Subject:	Continuous Glucose Monitoring in Interstitial Fluid	
Policy #:	MED	**Current Effective Date: 11/10/14**
Status:	New	**Last Review Date: 11/10/14**

Description/Scope

Tight glucose control in patients with diabetes has been associated with improved outcomes. Several devices are available to measure glucose levels automatically and frequently (eg, every 5-10 minutes). The devices measure glucose in the interstitial fluid and are approved as adjuncts to traditional self-monitoring of blood glucose levels.

The advent of blood glucose monitors for use by patients in the home over 20 years ago revolutionized the management of diabetes. Using fingersticks, patients could monitor their blood glucose level both to determine the adequacy of hyperglycemia control and to evaluate hypoglycemic episodes. Tight diabetic control, defined as a strategy involving frequent glucose checks and a target hemoglobin A1c (HgA1c) in the range of 7%, is now considered standard of care for diabetic patients. Randomized controlled trials (RCTs) of tight control have demonstrated benefits for type I diabetics in decreasing microvascular complications. The impact of tight control on type II diabetic patients and on macrovascular complications such as stroke or myocardial infarction is less certain.

However, tight glucose control requires multiple measurements of blood glucose each day (ie, before meals and at bedtime), a commitment that some patients may be unwilling or unable to meet. In addition, the goal of tight glucose control has to be balanced with an associated risk of hypoglycemia. An additional limitation of periodic self-measurements of blood glucose is that glucose values 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 HgA1c values.

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

Several devices have received U.S. Food and Drug Administration (FDA) approval. The first 2 approved devices were the Continuous Glucose Monitoring System (CGMS®) (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 with an electric current (referred to as reverse iontophoresis).

Additional devices that have subsequently been approved include those for pediatric use and those with more advanced software, more frequent measurements of glucose levels, more sophisticated alarm systems, etc. Devices initially measured interstitial glucose every 5 to 10 minutes and, with currently available devices the time intervals at which interstitial glucose is measured ranges from every 1 to 2 minutes to 5 minutes. While

CGMs potentially eliminate or decrease the number of required daily fingersticks, it should be noted that, according to the FDA labeling, monitors are not intended to be an alternative to traditional self-monitoring of blood glucose levels but rather provide adjunct monitoring, supplying additional information on glucose trends that are not available from self-monitoring. In addition, it is important to note that devices may be used intermittently, eg, time periods of 72 hours, or on a long-term basis.

In addition to stand-alone CGMs, several insulin pump systems have included a built-in CGM. This policy addresses continuous glucose monitoring devices, not the insulin pump portion of these systems. Also, under development is what is known as an artificial pancreas or artificial pancreas device system (APDS). The proposed artificial pancreas is a series of devices, eg, a CGM, blood glucose device and an insulin pump, plus a computer algorithm that communicates with all of the devices. The goal of the APDS is to automatically monitor glucose levels and adjust insulin levels. These systems are also called closed-loop systems or autonomous systems for glucose control. One technology associated with artificial pancreas development is a "low glucose suspend (LGS)" feature included with an insulin pump. The LGS feature is designed to suspend insulin delivery when plasma glucose levels fall below a prespecified threshold.

Position Statement

Medically Necessary:

Except where regulatory requirements for a particular plan would apply:

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

- Insulin Dependent Diabetes Mellitus (IDDM),
- Non-Insulin Dependent Diabetes Mellitus (NIDDM), OR
- Gestational diabetes.

Professional (intermittent 72 hour) monitoring of glucose levels in interstitial fluid **may be considered medically necessary** for:

- Patients with Type I or Type II insulin dependent diabetes prior to insulin pump initiation to determine basal insulin levels; OR
- Patients with Type I or Type II insulin dependent diabetes whose diabetes is poorly controlled** despite current compliance with a regimen including four or more finger sticks each day, and either three or more insulin injections or use of an insulin pump.

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

- Unexplained hypoglycemic episodes;
- Hypoglycemic unawareness;
- Suspected postprandial hyperglycemia; OR

- Recurrent diabetic ketoacidosis.

Personal continuous glucose (long-term) monitoring (CGM) in interstitial fluid, including real-time monitoring, as a technique of diabetic monitoring, **may be considered medically necessary** in patients with Type I insulin dependent diabetes who:

- Are pregnant; OR
- Have been compliant with a regimen that includes:
    1. Four or more finger sticks and three or more insulin injections per day; OR
    2. Use of an insulin pump;

AND have not achieved adequate metabolic control as evidenced by at least **one** of the following:

1. Hypoglycemic unawareness or frequent hypoglycemia; OR
2. Frequent nocturnal hypoglycemia, less than 50 mg/dL; OR
3. Wide fluctuations in blood sugar patterns over time (<50 mg/dL, or >150 mg/dL); OR
4. Discordant hemoglobin A1c (HbA1c) and fingerstick blood glucose levels (i.e., patient with consistent normal blood glucose levels at home but high HbA1C levels).

Investigational and Not Medically Necessary:

Other uses of continuous monitoring of glucose levels in interstitial fluid, including real-time monitoring, as a technique of diabetic monitoring, not meeting above noted criteria **is considered experimental, investigational and/or unproven.**

Artificial Pancreas System

Use of an artificial pancreas system, with low-glucose suspend (LGS) features when performed according to FDA-approved indications for persons 16 years and older, **may be considered medically necessary** when:

- Patient meets criteria for insulin infusion pump (see separate policy DME101.048 Insulin Infusion Pump) and
- Patient meets criteria for personal continuous glucose (long-term) monitoring noted above and
- Patient has **one** of the following:
    - Hypoglycemic unawareness **or**
    - Multiple documented episodes of nocturnal hypoglycemia, (less than 50mg/dL).

(Legislative mandates for insured (individual or group) business require coverage for diabetic equipment and supplies that are approved by the United States Food and Drug Administration, if such equipment or supplies are determined to be medically necessary and appropriate by a treating physician.)

Regulatory Status

Several continuous glucose monitoring systems have been approved by FDA through the premarket approval process:

- The Continuous Glucose Monitoring System (CGMS®) (MiniMed) in 1999 (approved for 3-day use in a physician's office).
- The GlucoWatch G2® Biographer in 2001. Of note, neither the GlucoWatch nor the autosensors have been available after July 31, 2008.
- The Guardian®-RT (Real-Time) CGMS (Medtronic, MiniMed) in July 2005. (MiniMed was purchased by Medtronic).
- The DexCom® STS CGMS system (DexCom) was approved by FDA in March 2006.
- The Paradigm® REAL-Time System (Medtronic, MiniMed) was approved by FDA in 2006. This system integrates a CGM with a Paradigm insulin pump. The second generation integrated system is called the MiniMed Paradigm Revel System.
- The FreeStyle Navigator® CGM System (Abbott) was approved in March 2008.
- The OmniPod® Insulin Management System (Insulet Corporation), integrating the Freestyle Navigator CGM system with the Pod insulin pump, was approved in December 2011.
- The DexCom G4 Platinum (DexCom) CGM was approved for use in adults 18 years and older in October 2012. The device can be worn for up to 7 days. In February 2014, FDA expanded use of the Dexcom Platinum CGM to include patients with diabetes, age 2 to 17 years-old.

Artificial pancreas device systems:

- The Minimed 530G System (Medtronic) integrating an insulin pump and glucose meter, and including a low glucose suspend feature, was cleared for marketing in September 2013. The threshold suspend tool temporarily suspends insulin delivery when the sensor glucose level is equal to or lower than a preset threshold within the 60 mg/dL to 90 mg/dL range. When the glucose value reaches this threshold, an alarm sounds. If patients respond to the alarm, they can choose to continue or cancel the insulin suspend feature. If patients fail to respond to the alarm, the pump automatically suspends action for 2 hours, and then insulin therapy resumes. The device is approved only for use in patients 16 years and older.

Rationale

This is a new policy. The most recent literature review was performed through February 3, 2014. Following is a summary of the key literature to date:

Continuous glucose monitoring systems

Most of the following discussion focuses on the clinical utility of continuous glucose monitoring (CGM) systems. That is, their ability to provide either additional information on glucose levels, leading to improved glucose control or to improve the morbidity/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, randomized controlled trials (RCTs) are important to isolate

the contribution of interstitial glucose measurements to the overall diabetic management. Data on patients with type 1 diabetes and type 2 diabetes are discussed separately.

<u>Type 1 diabetes</u>

Several meta-analyses of RCTs have been published; they have focused on slightly different populations e.g, age and/or type of diabetes, and different study designs, e.g, by length of follow-up. Two 2011 meta-analyses included studies on adults and/or children. The study by Gandhi et al. identified studies conducted among patients with type 1 and/or type 2 diabetes and stratified findings by type of diabetes. (2) The investigators identified 19 RCTs evaluating CGM interventions lasting at least 8 weeks and conducted in the outpatient setting. Mean baseline hemoglobin A1c (HbA1c) was at least 7.0% in all studies but included 1 in which the mean baseline HbA1c was 6.4%. Overall, compared with self-monitoring of blood glucose, CGM was associated with a statistically significant reduction in mean HbA1c (weighted mean difference [WMD], -0.27%; 95% confidence interval [CI], -0.44% to -0.10%). When stratified by age and type of diabetes, there was a statistically significant reduction in HbA1c in adults with type 1 diabetes and adults with type 2 diabetes, but not in studies of children and adolescents with type 1 diabetes.

Another 2011 meta-analysis of RCTs on CGM included trials conducted in adults and children with type 1 diabetes who were on an intensive insulin regimen (studies of type 2 diabetes were not included).(3) This meta-analysis required a minimum of 12 weeks of follow-up in the studies (as compared with at least 8 weeks in the Gandhi meta-analysis). Studies compared CGM with self-monitored blood glucose (SMBG); there was no restriction related to type of CGM device, but the CGM readings had to be used to adjust insulin dose or modify diet. A total of 14 RCTs met eligibility criteria. In a pooled analysis, there was a statistically significant reduction in HbA1c with CGM compared with SMBG (WMD= -0.26%; 95% CI, -0.34% to -0.19%). In a subgroup analysis by age, there were significant reductions in HbA1c with CGM in studies of adults (n=5) (WMD= -0.33; 95% CI, -0.46 to -0.20) and in studies with children and/or adolescents (n=8) (WMD= -0.25; 95% CI, -0.43 to -0.08).

Two 2012 meta-analyses evaluating the efficacy of CGM in patients with type 1 diabetes had similar findings: overall, use of CGM to result in significantly greater reductions in HbA1c compared with SMBG. (4,5) Most recently, a 2013 systematic review by Poolsup et al. included RCTs that compared CGM with SMBG, had interventions lasting at least 8 weeks, and reported HbA1c as an outcome.(6) For type 1 diabetes, only studies in children were included. Ten RCTs including pediatric patients with type 1 diabetes met inclusion criteria and were included in a meta-analysis. Overall, the investigators did not find that CGM had a significantly greater impact on HbA1c than SMBG. The pooled estimate of the difference in HbA1c between groups was -0.13% (95% CI, -0.38% to 0.11%). In a subgroup analysis by approach to CGM, devices that provided data retrospectively (retrospective CGM) did not result in better glucose control than SMBG (5 studies; pooled mean difference, -0.05%; 95% CI, 0.46% to 0.35%). However, real-time CGM was superior to SMBG in terms of improving glycemic control (5 studies; pooled mean difference, 0.18%; 95% CI, 0.35% to 0.02%).

Representative RCTs follow:

In 2008, the Juvenile Diabetes Research Foundation (JDRF) published results of a study that randomly assigned 322 adults and children with type I diabetes to CGM or self-(home) monitoring. (7) With HbA1c as the primary outcome measure, there was a significant difference among patients 25 years of age or older that favored continuous monitoring (mean HbA1c difference, 0.53%), while the difference between groups was not statistically significant for those ages 15 to 24 years or 8 to 14 years. The population in this study had relatively

well-controlled diabetes in that entry criterion was glycated Hb of 7% to 10%, but approximately 70% had levels between 7% and 8%; in addition, more than 70% of patients were using an insulin pump. No significant differences were noted in rates of hypoglycemic events, but the study was likely not sufficiently large to detect potential differences. The authors also reported that monitor use was greatest in those patients ages 25 or older, the group in which 83% of patients used the monitor 6 or more days per week. The investigators also conducted a nonblinded single-arm 6-month extension to the randomized trial in which patients in the control group were offered a CGM device. (8) A total of 214 of 219 (98%) in the control group participated in the extension. This included 80 (37%) who were at least 25 years old, 73 (34%) who were 15 to 24-years old, and 61 (29%) who were 8 to 14-years old. The mean HbA1c level at the time of initiation of CGM use was 7.4%±0.7%. Patients were instructed to use the device on a daily basis. Among the 154 patients with baseline A1c at least 7%, there was a significant decrease in A1c 6 months after initiating device use in the older age group (mean change in A1c, -0.4%±0.5%; p<0.001). HbA1c did not decrease significantly in the 15 to 24-year olds (0.01%±0.7%, p=0.95) or in the 8 to 14-year olds (0.02±0.7%, p=0.85). Greater decrease in HbA1c was associated with more frequent use of the CGM device (p=0.001, adjusted for age group). Frequency of device use tended to decrease over time, with less of a decrease in the older age group. At month 6, median use of CGM devices was 6.5 days per week among the older age group, 3.3 days among the 15 to 24-year olds, and 3.7 days per week among the children. During the 6-month extension, the rate of severe hypoglycemic events was 15 per 100 person-years of follow-up.

An additional randomized trial by the JDRD, published in 2009, studied the potential benefits of CGM in the management of adults and children with well-controlled type 1 diabetes.(9) In this study, 129 adults and children with intensively treated type 1 diabetes (age range, 8-69 years) and HbA1c less than 7.0% were randomly assigned to either continuous or standard glucose monitoring for 26 weeks. The main study outcomes were time with glucose level at or below 70 mg/dL, HbA1c level, and severe hypoglycemic events. At 26 weeks, biochemical hypoglycemia (≤70 mg/dL) was less frequent in the CGM group than in the control group (median 54 vs 91 min/d, respectively), but the difference was not statistically significant (p=0.16). Time out of range (≤70 or >180 mg/dL) was significantly lower in the CGM group than in the control group (377 vs 491 min/d, respectively, p=0.003).There was a significant treatment group difference favoring the CGM group in mean HbA1c at 26 weeks adjusted for baseline values. One or more severe hypoglycemic events occurred in 10% and 11% of the 2 groups, respectively (p not significant). The authors concluded that the weight of evidence suggests that CGM is beneficial for individuals with type 1 diabetes who have already achieved excellent control with HbA1c of less than 7.0%. This is a relatively small study. In addition, the clinical significance of some of these findings is not certain. Some of the patients in this group would likely meet policy statements for use of CGM.

The MITRE trial, published by Newman et al. in 2009, was conducted to evaluate whether the additional information provided by use of minimally invasive glucose monitors resulted in improved glucose control in patients with poorly controlled insulin-requiring diabetes. (10) This was a 4-arm RCT conducted at secondary care diabetes clinics in 4 hospitals in England. In this study, 404 people aged older than 18 years, with insulin-treated diabetes mellitus (types 1 or 2) for at least 6 months, who were receiving 2 or more injections of insulin daily, were eligible. Most participants, 57%, had type 1 diabetes, 41% had type 2 diabetes, and 2% were classified as "other." Participants had 2 HbA1c values of at least 7.5% in the 15 months prior to 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 CGM was used i.e.,

monitoring was performed over several days at various points in the study. 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). Change in HbA1c from baseline to 3, 6, 12, and 18 months was the primary indicator of short- to long-term efficacy in this study. At 18 months, all groups demonstrated a decline in HbA1c levels from baseline. Mean percentage changes in HbA1c 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 (ITT) analysis, no significant differences were found between any of the groups at any of the assessment times. There was no evidence that the additional information provided by the devices resulted in any change in the number or nature of treatment recommendations offered by the nurses. Use and acceptability indicated a decline in use of 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 study of unselected patients, use of CGMs (CGMS on an intermittent basis) did not lead to improved clinical outcomes.

In 2011, Mauras et al. published an analysis from the Diabetes Research in Children Network (DirecNet) Study Group that evaluated CGM in the management of young children aged 4 to less than 10 years with type 1 diabetes.(11) A total of 146 children (mean age, 7.5 years) were randomized to CGM or usual care. At baseline, 30 children (42%) had an HbA1c of at least 8%. The primary outcome was clinical success as defined as reduction in HbA1c by at least 0.5% without the occurrence of severe hypoglycemia at 26 weeks. Clinical success was attained by 19% in the CGM group and 28% in the usual care group (p=0.17). Mean change in HbA1c, a secondary outcome, did not differ significantly between groups (-0.1 in each group, p=0.79).

<u>Section summary</u>

There are numerous RCTs and several systematic reviews of RCTs evaluating CGM in patients with type 1 diabetes. Systematic reviews generally found that CGM use resulted in improved glycemic control for adults with type 1 diabetes and for children with type 1 diabetes who used real-time CGM devices.

<u>Type 2 diabetes</u>

Two of the systematic reviews previously described in the section on type 1 diabetes also reported on the efficacy of CGM in patients with type 2 diabetes. Gandhi et al.(2) identified 3 RCTs that included patients with type 2 diabetes (one of these included patients with either type of diabetes). There was a mixture of patients with type 2 diabetes who did and did not require insulin. In a meta-analysis of the 3 trials, there was a statistically significant reduction in HbA1c with CGM compared with SMBG in adults with type 2 diabetes (WMD= -0.70; 95% CI, -1.14 to -0.27). In 2013, Poolsup et al.(6) conducted a meta-analysis of 4 trials conducted with adults with type 2 diabetes. In a pooled analysis, CGM had greater efficacy in terms of HbA1c than usual care. The pooled mean difference in HbA1c was -0.31% (95% CI, -0.6 to 0.02, p=0.04). Because of a lack of statistical heterogeneity among studies, subgroup analyses (eg, by type of CGM device) were not performed. However, there were some differences among studies; one used retrospective CGM and 2 used real-time CGM. Also, there was variability in the frequency of CGM use, making it difficult to determine the optimal frequency of use.

A representative study included in the 2013 meta-analysis evaluated intermittent use of a CGM device in 100 patients with type 2 diabetes who did not use prandial insulin.(12,13) Eligible participants were 18 or older, had type 2 diabetes for at least 3 months, and had an initial HbA1c of at least 7% but not more than 12%. The study

compared real-time continuous monitoring with the DexCom device used for four 2-week cycles (2 weeks on/1 week off) with SMBG. The primary efficacy outcome was mean change in HbA1c. The mean decline from baseline in HbA1c in the CGM versus the SMBG group was 1.0% versus 0.5% at 12 weeks, 1.2% versus 0.5% at 24 weeks, 0.8% versus 0.5% at 38 weeks, and 0.8% versus 0.2% at 1 year, respectively. Over the course of the study, the reduction in HbA1c was significantly greater than in the SMBG group (p=0.04). After adjusting for potential confounding variables including age, sex, baseline therapy, and whether the individual started taking insulin during the study, the difference between groups over time remained statistically significant (p<0.001).

Section summary

There are fewer RCTs on CGM in patients with type 2 diabetes than for patients with type 1 diabetes. Systematic reviews that included 3 to 4 RCTs found that there was variability in the intervention, eg, type of CGM device, frequency of use and patient populations eg, adults and/or children. Although systematic reviews have found a statistically significant benefit of CGM in terms of glycemic control, the small number of RCTs and variability among interventions makes it difficult to identify an optimal approach to CGM use or subgroup of type 2 diabetes patients who might benefit.

Pregnant women with diabetes

In 2013, Voormolen et al. published a systematic review of the literature on CGM during pregnancy. (14) The authors identified 11 relevant studies (i.e., published in peer-review journals and evaluating the utility of CGM in pregnancy). Two of the studies were RCTs. The 11 studies included a total of 534 women; the largest study was an RCT that had 154 participants. Seven of the studies used retrospective CGM, and the remaining 4 studies used real-time CGM. The authors did not pool study findings; they concluded that evidence is limited on the efficacy of CGM during pregnancy. The 2 published RCTs are described next:

The larger RCT was published by in 2013 by Secher et al. in Denmark.(15) The investigators randomized 154 women to real-time CGM in addition to routine pregnancy care (n=79) or routine pregnancy care alone (n=75). There were 123 women with type 1 diabetes and 31 with type 2 diabetes. 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. Participants in both groups were instructed to perform 8 daily self-monitored plasma glucose measurements for 6 days before each visit. Baseline mean HbA1c was 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). In addition, 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 study had low baseline HbA1c, which might help explain the lack of impact of CGM on outcomes. Other factors potentially contributing to the negative findings include the intensive SMBG routine in both groups and the relatively low compliance rate (64%) in the CGM group with the instruction of use the CGM devices for 6 days before each of 5 study visits.

In 2008, Murphy et al. in the U.K. randomized 71 pregnant women with type 1 (n=46) or type 2 (n=25) diabetes to CGM or usual care.(16) The intervention consisted of up to 7 days of CGM at intervals of 4 to 6 weeks between 8 and 32 weeks' gestation. In addition to CGM, the women were advised to measure blood glucose levels at least 7 times a day. Baseline HbA1c was 7.2% (SD=0.9) in the CGM group and 7.4% (SD=1.5) in the

usual care group. The primary study outcome was maternal glycemic control during the second and third trimesters. Mean HbA1c levels were consistently lower in the intervention arm, but differences between groups were not statistically significant at any time point. For example, between 28 and 32 weeks' gestation, mean HbA1c levels were 6.1% (SD=0.60) in the CGM group and 6.4% (SD=0.8) 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 of 37 (35%) infants in the CGM group were large-for-gestational age compared with 18 of 30 (60%) in the usual care group. The odds ratio 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).

Neither RCT found a statistically significant difference in their primary outcome. The Murphy study found a borderline statistically significantly lower rate of large-for-gestational age infants in women who used CGM while pregnant. Taken together, 2 published RCTs on CGM in pregnancy do not provide strong evidence that routine CGM during pregnancy is beneficial. However, it is difficult to draw definitive conclusions from this limited evidence.

<u>Other diabetic subgroups</u>

CGM has been proposed for specific diabetic subgroups such as patients with poor diabetic control, as evidenced by recurrent hypoglycemia, hypoglycemia unawareness, postprandial hyperglycemia, and/or recurrent diabetic ketoacidosis. For these groups, CGM provides different types of information than single glucose measurements, such as trends in glucose and rates of change. There is only anecdotal evidence for the efficacy of this approach; there is no high-quality evidence available to evaluate the impact of this approach on health outcomes.

Continuous glucose monitoring systems integrated with an insulin pump

Recent advances in technology now allow linkage between the CGM device and an insulin pump. In a randomized study of 132 adults and children from France reported in 2009, Raccah et al. reported improved HbA1c levels (change in A1c of 0.96% vs 0.55%, respectively) in patients who were fully protocol compliant for use of an insulin pump integrated with CGMS compared with those using a pump with standard glucose self-monitoring.(17) In 2012, Battelino et al. published findings of a multicenter crossover study conducted in several European countries that included 153 children and adults with type 1 diabetes.(18) The study used the MiniMed Paradigm REAL-Time system, which integrates a CGM device and an insulin pump system. Patients were randomized to use of the system for 6 months with the sensor on and 6 months with the sensor off, in random order, with a washout period of 4 months between interventions. Baseline HbA1c ranged from 7.5% to 9.5%. After treatment, mean HbA1c was 8.04% in the sensor on arm and 8.47% in the sensor off arm. The mean difference in HbA1c between groups was -0.43% (95% CI, -0.32% to -0.55%; p<0.001). Neither of the above trials was blinded, and neither compared continuous with intermittent use of the CGM.

Artificial pancreas device systems, including low glucose suspend technology

The first device categorized by the FDA as an artificial pancreas device system was cleared for marketing by FDA in September 2013. The system integrates a CGM and insulin pump and includes a low glucose suspend (LGS) feature that can automatically temporarily suspend insulin delivery when glucose levels fall below a prespecified level.

A December 2013 BCBSA TEC Assessment addressed artificial pancreas device systems.(19) The Assessment included the following conclusion:

"The evidence is insufficient to permit conclusions on the impact of the artificial pancreas device system, with low glucose suspend feature, on health outcomes. A single trial has reported the results of its use in a home setting. Although the trial results are generally favorable, the study has limitations and further studies are needed."

The study referred to in the TEC Assessment was the in-home arm of the Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial, published by Bergenstal et al. in 2013.(20) This was an industry-sponsored trial using the Medtronic Paradigm Veo pump. A total of 247 patients were randomly assigned to an experimental group, in which the low glucose suspend feature was used (n=121), or a control group that did not use the LGS feature (n=126). Key eligibility criteria were 16 to 70 years old, type 1 diabetes, and an HbA1c level between 5.8% and 10.0%. In addition, patients needed to have at least 2 nocturnal hypoglycemic events (≤65 mg/dL) lasting more than 20 minutes during a 2-week run-in phase. The randomized intervention phase lasted 3 months. Patients in the low glucose suspend group were required to use the feature at least between 10 pm and 8 am. The threshold value was initially set at 70 mg/dL and could be adusted to a value between 70 to 90 mg/dl. The primary efficacy outcome was the area under the curve (AUC) for nocturnal hypoglycemia events during the intervention phase and the primary safety outcome was change in HbA1c. Seven patients withdrew early from the study; all 247 were included in the ITT analysis.

Mean HbA1c changed from 7.26 to 7.24 in the low glucose suspend group and from 7.21 to 7.14 in the control group. Change was minimal and there was not a statistically significant difference between groups. The AUC for nocturnal events was 980 (SD=1200) in the low glucose suspend group and 1568 (SD=1995) in the control group. The difference between groups was statistically significant, $p < 0.001$, favoring the intervention group. As cited in the TEC Assessment, among secondary outcomes, the LGS group also experienced fewer hypoglycemic episodes, 1 per week than the control group (3.3±2.0 vs 4.7±2.7; $p < 0.001$), and the percentage of 2 sensor glucose values at or below 50 mg/dL was 57.1% lower in the LGS group 3 (0.9% vs 1.9%, respectively; $p < 0.01$). For patients in the LGS group, the mean number of times the feature was triggered per patient was 2.08 per day, for a median of 1.42 minutes (mean, 25.5 minutes), and 0.77 times per night. Insulin infusion was suspended for the whole 2 hours in only 19.6% of episodes.

The TEC Assessment had the following comments on potential limitations of the Bergenstal et al. study:

"1. The authors reported that 43.1% of low glucose suspend events lasted less than 5 minutes, and 19.4% of the low suspend episodes were 120 minutes. Thus, most of the events were very short, for reasons that are not discussed. Also, the study did not track whether or not subjects who underwent low glucose suspend for 2 hours ate or drank food or glucose during that time or in the 2 hours afterward. Therefore, it is not clear whether changes in hemoglobin levels were due to the suspension of insulin infusion or to the subject's response. The latter might produce overestimates of the impact of the low glucose suspend feature by attributing all improvements to it.

2. It was not reported whether subgroup results, grouped by age, HbA1c at randomization, and duration of diabetes, were prespecified.

3. There was 1 equipment malfunction (prolonged pump suspension in 1 patient with no adverse events), which might have had serious effects. Also, there were 3 adverse events in which the infusion-set malfunctioned resulting in severe hyperglycemia (>300 mg/dL). All were in the low glucose suspend group; none were in the control group."

Before reporting on in-home findings, in 2012 the ASPIRE researchers (Garg et al.) published data from the in-clinic arm.(21) This was a randomized crossover trial that included 50 patients with type 1 diabetes who had at least 3 months' experience with an insulin pump system. After a 2-week run-in period to verify and optimize basal rates, patients underwent 2 in-clinic exercise sessions to induce hypoglycemia. The LGS feature on the insulin pump was turned on in one session and off in the other session, in random order. When on, the LGS feature was set to suspend insulin delivery for 2 hours when levels reached 70 mg/dL or less. The goal of the study was to evaluate whether the severity and duration of hypoglycemia was reduced when the LGS feature was used. The study protocol called for patients to start exercise with a glucose level of 100 to 140 mg/dL, and to use a treadmill or stationary bicycle until their plasma glucose level was 85 mg/dL or less. The study outcome, duration of hypoglycemia, was defined as the period of time glucose values were lower than 70 mg/dL and above 50 mg/dL, and hypoglycemia severity was defined as the lowest observed glucose value. A successful session was defined as an observation period of 3 to 4 hours and with glucose levels above 50 mg/dL. Patients who did not attain success could repeat the experiment up to 3 times.

The 50 patients attempted 134 exercise sessions; 98 of these were successful. Duration of hypoglycemia was significantly less during the LGS-on sessions (mean, 138.5 minutes; SD=68 minutes) than the LGS-off sessions (mean, 170.7 minutes; SD=91) (p=0.006). Hypoglycemia severity was significantly lower in the LGS-on group. The mean lowest glucose level was 59.5 mg/dL (SD=72) in the LGS-on group and 57.6 mg/dL (SD=5.7) in the LGS-off group (p=0.015). The Garg study evaluated the LGS feature in a research setting and over a short time period.

Several small trials conducted outside the U.S. have evaluated a non-FDA-approved device, the MD-Logic artificial pancreas. This device is a closed-loop system that provides safety alerts before hypoglycemia and hypoglycemia events. A 2013 study included 56 type I diabetic children (10-18 years old) who were attending a diabetes camp and had used an insulin pump for at least 3 months.(22) The study was done over 2 consecutive nights, during which each patient received an artificial pancreas one night and a continuous glucose monitor the other night, in random order. The primary end points were the number of hypoglycemic episodes (defined as glucose <63 mg/dL for at least 10 minutes), the total time that glucose levels were less than 60 mg/dL, and the mean overnight glucose levels. There were fewer episodes of hypoglycemia recorded in the artificial pancreas group compared with the CGM group (7 vs 22, p=0.003). The median time that patients had a glucose level less than 60 was 0 minutes in both groups, but the time was significantly less in the artificial pancreas group (p=0.02). There was no significant difference in the mean glucose level in the artificial pancreas group compared with the CGM group (126.4 mg/dL vs 140.4 mg/dL).

Also in 2013, Nimri et al. published a randomized crossover trial that included 12 patients at least 10 years-old who had type 1diabetes and had used an insulin pump for at least 3 months.(23) The study was conducted in the inpatient setting over 2 consecutive nights. The artificial pancreas was used 1night and an insulin pump was used the other night, in random order. The primary end point, number of hypoglycemic episodes defined as glucose less than 63 mg/dL for at least 10 minutes, did not differ significantly between groups (p=0.18). There were no events in the artificial pancreas group and 3 in the insulin pump group. A secondary outcome

was the percentage of time spent in the target range, ie, a glucose level between 80 and 120 mg/dL. Time in the target range was significantly higher when the artificial pancreas device was used than when the insulin pump alone was used (p=0.002). The percentage of time in the target range was 94% (95% CI, 86 to 100) when the artificial pancreas device was used and 74% when it was not used (95% CI, 42 to 96).

Section summary

There are several RCTs evaluating the first FDA-approved artificial pancreas device, which includes a LGS feature. Only 1 of these studies was conducted in a real-life in-home setting. This study did not find a statistically significant difference in glucose control in the artificial pancreas device and control groups. The study showed an improvement in the primary outcome, AUC for nocturnal hypoglycemic events.

Ongoing Clinical Trials

A search of online site ClinicalTrials.gov on February 10, 2014, identified a number of open-label randomized crossover trials evaluating artificial pancreas device systems. This includes the following trials:

The Performance of an Artificial Pancreas at Home in People With Type 1 Diabetes (NCT02040571) (24): This randomized crossover study includes patients age 14 and older with type 1 diabetes. There will be a 1-night in-hospital phase and a 5-night in-home phase. A closed-loop artificial pancreas device will be compared with an open-loop insulin pump system. A Medtronic artificial pancreas device will be used. The study is currently recruiting patients; estimated enrollment is 24 patients. The expected date of study completion is January 2015.

Overnight Type 1 Diabetes Control Under MD-Logic Closed Loop System at the Patient's Home (NCT01726829)(25): This randomized crossover trial that is evaluating blood glucose control overnight with MD-Logic Artificial Pancreas system in patients with type 1 diabetes. The intervention consists of 4 consecutive nights using the artificial pancreas device and 4 nights using regular pump therapy, with a 10-day washout period between arms. The study is currently recruiting patients; estimated enrollment is 75 patients. An interim analysis of this ongoing study was published in 2013. (26)

Summary

The available studies demonstrate that glucose monitoring may improve glucose control in type I diabetic patients. However, the data on the impact of long-term continuous glucose monitoring are still limited. Studies such as that of the Juvenile Diabetes Research Foundation (JDRF) suggest that more frequent use of continuous glucose monitors (CGMs) may result in better outcomes, but this finding is not consistent across all available studies. In addition, the magnitude of effect is modest, suggesting that either the efficacy is of a small magnitude or that only a subset of patients benefit from this type of monitoring. Thus, the impact of CGM use on glucose control for the general diabetic population is uncertain, and CGM is considered investigational for the purpose of improving glucose control in the general diabetic population.

CGM provides more data points on glucose levels, and also provides information about trends. This additional information is most likely to benefit subgroups of diabetic patients, ie, those patients with type I diabetes who do not have adequate control, including episodes of hypoglycemia, despite use of current best practices including multiple (≥4) daily checks of blood glucose and use of an insulin pump. Based on the available data, intermittent, ie, 72-hour, glucose monitoring may be considered medically necessary in those whose diabetes is poorly controlled, despite use of best practices.

Rationale similar to that just noted for intermittent monitoring, continuous monitoring can also be used in diabetic subpopulations. Continuous glucose monitoring may be considered medically necessary to provide additional data for management of those who have recurrent, unexplained, severe hypoglycemia that puts the patient or others at risk, despite use of current best practices, and also for pregnant patients with type I diabetes.

The available literature suggests that CGM systems may improve glycemic control in patients with type 2 diabetes but too few studies have focused on this population, and it is not clear what subset of patients with type 2 diabetes might benefit from intermittent or continuous glucose monitoring. Due to the limited evidence, use of CGM systems in patients with type 2 diabetes is considered experimental, investigational and/or unproven.

Although conclusions from a single RCT using an FDA-approved artificial pancreas device conducted in a real-life in-home setting resulted in noting that changes in glycated hemoglobin values had no statistically significant difference between the two groups; it was noted that the low glucose suspend (LGD) group experienced fewer hypoglycemic episodes.

Practice Guidelines and Position Statements

In 2013, the American Diabetes Association made the following recommendations concerning continuous glucose monitoring (27):

- CGM in conjunction with intensive insulin regimens can be a useful tool to lower A1c in selected adults (age at least 25 years) with type 1 diabetes. (Level of evidence A)
- Although the evidence of A1c lowering is less strong in children, teens, and younger adults, CGM may be helpful in those groups. Success correlates with adherence to ongoing use of the device. (Level of evidence C)
- CGM may be a supplemental tool to SMBG [self-monitoring of blood glucose] in those with hypoglycemic unawareness and/or frequent hypoglycemic episodes. (Level of evidence E)

In 2011, the Endocrine Society published a clinical practice guideline developed by a task force that included the following recommendations on continuous glucose monitoring (28):

1. Real-time continuous glucose monitoring (RT-CGM) in adult hospital settings

   1. We recommend against the use of RT-CGM alone for glucose management in the intensive care unit or operating room until further studies provide sufficient evidence for its accuracy and safety in those settings.

2. Children and adolescent outpatients

   1. We recommend that RT-CGM with currently approved devices be used by children and adolescents with type 1 diabetes mellitus who have achieved HbA1c levels below 7.0%.
   2. We recommend RT-CGM devices be used with children and adolescents with type 1 diabetes who have HbA1c levels 7.0% or higher who are able to use these devices on a nearly daily basis.

3. We make no recommendations for or against the use of RT-CGM by children with type 1 diabetes who are less than 8 yr of age.
4. We suggest that treatment guidelines regarding use of RT-CGM be provided to patients.
5. We suggest the intermittent use of CGM systems designed for short-term retrospective analysis in pediatric patients with diabetes in whom clinicians worry about nocturnal hypoglycemia, dawn phenomenon, and postprandial hyperglycemia; in patients with hypoglycemic unawareness; and in patients experimenting with important changes to their diabetes regimen.

3. Adult outpatients

1. We recommend that RT-CGM devices be used by adult patients with type 1 diabetes who have HbA1c levels of at least 7.0% and who have demonstrated that they can use these devices on a nearly daily basis.
2. We recommend that RT-CGM devices be used by adult patients with type 1 diabetes who have HbA1c levels less than 7.0% and who have demonstrated that they can use these devices on a nearly daily basis.
3. We suggest that intermittent use of CGM systems designed for short-term retrospective analysis may be of benefit in adult patients with diabetes to detect nocturnal hypoglycemia, the dawn phenomenon, and postprandial hyperglycemia, and to assist in the management of hypoglycemic unawareness and when significant changes are made to their diabetes regimen.

Coding:

Disclaimer for coding information on Medical Policies

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

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

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

CPT/HCPCS/ICD-9/ICD-10 Codes
The following codes may be applicable to this Medical policy and may not be all inclusive.
CPT Codes
95250, 95251
HCPCS Codes

A4233, A4234, A4235, A4236, A4253, A9275, A9276, A9277, A9278, E0607, E0784, E1399,E2100, E2101, S1030, S1031, S1034, S1035, S1036, S1037
ICD-9 Diagnosis Codes
250.00-250.93, 648.80, 648.81, 648.82, 648.83, 648.84, V58.67
ICD-9 Procedure Codes
None
ICD-10 Diagnosis Codes
E10.10-E13.9, O24.414, O24.424, O24.429, O24.434, O99.810, O99.815, Z79.4
ICD-10 Procedure Codes
None

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

Document History		
Status	**Date**	**Action**