Clinical Implications of Real-time and Intermittently Scanned Continuous Glucose Monitoring

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Two types of continuous glucose monitoring (CGM) systems are now available: real-time CGM (rtCGM) and intermittently scanned (isCGM). Current rtCGM systems automatically transmit a continuous stream of glucose data to the user, provide alerts and active alarms, and transmit glucose data (trend and numerical) in real time to a receiver, smart watch, or smartphone. The current isCGM system provides the same type of glucose data but requires the user to purposely scan the sensor to obtain information, and it does not have alerts and alarms. Both CGM technologies have significant advantages over self-monitoring of blood glucose; however, differences in the features and capabilities of the two approaches must be considered when guiding patient selection of the system that meets their individual needs.

Over the past decade, personal continuous glucose monitoring (CGM) has emerged as a new standard of care for many individuals with insulin-treated diabetes (1–6). Unlike self-monitoring of blood glucose (SMBG) measurements, CGM systems provide continuous measurement at 1–5 min increments of glucose concentrations in the interstitial fluid, which correlate with blood glucose levels (7).

CGM provides information about the immediate glucose level to the user, as well as information about previous glucose trends and the current direction and rate of change. Analysis of CGM data by either the user or clinician allows for a more complete picture of glycemic patterns throughout the day and night, including not only the mean but also time in ranges and the degree of glycemic variability. It can provide insight into the duration, frequency, and causes of fluctuations in blood glucose levels. This information can help identify and prevent unwanted periods of hypoglycemia and hyperglycemia and, thus, improve overall glycemic control (8–10).

Two types of CGM systems are now available: real-time (rtCGM) and intermittently scanned (isCGM). Current rtCGM systems automatically transmit a continuous stream of glucose data to the user in real time, provide alerts and active alarms, and transmit glucose data (trend and numerical) to a receiver, smart watch, or smartphone. The current isCGM system provides the same type of glucose data but requires the user to purposely scan the sensor to obtain information, and it does not have alerts and alarms. Both CGM technologies have significant advantages over SMBG; however, differences in the features and capabilities of the two approaches must be considered when guiding patient selection of the system that meets their individual needs.

The purpose of this article is to *1*) discuss the strengths and limitations of traditional methods to evaluate glucose control, *2*) review the data on the currently available rtCGM and isCGM systems, *3*) discuss the strengths and limitations of each CGM approach, *4*) review the recent literature of isCGM and rtCGM studies, and *5*) provide guidance to clinicians regarding possible clinical indications for specific patient groups. The

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opinions and guidance expressed in this review are based on our clinical experiences treating diabetes patients and our personal experiences with diabetes; the authors all have been living with type 1 diabetes (T1D) for well over 175 combined years.

LIMITATIONS OF TRADITIONAL METHODS TO EVALUATE GLUCOSE CONTROL

Glycated Hemoglobin

Glycated hemoglobin (HbA_{1c}) is a validated reference marker for assessing glycemic control and predicting the risk of developing long-term complications (11,12). The assay has been rigorously standardized, can be drawn in the nonfasting state, and is widely available. As such, HbA_{1c} is a valuable measure of population health and is used by regulators and payers as the primary intermediate outcome measure to assess risk of developing complications and the efficacy of treatments.

However, HbA_{1c} has limited utility in personalized diabetes management for the following reasons. HbA_{1c} only provides an average of glucose levels over the previous 2–3 months, and although its value is weighted toward more recent events (13), it does not reflect daily glucose fluctuations, variability, or time in range (14). Likewise, does it not reflect intra- and interday glycemic excursions that may result in acute events such as hypoglycemia or postprandial hyperglycemia. Both of these conditions have been linked to microvascular and macrovascular complications with potential interactions with other risk factors (15,16); however, the clinical impact of time in range and glycemic variability on these complications has not been fully proven in long-term clinical trials. Nevertheless, increased glucose variability is consistently associated with mortality in the intensive care unit (17,18) and is a consistent predictor of hypoglycemia, both in prospective studies and within the setting of randomized clinical trials (19,20). The authors can attest to the fact that glucose variability and unpredictable fluctuations are the most bothersome, dangerous, and irritating issues, none of which are captured by the HbA_{1c} level.

HbA_{1c} is an unreliable measure in patients with some types of anemia (21), hemoglobinopathies (22), and iron deficiency (23), as well as during pregnancy (24), and its correlation with mean glucose differs significantly between races (25). Perhaps most importantly, the correlation of HbA_{1c} with mean glucose within individuals is highly variable even in those who do not have a condition known to alter red blood cell life (25,26). There is no question that the best indicator of average glucose over the prior 2–3 months is, quite simply, the average glucose measured over the past 2–3 months. These data are now readily available with CGM technology.

Setting glycemic goals based on HbA_{1c} thus represents applying a population average to the individual (14). This can lead to false reassurance in those who have a significantly higher mean glucose than expected at a given HbA_{1c} and potentially inappropriate treatment intensification with possible increases in hypoglycemic burden in those with lower-than-expected mean glucose at a given HbA_{1c}. Therefore, even though HbA_{1c} is a robust and core glycemic measure, it is incomplete and potentially misleading for individual patients. Moreover, it does not provide the clinician guidance for specifically adjusting treatment regimens, particularly insulin in patients with T1D.

SMBG

SMBG has traditionally been considered a key component in effective management in insulin-treated and non–insulin-treated diabetes (11,27–31). SMBG will continue to play an important role in diabetes care worldwide for many years to come. However, it also has inherent limitations that can impact its utility, especially in insulin-treated individuals with T1D and type 2 diabetes (T2D). The requirement to perform a fingerstick to obtain a blood sample can negatively influence patient adherence to prescribed SMBG regimens. Moreover, SMBG may not be feasible (or desirable) at work or school, and it is susceptible to user error due to poor testing technique, inadequate blood sample, presence of contaminating substances on fingers, and other factors (32), all of which can lead to primarily falsely high, but also low, readings. Additionally, postmarketing data on the accuracy and consistency of commercially available SMBG systems demonstrated that many did not meet recommended standards (33).

The utility of SMBG is also limited because it only measures glucose at a single "point in time" and provides no indication of changing glucose (direction or rate of change). Because it cannot predict impending hypoglycemia or alert for hypoglycemia (34,35), use of SMBG data in isolation may result in inappropriate therapy decisions. Importantly, SMBG is dependent upon the patient's decision and ability to measure glucose at a given time, which limits its use during the night unless the patient or patient caretaker awakens to perform a fingerstick. As a result, nocturnal and asymptomatic hypoglycemia can often go undetected (34,35). These issues are exacerbated during illness, stress, or major alterations in daily routine. Similarly, our observation is that during illness severe enough to result in hospitalization, CGM provides the advantages predicted from knowing blood glucose trends.

CURRENT CGM SYSTEMS

rtCGM

Five rtCGM sensors are currently available or being evaluated by the U.S. Food and Drug Administration (FDA): Medtronic Enlite and Medtronic Guardian 3 sensors (Medtronic, Inc., Northridge, CA); Dexcom G5 and Dexcom G6 sensors (Dexcom, Inc., San Diego, CA); and the Eversense sensor (Senseonics, Inc., Germantown, MD). The Medtronic Enlite sensor functions as a component of the MiniMed 530G, 630G, and 640G insulin pump systems, whereas the Medtronic Guardian 3 functions both as a component of the MiniMed 670G insulin pump system and was recently approved by the FDA for use in the U.S. as a stand-alone sensor (Guardian Connect). The Dexcom G5 and the recently approved G6 rtCGM sensors are stand-alone devices that can be used with both insulin pump and injection therapies, and they feature options for interoperability with numerous devices and apps. The FDA approved use of the Dexcom G6 sensor as first in a new device category (Class II Special Controls) as an integrated CGM system that is compatible with other medical devices and electronic interfaces. These devices and interfaces may include automated insulin dosing

systems (e.g., bolus calculators), insulin pumps, blood glucose meters, and other diabetes management devices. It should be noted that although the Dexcom G4 sensor is being phased out, it is still being used with the older Animas and Tandem insulin pumps.

The Medtronic and Dexcom systems utilize transcutaneous sensing and consist of three components: a disposable sensor that is inserted into the subcutaneous tissue to measure glucose levels, a transmitter that attaches to the sensor, and a receiver (stand-alone device, insulin pump, smartphone, smart watch) that displays and stores glucose information. In addition, the Dexcom device can transmit data to the cloud for information sharing in real time. Guardian Connect users can opt to send text messages to care partners when they drop below their target range.

After a 2-h warm-up period and calibration with two SMBG values (Medtronic Enlite and Guardian, Dexcom G5 only), these systems provide a continuous stream of real-time numerical and graphical information about the current glucose level and direction/velocity or rate of change to the receiver. The systems also feature programmable alerts/alarms that can be used to warn users of immediate and/or impending hypoglycemia or hyperglycemia. Use of the Dexcom G5 with the data sharing app is now covered by Medicare. It is also our understanding that Dexcom has applied for Medicare coverage of the Dexcom G6, which (as discussed earlier) received FDA approval as an integrated system, and that use with the data sharing app will likely be covered.

The Eversense rtCGM system consists of an implantable, fluorescence-based, cylindrical glucose sensor (3.3 × 15.7 mm); a removable external smart transmitter; and a mobile medical application that displays glucose information and operates on a mobile device that allows users to review current and historical glucose data in real time. The Eversense system is approved in European markets and is indicated for 180-day wear time, and it recently received FDA clearance for a 90-day wear time in the U.S. As with the Medtronic sensors, the Eversense sensor requires twice-daily calibration and is currently indicated only for adjunctive use, thus requiring verification with SMBG.

isCGM

The FreeStyle Libre Flash Glucose Monitoring System (Abbott Diabetes Care, Alameda, CA) is the only isCGM system currently available. The system utilizes two components: a combined glucose sensor/transmitter (inserted in the user's upper arm) and a separate touch-screen reader device. After the sensor is inserted, there is a 12-h warm-up time, and no initial or daily calibration is required during the 10-day wear period (current U.S. version). When the reader device is swiped close to the sensor, the sensor transmits a glucose level and the direction and velocity of changing glucose as well as an 8-h trend graph to the reader. If more than 8 h pass between scans, only the most recent 8 h of data will be retained and available to the user for review. The FreeStyle Libre is indicated for nonadjunctive use and, as with Dexcom G5 and G6, the system is covered by Medicare.

COMPARISON OF CGM SYSTEM FEATURES AND REQUIREMENTS FOR USE

Current rtCGM and isCGM devices share some common features and functions. Both technologies measure glucose concentrations in the interstitial space after subcutaneous sensor insertion, translate these values into blood glucose values for clinical use, and display current glucose values and trend information (e.g., graphs, trend arrows) on an external device. Software is also available for retrospective data review and analysis. No systems have been approved for use in dialysis or critically ill patients. All systems are indicated for nonpregnant adults with T1D and T2D; however, pediatric and pregnancy indications vary (Table 1).

Availability of Alarms/Alerts

A key difference between rtCGM and isCGM is the availability of alerts and alarms for current and/or impending glycemic events, such as hypoglycemia and hyperglycemia. All current rtCGM devices offer these functions, with individualized upper and lower limits, and rapidity of change alerts as well. For example, some patients who want to be notified early can set a lower threshold alert for rising glucose as an early warning of impending hyperglycemia. In addition, patients with problematic hypoglycemia can set a higher threshold alert for rapidly falling glucose, which is especially important for individuals with frequent episodes of severe hypoglycemia, frequent nocturnal hypoglycemia, and/or impaired hypoglycemia awareness. The Dexcom G6 has an optional alert when glucose is above the low threshold but rapidly falling and is estimated to reach <55 mg/dL ("Urgent Low Soon") in 20 min. This may negate the need to elevate the threshold alert in people with problematic hypoglycemia. The Guardian Connect offers predictive high and low alerts 10–60 min ahead of time. The Eversense sensor also features predictive alerts for impending hypoglycemia. isCGM technology does not offer alerts and alarms but rather requires the user to manually scan the sensor to obtain a glucose value.

Accessing and Archiving Data

Another key difference is how users obtain and archive their data. Whereas all rtCGM devices automatically transmit a continuous stream of data to the user's receiver and/or smart device, isCGM technology (FreeStyle Libre sensor) requires a conscious decision by the user to scan the sensor in order to obtain glucose information, and to do so at least every 8 h to avoid data gaps in the glycemic data archive. This could be problematic for patients who tend to sleep longer than 8 h. isCGM systems will not notify the user or the caretaker for impending hypoglycemia or hyperglycemia.

Nonadjunctive Use With SMBG

The indication for nonadjunctive use for making treatment decisions is particularly important as it applies to insulin therapy dosing. In the past, all CGM systems were indicated only for adjunctive use with SMBG to confirm current glucose levels prior to making insulin adjustments and other diabetes treatment decisions. Today, three systems carry this nonadjunctive indication: FreeStyle Libre (36,37), Dexcom G5 (38), and Dexcom G6 (39). The current Medtronic systems require confirmatory testing with SMBG prior to bolus insulin dosing (40,41), but the sensors integrated into the 530G, 630G, 640G, and 670G insulin pumps can alter basal rates without confirmation. The Eversense sensor is also indicated for adjunctive use with confirmatory fingerstick testing (42).

Table 1—Key features of current stand-alone rtCGM and isCGM devices

	isCGM	rtCGM				
Feature	FreeStyle Libre (36,37)	Dexcom G6 (39)	Dexcom G5 (38)*	Guardian 3 (40)	Enlite (41)	Eversense (65)
Minimum age for use, years	≥18 (U.S.) ≥4 (ex-U.S.)	≥2	≥2	≥7	≥16	≥18
Indicated for use in pregnancy	No (U.S.) Yes (ex-U.S.)	No	No	No	No	No
Sensor wear time, days	10 (U.S.)*f* 14 (ex-U.S.)	10	7	7	6	≤90 (U.S.) ≤180 (ex-U.S.)
Calibration with SMBG is required	No	No	2×/day	2×/day	2×/day	2×/day
Allows optional calibration	No	Yes	Yes	Yes	Yes	Yes
Warm-up period, h	12 (U.S.)*f* 1 (ex-U.S.)	2	2	2	2	24 (only upon insertion of sensor)
Insulin dosing approved without confirmatory fingerstick testing	Yes	Yes	Yes	No	No	No
Provides trend arrows	Yes	Yes	Yes	Yes	Yes	Yes
Provides active alarms/alerts for current and impending hyperglycemia and hypoglycemia	No	Yes	Yes	Yes	Yes	Yes
Real-time remote monitoring (data sharing)	No	Yes	Yes	No	Yes	Yes
Connects with insulin pump	No	Yes	Yes	Yes	Yes	No
Interoperability with other devices	No	Yes	Yes	No	Yes	Yes
Accuracy: overall MARD, %†	9.7 (66)	9.0 (39)	9.0‡ (38)	10.6‡ (67)	16.1‡ (68)	8.8‡ (65)
Accuracy: low glucose range‡						
MARD, % [range, mg/dL]	24.0 [≤70] (69)	–	–	9.4 [61–80] (67)	13.0 [61–80] (68)	9.0 [55–70] (65)
MAD, mg/dL§ [range, mg/dL]	13.0 [≤70] (69)	11.5 [54–69] (39)	6.7 [61–80] (38)	–	–	–

Numbers in parentheses are references. ex-U.S., outside the U.S. *Results are from assessment of the Dexcom G4 sensor with Software 505, which is used in the Dexcom G5 system. †Mean absolute relative difference (MARD) between sensor readings and reference values, expressed as %. ‡Derived from twice-daily calibration; Guardian 3 accuracy is improved with 3–4 calibrations per day (9.7%). §Mean absolute difference (MAD) between sensor readings and reference values, expressed as mg/dL. *f* Recently approved in the U.S. for 14-day wear and 1-h warm-up period. Not currently available at the time of this publication.

Confirmatory SMBG with all rtCGM and isCGM sensors is recommended when the CGM reading does not match symptoms, if there is no trend arrow displayed, or if the user suspects that the reading may be inaccurate. In the U.S., confirmatory SMBG with FreeStyle Libre use is also recommended during times of rapidly changing glucose (>2 mg/dL/min) and in order to confirm hypoglycemia or impending hypoglycemia.

Accuracy

Differences in accuracy are also important to distinguish between and among isCGM and rtCGM systems. Although the clinical implications of inaccuracy are obvious, particularly when CGM values are used for insulin dosing decisions, failure to consistently provide accurate glucose data can have an impact on patient adherence and persistence in using appropriately set alerts and alarms due to alarm fatigue and/or use of the devices entirely (43). Continued CGM use has been shown to be related to users' trust in the accuracy and reliability of the data and the usability of the device (44).

Numerous laboratory studies have been conducted to assess accuracy as measured by common metrics such as mean absolute relative difference (MARD). As shown in Table 1, there are measurable differences between isCGM and rtCGM technologies and between rtCGM systems. Moreover, all current systems are less accurate in the lower glucose ranges. However, it is difficult to draw direct comparisons between systems owing to differences in study designs, methodologies, metrics, and other factors used in the various studies. For example, there is no standardization in reporting sensor accuracy in the lower glucose ranges, which further confounds reliable comparisons.

Calibration

Both the Dexcom G6 and FreeStyle Libre systems are factory calibrated, which eliminates the need for daily calibration with SMBG. The Dexcom G6 also allows for optional calibration with SMBG. Although factory calibration is convenient, the ability to calibrate the Dexcom G6 may be an advantage in terms of aligning the CGM values to blood glucose measurements for people who choose to perform SMBG. The Eversense and Medtronic sensors require a minimum of two calibrations per day.

Additionally, more frequent calibration has been shown to improve accuracy of some rtCGM systems. For those patients using the 670G hybrid closed-loop system, a minimum of two calibrations are required; however, four or more calibrations may be needed to stay in auto mode (40,41). CGM systems that cannot be recalibrated when sensor

glucose values consistently do not match results from SMBG, perhaps because of a defective sensor or local problem such as excessive bleeding at the insertion site, may need to be discontinued by the user prior to their indicated wear time.

Remote Monitoring

The Dexcom G5, Dexcom G6, and Eversense systems offer the ability to share real-time glucose data with family members, caregivers, and clinicians. This capability is particularly valuable for parents and caregivers of pediatric patients, allowing them to monitor their child's glycemic status at school, during physical activity, and throughout the night. Data sharing also provides a safety net for elderly patients and adults who frequently travel alone. Importantly, Medicare beneficiaries can now use their smartphones to monitor and share their CGM data. The FreeStyle Libre (outside the U.S.), Guardian 3, and Enlite systems allow data sharing, but not in real time.

Sensor Wear Life

The FreeStyle Libre system offers a 10-day (U.S.) to 14-day (outside the U.S.) wear life (Table 1). The Dexcom G5 and G6 offer a 7-day and 10-day wear life, respectively. The Enlite and Guardian sensors have 6- and 7-day wear, respectively. The Eversense sensor, which requires an office-based procedure to insert the sensor in the subcutaneous tissue, is currently indicated for up to 180 days outside the U.S. and for 90 days in the U.S.

EVIDENCE SUPPORTING CGM USE

rtCGM

Numerous recent studies have demonstrated the clinical efficacy and other benefits of rtCGM use in individuals with T1D and T2D regardless of the insulin delivery method used (9,10,45–52). Many of the earlier studies focused primarily on use of rtCGM in conjunction with insulin pump therapy (53); however, more recent studies have investigated the potential benefits of rtCGM use in conjunction with multiple daily injections (MDI) therapy (9,10,45,47–50). For example, the large, randomized Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND) trial, which included T1D and T2D participants, showed that use of rtCGM improved HbA_{1c}, reduced time spent in the hypoglycemic (T1D only) and hyperglycemic ranges, and demonstrated reductions in moderate to severe hypoglycemia in individuals with MDI-treated T1D and T2D compared with traditional SMBG (9,10). Improvements in diabetes-related distress and hypoglycemic confidence among the rtCGM users were also observed (48).

Recent studies have also demonstrated the benefits of rtCGM as an integrated component of sensor-augmented insulin pumps with predictive low glucose suspend functionality (54,55). Automatic insulin pump suspension can help individuals with T1D avoid hypoglycemia without significantly increasing hyperglycemia, including the risk of diabetic ketoacidosis (54). A recent single-arm pivotal trial, which included 124 adults with T1D, showed that use of a hybrid closed-loop insulin delivery system was associated with notable reductions in time spent in the low glycemic ranges, as well as lower HbA_{1c}, lower variability, and improved time in target range (55).

Reduction in hypoglycemia is considered an important clinical outcome; however, the impact of rtCGM use in individuals with problematic hypoglycemia has not been widely studied until recently. Findings from a recent randomized trial using a crossover study design assessed the impact of rtCGM versus SMBG use in T1D patients with impaired hypoglycemia awareness (51). Investigators found that rtCGM use significantly increased time spent in normoglycemia and reduced severe hypoglycemia in this high-risk population. The recent HypoDE (Hypoglycemia in Deutschland) study found similar results, reporting that use of rtCGM reduced the number of low glucose events and episodes of severe hypoglycemia in individuals with MDI-treated T1D and problematic hypoglycemia (56).

A recent head-to-head comparative study demonstrated that use of Dexcom G5 rtCGM effectively reduces time spent in hypoglycemia in MDI-treated T1D adults with impaired hypoglycemia awareness compared with isCGM use, which showed no meaningful improvement (57). These findings lend support to the recommendations regarding T1D in adults of the National Institute for Health and Care Excellence (U.K.) for the use of rtCGM in individuals with recurrent severe hypoglycemia and/or impaired hypoglycemia awareness (1).

isCGM

Two large randomized controlled trials have also demonstrated significant improvements in hypoglycemia, time in range, glycemic variability, and patient satisfaction in individuals with well-controlled T1D (58) and T2D (59) who were treated with intensive insulin therapy. In the Randomised Controlled Study to Evaluate the Impact of Novel Glucose Sensing Technology on Hypoglycaemia in Type 1 Diabetes (IMPACT), which included 239 participants with well-controlled T1D (6.7% baseline HbA_{1c}), use of the FreeStyle Libre system was associated with a 38% reduction in time spent in hypoglycemia (<70 mg/dL) (58). In addition, an increase in time spent in range and reductions in glycemic variability were also observed. FreeStyle Libre users scanned their sensor an average of 15 times/day. The FreeStyle Libre system was also assessed in a large T2D population treated with intensive insulin therapy (Randomised Controlled Study to Evaluate the Impact of Novel Glucose Sensing Technology on HbA_{1c} in Type 2 Diabetes [REPLACE]) (59). Findings were similar to those reported in the IMPACT trial, with a 43% reduction in time spent in hypoglycemia despite less frequent scanning (8 vs. 15 times/day). In both studies, participants spent a notable amount of time <55 mg/dL—from 11 (59) to 22 min (58) compared with the high-risk participants in the HypoDE study (3 min) (56). Reductions in HbA_{1c} were not seen in either of these two studies; however, smaller observational and prospective studies have shown notable improvements in both HbA_{1c} and hypoglycemia (60–63).

SUGGESTIONS FOR PATIENT SELECTION

As discussed, there are significant differences in capabilities and limitations between and within the classes of CGM devices. Therefore, it is important that clinicians consider the strengths and limitations of each system and how they align with the individual needs and circumstances of the patient (Table 2). The following suggestions for matching patients to appropriate CGM systems are

Table 2—Strengths and limitations of rtCGM and isCGM systems

Strengths	Limitations
rtCGM	
Dexcom G6 sensor • Indicated for use in children ≥2 years • 10-day sensor wear with single use automatic inserter • Can be used to dose insulin without confirmatory testing in most circumstances • Automatic transmission of glucose data to the user; no action required to obtain data • Provides active alarms/alerts for current and impending hyperglycemia and hypoglycemia (allows for different settings for daytime and nighttime) • Predictive low glucose alert setting • Factory calibrated • Allows optional calibration when glucose data do not match symptoms or confirmatory SBMG • Real-time results can be shared with up to five individuals via G6 Mobile app (Android and iPhone) • Interoperability with other devices • Passive downloading with Dexcom Clarity software • No interference by acetaminophen • Meets Medicare coverage requirement	• Confirmatory SMBG is recommended when - the CGM reading does not match symptoms, - if there is no trend arrow displayed, or - if the user suspects that the reading may be inaccurate. • Cost is higher than isCGM
Dexcom G5 sensor • Indicated for use in children ≥2 years • Can be used to dose insulin without confirmatory testing in most circumstances • Provides active alarms/alerts for current and impending hyperglycemia and hypoglycemia • Automatic transmission of glucose data to the user; no action required to obtain data • Allows optional calibration when glucose data do not match symptoms or confirmatory SBMG • Real-time results can be shared with up to five individuals via G5 Mobile app (iPhone and Android) • Interoperability with other devices • Accurate across glucose levels 40–400 mg/dL • Medicare approved	• 7-day sensor wear life • Requires twice-daily calibration, the accuracy of which can be limited by poor user SMBG technique or less accurate SMBG • Confirmatory SMBG with all rtCGM and isCGM sensors is recommended when - the CGM reading does not match symptoms, - if there is no trend arrow displayed, or - if the user suspects that the reading may be inaccurate. • Cost is higher than isCGM • Acetaminophen interference • Less optimal performance on day 1
Guardian 3 • Automatic transmission of glucose data to the user; no action required to obtain data • Provides active alarms/alerts for current and impending hyperglycemia and hypoglycemia • Allows optional calibration when glucose data do not match symptoms or confirmatory SBMG • Integrates with insulin pumps (e.g., hybrid AP) and can be used as a stand-alone system	• Not indicated for use in children <7 years • Nonadjunctive—requires confirmatory fingerstick testing for insulin dosing • 7-day sensor wear life • Requires twice-daily calibration, the accuracy of which can be limited by poor user SMBG technique or less accurate SMBG • Best accuracy requires 3–4 calibrations per day; the Medtronic 670G may require >2 calibrations to stay in auto mode • Stops displaying data with late calibrations, potentially leaving the patient without data or active alerts • Suboptimal performance on day 1 • Cost is higher than isCGM • Less optimal performance on day 1 • Acetaminophen interference
Enlite • Automatic transmission of glucose data to the user; no action required to obtain data • Provides active alarms/alerts for current and impending hyperglycemia and hypoglycemia • Allows optional calibration when glucose data do not match symptoms or confirmatory SBMG • Integrates with insulin pumps (e.g., hybrid AP)	• Not indicated for use in children <16 years • Nonadjunctive—requires confirmatory fingerstick testing for insulin dosing • 6-day sensor wear life • Requires twice-daily calibration, the accuracy of which can be limited by poor user SMBG technique or less accurate SMBG • Less optimal performance on day 1 • Cost is higher than isCGM • Acetaminophen interference

Continued on p. 2271

Table 2—Continued

Strengths	Limitations
Eversense	
• 90-day sensor wear • Automatic transmission of glucose data to the user; no action required to obtain data • Sensor cannot be accidentally dislodged • Provides active alarms/alerts for current and impending hyperglycemia and hypoglycemia • Transmitter can be removed and reattached • Vibratory on-body alerts via the transmitter to alert user to hypoglycemia and hyperglycemia, even without the smartphone in range • Interoperability with other devices • Wireless upload to a browser-based application • No interference by acetaminophen	• Not indicated for use in children <18 years • Requires in-office surgical procedure • Nonadjunctive—requires confirmatory fingerstick testing for insulin dosing • Requires twice-daily calibration, the accuracy of which can be limited by poor user SMBG technique or less accurate SMBG • Stops displaying data with late calibrations, potentially leaving the patient without data or active alerts • 24-h warm-up period after sensor insertion • Cost is higher than isCGM
isCGM	
FreeStyle Libre	
• Requires no daily calibration; however, fingerstick testing may still be needed in certain situations (see Limitations) • Ease of use by the patient • Up to 14-day sensor wear (ex-U.S.) and up to 10 days in the U.S. version* • Can be used to dose insulin without confirmatory testing under most circumstances • Results can be shared with clinician via LibreLink app (via Android phone only) • Can be used in children/adolescents 4–17 years (ex-U.S.) • Measures glucose 40–500 mg/dL • Can be used in pregnancy (ex-U.S.) • No interference by acetaminophen • Lower cost than rtCGM systems • Medicare approved • Measures blood ketones with special test strips	• Not indicated for children <18 years (US) • No data available for the first 12 h during warm-up period* • Does not have real-time sharing capabilities • Not recommended for those with hypoglycemia unawareness • Does not provide alarms for current/impending glucose events • Is a "passive" system—data not transmitted continuously from sensor; results are available only when the sensor is scanned with a reading device (however, this may not be a limitation in less intensively managed patients not on insulin) • Full 24-h data can be captured and downloaded only if the sensor is scanned at least every 8 h • Does not allow for "recalibration" or detection of poor individual sensor function • In the U.S., currently is indicated for adults only • Requires fingerstick confirmatory testing under the following conditions: - Hypoglycemia (≤70 mg/dL) - Impending hypoglycemia - Rapidly changing glucose - Symptoms of low or high blood glucose - 12-h warm-up period - When symptoms do not match system readings or when inaccurate readings are suspected • Accuracy in hypoglycemic and hyperglycemic ranges is suboptimal • Does not currently connect to insulin pumps or other platforms (e.g., smart pens, apps)

AP, artificial pancreas; ex-U.S., outside the U.S. *Recently approved in the U.S. for 14-day wear and 1-h warm-up period. Not currently available at the time of this publication.

based on our professional experience as clinicians and our personal experience as individuals living with T1D.

rtCGM

All individuals with increased risk for hypoglycemia should consider rtCGM use, including those with impaired hypoglycemia awareness (these individuals should obtain rtCGM systems that have real-time sharing capabilities), frequent nocturnal hypoglycemia, frequent severe hypoglycemia, and/or significant glycemic variability and who are trying to increase time in range (e.g., 70–180 mg/dL). Individuals who could benefit from data sharing capability (e.g., pediatric patients, the elderly, people who travel alone) are also good candidates for rtCGM. It should also be considered for individuals with frequent hypoglycemia (even those with adequate hypoglycemia awareness) owing to the increased accuracy in the lower glucose ranges with rtCGM. Individuals with high HbA_{1c} also benefit from rtCGM use (64). Other candidates for rtCGM use include individuals who are physically active, want to use insulin pump systems that offer predictive low glucose suspend functionality, experience hypoglycemia fear, or desire tighter glucose control than obtained with their current monitoring system.

isCGM

isCGM systems are especially beneficial for most patients with T2D who are not willing or able to perform SMBG as often as needed for clinical decision making. Periodic or long-term isCGM use has potential benefits in prediabetes, patients on oral agents only, and those on basal insulin needing titration. isCGM in some of these latter patient groups could have important effects on behavior

modification. isCGM is indicated for individuals with limited risk for hypoglycemia and who do not have any degree of hypoglycemia unawareness. Clinical benefit can be seen when patients and providers can accurately interpret and make appropriate therapy changes based on retrospective review of data. It may also be valuable for patients who have difficulty performing fingersticks because of manual dexterity issues due to neuropathy, poor circulation to the extremities, cheiroarthropathy, or skin changes that make SMBG challenging. isCGM is also a good option for individuals who do not need to monitor glucose values with alerts and alarms and are motivated to scan their device several times per day. In situations where cost of rtCGM is prohibitive or burdensome, isCGM may be a less costly alternative that still improves outcomes compared with SMBG alone. Patients who "refuse" rtCGM for various reasons should also be considered. Although use of isCGM could be applicable to many individuals with T2D across the natural history, no matter what type of therapy they are on, the cost and accessibility may be an issue depending on health care coverage. In addition, SMBG still remains an important tool for many individuals with T2D.

SUMMARY

Recent advances in glucose monitoring technologies have led to the development of a new generation of CGM systems that are both accurate and reliable. Numerous clinical trials have demonstrated the safety and efficacy of these systems as stand-alone devices (9,10, 45–52) and as integrated components of advanced insulin pump systems (54,55). Based upon the growing body of supporting evidence, use of CGM is now recognized as the standard of care for individuals with T1D and a subset of those with insulin-requiring T2D (1–6).

Two approaches to CGM are currently available, isCGM and rtCGM. Both approaches provide patients with actionable information about their current glucose level as well as glucose trend and predictive information while avoiding the pain and inconvenience of frequent SMBG. However, each system has its own unique features, capabilities, and limitations that must be considered when helping patients select the system that meets their individual clinical needs and life circumstances.

CGM is also an important component of the artificial pancreas backbone. CGM is currently being used with success in both commercial and do-it-yourself hybrid closed-loop systems, and there are at least five major research groups (e.g., Nightscout) working on a fully functioning artificial pancreas where the user will not have to think about his or her diabetes on a daily basis. The authors will probably have a hard time adjusting to NOT having to count carbohydrates, determining the right insulin dose in response to anticipated food intake and exercise, dealing with hypoglycemia and hyperglycemia on a daily basis, and many other variables that cause havoc with our diabetes.

Duality of Interest. S.V.E. is a member of the board for Senseonics and serves as a medical advisory board member for Eli Lilly and Company, MannKind, Novo Nordisk, Sanofi U.S., Merck, and AstraZeneca. N.B.A. has received educational grants, presented promotional programs, and served on the clinical advisory board for Dexcom; served on a consulting board and has done promotional programs for Eli Lilly and MannKind; served on an advisory board for Senseonics; has done consulting and served on a speakers' bureau for Insulet; has done consulting for Becton Dickinson, UnoMedical, LifeScan, and Intuity; and has served on speakers' bureaus for Novo Nordisk and Boehringer Ingelheim. J.P. has received consulting fees from Sanofi, Novo Nordisk, MannKind, Eli Lilly and Company, Insulet, and Senseonics. I.B.H. serves as an advisory board member for Abbott Diabetes Care, Roche, and Becton Dickinson and receives research grant support from Novo Nordisk and Sanofi U.S. No other potential conflicts of interest relevant to this article were reported.

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