degree of heterogeneity across studies, with significant range of mean differences reported (-6.3% to 26.68%). Overall, the artificial "pancreas system" groups demonstrated a greater difference for time in target in overnight studies vs. standard care (14.2%, p<0.0001). Looking at time spent in hypoglycemia, 21 studies involving 463 subjects were included in the analysis. The results showed that time in hypoglycemia was 2.45% in the artificial pancreas group vs. 4.88% in the standard care group (p<0.0001). It was noted that this equates to a 50% relative risk reduction. An analysis looking at change in insulin dose included 18 studies involving 389 subjects. Overall, no differences between device groups were noted, but a sub-analysis looking at the closed-loop group only indicated that children using closed-loop devices had a significantly higher insulin dose vs. adults using this type of device. (p<0.0001). Episodes of severe hypoglycemia were reported in 22 studies, with no significant differences reported between groups. No sub-analysis was provided for single hormone-only devices, and it was not clear if data involving hybrid closed-loop devices was included in the analysis.

Brown (2017) reported on the results of a randomized crossover study involving 40 subjects with type 1 diabetes comparing the use of an SAP (Roche Accu-Chek Spirit Combo connected to either a DexCom G4 Platinum or AP Share CGM) vs. a closed-loop system (Diabetes Assistant [DiAs] portable artificial pancreas platform, which connected the pumps and CGM devices wirelessly to a smartphone running the DiAs algorithm) to evaluate performance in controlling overnight glycemic control. Subjects were evaluated in 5 consecutive day periods wearing either the SAP or the closed-loop device. The closed-loop evaluations were conducted at either a hotel or study center and the pump trials were done at the subjects' home or usual environment. The primary endpoint of time in the target range of 70 to 180 mg/dL improved in closed-loop trials vs. the pump trials (mean=78.3% vs. 71.4%; p=0.003) when measured for 24 hours during the study period. The time in the target range was also improved in the overnight hours (23:00 to 07:00) in closed-loop trials vs. the pump trials (85.7% vs. 67.6%;

p<0.001). Mean overnight glucose concentrations were significantly lower during the closed-loop trials vs. the pump trials (137.2 vs 154.9 mg/dL; p<0.001). Mean glucose concentrations upon awakening were closer to the algorithm target of 120 mg/dL in the closed-loop trials vs. pump trials (123.7 vs. 145.3 mg/dL; p<0.001). The time spent in range during both overnight and during the 24-hour observation periods was significantly better in the closed-loop trials vs. the pump trials (p=0.002 and p<0.001, respectively), likewise, the time spent in the hyperglycemic range (< 180 mg/dL) was significantly less in the closed-loop trials (p<0.001). The authors reported data for a subset of subjects who completed the trials at home. However, this data involved only 10 subjects and is not generalizable. No instances of ketoacidosis or hypoglycemia requiring outside intervention were reported. This system is not currently approved by the FDA and not commercially available in the U.S.

An RCT involving 136 hospitalized subjects with type 2 diabetes aged 18 years and older in noncritical care was described by Bally in 2018. Subjects were assigned to either standard care with manual blood glucose monitoring and conventional subcutaneous insulin therapy (n=66) or treatment with an experimental closed-loop system (n=70). The system used a Dana Diabecare insulin pump, Abbott Freestyle Navigator II CGM, and a proprietary control algorithm run on a tablet computer. The mean percentage of time that the sensor glucose measurement was in the target range of 100-180 mg/dL was reported to be 65.8% in the closed-loop group vs. 41.5% in the control group (p<0.001). Values above the target range were reported in 23.6% and 49.5% of subjects, respectively (p<0.001). The mean glucose level was 154 mg/dL in the closed-loop group vs. 188 mg/dL (p<0.001). No significant between-group differences were reported with regard to the duration of hypoglycemia or daily insulin usage. Finally, no episode of severe hypoglycemia or clinically significant hyperglycemia with ketonemia occurred in either group.

The results of these studies are promising. However, it is not clear which one of these devices, if any, will receive FDA approval and reach market. Until that time, questions of clinical utility of closed-loop automated insulin deliver devices are academic.

Other Information

In addition to the threshold suspend-type devices, there are also “control-to-range” and “control-to-target” devices which operate on different principles (below). At this time, there are no “control-to-range” automated insulin delivery devices which have been cleared to market in the US. Additionally, the available evidence addressing their use involves mostly small case series which are insufficient to properly evaluate their safety and efficacy (Nimri, 2014a, 2014b).

There are other automated insulin delivery devices under development which attempt to more fully mimic the action of the pancreas. One such device type is referred to as a *bionic pancreas* or *dual-hormone artificial pancreas.* These systems involve the administration of both insulin and glucagon to maintain blood glucose within a targeted range. These automated insulin delivery devices are not addressed in this document.

Major Specialty Medical Society Recommendations

Continuous Glucose Monitoring Devices and External Insulin Infusion Pumps

The ADA Standards of Medical Care in Diabetes-2022 has recommendations regarding the use of continuous glucose monitoring. These recommendations state:

7.11 Real-time continuous glucose monitoring 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.

7.12 Real-time continuous glucose monitoring A or intermittently scanned continuous glucose monitoring C can 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.

7.13 Real-time continuous glucose monitoring 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.

7.14 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 devices safely (either by themselves or with a caregiver). The choice of device should be made based on patient circumstances, desires, and needs. E

7.15 In patients on multiple daily injections and continuous subcutaneous insulin infusion, real-time continuous glucose monitoring devices should be used as close to daily as possible for maximal benefit. A Intermittently scanned continuous glucose monitoring devices should be scanned frequently, at a minimum once every 8 h. A

7.16 When used as an adjunct to pre- and postprandial blood glucose monitoring, continuous glucose monitoring can help to achieve A1C targets in diabetes and pregnancy. B

7.17 Periodic use of real-time or intermittently scanned continuous glucose monitoring or use of professional continuous glucose monitoring can be helpful for diabetes management in circumstances where continuous use of continuous glucose monitoring is not appropriate, desired, or available. C

7.18 Skin reactions, either due to irritation or allergy, should be assessed and addressed to aid in successful use of devices. E

14.18 All children and adolescents with type 1 diabetes should monitor glucose levels multiple times daily (up to 6–10 times/day by blood glucose meter or continuous glucose monitoring), including prior to meals and snacks, at bedtime, and as needed for safety in specific situations such as exercise, driving, or the presence of symptoms of hypoglycemia. B

14.19 Real-time continuous glucose monitoring B or intermittently scanned continuous glucose monitoring E should be offered for diabetes management in youth with diabetes on multiple daily injections or insulin pump therapy who are capable of using the device safely (either by themselves or with caregivers). The choice of device should be made based on patient circumstances, desires, and needs.

14.20 Automated insulin delivery systems should be offered for diabetes management to youth with type 1 diabetes who are capable of using the device safely (either by themselves or with caregivers). The choice of device should be made based on patient circumstances, desires, and needs. A

7.23 Automated insulin delivery systems should be offered or 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 patient circumstances, desires, and needs.

7.24 Insulin pump therapy alone with or without sensor-augmented low glucose suspend 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/interested in an automated insulin delivery system. The choice of device should be made based on patient circumstances, desires, and needs. A

7.25 Insulin pump therapy can be offered for diabetes management to youth and adults on multiple daily injections with type 2 diabetes 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. A

14.21 Insulin pump therapy alone should be offered for diabetes management to youth on multiple daily injections with type 1 diabetes who are capable of using the device safely (either by themselves or with caregivers). The choice of device should be made based on patient circumstances, desires, and needs. A

14.27 Continuous glucose monitoring metrics derived from continuous glucose monitor use over the most recent 14 days (or longer for patients with more glycemic variability), including time in range (70–180 mg/dL), time below target (<70 and <54 mg/dL), and time above target (>180 mg/dL)], are recommended to be used in conjunction with A1C whenever possible. E

14.61 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 device safely (either by themselves or with a caregiver). The choice of device should be made based on patient circumstances, desires, and needs. E

14.72 Patients treated with metformin, a glucagon-like peptide 1 receptor agonist, and basal insulin who do not meet glycemic targets should be moved to multiple daily injections with basal and premeal bolus insulins or insulin pump therapy. E

15.9 When used in addition to pre- and postprandial blood glucose monitoring, continuous glucose monitoring can help to achieve A1C targets in diabetes and pregnancy. B

15.10 When used in addition to blood glucose monitoring targeting traditional pre- and postprandial targets, real-time continuous glucose monitoring can reduce macrosomia and neonatal hypoglycemia in pregnancy complicated by type 1 diabetes. B

15.11 Continuous glucose monitoring metrics may be used in addition to but should not be used as a substitute for self-monitoring of blood glucose to achieve optimal pre- and postprandial glycemic targets. E

15.18 Either multiple daily injections or insulin pump technology can be used in pregnancy complicated by type 1 diabetes. C

The Endocrine Society also has recommendations for the use of CGM devices in their 2018 clinical practice guideline addressing this topic (Peters, 2018):

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 who have A1C levels above target and who are willing and able to use these devices on a nearly daily basis. (1⊕⊕⊕⊕)
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. (1⊕⊕⊕⊕)
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. (2⊕⊕◯◯)

Children and Adolescents (2011 guideline)
2.1 We recommend that RT-CGM with currently approved devices be used by children and adolescents with T1DM who have achieved glycosylated hemoglobin (HbA1c) levels below 7.0% because it will assist in maintaining target HbA1c levels while limiting the risk of hypoglycemia (1|⊕⊕⊕).
2.2 We recommend RT-CGM devices be used with children and adolescents with T1DM who have HbA1c levels ≤ 7.0% who are able to use these devices on a nearly daily basis (1|⊕⊕⊕◯).
2.3 We make no recommendations for or against the use of RT-CGM by children with T1DM who are less than 8 years of age.
2.4 We suggest that treatment guidelines be provided to patients to allow them to safely and effectively take advantage of the information provided to them by RT-CGM (2|⊕◯◯◯).
2.5 We suggest the intermittent use of CGM systems designed for short-term retrospective analysis in pediatric patients with diabetes in whom clinicians worry about nocturnal hypoglycemia, dawn phenomenon, and postprandial hyperglycemia; in patients with hypoglycemic unawareness; and in patients experimenting with important changes to their diabetes regimens [such as instituting new insulin or switching from multiple daily injections (MDI) to pump therapy] (2|⊕◯◯◯).

The Endocrine Society uses the following scheme to grade their recommendations:
Strength of the recommendation:
- Strong recommendations use the phrase “we recommend” and the number 1; and
- Weak recommendations use the phrase “we suggest” and the number 2.

Quality of the evidence:
- ⊕◯◯◯, denotes very low quality evidence; and
- ⊕⊕◯◯, low quality; and
- ⊕⊕⊕◯, moderate quality; and
- ⊕⊕⊕⊕, high quality.

It should be noted that recommendation 6.3 was graded “weak” and based on low quality evidence.

Continuous Glucose Monitoring Devices and External Insulin Infusion Pumps

The American Association of Clinical Endocrinologist (AACE) and the American College of Endocrinology (ACE) produced a consensus statement addressing outpatient glucose monitoring in 2016 (Bailey, 2016). This document makes the following recommendations for the use of CGM:

- Type 1 Adult: CGM recommended, particularly for patients with history of severe hypoglycemia, hypoglycemia unawareness and to assist in the correction of hyperglycemia in patients not at goal. CGM users must know basics of sensor insertion, calibration, and real-time data interpretation.
- Type 1 – Pediatric: Same as Adult Type 1. Both prevalence and persistent use of CGM is lower in children than adults. More in-depth training as well as more frequent follow-up is recommended to enable children to adopt the technology more successfully.
- Type 2 – Receiving insulin/ sulfonylureas, glinides: Data on CGM in T2DM are limited at this time. Trials assessing the use of CGM in T2DM patients are ongoing.
- Type 2 – Low risk of hypoglycemia: No recommendation.
- Gestational: Benefits of CGM in pregnant females with pre-existing diabetes are unclear based on current data; additional studies are ongoing. CGM during pregnancy can be used as a teaching tool, to evaluate glucose patterns, and to fine-tune insulin dosing. CGM in pregnancy can supplement BGM, in particular for monitoring nocturnal hypoglycemia or hyperglycemia and postprandial hyperglycemia.

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) published a position statement on the integration of insulin pumps and continuous glucose monitoring in patients with diabetes mellitus (Grunberger, 2018). This document states the following:

> The AACE/ACE recommends that CGM be considered for all insulin-using patients, regardless of diabetes type. Insulin pump usage is recommended in patients with intensively managed insulin-dependent T1DM or T2DM (those who perform at least 4 insulin injections and 4 SMBG measurements daily). Integration of CGM and CSII may be considered in patients already on SII or appropriate for initiating CSII.
>
> Personal CGM should ideally be considered in all patients with T1DM, especially those with a history of severe hypoglycemia, hypoglycemia unawareness, and to assist in the correction of hyperglycemia in patients not at goal. Of note, usage and persistence of usage of CGM is lower in pediatric patients. The benefits of CGM in patients with T2DM have not been investigated to the same degree. A key aspect of successful glycemic control with CGM, however, is patients' ability to understand and respond to the data they receive in real time. Recent results show there is some variation in how patients adjust insulin therapy. Nonetheless, CGM users do rely on glucose rate of change arrows to adjust insulin delivery.

Appropriate candidates for pump therapy include:

- Patients with T1DM who are not at glycemic goal, despite adherence to maximum MDI, in particular
  - Those with erratic and wide glycemic excursions (including recurrent DKA)

  - Frequent severe hypoglycemia and/or hypoglycemia unawareness
  - Significant "dawn phenomenon," extreme insulin sensitivity
- T1DM special populations (including preconception, pregnancy, children, adolescents, and competitive athletes)
- Patients with T1DM who feel CSII would help achieve and maintain glycemic targets
- Select patients with insulin-dependent T2DM with any or all of the following:
  - C-peptide positivity with suboptimal control on maximal basal/bolus injections
  - Substantial "dawn phenomenon"
  - Erratic lifestyle (e.g., frequent long-distance travel, shift work, and unpredictable schedules)
  - Severe insulin resistance
- Select patients with other DM types (e.g., postpancreatectomy).

Importantly, patients who are unable or unwilling to perform MDI, frequent SMBG, and carbohydrate counting; lack motivation to achieve tighter glucose control or have a history of nonadherence; have a history of serious psychological or psychiatric conditions; or have either substantial reservations or unrealistic expectations about pump therapy are not good candidates.

Use of CGM with integrated pump requires patient self-management. The ideal candidate must be willing and able to carry out tasks associated with using the system, self-monitor and react to collected data, and maintain frequent contact with the healthcare team. Intensive education is needed, and patients must be willing to complete the necessary training. Family support, particularly with pediatric patients, is paramount to success. The increased burden on patients and their families, as well as health-economic and ethical concerns, must be considered carefully, and this strategy may not be ideal for all patients.

Additionally, in 2018 the Endocrine Society published *Advances in Glucose Monitoring and Automated Insulin Delivery: Supplement to Endocrine Society Clinical Practice Guidelines* (Peters, 2018). In this document they make the following recommendations:

1. Insulin pump therapy without sensor augmentation

1.1 We recommend continuous subcutaneous insulin infusion (CSII) over analog-based basal-bolus multiple daily injections (MDI) in patients with type 1 diabetes mellitus (T1DM) who have not achieved their A1C goal, as long as the patient and caregivers are willing and able to use the device. (1|⊕⊕⊕◯)

1.2 We recommend CSII over analog-based basal-bolus MDI in patients with T1DM who have achieved their A1C goal but continue to experience severe hypoglycemia or high glucose variability, as long as the patient and caregivers are willing and able to use the device. (1|⊕⊕◯◯)

1.3 We suggest CSII in patients with T1DM who require increased insulin delivery flexibility or improved satisfaction and are capable of using the device. (2|⊕⊕◯◯)

2. Insulin pump therapy in type 2 diabetes mellitus

2.1 We suggest CSII with good adherence to monitoring and dosing in patients with type 2 diabetes mellitus (T2DM) who have poor glycemic control despite intensive insulin therapy, oral agents, other injectable therapy, and lifestyle modifications. (2|⊕⊕〇〇)

4. Selection of candidates for insulin pump therapy

4.1 We recommend that before prescribing CSII, clinicians perform a structured assessment of a patient's mental and psychological status, prior adherence with diabetes self-care measures, willingness and interest in trying the device, and availability for the required follow-up visits. (1|⊕⊕〇〇)

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 who have A1C levels above target and who are willing and able to use these devices on a nearly daily basis. (1|⊕⊕⊕⊕)

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. (1|⊕⊕⊕⊕) Use of continuous glucose monitoring in adults with type 2 diabetes mellitus

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. (2|⊕⊕〇〇)

In 2021 the AACE published clinical practice guidelines addressing the use of advanced technology in the management of persons with diabetes mellitus. Their recommendations in that document include the following:

R2.1.3 CGM is recommended for all individuals with problematic hypoglycemia (frequent/severe hypoglycemia, nocturnal hypoglycemia, hypoglycemia unawareness). Grade A; Intermediate-High Strength of Evidence; BEL 1

R2.1.4 CGM is recommended for children/adolescents with T1D. Grade A; Intermediate-High Strength of Evidence; BEL 1

R2.1.5 CGM is recommended for pregnant women with T1D and T2D treated with intensive insulin therapy. Grade A; Intermediate-High Strength of Evidence; BEL 1

R2.1.6 CGM is recommended for women with gestational diabetes mellitus (GDM) on insulin therapy. Grade A; Intermediate Strength of Evidence; BEL 1

R2.1.7 CGM may be recommended for women with GDM who are not on insulin therapy. Grade B; Intermediate Strength of Evidence; BEL 1

R2.1.8 CGM may be recommended for individuals with T2D who are treated with less intensive insulin therapy. Grade B; Intermediate Strength of Evidence; BEL 1

R2.2.1 The AGP may be utilized to assess glycemic status in persons with diabetes. Grade B; Low Strength of Evidence; BEL 1

R2.2.2 When using the AGP, a systematic approach to interpret CGM data is recommended:

1. Review overall glycemic status (eg, GMI, average glucose)
2. Check TBR, TIR, and TAR statistics, focusing on hypoglycemia (TBR) first. If the TBR statistics are above the cut-point for the clinical scenario (ie, for most with

3. T1D >4% <70 mg/dL; >1% <54 mg/dL), the visit should focus on this issue. Otherwise, move on to the TIR and TAR statistics.
4. Review the 24-hour glucose profile to identify the time(s) and magnitude(s) of the problem identified.
5. Review treatment regimen and adjust as needed.

Grade B; Low Strength of Evidence; BEL 1

R2.3.1 Real-time continuous glucose monitoring (rtCGM) should be recommended over intermittently scanned continuous glucose monitoring (isCGM) to persons with diabetes with problematic hypoglycemia (frequent/severe hypoglycemia, nocturnal hypoglycemia, hypoglycemia unawareness) who require predictive alarms/ alerts; however, the lifestyle of persons with diabetes and other factors should also be considered. Grade B; Low-Intermediate Strength of Evidence; BEL 1

R2.3.2 isCGM should be considered for persons with diabetes who meet 1 or more of the following criteria: Newly diagnosed with T2D Treated with nonhypoglycemic therapies Motivated to scan device several times per day at low risk for hypoglycemia, but desire more data than SMBG provides Grade D; Low Strength of Evidence/Expert Opinion of Task Force; BEL 4

R2.4.1 Diagnostic/professional CGM should be used in the management of persons with diabetes who meet 1 or more of the following criteria: Newly diagnosed with diabetes mellitus Not using CGM May have problematic hypoglycemia, but no access to personal CGM Persons with T2D treated with non-insulin therapies who would benefit from episodic use of CGM as an educational tool Persons who would like to learn more about CGM before committing to daily use Importantly, in those using "masked" or "blinded" diagnostic/professional CGM, they must have and continue using adjunctive SMBG to assist in daily diabetes self-care. Grade B; Intermediate Strength of Evidence; BEL 1

R2.7.1 The use of an insulin pump without CGM could be used to manage persons with diabetes who are achieving glycemic targets with minimal TBR, who report infrequent episodes of symptomatic hypoglycemia, and who are using SMBG on a regular basis (at least 4 times per day for persons with T1D). Grade B; Intermediate-High Strength of Evidence; BEL 1

R2.8.1 Insulin pump with CGM or SAP is recommended to manage all persons with diabetes treated with intensive insulin management who prefer not to use automated insulin suspension/dosing systems or have no access to them. Grade A; Intermediate-High Strength of Evidence; BEL 1

R2.9.1 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; BEL 1

R2.9.2 AID systems are strongly recommended for all persons with T1D, since their use has been shown to increase TIR, especially in the overnight period, without causing an increased risk of hypoglycemia. Given the improvement in TIR and the reduction in hyperglycemia with AID, this method of insulin delivery is preferred above other modalities. For persons with diabetes with suboptimal glycemia,

significant glycemic variability, impaired hypoglycemia awareness, or who allow for permissive hyperglycemia due to the fear of hypoglycemia, such AID systems should be considered. Grade A; High Strength of Evidence; BEL 1

R2.10.2 rtCGM is recommended for persons 65 years old with insulin-requiring diabetes to achieve improved glycemic control, reduce episodes of severe hypoglycemia, and improve QoL; however, glycemic goals should be individualized due to increased comorbidities and reduced capacity to detect and counter-regulate against severe hypoglycemia in this population. Grade A; Intermediate-High Strength of Evidence; BEL 1

R2.10.3 Clinicians should prescribe CGM as a tool to track glucose before, during, and after exercise in persons with diabetes; monitor the glycemic response to exercise; and help direct insulin and carbohydrate consumption to avoid hypoglycemia and hyperglycemia. When this technology is utilized as part of AID systems, it can reduce glycemic excursions during exercise. Grade A; Intermediate Strength of Evidence; BEL 1

R3.4.1 Clinicians should caution persons with diabetes who are using do-it-yourself systems that these devices have not undergone rigorous review by the FDA for safety and efficacy. Grade B; Low Strength of Evidence/Expert Opinion of Task Force; BEL 4

Definitions

Automated insulin delivery systems: A device that combines the functions of an external insulin pump and a CGM device to create a device that attempts to mimic normal physiological functioning. Such devices control the majority of insulin administration tasks, such as measuring blood glucose concentrations and calculation and management of insulin administration. As noted above, there are several categories of this type of device: open-loop systems, hybrid closed-loop systems, and closed-loop systems.

Closed-loop systems: A type of automated insulin delivery device consisting of an external insulin infusion pump device and a CGM device. This type of system is able to increase, decrease or stop insulin delivery automatically beyond pre-set infusion rates in response glucose concentration measurements taken by the CGM. Individuals using this type of device do not need to calculate and adjust infusion rates to compensate for prandial boluses, and little to no input is needed by the individual during normal functioning.

Continuous interstitial glucose monitoring (CGM) device: A device applied to the skin that contains a sensor implanted into the skin to measure glucose concentrations in the interstitial fluid. Such devices may be used to create a record of glucose concentrations over time to allow analysis by a medical professional. They may also measure and provide real-time glucose concentration data to allow an individual or automated insulin delivery system to adjust insulin delivery rates to provide better control of blood glucose concentrations.

External insulin infusion pumps: A device that is worn externally and attached to a temporary subcutaneous insulin catheter. An integrated computer controls a pump mechanism that administers insulin at a set rate or provide bolus injections as needed.

Flash CGM: A type of CGM device that requires the use of a device access glucose data from a sensor on a per-need basis. Glucose concentration data is not continuously visible with this type of device.

Glycemic: Having to do with blood sugar (glucose) levels.

Glycemic control: The ability of an individual's body to control blood glucose concentrations within a specific physiologic range, either on its own or with the assistance of medical therapy.

Glycosylated hemoglobin (HbA1c) test: A laboratory test that provides the percentage of a specific type of modified hemoglobin in the blood. This test ascertains the level of diabetic blood glucose control over the past three to four months.

Hybrid closed-loop systems: A type of automated insulin delivery device consisting of an external insulin infusion pump device and a CGM device. This type of system is able to increase, decrease or stop insulin delivery automatically beyond pre-set infusion rates in response glucose concentration measurements taken by the CGM. Individuals using this type of device need to calculate and adjust infusion rates for prandial boluses.

Hyperglycemia: A condition characterized by excessively high blood glucose concentrations, generally considered greater than 150 mg/dL.

Hypoglycemia: A condition characterized by excessively low blood glucose concentrations, generally considered less than 50 mg/dL.

Interstitial glucose: Glucose present in the fluid present in spaces between the tissue cells of the body.

Low glucose suspend feature: A function of an automated insulin delivery system that uses the data from a CGM to detect when blood glucose concentrations pass below a pre-set threshold. When that occurs, the pump function temporarily stops insulin delivery with the goal of avoiding or shortening hypoglycemic events.

Open-loop system: A type of automated insulin delivery system that integrates an external insulin pump and CGM device. This type of device requires manual adjustment of insulin administration rates based on CGM data, as well as manual calculation and administration of pre-meal insulin bolus doses. These types of devices require self-adjustment of the basal insulin infusion rate and most require a blood glucose measurement to confirm CGM data.

Predictive low glucose management (PLGM): A feature of some CGM systems that uses a computer algorithm to monitor blood glucose concentration trend data to predict when concentrations will be approaching the preset low threshold and decrease or stop insulin administration to avoid hypoglycemic events.

Real time CGM: A type of CGM device that provides real-time, continuously visible glucose concentration data to the user.

Type 1 diabetes: A condition characterized by the impaired or inability of the pancreas to produce insulin. Sometimes known as 'juvenile diabetes.'

Type 2 diabetes: A condition characterized by a person's body losing the ability to use insulin properly, a problem referred to as insulin resistance.

References

External Insulin Infusion Pumps

Peer Reviewed Publications:

1. Aronson R, Reznik Y, Conget I, et al.; OpT2mise Study Group. Sustained efficacy of insulin pump therapy compared with multiple daily injections in type 2 diabetes: 12-month data from the OpT2mise randomized trial. Diabetes Obes Metab. 2016; 18(5):500-507.
2. Bergenstal RM, Peyrot M, Dreon DM, et al.; Calibra Study Group. Implementation of basal-bolus therapy in type 2 diabetes: a randomized controlled trial comparing bolus insulin delivery using an insulin patch with an insulin pen. Diabetes Technol Ther. 2019; 21(5):273-285.
3. Berghaeuser MA, Kapellen T, Heidtmann B, et al. Continuous subcutaneous insulin infusion in toddlers starting at diagnosis of type 1 diabetes mellitus. A multicenter analysis of 104 patients from 63 centres in Germany and Austria. Pediatric Diabetes. 2008; 9(6):590-595.
4. Berthe E, Lireux B, Coffin C, et al. Effectiveness of intensive insulin therapy by multiple daily injections and continuous subcutaneous infusion: a comparison study in type 2 diabetes with conventional insulin regimen failure. Horm Metab Res. 2007; 39(3):224-229.
5. Bode BW, Steed RD, Davidson PC. Reduction in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type I diabetes. Diabetes Care. 1996; 19(4):324-327.
6. Bohannon N, Bergenstal R, Cuddihy R, et al. Comparison of a novel insulin bolus-patch with pen/syringe injection to deliver mealtime insulin for efficacy, preference, and quality of life in adults with diabetes: a randomized, crossover, multicenter study. Diabetes Technol Ther. 2011; 13(10):1031-1037.
7. Boonin A, Balinski B, Sauter J, et al. A retrospective chart review of two different insulin administration systems on glycemic control in older adults in long-term care. J Gerontol Nurs. 2017; 43(1):10-16.
8. Bruttomesso D, Pianta A, Crassolara D, et al. Continuous subcutaneous insulin infusion (CSII) in the Veneto region: efficacy, acceptability, and quality of life. Diabet Med. 2002; 19(8):628-634.
9. Carlsson BM, Attvall S, Clements M, et al. Insulin pump-long-term effects on glycemic control: an observational study at 10 diabetes clinics in Sweden. Diabetes Technol Ther. 2013; 15(4):302-307.
10. Conget I, Castaneda J, Petrovski G, et al.; OpT2mise Study Group. The impact of insulin pump therapy on glycemic profiles in patients with type 2 diabetes: data from the OpT2mise study. Diabetes Technol Ther. 2016; 18(1):22-28.

11. Danne T, Battelino T, Jarosz-Chobot P, et al.; PedPump Study Group. Establishing glycaemic control with continuous subcutaneous insulin infusion in children and adolescents with type 1 diabetes: experience of the PedPump Study in 17 countries. Diabetologia. 2008; 51(9):1594-1601.
12. DeVries JH, Snoek FJ, Kostense PJ, et al. A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with long-standing poor glycemic control. Diabetes Care. 2002; 25(11):2074-2080.
13. Diabetes Control and Complications Trial (DCCT) Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993; 329(14):977-986.
14. Fatourechi MM, Kudva YC, Murad MH, et al. Clinical review: Hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. J Clin Endocrinol Metab. 2009; 94(3):729-740.
15. Feig DS, Corcoy R, Donovan LE, et al.; CONCEPTT Collaborative Group. Pumps or multiple daily injections in pregnancy involving type 1 diabetes: a prespecified analysis of the CONCEPTT randomized trial. Diabetes Care. 2018; 41(12):2471-2479.
16. Grunberger G, Rosenfeld CR, Bode BW, et al. Effectiveness of V-Go® for patients with type 2 diabetes in a real-world setting: a prospective observational study. Drugs Real World Outcomes. 2020; 7(1):31-40.
17. Halvorson M, Carpenter S, Kaiserman K, Kaufman FR. A pilot trial in pediatrics with the sensor-augmented pump: combining real-time continuous glucose monitoring with the insulin pump. J Pediatr. 2007; 150(1):103-105.
18. Hanaire-Broutin H, Melki V, Bessieres-Lacombe S, Tauber JP. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using insulin lispro in type 1 diabetic patients on intensified treatment: a randomized study. The Study Group for the Development of Pump Therapy in Diabetes. Diabetes Care. 2000; 23(9):1232-1235.
19. Hirsch IB, Farkas-Hirsch R, Skyler JS. Intensive insulin therapy for treatment of Type 1 diabetes. Diabetes Care. 1990; 13(12):1265-1283.
20. Jakisch BI, Wagner VM, Heidtmann B, et al. Comparison of continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI) in paediatric Type 1 diabetes: a multicentre matched-pair cohort analysis over 3 years. Diabet Med. 2008; 25(1):80-85.
21. Jeitler K, Horvath K, Berghold A, et al. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. Diabetologia. 2008; 51(6):941-951.
22. Johns BR, Jones TC1 Sink JH 2nd, Cooke CE. Real-world assessment of glycemic control after V-Go® initiation in an endocrine practice in the southeastern United States. J Diabetes Sci Technol. 2014; 8(5):1060-1061.
23. Kitzmiller JL, Gavin LA, Gin GD, et al. Preconception care of diabetes. Glycemic control prevents congenital anomalies. JAMA. 1991; 265(6):731-736.
24. Lajara R, Davidson JA, Nikkel CC, Morris TL. Clinical and cost-effectiveness of insulin delivery with V-Go(®) disposable insulin delivery device versus multiple daily injections in patients with type 2 diabetes inadequately controlled on basal insulin. Endocr Pract. 2016; 22(6):726-735.

25. Lajara R, Fetchick DA, Morris TL, Nikkel C. Use of V-Go® insulin delivery device in patients with sub-optimally controlled diabetes mellitus: a retrospective analysis from a large specialized diabetes system. Diabetes Ther. 2015; 6(4):531-545
26. Lajara R, Nikkel C, Abbott S. The clinical and economic impact of the V-Go® disposable insulin delivery device for insulin delivery in patients with poorly controlled diabetes at high risk. Drugs Real World Outcomes. 2016; 3(2):191-199
27. Layne JE, Parkin CG, Zisser H. Efficacy of the omnipod insulin management system on glycemic control in patients with type 1 diabetes previously treated with multiple daily injections or continuous subcutaneous insulin infusion. J Diabetes Sci Technol. 2016; 10(5):1130-1135.
28. Mastrototaro JJ, Cooper KW, Soundararajan G, et al. Clinical experience with an integrated continuous glucose sensor/insulin pump platform: a feasibility study. Adv Ther. 2006; 23(5):725-732.
29. Meade LT, Battise D. Evaluation of clinical outcomes with the V-Go wearable insulin delivery device in patients with type 2 diabetes. Clin Diabetes. 2021; 39(3):297-303.
30. Nathan DM, Zinman B, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). Arch Intern Med. 2009; 169(14):1307-1316.
31. Nuboer R, Borsboom GJ, Zoethout JA, et al. Effects of insulin pump vs. injection treatment on quality of life and impact of disease in children with type 1 diabetes mellitus in a randomized, prospective comparison. Pediatr Diabetes. 2008; 9(4 Pt 1):291-296.
32. Pańkowska E, Błazik M, Dziechciarz P, et al. Continuous subcutaneous insulin infusion vs. multiple daily injections in children with type 1 diabetes: a systematic review and meta-analysis of randomized control trials. Pediatr Diabetes. 2009; 10(1):52-58.
33. Pickup J, Keen H. Continuous subcutaneous insulin infusion at 25 years: evidence base for expanding use of insulin pump therapy in type 1 diabetes. Diabetes Care. 2002; 25(3):593-598.
34. Pohar SL. Subcutaneous open-loop insulin delivery for type 1 diabetes: Paradigm Real-Time System. Issues Emerg Health Technol. 2007; (105):1-6.
35. Raskin P, Bode BW, Marks JB, et al. Continuous subcutaneous insulin infusion and multiple daily injection therapy are equally effective in type 2 diabetes: a randomized, parallel-group, 24-week study. Diabetes Care. 2003; 26(9):2598-2603.
36. Raval AD, Nguyen MH, Zhou S, et al. Effect of V-Go versus multiple daily injections on glycemic control, insulin use, and diabetes medication costs among individuals with type 2 diabetes mellitus. J Manag Care Spec Pharm. 2019; Jul 5:1-14.
37. Reznik Y, Cohen O, Aronson R, et al.; OpT2mise Study Group. Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. Lancet. 2014; 384(9950):1265-1272.

38. Rosenfeld CR, Bohannon NJ, Bode B, et al. The V-Go insulin delivery device used in clinical practice: patient perception and retrospective analysis of glycemic control. Endocr Pract. 2012; 18(5):660-667.
39. Sanfield, JA, Hegstad M, Hanna RS. Protocol for outpatient screening and initiation of continuous subcutaneous insulin infusion therapy: impact on cost and quality. Diabetes Educ. 2002; 28(4):599-607.
40. Selam JL, Charles MA, Devices for insulin administration. Diabetes Care. 1990; 13(9):955-979.
41. Sutton D, Higdon C, Carmon M, Abbott S. Regular insulin administered with the V-Go disposable insulin delivery device in a clinical diabetes setting: a retrospective analysis of efficacy and cost. Clin Diabetes. 2016; 34(4):201-205.
42. Winter A, Lintner M, Knezevich E. V-Go insulin delivery system versus multiple daily insulin injections for patients with uncontrolled type 2 diabetes mellitus. J Diabetes Sci Technol. 2015; 9(5):1111-1116.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Diabetes Association. Standards of Care in Diabetes-2022. Diabetes Care. 2022; 45(Suppl 1):S1-S270.
2. American Association of Clinical Endocrinologists (AACE). American Association of Clinical Endocrinologists medical guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan. Endocr Pract. 2011; 17(2):287-302.
3. Centers for Medicare and Medicaid Services. National Coverage Determination for Infusion Pumps. NCD #280.14. Effective February 4, 2005. Available at: https://www.cms.gov/medicare-coverage-database/search.aspx?redirect=Y&from=Overview&list_type=ncd. Accessed on Accessed on April 25, 2023.
4. Fullerton B, Jeitler K, Seitz M, et al. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2014;(2):CD00912.
5. Grunberger G, Abelseth J, Bailey T, et al. Consensus statement by the American Association of Clinical Endocrinologists/American College of Endocrinology Insulin Pump Management Task Force. Endocr Pract. 2014; 20(5):463-489.
6. Misso ML, Egberts KJ, Page M, et al. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2010;(1):CD005103.
7. Silverstein J, Klingensmith G, Copeland K, et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. Diabetes Care. 2005; 28(1):186-212.

Continuous Interstitial Glucose Monitoring Devices

Peer Reviewed Publications:

1. Abraham MB, Nicholas JA, Smith GJ, et al.; PLGM Study Group. Reduction in hypoglycemia with the predictive low-glucose management system: a long-term randomized controlled trial in adolescents with type 1 diabetes. Diabetes Care. 2018; 41(2):303-310.
2. Al Hayek AA, Robert AA, Al Dawish MA. Evaluation of FreeStyle Libre Flash Glucose Monitoring System on glycemic control, health-related quality of life, and fear of hypoglycemia in patients with type 1 diabetes. Clin Med Insights Endocrinol Diabetes. 2017; 10:1179551417746957.

3. Aronson R, Abitbol A, Tweden KS. First assessment of the performance of an implantable continuous glucose monitoring system through 180 days in a primarily adolescent population with type 1 diabetes. Diabetes Obes Metab. 2019; 21(7):1689-1694.
4. Battelino T, Conget I, Olsen B, et al. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. Diabetologia. 2012; 55(12):3155-3162.
5. Battelino T, Nimri R, Dovc K, et al. Prevention of hypoglycemia with predictive low glucose insulin suspension in children with type 1 diabetes: a randomized controlled trial. Diabetes Care. 2017; 40(6):764-770.
6. Battelino T, Phillip M, Bratina N, et al. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care. 2011; 34(4):795-800.
7. Beck RW, Riddlesworth T, Ruedy K, et al.; DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. JAMA. 2017a; 317(4):371-378.
8. Beck RW, Riddlesworth TD, Ruedy K, et al. Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: a randomized trial. Ann Intern Med. 2017b; 167(6):365-374.
9. Benkhadra K, Alahdab F, Tamhane S, et al. Real-time continuous glucose monitoring in type 1 diabetes: a systematic review and individual patient data meta- analysis. Clin Endocrinol (Oxf). 2017; 86(3):354-360.
10. Blackberry ID, Furler JS, Ginnivan LE, et al. An exploratory trial of basal and prandial insulin initiation and titration for type 2 diabetes in primary care with adjunct retrospective continuous glucose monitoring: INITIATION study. Diabetes Res Clin Pract. 2014; 106(2):247-255.
11. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, et al. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet. 2016; 388(10057):2254-2263.
12. Boscari F, Vettoretti M, Amato AML, et al. Comparing the accuracy of transcutaneous sensor and 90-day implantable glucose sensor. Nutr Metab Cardiovasc Dis. 2021a; 31(2):650-657.
13. Boscari F, Vettoretti M, Cavallin F, et al. Implantable and transcutaneous continuous glucose monitoring system: a randomized cross over trial comparing accuracy, efficacy and acceptance. J Endocrinol Invest. 2021b:1-10.
14. Charleer S, Mathieu C, Nobels F, et al.; RESCUE Trial Investigators. Effect of continuous glucose monitoring on glycemic control, acute admissions, and quality of life: a real-world study. J Clin Endocrinol Metab. 2018; 103(3):1224-1232.
15. Choudhary P, Ramasamy S, Green L, et al. Real-time continuous glucose monitoring significantly reduces severe hypoglycemia in hypoglycemia-unaware patients with type 1 diabetes. Diabetes Care. 2013; 36(12):4160-4162.
16. Christiansen MP, Klaff LJ, Bailey TS, et al. A prospective multicenter evaluation of the accuracy and safety of an implanted continuous glucose sensor: The PRECISION study. Diabetes Technol Ther. 2019; 21(5):231-237.
17. Christiansen MP, Klaff LJ, Brazg R, et al. A prospective multicenter evaluation of the accuracy of a novel implanted continuous glucose sensor: PRECISE II. Diabetes Technol Ther. 2018; 20(3):197-206.

18. Cooke D, Hurel SJ, Casbard A, et al. Randomized controlled trial to assess the impact of continuous glucose monitoring on HbA1c in insulin-treated diabetes (MITRE Study). Diabet Med. 2009; 26(5):540-547.
19. Dehennis A, Mortellaro MA, Ioacara S. Multisite study of an implanted continuous glucose sensor over 90 days in patients with diabetes mellitus. J Diabetes Sci Technol. 2015; 9(5):951-956.
20. Deiss D, Irace C, Carlson G, et al. Real-world safety of an implantable continuous glucose sensor over multiple cycles of use: a post-market registry study. Diabetes Technol Ther. 2020; 22(1):48-52.
21. Dunn TC, Xu Y, Hayter G, Ajjan RA. Real-world flash glucose monitoring patterns and associations between self-monitoring frequency and glycaemic measures: a European analysis of over 60 million glucose tests. Diabetes Res Clin Pract. 2018; 137:37-46.
22. Ehrhardt NM, Chellappa M, Walker MS, et al. The effect of real-time continuous glucose monitoring on glycemic control in patients with type 2 diabetes mellitus. J Diabetes Sci Technol. 2011; 5(3):668-675.
23. Feig DS, Donovan LE, Corcoy R, et al.; CONCEPTT Collaborative Group. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet. 2017; 390(10110):2347-2359.
24. Floyd B, Chandra P, Hall S, et al. Comparative analysis of the efficacy of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes mellitus. J Diabetes Sci Technol. 2012; 6(5):1094-1102.
25. Furler J, O'Neal D, Speight J, et al. Use of professional-mode flash glucose monitoring, at 3-month intervals, in adults with type 2 diabetes in general practice (GP-OSMOTIC): a pragmatic, open-label, 12-month, randomised controlled trial. Lancet Diabetes Endocrinol. 2020; 8(1):17-26.
26. Gandhi GY, Kovalaske M, Kudva Y, et al. Efficacy of continuous glucose monitoring in improved glycemic control and reducing hypoglycemia: a systematic review and meta-analysis of randomized trials. J Diabetes Sci Technol. 2011; 5(4):952-965.
27. Haak T, Hanaire H, Ajjan R, et al. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. Diabetes Ther. 2017a; 8(1):55-73.
28. Haak T, Hanaire H, Ajjan R, et al. Use of flash glucose-sensing technology for 12 months as a replacement for blood glucose monitoring in insulin-treated type 2 diabetes. Diabetes Ther. 2017b; 8(3):573-586.
29. Heinemann L, Freckmann G, Ehrmann D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet. 2018; 391(10128):1367-1377.
30. Irace C, Cutruzzolà A, Nuzzi A, et al. Clinical use of a 180-day implantable glucose sensor improves glycated haemoglobin and time in range in patients with type 1 diabetes. Diabetes Obes Metab. 2020; 22(7):1056-1061.
31. Jafri RZ, Balliro CA, El-Khatib F, et al. A three-way accuracy comparison of the Dexcom G5, Abbott Freestyle Libre Pro, and Senseonics Eversense continuous glucose monitoring devices in a home-use study of subjects with type 1 diabetes. Diabetes Technol Ther. 2020; 22(11):846-852.
32. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Effectiveness of continuous glucose monitoring in a clinical care environment. Diabetes Care. 2010; 33(1):17-22.
33. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care. 2009; 32(8):1378-1383.
34. Kropff J, Choudhary P, Neupane S, et al. Accuracy and longevity of an implantable continuous glucose sensor in the PRECISE study: A 180-day, prospective, multicenter, pivotal trial. Diabetes Care. 2017; 40(1):63-68.

35. Laffel LM, Kanapka LG, Beck RW, et al. Effect of continuous glucose monitoring on glycemic control in adolescents and young adults with type 1 diabetes: a randomized clinical trial. JAMA. 2020; 323(23):2388-2396.
36. Lind M, Polonsky W, Hirsch IB, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: the GOLD randomized clinical trial. JAMA. 2017; 317(4):379-387.
37. Little SA, Speight J, Leelarathna L, et al. Sustained reduction in severe hypoglycemia in adults with type 1 diabetes complicated by impaired awareness of hypoglycemia: two-year follow-up in the HypoCOMPaSS randomized clinical trial. Diabetes Care. 2018; 41(8):1600-1607.
38. Martens T, Beck RW, Bailey R, et al; MOBILE Study Group. Effect of continuous glucose monitoring on glycemic control in patients with type 2 diabetes treated with basal insulin: A randomized clinical trial. JAMA. 2021; 325(22):2262-2272.
39. Mauras N, Beck R, Xing D, et al. A randomized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to <10 years. Diabetes Care. 2012; 35(2):204-210.
40. Murphy HR, Rayman G, Lewis K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. BMJ. 2008; 337:a1680.
41. Newman SP, Cooke D, Casbard A, et al. A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE). Health Technol Assess. 2009; 13(28):iii-iv, ix-xi, 1-194.
42. Poolsup N, Suksomboon N, Kyaw AM. Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes. Diabetol Metab Syndr. 2013; 5(1):39.
43. Raccah D, Sulmont V, Reznik Y, et al. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study. Diabetes Care. 2009; 32(12):2245-2250.
44. Renard E, Riveline JP, Hanaire H, Guerci B; on behalf of the investigators of France Adoption Clinical Trial. Reduction of clinically important low glucose excursions with a long-term implantable continuous glucose monitoring system in adults with type 1 diabetes prone to hypoglycaemia: the France Adoption Randomized Clinical Trial. Diabetes Obes Metab. 2022 Jan 4. Epub ahead of print.
45. Saboo B, Sheth SV, Joshi S, et al. Use of ambulatory glucose profile for improving monitoring and management of T2DM. J Assoc Physicians India. 2018; 66(7):69-71.
46. Sanchez P, Ghosh-Dastidar S, Tweden KS, Kaufman FR. Real-world data from the first U.S. commercial users of an implantable continuous glucose sensor. Diabetes Technol Ther. 2019; 21(12):677-681.
47. Secher AL, Ringholm L, Andersen HU, et al. The effect of real-time continuous glucose monitoring in pregnant women with diabetes: a randomized controlled trial. Diabetes Care. 2013; 36(7):1877-1883.
48. Sierra JA, Shah M, Gill MS, et al. Clinical and economic benefits of professional CGM among people with type 2 diabetes in the United States: analysis of claims and lab data. J Med Econ. 2018, 21(3):225-230
49. Tamborlane WV, Beck RW, Bode BW, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med. 2008; 359(14):1464-1476.

50. Tweden KS, Deiss D, Rastogi R, et al. Longitudinal analysis of real-world performance of an implantable continuous glucose sensor over multiple sensor insertion and removal cycles. Diabetes Technol Ther. 2020; 22(5):422-427.
51. Vigersky RA, Fonda SJ, Chellappa M, et al. Short- and long-term effects of real-time continuous glucose monitoring in patients with type 2 diabetes. Diabetes Care. 2012; 35(1):32-38.
52. Voormolen DN, DeVries JH, Evers IM, et al. The efficacy and effectiveness of continuous glucose monitoring during pregnancy: a systematic review. Obstet Gynecol Surv. 2013; 68(11):753-763.
53. Voormolen DN, DeVries JH, Sanson RME, et al. Continuous glucose monitoring during diabetic pregnancy (GlucoMOMS): a multicentre randomized controlled trial. Diabetes Obes Metab. 2018; 20(8):1894-1902.
54. Wang X, Ioacara S, DeHennis A. Long-term home study on nocturnal hypoglycemic alarms using a new fully implantable continuous glucose monitoring system in type 1 diabetes. Diabetes Technol Ther. 2015; 17(11):780-786.
55. Yaron M, Roitman E, Aharon-Hananel G, et al. Effect of flash glucose monitoring technology on glycemic control and treatment satisfaction in patients with type 2 diabetes. Diabetes Care. 2019; 42(7):1178-1184.
56. Yeh HC, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. Ann Intern Med. 2012; 157(5):336-347.
57. Yoo HJ, An HG, Park SY, et al. Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. Diabetes Res Clin Pract. 2008; 82(1):73-9.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Diabetes Association. Standards of Care in Diabetes-2022. Diabetes Care. 2022; 45(Suppl 1):S1-S270.
2. Bailey TS, Grunberger G, Bode BW, et al. American Association of Clinical Endocrinologists and American College of Endocrinology 2016 outpatient glucose monitoring consensus statement. Endocr Pract. 2016; 22(2):231-261.
3. Grunberger G, Bailey T, Camacho PM, et al.; Glucose Monitoring Consensus Conference Writing Committee. Proceedings from the American Association of Clinical Endocrinologists and American College of Endocrinology consensus conference on glucose monitoring. Endocr Pract. 2015; 21(5):522-533.
4. Fonseca VA, Grunberger G, Anhalt H, et al.; Consensus Conference Writing Committee. Continuous glucose monitoring: a consensus conference of the American Association of Clinical Endocrinologists and American College of Endocrinology. Endocr Pract. 2016; 22(8):1008-1021
5. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015; 21(Suppl 1):1-87.
6. Klonoff DC, Buckingham B, Christiansen JS, et al. Continuous glucose monitoring: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011; 96(10):2968-2979.
7. Langendam M, Luijf YM, Hooft L, et al. Continuous glucose monitoring systems for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2012;(1):CD008101.
8. Moy FM, Ray A, Buckley BS. Techniques of monitoring blood glucose during pregnancy for women with pre-existing diabetes. Cochrane Database Syst Rev. 2014;(4):CD009613.

9. Peters AL, Ahmann AJ, Battelino T, et al. Diabetes technology-continuous subcutaneous insulin infusion therapy and continuous glucose monitoring in adults: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016; 101(11):3922-3937.
10. United States Food and Drug Administration. Premarket approval Dexcom G7 Continuous Glucose Monitoring (CGM) System. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf21/K213919.pdf. Accessed on April 25, 2023.
11. United States Food and Drug Administration. Premarket approval Eversense Continuous Glucose Monitoring System. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160048. Accessed on April 25, 2023.
12. United States Food and Drug Administration. Premarket approval FreeStyle Libre 2 Flash Glucose Monitoring System; FreeStyle Libre 3 Continuous Glucose Monitoring System. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf22/K223435.pdf. Accessed on April 25, 2023.
13. U.S Food and Drug Administration. Summary of safety and effectiveness data for the FreeStyle Libre Flash Glucose Monitoring System. September 27, 2017. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160030B.pdf. Accessed on April 25, 2023.

Automated Insulin Delivery Systems

Peer Reviewed Publications:

1. Abraham MB, de Bock M, Paramalingam N, et al. Prevention of insulin-induced hypoglycemia in Type 1 diabetes with predictive low glucose management system. Diabetes Technol Ther. 2016; 18(7):436-443.
2. Agrawal P, Zhong A, Welsh JB, et al. Retrospective analysis of the real-world use of the threshold suspend feature of sensor-augmented insulin pumps. Diabetes Technol Ther. 2015; 17(5):316-319.
3. Anderson SM, Raghinaru D, Pinsker JE, et al.; Control to Range Study Group. Multinational home use of closed-loop control is safe and effective. Diabetes Care. 2016; 39(7):1143-1150.
4. Bally L, Thabit H, Hartnell S, et al. Closed-loop insulin delivery for glycemic control in noncritical care. N Engl J Med. 2018; 379(6):547-556
5. Bally L, Thabit H, Kojzar H, et al. Day-and-night glycaemic control with closed-loop insulin delivery versus conventional insulin pump therapy in free-living adults with well controlled type 1 diabetes: an open-label, randomised, crossover study. Lancet Diabetes Endocrinol. 2017; 5(4):261-270.
6. Benhamou PY, Huneker E, Franc S, et al.; Diabeloop Consortium. Customization of home closed-loop insulin delivery in adult patients with type 1 diabetes, assisted with structured remote monitoring: the pilot WP7 Diabeloop study. Acta Diabetol. 2018; 55(6):549-556.
7. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a hybrid closed-loop insulin delivery system in patients with Type 1 diabetes. JAMA. 2016; 316(13):1407-1408.
8. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med. 2013; 369(3):224-232.
9. Breton MD, Kanapka LG, Beck RW, et al. A randomized trial of closed-loop control in children with type 1 diabetes. N Engl J Med. 2020; 383(9):836-845.
10. Breton MD, Kovatchev BP. One year real-world use of the Control-IQ advanced hybrid closed-loop technology. Diabetes Technol Ther. 2021; 23(9):601-608.

11. Brown SA, Beck RW, Raghinaru D, et al.; iDCL Trial Research Group. Glycemic outcomes of use of CLC versus PLGS in type 1 diabetes: a randomized controlled trial. Diabetes Care. 2020; 43(8):1822-1828.
12. Brown SA, Breton MD, Anderson SM, et al. Overnight closed-loop control improves glycemic control in a multicenter study of adults with type 1 diabetes. J Clin Endocrinol Metab. 2017; 102(10):3674-3682.
13. Brown SA, Kovatchev BP, Breton MD, et al. Multinight "bedside" closed-loop control for patients with type 1 diabetes. Diabetes Technol Ther. 2015; 17(3):203-209.
14. Brown SA, Kovatchev BP, Raghinaru D, et al.; iDCL Trial Research Group. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. N Engl J Med. 2019; 381(18):1707-1717.
15. Buckingham BA, Bailey TS, Christiansen M, et al. Evaluation of a predictive low-glucose management system in-clinic. Diabetes Technol Ther. 2017; 19(5):288-292.
16. Carlson AL, Sherr JL, Shulman DI, et al. Safety and glycemic outcomes during the MiniMed™ advanced hybrid closed-loop system pivotal trial in adolescents and adults with type 1 diabetes. Diabetes Technol Ther. 2022 Mar;24(3):178-189.
17. Collyns OJ, Meier RA, Betts ZL, et al. Improved glycemic outcomes with Medtronic MiniMed Advanced hybrid closed-loop delivery: results from a randomized crossover trial comparing automated insulin delivery with predictive low glucose suspend in people with type 1 diabetes. Diabetes Care. 2021; 44(4):969-975.
18. de Bock M, Dart J, Roy A, et al. Exploration of the performance of a hybrid closed-loop insulin delivery algorithm that includes insulin delivery limits designed to protect against hypoglycemia. J Diabetes Sci Technol. 2017; 11(1):68-73.
19. DeBoer MD, Breton MD, Wakeman C, et al. Performance of an artificial pancreas system for young children with type 1 diabetes. Diabetes Technol Ther. 2017; 19(5):293-298.
20. Del Favero S, Place J, Kropff J, et al.; AP@home Consortium. Multicenter outpatient dinner/overnight reduction of hypoglycemia and increased time of glucose in target with a wearable artificial pancreas using modular model predictive control in adults with type 1 diabetes. Diabetes Obes Metab. 2015; 17(5):468-476.
21. Ekhlaspour L, Forlenza GP, Chernavvsky D, et al. Closed loop control in adolescents and children during winter sports: use of the Tandem Control-IQ AP system. Pediatr Diabetes. 2019; 20(6):759-768.
22. Forlenza GP, Li Z, Buckingham BA, et al. Predictive low-glucose suspend reduces hypoglycemia in adults, adolescents, and children with type 1 diabetes in an at-home randomized crossover study: results of the PROLOG trial. Diabetes Care. 2018; 41(10):2155-2161.
23. Forlenza GP, Nathan BM, Moran AM, et al. Successful application of closed-loop artificial pancreas therapy after islet autotransplantation. Am J Transplant. 2016; 16(2):527-534.
24. Forlenza GP, Pinhas-Hamiel O, Liljenquist DR, et al. Safety evaluation of the MiniMed 670G System in children 7-13 years of age with type 1 diabetes. Diabetes Technol Ther. 2019; 21(1):11-19.
25. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. Diabetes Technol Ther. 2017; 19(3):155-163.
26. Gill M, Chhabra H, Shah M, et al. C-peptide and beta-cell autoantibody testing prior to initiating continuous subcutaneous insulin infusion pump therapy did not improve utilization or medical costs among older adults with diabetes mellitus. Endocr Pract. 2018; 24(7):634-645.

27. Gómez AM, Marín Carrillo LF, Muñoz Velandia OM, et al. Long-term efficacy and safety of sensor augmented insulin pump therapy with low-glucose suspend feature in patients with Type 1 diabetes. Diabetes Technol Ther. 2017; 19(2):109-114.
28. Isganaitis E, Raghinaru D, Ambler-Osborn L, et al.; iDCL Trial Research Group. Closed-loop insulin therapy improves glycemic control in adolescents and young adults: outcomes from the international diabetes closed-loop trial. Diabetes Technol Ther. 2021; 23(5):342-349.
29. Kanapka LG, Wadwa RP, Breton MD, et al.; iDCL Trial Research Group. Extended use of the Control-IQ closed-loop control system in children with type 1 diabetes. Diabetes Care. 2021; 44(2):473-478.
30. Kovatchev B, Cheng P, Anderson SM, et al. Feasibility of long-term closed-loop control: a multicenter 6-month trial of 24/7 automated insulin delivery. Diabetes Technol Ther. 2017; 19(1):18-24.
31. Kovatchev BP, Renard E, Cobelli C, et al. Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas. Diabetes Care. 2014; 37(7):1789-1796.
32. Kropff J, Del Favero S, Place J, et al.; AP@home Consortium. 2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial. Lancet Diabetes Endocrinol. 2015; 3(12):939-947.
33. Leelarathna L, Dellweg S, Mader JK, et al.; AP@home Consortium. Day and night home closed-loop insulin delivery in adults with type 1 diabetes: three-center randomized crossover study. Diabetes Care. 2014; 37(7):1931-1937.
34. Ly TT, Breton MD, Keith-Hynes P, et al. Overnight glucose control with an automated, unified safety system in children and adolescents with type 1 diabetes at diabetes camp. Diabetes Care. 2014; 37(8):2310-2316.
35. Ly TT, Nicholas JA, Retterath A, et al. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. JAMA. 2013; 310(12):1240-1247.
36. McAuley SA, Lee MH, Paldus B, et al.; Australian JDRF Closed-Loop Research Group. Six months of hybrid closed-loop versus manual insulin delivery with fingerprick blood glucose monitoring in adults with type 1 diabetes: a randomized, controlled trial. Diabetes Care. 2020; 43(12):3024-3033.
37. Messer LH, Berget C, Pyle L, et al. Real-world use of a new hybrid closed loop improves glycemic control in youth with type 1 diabetes. Diabetes Technol Ther. 2021; 23(12):837-843.
38. Messer LH, Forlenza GP, Sherr JL, et al. optimizing hybrid closed-loop therapy in adolescents and emerging adults using the MiniMed 670G system. Diabetes Care. 2018; 41(4):789-796.
39. Nimri R, Bratina N, Kordonouri O, et al. MD-Logic overnight type 1 diabetes control in home settings: a multicentre, multinational, single blind randomized trial. Diabetes Obes Metab. 2017; 19(4):553-561.
40. Nimri R, Muller I, Atlas E, et al. Night glucose control with MD-Logic artificial pancreas in home setting: a single blind, randomized crossover trial-interim analysis. Pediatr Diabetes. 2014a; 15(2):91-99.
41. Nimri R, Muller I, Atlas E, et al. MD-Logic overnight control for 6 weeks of home use in patients with type 1 diabetes: randomized crossover trial. Diabetes Care. 2014b; 37(11):3025-3032.
42. Pulkkinen MA, Varimo TJ, Hakonen ET, et al. 780G™ in 2- to 6-year-old children: safety and clinical outcomes after the first 12 weeks. Diabetes Technol Ther. 2023; 25(2):100-107.
43. Renard E, Farret A, Kropff J, et al.; AP@home Consortium. Day-and-night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: results of a single-arm 1-month experience

compared with a previously reported feasibility study of evening and night at home. Diabetes Care. 2016; 39(7):1151-1160.
44. Sharifi A, De Bock MI, Jayawardene D, et al. Glycemia, treatment satisfaction, cognition, and sleep quality in adults and adolescents with Type 1 diabetes when using a closed-loop system overnight versus sensor-augmented pump with low-glucose suspend function: a randomized crossover study. Diabetes Technol Ther. 2016; 18(12):772-783.
45. Sherr JL, Buckingham BA, Forlenza GP, et al. Safety and performance of the Omnipod hybrid closed-loop system in adults, adolescents, and children with type 1 diabetes over 5 days under free-living conditions. Diabetes Technol Ther. 2020; 22(3):174-184.
46. Stewart ZA, Wilinska ME, Hartnell S, et al. Closed-loop insulin delivery during pregnancy in women with Type 1 diabetes. N Engl J Med. 2016; 375(7):644-654.
47. Tauschmann M, Allen JM, Wilinska ME, et al. Day-and-night hybrid closed-loop insulin delivery in adolescents with Type 1 diabetes: a free-living, randomized clinical trial. Diabetes Care. 2016a; 39(7):1168-1174.
48. Tauschmann M, Allen JM, Wilinska ME, et al. Home use of day-and-night hybrid closed-loop insulin delivery in suboptimally controlled adolescents with Type 1 diabetes: a 3-week, free-living, randomized crossover trial. Diabetes Care. 2016b; 39(11):2019-2025.
49. Tauschmann M, Allen JM, Wilinska ME, et al. Sensor life and overnight closed-loop: a randomized clinical trial. J Diabetes Sci Technol. 2017; 11(3):513-521.
50. Thabit H, Hartnell S, Allen JM, et al. Closed-loop insulin delivery in inpatients with type 2 diabetes: a randomised, parallel-group trial. Lancet Diabetes Endocrinol. 2017; 5(2):117-124.
51. Tauschmann M, Thabit H, Bally L, et al; APCam11 Consortium. closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. Lancet. 2018; 392(10155):1321-1329.
52. van Beers CA, DeVries JH, Kleijer SJ, et al. Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial. Lancet Diabetes Endocrinol. 2016; 4(11):893-902.
53. Vigersky RA, Huang S, Cordero TL, et al. OpT2mise Study Group. Improved HbA1c, total daily insulin dose, and treatment satisfaction with insulin pump therapy compared to multiple daily insulin injections in patients with type 2 diabetes irrespective of baseline c-peptide levels. Endocr Pract. 2018; 24(5):446-452.
54. Weisman A, Bai JW, Cardinez M, et al. Effect of artificial pancreas systems on glycaemic control in patients with type 1 diabetes: a systematic review and meta-analysis of outpatient randomised controlled trials. Lancet Diabetes Endocrinol. 2017; 5(7):501-512.
55. Zisser H, Renard E, Kovatchev B, et al.; Control to Range Study Group. Multicenter closed-loop insulin delivery study points to challenges for keeping blood glucose in a safe range by a control algorithm in adults and adolescents with type 1 diabetes from various sites. Diabetes Technol Ther. 2014; 16(10):613-622.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Diabetes Association. Standards of Care in Diabetes-2022. Diabetes Care. 2022; 45(Suppl 1):S1-S2702.
2. Grunberger G, Handelsman Y, Bloomgarden ZT, Fonseca VA, Garber AJ, Haas RA, Roberts VL, Umpierrez GE. American Association of Clinical Endocrinologists and American College of Endocrinology 2018

position statement on integration of insulin pumps and continuous glucose monitoring in patients with diabetes mellitus. Endocr Pract. 2018; 24(3):302-308.
3. Grunberger G, Sherr J, Allende M, et al. American Association of Clinical Endocrinology clinical practice guideline: the use of advanced technology in the management of persons with diabetes mellitus. Endocr Pract. 2021; 27(6):505-537.
4. Peters AL, Ahmann AJ, Hirsch IB, Raymond JK. Advances in glucose monitoring and automated insulin delivery: supplement to Endocrine Society Clinical Practice Guidelines. J Endocr Soc. 2018; 2(11):1214-1225.
5. U.S Food and Drug Administration. Summary of safety and effectiveness data for the MiniMed 670G system. September 28, 2016. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf16/P160017b.pdf. Accessed on April 25, 2023.
6. U.S Food and Drug Administration. Summary of safety and effectiveness data for the MiniMed 780G system. April 21, 2023. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160017S091B.pdf . Accessed on April 25, 2023.
7. U.S Food and Drug Administration. Types of Artificial Pancreas Device Systems. Updated December 17, 2017. Available at: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/ArtificialPancreas/ucm259555.htm. Accessed on April 25, 2023.

Websites for Additional Information

1. Abbott. Freestyle Libre. Available at: https://www.freestyle.abbott/us-en/home.html. Accessed on April 25, 2023.
2. American Diabetes Association. 2020 Consumer guides. Available at: https://consumerguide.diabetes.org/. Accessed on April 25, 2023.
3. American Diabetes Association. Type 1 diabetes. Available at: http://www.diabetes.org/diabetes-basics/type-1/. Accessed on April 25, 2023.
4. American Diabetes Association. Type 2 diabetes. Available at: http://www.diabetes.org/diabetes-basics/type-2/?loc=db-slabnav/. Accessed on April 25, 2023.

Index

A6 TouchCare
Accu-Check Solo®
Control IQ
Dexcom G5
Dexcom G6
Dexcom G7
Enlite Sensor
Eversense Continuous Glucose Monitoring System
FreeStyle Insulin Infusion Systems

Continuous Glucose Monitoring Devices and External Insulin Infusion Pumps

Freestyle Libre 2
Freestyle Libre 3
Libre 14 Day Flash Glucose Monitoring System
JewelPUMP™
JewelPUMP™ 2
MiniMed 530G
MiniMed 630G
MiniMed 670G
MiniMed 770G
MiniMed 780G
Omnipod
Paradigm REAL-Time System
Portable External Insulin Pump
Senseonics Eversense Continuous Glucose Monitoring System
Solo™ MicroPump
Subcutaneous External Insulin Pump
Tandem t:slim X2 with Basal-IQ
Tandem t:slim X2 with Control-IQ

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Revised	05/11/2023	Medical Policy & Technology Assessment Committee (MPTAC). Revised hierarchy and formatting of external infusion pump criteria. Revised MN criteria for external insulin infusion pumps (group A). Revised the MN criteria for *personal long-term use* of continuous interstitial glucose monitoring devices so that the HbA1c range of "7% to 10%" was changed to "7% or greater". Added MN and NMN continued use criteria for external insulin pumps, continuous interstitial glucose monitoring devices, and open-loop or hybrid closed-loop automated insulin delivery systems. Updated Discussion, References, and Index sections.
	12/28/2022	Updated Coding section with 01/01/2023 HCPCS changes; added A4239, E2103 replacing K0553, K0554 deleted 12/31/2022, and revised descriptors for A4238, A9276, A9277, A9278, E2102.
Revised	05/12/2022	MPTAC. Revised title. Added MN statements addressing implantable CGM device implantation and replacement (formerly in MED.00121 Implantable Interstitial Glucose Monitors) to this document. Updated Description,

		Discussion, and References sections. Updated Coding section to add 0446T, 0448T previously addressed in MED.00121; also updated with 07/01/2022 HCPCS changes to add G0308, G0309.
	04/01/2022	Updated Coding section with 04/01/2022 HCPCS changes; added A4238, E2102.
Revised	05/13/2021	MPTAC. Clarified MN statement for external insulin pumps. Updated References section.
	01/11/2021	Corrected typographical error in references section.
	11/17/2020	Corrected criteria B in Clinical Indications section for personal long-term use of CGMs regarding type of diabetes.
Revised	11/05/2020	MPTAC review. Clarified type of diabetes throughout Clinical Indications section. Simplified blood glucose testing criteria throughout Clinical Indications section. Simplified hyper- and hypoglycemia criteria throughout Clinical Indications section. Added use of a CGM to insulin pump MN criteria. Simplified criteria for duration of professional CGM use. Lowered age criteria from > 24 y/o to > 14 y/o for use of CGMs by individuals in the absence of frequent hypoglycemic episodes. Expanded professional (short-term) and personal (long-term) CGM criteria to include treatment of individuals with all types of diabetes mellitus. Lowered MN age criteria for open-loop or hybrid closed-loop automated insulin delivery systems from 7 to 2 years of age. Updated Description, Discussion/General Information, References, and Index sections. Reformatted Coding section.
Revised	05/14/2020	MPTAC review. Relocated information regarding device details from Description section to the Websites section. Added additional example of disposable external insulin pump without wireless communication capability to NMN statement. Updated Discussion, Rationale and References sections.
	12/31/2019	Updated Coding section with 01/01/2020 HCPCS changes; added E0787.
Revised	06/06/2019	MPTAC review. Added notes to Description section addressing device types. Clarified and updated formatting in the Clinical Indications section. Updated Discussion, Definitions, References, and Index sections.
Reviewed	09/13/2018	MPTAC review. Updated Discussion and References sections.
New	01/25/2018	MPTAC review. Initial document development. Combined content from three documents into this document: CG-DME-01 External (Portable) Continuous Insulin Infusion Pumps, CG-DME-38 Continuous Interstitial Glucose Monitoring, and DME.00040 Automated Insulin Delivery Devices.