Medical Policy

BlueCross BlueShield of Kansas
An independent licensee of the Blue Cross Blue Shield Association

Title: Continuous or Intermittent Monitoring of Glucose in Interstitial Fluid

Professional
Original Effective Date: June 27, 2001
Revision Date(s): September 3, 2003; January 26, 2004; April 21, 2005; November 2, 2006; July 17, 2007; September 3, 2008; September 9, 2009; March 25, 2011; October 4, 2013; March 6, 2015; August 4, 2016; October 1, 2016; November 22, 2016; July 1, 2017; September 1, 2017; December 1, 2017; January 1, 2018; May 11, 2018; November 7, 2018; January 16, 2019
Current Effective Date: May 11, 2018

Institutional
Original Effective Date: July 1, 2005
Revision Date(s): November 2, 2006; July 17, 2007, September 3, 2008; September 9, 2009; March 25, 2011; October 4, 2013; March 6, 2015; August 4, 2016; October 1, 2016; November 22, 2016; July 1, 2017; September 1, 2017; December 1, 2017; January 1, 2018; May 11, 2018; November 7, 2018; January 16, 2019
Current Effective Date: May 11, 2018

Populations	Interventions	Comparators	Outcomes
Individuals: • With type 1 diabetes who are willing and able to use the device, and have adequate medical supervision	Interventions of interest are: • Long-term (continuous) glucose monitoring	Comparators of interest are: • Self-monitoring of blood glucose	Relevant outcomes include: • Symptoms • Morbid events • Quality of life • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With type 1 diabetes	Interventions of interest are: • Short-term (intermittent) glucose monitoring	Comparators of interest are: • Self-monitoring of blood glucose	Relevant outcomes include: • Symptoms • Morbid events • Quality of life • Treatment-related morbidity
Individuals: • With type 2 diabetes	Interventions of interest are: • Long-term (continuous) glucose monitoring	Comparators of interest are: • Self-monitoring of blood glucose	Relevant outcomes include: • Symptoms • Morbid events • Quality of life • Treatment-related morbidity
Individuals: • With type 2 diabetes	Interventions of interest are: • Short-term (intermittent) glucose monitoring	Comparators of interest are: • Self-monitoring of blood glucose	Relevant outcomes include: • Symptoms • Morbid events • Quality of life • Treatment-related morbidity
Individuals: • Who are pregnant with gestational diabetes	Interventions of interest are: • Long-term (continuous) or short-term (intermittent) glucose monitoring	Comparators of interest are: • Self-monitoring of blood glucose	Relevant outcomes include: • Symptoms • Morbid events • Quality of life • Treatment-related morbidity

DESCRIPTION

Tight glucose control in patients with diabetes has been associated with improved outcomes. Several devices are available to measure glucose levels automatically and frequently (eg, every 5-10 minutes). The devices measure glucose in the interstitial fluid and are approved as adjuncts to traditional self-monitoring of blood glucose levels. Devices can be used on an intermittent (short-term) basis or a continuous (long-term) basis.

OBJECTIVE

The objective of this policy is to evaluate whether continuous glucose monitoring improves the net health outcome in patients with type 1, type 2, or gestational diabetes.

BACKGROUND

Blood Glucose Control

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

decrease in risk for progression of diabetic retinopathy and 25% decrease in risk for progression of renal disease.[1]

Due to an increase in turnover of red blood cells during pregnancy, HbA_{1c} is slightly lower in women with a normal pregnancy compared with nonpregnant women. The target A_{1c} in women with diabetes is also lower in pregnancy. The American Diabetes Association recommends that, if achievable without significant hypoglycemia, the A_{1c} should range between 6.0 to 6.5%; an A_{1c} less than 6% may be optimal as the pregnancy progresses.[2]

Tight glucose control requires multiple daily measurements of blood glucose (ie, before meals and at bedtime), a commitment that some patients may be unwilling or unable to meet. Also, the goal of tight glucose control has to be balanced with an associated risk of hypoglycemia. Hypoglycemia is known to be a risk in patients with type 1 diabetes. While patients with insulin-treated type 2 diabetes may also experience severe hypoglycemic episodes, there is a lower relative likelihood of severe hypoglycemia compared with patients who had type 1 diabetes.[3,4] An additional limitation of periodic self-measurements of blood glucose is that glucose levels are seen in isolation, and trends in glucose levels are undetected. For example, while a diabetic patient's fasting blood glucose level might be within normal values, hyperglycemia might be undetected postprandially, leading to elevated HbA_{1c} levels.

Management

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

Several devices have received approval from the U.S. Food and Drug Administration (FDA). The first approved devices were the Continuous Glucose Monitoring System (MiniMed), which uses an implanted temporary sensor in the subcutaneous tissues, and the GlucoWatch G2 Biographer, an external device worn like a wristwatch that measures glucose in interstitial fluid extracted through the skin by electric current (referred to as reverse iontophoresis).

Devices subsequently approved include those for pediatric use and those with more advanced software, more frequent measurements of glucose levels, or more sophisticated alarm systems. Devices initially measured interstitial glucose every 5 to 10 minutes and stored data for download and retrospective evaluation by a clinician. With currently available devices, the intervals at which interstitial glucose is measured ranges from every 1 to 2 minutes to 5 minutes, and most provide measurements in real-time directly to patients. While CGM potentially eliminates or decreases the number of required daily fingersticks, it should be noted that, according to the FDA labeling, monitors are not intended as an alternative to traditional self-monitoring of blood glucose

levels but rather as adjuncts to monitoring, supplying additional information on glucose trends not available from self-monitoring. Also, devices may be used intermittently (ie, for periods of 72 hours) or continuously (ie, on a long-term basis).

In addition to stand-alone continuous glucose monitors, several insulin pump systems have a built-in CGM. This evidence review addresses CGM devices, not the insulin pump portion of these systems.

REGULATORY STATUS

Several continuous glucose monitoring systems have been approved by the FDA through the premarket approval process (see Table 1):

Table 1. CGM Systems Approved by the Food and Drug Administration

Device	Manufacturer	Approval	Indications
Continuous Glucose Monitoring System (CGMS®)	MiniMed	1999	3-d use in physician's office
GlucoWatch G2® Biographer		2001	Not available since 2008
Guardian®-RT (Real-Time) CGMS	MiniMed (now Medtronic)	2005	
Dexcom® STS CGMS system	Dexcom	2006	
Paradigm® REAL-Time System (second generation called Paradigm Revel System)	MiniMed (now Medtronic)	2006	Integrates a CGM with a Paradigm insulin pump
FreeStyle Navigator® CGM System	Abbott	2008	
Dexcom® G4 Platinum	Dexcom	2012	Adults ≥18 y; can be worn for up to 7 d
		2014	Expanded to include patients with diabetes 2-17 y
Dexcom® G5 Mobile CGM	Dexcom	2016[a]	Replacement for fingerstick blood glucose testing in patients ≥2 y. System requires at least 2 daily fingerstick tests for calibration purposes, but additional fingersticks are not necessary because treatment decisions can be made based on device readings[5]
Freestyle Libre® Pro Flash Glucose Monitoring System	Abbott	2017	Adults ≥18 y. Readings are only made available to patients through consultation with a health care professional. Does not require user calibration with blood glucose values
Dexcom® G6 Mobile CGM	Dexcom	2018	For determining blood glucose levels in children ages ≥2 and adults with diabetes

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

FDA product codes: MDS, PQF.

POLICY

A. Intermittent monitoring, ie, up to 72 hours, of glucose levels in interstitial fluid may be considered **medically necessary** in patients with type 1 diabetes whose diabetes is poorly controlled, despite current use of best practices (see Policy Guidelines). Poorly controlled type 1 diabetes includes the following clinical situations:

   1. Unexplained hypoglycemic episodes;

   2. Hypoglycemic unawareness;

   3. Suspected postprandial hyperglycemia; and

   4. Recurrent diabetic ketoacidosis.

B. Intermittent monitoring of glucose levels in interstitial fluid may also be considered **medically necessary** in patients with type 1 diabetes prior to insulin pump initiation to determine basal insulin levels.

C. Continuous, ie, long-term, monitoring of glucose levels in interstitial fluid, including real-time monitoring, as a technique of diabetic monitoring, may be considered **medically necessary** when the following situations occur, despite use of best practices:

   1. Patients with type 1 diabetes who have recurrent, unexplained, severe (generally blood glucose levels less than 50 mg/dL) hypoglycemia or impaired awareness of hypoglycemia that puts the patient or others at risk; **OR**

   2. Patients with type 1 diabetes who have recurrent diabetic ketoacidosis (DKA) requiring emergency room visits and admissions; **OR**

   3. Patients with poorly controlled type 1 diabetes who are pregnant. Poorly controlled type 1 diabetes includes unexplained hypoglycemic episodes, hypoglycemic unawareness, suspected postprandial hyperglycemia, and recurrent diabetic ketoacidosis; **OR**

   4. Patients with type 1 diabetes who have demonstrated an understanding of the technology, are motivated to use the device correctly and consistently, are expected to adhere to a comprehensive diabetes treatment plan supervised by a qualified provider, and are capable of using the device to recognize alerts and alarms.

D. Other uses of continuous and intermittent monitoring of glucose levels in interstitial fluid as a technique of diabetic monitoring are considered **experimental / investigational**.

Note: Hypoglycemic unawareness is reversible. Meticulous avoidance of hypoglycemia for several weeks is sufficient to restore awareness of hypoglycemia. Hypoglycemia Anticipation, Awareness and Treatment Training/Blood Glucose Awareness Training (HAATT/BGAT) has been proven to reduce the occurrence of severe hypoglycemia.

Policy Guidelines

1. Several insulin pump systems (eg, Paradigm® REAL-Time System) have a built-in continuous glucose monitor (CGM). This policy is evaluating the CGM-device only; the policy does not evaluate insulin pumps. In the case of insulin pumps systems with a built-in CGM and low glucose suspend (LGS) feature, the CGM device and the low glucose suspend feature are evaluated in this policy, not the insulin pump.
2. Best practices in diabetes control include compliance with a regimen of an average of 4 or more fingersticks each day (at least 30 days [1 month] prior to initiation) and use of an insulin pump or multiple daily injections. Compliance will also be required for other aspects of diabetic management including insulin bolusing or diet. During pregnancy, 3 or more insulin injections daily could also be considered best practice for patients not on an insulin pump prior to the pregnancy. Prior use of an intermittent (72-hour) glucose monitor would be considered a part of best practices for those considering use of a continuous glucose monitor.
3. Individuals with type 1 diabetes taking insulin who are pregnant or about to become pregnant with poorly controlled diabetes are another subset of patients to whom the policy statement on intermittent monitoring may apply.
4. Intermittent monitoring is generally conducted in 72-hour periods. It may be repeated at a subsequent time depending on the patient's level of diabetes control.
5. The strongest evidence exists for use of CGM devices in patients age 25 and older. However, age may be a proxy for motivation and good control of disease, so it is also reasonable to select patients based on their ability to self-manage their disease, rather than age.
6. Providers board certified in endocrinology, perinatologists, and/or providers with a focus on the practice of diabetes care may be considered qualified to evaluate and oversee individuals for continuous (ie, long-term) monitoring.

RATIONALE

A TEC Assessment was published in 2003.[6] The most recent literature review was performed for the period through July 7, 2018. Following is a summary of the key literature to date.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific

outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

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

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

Type 1 Diabetes

In some parts of the analysis of type 1 diabetes, BCBSA combines discussion of indications 1 (long-term) and 2 (short-term) glucose monitoring because several systematic reviews and RCTs provided information relevant to both indications.

Clinical Context and Therapy Purpose

The purpose of long-term CGM and short-term (intermittent) glucose monitoring devices is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with type 1 diabetes.

The question addressed in this evidence review is: Does use of a CGM device or a short-term (intermittent) glucose monitor device improve the net health outcome for individuals with type 1 diabetes?

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

Patients

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

Interventions

The therapies being considered are a CGM device to direct insulin regimens and an intermittent (ie, 72 hours) short-term glucose monitor device to optimize management.

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

Outcomes
The general outcomes of interest are change in hemoglobin A_{1c} (HbA_{1c}) levels, time spent in hypoglycemia, incidence of hypoglycemic events, complications of hypoglycemia, and quality of life.

Timing
To assess short-term outcomes such as HbA_{1c} levels, a minimum follow-up of 8 to 12 weeks is appropriate. To assess long-term outcomes such as time spent in hypoglycemia, incidence of hypoglycemic events, complications of hypoglycemia and quality of life, follow-up of 6 months to 1 year would be appropriate.

Setting
CGM devices and intermittent short-term glucose monitor devices may be used in home, outpatient, or inpatient setting and monitored patients and multispecialty physicians.

CGM Devices for Long-Term Use
Systematic Reviews
A number of systematic reviews and meta-analyses have assessed RCTs evaluating CGM for long-term, daily use in treating type 1 diabetes.[7-12] These systematic reviews have focused on slightly different populations, and some did not separate long-term CGM from intermittent glucose monitoring.[10] The most recent meta-analysis, and the only analysis to use individual patient data, was published by Benkhadra et al (2017).[13] The meta-analysis evaluated data from 11 RCTs that enrolled patients with type 1 diabetes and compared real-time CGM with a control intervention. Studies in which patients used insulin pumps or received multiple daily insulin injections were included. Reviewers contacted corresponding study authors requesting individual patient data; data were not obtained for 1 trial. Mean baseline HbA_{1c} levels were 8.2% in adults and 8.3% in children and adolescents. The overall risk of bias in the studies was judged to be moderate. In pooled analyses, there was a statistically significantly greater decrease in HbA_{1c} levels with real-time CGM vs control conditions. Overall, the degree of difference between groups was 0.26%. In subgroup analyses by age, there was a significantly greater change in HbA_{1c} levels among individuals 15 years and older, but not among the younger age groups. There were no significant differences between groups in the time spent in hypoglycemia or the incidence of hypoglycemic events. Key findings are shown in Table 2.

Table 2. Individual Patient Data Meta-Analytic Outcomes for Real-Time CGM in Type 1 Diabetes

No. of Trials	N	Group	Point Estimate	95% Confidence Intervals	p
Change in HbA_{1c} levels, %					
8	1371	Overall	-0.258	0.464 to -0.052	0.014
7	902	Age >15 y	-0.356	0.551 to -0.160	<0.001
7	178	Age 13-15 y	-0.039	-0.320 to 0.242	0.787
7	291	Age ≤12 y	-0.047	0.217 to 0.124	0.592
Time spent in hypoglycemia <60 mg/dL, min					
4	706	Overall	-8.549	-31.083 to 13 985	0.457
4	467	Age >15 y	-8.095	-32.615 to 16.425	0.518
3	109	Age 13-15 y	-13.966	31.782 to 3.852	0.124

No. of Trials	N	Group	Point Estimate	95% Confidence Intervals	p
3	130	Age ≤12 y	-9.366	19.898 to 1.167	0.081
Incidence of hypoglycemic events <70 mg/dL, mean no. events					
3	351	Overall	0.051	-0.314 to 0.416	0.785
3	277	Age >15 y	-0.074	-0.517 to 0.368	0.742
2	47	Age 13-15 y	0.536	0.243 to 1.316	0.177
2	27	Age ≤12 y	0.392	0.070 to 0.854	0.097

Adapted from Benkhadra et al (2017).[13]
CGM: continuous glucose monitoring: HbA_{1c}: hemoglobin A_{1c}.

Earlier meta-analyses of glucose monitoring devices for type 1 diabetes tended to combine studies of intermittent glucose monitoring with studies of long-term CGM. Several reported separate subgroup analyses for long-term CGM. A Cochrane review by Langendam et al (2012) assessed CGM in type 1 diabetes in adults and children included RCTs; it compared CGM with conventional self-monitored blood glucose (SMBG).[9] In pooled analysis (6 studies; n=963 patients) of studies of long-term CGM, the average decline in HbA_{1c} levels 6 months after baseline was statistically significantly larger for CGM users than for SMBG users (mean difference [MD], -0.2%; 95% confidence interval [CI], -0.4% to -0.1%), but there was no difference in the decline in HbA_{1c} levels at 12 months (1 study, n=154 patients; MD, 0.1%; 95% CI, -0.5% to 0.7%). In a meta-analysis of 4 RCTs (n=689 patients), there was no significant difference in the risk of severe hypoglycemia between CGM and SMBG users and the CI for the relative risk was wide (relative risk, 1.05; 95% CI, 0.63 to 1.77), indicating lack of precision in estimating the effect of CGM on hypoglycemia risk. Reviewers were unable to compare longer term change in HbA_{1c} levels or hypoglycemia outcomes for real-time CGM. Trials reporting results by compliance subgroups found larger treatment effects in highly compliant patients.

A systematic review by Wojciechowski et al (2011) evaluating CGM included RCTs conducted in adults and children with type 1 diabetes.[11] Reviewers selected studies having a minimum of 12 weeks of follow-up and requiring patients be on intensive insulin regimens. Studies compared CGM with SMBG; there was no restriction on the type of CGM device, but CGM readings had to be used to adjust insulin dose or modify diet. Fourteen RCTs met eligibility criteria. Study durations ranged from 3 to 6 months. Baseline mean HbA_{1c} levels ranged from 6.4% to 10%. Five included studies found a statistically significant decrease in HbA_{1c} levels favoring CGM, while nine did not. In a pooled analysis, there was a statistically significant reduction in HbA_{1c} levels with CGM compared with SMBG (weighted mean difference [WMD], -0.26%; 95% CI, -0.34% to -0.19%). For the subgroup of 7 studies that reported on long-term CGM, this difference was statistically significant (WMD = -0.26; 95% CI, -0.34 to -0.18). In a subgroup analysis by age, there were significant reductions in HbA_{1c} levels with CGM in 5 studies of adults (WMD = -0.33; 95% CI, -0.46 to -0.20) and in 8 studies with children and/or adolescents (WMD = -0.25; 95% CI, -0.43 to -0.08). Four of the studies provided data on the frequency of hypoglycemic episodes. Pooled results showed a significant reduction in hypoglycemic events for CGM vs SMBG (standardized mean difference, -0.32; 95% CI, -0.52 to -0.13). In 5 studies reporting the percentage of patients with severe hypoglycemic episodes, there were no differences in the percentages of patients with severe hypoglycemic episodes using CGM and SMBG.

Randomized Controlled Trials

Recent RCTs not included in the meta-analyses above are described next. For example, van Beers et al (2016) published a crossover RCT comparing CGM with SMBG and focused on patients with impaired hypoglycemia awareness.[14] Eligible patients were 18 to 75 years old, were treated

with insulin infusion pumps or multiple daily insulin injections, undertook at least 3 SMBG measurements per day, and had impaired awareness of hypoglycemia (ie, Gold score ≥4[15]). The trial used an artificial pancreas device system without using the low-glucose suspend feature. After a 6-week run-in phase (during which patients received education about diabetes management), 52 patients received both 16 weeks of CGM and 16 weeks of SMBG, in random order. There was a 12-week washout period between interventions. All patients were included in the primary intention-to-treat analysis. Six patients withdrew early from the study.

The primary outcome (time spent in normoglycemia [4-10 mmol/L]) was significantly higher in the CGM phase than in the SMBG phase. The percentage of time spent in normoglycemia was 65.0% in the CGM phase and 55.4% in the SMBG group (MD=9.6%; p<0.001). The sequence allocation did not affect the primary end point. Most other CGM-derived outcomes (eg, number and duration of nocturnal hypoglycemia events) also significantly favored the CGM group. The total number of severe hypoglycemic events (ie, those needing third-party assistance) was 14 in the CGM phase and 34 in the SMBG phase, which differed significantly between groups (p=0.033). The number of patients with 1 or more severe hypoglycemic event during the intervention period, however, did not differ significantly between phases 10 in the CGM phase and 18 in the SMBG phase (p=0.062). HbA_{1c} outcomes did not differ significantly (eg, change in HbA_{1c} levels from baseline was -0.1% in both phases; p=0.449). Regarding hypoglycemia awareness (one of 4 variables), Gold score at the study end point differed significantly (mean, 4.6 for the CGM phase vs 5.0 for the SMBG phase, p=0.035); 3 other variables related to hypoglycemia awareness did not differ between groups.

Two 2017 RCTs evaluated long-term CGM in patients with type 1 diabetes treated with multiple daily insulin injections. Both trials used the Dexcom G4 CGM device. Lind et al (2017) reported on a crossover study with 142 adults ages 18 and older who had baseline HbA_{1c} levels of 7.5% or higher (mean baseline HbA_{1c} level, ≈8.5%).[16] There was a 6-week run-in period using a CGM device with masked data and patients were excluded from further participation if they did not believe they would use the device more than 80% of the time or did not perform an adequate number of calibrations during the run-in period. Enrolled patients underwent 26-week treatment periods with a CGM device and conventional therapy using SMBG, in random order. There was a 17-week washout period between intervention phases. The primary end point was the difference in HbA_{1c} levels at the end of each treatment period. Mean HbA_{1c} levels were 7.9% during CGM use and 8.4% during conventional therapy (MD = -0.4%; p<0.01). There were a large number of secondary end points. A portion of them were prespecified, and analyses took into consideration the statistical impact of multiple comparisons; the remaining secondary outcomes were considered descriptive, and p values were not reported. Among the prespecified secondary outcomes, treatment satisfaction (measured by the Diabetes Treatment Satisfaction Questionnaire) was significantly higher in the CGM phase than in the conventional treatment phase (p<0.001). Hypoglycemia outcomes were secondary descriptive outcomes. There was 1 (0.7%) severe hypoglycemic event during the CGM phase and 5 (3.5%) events during conventional therapy. The percentage of time with hypoglycemia (<70 mmol/L) was 2.8% during CGM treatment and 4.8% during conventional therapy.

In the second study, Beck et al (2017) randomized 158 patients on a 2:1 basis to 24 weeks of CGM (n=105) or usual care (n=53).[17] The trial included patients with type 1 diabetes who were ages 25 or older and had baseline HbA_{1c} levels between 7.5% and 10%. Before randomization, patients underwent a 2-week period using a CGM system (without seeing data from the CGM) to

ensure compliance. To be eligible, patients had to wear the CGM on at least 85% of days, calibrate the device at least twice daily, and perform SMBG at least 3 times daily. The primary outcome (change in HbA_{1c} levels at 24 weeks) was 1.0% in the CGM group and 0.4% in the usual care group ($p<0.001$), with a between-group difference of 0.6%. Prespecified secondary outcomes on the proportion of patients below a glycemic threshold at 24 weeks also favored the CGM group. The proportion of patients with HbA_{1c} levels less than 7.0% was 18 (18%) in the CGM group and 2 (4%) in the control group ($p=0.01$). The proportion of patients with HbA_{1c} levels less than 7.5% was 39 (38%) in the CGM group and 6 (11%) in the control group ($p<0.001$). Moreover, prespecified secondary outcomes related to hypoglycemia also differed significantly between groups, favoring the CGM group. The time spent in hypoglycemia less than 70 mg/dL was 43 minutes per day in the CGM group and 80 minutes per day in the usual care group ($p=0.002$). Comparable numbers for time spent at less than 50 mg/dL were 6 minutes per day in the CGM group and 20 minutes per day in the usual care group ($p=0.001$). The median change in the rate per 24 hours of hypoglycemia events lasting at least 20 minutes at less than 3.0 mmol/L (54 mg/dL) fell by 30% from 0.23 at baseline to 0.16 during follow-up in the CGM group but was practically unchanged (0.31 at baseline and 0.30 at follow-up) in the usual care group ($p=0.03$).[18] Quality of life measures assessing overall well-being (World Health Organization Well-Being Index), health status (EQ-5D-5L), diabetes distress (Diabetes Distress Scale), hypoglycemic fear (worry subscale of the Hypoglycemia Fear Survey), and hypoglycemic confidence (Hypoglycemic Confidence Scale) have also been reported.[19] There were no significant differences between CGM and usual care in changes in well-being, health status, or hypoglycemic fear. The CGM group demonstrated a greater increase in hypoglycemic confidence ($p=0.01$) and a greater decrease in diabetes distress ($p=0.01$) than the usual care group.

Pregnant Women

One trial of real-time CGM in pregnant women with type 1 diabetes has been reported. Study characteristics, results, and gaps are summarized here and in Tables 3 to 6. Feig et al (2017) reported results of 2 multicenter RCTs in women ages 18 to 40 with type 1 diabetes who were receiving intensive insulin therapy and who were either pregnant (≤13 weeks and 6 days of gestation) or planning a pregnancy.[20] The trial enrolling pregnant women is reviewed here. Women were eligible if they had a singleton pregnancy and HbA_{1c} levels between 6.5% and 10.0%. The trial was conducted at 31 hospitals in North America and Europe. Women were randomized to CGM (Guardian REAL-Time or MiniMed Minilink system) plus capillary glucose monitoring or capillary glucose monitoring alone. Women in the CGM group were instructed to use the devices daily. Women in the control group continued their usual method of capillary glucose monitoring. The target glucose range was 3.5 to 7.8 mmol/L and target HbA_{1c} levels were 6.5% or less in both groups. The primary outcome was the difference in change in HbA_{1c} levels from randomization to 34 weeks of gestation. The proportion of completed scheduled study visits was high in both groups; however, participants using CGM had more unscheduled contacts, which were attributed both to sensor issues and to sensor-related diabetes management issues. The median frequency of CGM use was 6.1 days per week (interquartile range, 4.0-6.8 d/wk) and 70% of pregnant participants used CGM for more than 75% of the time. The between-group difference in the change in HbA_{1c} levels from baseline to 34 weeks of gestation was statistically significant favoring CGM (MD = -0.19%; 95% CI, -0.34 to -0.03; $p=0.02$). Women in the CGM group spent an increased percentage of time in the recommended glucose control target range at 34 weeks of gestation (68% vs 61%, $p=0.003$). There were no between-group differences in maternal hypoglycemia, gestational weight gain, or total daily insulin dose. A smaller proportion of infants of mothers in the CGM group were large-for-

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

Table 3. RCT Characteristics for Real-Time CGM in Pregnant Women With Type 1 Diabetes

Study; Registration	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Feig et al (2017)[20]; NCT01788527	Canada, England, Scotland, Spain, Italy, Ireland, U.S.	31	2013-2016	Pregnant women (<14 wk gestation) with type 1 diabetes receiving intensive insulin therapy with HbA_{1c} levels between 6.5% and 10.0% (mean, 6.9%); mean age, 31 y	CGM (real-time) (n=108)	SMBG (n=107)

CGM: continuous glucose monitoring: HbA_{1c}: hemoglobin A_{1c}; RCT: randomized controlled trial; SMBG: self-monitored blood glucose.

Table 4. RCT Outcomes for Real-Time CGM in Pregnant Women With Type 1 Diabetes

	Infant				Maternal	
Study	Large-for-Gestational Age	Gestational Age at Delivery, wk	Severe Hypoglycemia	Caesarean Section	HbA_{1c} Levels: Change From Baseline to 34 Wk of Gestation	Severe Hypoglycemia
Feig et al (2017)[20]						
n	211	201	200	202	173	214
CGM	53 (53%)	Median, 37.4	15 (15%)	63 (63%)	-0.54	11 (11%)
Control	69 (69%)	Median, 37.3	28 (28%)	74 (73%)	-0.35	12 (12%)
TE (95% CI)	OR=0.51 (0.28 to 0.90)	NR	OR=0.45 (0.22 to 0.89)	NR	-0.19% (-0.34% to -0.03%)	NR
p	0.02	0.50	0.025	0.18	0.02	1.0

Values are n or n (%) or as otherwise indicated.
CI: confidence interval; CGM: continuous glucose monitoring; HbA_{1c}: hemoglobin A_{1c}; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; TE: treatment effect.

The purpose of the gaps tables (see Tables 5 and 6) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 5. Relevance Gaps of RCTs for Real-Time CGM in Pregnant Women With Type 1 Diabetes

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Feig et al (2017)[20]	4. Run-in period requirement may have biased selection to highly compliant participants	3. More unscheduled contacts in CGM group	3. More unscheduled contacts in CGM group		

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

Table 6. Study Design and Conduct Gaps of RCTs for Real-Time CGM in Pregnant Women With Type 1 Diabetes

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
Feig et al (2017)[20]		1. Not blinded; chance of bias in clinical management				3, 4. Treatment effects and confidence intervals not calculated for some outcomes

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

Section Summary: CGM Devices for Long-Term Use in Type 1 Diabetes

Numerous RCTs and several systematic reviews of RCTs have evaluated CGM in patients with type 1 diabetes. A 2017 individual patient data analysis, using data from 11 RCTs, found that reductions in HbA_{1c} levels were significantly greater with real-time CGM compared with a control intervention. In addition, a 2012 meta-analysis of 6 RCTs found a significantly larger decline in HbA_{1c} levels at 6 months in the CGM group than the SMBG group. There are few studies beyond 6 months. Two recent RCTs in patients who used multiple daily insulin injections and were highly compliant with CGM devices during run-in phases found that CGM was associated with a larger reduction in HbA_{1c} levels than previous studies. Reductions were 0.4% and 0.6%, respectively, compared with approximately 0.2% to 0.3% in previous analyses. One of the 2 RCTs prespecified hypoglycemia-related outcomes and time spent in hypoglycemia was significantly lower in the CGM group.

One RCT in pregnant women with type 1 diabetes (n=215) has compared CGM with SMBG. Adherence was high in the CGM group. The difference in the change in HbA_{1c} levels from baseline to 34 weeks of gestation was statistically significant favoring CGM, and women in the CGM group spent an increased percentage of time in the recommended glucose control target range at 34 weeks of gestation. There were no between-group differences in maternal hypoglycemia,

gestational weight gain, or total daily insulin dose. A smaller proportion of infants of mothers in the CGM group were large for gestational age, had neonatal intensive care admissions lasting more than 24 hours, and had neonatal hypoglycemia requiring treatment. The total hospital length of stay was shorter by almost 1 day in the CGM group.

Glucose Monitoring Devices for Short-Term (Intermittent) Use

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

Systematic Reviews

Two meta-analyses were identified that reported separate subgroup analyses for intermittent monitoring. In a Cochrane review by Langendam et al (2012), 4 studies (total N=216 patients) compared real-time intermittent glucose monitoring systems with SMBG, and the pooled effect estimate for change in HbA_{1c} levels at 3 months was not statistically significant (MD change, -0.18; 95% CI, -0.42 to 0.05).[9] The meta-analysis by Wojciechowski et al (2011), which assessed RCTs on CGM (described previously), also included a separate analysis of 8 RCTs of intermittent monitoring.[11] On pooled analysis, there was a statistically significant reduction in HbA_{1c} levels with intermittent glucose monitoring compared with SMBG (WMD = -0.26; 95% CI, -0.45 to -0.06).

Randomized Controlled Trials

The largest RCT was the Management of Insulin-Treated Diabetes Mellitus (MITRE) trial, published by Newman et al (2009); it evaluated whether the use of the additional information provided by minimally invasive glucose monitors improved glucose control in patients with poorly controlled insulin-requiring diabetes.[21] This 4-arm RCT was conducted at secondary care diabetes clinics in 4 hospitals in England. This trial enrolled 404 people over the age of 18 years, with insulin-treated diabetes (types 1 or 2) for at least 6 months, who were receiving 2 or more injections of insulin daily. Most (57%) participants had type 1 diabetes (41% had type 2 diabetes, 2% were classified as "other"). Participants had to have 2 HbA_{1c} values of at least 7.5% in the 15 months before trial entry and were randomized to 1 of 4 groups. Two groups received minimally invasive glucose monitoring devices (GlucoWatch Biographer or MiniMed Continuous Glucose Monitoring System [CGMS]). Intermittent glucose monitoring was used (ie, monitoring was performed over several days at various points in the trial). These groups were compared with an attention control group (standard treatment with nurse feedback sessions at the same frequency as those in the device groups) and a standard control group (reflecting common practice in the clinical management of diabetes). Changes in HbA_{1c} levels from baseline to 3, 6, 12, and 18 months were the primary indicator of short- to long-term efficacy. At 18 months, all groups demonstrated a decline in HbA_{1c} levels from baseline. Mean percentage changes in HbA_{1c} levels were -1.4% for the GlucoWatch group, -4.2% for the CGMS group, -5.1% for the attention control group, and -4.9% for the standard care control group. In the intention-to-treat analysis, no significant differences were found between any groups at any assessment times. There was no evidence that the additional information provided by the devices changed the number or nature of treatment recommendations offered by the nurses. Use and acceptability indicated a decline for both devices, which was most marked in the GlucoWatch group by 18 months (20% still using GlucoWatch vs 57% still using the CGMS). In this trial of unselected patients, glucose monitoring (CGMS on an intermittent basis) did not lead to improved clinical outcomes.

Pregnant Women

Systematic Reviews: Voormolen et al (2013) published a systematic review of the literature on CGM during pregnancy.[22] They identified 11 relevant studies (total N=534 women). Two were RCTs, one of which was the largest of the studies (N=154). Seven studies used CGMs that did not have data available in real-time; the remaining 4 studies used real-time CGM. Reviewers did not pool study findings; they concluded that the evidence was limited on the efficacy of CGM during pregnancy. The published RCTs are described next.

Randomized Controlled Trials: Two RCTs of intermittent glucose monitoring in pregnant women with type 1 or type 2 diabetes are summarized in Tables 7 to 10 and the following paragraphs. While both trials included a mix of women with type 1 and type 2 diabetes, most women had type 1 diabetes in both trials, so the trials are reviewed in this section.

Secher et al (2013) randomized 154 women with type 1 (n=123) and type 2 (n=31) diabetes to real-time CGM in addition to routine pregnancy care (n=79) or routine pregnancy care alone (n=75). [23] Patients in the CGM group were instructed to use the CGM device for 6 days before each of 5 study visits and were encouraged to use the devices continuously; 64% of participants used the devices per-protocol. Participants in both groups were instructed to perform 8 daily self-monitored plasma glucose measurements for 6 days before each visit. Baseline mean HbA_{1c} levels were 6.6% in the CGM group and 6.8% in the routine care group. The 154 pregnancies resulted in 149 live births and 5 miscarriages. The prevalence of large-for-gestational age infants (at least 90th percentile), the primary study outcome, was 45% in the CGM group and 34% in the routine care group. The difference between groups was not statistically significant (p=0.19). Also, no statistically significant differences were found between groups for secondary outcomes, including the prevalence of preterm delivery and the prevalence of severe neonatal hypoglycemia. Women in this trial had low baseline HbA_{1c} levels, which might explain the lack of impact of CGM on outcomes. Other factors potentially contributing to the negative findings included the intensive SMBG routine in both groups and the relatively low compliance rate in the CGM group.

Murphy et al (2008) in the U.K. randomized 71 pregnant women with type 1 (n=46) and type 2 (n=25) diabetes to CGM or usual care.[24] The intervention consisted of up to 7 days of CGM at intervals of 4 to 6 weeks between 8 weeks and 32 weeks of gestation. Neither participants nor physicians had access to the measurements during sensor use; data were reviewed at study visits. In addition to CGM, the women were advised to measure blood glucose levels at least 7 times a day. Baseline HbA_{1c} levels were 7.2% in the CGM group and 7.4% in the usual care group. The primary study outcome was maternal glycemic control during the second and third trimesters. Eighty percent of women in the CGM group wore the monitor at least once per trimester. Mean HbA_{1c} levels were consistently lower in the intervention arm, but differences between groups were statistically significant only at week 36. For example, between 28 weeks and 32 weeks of gestation, mean HbA_{1c} levels were 6.1% in the CGM group and 6.4% in the usual care group (p=0.10). The prevalence of large-for-gestational age infants (at least 90th percentile) was a secondary outcome. Thirteen (35%) of 37 infants in the CGM group were large-for-gestational age compared with 18 (60%) of 30 in the usual care group. The odds for reduced risk of a large-for-gestational age infant with CGM was 0.36 (95% CI, 0.13 to 0.98; p=0.05).

Table 7. RCT Characteristics for Intermittent CGM in Pregnant Women With Type 1 Diabetes

Study; Registration	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Secher et al (2013)[23]; NCT00994357	Denmark	1	2009-2011	Pregnant women with type 1 (80%) or type 2 (20%) diabetes; mean gestational age, <14 wk); median HbA_{1c} level, 6.7%; median age, 32 y	CGM (for 6 d before each study visits; encouraged to used continuously) plus SOC (n=79)	SOC (n=75)
Murphy et al (2008)[24]; ISRCTN84461581	U.K.	2	2003-2006	Pregnant women with type 1 (65%) or type 2 (35%) diabetes; mean gestational age, 9.2 wk; mean HbA_{1c} level, 7.3%; mean age, 31 y	CGM (up to 7 d of CGM at intervals of 4-6 wk) plus SOC (n=38)	SOC (n=33)

CGM: continuous glucose monitoring; HbA_{1c}: hemoglobin A_{1c}; RCT: randomized controlled trial; SOC: standard of care.

Table 8. RCT Results for Intermittent CGM in Pregnant Women with Type 1 Diabetes

Study	Infant				Maternal	
	Large-for-Gestational Age	Gestational Age at Delivery	Severe Hypoglycemia	Caesarean Section	HbA_{1c} Levels at 36 Weeks of Gestation[a]	Severe Hypoglycemia
		Days				
Secher et al (2013)[23]						
n	154	154	145	154		154
CGM	34 (45%)	Median, 263	9 (13%)	28 (37%)	Median, 6.0%	16%
Control	25 (34%)	Median, 264	10 (14%)	33 (45%)	Median, 6.1%	16%
TE (95% CI)	NR	NR	NR	NR	NR	NR
p	0.19	0.14	0.88	0.30	0.63	0.91
		Weeks				
Murphy et al (2008)[24]						
n	71	71	68	69	71	NR
CGM	13 (35%)	Mean, 37.6	3 (8%)	27 (71%)	Mean, 5.8%	
Control	18 (60%)	Mean, 37.5	5 (17%)	21 (61%)	Mean, 6.4%	
TE (95% CI)	OR=0.36 (0.13 to 0.98)	NR	NR	NR	0.6% (CI NR)	
p	0.05	0.80	0.50	0.40	0.007	

Values are n or n (%) or as otherwise indicated.
CGM: continuous glucose monitoring; CI: confidence interval; HbA_{1c}: hemoglobin A_{1c}; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; TE: treatment effect.
[a] N inconsistently reported for HbA_{1c} outcome.

In summary, 2 trials of intermittent glucose monitoring conducted in Europe included pregnant women with type 1 or 2 diabetes, with most having type 1 diabetes. Secher et al (2013) included intermittent, real-time monitoring[23]; Murphy et al (2008) included intermittent, retrospective monitoring with CGM.[24] The intervention started in early pregnancy in these studies; mean age was in the early thirties and mean baseline HbA_{1c} level was greater than 6.5%. There was no statistically significant difference between CGM and routine care for maternal HbA_{1c} levels at 36 weeks in Secher; the difference in HbA_{1c} levels at 36 weeks was about 0.6% (p=0.007) in Murphy. Secher also reported no difference in severe maternal hypoglycemia. The proportion of infants that were large for gestational age (>90th percentile) was higher in the CGM group in Secher, although not statistically significantly higher; the difference in large for gestational age was statistically significantly lower for CGM in Murphy. The differences in the proportions of

infants born via caesarean section, gestational age at delivery, and infants with severe hypoglycemia were not statistically significant in either trial.

Tables 9 and 10 display notable gaps identified in each study.

Table 9. Relevance Gaps of RCTs of Intermittent CGM in Pregnant Women with Type 1 Diabetes

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Secher et al (2013)[23]	4. Study population had relatively low HbA_{1c} levels	4. Only 64% of the participants used devices per protocol			
Murphy et al (2008)[24]					

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

Table 10. Study Design and Conduct Gaps of RCTs of Intermittent Glucose Monitoring in Pregnant Women with Type 1 Diabetes

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
Secher et al (2013)[23]		1. Not blinded; chance of bias in clinical management				3, 4. Treatment effects and confidence intervals not calculated
Murphy et al (2008)[24]		1. Not blinded; chance of bias in clinical management				3, 4. Treatment effects and confidence intervals not calculated for some outcomes

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

Section Summary: Glucose Monitoring Devices for Short-Term (Intermittent) Use in Type 1 Diabetes
For short-term (intermittent) monitoring of type 1 diabetes, there are few RCTs and systematic reviews. Some trials have reported improvements in glucose control for the intermittent monitoring group, but limitations in this body of evidence preclude conclusions. The definitions of intermittent control and the specific monitoring protocols varied. In some studies, intermittent monitoring was part of a larger strategy aimed at optimizing glucose control, and the impact of monitoring cannot be separated from the impact of other interventions.

Two RCTs of intermittent glucose monitoring have been conducted in pregnant women with both type 1 and 2 diabetes, with most having type 1 diabetes. One trial reported a difference in HbA_{1c} levels at 36 weeks; the proportion of infants that were large for gestational age (>90th percentile) favored CGM while the second trial did not. The differences in the proportions of infants born via caesarean section, gestational age at delivery, and infants with severe hypoglycemia were not statistically significant in either study.

Type 2 Diabetes for Long- and Short-Term Glucose Monitoring
The analysis of type 2 diabetes does not distinguish between indications 3 (long-term) and 4 (short-term) glucose monitoring, consistent with the literature.

Clinical Context and Therapy Purpose
The purpose of long-term CGM and short-term (intermittent) glucose monitoring devices is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with type 2 diabetes.

The question addressed in this evidence review is: Does the use of long-term CGM and short-term (intermittent) glucose monitoring devices improve the net health outcome for individuals with type 2 diabetes?

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

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

Interventions
The therapies being considered are long-term CGM devices to direct insulin regimens and intermittent (ie, 72 hours), short-term glucose monitoring devices to optimize management.

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

Outcomes
The general outcomes of interest are change in HbA_{1c} levels, time spent in hypoglycemia, incidence of hypoglycemic events, complications of hypoglycemia, and quality of life.

Timing
To assess short-term outcomes such as HbA_{1c} levels, a minimum follow-up of 8 to 12 week is appropriate. To assess long-term outcomes such as time spent in hypoglycemia, incidence of hypoglycemic events, complications of hypoglycemia, and quality of life, follow-up of 6 months to 1 year would be appropriate.

Setting
CGM devices may be used in home, outpatient or inpatient setting by patients and evaluation of results is by general as well as subspecialty physicians.

Systematic Reviews
The systematic reviews by Poolsup et al (2013)[10] and Gandhi et al (2011),[8] previously described, also reported on the efficacy of CGM in patients with type 2 diabetes. A comparison of the trials of type 2 diabetes included in the systematic reviews and meta-analyses in these reviews is shown in Table 11.

Table 11. Comparison of CGM Trials for Type 2 Diabetes Included in Systematic Reviews

Primary Study	Poolsup et al (2013)[10]	Gandhi et al (2011)[8]
Ehrhardt et al (2011)[25]	•	
Cosson et al (2009)[26]	•	•
Allen et al (2008)[27]	•	•
Yoo et al (2008)[28]	•	•

CGM: continuous glucose monitoring.

A summary of the characteristics of the systematic reviews is shown in Table 12. Results are briefly described in Table 13 and the following. Gandhi et al (2011) identified 3 RCTs studying patients with type 2 diabetes (1 study included both types of diabetes).[8] There was a mix of patients with type 2 diabetes who did and did not require insulin. Two of the 3 trials evaluated retrospective CGM of different lengths and durations, and the third evaluated real-time intermittent glucose monitoring. Patients in the trials had baseline HbA_{1c} levels greater than 8%. In a meta-analysis of the 3 trials, there was a statistically significant reduction in HbA_{1c} levels for CGM compared with SMBG in adults with type 2 diabetes (WMD = -0.70; 95% CI, -1.14 to -0.27). Poolsup et al (2013) conducted a meta-analysis of 4 trials evaluating adults with type 2 diabetes.[10] Three trials in Poolsup overlapped with those of Gandhi; the remaining trial also evaluated real-time CGM but with a longer period of use (2 weeks on and 1 week off for 3 months). In a pooled analysis, CGM had greater efficacy regarding HbA_{1c} levels than SMBG. The pooled mean difference in HbA_{1c} level was -0.31% (95% CI, -0.6% to 0.02%; p=0.04). Because of a lack of statistical heterogeneity among studies, subgroup analyses (eg, by type of CGM device) were not performed.

Table 12. Systematic Review Characteristics for CGM in T2D

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Poolsup et al (2013)[10]	To 2013	4	Adults with T2D	228 (25-100)	RCT	At least 8 wk (median, 3 mo)
Gandhi et al (2011)[8]	1996-2010	3	Adult outpatients with T2D; mean baseline HbA_{1c} level >8%	128 (25-57)	RCT	At least 8 wk (median, 3 mo)

CGM: continuous glucose monitoring; HbA_{1c}: hemoglobin A_{1c}; RCT: randomized controlled trial; T2D: type 2 diabetes.

Table 13. Meta-Analytic Results for CGM in Type 2 Diabetes

Study	Reduction in HbA_{1c} Levels (Mean Difference)	Hypoglycemic Events	Diabetes Complications (retinopathy, nephropathy, neuropathy, diabetic foot)	Health-Related Quality of Life
Poolsup et al (2013)[10]				
Total N	228	NR	NR	NR
PE (95% CI)	-0.31 (-0.60 to -0.02)			
p	0.04			
I^2	0%			
Gandhi et al (2011)[8]				
Total N	128	NR	NR	NR
PE (95% CI)	-0.70 (-1.14 to -0.27)			
p	NR			
I^2	0%			

CGM: continuous glucose monitoring; CI: confidence interval; HbA_{1c}: hemoglobin A_{1c}; NR: not reported; PE: pooled effect.

Randomized Controlled Trials

Several RCTs of CGM in adults with type 2 diabetes are summarized in Tables 14 to 17. The largest and most recent studies are also briefly summarized in the following paragraphs. The trials were conducted in North America, Europe, and Asia. Baseline HbA_{1c} levels were between 8.5% and 9.0% in the RCTs, with participants having a mean baseline age range in the mid-50s and early-60s. The RCTs used a mixed of intermittent and continuous, real-time monitoring.

A large RCT, Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND), was reported by Beck et al (2017).[29] DIAMOND was performed at 25 endocrinology practices in North America (22 in the United States, 3 in Canada) and enrolled adults with type 2 diabetes receiving multiple daily injections of insulin. One-hundred fifty-eight patients were randomized 2 groups: CGM and usual care (n=79 in each group). Patients compliant during a run-in period were eligible for randomization. Patients in both groups were given a blood glucose meter. Participants in the CGM group were given a Dexcom G4 Platinum CGM System (Dexcom) and instructions on use. Change in HbA_{1c} level from baseline to 24 weeks was the primary outcome. Analyses were adjusted for baseline HbA_{1c} levels and clinic were performed using intention-to-treat analysis with missing data handling by multiple imputation. At baseline, the mean total daily insulin dose was 1.1 U/kg/d. Week 24 follow-up was completed by 97% of the CGM group and 95% of the control group. Mean CGM use was greater than 6 d/wk at 1 month, 3 months, and 6 months. The adjusted difference in mean change in HbA_{1c} level from baseline to 24 weeks was -0.3% (95% CI, -0.5% to 0.0%; p=0.022) favoring CGM. The adjusted difference in the proportion of patients with a relative reduction in HbA_{1c} level of 10% or more was 22% (95% CI, 0% to 42%; p=0.028) favoring CGM. There were no events of severe hypoglycemia or diabetic ketoacidosis in either group. The treatment groups did not differ in any of the quality of life measures.

The RCT by Sato et al (2016) included 34 patients with type 2 diabetes who were at least 20 years old and on insulin injection therapy, had HbA_{1c} levels between 6.9% and 11.0% during the previous 3 months, with HbA_{1c} fluctuations within 0.5%.[30] All patients conducted SMBG and used CGM devices that do not have data available in real-time (ie, data were viewed retrospectively by physicians). Devices were used for 4 to 5 days before each of 3 clinic visits, 2 months apart. At clinic visits, patients were evaluated and suggestions made to improve glucose control by lifestyle

changes and by changing medication doses. In the intervention group, but not the control group, patients and physicians had access to CGM data at the clinic visits. The primary end point was change in HbA_{1c} levels from baseline, which did not differ significantly between groups at the end of the trial, between the first and second visits, or between the second and third visits. HbA_{1c} levels changed little in either group. In the intervention group, the mean baseline HbA_{1c} level was 8.2%, and the mean final HbA_{1c} level was also 8.2%. Comparable percentages in the control group were 8.2% and 7.9%. In this trial, conducted in Japan, decisions on medication doses were made only by the physician at clinic visits, and practices may differ in other countries.

Ehrhardt and colleagues published 2 reports (2011, 2012) from an RCT evaluating the largest sample (N=100) in the Poolsup et al (2013) systematic review (accounting for 45% of the weight in the pooled analysis of HbA_{1c} levels).[25,31] The trial evaluated the intermittent use of a CGM device in adults with type 2 diabetes treated with diet/exercise and/or glycemia-lowering medications but not prandial insulin who had an initial HbA_{1c} level of at least 7% but not more than 12%. The trial compared real-time CGM with the Dexcom device used for four, 2-week cycles (2 weeks on and 1 week off) with SMBG. The primary efficacy outcome was mean change in HbA_{1c} levels. Mean HbA_{1c} levels in the CGM group were 8.4% at baseline, 7.4% at 12 weeks, 7.3% at 24 weeks, and 7.7% at 52 weeks. In the SMBG group, these values were 8.2% at baseline, 7.7% at 12 weeks, 7.6% at 24 weeks, and 7.9% at 52 weeks. During the trial, the reduction in HbA_{1c} levels was significantly greater in the CGM group than in the SMBG group (p=0.04). After adjusting for potential confounders (eg, age, sex, baseline therapy, whether the individual started taking insulin during the study), the difference between groups over time remained statistically significant (p<0.001). The investigators also evaluated SMBG results for both groups. The mean proportions of SMBG tests less than 70 mg/dL were 3.6% in the CGM group and 2.5% in the SMBG group (p=0.06).

Table 14. RCT Characteristics for Glucose Monitoring in T2D

Study; Registration	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Beck et al (2017) (DIAMOND)[29]; NCT02282397	U.S., Canada	25	2014-2016	Adults with T2D using multiple daily injections of insulin with HbA_{1c} levels 7.5%-10.0% (baseline mean, 8.5%); mean age, 60 y	Real-time CGM (n=79)	SMBG (n=79)
Sato et al (2016)[30]; UMIN: 000012034[a]	Japan	1	2012-2014	Adults with T2D using insulin with HbA_{1c} levels 6.9%-11.0% (baseline mean, 8.2%); mean age, 62 y	CGM for 4-5 d every 4 mo; reviewed at study visits (n=17)	"Blinded" CGM (n=17)
Ehrhardt et al (2011)[25]	U.S.	1	NR	Adults with T2D using oral antidiabetic agents without prandial insulin with HbA_{1c} levels 7.0%-12.0% (baseline mean, 8.3%), mean age, 58 y	Real-time CGM for 4 cycles of 3 wk (n=50)	SMBG (n=50)
Cosson et al (2009)[26]	France	5	NR	Adults with T1D or T2D treated with oral antidiabetic agents with or without insulin with HbA_{1c} levels 8.0%-10.5% (baseline mean, 9.1% in T2D); mean age, 57 y in T2D	CGM for 48 h at baseline and 3 mo; CGM data shared with physician and patient (n=11 with T2D)	"Blinded" CGM (n=14 in T2D)

Study; Registration	Countries	Sites	Dates	Participants	Interventions	
Allen et al (2008)[27]	U.S.	2	NR	Adults with T2D not receiving insulin with HbA_{1c} levels >7.5% (baseline mean, 8.6%), not participating in physical activity; mean age, 57 y	Diabetes education plus CGM for 3 d (n=27)	Diabetes education (n=25)
Yoo et al (2008)[28]	Korea	4	2007	Adults with T2D using oral antidiabetic agents or insulin with HbA_{1c} levels 8.0%-10.0% (baseline mean, 9%); mean age, 56 y	CGM (3 d at a time for 3 mo) (n=32)	SMBG (n=33)

CGM: continuous glucose monitoring; HbA_{1c}: hemoglobin A_{1c}; NR: not reported; RCT: randomized controlled trial; SMBG: self-monitored blood glucose; T1D: type 1 diabetes; T2D: type 2 diabetes.
[a] Registered with the University Hospital Medical Information Network in Japan.

Most RCTs used a type of intermittent monitoring; some reported data for patients in real-time while others provided data reviewed only at study visits. Four of the 6 RCTs of CGM in type 2 diabetes reported a statistically significant larger decrease in HbA_{1c} levels with CGM than with control. Beck et al (2017) reported more patients in CGM with a relative reduction in HbA_{1c} levels of greater than 10% at 24 weeks but no difference in the quality of life measures.[29] In Cosson et al (2009), the comparative treatment effect was not reported, but the CGM group had a statistically significant reduction in HbA_{1c} levels from baseline to 3 months.[26] Few other outcomes were reported. No trials reported on follow-up beyond 6 months. Thus the effect of CGM on outcomes related to diabetic complications is unknown. Only 2 RCTs used blinded CGM; in one, there was no difference in reduction in HbA_{1c} levels between CGM and control.

Table 15. RCT Outcomes for Glucose Monitoring in Type 2 Diabetes

Study	Reduction in HbA_{1c} Levels (Mean Range), %	HbA_{1c} Level <7.0%, n (%)	Relative Reduction in HbA_{1c} Level ≥10%, n (%)	Hypoglycemic or Ketoacidosis Events	Diabetes Complications (retinopathy, nephropathy, neuropathy, diabetic foot)	Health-Related Quality of Life
	Baseline to 24 Wk	**At 24 Wk**	**At 24 Wk**			**DDS Overall Mean Score at 24 Wk**
Beck et al (2017)[29]						
N	158	158	158	158	NR	150
CGM	8.6 to 7.7	11 (14%)	40 (52%)	0		Baseline: 1.78 24 weeks: 1.61
Control	8.6 to 8.2	9 (12%)	24 (32%)	0		Baseline: 1.69 24 weeks: 1.78
TE (95% CI)	-0.3 (-0.5 to 0.0)	3% (-9% to 14%)	22% (0% to 42%)			0.22 (0.08 to 0.36)
p	0.022	0.88	0.028			0.009
	Baseline to 8 Mo					

Study	Reduction in HbA_{1c} Levels (Mean Range), %	HbA_{1c} Level <7.0%, n (%)	Relative Reduction in HbA_{1c} Level ≥10%, n (%)	Hypoglycemic or Ketoacidosis Events	Diabetes Complications (retinopathy, nephropathy, neuropathy, diabetic foot)	Health-Related Quality of Life
Sato et al (2016)[30]						
N	34	NR	NR	NR	NR	NR
CGM	8.2 to 8.2					
Control	8.2 to 7.9					
TE (95% CI)	NR					
p	>0.05					
	Baseline to 12 Wk					
Ehrhardt et al (2011)[25]						
N	100	NR	NR	NR	NR	NR
CGM	8.4 to 7.4					
Control	8.2 to 7.7					
TE (95% CI)	NR					
p	0.006					
	Baseline to 3 Mo			**Time Spent With Hypoglycemia, min**		
Cosson et al (2009)[26]						
N	25	NR	NR	19	NR	NR
CGM	9.2 to 8.6			18		
Control	9.0 to 8.8			11		
TE (95% CI)	NR			NR		
	Baseline to 8 Wk					
Allen et al (2008)[27]						
N	46	NR	NR	NR	NR	NR
CGM	8.9 to 7.7					
Control	8.4 to 8.1					
TE (95% CI)	NR					
p	<0.05					
	Baseline to 3 Mo					
Yoo et al (2008)[28]						
N	57	NR	NR	NR	NR	NR
CGM	9.1 to 8.0					
Control	8.7 to 8.3					
TE (95% CI)	NR					
p	0.004					

CGM: continuous glucose monitoring; CI: confidence interval; DDS: Diabetes Distress Scale; HbA_{1c}: hemoglobin A_{1c}; NR: not reported; RCT: randomized controlled trial; TE: treatment effect.
Tables 16 and 17 display notable gaps identified in each study.

Table 16. Relevance Gaps of RCTs for Glucose Monitoring in Type 2 Diabetes

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Beck et al (2017)[29]; DIAMOND				1. Did not include outcomes on diabetic complications	1. Follow-up not sufficient to determine effects on diabetic complications
Sato et al (2016)[30]				1. Focused on HbA_{1c}; did not include outcomes on adverse events, QOL, or diabetic complications	1. Follow-up not sufficient to determine effects on diabetic complications
Ehrhardt et al (2011)[25]				1. Focused on HbA_{1c}; did not include outcomes on adverse events, QOL, or diabetic complications 6. No justification for clinically significant difference	1. Follow-up not sufficient to determine effects on diabetic complications; patients reportedly followed for 52 wk but data not reported.
Cosson et al (2009)[26]				1. Focused on HbA_{1c}; did not include outcomes on adverse events, QOL, or diabetic complications	1. Follow-up not sufficient to determine effects on diabetic complications
Allen et al (2008)[27]				1. Focused on HbA_{1c}; did not include outcomes on adverse events, QOL, or diabetic complications	1. Follow-up not sufficient to determine effects on diabetic complications
Yoo et al (2008)[28]				1. Focused on HbA_{1c}; did not include outcomes on adverse events, QOL, or diabetic complications	1. Follow-up not sufficient to determine effects on diabetic complications

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

Table 17. Study Design and Conduct Gaps of RCTs for Glucose Monitoring in Type 2 Diabetes

Study; Trial	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
Beck et al (2017)[29]; DIAMOND		1. Not blinded; chance of bias in				

Study; Trial	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
		clinical management				
Sato et al (2016)[30]						3, 4. Treatment effects and CIs not calculated
Ehrhardt et al (2011)[25]		1. Not blinded; chance of bias in clinical management	1. Registration not reported		3. No justification for difference used for power calculation	3, 4. Treatment effects and CIs not calculated
Cosson et al (2009)[26]			1. Registration not reported	2. Unclear how missing data were handled in analyses	1.-3. No power calculations	3, 4. Treatment effects and CIs not calculated
Allen et al (2008)[27]		1. Not blinded; chance of bias in clinical management	1. Registration not reported		2, 3. Power not calculated a priori; convenience sample size	3, 4. Treatment effects and CIs not calculated
Yoo et al (2008)[28]		1. Not blinded; chance of bias in clinical management	1. Registration not reported			3, 4. Treatment effects and CIs not calculated

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

Pregnant Women

As discussed in the section on CGM in pregnant women, 2 RCTs have evaluated intermittent glucose monitoring in pregnant women with type 1 and type 2 diabetes. Most women had type 1 diabetes in both trials. There were 25 (35%) women with type 2 diabetes in Murphy et al (2008)[24] and 31 (20%) with type 2 diabetes in Secher et al (2013).[23] Results for women with type 2 diabetes were not reported in Murphy. Secher reported that 5 (17%) women with type 2 diabetes experienced 15 severe hypoglycemic events, with no difference between groups; other analyses were not stratified by diabetes type.

Section Summary: Type 2 Diabetes for Long- and Short-Term Glucose Monitoring

Most RCTs of CGM in patients with type 2 trials found statistically significant benefits of CGM regarding glycemic control. However, the degree of HbA_{1c} reduction and the difference in HbA_{1c} reduction between groups might not be clinically significant. Also, the variability among

interventions makes it difficult to identify an optimal approach to CGM use; the studies used a combination of intermittent and continuous monitoring with a review of data in real-time or at study visits only. Only the DIAMOND trial (N=158) used real-time CGM. Entry criteria regarding the use of insulin and HbA_{1c} levels also varied across studies, and a subgroup of type 2 diabetes patients who might benefit has not been identified. Moreover, studies of CGM in patients with type 2 diabetes generally do not address the clinically important issues of severe hypoglycemia and diabetic complications. The DIAMOND trial reported a larger reduction in change in HbA_{1c} level from baseline to 24 weeks with CGM and a larger proportion of patients with a relative reduction in the HbA_{1c} level of 10% or higher at 24 weeks favoring CGM but no differences in quality of life. There were no events of severe hypoglycemia or diabetic ketoacidosis in either group.

Two trials of CGM have enrolled pregnant women with type 2 diabetes, but the total number of women with type 2 diabetes included in both trials is only 58. One study reported a difference in HbA_{1c} levels at 36 weeks, and the proportion of infants that were large for gestational age (>90th percentile) favored CGM while the second study did not. Neither trial reported analyses stratified by diabetes type.

Pregnant Women with Gestational Diabetes

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: Does the use of long-term (continuous) CGM and short-term (intermittent) glucose monitoring devices improve the net health outcome for women with gestational diabetes?

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

Patients

The relevant population of interest is women with gestational diabetes.

Interventions

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

Comparators

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

Outcomes

The general outcomes of interest are change in HbA_{1c} levels, time spent in hypoglycemia, incidence of hypoglycemic events, complications of hypoglycemia and quality of life.

Timing

To assess short-term outcomes such as HbA_{1c} levels, time spent in hypoglycemia, incidence of hypoglycemic events and, complications of hypoglycemia, a minimum follow-up of 8 to 12 week is appropriate. To assess long-term outcomes such as quality of life and maternal and infant outcomes, follow-up of 24 to 36 weeks would be appropriate.

Setting

CGM devices may be used in home, outpatient or inpatient setting by patients and evaluation of results is by general as well as subspecialty physicians.

Randomized Controlled Trials

One trial of glucose monitoring in women with gestational diabetes has been published. Trial characteristics, results, and gaps are shown in Tables 18 to 21. In the RCT, Wei et al (2016) evaluated the use of CGM in 120 women with gestational diabetes at 24 to 28 weeks.[32] Patients were randomized to prenatal care plus CGM (n=58) or SMBG (n=62). The CGM sensors were reportedly inserted for 48 to 72 hours on weekdays; it is not clear whether the readings were available in real-time. The investigators assessed a number of end points and did not specify primary outcomes; a significance level of p less than 0.05 was used for all outcomes. The groups did not differ significantly in a change in most outcomes, including a change in maternal HbA_{1c} levels, rates of preterm delivery before the 35th gestational week, cesarean delivery rates, proportions of large-for-gestational age infants, or rates of neonatal hypoglycemia. Women in the CGM group gained significantly less weight than those in the SMBG group.

Table 18. Key RCT Characteristics for CGM in Pregnant Women with Gestational Diabetes

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Wei et al (2016)[32]	China	1	2011-2012	Pregnant women with gestational diabetes diagnosed between 24 and 28 wk of gestation; mean HbA_{1c} level, 5.8%; mean age, 30 y	CGM (48- 721 on weekdays) (n=51)	SMBG (n=55)

CGM: continuous glucose monitoring; HbA_{1c}: hemoglobin A_{1c}; RCT: randomized controlled trial; SMBG: self-monitored blood glucose.

Table 19. RCT Outcomes for CGM in Pregnant Women with Gestational Diabetes

Study	Infant			Maternal		
	Large-for-Gestational Age, n (%)	Gestational Age at Delivery, wk	Severe Hypoglycemia, n (%)	Caesarean Section, n (%)	HbA_{1c} Levels at 36 Wk of Gestation[a]	Severe Hypoglycemia
Wei et al (2016)[32]						
N	106	106	106	106		NR
CGM	18 (35)	Mean, 37.4	4 (8)	31 (60)	Mean, 5.5%	
Control	29 (53)	Mean, 37.5	7 (13)	38 (69)	Mean, 5.6%	
TE (95% CI)	NR	NR	NR	NR	NR	
p	0.07	0.92	0.41	0.37	0.09	

Values are n (%) or as otherwise indicated.
CGM: continuous glucose monitoring; CI: confidence interval; HbA_{1c}: hemoglobin A_{1c}; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; TE: treatment effect.
[a] N inconsistently reported for HbA_{1c} outcome.

Tables 20 and 21 display notable gaps identified in each study.

Table 20. Relevance Gaps of RCTs for CGM in Pregnant Women with Gestational Diabetes

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Wei et al (2016)[32]	4. Study population had relatively low HbA_{1c} level	4. Compliance with CGM not reported			

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

Table 21. Study Design and Conduct Gaps of RCTs for CGM in Pregnant Women With Gestational Diabetes

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
Wei et al (2016)[32]	3. Not reported	1. Not blinded; chance of bias in clinical management	1. Registration not reported	5. Exclusions not well justified	1. No power calculations reported; primary outcome not specified	3, 4. Treatment effects and CIs not calculated

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

Section Summary: Pregnant Women with Gestational Diabetes

The RCT in women with gestational diabetes was conducted in China with the intervention starting in the 2nd or 3rd trimester and mean baseline HbA_{1c} level less than 6.0%. The type of CGM monitoring was unclear. Trial reporting was incomplete; however, there were no differences between groups for most reported outcomes.

SUMMARY OF EVIDENCE

Type 1 Diabetes

For individuals who have type 1 diabetes who are willing and able to use the device, and have adequate medical supervision, who receive long-term CGM, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related morbidity. Systematic reviews have generally found that at least in the short-term, long-term CGM resulted in significantly improved glycemic control for adults and children with type 1 diabetes, particularly highly compliant patients. A 2017 individual patient data analysis, pooling data from 11 RCTs, found that reductions in HbA_{1c} levels were significantly greater with real-time CGM than with a control intervention. Two RCTs in patients who used multiple daily insulin injections and were highly compliant with CGM devices during run-in phases found that CGM was associated with a larger reduction in HbA_{1c} levels than previous studies. One of the 2 RCTs prespecified hypoglycemia-related outcomes and reported that time spent in hypoglycemia was significantly less in the CGM group. One RCT in pregnant women with type 1 diabetes, which compared real-time CGM with self-monitoring of blood glucose, has also reported a difference in change in HbA_{1c} levels, an increased percentage of time in the recommended glucose control target range, a smaller proportion of infants who were large for gestational age, a smaller proportion of infants who had neonatal intensive care admissions lasting more than 24 hours, a smaller proportion of infants who had neonatal hypoglycemia requiring treatment, and reduced total hospital length of stay all favoring CGM. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome

For individuals who have type 1 diabetes who receive short-term (intermittent) glucose monitoring, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related morbidity. The evidence for intermittent short-term monitoring on glycemic control is mixed, and there was no definite improvement in HbA_{1c} levels. Studies have not shown an advantage for intermittent glucose monitoring in reducing severe hypoglycemia events, but the number of events reported is generally small and effect estimates imprecise. The evidence is insufficient to determine the effects of the technology on health outcomes.

Type 2 Diabetes

For individuals who have type 2 diabetes who receive long-term CGM, the evidence includes RCTs. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related morbidity. Only the DIAMOND RCT (N=158) has used real-time CGM in type 2 diabetes. Selected patients were highly compliant during a run-in phase. The difference in change in HbA_{1c} levels from baseline to 24 weeks was -0.3% favoring CGM. The difference in the proportion of patients with a relative reduction in HbA_{1c} level by 10% or more was 22% favoring CGM. There were no differences in the proportions of patients with an HbA_{1c} level less than 7% at week 24. There were no events of severe hypoglycemia or diabetic ketoacidosis in either group. The treatment groups did not differ in any of the quality of life measures. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have type 2 diabetes who receive short-term (intermittent) glucose monitoring, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related morbidity. Systematic reviews of 3 to 4 RCTs have found statistically significant benefits from CGM regarding glycemic control. However, the degree of HbA_{1c} reduction and the difference in HbA_{1c} reductions between groups

may not be clinically significant. Also, the small number of RCTs and variability among interventions make it difficult to identify an optimal approach to CGM or a subgroup of type 2 diabetes patients who might benefit. Moreover, studies of CGM in patients with type 2 diabetes have generally not addressed the clinically important issues of severe hypoglycemia and diabetic complications. Very few pregnant women with type 2 diabetes have been included in RCTs. The evidence is insufficient to determine the effects of the technology on health outcomes.

Gestational Diabetes

For individuals who are pregnant with gestational diabetes who receive long-term CGM or short-term (intermittent) glucose monitoring, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related morbidity. In the RCT, the type of glucose monitoring was unclear. Trial reporting was incomplete; however, there was no difference between the groups for most reported outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

CLINICAL INPUT RECEIVED THROUGH PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

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

In response to requests, input was received from 1 physician specialty society and 4 academic medical centers while this policy was under review in 2008. Input concurred that continuous glucose monitoring, particularly intermittent glucose monitoring, was helpful in a subset of patients with diabetes. Reviewers commented that this monitoring can improve diabetes care by reducing glucose levels (and improving hemoglobin A_{1c} levels) and/or by reducing episodes of hypoglycemia. Reviewers argued that there is persuasive data from case reports to demonstrate the positive impact of intermittent glucose monitoring.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Association of Clinical Endocrinologists and American College of Endocrinology

In 2016, the American Association of Clinical Endocrinologists and American College of Endocrinology published a consensus statement on outpatient glucose monitoring.[33] Following are their recommendations on CGM:

- Type 1 diabetes, adults: "CGM recommended, especially 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 diabetes, children: Same as adults, except that more training and follow-up is needed.
- Type 2 diabetes receiving insulin, sulfonylureas, or glinides: "Data on CGM in T2DM [type 2 diabetes mellitus] are limited at this time. Trials assessing the use of CGM in T2DM are ongoing."

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence updated its guidance on the diagnosis and management of type 1 diabetes in adults in 2016.[34] The guidance stated that real-time CGM

should not be offered "routinely to adults with type 1 diabetes" but that it can be considered in the following:

"…adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimised use of insulin therapy and conventional blood glucose monitoring:

- More than 1 episode a year of severe hypoglycaemia with no obviously preventable precipitating cause.
- Complete loss of awareness of hypoglycaemia.
- Frequent (more than 2 episodes a week) asymptomatic hypoglycaemia that is causing problems with daily activities.
- Extreme fear of hypoglycaemia.
- Hyperglycaemia (HbA1c [hemoglobin A_{1c}] level of 75 mmol/mol [9%] or higher) that persists despite testing at least 10 times a day. Continue real-time continuous glucose monitoring only if HbA1c can be sustained at or below 53 mmol/mol (7%) and/or there has been a fall in HbA1c of 27 mmol/mol (2.5%) or more."

American Diabetes Association

The 2018 American Diabetes Association "Standards of Medical Care in Diabetes on Glycemic Targets" included the following recommendations on CGM (see Table 22).[35]

Table 22. Recommendations on Diabetes Care

Recommendations	LOE
"When used properly, continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens is a useful tool to lower A1C in adults with type 1 diabetes who are not meeting glycemic targets"	A
"CGM may be a useful tool in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes."	C
"Given the variable adherence to CGM, assess individual readiness for continuing CGM use prior to prescribing"	E
When prescribing CGM, robust diabetes education, training, and support are required for optimal CGM implementation and ongoing use.	E
People who have been successfully using CGM should have continued access after they turn 65 years of age.	E

LOE: level of evidence.

[a] LOE: A: Clear evidence from 1. Well-conducted, generalizable randomized controlled trials that are adequately powered, including evidence from a well-conducted multicenter trial, evidence from a meta-analysis that incorporated quality ratings in the analysis or 2. Compelling nonexperimental evidence, i.e., "all or none" rule developed by the Centre for Evidence-Based Medicine at the University of Oxford or 3. Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including evidence from a well-conducted trial at one or more institutions or evidence from a meta-analysis that incorporated quality ratings in the analysis

LOE C: 1. Supportive evidence from poorly controlled or uncontrolled studies including evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results or evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) or evidence from case series or case reports 2. Conflicting evidence with the weight of evidence supporting the recommendation.

LOE E Expert consensus or clinical experience.

Endocrine Society

In 2016, the Endocrine Society published clinical practice guidelines that included the following recommendations on CGM[36]:

6. "Real-time continuous glucose monitors in adult outpatients
   - 6.1 We recommend real-time continuous glucose monitoring (RT-CGM) devices for adult patients with T1DM [type 1 diabetes mellitus] who have Ab1C levels above target and who are willing and able to use these devices on a nearly daily basis.
   - 6.2 We recommend RT-CGM devices for adult patients with well-controlled T1DM who are willing and able to use these devices on a nearly daily basis.

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

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."

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 23.

Table 23. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03263494	CGM Intervention in Teens and Young Adults With T1D (CITY): A Randomized Clinical Trial to Assess the Efficacy and Safety of Continuous Glucose Monitoring in Young Adults 14-<25 With Type 1 Diabetes	200	Jul 2019
NCT02838147	Effect of a Continuous Glucose Monitoring on Maternal and Neonatal Outcomes in Gestational Diabetes Mellitus: A Randomized Controlled Trial	200	Jul 2019
Unpublished			
NCT01787903[a]	The Effects of Real-time Continuous Glucose Monitoring on Glycemia and Quality of Life in Patients With Type 1 Diabetes Mellitus and Impaired Hypoglycemia Awareness)	52	Apr 2016 (completed)
NCT02671968[a]	Real-Time Continuous Glucose Monitoring (RT-CGM) in Patients With Type 1 Diabetes at High Risk for Low Glucose Values Using Multiple Daily Injections (MDI) in Germany (HYPODE-STUDY)	141	Oct 2017 (completed)

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

CODING

The following codes for treatment and procedures applicable to this policy 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. 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.

CPT/HCPCS

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
0447T	Removal of implantable interstitial glucose sensor from subcutaneous pocket via incision
0448T	Removal of implantable interstitial glucose sensor with creation of subcutaneous pocket at different anatomic site and insertion of new implantable sensor, including system activation
A9276	Sensor; invasive (e.g., subcutaneous), disposable, for use with interstitial continuous glucose monitoring system, 1 unit = 1 day supply
A9277	Transmitter; external, for use with interstitial continuous glucose monitoring system
A9278	Receiver (monitor); external, for use with interstitial continuous glucose monitoring system
K0553	Supply allowance for therapeutic continuous glucose monitor (CGM), includes all supplies and accessories, 1 month supply = 1 Unit of Service
K0554	Receiver (monitor), dedicated, for use with therapeutic glucose continuous monitor system
S1030	Continuous noninvasive glucose monitoring device, purchase (for physician interpretation of data, use CPT code)
S1031	Continuous noninvasive glucose monitoring device, rental, including sensor, sensor replacement, and download to monitor (for physician interpretation of data, use CPT code)

ICD-10 Diagnoses

E10.10	Type 1 diabetes mellitus with ketoacidosis without coma
E10.11	Type 1 diabetes mellitus with ketoacidosis with coma
E10.21	Type 1 diabetes mellitus with diabetic nephropathy
E10.22	Type 1 diabetes mellitus with diabetic chronic kidney disease
E10.29	Type 1 diabetes mellitus with other diabetic kidney complication
E10.311	Type 1 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E10.319	Type 1 diabetes mellitus with unspecified diabetic retinopathy without macular edema
E10.3211	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, right eye
E10.3212	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, left eye
E10.3213	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, bilateral
E10.3291	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, right eye
E10.3292	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, left eye
E10.3293	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, bilateral

E10.3311 Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, right eye
E10.3312 Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, left eye
E10.3313 Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, bilateral
E10.3391 Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, right eye
E10.3392 Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, left eye
E10.3393 Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, bilateral
E10.3411 Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, right eye
E10.3412 Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, left eye
E10.3413 Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, bilateral
E10.3491 Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, right eye
E10.3492 Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, left eye
E10.3493 Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, bilateral
E10.3511 Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye
E10.3512 Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye
E10.3513 Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral
E10.3521 Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye
E10.3522 Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye
E10.3523 Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral
E10.3531 Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye
E10.3532 Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye
E10.3533 Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral
E10.3541 Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye
E10.3542 Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye
E10.3543 Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral

E10.3551	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, right eye
E10.3552	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, left eye
E10.3553	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, bilateral
E10.3591	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, right eye
E10.3592	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye
E10.3593	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral
E10.36	Type 1 diabetes mellitus with diabetic cataract
E10.37X1	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, right eye
E10.37X2	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, left eye
E10.37X3	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral
E10.39	Type 1 diabetes mellitus with other diabetic ophthalmic complication
E10.40	Type 1 diabetes mellitus with diabetic neuropathy, unspecified
E10.41	Type 1 diabetes mellitus with diabetic mononeuropathy
E10.42	Type 1 diabetes mellitus with diabetic polyneuropathy
E10.43	Type 1 diabetes mellitus with diabetic autonomic (poly)neuropathy
E10.44	Type 1 diabetes mellitus with diabetic amyotrophy
E10.49	Type 1 diabetes mellitus with other diabetic neurological complication
E10.51	Type 1 diabetes mellitus with diabetic peripheral angiopathy without gangrene
E10.52	Type 1 diabetes mellitus with diabetic peripheral angiopathy with gangrene
E10.59	Type 1 diabetes mellitus with other circulatory complications
E10.610	Type 1 diabetes mellitus with diabetic neuropathic arthropathy
E10.618	Type 1 diabetes mellitus with other diabetic arthropathy
E10.620	Type 1 diabetes mellitus with diabetic dermatitis
E10.621	Type 1 diabetes mellitus with foot ulcer
E10.622	Type 1 diabetes mellitus with other skin ulcer
E10.628	Type 1 diabetes mellitus with other skin complications
E10.630	Type 1 diabetes mellitus with periodontal disease
E10.638	Type 1 diabetes mellitus with other oral complications
E10.641	Type 1 diabetes mellitus with hypoglycemia with coma
E10.649	Type 1 diabetes mellitus with hypoglycemia without coma
E10.65	Type 1 diabetes mellitus with hyperglycemia
E10.69	Type 1 diabetes mellitus with other specified complication
E10.8	Type 1 diabetes mellitus with unspecified complications
E10.9	Type 1 diabetes mellitus without complications
O24.011	Pre-existing type 1 diabetes mellitus, in pregnancy, first trimester
O24.012	Pre-existing type 1 diabetes mellitus, in pregnancy, second trimester
O24.013	Pre-existing type 1 diabetes mellitus, in pregnancy, third trimester

REVISIONS

01-26-2004	Deleted "Certain diabetic and newly pregnant or who are about to conceive" and "Patients who are about to start insulin for the first time using an insulin pump regimen"

	Added "Suboptimal glycemic control as reflected by a glycohemoglobin (HbA1c) value of greater than 7.0 percent."
	Added "Repeat testing for Continuous Glucose Monitoring System® (CGMS®): a. Prior Approval is recommended; and b. Patient is compliant on a prescribed intensive insulin program/therapy; and c. May occur four to six weeks following the initial study."
	Added "Use of noninvasive continuous glucose monitoring devices (eg Gluco Watch Biographer®) and related supplies is considered experimental/investigational for all indications."
04-21-2005	Added the definition of "intensive insulin therapy".
	Added, "The use of combined insulin, such as 70/30 insulin did not meet the criteria for "program involvement" of multiple daily injections."
11-02-2006 effective 01-02-2007	In "Description" section, deleted the paragraph starting with "The GlucoWatch is similar in appearance to a wristwatch that is worn on the inner or" as recommended by the Medical Director.
	In "Description" section, deleted the paragraph starting with "Although the noninvasiveness is an attractive quality of the device, it should be…" as recommended by the Medical Director..
	In "Description" section, deleted "For calibration purposes, the manufacturer recommends that the patient enter the results of 4 fingerstick blood glucose measurements per day into the monitor. For the Guardian CGMS, it is recommended that the device be calibrated with fingerstick blood glucose levels every 12 hours at a minimum. The Guardian CGMS does feature an audible alarm that sounds when glucose levels become too high or too low per parameters set by the patient and physician." as recommended by the Medical Director.
	In "Description" section, deleted the paragraph starting with "The definition of 'Intensive Insulin Therapy' is the use of an insulin regimen that…" as recommended by the Medical Director..
	In "Policy" section, first paragraph, added "(multiple daily injections (MDI) of 4-5 injections of insulin per day or insulin pump)." as recommended by the Medical Director.
	In "Policy" section, deleted "and one of the following conditions have been met:" and the "or" at the end of #1, #2, and #3 sentences per November MAC.
	In "Policy" section, added to the end of the opening sentence "The following conditions will be considered to determine medical necessity:" per November MAC.
	In "Policy" section, added "Unexplained" to the beginning of #3 and #4 per November MAC.
	In "Documentation" section, deleted "Program Involvement (all required):" as recommended by the Medical Director.
	In "Documentation" section, deleted #2 "Basal insulin usually involves "Ultralente" and "Lantus" insulin." as recommended by the Medical Director.
	In "Documentation" section, deleted #3 "Bolus insulin (insulin analogue) usually involves "Humalog" or "Novolog" insulin." as recommended by the Medical Director.
	In "Coding" Covered Diagnosis, deleted ICD-9 codes (for type II) 250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, and 250.92 as recommended by the Medical Director.
	In "Reference" Government Agency; Medical Society; and Other Authoritative Publications section, added new #3 through #7.
07-17-2007	In Policy section: ▪ Added clarification to policy that continuous glucose monitoring system is limited to 72 hours. Extended use beyond 72 hours is considered patient deluxe, patient responsibility/non-covered. In Coding section:

	▪ Removed code 99091.
01-01-2008	In Coding section: ▪ Added codes and nomenclature for A9276, A9277, A9278.
09-03-2008	In Coding section: ▪ Added codes and nomenclature for S1030, S1031. ▪ Corrected nomenclature for 95250.
	In Policy section: Revised wording from "requires prior approval" to "prior approval is encouraged".
09-09-2009	In Header: ▪ Revised title from Continuous Glucose Monitoring System (CGMS) to Continuous or Intermittent Monitoring of Glucose in Interstitial Fluid. In Description section: ▪ Updated wording. In Policy section: ▪ Updated wording on intermittent monitoring, no change in policy position. ▪ Added indication of: Continuous, ie, long-term, monitoring of glucose levels in interstitial fluid, including real-time monitoring, as a technique of diabetic monitoring, may be considered medically necessary when the following situations occur despite use of best practices: • Patients with type I diabetes who have recurrent, unexplained, severe, symptomatic (generally blood glucose levels less than 50 mg/dl) hypoglycemia for whom hypoglycemia puts the patient or others at risk; or • Patients with type I diabetes who have recurrent diabetic ketoacidosis (DKA) requiring emergency room visits and admissions. • Patients with type I diabetes who are pregnant whose diabetes is poorly controlled. Poorly controlled type I diabetes includes unexplained hypoglycemic episodes, hypoglycemic unawareness, suspected postprandial hyperglycemia, and recurrent diabetic ketoacidosis. Other uses of continuous monitoring of glucose levels in interstitial fluid as a technique of diabetic monitoring are considered investigational.
	Added Rationale section.
	In Coding section: ▪ Added CPT/HCPCS codes: 99091, A9278 ▪ Added Diagnoses codes: 648.80, 648.83
03-25-2011	In Policy Guidelines section: ▪ Added "or multiple daily injections" to read "Best practices in diabetes control for patients with type I diabetes include compliance with a regimen of 4 or more fingersticks each day and the use of an insulin pump, or multiple daily injections."
	Updated Reference section.
10-04-2013	Updated Description section.
	In Policy section: ▪ Formatted medical policy language. ▪ In Item C, #1, removed "symptomatic" to read "Patients with type I diabetes who have recurrent, unexplained, severe (generally blood glucose levels less than 50 mg/.dl) hypoglycemia…" ▪ In Item D, inserted "experimental/" to read "Other uses of continuous monitoring of glucose levels in interstitial fluid as a technique of diabetic monitoring are considered experimental / investigational." ▪ Added Item E, "Use of artificial pancreas system, including but not limited to closed-loop monitoring devices with low-glucose suspend (LGS) features, are considered experimental / investigational."

	▪ In Policy Guidelines, add the following statements: o "Several insulin pump systems (eg, Omnipod Insulin Management System, Paradigm REAL-Time System) have a built-in continuous glucose monitor (CGM). This policy is evaluating the CGM-device only; the policy does not evaluate insulin pumps. In the case of inslin pumps systems with built-in CGM and low glucose feature, the CGM device and the low glucose suspend feature are evaluated in the policy, not the insulin pump." o "The strongest evidence exists for use of the CGM devices in patients age 25 and older. However, age may be a proxy for motivation and good control of disease, so it is also reasonable to select patients based on their ability to self manage their disease rather than age."
	In Coding section: ▪ Added ICD-10 Diagnosis *(Effective October 1, 2014)*
	Updated Reference section.
03-06-2015	Updated Description section.
	In Policy section: ▪ Removed Item E, "Use of an artificial pancreas system, including but not limited to closed loop monitoring devices with low glucose suspend (LGS) features, are considered experimental/investigational."
	In Policy Guidelines section: ▪ In Item #2, removed "type I" and added "mellitus" to read, "Best practices in diabetes control for patients with diabetes mellitus include compliance with a regimen …" ▪ In Item #3, added "mellitus" to read, "Women with type I diabetes mellitus who are present or about to become …" ▪ In Item #4, removed "four weeks depending on the patient's level of diabetes control and medical necessity", and added "a subsequent time depending on the patient's level of diabetes control", to read, "Intermittent monitoring is generally conducted in 72-hour periods. It may be repeated at a subsequent time depending on the patient's level of diabetes control."
	Updated Rationale section.
	Updated References section.
08-04-2016	Updated Description section.
	In Policy section: ▪ In Policy Guidelines Item 1, removed "Omnipod Insulin Management System," to read "Several insulin pump systems (eg, Paradigm® REAL-Time System) have a built-in continuous glucose monitor (CGM). This policy is evaluating the CGM-device only; the policy does not evaluate insulin pumps. In the case of insulin pumps systems with a built-in CGM and low glucose suspend (LGS) feature, the CGM device and the low glucose suspend feature are evaluated in the policy, not the insulin pump."
	Updated Rationale section.
	Updated References section.
10-01-2016	In Coding section: ▪ Added ICD-10 codes effective 10-01-2016: E10.3211, E10.3212, E10.3213, E10.3291, E10.3292, E10.3293, E10.3311, E10.3312, E10.3313, E10.3391, E10.3392, E10.3393, E10.3411, E10.3412, E10.3413, E10.3491, E10.3492, E10.3493, E10.3511, E10.3512, E10.3513, E10.3521, E10.3522, E10.3523, E10.3531, E10.3532, E10.3533, E10.3541, E10.3542, E10.3543, E10.3551, E10.3552, E10.3553, 310.3591, E10.3592, E10.3593, E10.37X1, E10.37X2, E10.37X3, O24.415 ▪ Termed ICD-10 codes effective 09-30-2016: E10.321, E10.329, E10.331, E10.339, E10.341, E10.349, E10.351, E10.359
11-22-2016	In Policy section: ▪ In Policy Guidelines Item 3, removed "Women" and added "Individuals" to read,

	"Individuals with type I diabetes mellitus who are pregnant or about to become pregnant with poorly controlled diabetes are another subset of patients to whom the policy statement on intermittent monitoring may apply."
	In Coding section: ▪ Added CPT codes: 0446T, 0447T, 0448T.
07-01-2017	In Coding section: ▪ Added HCPCS codes: K0553, K0554 (Effective July 1, 2017).
09-01-2017	Updated Description section.
	In Policy section: ▪ In Item A, removed "mellitus" to read, "Intermittent monitoring, ie, up to 72 hours, of glucose levels in interstitial fluid may be considered medically necessary in patients with type 1 diabetes whose diabetes is poorly controlled, despite current use of best practices (see Policy Guidelines). Poorly controlled type 1 diabetes includes the following clinical situations:" ▪ In Item C 1, added "or impaired awareness of hypoglycemia that" and removed "for whom hypoglycemia" to read, "Patients with type 1 diabetes who have recurrent, unexplained, severe (generally blood glucose levels less than 50 mg/dL) hypoglycemia or impaired awareness of hypoglycemia that puts the patient or others at risk;" ▪ Added new Item C 3, "Patients with poorly controlled type 1 diabetes who are pregnant. Poorly controlled type 1 diabetes includes unexplained hypoglycemic episodes, hypoglycemic unawareness, suspected postprandial hyperglycemia, and recurrent diabetic ketoacidosis;" ▪ Updated Policy Guidelines.
	Updated Rationale section.
	Updated References section.
12-01-2017	In Policy section: ▪ In Policy Guidelines, Item 2, added "an average of", "(at least 30 days [1 month] prior to initiation)", and "or multiple daily injections. Compliance will also be required for other aspects of diabetic management including insulin bolusing or diet." to read, "Best practices in diabetes control include compliance with a regimen of 4 or more fingersticks each day (at least 30 days [1 month] prior to initiation) and use of an insulin pump or multiple daily injections. Compliance will also be required for other aspects of diabetic management including insulin bolusing or diet."
	In Coding section: ▪ Added ICD-10 codes: O24.011, O24.012, O24.013. ▪ Removed ICD-10 codes: O24.410, O24.414, O24.415, O24.419, O99.810.
01-01-2018	In Coding section: ▪ Added CPT code: 95249. ▪ Revised nomenclature to CPT codes: 95250, 95251. ▪ Removed ICD-9 codes.
05-11-2018	Updated Description section.
	In Policy section: ▪ In Item D, added "and intermittent" to read, "Other uses of continuous and intermittent monitoring of glucose levels in interstitial fluid as a technique of diabetic monitoring are considered experimental / investigational."
	Updated Rationale section.
	Updated References section.
11-07-2018	In Policy section: ▪ Updated Policy Guidelines.
	Updated References section.
01-16-2019	Updated Description section.
	Updated Rationale section.

	In Revisions section: ▪ In Revision of 09-09-2009, CPT code 99091 was not added to the policy at that time and will remain omitted from the policy.
	Updated References section.

REFERENCES

1. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *Jama.* May 15 2002;287(19):2563-2569. PMID 12020338
2. 13. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2018. *Diabetes Care.* Jan 2018;41(Suppl 1):S137-s143. PMID 29222384
3. Pazos-Couselo M, Garcia-Lopez JM, Gonzalez-Rodriguez M, et al. High incidence of hypoglycemia in stable insulin-treated type 2 diabetes mellitus: continuous glucose monitoring vs. self-monitored blood glucose. Observational prospective study. *Can J Diabetes.* Oct 2015;39(5):428-433. PMID 26254702
4. Gehlaut RR, Dogbey GY, Schwartz FL, et al. Hypoglycemia in type 2 diabetes--more common than you think: a continuous glucose monitoring study. *J Diabetes Sci Technol.* Sep 2015;9(5):999-1005. PMID 25917335
5. Food and Drug Administration (FDA). Summary of Safety and Effectiveness (SSED): Dexcom G5 Mobile Continuous Glucose Monitoring System. 2016; https://www.accessdata.fda.gov/cdrh_docs/pdf12/P120005S041b.pdf. Accessed February 26, 2018.
6. Blue Cross and Blue Shield Technology Evaluation Center (TEC). Use of intermittent or continuous interstitial fluid glucose monitoring in patients with diabetes mellitus. *TEC Assessments.* 2003;Volume 18:Tab 16.
7. 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.* Sep 2012;6(5):1094-1102. PMID 23063035
8. Gandhi GY, Kovalaske M, Kudva Y, et al. Efficacy of continuous glucose monitoring in improving glycemic control and reducing hypoglycemia: a systematic review and meta-analysis of randomized trials. *J Diabetes Sci Technol.* Jul 2011;5(4):952-965. PMID 21880239
9. Langendam M, Luijf YM, Hooft L, et al. Continuous glucose monitoring systems for type 1 diabetes mellitus. *Cochrane Database Syst Rev.* Jan 18 2012;1:CD008101. PMID 22258980
10. 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.* Jul 23 2013;5(1):39. PMID 23876067
11. Wojciechowski P, Rys P, Lipowska A, et al. Efficacy and safety comparison of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes: systematic review and meta-analysis. *Pol Arch Med Wewn.* Oct 2011;121(10):333-343. PMID 22045094
12. Yeoh E, Choudhary P, Nwokolo M, et al. Interventions that restore awareness of hypoglycemia in adults with type 1 diabetes: a systematic review and meta-analysis. *Diabetes Care.* Aug 2015;38(8):1592-1609. PMID 26207053
13. 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).* Mar 2017;86(3):354-360. PMID 27978595
14. 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.* Nov 2016;4(11):893-902. PMID 27641781
15. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. *Diabetes Care.* Jul 1994;17(7):697-703. PMID 7924780
16. 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.* Jan 24 2017;317(4):379-387. PMID 28118454

17. Beck RW, Riddlesworth T, Ruedy K, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: The DIAMOND randomized clinical trial. *Jama.* Jan 24 2017;317(4):371-378. PMID 28118453
18. Riddlesworth T, Price D, Cohen N, et al. Hypoglycemic event frequency and the effect of continuous glucose monitoring in adults with type 1 diabetes using multiple daily insulin injections. *Diabetes Ther.* Aug 2017;8(4):947-951. PMID 28616804
19. Polonsky WH, Hessler D, Ruedy KJ, et al. The impact of continuous glucose monitoring on markers of quality of life in adults with type 1 diabetes: further findings from the DIAMOND randomized clinical trial. *Diabetes Care.* Jun 2017;40(6):736-741. PMID 28389582
20. Feig DS, Donovan LE, Corcoy R, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. *Lancet.* Nov 25 2017;390(10110):2347-2359. PMID 28923465
21. 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.* May 2009;13(28):iii-iv, ix-xi, 1-194. PMID 19476724
22. Voormolen DN, Devries JH, Evers IM, et al. The efficacy and effectiveness of continuous glucose monitoring during pregnancy: a systematic review. *Obstet Gynecol Surv.* Nov 2013;68(11):753-763. PMID 24193194
23. 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.* Jul 2013;36(7):1877-1883. PMID 23349548
24. Murphy HR, Rayman G, Lewis K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. *BMJ.* Sep 25 2008;337:a1680. PMID 18818254
25. 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.* May 2011;5(3):668-675. PMID 21722581
26. Cosson E, Hamo-Tchatchouang E, Dufaitre-Patouraux L, et al. Multicentre, randomised, controlled study of the impact of continuous sub-cutaneous glucose monitoring (GlucoDay) on glycaemic control in type 1 and type 2 diabetes patients. *Diabetes Metab.* Sep 2009;35(4):312-318. PMID 19560388
27. Allen NA, Fain JA, Braun B, et al. Continuous glucose monitoring counseling improves physical activity behaviors of individuals with type 2 diabetes: A randomized clinical trial. *Diabetes Res Clin Pract.* Jun 2008;80(3):371-379. PMID 18304674
28. 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.* Oct 2008;82(1):73-79. PMID 18701183
29. 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.* Sep 19 2017;167(6):365-374. PMID 28828487
30. Sato J, Kanazawa A, Ikeda F, et al. Effect of treatment guidance using a retrospective continuous glucose monitoring system on glycaemic control in outpatients with type 2 diabetes mellitus: A randomized controlled trial. *J Int Med Res.* Feb 2016;44(1):109-121. PMID 26647072
31. 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.* Jan 2012;35(1):32-38. PMID 22100963
32. Wei Q, Sun Z, Yang Y, et al. Effect of a CGMS and SMBG on maternal and neonatal outcomes in gestational diabetes mellitus: a randomized controlled trial. *Sci Rep.* Jan 27 2016;6:19920. PMID 26814139
33. 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.* Feb 2016;22(2):231-261. PMID 26848630

34. National Institute for Health and Care Excellence (NICE). Type 1 diabetes in adults: diagnosis and management [NG17]. 2016; https://www.nice.org.uk/guidance/ng17?unlid=382286372016220232952. Accessed February 26, 2018.
35. American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2018. *Diabetes Care.* Jan 2018;41(Suppl 1):S55-S64. PMID 29222377
36. 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.* Nov 2016;101(11):3922-3937. PMID 27588440
37. Centers for Medicare & Medicare Services. Durable Medical Equipment, Prosthetics/Orthotics & Supplies Fee Schedule 2017; https://www.cms.gov/medicare/medicare-fee-for-service-payment/dmeposfeesched/index.html. Accessed February 26, 2018.

Other References

1. Blue Cross and Blue Shield of Kansas Pediatric Liaison Committee, July 2008; July 2009; July 2010; July 2011; July 2013; July 2014; July 2018.
2. Blue Cross and Blue Shield of Kansas Internal Medicine Liaison Committee, August 2008; August 2009; August 2013; August 2014; August 2018.
3. Blue Cross and Blue Shield of Kansas Family Practice Liaison Committee, July 2009.
4. Blue Cross and Blue Shield of Kansas Consent Ballot, June 2009: Family Practice Liaison Committee; Internal Medicine Liaison Committee; Pediatric Liaison Committee.