

CME Review Paper

Clinical Application of Emerging Sensor Technologies in Diabetes Management: Consensus Guidelines for Continuous Glucose Monitoring (CGM)

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NEEDS ASSESSMENT

Continuous glucose monitoring (CGM) is an evolving technology with the potential to revolutionize current concepts of glycemic control and optimal diabetes management. Unlike traditional blood glucose meters, glucose sensors continuously record glucose levels over a 24-hour period, showing the rate and direction of glucose change and alerting patients to trends that could lead to dangerous hypo- or hyperglycemia. With few randomized studies examining how to most effectively use this new tool, this article presents the recommendations of eight recognized diabetes specialists who discussed their experience with CGM to identify fundamental considerations, objectives, and methods for its optimal application in clinical practice.

TARGET AUDIENCE

This activity is for healthcare providers interested in optimizing the management of diabetes.

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Abstract

Continuous glucose monitoring (CGM) is an evolving technology poised to redefine current concepts of glycemic control and optimal diabetes management. To date, there are few randomized studies examining how to most effectively use this new tool. Therefore, a group of eight diabetes specialists heard presentations on continuous glucose sensor technology and then discussed their experience with CGM in order to identify fundamental considerations, objectives, and methods for applying this technology in clinical practice. The group concluded that routine use of CGM, with real-time data showing the rate and direction of glucose change, could revolutionize current approaches to evaluating and managing glycemia. The need for such progress is indicated by the growing prevalence of inadequately treated hyperglycemia. Coordinating financial and educational resources and developing clear protocols for using glucose sensor technology are urgent priorities in promoting wide adoption of CGM by patients and health care providers. Finally, researchers, manufacturers, payers, and advocacy groups must join forces on the policy level to create an environment conducive to managing continuous data, measuring outcomes, and formalizing best practices.

Introduction

CONTINUOUS GLUCOSE MONITORING (CGM) is an evolving technology poised to redefine current concepts of glycemic control and optimal diabetes management. Unlike handheld blood

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EDUCATIONAL OBJECTIVES

Upon completion of this activity, clinicians should be able to:

- * Describe the difference between the information provided by glucose sensors versus traditional blood glucose meters
- * Understand how continuous glucose monitoring (CGM) can help stabilize glycemic control even under conditions of optimal diabetes management
- * Specify the steps for initiating CGM in the clinical setting
- * Advise patients on interpreting CGM data for more reliable prevention of hypo- and hyperglycemia and achievement of better long-term glycemic control

glucose meters, which reveal a glucose value at a single point in time determined by the user, new CGM technology automatically provides patients with “real-time” information about the rate and direction of glucose change, and alerts them to trends that could lead to dangerous hypo- or hyperglycemia.¹

The basic mechanics of CGM involve attaching (or inserting) a sensor to the body that measures the amount of glucose in the interstitial fluid. The latest sensor models display glucose values approximately every 1–5 min and then transmit the results to a data storage device (the generated data are, in fact, “near continuous”). Because interstitial glucose is measuring glucose in a different physiologic compartment than blood, when blood glucose levels are changing rapidly, there will be a lag in the interstitial glucose values. Animal studies indicate that temporal changes in interstitial glucose values correlate better with central nervous system glucose levels than do blood glucose measurements, which may also be true in humans.²

Present-day CGM systems are approved for adjunctive use only, meaning that they are intended to augment traditional blood glucose testing. Current-day sensors are approved in a range of 3–7 days.

The clinical utility of any particular CGM system will depend on how it provides data to patients and clinicians. Every CGM manufacturer now produces at least one model that alerts the wearer if glucose levels fall outside the programmable low or high value.

In April 2006, an informal panel of eight clinicians shared presentations on continuous glucose sensor technology and then discussed their experience with CGM in order to identify fundamental considerations, objectives, and methods for applying this technology in clinical practice. Their consensus recommendations are presented in this article. Note that these recommendations are intended for health care professionals and should be viewed as an initial step in furthering wide adoption of CGM, and ensuring its effective application, in the foreseeable future.

Why Do We Need A Different Way of Assessing Glycemia?

Optimal glycemic control—defined by the American Diabetes Association (ADA) as a glycosylated hemoglobin (A1C) value of <7.0% for a population, or as close to normal (<6.0%) as possible without unacceptable risk of hypoglycemia for an individual—can be elusive despite the best efforts of patients to monitor and manage blood glucose. This is because blood glucose levels are influenced by numerous changing variables, including diet, insulin dosage, stress, physical activity, and the rate of nutrient absorption. Because traditional blood glucose meters provide only a snapshot of glucose status at a given moment, with no indication of whether the level is moving upward or downward at a particular rate, adjusting treatment can involve considerable guesswork. Increasing insulin in response to an elevated self-monitoring of blood glucose (SMBG) value could trigger hypoglycemia, for example, if the patient’s blood glucose level is, in fact, rapidly declining because of an unrecognized risk factor (e.g., a glycemic spike due to an unfamiliar food). In light of this unpredictability, it is not uncommon for patients to maintain consistently elevated blood glucose levels rather than run the risk of an acute hypoglycemic episode. When other barriers, such as inconvenience, pain, and lack of reimbursement for test strips, are added to this concern, advice to increase the frequency of blood glucose testing may often go unheeded.³

Glycemic variability

The inability to detect glycemic fluctuations throughout the day is another limitation of traditional blood glucose meters; glycemic variability may play an important role in the development of complications of diabetes, even when A1C levels are within normal range.^{4–6} Specifically, several studies indicate that the original deleterious effect of hyperglycemia on the vasculature may be magnified by overproduction of the reactive free radical molecule superoxide.^{7–10} This imbalance leads to increased oxidative stress stemming from both chronically elevated blood glucose levels and frequent oscillations of glycemia.⁶

In a recent study, Monnier et al.⁶ used CGM to compare the respective contributions of chronic hyperglycemia and glycemic variability with oxidative stress, measured by 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-PGF_{2 α}) excretion. The investigators found that, compared with healthy controls, patients with poorly controlled type 2 diabetes showed higher levels of 8-iso-PGF_{2 α} in urine. Moreover, urinary excretion of 8-iso-PGF_{2 α} was strongly correlated with acute fluctuations of blood glucose (calculated as the mean amplitude of glycemic excursion [MAGE]) (Fig. 1) but showed no relationship with chronic hyperglycemia (determined by A1C and mean blood glucose measurements). These findings support the contention that frequent wide excursions of blood glucose are a greater risk factor for oxidative stress and, by extension, complications of diabetes than chronic sustained hyperglycemia.

The negative effects of postprandial glucose excursions, in particular, have received wide attention.¹¹ The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study¹² and the Honolulu Heart study¹³ demonstrated a strong association between postprandial and post-challenge glucose and risk for macrovascular disease. Additionally, a number of experimental trials have linked postprandial glucose fluctuations with vascular tissue damage. In one study, post-challenge glucose and glycemic spikes were more strongly associated with carotid intima-media thickening than fasting glucose and A1C in patients at risk for or in the early stages of type 2 diabetes.¹⁴

Although studies of glucose variability have been largely focused on the increased potential for long-term complications due to hyperglycemia-induced oxidative stress, there

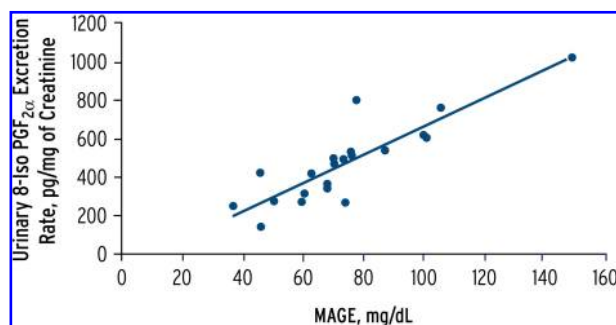


FIG. 1. Linear correlation between 24-h urinary excretion rate of 8-iso-PGF_{2 α} and MAGE. Copyright ©2006 American Medical Association. Reprinted with permission from Monnier et al.⁶

are now compelling data associating fluctuating glucose levels with increased risk for hypoglycemia. Specifically, recent analysis of the Diabetes Control and Complications Trial (DCCT) data base showed that severe hypoglycemia was independently related to A1C, mean blood glucose, and glycemic variability.¹⁵ The hypoglycemia risk for glucose variability measured as seven-point capillary glucose profiles was 1.07 (95% confidence interval 1.02–1.12; $P = 0.004$).¹⁵

It is also important to emphasize that controlling postprandial hyperglycemia will not by itself overcome glycemic variability, as illustrated in a 21-day study using CGM to track daily glycemic patterns. At the outset of the study, approximately 100 intensively managed patients with type 1 or type 2 diabetes were blinded to CGM data but were instructed to perform fingerstick blood glucose measurements 10 times per day.¹⁶ Figure 2 shows that, despite the high frequency of fingerstick testing throughout the study period, there was striking variability both within and among patients regarding duration of euglycemia, as well as the number, timing, and magnitude of diurnal glucose fluctuations. Indeed, even with frequent SMBG, subjects were within the former ADA target glycemic range (90–130 mg/dL) <30% of the time, and >2 h/day was spent in a state of overt hypoglycemia (<60 mg/dL). Such results affirm that current approaches to SMBG and antihyperglycemic therapy are inadequate for stabilizing glycemia even under conditions of “optimal” diabetes management.

Redefining glycemic control

Some researchers have proposed that glycemic control may be better expressed in terms of glycemic variability in conjunction with A1C, rather than A1C alone.^{4,5} Debate surrounding this issue has increased since publication of an 11-year follow-up to the DCCT, which demonstrated that intensive therapy aimed at both fasting and postprandial hyperglycemia to achieve near-normal blood glucose control (A1C <7.0%) significantly reduced complications of type 1 diabetes compared with conventional therapy. The subsequent DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) study, which followed 93% of DCCT participants, showed that subjects from the intensively treated group not only maintained significantly lower risk for retinopathy ($P < 0.001$) and nephropathy ($P < 0.001$), but also exhibited reduced carotid intima-media thickness ($P = 0.02$) and coronary calcification ($P = 0.01$) even though differences in A1C levels between the two groups became nonsignificant after 5 years.^{17–20} Further, intensive treatment reduced the risk of any cardiovascular event by 42% ($P = 0.02$) and the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease by 57% ($P = 0.02$).²¹ In the absence of a clear explanation for these dramatic results, Brownlee and Hirsch have proposed a possible link to the phenomenon known as “metabolic memory,” whereby an extended early period of stable glycemic control associated with early intensive insulin therapy provides continued protection against complications of diabetes despite worsening A1C levels over time.⁵ While the DCCT/EDIC Research Group urges caution in ascribing the difference in risk of complications between treatment groups to any single determinant, it acknowledges that almost 90% of the variation in risk among subjects may

be attributed to factors independent of A1C.²² Further investigation of this concept, combined with wider availability of CGM data, may eventually lead to tools that augment or replace A1C as a means of evaluating glycemic control and attendant complication risk.

How Can CGM Be Used To Improve Diabetes Management?

While CGM devices vary in terms of their specifications, mechanisms, and performance records, all capture near-continuous glucose data without the need for patient intervention to obtain individual readings. Thus far, no continuous sensor has been approved for replacement of traditional blood glucose monitoring. Traditional blood glucose testing

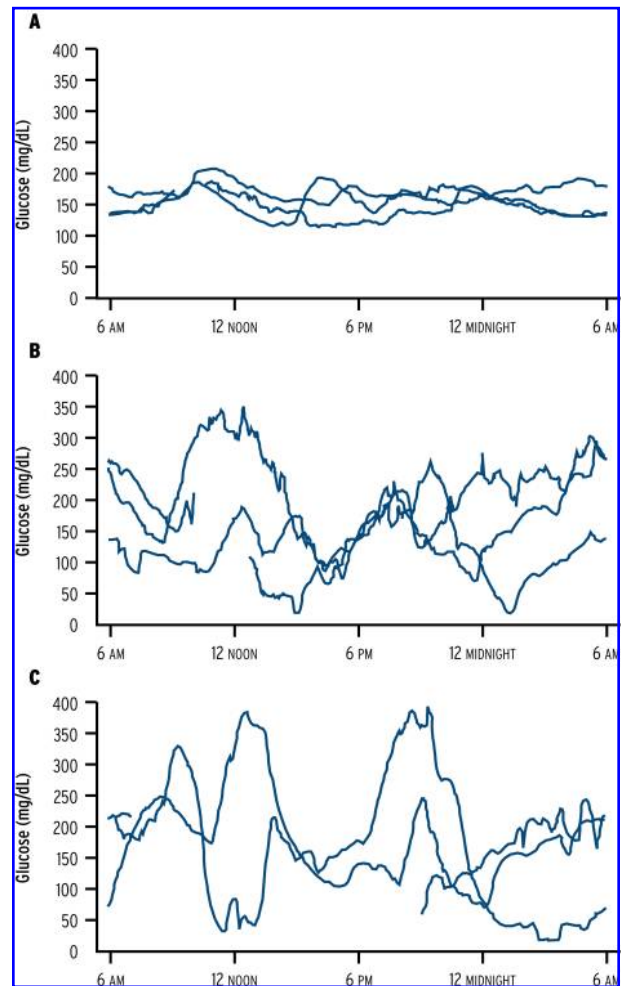


FIG. 2. Overlapping continuous glucose profiles representing 3 consecutive days of monitoring in (A) an obese (body mass index 33 kg/m²) 65-year-old woman with type 2 diabetes, (B) an obese (body mass index 31 kg/m²) 29-year-old woman with type 1 diabetes, and (C) a normal-weight (body mass index 22 kg/m²) 14-year-old male adolescent with type 1 diabetes. There is noteworthy variability both within and among subjects with respect to the duration and time in euglycemia and in the frequency, timing, and magnitude of day-to-day glycemic excursions. Copyright ©2005 American Diabetes Association. Reprinted with permission from Bode et al.¹⁶

must be performed: (1) to determine insulin doses; (2) when continuous monitoring results do not match the way the patient feels; (3) prior to administering diabetes medication or responding to threshold alarms; (4) when the CGM system is being calibrated to ensure accurate calculation of glucose readings; (5) before driving a motor vehicle; and (6) to assess the response to treatment of hypoglycemia.

A comparison of CGM features with those of traditional blood glucose meters appears in Table 1. It is expected that the characteristics of CGM will improve diabetes management by allowing (1) concurrent adjustment of therapy or diet in response to real-time data, (2) preemptive action guided by glucose trends, and (3) pattern adjustment based on retrospective data review.

Concurrent data analysis

The latest CGM devices enable patients to read real-time glucose values, review trend graphs of recent glucose values, and observe indicators, often in the form of trend arrows, that show whether glucose is rising or falling. They also feature alarms/alerts signaling hypo- or hyperglycemia.

Using the glucose values and trend arrows, as well as the continuous data output, patients may intervene to prevent hypo- or hyperglycemia and more easily relate diet (particularly meal composition), exercise, missed insulin doses, and other external factors to glucose levels.²³ For example, in a randomized controlled study of insulin-requiring patients using CGM, those given access to continuous glucose read-

ings and alerts/alerts managed episodes of hyperglycemia and hypoglycemia more effectively than control subjects blinded to this information.²⁴ On average, the unblinded group spent 21% ($P < 0.0001$) less time hypoglycemic (<55 mg/dL), 23% ($P < 0.0001$) less time hyperglycemic (>240 mg/dL), and 26% ($P < 0.0001$) more time in the target glycemic range (81–140 mg/dL). Interestingly, these improvements occurred within 6 days of unblinded device use and without any prescribed regimen to adjust therapy, raising the question of whether active decision support might have resulted in even greater benefit.

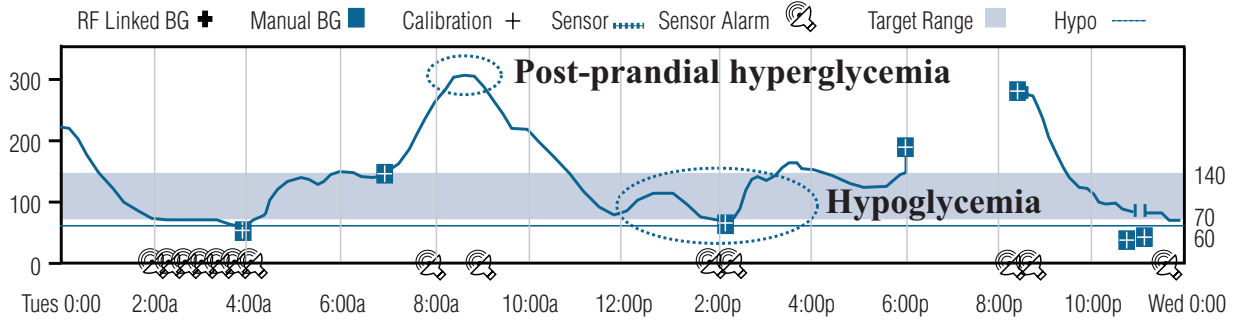
Prospective data analysis

Some real-time CGM systems feature alarms that signal pending hypo- or hyperglycemia, so that patients can take action before acute complications occur. These projected alarms can be especially helpful to patients predisposed to severe hypoglycemia (e.g., patients with hypoglycemia unawareness or nocturnal hypoglycemia). It should be noted, however, that while treatment to preempt hypoglycemia is usually straightforward (i.e., ingesting glucose or a fast-acting carbohydrate), addressing hyperglycemia detected by CGM requires judicious assessment of multiple factors. This is because making patients aware of previously undetectable elevations in blood glucose could promote “overcorrection” in that patients might be prompted to administer insulin too often, leading to insulin stacking (overlapping action) and subsequent hypoglycemia (Fig. 3). To avoid this potentially dangerous practice, patient

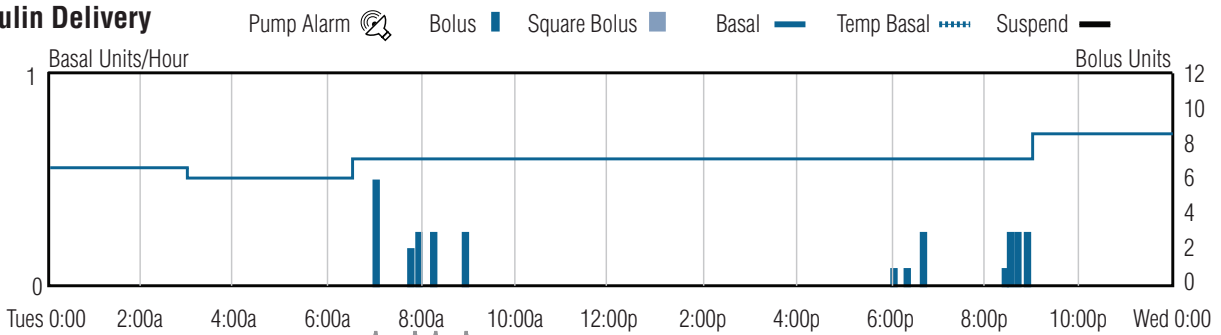
TABLE 1. COMPARISON OF TRADITIONAL BLOOD GLUCOSE METERS AND GLUCOSE SENSORS

Blood glucose meters	Glucose sensors
<p>Form and function</p> <ul style="list-style-type: none"> • Handheld devices that read glucose levels from a blood sample placed on a disposable test strip • Some meters have the capacity for data storage; results can be downloaded into a computer using diabetes management software. 	<ul style="list-style-type: none"> • Sensors are inserted subcutaneously and continuously record glucose levels over a 24-h period; a sensor can be worn for up to 7 days, depending on the model, before it is replaced by the patient. • Glucose data are transmitted to a receiver or an insulin pump where the values are displayed on a screen; trend reports and graphs can be viewed by downloading data into a computer.
<p>Data characteristics</p> <ul style="list-style-type: none"> • Reveals glucose values at a single point in time—much like a snapshot. • Diabetes management decisions are made on the basis of discrete data points reflecting changes in diet, medication, physical activity, and other lifestyle factors. • Meters can be downloaded to get a retrospective look at glucose patterns. Patterns often amount to a few data points collected at similar times of day with sparse post-meal data and overnight data. 	<ul style="list-style-type: none"> • Continuous data convey the progression of events—much like a movie. • Glucose changes in response to diet, medication, physical activity, and other lifestyle factors can be continually observed, providing cues for immediate and retrospective blood glucose management. • Availability of glucose trend data (i.e., the rate and direction of change) helps patients understand what, if any, action is needed to prevent hypo- or hyperglycemia.
<p>Measurement logistics</p> <ul style="list-style-type: none"> • Measures glucose in blood • Blood can be drawn from the fingertip or alternate sites, such as the arm, hand, thigh, or calf, using a lancet and test strip. 	<ul style="list-style-type: none"> • Measures glucose in the interstitial fluid found under the skin. In this fluid, cells receive oxygen and nutrients, including glucose. • Glucose values are converted to an electrical signal, representing the amount of glucose present in the blood. • Sensors are usually inserted in the abdominal area but may be located elsewhere, such as the arm.

Glucose (mg/dL)



Insulin Delivery



Boluses: 1 2 3 4

FIG. 3. Sample graph from Medtronic (Northridge, CA) CareLink™ Personal Therapy Management Software for Diabetes illustrating that excessive administration of insulin to correct postprandial glucose excursions, as detected by CGM, can lead to hypoglycemia and rebound hyperglycemia. To prevent this cycle, patients should understand insulin pharmacodynamics and pharmacokinetics, as well as factors affecting postprandial glucose patterns. BG, blood glucose; RF, radiofrequency. Copyright ©2008 American Diabetes Association. Reprinted with permission from Wolpert.³¹

education about insulin—including pharmacodynamics as well as pharmacokinetics—and guidance with respect to interpreting alarms and trend arrows are critical when initiating CGM (see Setting Alarms and Interpreting trend arrows).²³

Retrospective data analysis

One of the most valuable uses of CGM is guiding therapy adjustments, so that near-normal glycemia is maintained throughout the day and night.¹ Using the “event marker” feature to record information about meals, insulin administration, and other events can aid in identifying glucose patterns requiring correction. Potential changes include raising or lowering the prandial insulin dose, increasing or decreasing basal insulin, modifying the insulin-to-glucose correction algorithm, fine-tuning adjustments to accommodate exercise and foods shown to result in significant hyperglycemia, and other special situations. In some patients, particularly individuals with type 2 diabetes, intermittent CGM may identify glucose patterns that help define the most effective timing for continued SMBG or the selection of the most appropriate next glucose-lowering agent. Moreover, patients may wish to maximize the benefit of CGM by transitioning from a multiple daily injection regimen to insulin pump therapy for more accurate and timely insulin delivery.

Accuracy of dynamic readings

Traditional models for assessing the accuracy of single point-in-time blood glucose testing are not suited to measure the functionality of CGM because they fail to take into account direction and rate of glucose change. The Continuous Glucose-Error-Grid analysis (CG-EGA), developed by a member of the consensus panel, is one of the methods commonly used to capture these dynamic properties, although evaluation protocols of CGM are still evolving and have yet to be standardized.²⁵ The CG-EGA works by analyzing pairs of reference and sensor readings as a process in time, with point and rate comparisons combined into a single accuracy analysis for each of three blood glucose ranges: hypoglycemia (<70 mg/dL), euglycemia (70–180 mg/dL), and hyperglycemia (>180 mg/dL). Results are then plotted on a grid subdivided into five zones representing the clinical outcome that might occur if the patient acted on the CGM data: values in zones A and B represent accurate or benign error readings, values in zone C may result in unnecessary corrections, values in zone D signify a dangerous failure to detect and treat, and values in zone E denote erroneous treatment.

Another factor impacting accuracy evaluation is the difference in timing between the concentration of glucose in in-

terstitial fluid and the concentration in blood, which varies among monitors depending on the specific technology. Interstitial glucose can lag behind blood glucose by as much as 20 min when blood glucose levels are changing rapidly.²⁶ Yet, depending on the situation, gains in “predictive accuracy”—stemming from the ability to observe glycemic trends and take preemptive action to avoid adverse events—may offset deficiencies of point-in-time accuracy due to lag-time issues. The guidelines in the next section are intended, in part, to help health care professionals weigh this trade-off and, in so doing, determine when and how CGM may be best applied in clinical practice.

Guidelines for Clinical Use

The ability to obtain near-immediate access to glucose changes holds vast potential for modifying diabetes management strategies to improve outcomes. However, several possible barriers must be addressed to ensure acceptance of this technology among health care professionals, patients, and payers (Table 2).²⁷ Among these are inadequate time and reimbursement for comprehensive diabetes education, fear of information overload, and concern that real-time readings will result in excessive intervention and overcorrection. The following preliminary recommendations are intended as a starting point for developing protocols that can promote effective use of CGM in clinical practice.

Who should use CGM?

Patient selection. Pediatric patients and their families are among the strongest proponents and likeliest beneficiaries of this emerging technology. The National Institute of Diabetes and Digestive Kidney Diseases and the National Institute of Child Health and Human Development

have therefore funded a study called DirecNet designed to test the clinical utility of CGM in children with type 1 diabetes.²⁸ The Juvenile Diabetes Research Foundation (JDRF) is also funding a large trial utilizing CGM in both children and adults. For more information go to the study website (<http://clinicaltrials.gov/ct/show/NCT00406133?order=1>).

Among adults, the consensus panel cited several main patient groups as good candidates for current sensor technology: (1) patients with type 1 diabetes who are not reaching treatment goals in terms of A1C and/or glycemic variability despite adequate SMBG; (2) patients who intentionally keep blood glucose levels above target because of fear of hypoglycemia; (3) patients with type 2 diabetes who would wear the sensor intermittently to learn about their own diabetes and the rationale for initiating or changing a specific therapy, or using SMBG more effectively; and (4) patients with hypoglycemia unawareness, or frequent episodes of severe hypoglycemia.

While highly motivated patients are considered the ideal candidates for CGM, the panel stressed that CGM can itself be a motivational tool—especially among patients with limited understanding of how eating and other factors affect blood glucose. Such patients can benefit greatly from CGM, provided they receive appropriate education and decision support.

As a rule of thumb, continuous data should not be used to guide medication adjustment unless patients understand:

- Rationale and methods for emulating physiologic basal-prandial insulin secretion
- Action profiles of different insulin products
- Relationship between overlapping insulin action (also known as “insulin-on-board”) and the potential for hypoglycemia (Fig. 4)²⁹

TABLE 2. ADDRESSING POTENTIAL BARRIERS TO THE ADOPTION OF CGM

<i>Barrier</i>	<i>Comment</i>
Uncertainties about accuracy	<ul style="list-style-type: none"> • Continuous data and trend information (i.e., rate and direction of change) require a new standard of accuracy. • There is the potential for lag between interstitial and blood glucose measurements; this lag is usually more pronounced during periods of rapid changes in glucose levels. • Confirmation with a standard blood glucose meter is required before making treatment adjustments.
Inadequate reimbursement	<ul style="list-style-type: none"> • Under the current system, broad-scale coverage will depend on demonstrating the value of CGM in terms of current point-in-time monitoring methods and patient outcomes. • Support services for high-quality diabetes management (e.g., education, telephone, and e-mail consultation) typically do not cover physicians’ overhead.
Need for educational infrastructure	<ul style="list-style-type: none"> • Patients and clinicians require education to realize full benefit of continuous data and to avoid “information overload.” • Understanding of insulin pharmacodynamics and other factors affecting blood glucose is necessary to ensure appropriate use of continuous data and improved outcomes.
Concerns about workload and workflow in daily clinical practice	<ul style="list-style-type: none"> • Group education, standardized check sheets, data downloading prior to the office visit, manufacturer-generated medical necessity letters, and the ability to automatically integrate continuous data into electronic medical records can increase the efficiency of CGM for time-pressed clinicians.

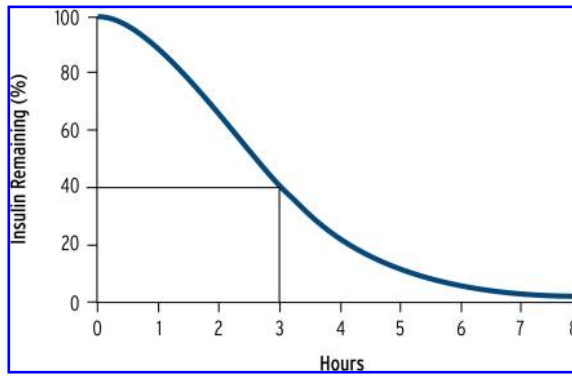


FIG. 4. Example of “insulin-on-board.” This graph depicting delivery of insulin aspart (0.2 units/kg of body weight, delivered into the abdomen) shows, for example, that 3 h after the administration of 10 units of insulin aspart, there is still approximately 40% × 10 units, or 4 units, remaining (i.e., insulin-on-board). Awareness of insulin-on-board can help patients avoid “insulin stacking.” Copyright ©2005 Massachusetts Medical Society. All rights reserved. Reprinted with permission from Hirsch.²⁹

- Physiologic lag time between the blood glucose and interstitial glucose
- Need for traditional blood glucose testing to confirm the continuous glucose result

Clinician acceptance. Clinician acceptance is vital to realizing the full potential of CGM, yet time limitations, lack of reimbursement for patient education, and a health care system ill-equipped to meet the demands of chronic disease care may prevent many health care professionals from embracing this technology. The panel made several recommendations to help overcome these barriers to adoption (Table 2).

To meet the considerable need for education about the scientific, therapeutic, and mechanical aspects of CGM technology, the panel suggested that a multifaceted, web-based program be established for physicians, diabetes educators, registered dietitians, and patients. Depending on the target audience, topics would range from calibrating the device and setting alarms to interpreting data and adjusting therapy. Printed materials and other media platforms were also recommended to reinforce basic concepts of diabetes care and underscore the differences between traditional SMBG and CGM (Table 1). The following list provides additional suggestions for some future improvements that can support clinicians:

- Technology that allows patients to download their continuous glucose data and either bring print-outs of their results to an office visit, or download their sensor data to a website also accessible to the physician; trouble spots can then be flagged on a standardized checklist and submitted to the clinician for more focused investigation.
- Technology and software to allow medical practices to download multiple CGM devices easily and generate a common printout or series of printouts customized to the provider’s and patient’s preference regardless of the CGM device
- Specially trained CGM educators to guide initiation of sensor use and ongoing application of data, both real-time and retrospectively

- Software that enables direct downloading of continuous data to electronic medical records
- Issuing medical necessity letters directly to payers

How should CGM be initiated in the clinical setting?

The panel discussed the logistics of starting a patient on CGM, moving from preparation to the actual office visit and follow-up. Encouraging patients to do “homework” before the office visit (e.g., by consulting online or print materials describing CGM and the particular device they will be using) can help in setting realistic expectations with respect to sensor mechanics and continuous readings.

Initial training is often more efficient when conducted in groups. The first session may take 1–2 h, during which time the sensor would be inserted and the following topics would be covered:

- Setting realistic expectations of sensor therapy
- All preparation procedures through calibration, including placement of the sensor and appropriate calibration of the sensor when the glucose is in a steady state
- Setting target ranges
- Setting low and high alarms
- Setting projected low and high alarms
- Review of other alarms
- Reading the receiver
- Cleaning the system
- Review of the procedure for adding events
- Review of testing in the Blood Glucose Mode
- Troubleshooting common alarms

The panel recommended that no action be taken by the patient during the first 3–7 days, although alarms can be set in stages (i.e., turned on one at a time) so that patients can master one before moving on to another. Patients must be reminded to adhere to their usual diabetes care regimen using traditional SMBG.

Follow-up. Patients should be instructed to return within 1 week to review their first days of data and insert the next sensor. The panel recommended developing a standardized checklist of events (e.g., first low alarm, first high alarm, first projected alarm), so patients can record their experiences in preparation for the follow-up visit. After this second visit, training will need to be individualized, with most patients requiring some contact, either web-based or face-to-face, within 2–4 weeks.

What are the keys to an actionable assessment?

Calibration. To ensure the accuracy of continuous data, patients wearing a real-time monitoring device must calibrate the sensor reading to a fingerstick reading. To increase the chance of a successful calibration, it is important that patients verify that their hands are clean and dry, verify that the meter to be used is accurate (i.e., the correct test strip code has been entered and periodic validation of the accuracy has been confirmed with the use of control solution), and draw blood from the fingertips only. Calibration is best done when the glucose is not rapidly changing, such as before meals or in the fasting state. Since calibration procedures vary with model and manufacturer, users should follow instructions carefully.

Setting targets. Programmable glucose targets allow for reports and line graphs that depict actual glucose performance in relation to glycemic targets or goals (Table 3). Although the ideal preprandial and postprandial blood glucose targets recommended by the ADA are 70–130 mg/dL and <180 mg/dL, respectively, patients beginning CGM may want to start with more modest goals.³⁰

To establish realistic targets, the panel recommended checking pre-meal and post-meal glucose levels for 5 days prior to sensor insertion for evaluation of baseline glycemic status. This preview can also prepare patients for the frequent glucose excursions typically detected by continuous monitoring even when A1C testing indicates good overall control.

In some cases, patients can set separate glucose targets for the CGM device and the data management software. In the event a system allows for separate pre-meal and post-meal target ranges, a pre-meal target range of 80–130 mg/dL and a post-meal range of 140–180 mg/dL were considered reasonable by the panel.

Setting a wide glucose target range initially may help to prevent patient burnout as it can be frustrating to see many glucose values outside of the target range. Patients should be reassured that it is not unusual to be out of target range >50% of the time when starting out and that these fluctuations can be corrected over time. The issue of lag times should also be discussed (see Accuracy of dynamic readings), with the important caveat that they can be overcome by paying close attention to glucose trends and projected alarms.

Setting alarms (threshold and projected). High and low glucose alarms may alert the user when glucose levels are above or below the glucose threshold values established by the diabetes management team (Table 3). It is important to note that projected alarms correctly warn the patient of only a fraction of the actual hypoglycemic events that occur. When there are fluctuations in the glucose it is possible that the “20-min warning” may be less likely to detect a pending event.

The panel stressed the need to actively discourage patients using any CGM device from relying solely on alarms for general diabetes management. Note that alarms should always be used in tandem with other indicators of glycemic status, such as fingerstick blood glucose readings, trend arrows, line

graphs, and, when available, selected data management features. Suggested threshold alarm settings include:

- Initially, the low alarm might be set at 70 mg/dL, unless the patient has a history of hypoglycemia unawareness, in which case setting a higher low threshold value (e.g., 80 mg/dL) may increase event detection.
- The high alarm might be set at 250 mg/dL, as this range prevents alarms from sounding too frequently during the first few weeks of use.
- After several weeks, however, the high alarm may be reset to a lower value (e.g., 180–200 mg/dL).

The alarm programming should take into consideration individual patient needs. The panel identified situations that might warrant a different projected alarm:

- Desire for fewer alarms (e.g., 10-min warning for people with type 2 diabetes who do not have hypoglycemia unawareness and are willing to forgo greater sensitivity for fewer alarms)
- Hypoglycemia unawareness (e.g., 30-min warning and a higher glucose alarm threshold value for individuals with type 1 diabetes who have hypoglycemia unawareness and prefer a higher sensitivity despite more frequent alarms)

Other alarm considerations. Depending on the device, alarms may be set to beep or vibrate. They can also be muted for a period of time, or turned off at night if preferred. These options are particularly useful for accommodating individual sleeping habits. However, it is not generally recommended that the low alarm be turned off at night, because of safety concerns. The common phenomenon of postprandial glucose excursions can trigger repeated high alarms, causing patients to overadminister correction dose insulin between meals. Such insulin stacking is often a precursor to overlapping insulin action (insulin-on-board) and attendant hypoglycemia (Fig. 4).²⁹

Inappropriate basal insulin may also affect post-meal excursions signaled by alarms. Therefore, it is imperative that patients beginning CGM have a thorough understanding of how insulin works in their own bodies before deciding whether or not to treat high glucose. For patients experiencing frequent postprandial glucose spikes, the panel suggests resetting the high alarm to the maximum limit of 300 mg/dL as a precaution until blood glucose is stabilized and the normal treatment regimen can be resumed.

Special situations. Continuous monitoring may be of particular benefit to patients with hypoglycemia unawareness or gastroparesis, inpatients, athletes, and pregnant women. However, until the full impact of sensor technology in these situations is understood and studied, caution is advised. For example, patients with hypoglycemia unawareness need to understand the lag time between blood glucose and interstitial glucose readings and reset their alarms accordingly. With gastroparesis and other disorders of malabsorption, or when patients are using medications that affect the rate of gastric emptying (e.g., pramlintide or exenatide), anecdotal evidence indicates that care must be taken to avoid insulin stacking. More research is needed to define the best application of adjunctive CGM under these and other special metabolic circumstances.

TABLE 3. GLUCOSE TARGETS AND ALARMS: KEY CONCEPTS FOR CGM

-
- Glucose targets—Glucose goals that are reviewed by the health care provider and appear on the CGM receiver and software report
 - Threshold glucose value—Glucose level of which patients must be aware to recognize that they are reaching a critical value possibly requiring some type of action
 - Threshold glucose alarm—An alarm that alerts the patient that the glucose level has risen or dropped to or beyond the threshold glucose value and that some type of action may be warranted
 - Projected glucose alarm—An alarm that, based on the glucose trend and rate of change, provides advanced notice of a threshold glucose value being reached
-

TABLE 4. SUMMARY OF ISSUES RELATED TO THE CLINICAL APPLICATION OF CGM TECHNOLOGY

How to apply CGM to clinical practice	<ul style="list-style-type: none"> • Provides patients with “real-time” information about the rate <i>and</i> direction of glucose change and alerts them to trends that could lead to hypoglycemia or hyperglycemia • Allows patients to more tightly manage their diabetes • Promotes understanding of how food, exercise, stress, and other factors affect blood glucose
What health care professionals need to know to use CGM effectively	<ul style="list-style-type: none"> • CGM systems are approved for adjunctive use only—augment traditional blood glucose testing and require a blood glucose test be used as the basis for management decisions • Education on calibrating the device, setting alarms, interpreting data, and adjusting therapy • Should be thoroughly familiar with physiology of glycemic control and insulin action
Patient selection	<ul style="list-style-type: none"> • CGM devices are currently approved for use in adults • While not currently Food and Drug Administration-approved for use in pediatrics, the pediatric population may benefit from the technology. • Special populations that may also benefit include: <ul style="list-style-type: none"> ◦ Patients with type 1 diabetes mellitus who have not met A1C and/or glycemic variability goals despite adequate SMBG ◦ Patients who intentionally keep blood glucose levels above target because of fear of hypoglycemia ◦ Patients with type 2 diabetes mellitus who would wear the sensor intermittently to learn about their own diabetes and the rationale for initiating or changing a specific therapy ◦ Patients with hypoglycemia unawareness, or frequent episodes of severe hypoglycemia
Use in special situations	<ul style="list-style-type: none"> • CGM allows patients to see how numerous changing variables including exercise, illness, stress, insulin or medication, unusual foods, the rate of nutrient absorption, and other variables impact glucose and reduce glycemic variability from these events.
What patients need to know to use CGM effectively	<ul style="list-style-type: none"> • CGM systems are approved for adjunctive use only—augment traditional blood glucose testing and require a blood glucose test be used as the basis for management decisions • Initial training: patients should be guided through all preparation procedures and calibration and taught how to set target ranges and alarms and maintain and clean their system. • Patients should have a thorough understanding of how insulin works in their bodies before deciding whether or not to treat high glucose. This helps prevent insulin stacking. • Patients should be encouraged to research CGM before initiation of therapy so they have realistic expectations of what will be required and what they can gain from CGM.
Programming targets	<ul style="list-style-type: none"> • Although the ideal preprandial and postprandial blood glucose targets recommended by the ADA are 70–130 mg/dL and <180 mg/dL, respectively, patients beginning CGM may want to start with more modest goals. • Patients should check pre-meal and post-meal glucose levels for 5 days prior to sensor insertion to evaluate their baseline status and set reasonable goals.
Data management	<ul style="list-style-type: none"> • Retrospective analysis of CGM data can be used to identify glucose patterns that if confirmed with blood glucose testing may lead to therapy adjustments. • In discussing retrospective data with patients, clinicians should pay attention to patient preference regarding format (e.g., statistics report vs. pie chart) to optimize communication within the limited amount of time available. • Downloading data before the office visit is a time-saving measure and should be used where possible. • Verify that the date and time on the monitor are correct. If the time on the monitor is incorrect, the downloaded results will also be in error, especially with respect to postprandial data.

(continued)

TABLE 4. SUMMARY OF ISSUES RELATED TO THE CLINICAL APPLICATION OF CGM TECHNOLOGY (CON'T)

Interstitial versus blood glucose and discussion of lag	<ul style="list-style-type: none"> • Interstitial glucose readings generally lag behind blood glucose readings, especially during periods of rapid change. • The lag time varies from 3 to 20 min. • Because of the lag time between CGM and traditional blood glucose monitoring, using the two methods in tandem is the best way to look at overall blood glucose dynamics.
Patient issues	<ul style="list-style-type: none"> • Patients can become frustrated and overwhelmed by the increased amount of data and information. • Patients should be reassured that it is not unusual to be out of the target range >50% of the time when starting CGM and that these fluctuations can be corrected over time.
How CGM may change current paradigms of diabetes care	<ul style="list-style-type: none"> • New evidence suggests that glycemic control depends on a combination of A1C and glycemic variability, both of which need to be minimized to prevent complications. CGM will allow patients to detect and control glycemic variability and to see how different daily activities affect their blood glucose. • Real-time data allow patients to control glucose more tightly.

How should CGM be used to adjust therapy?

Since present-day CGM devices are approved for adjunctive use only and have limitations due to the lag time between interstitial glucose and blood glucose, a confirmatory SMBG reading is necessary before any adjustment of therapy. Additionally, when contemplating an intervention, patients should always review the last food eaten, recent exercise, and previous insulin doses that may not have had their full effect.

Addressing projected low alerts. Projected low alerts generally warrant action on the part of the patient. Fingerstick testing of blood glucose is required to confirm glycemic status. Projected hypoglycemia requires “gentle” intervention in the form of approximately 10 g of carbohydrate. If the patient is already hypoglycemic (blood glucose, <70 mg/dL), 15–20 g of glucose is the preferred treatment.³⁰ Retesting with a traditional blood glucose meter is advised after approximately 15 min to verify that no additional treatment is needed. In the event of severe hypoglycemia (when a patient requires the assistance of another person and cannot be treated with oral carbohydrate), emergency glucagon should be administered.

When considering the response of insulin pump wearers to projected low alerts, it is prudent to confirm that patients are not cutting back or discontinuing their basal insulin as a means of warding off hypoglycemia. Some patients are especially prone to this behavior, which can lead to a vicious cycle of rebound hyperglycemia, overuse of correction dose insulin, projected low alerts, and so on.³¹ Clinicians can help break this cycle by urging patients to pay attention to trend arrows rather than to isolated glucose readings. Prompt response to projected low alerts also helps by reducing the number of calories required to prevent hypoglycemia.

Interpreting trend arrows. Trend arrows, or equivalent indicators depending on the device model, are an essential feature of today’s CGM technology because they provide patients with the rate and direction of glucose change (see Concurrent data analysis). Before using trend arrows to ad-

just therapy, however, patients must have a firm grounding in the physiology of glycemic control and a complete understanding of the effects of insulin, oral antidiabetic agents, carbohydrates, and exercise on their own metabolism. In addition, patients using the FreeStyle Navigator system should also be told that although a flat arrow implies minimal blood glucose change (<60 mg/dL/h or <1 mg/dL/min), the change could be as much as 59 mg/dL over the course of an hour. Thus, despite the predictive advantages of trend arrows and corresponding alarms, complacency or overconfidence is never warranted. This is especially true of patients striving to maintain near-normal blood glucose levels.

When considering glucose trends, it is necessary to factor in the lag time between interstitial glucose and blood glucose readings (estimated between 3 and 20 min).²⁶ While lag time is more pronounced during periods of rapidly changing glucose (up or down), it requires particular attention when glucose is decreasing at a rapid rate, since hypoglycemia could ensue. Because of the lag time between CGM and traditional blood glucose monitoring, using the two methods in tandem is the best way to look at overall blood glucose dynamics. Whereas traditional monitoring provides the glucose value at a single point in time, CGM shows the trend when glucose levels are changing.

Data downloading and analyzing glucose patterns. Real-time CGM systems allow downloading of continuous data through a variety of diabetes management software programs. Approaches to using diabetes management software vary according to the patient and the clinician. Clinicians should pay attention to patient preference regarding format (e.g., statistics report, pie chart, or modal day) to optimize communication within the limited amount of time available. Downloading data before the office visit is another time-saving measure. It is also important to make sure that the date and time on the monitor are correct. If the time on the monitor is incorrect, the downloaded results will also be in error, especially with respect to postprandial data. Standardization of diabetes management software, including capabilities for web-based computer downloading programs that allow immediate graphing, faxing, and e-mailing of glu-

case results to health care providers, should increase the feasibility of using continuous data in clinical practice.

While there appears to be great value in utilizing real-time glucose data and trends in glucose readings, clinicians are also finding value in analyzing the downloaded CGM data. For instance, several of the authors and others have noted in many patients that the so-called rapid-acting insulins may not be rapid enough as currently delivered to optimize post-meal glucose control. Based on CGM data, in certain individuals, we suggest giving rapid-acting insulin further ahead of the meal than currently recommended. In addition, the plot of thousands of glucose values collapsed into a single day's picture can help identify how to modify therapy or which therapy would best be added next.

What Are The Priorities For The Near Future?

Given the practical challenges of diabetes care, wide acceptance of CGM will depend on minimizing the amount of time, investment, and inconvenience necessary for clinical use.²⁷ To ensure that technology design and support systems fit real-world needs, researchers and payers will need to create opportunities for "early adopters" to describe their experiences and concerns. With the benefit of this input, the best application of CGM can be determined in relation to specific therapeutic objectives. Coordinating stakeholders in a united effort to address the regulatory, clinical, economic, and patient-related barriers that have historically impeded high-quality diabetes care will be fundamental.

The need for education in transitioning from a care model based on point-in-time blood glucose analysis to one guided by continuous data cannot be overstated. It will be incumbent on advocacy groups such as the American Association of Diabetes Educators, the ADA, the JDRF, and the American Association of Clinical Endocrinologists to assume a leadership role in developing and disseminating specific CGM protocols and consistent CGM download options.²⁷ Clinical studies will be necessary to clarify methods for treating predicted hypo- and hyperglycemia and adjusting insulin on the basis of glucose trends.²⁶

Determining accuracy criteria is another priority with potentially far-reaching ramifications. New standards focusing on patients' ability to accurately anticipate glycemic events, and modify treatment accordingly, could conceivably lead to replacement labeling (as opposed to adjunctive) and a more favorable climate for reimbursement. Measurable gains in clinical and quality-of-life outcomes will have to be shown; in addition, it must be demonstrated that these improvements justify the cost differences between CGM and traditional blood glucose testing. Finally, establishing mechanisms by which clinicians can bill for time spent evaluating data and counseling patients is an urgent priority if CGM is to be optimally utilized.

Potential for a closed-loop insulin delivery system

The availability of reliable glucose sensing technology is considered a prerequisite for the development of a closed-loop insulin delivery system. Closed-loop systems now being tested incorporate a continuous glucose monitor that transmits data to an insulin pump.³² The pump is equipped

to adjust insulin doses in response to real-time readings. Because this technology requires minimal patient input, it is commonly referred to as an "artificial pancreas." Today's CGM systems are seen as an important evolutionary step toward realizing the goal of closed-loop insulin delivery in clinical practice.

Summary and Conclusions

In summary, coordinating financial and educational resources, as well as developing clear protocols for using glucose sensor technology, are urgent priorities in promoting wide adoption of CGM by patients and health care providers. Table 4 highlights issues related to the general application of CGM technology. Clinical issues that must be addressed are the lag times between blood glucose and interstitial glucose readings, the potential for over-correction in response to alarms, and the likelihood of detecting significant glycemic variability even when A1C results are in target range. Moreover, patients should be thoroughly familiar with the physiology of glycemic control and demonstrate clear understanding of insulin action before using CGM to adjust therapy. Finally, researchers, payers, and advocacy groups must join forces on the policy level to create an environment conducive to managing continuous data, measuring outcomes, and formalizing best practices.

Acknowledgments

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Posttest Questions

1. CGM provides information about the rate and ____ of changing glucose levels.
 - A. impact
 - B. direction
 - C. speed
 - D. quantity
2. There will be a ____ in interstitial glucose values when blood glucose levels are changing rapidly.
 - A. lag
 - B. slight increase
 - C. significant increase
 - D. minute-by-minute fluctuation
3. A key limitation of traditional hand-held blood glucose monitoring systems is _____.
 - A. lack of portability
 - B. overcompensation for inadequate blood sample size
 - C. inability to detect glucose fluctuations throughout the day
 - D. inaccuracy of test results when glucose levels are high
4. Because traditional handheld glucose monitoring devices provide only a "snap-shot" of the current glucose level, patients may miss identifying ____ unless they are testing their blood glucose frequently throughout the day.
 - A. impending hypoglycemia
 - B. extended periods of hyperglycemia
 - C. significant postprandial glucose excursions
 - D. all of the above
5. CGM provides meaningful data that enables patients to ____ hypoglycemia.
 - A. more effectively treat
 - B. detect and prevent impending
 - C. monitor
 - D. induce
6. Before using CGM trend data to adjust therapy, patients must have a firm grounding in _____.
 - A. the rationale and methods for emulating physiologic basal-prandial insulin secretion
 - B. the relationship between "insulin-on-board" and the potential for hypoglycemia
 - C. physiologic lag time between the blood glucose and interstitial glucose
 - D. all of the above
7. After the initial training session, no action should be taken by the patient for _____.
 - A. 2 weeks
 - B. 1 day
 - C. 3-7 days
 - D. 12 hours
8. To establish realistic targets, patients should check their _____ for 5 days prior to sensor insertion.
 - A. pre-meal and post-meal glucose levels
 - B. total daily insulin dose
 - C. insulin-to-glucose correction algorithm
 - D. insulin-on-board
9. Education on _____, setting alarms, interpreting data, and adjusting therapy is vital to effective use of CGM.
 - A. device calibration
 - B. insulin pump use
 - C. carbohydrate counting
 - D. none of the above
10. To address concerns and barriers about workload and workflow in daily clinical practice, it is recommended that clinicians _____.
 - A. offer patient education on a one-on-one basis
 - B. automatically integrate CGM data into electronic medical records
 - C. download patients' CGM data once they arrive at an office visit
 - D. all of the above

Activity Evaluation

Please visit www.bcmeonline.com to complete this evaluation and to receive your certificate.
Please rate the effectiveness of this activity. Your input and comments are encouraged and appreciated.

1. Please rate the overall content of this activity.

<u>Poor</u>					<u>Excellent</u>
1	2	3	4	5	6

2. Please rate how well the educational objectives of this activity were met.

- | | | | | | | |
|--|-------------------|---|---|---|-------------------|---|
| | <u>Not at all</u> | | | | <u>Completely</u> | |
| | 1 | 2 | 3 | 4 | 5 | 6 |
- Describe the difference between the information provided by glucose sensors versus traditional blood glucose meters
 - Understand how continuous glucose monitoring (CGM) can help stabilize glycemic control even under conditions of optimal diabetes management
 - Specify the steps for initiating CGM in the clinical setting
 - Advise patients on interpreting CGM data for more reliable prevention of hypo- and hyperglycemia and achievement of better long-term glycemic control
- | | | | | | | |
|--|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
|--|---|---|---|---|---|---|

3. Do you believe the subject matter was presented objectively, with fair balance, and that it was free of commercial bias?

Yes No

If no, please explain. _____

4. Please select confidence levels below regarding use of CGM technology:

	Not Confident		Somewhat Confident		Very Confident	
I am _____ about my ability to provide adequate instruction to patients regarding how to effectively use CGM technology.	1	2	3	4	5	6
I am _____ about my ability to analyze CGM retrospective trend data and use it to analyze the source of a problem and/or adjust medications.	1	2	3	4	5	6

5. On a scale of 1 to 6 with 1=not at all, and 6=completely, to what extent will you attempt to implement the following changes in practice:

Intended Changes in Practice	Not at all		Partially		Completely	
Expand the use of CGM to assist in identifying patients' glucose patterns and directing changes in therapy.	1	2	3	4	5	6
Commit to the education of my patients in order to support their appropriate use of CGM technology.	1	2	3	4	5	6

6. To what degree will the content of this activity influence changes to your management of diabetes?

Low Degree					High Degree
1	2	3	4	5	6

7. What related topics would you like to be offered as CME activities in the future?

8. Please rate the following educational media in order of your preference (from 1 to 6, 1 being the most preferred) for CME activities:

- | | | |
|----------------------|----------------------------|---------------------------|
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| ____Print | ____Live local programs | ____Podcast/Mobile CE/CME |

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