Continuous or Intermittent Monitoring of Glucose in Interstitial Fluid

Policy # 00019
Original Effective Date: 03/25/2002
Current Effective Date: 09/19/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Intermittent 72 Hour Glucose Monitoring

Based on review of available data, the Company may consider intermittent 72 hour continuous monitoring of glucose levels in the interstitial fluid using an implantable sensor as a technique of diabetic monitoring to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility for 72 hour continuous monitoring of glucose levels in the interstitial fluid using an implantable sensor as a technique of diabetic monitoring will be considered when the following patient selection criteria are met:

- Insulin dependent diabetic using 3 or more insulin injections per day or insulin pump; AND
    - Despite current use of best practices (per Policy Guidelines), diabetes is poorly controlled as evidenced by unexplained or frequent hypoglycemic episodes, hypoglycemic unawareness, suspected postprandial hyperglycemia or recurrent diabetic ketoacidosis; OR,
    - Prior to insulin pump initiation to determine basal insulin levels.

Note: Monitoring would be for 72 consecutive hours, and approved for a maximum of 2 times per year.

Continuous Long-term Glucose Monitoring

Based on review of available data, the Company may consider chronic continuous monitoring of glucose levels in interstitial fluid, including real-time monitoring, as a technique of diabetic monitoring, may be considered **eligible for coverage.**

Patient Selection Criteria

Coverage eligibility for chronic continuous monitoring of glucose levels in interstitial fluid, including real-time monitoring, as a technique of diabetic monitoring will be considered when the following patient selection criteria are met, despite use of best practices:

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

- 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.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers other uses of continuous monitoring of glucose levels in interstitial fluid as a technique of diabetic monitoring to be **investigational.***

Based on review of available data, the Company considers the use of continuous monitoring of glucose in the interstitial fluid when patient selection criteria are not met to be **investigational.***

Policy Guidelines

Several insulin pump systems (e.g., Paradigm® REAL-Time System)‡ have a built-in continuous glucose monitor. This policy only evaluates the continuous glucose monitor; it does not evaluate insulin pumps.

Best practices in diabetes control include compliance with a regimen of 4 or more fingersticks each day and use of an insulin pump. 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.

Women 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.

Intermittent monitoring is generally conducted over 72-hour periods. It may be repeated subsequently depending on the patient's level of diabetes control.

The strongest evidence exists for use of continuous glucose monitoring (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 their age.

Providers board certified in endocrinology and/or providers with a focus on the practice of diabetes care may be considered qualified to evaluate and oversee individuals for continuous (i.e., long-term) monitoring.

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Background/Overview

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 (RCTs) assessing tight control have demonstrated benefits for patients with type 1 diabetes in decreasing microvascular complications. The impact of tight control on type 1 diabetes and macrovascular complications such as stroke or myocardial infarction is less certain. The Diabetes Control and Complications Trial (2002) demonstrated that a relative 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.

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.

Tight glucose control requires multiple daily measurements of blood glucose (i.e., 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. 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} values.

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 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 (i.e., for periods of 72 hours) or continuously (i.e., 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Several CGM systems have been approved by 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

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

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FDA product codes: MDS, PQF.

Centers for Medicare and Medicaid Services (CMS)
In January 2017, the Centers for Medicare & Medicaid Services issued a ruling that CGM devices approved by the FDA that can be used to make treatment decisions are considered durable medical equipment. To date, 1 device has met these criteria, the Dexcom G5.

Rationale/Source

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 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 CGM systems. That is, their ability to provide additional information on glucose levels leads to improved glucose control, or to improve 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
This evidence review assesses RCTs that have reported on outcomes of CGM devices. We categorized CGM devices as continuous, long-term, monitoring devices by the patient to direct insulin regimens, and intermittent (i.e., 72 hours), short-term monitoring used by the provider to optimize management.

In some parts of the analysis of type 1 diabetes, we combine discussion of the first 2 indications (long-term and short-term glucose monitoring) because several of the systematic reviews and RCTs provided information relevant to both indications. Separate sections and summaries follow after that.

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. These systematic reviews have focused on slightly different populations, and some did not separate long-term CGM from intermittent glucose monitoring. The most recent meta-analysis, and the only analysis to use individual patient data was published by Benkhadra et al (2017). 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 hemoglobin A_{1c} (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 I 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
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).
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 (2012) of CGM in type 1 diabetes in adults and children included RCTs comparing CGM with conventional self-monitored blood glucose (SMBG). 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] change, -0.2%; 95% confidence interval [CI], -0.4% to -0.1%), but there was no difference in decline in HbA_{1c} levels at 12 months (1 study, n=154 patients; MD change, 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 (2011) of RCTs evaluating CGM included trials conducted in adults and children with type 1 diabetes. 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 MD, -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 are described next. For example, van Beers et al (2016) published a crossover RCT comparing CGM with SMBG and focusing on patients with impaired hypoglycemia awareness. 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). 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 (e.g., number and duration of nocturnal

hypoglycemia events) also significantly favored the CGM group. The total number of severe hypoglycemic events (i.e., 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%). 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). 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). Quality of life measures assessing overall well-being (WHO-5), health status (EQ-5D-5L), diabetes distress (DDS), hypoglycemic fear (worry subscale of the HFS-II), and hypoglycemic confidence (HCS) have also been reported. 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 HCS (p=0.01) and a greater decrease in DDS (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 design 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. 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) 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 length of hospital stay (3.1 days vs 4.0 days; p=0.0091). Skin reactions occurred in 49 (48%) of 103 CGM participants and 8 (8%) of 104 control participants.

Table 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); 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, continuous) (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)						
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.

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

Study	Population	Intervention	Comparator	Outcomes	Follow-Up
Feig et al (2017)	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	None noted	None noted
Key	1.Intended use population unclear 2.Clinical context for treatment is unclear 3.Study population unclear 4.Study population not representative of intended use 5.Study population is subpopulation of intended use	1.Not clearly defined 2.Version used unclear 3.Delivery not similar intensity as comparator 4.Not delivered effectively	1.Not clearly defined 2.Not standard or optimal 3.Delivery not similar intensity as intervention 4.Not delivered effectively	1.Key health outcomes not addressed 2.Physiologic measures, not validated surrogates 3.Not CONSORT reporting of harms 4.Not established and validated measurements 5.Clinically significant difference not prespecified 6.Clinically significant difference not supported	1.Not sufficient duration for benefits 2.Not sufficient duration for harms

CGM: continuous glucose monitoring; RCT: randomized controlled trial.

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

Study	Allocation	Blinding	Selective Reporting	Follow-Up	Power	Statistical
Feig et al (2017)	None noted	1. Not blinded; chance of bias in clinical management	None noted	None noted	None noted	3, 4. Treatment effects and confidence intervals not calculated for some outcomes
Key	1.Participants not randomly allocated 2.Allocation not concealed 3.Allocation concealment unclear 4.Inadequate control for selection bias	1.Not blinded to treatment assignment 2.Not blinded outcome assessment 3.Outcome assessed by treating physician	1.Not registered 2.Evidence of selective reporting 3.Evidence of selective publication	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)	1.Power calculations not reported 2.Power not calculated for primary outcome 3.Power not based on clinically important difference	1.Test is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event 2.Test is not appropriate for multiple observations per patient 3.Confidence intervals and/or p values not reported 4.Comparative treatment effects not calculated

CGM: continuous glucose monitoring; RCT: randomized controlled trial.

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 reduction in HbA_{1c} levels was 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 length of hospital 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 (e.g., education, lifestyle modifications).

Two meta-analyses were identified that reported separate subgroup analyses for intermittent monitoring. In a Cochrane review (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). The meta-analysis (2011) of RCTs on CGM (described previously) also included a separate analysis of 8 RCTs of intermittent monitoring. 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).

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. 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 (i.e., monitoring was performed over several days at various points in the trial). These groups were compared with an attention control group (standard treatment with nurse feedback sessions at the same frequency as those in the device groups) and a standard control group (reflecting common practice in the clinical management of diabetes). Changes in 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 resulted in any changes in 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. 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 do not have data available in real-time; the remaining 4 studies used real-time CGM. Reviewers did not pool study findings; they concluded that the evidence was limited on the efficacy of CGM during pregnancy. The published RCTs are described next.

Randomized Controlled Trials
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.

Murphy et al (2008) in the U.K. 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).

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). 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.

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

Author; Registration	Countries	Sites	Dates	Participants	Active	Comparator
Murphy et al (2008); ISRCTN84461581	U.K.	2	2003-2006	Pregnant women with type 1 (65%) and 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)
Secher et al (2013); 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 routine care (n=79)	Routine care (n=75)

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

Table 8. RCT Outcomes of Intermittent CGM in Pregnant Women With Type 1 Diabetes

	Infant				Maternal	
Study	Large-for-Gestational Age	Gestational Age at Delivery Weeks	Severe Hypoglycemia	Caesarean Section	HbA_{1c} Levels: At 36 Wk' Gestation[a]	Severe Hypoglycemia
Murphy et al (2008)						
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	
			Days			
Secher et al (2013)						
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

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 studies of intermittent glucose monitoring conducted in Europe included pregnant women with type 1 or 2 diabetes, with most having type 1 diabetes. Murphy et al (2008) included intermittent, retrospective monitoring with CGM; Secher et al (2013) included intermittent, real-time monitoring. 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.

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

Study	Population	Intervention	Comparator	Outcomes	Follow-Up
Murphy et al (2008)	None noted	None noted	None noted	None noted	None noted
Secher et al (2013)	4. Study population had relatively low HbA_{1c}	4. Only 64% of the participants used devices per protocol	None noted	None noted	None noted
Key	1.Intended use population unclear 2.Clinical context for treatment is unclear 3.Study population unclear 4.Study population not representative of intended use 5.Study population is subpopulation of intended use	1.Not clearly defined 2.Version used unclear 3.Delivery not similar intensity as comparator 4.Not delivered effectively	1.Not clearly defined 2.Not standard or optimal 3.Delivery not similar intensity as intervention 4.Not delivered effectively	1.Key health outcomes not addressed 2.Physiologic measures, not validated surrogates 3.Not CONSORT reporting of harms 4.Not established and validated measurements 5.Clinically significant difference not prespecified 6.Clinically significant difference not supported	1.Not sufficient duration for benefits 2.Not sufficient duration for harms

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

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

Study	Allocation	Blinding	Selective Reporting	Follow-Up	Power	Statistical
Murphy et al (2008)	None noted	1. Not blinded; chance of bias in clinical management	None noted	None noted	None noted	3, 4. Treatment effects and confidence intervals not calculated for some outcomes
Secher et al (2013)	None noted	1. Not blinded; chance of bias in clinical management	None noted	None noted	None noted	3, 4. Treatment effects and confidence intervals not calculated
Key	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician	1. Not registered 2. Evidence of selective reporting 3. Evidence of selective publication	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)	1. Power calculations not reported 2. Power not calculated for primary outcome 3. Power not based on clinically important difference	1. Test is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event 2. Test is not appropriate for multiple observations per patient 3. Confidence intervals and/or p-values not reported 4. Comparative treatment effects not calculated

CGM: continuous glucose monitoring; RCT: randomized controlled trial.

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 study reported a difference in HbA_{1c} levels at 36 weeks and the proportion of infants that were large for gestational age (>90th percentile) favoring CGM while the second study 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 and 4 (long-term and short-term glucose monitoring), consistent with the literature.

Systematic Reviews

Two systematic reviews (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	Gandhi et al (2011)	Poolsup et al (2013)
Allen et al (2008)	●	●
Yoo et al (2008)	●	●
Cosson et al (2009)	●	●
Ehrhardt et al (2011)		●

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). 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. 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 MD 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 (e.g., by type of CGM device) were not performed.

Table 12. Systematic Review Characteristics for CGM in Type 2 Diabetes

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Gandhi et al (2011)	1996-2010	3	Adult outpatients with T2D; mean baseline HbA_{1c} level >8%	128 (25-57)	RCT	At least 8 wk (median, 3 mo)
Poolsup et al (2013)	Up to 2013	4	Adults with T2D	228 (25-100)	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
Gandhi et al (2011)				
Total N	128	NR	NR	NR
PE (95% CI)	-0.70 (-1.14 to -0.27)			
p	NR			
I^2	0%			
Poolsup et al (2013)				
Total N	228	NR	NR	NR
PE (95% CI)	-0.31 (-0.60 to -0.02)			
p	0.04			
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 studies 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.

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). 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 (e.g., 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).

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%. All patients conducted SMBG and used CGM devices that do not have data available in real-time (i.e., 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.

The largest RCT, Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND), was reported by Beck et al (2017). 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 into 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.

Table 14. RCT Characteristics for Glucose Monitoring in Type 2 Diabetes

					Interventions	
Study; Registration	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
Allen et al (2008)	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)	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)
Cosson et al (2009)	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)
Ehrhardt et al (2011)	U.S.	1	NR	Adults with T2D using oral antidiabetic agents without prandial insulin with HbA_{1c} levels 7.0%-12.0%	Real-time CGM for 4 cycles of 3 wk (n=50)	SMBG (n=50)

				(baseline mean, 8.3%), mean age, 58 y		
Sato et al (2016); 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)
Beck et al (2017) (DIAMOND); 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, continuous, real-time (n=79)	SMBG (n=79)

CGM: continuous glucose monitoring; HbA_{1c}: hemoglobin A_{1c}; NR: not reported; 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. 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. Few other outcomes were reported. 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. 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%, %	Relative Reduction in HbA_{1c} Level ≥10%, %	Hypoglycemic or Ketoacidosis Events	Diabetes Complications (retinopathy, nephropathy, neuropathy, diabetic foot)	Health-Related Quality of Life
	Change From Baseline to 8 Wk					
Allen et al (2008)						
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					
	Change From Baseline to 3 Mo					
Yoo et al (2008)						
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					
				Time Spent With Hypoglycemia, min		
Cosson et al (2009)						
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		
	Change From Baseline to 12 Wk					
Ehrhardt et al (2011)						
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					
	Change From Baseline to 8 Mo					
Sato et al (2016)						
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					
	Change From Baseline to 24 Wk	**At 24 Wk**	**At 24 Wk**			**DDS Overall Mean Score at 24 Wk**
Beck et al (2017)						
N	158	158	158	158	NR	150
CGM	8.6% to 7.7%	11 (14%)	40 (52%)	0		1.8
Control	8.6% to 8.2%	9 (12%)	24 (32%)	0		1.8
TE (95% CI)	-0.3 (-0.5 to 0.0)	3% (-9% to 14%)	22% (0% to 42%)			NR
p	0.022	0.88	0.028			

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.

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

Study	Population	Intervention	Comparator	Outcomes	Follow-Up
Allen et al (2008)	None noted	None noted	None noted	1. Focused on HbA_{1c}; did not include outcomes on adverse events, quality of life, or diabetic complications	1. Follow-up not sufficient to determine effects on diabetic complications
Yoo et al (2008)	None noted	None noted	None noted	1. Focused on HbA_{1c}; did not include outcomes on adverse events, quality of life, or diabetic complications	1. Follow-up not sufficient to determine effects on diabetic complications
Cosson et al (2009)	None noted	None noted	None noted	1. Focused on HbA_{1c}; did not include outcomes on adverse events, quality of life, or diabetic complications	1. Follow-up not sufficient to determine effects on diabetic complications
Ehrhardt et al (2011)	None noted	None noted	None noted	1. Focused on HbA_{1c}; did not include outcomes on adverse events, quality of life, or diabetic complications 6. No justification for clinically significant difference	1. Follow-up not sufficient to determine effects on diabetic complications; patients reportedly followed for 52 wk but data not reported.
Sato et al (2016)	None noted	None noted	None noted	1. Focused on HbA_{1c}; did not include outcomes on adverse events, quality of life, or diabetic complications	1. Follow-up not sufficient to determine effects on diabetic complications
Beck et al (2017) (DIAMOND)	None noted	None noted	None noted	1. Did not include outcomes on diabetic complications	1. Follow-up not sufficient to determine effects on diabetic complications
Key	1. Intended use population unclear 2. Clinical context for treatment is unclear 3. Study population unclear 4. Study population not representative of intended use 5. Study population is subpopulation of intended use	1. Not clearly defined 2. Version used unclear 3. Delivery not similar intensity as comparator 4. Not delivered effectively	1. Not clearly defined 2. Not standard or optimal 3. Delivery not similar intensity as intervention 4. Not delivered effectively	1. Key health outcomes not addressed 2. Physiologic measures, not validated surrogates 3. Not CONSORT reporting of harms 4. Not established and validated measurements 5. Clinically significant difference not prespecified 6. Clinically significant difference not supported	1. Not sufficient duration for benefits 2. Not sufficient duration for harms

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

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

Study	Allocation	Blinding	Selective Reporting	Follow-Up	Power	Statistical
Allen et al (2008)	None noted	1. Not blinded; chance of bias in clinical management	1. Registration not reported	None noted	2, 3. Power not calculated a priori; convenience sample size	3, 4. Treatment effects and confidence intervals not calculated
Yoo et al (2008)	None noted	1. Not blinded; chance of bias in clinical management	1. Registration not reported	None noted	None noted	3, 4. Treatment effects and confidence intervals not calculated
Cosson et al (2009)	None noted	None noted	1. Registration not reported	2. Unclear how missing data were handled in analyses	1, 2,3. No power calculations	3, 4. Treatment effects and confidence intervals not calculated
Ehrhardt et al (2011)	None noted	1. Not blinded; chance of bias in clinical management	1. Registration not reported	None noted	3. No justification for difference used for power calculation	3, 4. Treatment effects and CIs not calculated
Sato et al (2016)	None noted	None noted	None noted	None noted	None noted	3, 4. Treatment effects and confidence intervals not calculated
Beck et al (2017) (DIAMOND)	None noted	1. Not blinded; chance of bias in clinical management	None noted	None noted	None noted	None noted
Key	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician	1. Not registered 2. Evidence of selective reporting 3. Evidence of selective publication	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)	1. Power calculations not reported 2. Power not calculated for primary outcome 3. Power not based on clinically important difference	1. Test is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event 2. Test is not appropriate for multiple observations per patient 3. Confidence intervals and/or p values not reported 4. Comparative treatment effects not calculated

CGM: continuous glucose monitoring; CI: confidence interval; RCT: randomized controlled trial.

Pregnant Women

As discussed in the section on CGM in pregnant women, 2 RCTs have evaluated intermittent CGM 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) and 31 (20%) with type 2 diabetes in Secher et al (2013). 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 the 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 continuous, 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 study reported analyses stratified by diabetes type.

PREGNANT WOMEN WITH GESTATIONAL DIABETES

One trial of glucose monitoring in women with gestational diabetes has been published. Trial design, results, and gaps are shown in Tables 18 to 21. In an RCT, Wei et al (2016) evaluated the use of CGM in 120 women with gestational diabetes at 24 to 28 weeks. Patients were allocated 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

					Interventions	
Author	Countries	Sites	Dates	Participants	Active	Comparator
Wei et al (2016)	China	1	2011-2012	Pregnant women with gestational diabetes diagnosed between 24 and 28 wk' 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

	Infant				Maternal	
Study	Large-for-Gestational Age	Gestational Age at Delivery, wk	Severe Hypoglycemia	Caesarean Section	HbA_{1c} Levels at 36 Wk' Gestation[a]	Severe Hypoglycemia
Wei et al (2016)						
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.

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

Study	Population	Intervention	Comparator	Outcomes	Follow-Up
Wei et al (2016)	4. Study population had relatively low HbA_{1c} level	4. Compliance with CGM not reported	None noted	None noted	None noted
Key	1. Intended use population unclear 2. Clinical context for treatment is unclear 3. Study population unclear 4. Study population not representative of intended use 5. Study population is subpopulation of intended use	1. Not clearly defined 2. Version used unclear 3. Delivery not similar intensity as comparator 4. Not delivered effectively	1. Not clearly defined 2. Not standard or optimal 3. Delivery not similar intensity as intervention 4. Not delivered effectively	1. Key health outcomes not addressed 2. Physiologic measures, not validated surrogates 3. Not CONSORT reporting of harms 4. Not established and validated measurements 5. Clinically significant difference not prespecified 6. Clinically significant difference not supported	1. Not sufficient duration for benefits 2. Not sufficient duration for harms

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

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 compares 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 length of hospital 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, real-time 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 continuous, 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 CGM, 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 (continuous) 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 CGM was unclear. Trial reporting was incomplete; however, there was no difference between the groups for the majority of the reported outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Continuous or Intermittent Monitoring of Glucose in Interstitial Fluid", 1.01.20; 3:2018.
2. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *Jama.* May 15 2002;287(19):2563-2569. PMID 12020338
3. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2018. *Diabetes Care.* Jan 2018;41(Suppl 1):S137-s143. PMID 29222384
4. 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
5. 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
6. 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.
7. 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.
8. 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
9. 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
10. 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
11. 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
12. 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
13. 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
14. 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
15. 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
16. 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

17. 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
18. 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
19. 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
20. 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
21. 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
22. 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
23. 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
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. 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
26. 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
27. 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
28. 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
29. 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
30. 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
31. 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
32. 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
33. 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
34. 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
35. 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.
36. American Diabetes Association (ADA). 6. Glycemic Targets. *Diabetes Care.* Jan 2017;40(Suppl 1):S48-S56. PMID 27979893
37. 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
38. 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.

Continuous or Intermittent Monitoring of Glucose in Interstitial Fluid

Policy # 00019
Original Effective Date: 03/25/2002
Current Effective Date: 09/19/2018

Policy History

Original Effective Date: 03/25/2002
Current Effective Date: 09/19/2018

03/21/2002	Medical Policy Committee review
03/25/2002	Managed Care Advisory Council approval
06/24/2002	Format revision. No substance change to policy.
01/29/2004	Medical Director Review
02/1720/04	Medical Policy Committee review. Format revision. No substance change to policy.
02/23/2004	Managed Care Advisory Council approval
02/01/2006	Medical Director review
02/15/2006	Medical Policy Committee review. Format revisions. Rationale updated.
02/23/2006	Quality Care Advisory Council approval
07/07/2006	Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged
03/14/2007	Medical Director review
03/21/2007	Medical Policy Committee approval. Real time monitoring added to policy statement. Coverage eligibility unchanged.
05/07/2008	Medical Director review
05/21/2008	Medical Policy Committee approval. 72 hour continuous glucose monitoring now eligible for coverage with criteria. The word “Continuous” was removed from the title.
12/03/2008	Medical Director review
12/17/2008	Medical Policy Committee approval. Separated criteria into type I and type II diabetes in the 72 Hour Glucose Monitoring coverage section. Added, “Type II diabetes in patients who are insulin dependent requiring three or more insulin injections per day.” to the 72 Hour Glucose Monitoring coverage section. Adopted BCBSA format, title and coverage for chronic continuous glucose monitoring as follows: Based on review of available data, the Company may consider continuous monitoring of glucose levels in interstitial fluid, including real-time monitoring, as a technique of diabetic monitoring, in the following situations to be **eligible for coverage**: • Patients with type 1 diabetes on an insulin pump with recurrent unexplained severe symptomatic hypoglycemia for whom hypoglycemia puts the patients or others at risk; or • Pregnant type 1 diabetics, when recurrent hypoglycemia cannot be resolved.
11/04/2010	Medical Policy Committee approval
11/16/2010	Medical Policy Implementation Committee approval. No change to coverage.
11/03/2011	Medical Policy Committee approval
11/16/2011	Medical Policy Implementation Committee approval. No change to coverage. Rationale rewritten.
03/01/2012	Medical Policy Committee approval
03/21/2012	Medical Policy Implementation Committee approval. Under the 72 hour glucose monitoring section, “Type 1” was removed and “as evidenced by four or more documented blood glucose checks per day with fasting blood glucose levels often greater than or equal to 150 and/or hypoglycemic levels of less than or equal to 50 for at least a month” was also removed from patient selection criteria.
09/06/2012	Medical Policy Committee approval
09/19/2012	Medical Policy Implementation Committee approval. Patient Selection Criteria for both 72 hour and chronic continuous glucose monitoring revised.
03/07/2013	Medical Policy Committee review
03/20/2013	Medical Policy Implementation Committee approval. Added “requiring 3 or more insulin injections per day or are” to the first bullet for Chronic Continuous Glucose Monitoring criteria.

Continuous or Intermittent Monitoring of Glucose in Interstitial Fluid

Policy # 00019
Original Effective Date: 03/25/2002
Current Effective Date: 09/19/2018

06/05/2014 Medical Policy Committee review
06/18/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/04/2015 Medical Policy Committee review
06/17/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
06/02/2016 Medical Policy Committee review
06/20/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/01/2016 Coding update
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes and CPT coding update
09/07/2017 Medical Policy Committee review
09/20/2017 Medical Policy Implementation Committee approval. Added "Intermittent" to the "72 Hour Glucose Monitoring" subtitle in the coverage section. Changed the first criteria bullet for "Intermittent 72 Hour Glucose Monitoring" as follows:

- Insulin dependent diabetic using 3 or more insulin injections per day or insulin pump; AND
  - Despite current use of best practices (per Policy Guidelines), diabetes is poorly controlled as evidenced by unexplained or frequent hypoglycemic episodes, hypoglycemic unawareness, suspected postprandial hyperglycemia or recurrent diabetic ketoacidosis.

Changed the "Chronic Continuous Glucose Monitoring" subtitle in the coverage section to "Continuous Long-term Glucose Monitoring. Impaired awareness of hypoglycemia added to eligible for coverage statement on long-term CGM.

01/01/2018 Coding update
09/06/2018 Medical Policy Committee review
09/19/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 09/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Continuous or Intermittent Monitoring of Glucose in Interstitial Fluid

Policy # 00019
Original Effective Date: 03/25/2002
Current Effective Date: 09/19/2018

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code			
CPT	0446T, 0447T, 0448T, 95250, 95251 New codes eff 1/1/18: 95249			
HCPCS	A9276, A9277, A9278, E0784, K0553, K0554, S1030, S1031, S1034, S1035, S1036, S1037			
ICD-10 Diagnosis	E08.3211-E08.3219	E08.3291-E08.3299	E08.3311-E08.3399	E08.3411-E08.3499
	E08.3511-E08.3519	E08.3521-E08.3529	E08.3531-E08.3539	E08.3541-E08.3549
	E08.3551-E08.3559	E08.3591-E08.3599	E08.37X1-E08.37X9	E09.3211-E09.3219
	E09.3291-E09.3299	E09.3311-E09.3399	E09.3411-E09.3419	E09.3491-E09.3499
	E09.3511-E09.3519	E09.3521-E09.3529	E09.3531-E09.3539	E09.3541-E09.3549
	E09.3551-E09.3559	E09.3591-E09.3599	E09.37X1-E09.37X9	E10.10-E10.39
	E10.3211-E10.3219	E10.3291-E10.3299	E10.3311-E10.3319	E10.3391-E10.3399
	E10.3411-E10.3419	E10.3491-E10.3499	E10.3511-E10.3519	E10.3521-E10.3529
	E10.3531-E10.3539	E10.3541-E10.3549	E10.3551-E10.3559	E10.37X1-E10.37X9
	E11.00-E11.9	E11.3211-E11.3219	E11.3291-E11.3299	E11.3311-E11.3319
	E11.3391-E11.3399	E11.3411-E11.3419	E11.3491-E11.3499	E11.3511-E11.3519
	E11.3521-E11.3529	E11.3531-E11.3539	E11.3541-E11.3549	E11.3551-E11.3559
	E11.3591-E11.3599	E11.37X1-E11.37X9	E13.00-E13.9	E13.3211-E13.3219
	E13.3291-E13.3299	E13.3311-E13.3319	E13.3391-E13.3399	E13.3511-E13.3519
	E13.3521-E13.3529	E13.3531-E13.3539	E13.3541-E13.3549	E13.3551-E13.3559
	E13.3591-E13.3599	E13.37X1-E13.37X9		

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.