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# MONITORING TECHNOLOGIES – CONTINUOUS GLUCOSE MONITORING, MOBILE TECHNOLOGY, BIOMARKERS OF GLYCEMIC CONTROL

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## ABSTRACT

It is recognized that traditional measures of glucose control (such as hemoglobin A1c [A1C]) provide little information regarding the need for day to day changes in therapies. While intermittent self-monitored blood glucose (SMBG) provides additional information with which to make treatment decisions, significant barriers to its use exist, such as inconvenience and lack of timely and regular feedback. Furthermore, important information regarding glucose trends may be missed. Continuous glucose monitoring (CGM) has become increasingly reliable and has demonstrated efficacy in terms of reducing A1C, reducing hypoglycemia and improving the time in target glucose range. Incremental progress continues to be made toward a fully functional artificial pancreas, of which CGM will play a vital role. As more and more data are presented to patients and providers, it has become increasingly paramount that the data are organized in a standardized way and that communication of data is streamlined using patients' mobile devices where available and within the existing clinic infrastructure. Systems that provide immediate feedback to patients and decision support tools for patients and providers have demonstrated superior outcomes compared to routine SMBG alone. Alternate markers of glucose control may provide complementary information about glucose control and long-term prognosis. This chapter will review the latest evidence for use of professional and personal CGM, mobile glucose monitoring approaches, and biomarkers of glycemic control. For complete coverage of this and all related areas of Endocrinology, please visit our FREE on-line web-textbook, www.endotext.org.

## INTRODUCTION

The current technology for monitoring of glucose levels has been well established since the 1980′s. This practice is beneficial to patients with diabetes from both a clinical and an economic standpoint when used optimally. Knowledge of the glucose levels that are measured can allow a patient to select an appropriate dose of insulin or implement dietary or other lifestyle changes to regulate their glucose levels. Expert groups provide recommendations for glucose targets, including HbA1c and self-monitored blood glucose (SMBG).[1,2] Although targets vary, expert groups recommend individualization based upon risk of hypoglycemia, polypharmacy, comorbidities and other characteristics that may affect long-term benefit, individual patient characteristics and resources.

The landscape of glucose monitoring technologies is expanding and rapidly changing. For a full review of glucose monitoring technologies, the reader is referred to one of many excellent reviews referenced throughout this chapter. In addition, Diabetes Forecast publishes an up to date description of glucometers, continuous glucose monitoring (CGM) devices, diabetes apps, and their features regularly.[3] Several trends are emerging in glucose monitoring and will be reviewed in more detail in this chapter:

- **CGM**: This practice is still not yet widely established, but evidence supporting its use is accumulating. The data available through CGM can permit significantly more fine-tuned adjustments in insulin dosing and other therapies than spot testing from self-monitoring of blood glucose (SMBG) can provide. CGM technologies for automatic collection of data have spurred interest in noninvasive glucose monitoring as an additional tool for obtaining information about glucose levels.
- **Closed loop control (CLC):** Also known as an "artificial" or "bionic" pancreas, this technology will link CGM with automatically controlled insulin delivery, using non-living components made of silicon, plastic, and metal. The first steps toward CLC are now available.
- **Mobile Technology and Decision Support**: In recent years, increasing connectivity between glucose monitoring technologies and mobile devices has facilitated ongoing improvements in self-care and communication of data.
- **Alternate Markers of Glucose Control:** Finally, the use of additional analytes besides glucose is still being established.

This chapter analyzes the technology, benefits, and problems with the use of intermittent SMBG and CGM, mobile technology and decision support, and alternate biomarkers of glycemic control.

## CONTINUOUS GLUCOSE MONITORS

CGM measures glucose levels (typically interstitial glucose) continuously and update the glucose level display every 1 to 5 minutes. Most CGMs consist of 1) a monitor to display the information (in some cases, this is the patient's mobile device), 2) a sensor that is usually inserted into the subcutaneous tissue, and 3) a transmitter that transmits the sensor data to the monitor. Previously, all devices were approved for adjunctive use only due to limitations in accuracy; in this case patients must still perform fingerstick glucose monitoring in order to guide therapy and perform calibrations. However, in 2016, the FDA approved the use of the Dexcom G5 as the first CGM for stand-alone use. The following year, the FDA approved the Freestyle Libre, which may also be used for treatment decisions, but in addition, eliminates the need for calibrations. The accuracy of all commercially available CGMs is still the lowest in the hypoglycemic range, which is where the need for sensitivity and specificity is great in terms of serving as an alarm for hypoglycemia.

CGM can provide both retrospective as well as real-time information to detect: 1) hypoglycemic and hyperglycemic excursions; 2) predict impending hypoglycemia; and 3) wide fluctuations in glucose levels, also known as glycemic variability. 24-hour telephone support is available for all FDA approved CGM devices. Use of CGM can help both the patient and their medical provider make fine tune adjustments to medication therapy and provide insight to the patient on behavioral changes to achieve glycemic control. Additionally, current efforts to link CGM measurement with automatically controlled insulin delivery, has progressed incrementally toward a fully functional artificial pancreas. Systems can be divided according to their intended use as professional CGM (which provides only retrospective glucose data) and personal CGM (which provides real-time glucose data).

## PROFESSIONAL CGM

Professional CGM describes CGM data that are obtained via healthcare provider owned equipment. It does not necessarily provide the glucose results in real time, but downloads the readings after they have been collected, the way a 24-hour cardiac Holter monitor provides information about cardiac rhythms after they have occurred. This allows the health care provider to obtain relatively unbiased glucose patterns during typical everyday life. The Endocrine Society recommendations state that professional CGM may be of benefit in adults with diabetes to detect nocturnal hypoglycemia, dawn phenomenon,

postprandial hyperglycemia and to assist in management of diabetes therapies.[4] Professional CGM is more readily reimbursed than personal CGM, but interpretation of both personal and professional CGM reports by qualified healthcare professionals may be reimbursed on a monthly basis.

Some personal CGM systems can be operated in a blinded fashion in order to provide professional glucose data. These systems will be discussed in more detail later (see "Personal [Real-time] Continuous Glucose Monitoring"). The first device for reading blood glucose levels continuously was a professional CGM that was approved by the FDA in June 1999. This device was the Continuous Glucose Monitor System (CGMS) manufactured by Medtronic MiniMed (Medtronic Diabetes, Northridge, CA).[5] Since then, newer models have shown improvements in accuracy and patient acceptance.

**_i_Pro2**

The *i*Pro2 was approved by the FDA in 2011 (Figure 1).[6] The device calculates and stores glucose readings every five minutes. The *i*Pro2 uses the Enlite sensor, which contains a wire with a supply of glucose oxidase at the tip which is inserted subcutaneously into the anterior abdominal wall with a dedicated inserting device, the Enlite Serter. This same enzyme for recognizing glucose molecules is used in many portable blood glucose monitors. Glucose oxidase catalyzes a biochemical reaction in the presence of glucose and oxygen that transfers electrons to a receiving molecule and creates an electronic current, whose magnitude can be measured and converted into a glucose concentration. After 5 days of measurements, the device is removed and plugged into a docking station to download its readings into a computer.

The *i*Pro2 is cordless and requires minimal patient interaction or training. It is activated, inserted, and downloaded in a few simple steps. All calibrations of the *i*Pro2 are performed at the time the device is downloaded by the healthcare provider, either via downloading compatible meters or manual entry. The sensor is identical to that used in the Medtronic Guardian Realtime CGM and Paradigm Revel sensor augmented pump. However, both retrospective and prospective time-points are available for calibration with the *i*Pro2, potentially improving overall accuracy compared to real-time CGM. The mean absolute relative difference (MARD) is reported to be 9.9-10.1% overall and lower sensor-meter agreement in the hypoglycemic range (40-80 mg/dl).[7] The docking station can be connected to a computer that contains dedicated software, called Carelink *i*Pro Software, for use with the system. Patients can now also use the *i*Pro2 myLog App log to log events that might be useful for interpretation of the data, such as blood glucose levels, diet and activity. These data are automatically integrated within the CareLink report.

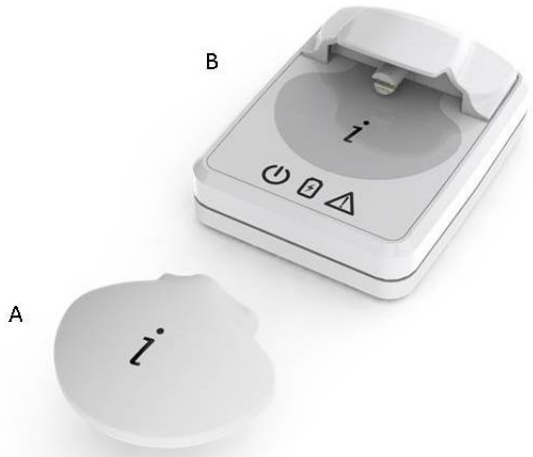



**Figure 1. iPro2 Continuous Glucose Monitor. A –Monitor. B – Docking station.**

**FreeStyle Libre Pro**

The FreeStyle Libre Pro utilizes the same sensor as the Libre personal CGM. Unlike the iPro2, the Libre is factory calibrated and therefore does not require self-monitored blood glucose calibrations. This actually may be a potential advantage since capillary blood glucose testing is subject to various system and user errors, which in addition to the physiologic lag time between blood and interstitial glucose (which is magnified in the postprandial period) could contribute to CGM error. It collects up to 14 days of glucose readings, which are recorded every 15 minutes. The glucose sensor is fully disposable and a single reader is used to activate and scan multiple devices, allowing multiple patients in one office to undergo the procedure simultaneously. Reports are obtained through the LibreView website, which offers a secure cloud-based system, or the FreeStyle Libre desktop reporting software. Reports provide daily patterns, an assessment of glucose variability and hypoglycemia risk, a daily glucose report, and an overall snapshot report.

The overall MARD for the FreeStyle Libre is 11.4%, 86.7% of readings were in Zone A of the Consensus Error Grid analysis, and 99.7% of results were in Zones A and B.[8] It is important to note that sensor accuracy is lower on day 1 and in the hypoglycemia range (MARD 20.3% for values <72 mg/dl in one study).[9,10] Accuracy improves and remains steady over the 14-day wear period. The Libre utilizes glucose oxidase in a "direct signaling" approach that is not dependent on oxygen and minimizes interference by other substances, such as acetaminophen, which may falsely elevated readings on other devices.

**Dexcom Professional**

The Dexcom G4 PLATINUM Professional CGM is a practice-owned system that offers real-time or blinded data depending upon whether the goal is to observe glucose patterns without intervention, to provide immediate feedback to educate and inform patients about their medications and behaviors, or to facilitate decisions about pursuing personal CGM. Patients are required to perform fingerstick calibration of the device twice daily when wearing the CGM. The sensor, transmitter, and receiver are essentially identical to the personal Dexcom G4 system. The device measures interstitial glucose levels every 5 minutes and is approved for 7 days of use. The device is downloaded using Dexcom CLARITY, a web-based software program that is also used to download and review personal data.

**Analysis of Retrospective Data**

Data from all CGM devices can be studied retrospectively after downloading.[11] It is recommended that diet, activity, symptom, and insulin data are collected during professional CGM to assist with interpretation, either via patient diary, direct entry of events into the device, or use of an accompanying app, depending on the system. Three time periods should be analyzed. These are:

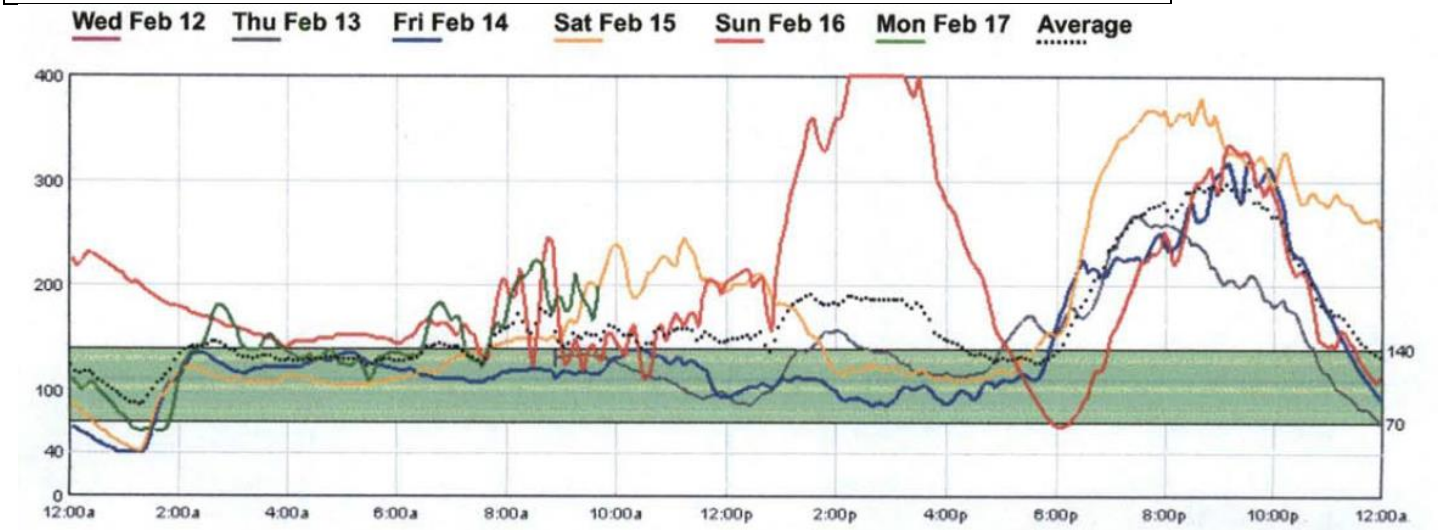
- **Overnight**: Out-of-target overnight glucose levels can be modified by adjusting the basal dose.
- **Pre-prandial Period**: Out-of-target pre-prandial glucose levels can be modified by adjusting the previous meal bolus, meal or exercise pattern.
- **Post-prandial period**: Out-of-target postprandial glucose levels can be modified by adjusting the immediate meal bolus, meal or exercise pattern.

In certain special situations, targets may need to be adjusted. Other important elements of a professional CGM analysis are shown in Table 1. An example of a patient who used CGM (with iPro2) is presented in Figure 2. The CGM demonstrated high glucose levels from 6:00 PM to 11:00 PM post-

supper and low glucose levels from 12:00 AM to 2AM. Recognition of these patterns allowed appropriately timed treatment interventions.

**Table 1. Elements of Professional Continuous Glucose Monitoring Analysis**

| |
|---|
| **ta Accuracy** |
| Frequency of Capillary Blood Glucose Monitoring, calibration (if applicable) |
| Sensor-meter agreement (MARD, correlation coefficient) |
| **Overall Control** |
| Mean Glucose |
| Glucose Variability (Standard Deviation, Coefficient of Variation, ADRR, MAGE) |
| **Daily Detail** |
| Diurnal Patterns: dawn phenomenon, overnight |
| Meal effects |
| Correction |
| Exercise effects |
| Other patterns (work days vs. weekend, menstrual cycles) |
| **Hypoglycemia** |
| Precipitating factors |
| Corresponding meter glucose (recognition) |
| **Recommendations** |
| Adherence (missed boluses, bolus calculator use, infrequent SMBG) |
| Medication dose adjustment |
| Diet (carbohydrate awareness or formal carbohydrate counting) |
| RT-CGM |




| | Wed Feb 12 | Thu Feb 13 | Fri Feb 14 | Sat Feb 15 | Sun Feb 16 | Mon Feb 17 | Average / Total |
|---|---|---|---|---|---|---|---|
| # Sensor Values | 0 | 182 | 288 | 288 | 288 | 116 | 1,162 |
| Highest | N/A | 267 | 322 | 379 | 400 | 224 | 400 |
| Lowest | N/A | 69 | 40 | 41 | 66 | 61 | 40 |
| Average | N/A | 150 | 138 | 179 | 202 | 140 | 166 |
| Standard Dev. | N/A | 50 | 62 | 88 | 81 | 39 | 75 |
| MAD % | N/A | 14.5 | 24.1 | 17.6 | 18.0 | 10.3 | 17.5 |
| Correlation | N/A | N/A | N/A | 0.97 | 0.94 | N/A | 0.95 |
| # Valid Calibrations | 0 | 3 | 2 | 4 | 4 | 1 | 14 |
| Designation | S | | X | | | X | |

X: Use Clinical Judgment S: No Sensor Data C: No Calibration BG's

**Figure 2. iPro2 tracing of a patient whose glucose levels were high from 6:00 PM to 11:PM post-supper and low from 12:00 AM to 2AM.**

**Ambulatory Glucose Profile**

The ambulatory glucose profile (AGP, Figure 3) is a standardized reporting format for glucose data that was developed by an expert panel of diabetes specialists and sponsored by the Helmsley Charitable Trust and is customized for insulin pumps or injection therapy.[12] The universal report is intended to simplify and facilitate interpretation of otherwise complex and lengthy reports with varying terminology. It is anticipated that a standardized report would "help clinicians develop expertise in CGM use, enhance quality of care through enhanced pattern recognition, improve practice efficiencies with minimal disruption of workflow, and engage patients, thereby reinforcing consistent use of CGM technology. The AGP is currently employed by many reporting systems and consists of 3 components:

1) Statistical Summary, which utilizes standard metrics and terminology to summarize the number of values, percentage of values and time in target, above target, and below target, as well as an assessment of glucose variability.
2) Modal day report which collapses data from days or weeks to a single day in order to identify patterns by time of day. Data are presented graphically as 5 distribution curves, representing the median, interquartile range, and $10^{th}$ to $90^{th}$ percentiles, on the backdrop of target range.
3) Daily View, which facilitates review of within day events.

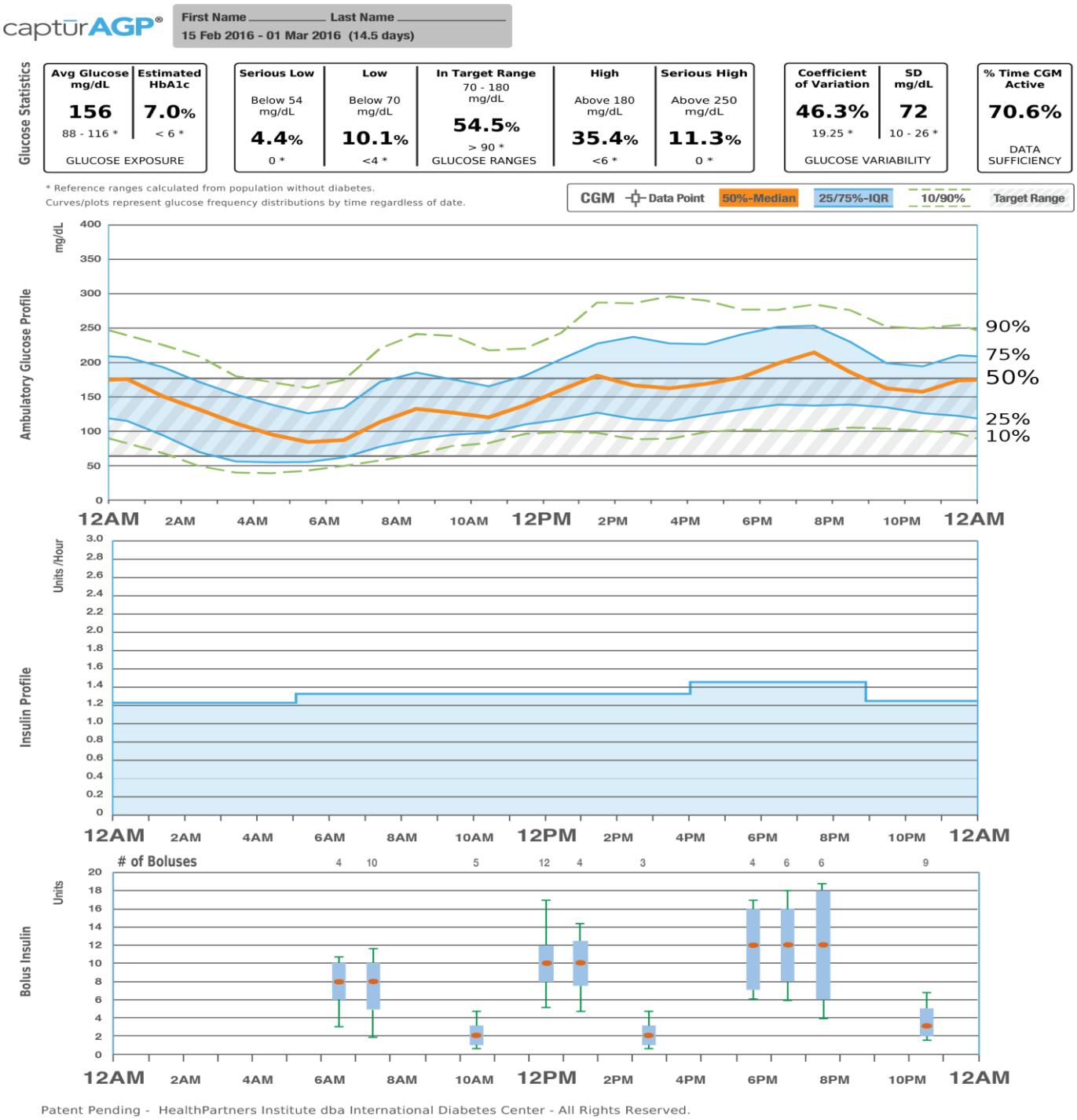





**Figure 3: Ambulatory Glucose Profile for Insulin Pumps**.

**Glucose Statistics:** Metrics include mean glucose, estimated A1C, glucose ranges, coefficient of variation and standard deviation.

**Glucose Profile:** Daily glucose profiles are combined to make a one day (24-hour) picture. Ideally, lines would stay within grey shaded area (target range)

**Orange:** median (middle) glucose line

**Blue:** area between blue lines shows 50% of the glucose values

**Green:** 10% of values are above (90% top line) and 10% are below (10% bottom line)

**Insulin Profile Graph:** Shows basal insulin pump settings over a 24-hour period

**Bolus Insulin Graph:** Combines all bolus insulin doses into one graph to make a one day (24-hour) picture. Each box on the graph covers 60 minutes of doses.

**Orange:** median (middle) dot

**Blue:** shaded box shows 50% of the bolus dosages in the hour

**Green:** lines above and below the shaded box (whiskers) show how many of the bolus dosages per hour were between 75 - 90% and between 10 - 25%

**PERSONAL (REAL-TIME) CONTINUOUS GLUCOSE MONITORING (RT-CGM)**

RT-CGM devices not only display the current glucose every few minutes, but may also alert the patient for impending (projected alert) or actual (threshold alert) hyperglycemia or hypoglycemia or rate of change in glucose. Over time, accuracy with RT-CGM has improved substantially.[13,14,15] In fact, two devices, the Dexcom and Freestyle Libre, are approved for stand-alone use, meaning that under specified conditions, the device may be used to make treatment decisions without confirmatory blood glucose measure. However, the user will still experience a tradeoff between a high alarm sensitivity and specificity for detecting hypoglycemic events, particularly where glucose levels are changing rapidly (Figure 4). Current and recent glucose levels, trend information, and a visual alarm are all presented so that a patient can predict future low or high glucose excursions (Figures 4-7). Using this information will allow the patient to take actions to spend more time in the euglycemic range and less time in the hypoglycemic or hyperglycemic ranges. This potential decrease in glycemic variability will not necessarily be reflected in an improved A1C value, which reflects mean glycemic levels.

| | High Sensitivity (Minimal false negative rate) | High Specificity (Minimal false positive rate) |
|---|---|---|
| **Advantages** | Safety will be maximized | Sleep and other activities will rarely be unnecessarily disturbed |
| **Disadvantages** | False alarms will be common | Some hypoglycemic events will be missed |

**Figure 4. Tradeoffs between emphasis on high sensitivity compared to emphasis on high specificity in a hypoglycemic alarm that is part of a continuous glucose monitor.**

**Evidence- Type 1 Diabetes**

Studies may be divided according to background therapies (insulin pump or injection therapy).

Studies utilizing either insulin pump or injections as background therapies

- The seven-country GuardControl Study was the first randomized controlled trial to ever demonstrate a statistically significant improvement in A1C levels with the use of RT-CGM. [16] The Guardian RT was used either continuously or biweekly for three months and both regimens were compared to control

treatment which did not include use of CGM. At one month and at three months the continuous users had significantly lower A1C levels than the controls. The biweekly users had intermediate improvement which did not reach statistical significance compared to the outcomes in the control group.

- In 2008, the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group evaluated 322 adults and children with type 1 diabetes (either injection or insulin pump therapy) and A1C 7-10% who were randomized to either RT-CGM or usual care.[17] RT-CGM was associated with a 0.53% reduction in A1C compared to usual care ($p<0.001$), but was only significant among subjects over age 24 due to lack of consistent use in younger patients. Hypoglycemia was infrequent and was no different between groups.
- In 2011, 120 children and adults with type 1 diabetes on insulin pump or injection therapy and A1C <7.5% were randomly assigned to RT-CGM (Freestyle Navigator—not available in the US) or masked CGM every other week.[18] The time spent in hypoglycemia was reduced over 50% at 26 weeks, and patients spent more time in 70-180 mg/dl range.
- In the IMPACT trial, 241 adults with type 1 diabetes with an A1C less than or equal to 7.5% were randomly assigned to Freestyle flash glucose monitoring (described in more detail under "Overview of Stand-Alone Personal CGM systems") vs. SMBG. In this group 68% of the patients were treated with multiple daily injections and 32% with CSII. The amount of time spent in hypoglycemia was decreased by nearly 90 minutes per day ($P<0.0001$) when patients had access to CGM data.[19] It must be noted that this technology does not provide real-time alerts for impending hypoglycemia or hyperglycemia and data are accessed via a hand-held device on demand. In a small study of patients with hypoglycemia unawareness or recent severe hypoglycemia, RT-CGM more effectively reduced the time spent in hypoglycemia compared to flash glucose monitoring.[20]

Studies utilizing insulin pump therapy as background

- In the largest study to date, the STAR3 study, 485 adults and children with A1C 7.4-9.5% were randomized to sensor-augmented pump therapy (Medtronic Paradigm Revel) or multiple daily injections per day.[21] Sensor-augmented pump therapy resulted in better A1C reduction with between-group difference of 0.6%, $p<0.001$. Hypoglycemia did not differ between groups, but only short-term CGM data were available for comparison and patients with a history of severe hypoglycemia were excluded.

Studies utilizing injection therapy as background

- In 2016, a 6-month randomized controlled trial, the DIAMOND study, compared RT-CGM (using Dexcom G4 system) versus SMBG in in 158 patients with type 1 diabetes on multi-dose injection therapy and demonstrated a significantly lower A1C (between group difference 0.6%, $p< 0.0001$), decrease in hypoglycemia (43 minutes vs. 80 minutes per day, $p=0.0002$) and less glucose variability with RT-CGM compared to SMBG. This study did not address hypoglycemia frequency in the two groups.[22]
- The GOLD trial studied 161 patients with type 1 diabetes receiving multiple daily injections with either RT-CGM (Dexcom G4) or standard care in a random order cross-over trial. The mean difference in A1C was 0.43% ($p<0.001$), favoring RT-CGM. One subject in the CGM group compared to 5 subjects in the standard care group experienced a severe hypoglycemic event. The percentage of time spent in hypoglycemia numerically favored the CGM group but statistical analyses were not presented. There was a significant reduction in standard deviation and MAGE (measures of glucose variability). Overall well-being, diabetes treatment satisfaction, and fear of hypoglycemia improved.[23]

A Cochrane review and another meta-analysis found modest A1c reductions, particularly among patients who were not using insulin pumps, patients under age 18, and among patients with lower adherence.[24] The results were heavily influenced by the STAR3 trial, and the JDRF study did not report a difference between pump users and patients using multiple dose injection therapy. Severe hypoglycemia rates did not differ. However, the quality of most studies was limited due to small sample size, lack of blinding, and lack of sufficient data to compare hypoglycemia rates. Meta-analyses may be hampered by the inclusion of studies with obsolete technology or lack of consideration for the intended use of the device in the study.[25,26] In another meta-analysis, studies that specifically enrolled patients at risk for hypoglycemia and used blinded CGM to assess it did show improvement in hypoglycemia.[27]

**Evidence- Patients with Hypoglycemia Unawareness**

Many older studies specifically excluded patients with a history of severe hypoglycemia or were underpowered to detect significant hypoglycemia. Two recent studies have examined the use of RT-CGM in patients with hypoglycemia unawareness, which is a risk factor for severe hypoglycemia (events requiring outside assistance to treat).

- In the HypoCOMPaSS trial, 96 patients with a history of hypoglycemia unawareness determined by the GOLD Score of at least 4 or more were randomly assigned in a 2x2 factorial design to insulin pump or injection therapy, both with access to a bolus insulin calculator, and either RT-CGM (Medtronic Continuous Glucose Monitoring System) or SMBG. All patients had diabetes education with a goal toward hypoglycemia avoidance. [28] The results demonstrated a similar reduction in severe hypoglycemia and improvement in hypoglycemia unawareness and fear of hypoglycemia without a significant treatment interaction between insulin or glucose monitoring interventions. Treatment satisfaction was higher with insulin pump compared to injection therapy but similar between RT-CGM and SMBG.
- The IN CONTROL trial evaluated patients with Type 1 diabetes and hypoglycemia unawareness receiving either injection or insulin pump therapy in a crossover study comparing RT-CTM (Medtronic Paradigm Veo system with a MiniLink transmitter and an Enlite glucose sensor) or SMBG.[29] Hypoglycemia was significantly reduced with RT-CGM compared to SMBG (including a 9.8% reduction in events <70 mg/dl and 44% reduction in events <40 mg/dl). Severe hypoglycemic events were significantly reduced but hypoglycemia unawareness was unchanged.

Differences between studies may be explained by differences in populations and the technologies utilized. In the In CONTROL study, contact with patients was less frequent, sensor use was greater (89 vs. 57% in HypoCOMPaSS) and there were no insulin adjustment protocols. Therefore, more studies are needed to understand the potential role of background therapy, other technologies, and clinical support.

**Evidence- Patient Reported Outcomes**

Generic Quality of life scores generally do not improve with RT-CGM but treatment-specific measures, such as diabetes distress, hypoglycemic confidence, fear of hypoglycemia and to a lesser extent, measures of convenience, efficacy and performance, may be improved.[22,30,31]

**Evidence- Type 2 Diabetes**

In patients with type 2 diabetes, even in patients not on insulin, RT-CGM may act as a motivator and positive influence for patients to improve lifestyle. The change in behavior can potentially lead to better glycemic control.[32]

- In 2012, Vigersky et al. randomized 100 patients with type 2 diabetes on basal insulin and anti-hyperglycemic agents into either a group that used real-time RT-CGM intermittently (2 weeks on, 1 week off) or a group that recorded SMBG four times per day for 12 weeks. At 12 weeks, they found a statistically significantly greater 1.0% reduction in A1c in the CGM group compared to 0.5% reduction in the SMBG group. The effect persisted up to the 40-week follow-up, 0.8% and 0.5% reduction in A1c in the RT-CGM versus SMBG group respectively.[33]
- In 2017, Beck et al conducted a randomized study to study benefit of RT-CGM use in 158 patients with type 2 diabetes with mean A1C of 8.5% treated using multiple daily injections.[34] Over a 24-week period the A1C decreased to 7.7% in the RT-CGM group compared to 8% in the group with usual care (mean difference -0.3%, p=0.022). RT-CGM derived hypoglycemia and quality of life did not differ.

**Recommendations**

Patients should be adequately informed of the benefits and importantly the limitations of this technology, particularly with respect to the role for SMBG. At a minimum, structured education programs encompassing concepts such as carbohydrate counting and active insulin time (insulin on board) should be completed prior to considering RT-CGM, and patients should demonstrate that they can reliably and consistently perform SMBG.[35] Several expert groups have issued guidance in the use of RT-CGM.

- In 2016, the Endocrine Society, co-sponsored by The American Association for Clinical Chemistry, the American Association of Diabetes Educators, and the European Society of Endocrinology, published guidelines for use of insulin pumps and CGM. The guidelines recommended RT-CGM in adults with type 1 diabetes and any A1C who are willing and able to use the devices nearly daily. The panel suggested short-term intermittent use for patients with type 2 diabetes (not requiring prandial insulin) who had an A1C ≥7% and are willing and able to use the device.[4] This recommendation stems from data from the RCT conducted by Vigersky, discussed in the Evidence section above.
- The American Diabetes Association (ADA) Standards of Care recommend CGM in adults with type 1 diabetes and those with hypoglycemia unawareness or frequent hypoglycemia. The guidelines specifically recommend that patients who are older than age 65 continue to have access to CGM. Among pediatric patients, the ADA notes that CGM may reduce missed school days with regular usage.[1]
- The 2016 American Association of Clinical Endocrinologists recommendations for use include all adults and children with type 1 diabetes, especially those with severe hypoglycemia or hypoglycemia unawareness, and all patients with type 2 diabetes on multiple insulin injections, basal insulin, or sulfonylureas who are at risk for hypoglycemia.[2]
- In 2017, the Advanced Technologies & Treatments for Diabetes (ATTD) Congress organized an international consensus panel, consisting of physicians, researchers, and individuals with diabetes to analyze the existing literature and to provide guidance for utilizing, interpreting, and reporting CGM data.[36] The panel made recommendations in 7 key areas (Table 2).
- Also in 2017 the ADA and the European Association for the Study of Diabetes published a joint statement providing recommendations for systematic improvements in clinical use and regulatory handling of CGM devices.[37]
- In 2016, the Diabetes Technology Society sponsored a panel of experts in inpatient diabetes management to review the evidence for us of CGM in the hospital.[38] The panel agreed that CGM had the potential to improve clinical outcomes, particularly for patients who are unable to communicate signs or symptoms of hypoglycemia, but use is limited by lack of data demonstrating accuracy (particularly in the hypoglycemic range or in case of diabetic ketoacidosis, poor perfusion, or acetaminophen use) and clinical utility, and a lack of decision support systems, including

infrastructure for communicating results to care teams and to the electronic medical record. The panel agreed that patients who are admitted with personal CGM devices should be allowed to continue use of such devices under the condition that they are able to self-manage the devices on their own and are followed by an endocrinologist or experienced practitioner who is specifically trained in their use. In particular, the panel advised implementing institutional policies that recommend continued capillary or blood glucose monitoring and CGM calibration using the hospital (rather than the home) glucose meter, ensuring that CGM data are not used for inpatient insulin dosing (since no CGM device is FDA approved in the inpatient setting), and requiring patients to sign safety waivers which illustrate the potential risks and benefits of continued use. Devices must be removed for any MR or CT imaging.

**Table 2. Summary of ATTD Recommendations for CGM**

| | |
|---|---|
| Limitations of A1C | • CGM should be utilized when there is a discrepancy in A1C and other measures of glucose control<br>• CGM should be utilized to assess hypoglycemia and glucose variability |
| Guiding management and assessing outcomes | • CGM should be considered for patients with type 1 diabetes and insulin treated type 2 diabetes who are not achieving targets or those with hypoglycemia<br>• All patients should receive training education regarding how to interpret and respond to their data, utilizing standardized programs with follow-up |
| Performance | No accepted standard exists for CGM system performance. However, a mean absolute relative difference ≤10% provides little additional benefit for insulin dosing. |
| Definition and assessment of hypoglycemia | Clinical classification<br>• Level 1: 54-70 mg/dl with or without symptoms<br>• Level 2: <54 mg/dl with or without symptoms (clinically significant)<br>• Level 3: cognitive impairment requiring external assistance for recovery<br>Quantification using CGM<br>• % of values or time below a given threshold (54 or 70 mg/dl)<br>• Number of events (defined as CGM readings persistently below threshold for at least 15 min. with recovery defined as persistent readings over the threshold for at least 15 min.) over a given reporting period) |
| Glycemic Variability | Coefficient of Variation should be the primary measure |
| Time in Range | The % time in hyperglycemia, hypoglycemia, and target range should be reported. |
| CGM Metrics | • Standardized reporting using the AGP and integration into electronic health records is recommended.<br>• A minimum of 14 consecutive days with 70-80% of data overall is recommended for analysis.<br>• Key metrics: mean glucose, % time in range (level 1 & level 2 hypoglycemia, target, level 1 [>180 mg/dl] & level 2 [<250 mg/dl] hyperglycemia, CV, SD, eA1C, number of hypoglycemic and hyperglycemic episodes, area under the curve (research use), and risk (low blood glucose index, high blood glucose index)<br>• Metrics should be reported overall and by time of day, |

**Limitations of Use**

It should be emphasized that most prospective randomized controlled trials enroll highly motivated patients. In the case of the STAR3 trial, access to a computer was required. It is less clear whether RT-

CGM can be useful for patients in the real-world setting, where there are fewer resources for training, and less motivated patients may be overwhelmed with the additional data, particularly where complex algorithms in addition to existing smart pump features are required. Only 37% of patients in the Type 1 Diabetes Exchange Registry reported using RT-CGM in 2017.[39] While this has improved substantially over time, more than half of respondents cited cost or insurance coverage as a significant barrier to use. Modifiable reasons for avoiding use include the hassle of devices (47%) and aversion to having a device attached to the body (35%). In a multi-national study of 263 patients, persistent sensor use for 12 months was only 30%.[40] Improvement in A1C was associated with higher A1C at baseline, older age, and more frequent sensor use. However, diabetes related hospital admissions were reduced following the initiation of sensor augmented pump therapy and fear of hypoglycemia (measured with the Hypoglycemia Fear Survey) improved. In the 6-month follow-up phase of the JDRF-CGM trial, RT-CGM was initiated in the control group in a manner that more closely approximates clinical practice.[41] Investigators found a significant reduction in CGM use in all age groups over time. However, increasing sensor use was associated with A1C reduction.

**Daily Use**

Patients must be aware that sensor readings can deviate from actual blood glucose measurements, particularly during rapid glucose changes such as that which occurs post-meal or during exercise. Calibration, where necessary, should not be performed when trend arrows indicate rapid swings in glucose. While systems are becoming more reliable, patients should be instructed when to verify sensor readings before taking action such as meal boluses or treatment of hypoglycemia (varies by device). Alarm thresholds should be set in order to maximize patient compliance, keeping in mind that the sensitivity for detecting hypoglycemia drops dramatically as the threshold is reduced below 70 mg/dl.[42] Conversely, specificity improves to a much smaller degree at lower thresholds, and thus false alarms may not be reduced substantially.

Several algorithms have been published that provide specific guidance to patients for responding to trend arrows and alarms. In addition, several algorithms advise patients how to review downloads of the data periodically (weekly) and make adjustments.

- The algorithm by Jenkins et al. provides tiered recommendations that are based upon the meter glucose and sensor trend arrows.[43] Patients who were randomly assigned to sensor augmented pump with the algorithm had lower A1C and reported better quality of life at 16 weeks compared to patients who did not get the algorithm. The effect on quality of life persisted at the 32-week follow-up, and was associated with A1C reduction. Importantly, patients who received the algorithm at 16 weeks after initiating sensor augmented pump did not benefit.
- The DirecNet study algorithm (for use with the Navigator system) recommended that patients increase or decrease the meal + correction bolus by 10-20% based upon the rate of change and provided specific instructions for responding to alarms. [44] Algorithm use was high in the first 3 weeks but dropped off by week 13, despite increasing insulin self-adjustments, suggesting patients became more independent over time.
- Subsequent methods recommended adjustment of only the correction insulin dose by the amount needed to cover a glucose level that is incrementally higher or lower than the current glucose, based upon the trend arrow.[45,46] However, these methods generally require complex calculations which may be difficult for many patients, particularly for those who are not already using a bolus calculator.
- Klonoff and Kerr proposed a more straightforward correction dose (in 0.5 unit increments), based upon the trend arrow, which incorporates the patient's insulin sensitivity.[47]

- A consensus statement facilitated by the Endocrine Society was recently developed that provides expert guidance on the use of trend arrows for making treatment decisions.[48] The guidance recommends adjustment of boluses pre-meal and at least 4 hours post-meal in 0.5 unit increments based upon the trend arrow and the patient's sensitivity. These instructions are complex and are not integrated within bolus calculators of existing insulin pumps. Therefore, they should only be implemented in patients who have demonstrated an understanding of CGM technology, including lag times between CGM and BGM, calibration procedures, alerts and trend arrows, as well as a thorough understanding of insulin action time and the risks of insulin stacking. In the 4 hours following a meal, the statement recommends no treatment within 2 hours of a previous meal bolus, and corrective action otherwise. Corrective action should utilize the bolus calculator or usual correction dose in the presence of one or two up arrows or carbohydrate intake for diagonal, one, or two down arrows, based upon the current glucose level.

**Overview of Stand-alone Personal CGM and Flash Glucose Monitoring Systems**
**Guardian**

The first RT-CGM (Guardian, Medtronic$^{R}$) was approved in 2004. Since then, additional models and other devices have entered the market, and accuracy and patient satisfaction have improved. Several personal continuous glucose monitors have been approved by the US Food and Drug Administration (FDA) for use in the United States or carry CE marking for use in Europe and are currently on the market.

**Guardian RT**

The Guardian RT was approved in 2005 for patients over 18 years of age. The sensor and monitor are connected through a wireless transmitter and the monitor displays real-time glucose results every five minutes. The continuous data can be stored up to 21 days and downloaded any time into a computer. The data can then be reviewed with proprietary software provided by the manufacturer.

The original Guardian and Guardian RT devices contained a large transmitter piece and were used primarily for research. A smaller data transmission system, known as the Minilink, to send glucose information from the sensor to the belt-attached monitor, was approved in 2007. This component was immediately incorporated into the Guardian RT. Sensors are FDA approved for 72 hours of use. The monitor is similar in appearance to the Paradigm Revel sensor augmented pump (discussed below). However, it functions only as a CGM and not as a pump.

**Guardian Connect CGM**

The Guardian Connect utilizes the Medtronic Enlite sensor, the Guardian Connect transmitter, and the Guardian Connect app to transmit data via Bluetooth every 5 minutes to the user's smart phone or device (initially only available on iOS devices). Data can be shared with others remotely, and SMS messages can be sent in times of hypoglycemia. The system is not available in the U.S. but is being launched in select countries in Asia, Latin America, Europe and Australia.

**Dexcom G4 Platinum**

The Dexcom CGM utilizes a glucose oxidase sensor at the tip of a wire that is implanted in the subcutaneous space (Figure 5). The G4 sensor is inserted via a dedicated applicator by the user or clinician just under the skin where it is held in place by an adhesive to the skin. The transmitter is

snapped into a platform located on top of the sensor. The data are transmitted wirelessly and are displayed on a separate receiver. This device is FDA approved to provide glucose readings for 168 hours or 7 days. The device must be calibrated every 12 hours. Real-time data may be shared with up to 5 other individuals using the Dexcom Share app. The G4 works with a Windows based software called DexCom Studio or Dexcom Clarity Web-based data management software for retrospective downloading and analysis of glucose data. The G4 is compatible with the Animas Vibe and the T-slim G4 insulin pumps but at this time, it consists only of the integration of glucose values and alerts within the pump display and glucose values do not affect insulin delivery. Dexcom devices can also be operated in blinded mode for professional CGM applications (discussed above). The mean absolute relative difference for the Dexcom G4 has been reported to be 13% and the mean absolute difference in the hypoglycemia (<70 mg/dl) range was 11 mg/dl, which was a significant improvement over the previous generation.[28] In the REPLACE-BG Trial, patients with type 1 diabetes were randomly assigned to use of Dexcom G4 with (N=77) or without (N=148) confirmatory blood glucose monitoring.[49] Patients in the CGM only group used blood glucose monitoring only for calibration, sick days, acetaminophen use, blousing if the glucose was >250 mg/dl or fasting or persistent glucose >300 mg/dl. After 26 weeks, the % time in target range 70-180 mg/dl was 63% in the CGM only group and 65% in the CGM plus blood glucose monitoring. There was no difference in hypoglycemia, hyperglycemia, or A1C. There were no cases of diabetic ketoacidosis or severe hypoglycemia, though patients at high risk for these events were excluded from participation in the study.


**Figure 5. Dexcom G4 Platinum (clockwise) applicator containing a sensor ready for insertion, transmitter which will be attached to the sensor after insertion, and receiver.**

**Dexcom G5 Mobile**

The Dexcom G5 mobile provides increasing sensor accuracy and allows users to obtain glucose monitoring data and alerts directly via their smart device and share data with others via the Dexcom Share App. A fingerstick confirmation is not needed for making treatment decisions, except in situations in which the glucose is rapidly changing, or glucose value is unexpected and does not match the patient's symptoms. Like the G4, calibration is required every 12 hours and the device is inaccurate in the setting of acetaminophen use.

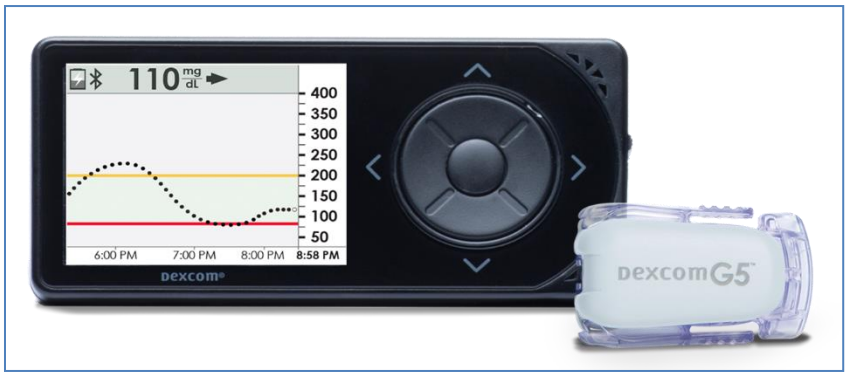


**Figure 6. Dexcom G5 System (transmitter shown with receiver. Data and alerts may alternatively be accessed using a smart device)**

**FreeStyle Libre**

The sensor utilizes Wired Enzyme ™ technology in which the enzyme and mediator are co-immobilized on the sensor. It is currently the only device that offers factory calibration, and therefore nearly eliminates the need for fingerstick monitoring. However, patients are still advised to perform SMBG whenever an alert appears on the reader display (which occurs when the glucose is rising or falling rapidly) or whenever the glucose value does not fit the patient's symptoms. The reader contains a built-in meter for this purpose. The sensor is FDA approved for 10 days of use. The system is not approved for use in children under age 18, or during pregnancy or in persons requiring hemodialysis. The Libre has minimized the interference by acetaminophen which is present in other devices but interference from other substances such as ascorbic acid or aspirin may be possible. The Libre also differs from other CGM devices in that the system does not alert the user for glucose values surpassing a high or low threshold. In addition, glucose values are not automatically made available to the user but are easily and instantly accessed by scanning the sensor with a handheld reader. However, the product may be attractive option for patients who are averse to the hassle imposed by other RT-CGM devices and SMBG only. Glucoses are measured every minute and recorded every 15 minutes. Data can be accessed using the reader or downloaded to LibreView cloud based online management system, or using the FreeStyle Libre desktop software. The MARD is reported by the manufacturer to be 9.7% overall, and as with other CGM devices, less accurate on day 1 of wear and in hypoglycemia range.[50]


**Figure 7. FreeStyle Libre continuous glucose monitor.**

**Eversense Implantable CGM**

The Eversense system (Senseonics) is a 90-day implantable sensor that uses fluorescent technology to send measures via a transmitter which rests just above the skin to a smartphone app. The system

received the CE mark and is under review at the FDA as of 2017.[51] The system is approved for adjunctive use, and thus may not replace SMBG.

**Sensor Augmented Pump**

To date the largest A1C reductions have been observed when sensors are initiated with insulin pump technology. In the observational (nonrandomized) COMISAIR study, patients initiating CGM (with or without insulin pump) achieved significantly larger reductions in A1C (-1.2%) compared to subjects initiating insulin pump alone (-0.6%) or remaining on injections alone (-0.3%).[52] There was no difference in outcomes between the DexCom G4 and Enlite sensor. A reduction in time spent in hypoglycemia was observed only in patients using CGM (8% vs 6%, p<0.001).

Currently, several sensor augmented insulin pump systems are available. The Minimed Paradigm REAL-time Revel sensor-augmented pump system (Medtronic Diabetes, Northridge, CA) utilizes the Guardian RT CGM and was the first such system to become available (Figure 8). In addition, Medtronic's mySentry device allows for remote monitoring of Minimed Paradigm RT-CGM up to 50 feet away and may have particular appeal for nighttime monitoring in children.[53] The other Medtronic systems with closed loop technologies are discussed in subsequent sections.

Other sensor and pump manufacturers have been in discussions or held agreements to develop and market sensor augmented pumps. The Animas Vibe features integrated Dexcom G4 Platinum CGM and but was discontinued by the manufacturer in 2017. Another system, the Tandom t:slim G4 insulin pump is available but does not interact with insulin administration. The t:slim X2 was FDA approved in 2017 and incorporates the Dexcom G5 CGM.

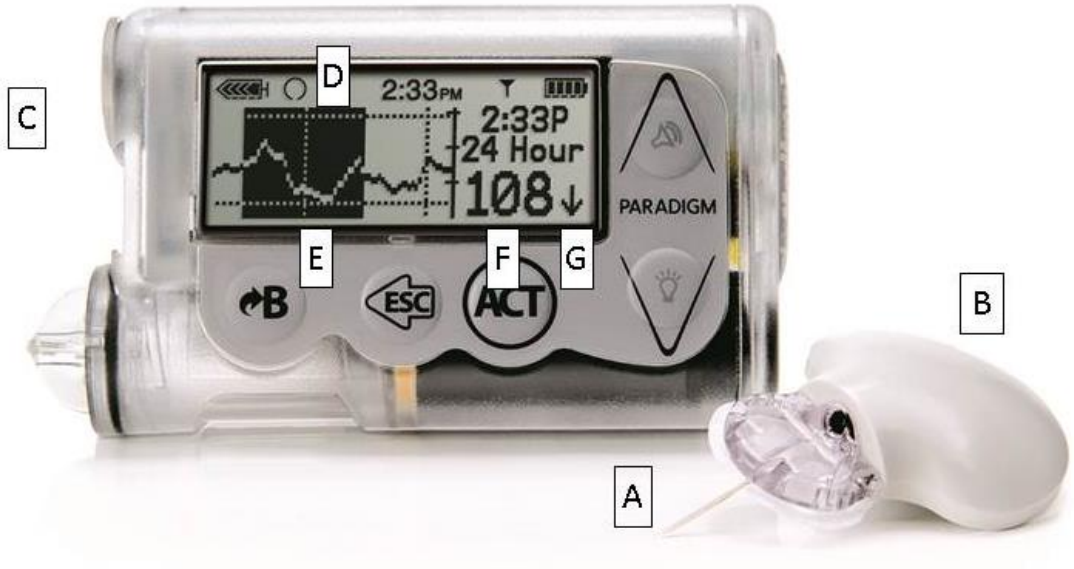



**Figure 8**. **The Paradigm sensor augmented pump** consisting of a sensor (A), which is attached to a Minilink transmitter (B) and communicating with an insulin infusion pump (C). Screen displays information about: (D) An alarm warning; (E) A trend graph portraying recent patterns of glycemia, (F) Glucose level, (G) Trend arrow for the direction and magnitude of trends in glycemia.

**STEPS TOWARDS AN ARTIFICIAL PANCREAS**

Until recently, RT-CGM technology has operated completely independently of insulin delivery. By combining continuous basal insulin delivery during fasting periods with discrete bolus doses of insulin at mealtimes, insulin delivery can be crafted to mimic the natural pattern of pancreatic insulin release. An artificial pancreas will consist of: 1) an automatic and continuous glucose monitor; 2) an implanted continuous insulin delivery system; 3) a control processor to link the insulin delivery rate to the glucose level; and 4) a radio to send the glucose level to the body surface for continuous display onto a monitor. Limitations to full implementation include sensor accuracy and lag time, inadequate onset and offset of currently available rapid acting insulin analogs, meal challenges, and changes in insulin sensitivity due to circadian rhythms, exercise, menstrual cycles, and intercurrent illness.[54] However, even incremental advances are likely to expand access of this technology to more patients since they may improve glucose control without increasing the complexity of decision-making on the part of the patient. The long-term safety, efficacy, cost, and cost-effectiveness of an artificial pancreas are still largely unknown at this time. However, the urgency of this technology cannot be emphasized enough, as demonstrated by the #WeAreNotWaiting movement, which has given rise to home-grown, crowd-sourced, patient driven systems that utilize existing devices which are linked by open-source software, such as Open Artificial Pancreas System, and Loop (for a recent blog entry, see http://www.diabettech.com/looping-a-guide/). None of these systems are FDA approved or even systematically studied, and therefore, carry obvious safety concerns, particularly among less tech-savvy patients.

**Threshold Suspend**

Progress is expected toward a fully functional closed loop system in incremental steps. The first step toward a fully automated “artificial pancreas”, the low glucose suspend feature, which is now available. The Medtronic 530G system, containing the Veo insulin pump and Enlite sensor, is the first sensor augmented pump with low threshold suspend and uses the same sensor as the more recent 630G system. The Enlite sensor accuracy is significantly improved over the previous Sof-sensor$^{R}$, with an MARD of 13.6% when used with the 530G.[55] The Enlite is also one-third of the size of Sof-sensor and the filament is 38% shorter. The Enlite sensor may be worn up to six days. The low threshold suspend SmartGard$^{TM}$ technology suspends the pump for up to two hours in the event of sensor detected hypoglycemia in which the user does not respond to the alarm. Prior to suspension, a “siren” sounds which is distinct from other high or low alerts, and the suspension can be overridden at any time. The MiniMed Connect mobile accessory sends sensor data to an app on a mobile device where data can be viewed (available only with the 530G system). A study that enrolled 247 patients with type 1 diabetes and documented nocturnal hypoglycemia to sensor-augmented pump with or without a low-glucose threshold-suspend feature demonstrated similar A1C between groups at 3 months but lower frequency of nocturnal hypoglycemia.[56] Similar findings were demonstrated in an Australian study of 95 patients, in which the incidence rate ratio for hypoglycemia was 3.6 (95% CI 1.7-7.5, $p<0.001$).[57] There were no reports of DKA in either study.

**Suspend Before Low**

The next incremental step in closed loop systems is the suspend before low feature, currently available in the Medtronic 640G (approved only in Europe) and the 670G systems. This feature automatically suspends insulin delivery 30 minutes before a low glucose threshold is predicted and resumes delivery once the glucose recovers, without alerting the patient.

**Hybrid Closed Loop**

This step refers to sensor glucose driven automatic adjustment of basal insulin, which still requires the patient to bolus for meals. The first system to gain FDA approval is the Medtronic 670G (Figure 9), which adjusts basal insulin delivery every 5 minutes when in auto mode. This system utilizes the Guardian sensor 3, which offers enhanced sensor accuracy, with an overall MARD of 9.64%.[58] The system was associated with a reduction in A1C from 7.4 to 6.9% and there were trends in improvement of time in target range and hypoglycemia in a non-randomized study of 124 patients with type 1 diabetes.[59] However, randomized studies are needed. T:slim (Tandem) is currently developing a similar device.


**Figure 9. The 670G Hybrid Closed Loop insulin delivery system** consisting of the Guardian sensor 3 (A), which is attached to a Guardian Link 3 transmitter (B) and communicating with an insulin infusion pump (C).

**Closed Loop Systems**

Additional steps toward closed loop control (CLC) insulin delivery require algorithmic insulin adjustments, which arguably present additional safety concerns. Overnight CLC insulin delivery is relatively straightforward, whereas post-meal control and exercise effects remain the most challenging of events to manage. Thus far, randomized studies have been small and reported only short-term outcomes, often in controlled settings. Systems have utilized single hormone (rapid acting insulin only) or dual hormone (both fast-acting insulin analog and glucagon to imitate normal physiology) as directed by a computer algorithm (Figure 10).[60] At this time, there are insufficient data demonstrating the superiority of one system or algorithm compared to others. A brief overview of recent studies is presented below.

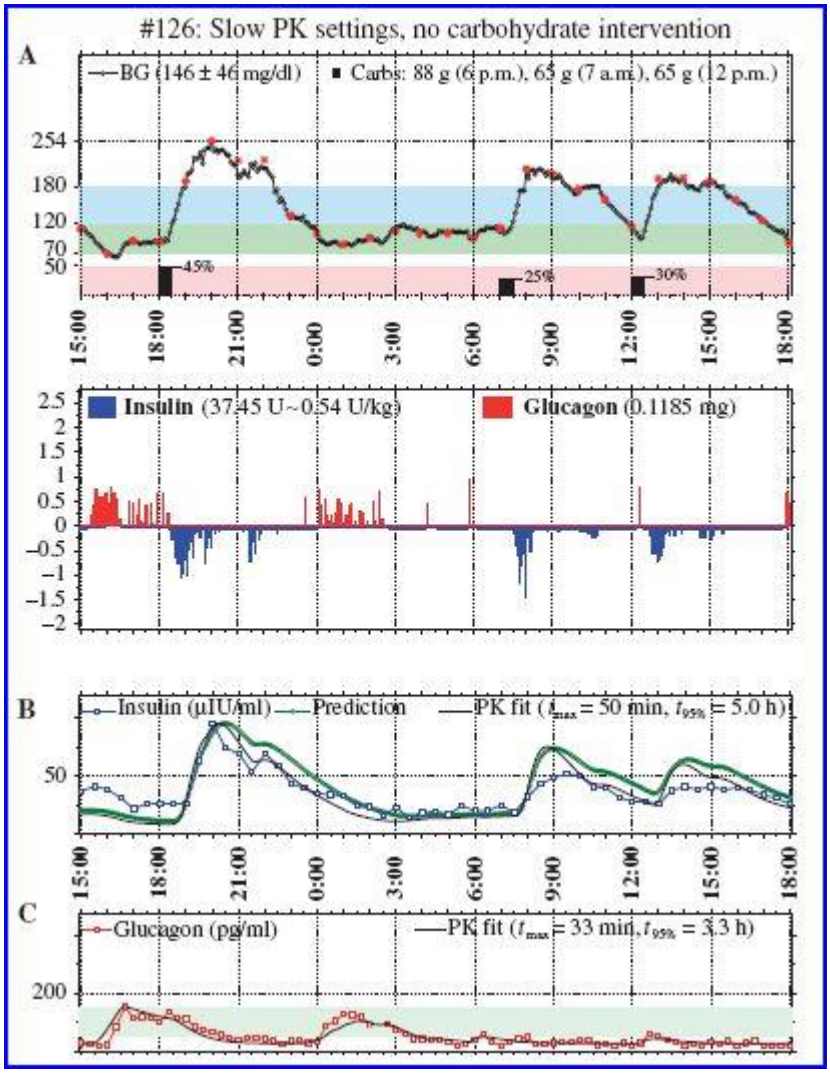



**Figure 10. Dual Hormone Closed Loop Control System.**

**Single Hormone CLC Systems**

- In one of the first randomized studies, 56 children and adolescents attending diabetes camps received sensor augmented pump or artificial pancreas (via fuzzy logic controller) on two separate nights in random order.[61] The artificial pancreas demonstrated markedly reduced hypoglycemic events (7 vs. 22 events in the artificial pancreas compared to the sensor augmented pump, p=0.003) and time in hypoglycemia, as well as better overall mean glucose and glycemic variability.
- In another study, 32 adolescents with type 1 diabetes attending a 5-day ski camp were randomized to CLC or remotely monitored sensor-augmented pump. In the CLC group time in range increased by 7% (1 hour and 40 minutes per day) when compared to the sensor-augmented pump group. At the beginner ski level, percent time spent in blood glucose <70mg/dl decreased by almost 50% but this was not observed in the advanced ski level, possibly due to more experience with prevention and management of hypoglycemia.[62]
- In a cross-over study of 40 patients with type 1 diabetes, there was a statistically significant increase in percentage of time in range with CLC when compared to sensor augmented pump over 24 hours, 78.3% vs 71.4% respectively during the day and 85.7% vs 67.6% overnight. The CLC group spent a lower percentage of time in low glucose range of less than 70mg/dl when

compared to the sensor augmented pump group, 2.5% vs 4.3% respectively with p-value=0.002.[63]

**Dual Hormone Control**

- In 2014, Russell et al conducted a random order cross-over study to evaluate glycemic control with a dual hormone (glucagon and insulin) CLC system compared to CSII in 32 adolescents and 20 adults with type 1 diabetes in a real-world outpatient setting. Over 5-days of use they noted a statistically significant reduction in mean sensor glucose from 158 mg/dl to 142 mg/dl and from 159 mg/dl to 133 mg/dl in adolescents and adults respectively. The percentage of time spent in glucose <70mg/dl was lower and statistically significant in the adults (7.3 vs. 4.1%, p=0.01), but did not reach statistical significance in adolescents with dual hormone CLC (4.9 vs. 3.1%, p=0.05).[64]
- The same group further evaluated whether an adaptive meal-priming insulin bolus that automatically adjusts the size of breakfast, lunch, and dinner doses by delivering 75% of the average prandial insulin provided for previous meals at that time of day improved glucose control compared to no meal announcement during dual hormone CLC system. Among 12 adults and 12 adolescents with type 1 diabetes, using only weight as the initial input, adaptive meal time boluses resulted in improved mean glucose without increasing time spent with glucose <60mg/dl.[65]
- In 2016, Haidar et al performed a 3-arm random order crossover study among 21 adults and 7 adolescents with type 1 diabetes comparing dual hormone CLC, single hormone CLC, or insulin pump on overnight glucose control following a high fat, high carb meal or exercise the previous evening.[66] The percentage of time spent in target range (70-180 mg/dl) was 81, 76, and 47% in the dual hormone, single hormone, and insulin pump (p<0.001 for each CLC system vs. sensor augmented pump alone). The percentage of time below 72 mg/dl was 5, 1, and 14% in the respective groups and was significantly lower for both CLC groups vs. conventional therapy.[67] However, in a subsequent study, the dual hormone system resulted in significantly less hypoglycemia than a single hormone system.[68]
- In 2017 this group further evaluated the impact of dual-hormone artificial pancreas on risk of hypoglycemia when compared to single hormone artificial pancreas in 23 adult patients with type 1 diabetes in an outpatient real world setting for 60 hours.[69] They noted a median difference of -2.3% between the dual and single hormone system for time spent below 4 mmol/L (72mg/dl) and a median difference of -1.3% between the two groups for time spent below BG of 3.5 mmol/L (63mg/dl). Although they noted numerically less risk of hypoglycemia with the dual hormone system, the results were not statistically significant. Both systems were superior to sensor augmented pump therapy in terms of percentage of time spent in hypoglycemia.
- Russell and colleagues recently performed an 11-day random-order cross-over study among 43 subjects with type 1 diabetes under free living conditions. The mean glucose was 140 vs. 162 mg/dl during dual hormone CLC vs. control periods (p<0.0001) and the time spent <60 mg/dl was reduced (0·6% versus 1·9%, p<0.0001).[70]

**FUTURE MINIMALLY INVASIVE CONTINUOUS GLUCOSE MONITORS**

Continuous hypoglycemia detection systems using current sensing technology must be either implanted (subcutaneously or into a blood vessel), or else wrapped around or attached to the body. Implantation is more secure, but may be associated with biocompatibility problems or local irritation. Wrapping around or attaching a monitor to the body avoids biocompatibility problems, but may be uncomfortable or inconvenient due to being constantly tethered to a device. Few devices (other than some interstitial

CGMs discussed above) have demonstrated high levels of accuracy recommended by expert groups, though several have been approved by CE or FDA.[71]

Methods for harvesting interstitial fluid from the body to measure with an external non-implanted sensor are being developed that disrupt the skin barrier and trap the fluid that rises to the surface (reverse iontophoresis). GlucoWatch G2 Biographer ("GlucoWatch") (formerly Cygnus, Inc., Redwood City, CA) is one such device which extracted glucose from the skin electrochemically but was taken off the market in 2007. In one study, only 20% of participants were still using the device at 18 months.[72] The device suffered from inaccuracy, and 49% of wearers reported skin reactions as the reason for discontinuation. Another device (Sugar BEAT, Nemaura Medical), consists of a patch on the abdomen or extremity that passes a small electric current through the skin to draw a measurable amount of interstitial fluid and was CE approved in 2016.

**Noninvasive Glucose Monitoring**

No monitor is currently approved by the FDA to measure blood glucose noninvasively. Methods utilizing near infrared, impedance, occlusion, Raman or radio wave spectroscopy on the wrist, finger, abdomen, or earlobe are completely noninvasive, but suffer from accuracy problems and none are currently available, though several methods were CE approved in the past.[71]

Devices under development can be classified as taking a measurement either intermittently or continuously. A large device that is not portable would have to be utilized on an intermittent basis, whereas a small monitoring device would have the potential to be wrapped around a body appendage or the waist to make continuous noninvasive readings. Noninvasive glucose monitoring depends either upon on the application of optical energy into tissue followed by measurement of the interaction of the optical energy with glucose in the intravascular, interstitial fluid, and intracellular compartments, or else measurement of a physiologic phenomenon which is proportionate to the blood glucose level. The optical energy is typically applied to an appendage, such as a fingertip, an earlobe, or a forearm.

Noninvasive testing using infrared light spectroscopy to measure reflection of infrared light from the skin in proportion to the glucose concentration must distinguish the signal of water (which is very large) from that of glucose (which is much smaller), as well as other potential interferents in the skin. Interest has been expressed in applying optical energy to the buccal mucosa within the mouth because this region contains no stratum corneum, the outermost dead layer of skin, to absorb the optical energy. In addition, the anterior chamber of the eye has been studied with various types of optical energy. Applications of light that interacts with ocular glucose must be carefully constructed to avoid excessive energy transmission and damage to the eyes. Optical measurement of glucose will avoid the problem of confounding analytes whose chemical properties resemble those of glucose. However, other analytes that are not a problem for existing invasive monitors can be confounding if their optical properties overlap those of glucose.

The GlucoTrack (Integrity Applications Ltd.) utilizes noninvasive ultrasonic, electromagnetic, and thermal methods to detect glucose-related shifts in earlobe tissue. The device is commercially available and CE approved, but accuracy remains a limiting factor with a MARD of only 22.8%.[73]

A high-profile example of noninvasive glucose monitoring is Google's smart contact lens, which contains a tiny microchip, glucose sensor, and antenna embedded in its periphery, but as of 2017, still had not begun clinical trials.[74]

Another novel approach is the estimation of glucose from analysis of acetone and other metabolites in the breath, a process that would potentially bypass the interfering effects of skin components and microcirculation present with other methods.[75]

## MOBILE TECHNOLOGY AND DECISION SUPPORT

It has become increasingly clear that the isolated use of glucose monitoring technologies without a plan for using the data provides minimal benefit, particularly among patients with type 2 diabetes or who are not using insulin.[76] In order for glucose monitoring to provide the most benefit, patients and providers must be able to easily obtain and communicate the data, data must be organized in such a way that patterns can be identified, and patients must receive feedback at the point of care. The widespread use of mobile devices provides opportunities for data collection, analysis, and communication of results with health care providers and caregivers. The demand for this capability is illustrated by recent patient driven efforts, such as the Nightscout Project, which provides a free mobile technology platform for patients who want to access their CGM devices in real time on any mobile device.[77] The project has raised concerns about safety, legal liability in a crowd sourced environment, and regulatory challenges since the code is not FDA regulated. Finally, as healthcare providers are inundated with more data and spend increasing amounts of time using electronic medical records, it has also become paramount that devices and or reports from the devices communicate or interface with these systems.

Hurdles to wider implementation of mobile technology include the lack of usability (both for patients, as well as providers who may be expected to review and act upon reports), safety, efficacy (including long-term adherence), and cost-effectiveness studies.[78] The lack of data is in part due to the rapidly changing technology itself, which renders the technology obsolete by the time a vigorous clinical trial is conducted and published. The fee for service model is a major barrier to adapting many glucose monitoring technologies, which often require frequent feedback and treatment adjustments, efforts that are not reimbursed without an actual office visit. Finally, cyber security is a big concern for all medical devices, especially for devices that are controlled by a smartphone. [79]

### Device Downloading and Connectivity

Manual recording of glucose data is fraught with inaccuracies.[80] Most meters can be downloaded, usually via a tethering cable or wireless connection, either by the patient or healthcare provider. Each glucose monitoring device generally works with its own proprietary management software. However, several programs (Tidepool, Glooko/Diasend, Carelink) are capable of downloading and organizing data for multiple different devices.[81] Reports are then standardized across all device downloads, facilitating efficient and actionable patient and healthcare provider review. These programs also facilitate population health and telehealth strategies (discussed below).

In actuality, a minority of patients with type 1 diabetes download and review their own glucose monitoring data, and few download routinely.[82] In the Type 1 Diabetes Exchange Registry, 65% never download their meter, and only 12% download at least monthly.[83] There are few data among patients with type 2 diabetes, but there is no reason to believe that the frequency is any better. Direct connectivity of blood glucose or CGM levels to cell phones or other devices not only improves data integrity but may also simplify the assimilation of glucose levels with other data such as insulin use, carbohydrate intake and activity levels for the purpose of facilitating insulin dose adjustments in real time or retrospectively. Cell phone connectivity may also improve communication with providers. A few meters with direct cellular capability are now available. Miniaturized glucometers that directly plug into a smart phone also allow

users to consolidate devices. Devices with direct cellular or Bluetooth connections may be paired with apps that facilitate collection, communication, and analysis of a variety of data and provide tools for education (such as nutrition information) at the point of care.

**Diabetes Apps**

A variety of stand-alone smart phone applications that support SMBG are also available. Most incorporate SMBG data that needs to be manually entered, some allow insulin or carbohydrate documentation, track activity and provide diabetes education, and a few provide an insulin dosing calculator. However, most of them do not connect directly with a glucose meter, and most have not been evaluated by the FDA or other regulatory agencies. Data privacy is also a concern, as no federal regulations currently prevent app developers from disclosing data to third parties. Most apps (81% in one survey of Android apps) do not have privacy policies, and of those that do, 49% share user data with third parties.[84] Expert groups have recently developed policy or guidance statements that may lead to standardization and increased functionality.[85,86]

**Efficacy**

While the data are still evolving with respect to mobile diabetes applications, several systematic reviews and meta-analyses are available. In 2016, Hou and colleagues conducted a meta-analysis of 14 randomized controlled trials among patients with type 2 diabetes.[87] There were insufficient data to analyze type 1 diabetes studies. The reported mean reduction in A1C was 0.49% (95% CI 0.30-0.68), with moderate grade evidence. Effect size was larger in younger patients and those with healthcare provider feedback. A similar, modest reduction in A1C was also reported in other meta-analyses.[88,89] Efficacy is variable, in part because app features vary but also because apps are often studied as part of a multi-component intervention, making it difficult to assess individual elements.

In another meta-analysis, investigators developed a taxonomy system to classify apps in order to facilitate understanding of the contribution of individual functions to outcomes.[90] Functions were classified according to functional (technical) characteristics (log, structured display, education, personalized feedback, and communication) and clinical features (glucose monitoring, medication management, lifestyle modification, complication prevention, and psychosocial care). A separate risk axis was specified based upon whether the app provided communication or administrative functions (low risk), health management (decision support and medication management—potential risk), or medical device interface (high risk). All 12 apps included glucose a monitoring function. Three apps were classified as high risk. The mean A1C reduction was 0.48% (95% CI 0.19-0.77) across studies, but was limited to patients with type 2 diabetes and the overall quality of evidence was low. A1C reduction was greater when the intervention included a complication prevention module, a structured display, no clinical decision making function, and wireless (vs manual) entry. The quality of evidence for severe hypoglycemia was low.

**Usability**

In a systematic review of 20 studies, only one third of the 20 apps met the authors' health literacy standards.[91] Usability was measured in 7 studies through satisfaction surveys from patients and experts, and ranged from 38-80%. The most common usability problems were multi-step tasks, limited functionality, and poor system navigation.

Recently, a Mobile App Rating Scale was utilized to assess the top free (without subscription), patient directed, English language apps in iTunes and Google Play for “diabetes” and “diabetes management”.[92] Most apps were rated by 3 reviewers to be high quality for a single task but only 4/89 apps integrated all diabetes management tasks (physical activity, nutrition, blood glucose monitoring, medication usage, health feedback, and education). The top scoring apps were Tactio Health: My Connected Health Logbook, and ACCU-CHEK 360 Diabetes Mgmt).

In a similar approach, Brzan and colleagues evaluated 65 freely available apps assessed by 3 expert reviewers for published criteria promoting diabetes self-management (SMBG, medication, nutrition, exercise, weight). Most apps (56/65) did not meet minimal requirements or did not function properly. Only 9 apps were determined to be versatile and useful for diabetes self-management.[93]

**Decision Support**

The use of pattern management software improves health care provider efficiency and accuracy in identifying needed therapeutic adjustments.[94,95] Software programs provide graphs or charts and may in some cases provide dosing advice, either for the healthcare provider or directly to the patient.

**Insulin Dosing Calculators**

Insulin dosing calculators have been used for years as a means of incorporating glucose measures into routine practice. Previously, only calculators that interface with continuous insulin infusion pumps were approved by the FDA, although calculators that interface with a glucometer (either within the device or through the use of a connected app) have become available. Bolus calculators are known to substantially improve dosing accuracy and glycemic control in outpatients with type 1 diabetes.[96,97,98] Subjects with diabetes feel more confident using the calculator and prefer it to manual calculations of insulin doses. Bolus calculators might be particularly helpful for patients with poor numeracy. A number of stand-alone smart-phone apps for bolus insulin calculation have been developed but as noted above, their safety and efficacy remains a concern.[99,100] Therefore, only evidence based applications with regulatory approval should be used. A review of several approved systems is presented here.

Bolus Calculators

- The Accuchek Aviva Expert system was a stand-alone glucose meter with a built-in bolus calculator that was recently discontinued by Roche and replaced by an Accu-Chek Connect meter that wirelessly transmits data to a smartphone app or web portal with a built-in FDA approved bolus calculator. The Bolus Insulin Advisor needs to be set up by the health care provider. The app also provides the ability to share data with others via automatic SMS messaging as well as with healthcare professionals via an online portal.[101] The Accu-Chek 360 View software can be used to view and process glucose, carbohydrate, and insulin doses to inform management decisions. The 26 week Accu-Chek Bolus Advisor Control and Usability Study (ABACUS) randomly assigned over 200 patients with diabetes to use of the bolus calculator or usual care.[102] Patients using the bolus advisor were more likely than controls to achieve >0.5% A1c reduction (56 vs. 34%, $p<0.01$).
- Another device, the Freestyle InsuLinx system (Abbott) has a touchscreen interface and contains a bolus calculator that is available in fixed meal or flexible meal dosing modes.[103] The bolus calculator incorporates correction dosing as well as an active insulin time. The bolus calculator is only available outside of the U.S., but a simplified version without the bolus advisor, which allows

the patient to record insulin and glucose data is FDA approved. There is an online portal FreeStyle Auto-Assist DM, for health care professionals to access and process data.

- The Dario (LabStyle Innovations) meter is a small glucose monitoring device that directly plugs into a smart phone, where glucose data is stored in the cloud via an app.[104] The app provides access to an insulin bolus calculator and carbohydrate counting tool and facilitates real-time data sharing with family and caregivers. The system will also send a text message plus GPS coordinates to designated individuals in the event of hypoglycemia. There are no published efficacy studies but the device has been FDA and CE approved.

Insulin Titration Calculators

More recently insulin dosing calculators have been approved to recommend ongoing adjustments in therapy. Unfortunately, efficacy and safety studies are not currently available for most apps. However, the following are approved by the FDA or in Europe.

- The Diabetes Insulin Guidance System (Hygieia) uses a d-Nav glucose monitor with built-in insulin dosing calculator that is set up by the healthcare provider to titrate the insulin doses based upon historical glucose values and insulin doses. The system is approved in Europe but not the US. Efficacy has only been demonstrated with a single observational study, in which users demonstrated a reduction in A1C and hypoglycemia compared to baseline.[105]
- My Dose Coach (Sanofi Aventis) is an app that was FDA cleared in 2017 to optimize basal insulin dosing.[106] The healthcare provider sets up the individualized dose plan on a separate provider portal and the user activates the app with a verification code, received via text message.
- Insulia (Voluntis, in partnership with Sanofi and Livongo) is a software management system with accompanying app available on a prescription basis. It was FDA approved for detemir and glargine U100 dose titration in 2016 and Glargine U300 dosing in 2017 and is also CE approved.[107]
- Go Dose (Eli Lilly) is an app (patient version and Go Dose Pro for healthcare providers) for adjusting prandial lispro one meal at a time and was FDA approved in 2017. The app is only available by prescription.[108]
- Other tools are under development including a partnership between Livongo and Glytec, and Glooko.[109]

**Integrated Telemedicine Approaches**

Integrated telemedicine approaches have received increasing attention as a means of providing cost-effective care.[110,111,112] Some results of telemonitoring studies have been somewhat disappointing, perhaps due to delayed or infrequent feedback to patients.[113,114] Approaches in which real-time feedback is provided, such as through the use of text messages, have shown more promising results. In fact, the benefit from these approaches may not necessarily derive from adjustment of medications such as insulin, but from a combination of increased self-efficacy and motivation as a result of better patient-provider communication and support.[112]

The WellDoc system consists of patient coaching as well as provider clinical decision support. Patients view data via their mobile device through a web portal and receive automated text messaging responses that are tailored to the data. Diabetes educators or other providers may view the data and send supplemental feedback as well. In a 12 month cluster randomized trial of patients with type 2 diabetes, the system was shown to reduce A1c by 1.2% vs. usual care.[115]

The Diabeo system consists of smartphone software that serves as a bolus calculator, enables self-titration of insulin, and transmits data to health care providers.[116] In a 6-month randomized controlled trial of 180 patients with type 1 diabetes, the Diabeo system resulted in an A1c reduction of 0.91 and 0.67% when used with or without biweekly teleconsultation when compared to placebo.

Livongo In Touch is a cellular enabled color touchscreen platform with a built-in glucose meter that directly uploads data to the cloud, without a need for Wi-Fi, Blue-tooth, or tethering cables.[117] It provides immediate personalized feedback to the patient based upon glucose levels, tailored text messages, and access to certified diabetes educators in real time. A patient portal also allows for integration of data from multiple sources including third party nutrition and exercise apps. Providers can easily access dashboard reports for population and telehealth programs. Test strips are unlimited with a monthly service fee. The system is accredited by the American Association of Diabetes Educators and FDA approved, but no peer-reviewed efficacy studies are available.

Telcare is another cellular enabled glucose meter that automatically uploads glucose data to a cloud and can be shared with family and health care providers. Users receive automated personalized messages in response to specific glucose values and providers can also send custom messages in real-time. Data can be accessed with the Diabetes Pal app or through an online portal. In a pragmatic clinical trial of 450 non-insulin requiring patients with type 2 diabetes randomized to no SMBG, once daily SMBG, or Telcare system, there was no difference in A1C or quality of life among groups.[118] However, in a small nonrandomized study (presented at the 2016 American Diabetes Association Scientific Sessions) of patients with type 1 or type 2 diabetes receiving multiple daily injections of insulin, the system was associated with a reduction in A1C when paired with Glucommander Outpatient (Glytec). [119]

Glucommander Outpatient is an FDA approved glucose management and titration platform that analyzes glucose patterns and provides insulin titration advice to healthcare providers.

## BIOMARKERS OF GLYCEMIC CONTROL

### Hemoglobin A1c (A1C)

A1C is the best biomarker indicator of glycemic control over the past 2-3 months due to strong data predicting complications.[1,2] In addition, the American Diabetes Association has recommended its use for the diagnosis of diabetes.[1]

Hemoglobin A1c refers to the non-enzymatic addition of glucose to the N-terminal valine of the hemoglobin beta chain. Assays are based upon charge and structural differences between hemoglobin molecules.[120,121] Therefore, variants in hemoglobin molecules may lead to analytic interferences. It should be noted that some homozygous hemoglobin variants (HbC or HbD, or sickle cell disease) also alter erythrocyte life span and therefore, even if the assay does not show analytic interference, other methods of monitoring glycemia should be utilized, as HbA1c will be falsely low. Individual assay interferences are available at the National Glycohemohemoglobin Standardization Program website: www.ngsp.org/interf.asp.[122] Several commercial home monitoring kits are also available. [123] A brief summary of assay methods is described below.

- HPLC methods utilize the fact that glycated hemoglobin has a lower isoelectric point and migrates faster than other hemoglobin components. As such it has variable interference with hemoglobinopathies that alter the charge of the molecule (such as HbF and carbamylated Hb), but these may be revealed through individual inspection of the chromatograms.

- Boronate affinity methods are based upon glucose binding to m-aminophenylboronic acid and measures glycation on the N-terminal valine on the beta chain but also glycation at other sites. There is minimal interference from hemoglobinopathies but this assay is not widely available.
- Immunoassays make use of antibody binding to glucose and N-terminal amino acids on the beta chain and therefore may be affected by hemoglobinopathies with structural changes at these sites, including HbF but not HbE, HbD, or carbamylated Hb. Some newer assays have attempted to correct for these interferences.
- Enzymatic methods lyse whole blood, releasing glycated N-terminal valines which are detected using a chromoagenic reaction and are not affected by hemoglobin variants.

An Organization with links to governmental regulatory agencies, the National Glycohemoglobin Standardization Program (NGSP) (<http://www.ngsp.org/news.asp >), evaluates every laboratory and home test for A1C, sets accuracy standards, and certifies which methods meet their standards.[124] The trend in industry is for monitors to become increasingly more accurate and the trend in regulatory organizations is to require increasing accuracy for ongoing certification.

A1C is an analyte found within red blood cells, comprised of glycated Hemoglobin. The glycation gap (formerly known as the glycosylation gap) (GG), based on fructosamine measurement, and the Hemoglobin Glycation Index (HGI), based on mean blood glucose, are two indices of between-individual differences in glycated hemoglobin adjusted for glycemia. GG is the difference between the measured A1C test and the A1C test result predicted from serum fructosamine testing based on a population regression equation of A1C on fructosamine,[125] and HGI is the difference between the measured A1C test and A1C results predicted from the mean blood glucose level (calculated from self-monitored blood glucose tests) based on a population regression equation of A1C tests on mean blood glucose levels[126]. These two indices are consistent within an individual over time and reflect an inherent tendency for an individual's proteins to glycate.[127,128] Patients with high GG and HGI indices might have falsely high A1C test results and might also be at increased risk of basement membrane glycosylation and development of microvascular complications. Whether between-individual biological variation in Hemoglobin A1c is an independent risk factor, distinct from that attributable to mean blood glucose or fructosamine levels, for diabetic microvascular complications is controversial.[129]

Because the A1C test is supposed to reflect the mean level of glycemia, attempts have been made to correlate this widely-accepted measure with empirically measured mean blood glucose levels. In 2008, the A1c-Derived Average Glucose (ADAG) study compared HbA1c and continuous glucose monitoring derived mean glucose and 7-point glucose profiles among 507 patients with type 1 and type 2 diabetes and without diabetes from 10 international centers to derive an estimated average glucose (eAG) from A1C levels using the following equation: eAG(mg/dl)=(28.7*HbA1c)-46.7 (Table 3).

**Table 3. A1C and Estimated Average Glucose**

| A1C (%) | eAG (mg/dl) | eAG (mmol/l) |
|---|---|---|
| 5 | 97 | 5.4 |
| 6 | 126 | 7.0 |
| 7 | 154 | 8.6 |
| 8 | 183 | 10.2 |
| 9 | 212 | 11.8 |
| 10 | 240 | 13.4 |
| 11 | 269 | 14.9 |
| 12 | 298 | 16.5 |

Several lines of evidence support this disconnect from a tight correlation between mean glycemia and A1C levels. First, improvements in mean glycemia may not necessarily be reflected by improvements in A1C in intensively treated patients.[130] A1C does not reflect short-term changes in glucose control, and therefore can be misleading where there have been recent changes in the clinical condition. In addition, glucose fluctuations, compared to chronic sustained hyperglycemia, have been shown to exhibit a more specific triggering effect on oxidative stress and endothelial function. [131,132] Glycemic variability cannot be assessed by a global measure of mean glycemia, such as A1C, but requires multiple individual glucose values, such as what can be obtained from continuous glucose monitoring or from seven-point-per-day (or greater) self-glucose testing. Third, A1C does not permit specific adjustments in therapy, particularly among patients requiring insulin titration. Finally, A1C reliability may be affected by several conditions that alter red blood cell lifespan and its use in these circumstances can be misleading. A comparison of the features and limitations in glucose markers is presented in Table 4.[133,134,135]

**Table 4. Comparison of Markers of Glycemic Control**

| | Biomarker mechanism | Interval of time reflecting glucose control | Cautions/Interferences |
|---|---|---|---|
| A1C | Hemoglobin glycation | 3 months | Hemoglobinopathy (↓/↑*)<br>Decrease in RBC survival (hemolysis, splenomegaly, pregnancy, drugs) (↓)<br>Increase in RBC survival (Erthyropoietin, iron replacement) (↑)<br>Transfusion (↓) |
| Fructosamine | Protein glycation | 2 weeks | Conditions resulting in hypoproteinemia (severe cirrhosis, nephrotic syndrome, enteropathy) (↓)<br>High dose Vitamin C, severe hyperbilirubinemia/uremia/ hypertriglyceridemia (↑) |
| 1,5-AG | Renal clearance | 1 week | Chronic kidney disease (stage 4, 5) (↓)<br>Glucosuria (pregnancy, renal tubular disorders SGLT2 inhibitors) (↓)<br>Advanced cirrhosis (↓)<br>High soy diet (↑) |

*Assay-dependent

Ethnic differences in A1C have also been reported. [136] For example, recent data from the Type 1 Diabetes Exchange demonstrates a 0.4% higher A1C at a given mean glucose among black patients compared to white patients with type 1 diabetes.[137] However NHANES data do not demonstrate an effect of ethnicity on the association between A1C and retinopathy.[138] Data from the ARIC study demonstrated that A1C, fructosamine, glycated albumin, and 1,5-AG were consistent with hyperglycemia among blacks compared to whites, but the prognostic value for incident cardiovascular disease, end stage renal disease and retinopathy were similar by race.[139] It should be noted that the range of available A1C was relatively narrow in NHANES and ARIC, and further data across an expansive range is needed.

**Fructosamine**

A medium-term marker (defined as reflecting the average degree of control over the past few days or weeks) may be useful for determining control over a period of days to weeks since A1C does not reflect recent changes in glucose control. Alternate markers may also be useful in patients with discrepant A1C and self-monitored blood glucose readings as well as patients with other hematologic conditions known

to affect A1C. Fructosamine is a term that refers to a family of glycated serum proteins and this family is comprised primarily of albumen and to a lesser extent, globulins, and to an even lesser extent, other circulating serum proteins. No product exists for home use that measures serum fructosamine. A home blood fructosamine monitor, Duet Glucose Control System, was marketed in the early 2000′s and then withdrawn from the market. No subsequent home fructosamine test has been available since then. Randomized controlled trials have reported inconsistent effects of frequent monitoring on A1C lowering, possibly due to differences in execution of therapeutic interventions.[140,141]

**Glycated Albumin**

The largest constituent of fructosamine is glycated albumin. Several investigators and companies are developing portable assays for glycated albumin to assess overall control during periods of rapidly changing glucose levels. In these situations, an A1C test may change too slowly to capture a sudden increase or decrease in mean glycemia. The components of the necessary technology appear to be in place to build a commercial instrument for home testing of glycated albumin. Epinex received U.S. Discovery Grant funding to develop such a product (G1A™) in 2010 but it is not currently available or FDA approved. The biggest obstacle to adoption of this test into routine clinical practice will be the extensive amount of education that will be necessary to convince physicians to adopt it. Whether the cost of this massive education program can be recouped by product sales remains to be seen.

Furthermore, there is no randomized controlled trial showing that the measurement of glycated albumin improves outcomes, but cohort data are accumulating. In in the Atherosclerosis Risk in Communities (ARIC) study, fructosamine, glycated albumin, and 1,5-AG were associated with incident diabetes, even after adjustment for baseline A1C and fasting glucose. In the Atherosclerosis Risk in Communities (ARIC) study, both fructosamine and glycated albumin predicted incident retinopathy and nephropathy, even after adjusting for A1C.[142] In addition, baseline glycated albumin and fructosamine were associated with cardiovascular outcomes over a 20 year follow-up period after adjusting for other risk factors, but the overall magnitude of associations was similar to A1C.[143] In the DCCT, glycated albumin had a similar association with retinopathy and nephropathy as A1C, but the combination of both markers provided even better prediction.[144]

**1,5-Anhyroglucitol**

The aforementioned biomarkers for measuring glycemic control, (A1C, fructosamine, and glycated albumin) only reflect mean levels of glycemia. These measures can fail to portray hyperglycemic excursions if they are balanced by hypoglycemic excursions. Plasma 1,5-anhydroglucitol (1,5-AG) is a naturally occurring dietary monosaccharide, with a structure similar to that of glucose. (Figure 8) This analyte has been proposed as a marker for postprandial hyperglycemia.[145] An automated laboratory grade assay named Glycomark is approved in the U.S. for measuring 1,5-AG as a short-term marker for glycemic control. A similar laboratory assay has been used in Japan. During normoglycemia, 1,5-AG is maintained at constant steady-state levels because of a large body pool compared with the amount of intake and because this substance is metabolically inert. Normally, 1,5-AG is filtered and completely reabsorbed by the renal tubules. During acute hyperglycemia when the blood glucose levels exceed 180 mg/dl, which is the renal threshold for spilling glucose into the urine, serum 1,5-AG falls. This fall occurs due to competitive inhibition of renal tubular reabsorption by filtered glucose. The greater the amount of glucose in renal filtrate (due to hyperglycemia), the less 1, 5-AG is reabsorbed by the kidneys. The 1,5-AG levels respond sensitively and rapidly to rises in serum glucose and a fall in the serum level of this analyte can indicate transient elevations of serum glucose occurring over as short a period as a few days. Measurement of 1,5-AG can be useful in assessing the prior 1-2 weeks for: 1) the degree of

postprandial hyperglycemia; and 2) the mean short-term level of glycemia. This assay might prove useful in assessing the extent of glycemic variability that is present in an individual with a close-to-normal A1C level, but who is suspected to be alternating between frequent periods of hyperglycemia and hypoglycemia. In such a patient, the 1,5-AG level would be low, which would indicate frequent periods of hyperglycemia, whereas in a patient with little glycemic variability, the 1,5-AG levels would not be particularly depressed because of a lack of frequent hyperglycemic periods.

Longitudinal data from the ARIC study showed that 1,5-AG was associated with ESRD over a 19-year follow-up period, but the relationship was no longer significant after adjusting for glucose control with other markers.[146] Among participants with diabetes and A1C <7%, each 5 mcg/mL decrease in 1,5-AG was associated with an increase in dementia risk by 16%, and at A1C >7%, there was also a significant association over a median 21 year follow-up period.[147] There was also an association of 1,5-AG and cardiovascular outcomes in ARIC, which persisted, though were attenuated after adjusting for A1C.[148] Therefore, it is not yet clear whether 1,5-AG, as a measure of glucose excursions, provides incremental value beyond A1C for predicting long-term complications.

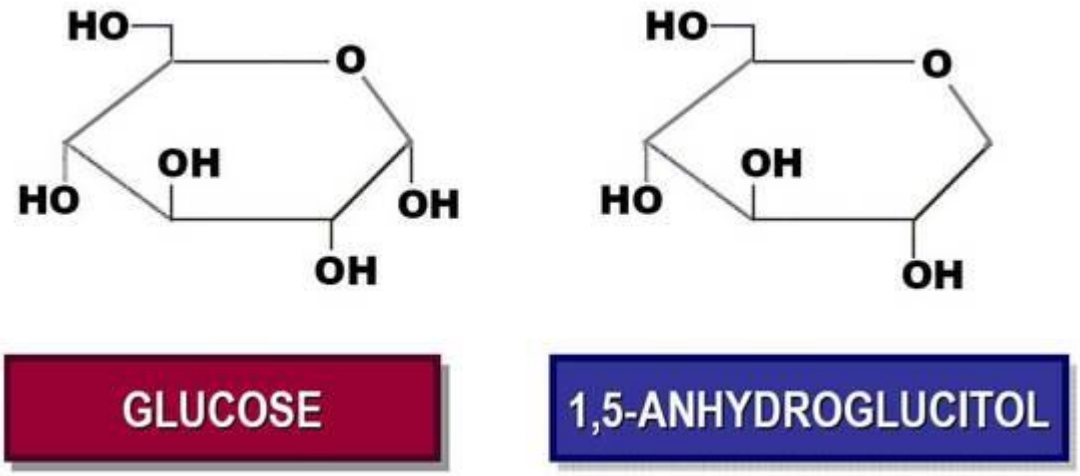



**Figure 11. Structure of glucose (left) and 1,5-anhydroglucitol (right)**

## CONCLUSIONS

Many new types of technology are increasingly being developed and applied to fight diabetes and its complications. New technologies will improve the lives of people with diabetes by measuring glucose and other biomarkers of glycemic control and linking glucose levels with insulin delivery to improve the lives of people with diabetes.

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