Meaningful Monitoring – an Integrative Approach: What glucose monitoring technology is most appropriate to use and how to implement it

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Meaningful Monitoring –
An Integrative Approach:
What glucose monitoring technology is most appropriate to use
and how to implement it by patient type

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Disclosures

• **Research:** Abbott, ACON, Ascensia, BD, Boehringer Ingelheim, Bristol Myers Squibb, Companion Medical, Dexcom, Elcelyx, Glysens, Insulet, Janssen, Lexicon, Lifescan, Lilly, Medtronic, Merck, Novo Nordisk, Sanofi, Senseonics, Versartis, Yofimeter

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• **Speaking:** Abbott, Insulet, Medtronic, Novo Nordisk, Sanofi
Definitions

- Integrative = “serving or intending to unify separate things”
- GM = Glucose Monitoring
- BGM = standard intermittent capillary monitoring (SMBG)
- CGM = continuous glucose monitoring
- Meaningful = “having a serious, important, or useful quality or purpose”
AACE/ACE Glucose Monitoring Consensus
Statement Objectives and Structure

This consensus statement provides recommendations to clinicians regarding the type and frequency of GM technology to be employed in the management of:

- T1DM (pediatric or adult)
- T2DM (with and without insulin therapy)
- Pregnancy complicated by preexisting diabetes or GDM

This statement also
- Provides a primer on GM accuracy
- Reviews measures of glycemic control (glucometrics)
- Presents graphical methods to display glycemic data

GDM = gestational diabetes mellitus; GM = glucose monitoring; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
Adult Patients With T1DM

- Frequent BGM is an essential element in effective T1DM management because it:
  - Detects glycemic variability and hypoglycemia
  - Informs treatment modifications and reflects the impact of food intake and physical activity
  - Provides important information on treatment efficacy

- All major clinical practice guidelines recommend individualized, frequent BGM for patients with T1DM

- CGM is particularly important for patients with a history of severe hypoglycemia or hypoglycemia unawareness

BGM = blood glucose monitoring; CGM = continuous glucose monitoring; T1DM = type 1 diabetes mellitus.

Pediatric Patients With T1DM

- Challenges of glycemic control in pediatric patients:
  - Changing insulin requirements
  - Unpredictable food intake and physical activity
  - Concerns about hypoglycemic risk
  - Close monitoring needed to recognize when the patient outgrows their insulin dose(s)¹

CGM should be considered for regular daily use in pediatric patients with T1DM who perform frequent blood glucose testing and have:²
- Severe hypoglycemic episodes
- Hypoglycemic unawareness (especially in young children)
- Nocturnal hypoglycemia
- Wide glucose excursions, regardless of A1C
- Suboptimal glycemic control, with A1C exceeding target range
- A1C levels <7%, to maintain target glycemic control while limiting hypoglycemia risk


T1DM = type 1 diabetes mellitus; A1C = glycated hemoglobin; CGM = continuous glucose monitoring.
Adult Patients With T2DM

- BGM should be individualized and accessible to all patients receiving any therapy for T2DM\(^1\)

**Patients receiving non-insulin agents associated with hypoglycemia:**
- Perform BGM at least once daily (fasting) and periodically at other times

**Patients at low risk for increased hypoglycemia risk and not at goal:**
- Perform structured testing (eg, before meals and at bedtime) at least weekly

- Limited data on the use of real-time CGM in patients with T2DM, although available evidence is promising\(^2-3\)
- Trials are ongoing to evaluate the potential use of CGM (masked or unmasked) in patients with T2DM

BGM = blood glucose monitoring; CGM = continuous glucose monitoring; T2DM = type 2 diabetes mellitus.

Adult Patients With T2DM

BGM is recommended for patients **not** taking insulin if\(^1\)\(^2\)

- Patients and/or caregivers have knowledge, skills, and willingness to incorporate BGM and therapeutic adjustments into diabetes care plan
- Patient is taking a medication with hypoglycemic potential (e.g. SU)

If the patient is on insulin therapy, BGM should be tailored by therapy type

- Patients taking prandial and basal insulin should perform BGM when fasting, premeal, at bedtime, and periodically during the night
- Patients taking only basal insulin (with or without other diabetes medications) should perform BGM at minimum when fasting and at bedtime

BGM = blood glucose monitoring; T2DM = type 2 diabetes mellitus.

Pregnancy Complicated by Diabetes

• BGM is integral to diabetes management in pregnancy
  — Real-time results enable women to make informed daily self-care decisions regarding diet, exercise, and insulin
  — Fasting and 1 hr post-prandial glucose are key
  — Retrospective analysis of BGM data helps to:
    • Enable clinicians to develop individualized care plans
    • Inform decisions related to insulin initiation and adjustment
    • Recognize the need for interventions to improve self-monitoring
• Potential benefit of CGM in pregnant women with preexisting diabetes is unclear

BGM = blood glucose monitoring; CGM = continuous glucose monitoring.

Pregnancy Complicated by Diabetes

GDM managed with MNT
- Check blood glucose levels 4 times per day:
  - Before breakfast (fasting) and after 3 largest meals of the day

Preexisting diabetes
- Before attempting to become pregnant, maintain glycemic control as close to normal as possible for 3 to 6 months

Diabetes managed with insulin
- Monitor glucose both before and 1 hour after each meal (ie, at least 6 times per day)

GDM = gestational diabetes mellitus; MNT = medical nutrition therapy.
Benefits and Drawbacks of CGM

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alerts patients to</td>
<td>Issues related to</td>
</tr>
<tr>
<td>• Episodes of hypoglycemia and hyperglycemia</td>
<td>• Accuracy</td>
</tr>
<tr>
<td>• <em>Predicted</em> episodes of hypoglycemia and hyperglycemia</td>
<td>• Comfort</td>
</tr>
<tr>
<td>Device displays help patients with clinical decision making</td>
<td>• Convenience</td>
</tr>
<tr>
<td></td>
<td>• Patient acceptance</td>
</tr>
<tr>
<td></td>
<td>• Expense</td>
</tr>
<tr>
<td></td>
<td>Most devices require frequent calibration</td>
</tr>
</tbody>
</table>

CGM = continuous glucose monitoring.
Glucose Monitoring Accuracy and Precision

- Accuracy is defined as the closeness of agreement between a glucose test result and an accepted reference value
  - Accuracy improves when it has minimal bias and relative error (%CV, MARD, and minimal absolute error)
  - Point accuracy refers to blood glucose values and sensor readings at single points in time

- Precision: measurement reproducibility (irrespective of accuracy)
  - It is possible to derive a measure of precision without knowing the true value

- Bias: systematic error in meter or sensor measurements
  - Measurements may cluster around an erroneous value
  - May be due to improper calibration, lack of calibration, or calibration with an inaccurate BGM

BGM = blood glucose monitoring; CV = coefficient of variation; MARD = mean absolute relative deviation.
Understanding Clinical Standards for Accuracy of BGMs and CGMs: Error Grids

- The Parkes Error Grid (2000) is one way to measure accuracy.
- Grid regions reflect the potential risk severity of incorrect treatment triggered by the measurement error.
- Device performance typically reported as percentage of glucose values in zone A or zones A + B (higher percentages indicate better performance).

BGM = blood glucose monitor; CGM = continuous glucose monitor.

Measures of Accuracy for BGM and CGM

- **Arithmetic deviation**
  - The difference between true value and measured value
- **Absolute deviation**
  - The absolute value of the arithmetic deviation
- **Absolute relative deviation (ARD)**
  - The absolute deviation in relation to true value
- **Mean absolute relative deviation (MARD):**
  - The mean value of individual absolute relative deviations
- **Median absolute relative deviation (MedARD):**
  - The median value of individual absolute relative deviations

BGM = blood glucose monitor/monitoring; CGM = continuous glucose monitor.
Measures of Accuracy May Change Over Time

• This graph shows an example of accuracy results and how MARD values for CGM can vary systematically by day (eg, day 1 vs day 3 vs day 7)\textsuperscript{1}

• Display shows:
  – Mean (diamonds)
  – Median (horizontal lines within boxes)
  – 25th and 75th percentiles (lower and upper box edges)
  – minimum and maximum values (antennae)

BGM = blood glucose monitor; CGM = continuous glucose monitor; MARD = mean absolute relative deviation.

Understanding Clinical Standards for Accuracy

ISO Meter Approval Standards

<table>
<thead>
<tr>
<th>ISO 15197 2013¹</th>
<th>&lt;100 mg/dL (&lt;5.55 mmol/L)</th>
<th>±15 mg/dL (±0.83 mmol/L)</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥100 mg/dL (≥5.55 mmol/L)</td>
<td>±15%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Both FDA and ISO standards allow 5% of meter values to be outside limits
- 99% of values must be within Consensus Error Grid zones A or B

BGM = blood glucose monitor; CGM = continuous glucose monitor; FDA = US Food and Drug Administration; ISO = International Organization for Standardization.

Understanding Clinical Standards for Accuracy

**FDA Draft Guidance (2014)**

<table>
<thead>
<tr>
<th>Range</th>
<th>Accuracy</th>
<th>Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-400 mg/dL</td>
<td>±15%</td>
<td>95%</td>
</tr>
<tr>
<td>(2.8-22.2 mmol/L)</td>
<td></td>
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<tr>
<td>and</td>
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<td>50-400 mg/dL</td>
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- The draft proposes smaller errors in the hypoglycemic range and fewer outliers
- Testing should be performed by non-trained people
  - If devices are only tested by trained technicians, greater accuracy might be seen than when used by untrained people

*BGM = blood glucose monitor; CGM = continuous glucose monitor; FDA = US Food and Drug Administration.*

## Clinical Situations Requiring Increased Accuracy

<table>
<thead>
<tr>
<th>Patients Requiring the Highest Possible Accuracy in Glucose Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of severe hypoglycemia</td>
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<tr>
<td>Hypoglycemia unawareness</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Infants and children receiving insulin therapy</td>
</tr>
<tr>
<td>Patients at risk for hypoglycemia, including:</td>
</tr>
<tr>
<td>- Patients receiving basal insulin</td>
</tr>
<tr>
<td>- Patients receiving basal bolus insulin therapy with multiple daily injections</td>
</tr>
<tr>
<td>- Patients receiving sulfonylureas or glinides (insulin secretagogues)</td>
</tr>
<tr>
<td>- Patients with irregular schedules, skipped or small meals, vigorous exercise, travel between time zones, disrupted sleep schedules, shift work</td>
</tr>
<tr>
<td>People with occupational risks that enhance possible risks from hypoglycemia (for example, driving or operating hazardous machinery)</td>
</tr>
</tbody>
</table>
What Impacts BGM Accuracy?

- Manufacturing defects and test-strip lot-to-lot variations impact BGM accuracy and introduce bias with differences up to 11%\(^1\)-\(^3\)
- Underfilling the test strip can introduce errors >20%\(^4\)
- Use of alternate sites (sampling from palm, upper arm, forearm, thigh, or calf) can generate inaccurate results
  - Particularly true when glucose levels are changing rapidly
    - after meals or exercise
    - when the patient is ill or under stress
    - shortly after insulin administration\(^5,\,^6\)

BGM = blood glucose monitor.
Other Factors Affecting Test Results

- Factors that interfere with glucose oxidase or glucose-1-dehydrogenase enzyme or BGM degrade overall accuracy:
  - Competing blood substrates (e.g., maltose, vitamin C)\(^1,2\)
  - Environmental issues (e.g., cold temperature, high altitude)
  - Contaminants on the skin from food sources and lotions\(^3\)
  - Acetaminophen use
  - Physical compression of the CGM sensor during sleep\(^4,5\)

- Reduced accuracy and precision in tests performed by patients/other lay users compared with trained health professionals\(^6\)

BGM = blood glucose monitor; CGM = continuous glucose monitor.
Communicating BGM Device Accuracy Data

- Recent FDA proposed guidance document suggests labeling each BGM device and its test strips or sensors with specific performance characteristics. This allows clinicians and patients to make informed choices.

Sample label information for meter and test-strip boxes

Your ABC meter result may vary slightly from your actual blood glucose value. This may be due to slight differences in technique and natural variation in the testing technology.

The chart below shows the results of a study where 350 typical users used the ABC meter to test their blood glucose levels. For example, in this study, the ABC meter gave results within 15% of their true blood glucose level 340 out of 350 times.

<table>
<thead>
<tr>
<th>Difference in range between the true blood glucose level and the ABC meter result</th>
<th>Within 5%</th>
<th>Within 10%</th>
<th>Within 15%</th>
<th>Within 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>The percent (and number) of meter results that match true blood glucose level within x%</td>
<td>57% (200/350)</td>
<td>94% (330/350)</td>
<td>97% (340/350)</td>
<td>100% (350/350)</td>
</tr>
</tbody>
</table>

Accuracy levels

- **Accurate**: 350 out of 350 ±15%
- **More Accurate**: 262 out of 350 ±10%
- **Most Accurate**: 175 out of 350 ±5%

BGM = blood glucose monitor; FDA = US Food and Drug Administration.
Improving the Quality of Glycemic Control: More Than Measurement Accuracy Is Needed

- Features that provide additional information and give context to raw glucose numbers include:
  - Weekly or monthly glucose averages to highlight glycemic variability patterns
  - On-screen analysis capabilities display glucose trend lines over time, and arrows reflect magnitude of current glucose rate-of-change
- BGM clock setting must be accurate, clearly visible, easy to adjust, and maintained during battery change¹
  - Clocks in meter, CGM, and insulin pump should be synchronized (automatically if possible), with accommodation for travel across time zones
- To effectively use these informative features, many users will require guidance
  - Clinicians should consider ease and speed of BGM data downloading

BGM = blood glucose monitor; CGM = continuous glucose monitor.

Post-approval Meter Accuracy

- Independent laboratories should confirm ongoing routine quality assurance verification of test-strip lots using a standardized methodology\(^1\)

- Studies confirm:
  - Review of post-approval accuracy of 27 meters under 2003 ISO 15197 standard; >40% of meters failed to meet standard by which they had received approval\(^2\)
  - 2014 study found only 12 (44.4%) of 27 available BGMs met most recent 2013 ISO 15197 standard\(^3\)

- FDA approval does not mean a BGM will continue to meet FDA accuracy requirements

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Glucometrics

- Glucometrics is the analysis and display of glucose data\(^1\) and can provide insights into how medications, diet, stress, and activity contribute to diabetes control\(^2,3\).
- Patient-to-health care team communication methods can include:
  - Logbook during office visit
  - Computer outputs
  - Periodic phone calls, faxes, or emails to office
  - Automated transfer from meter or sensor to Internet for review
  - Automated interpretation by glucose monitoring device
- Glucose and related data should be integrated with an electronic health record

GM = glucose monitoring.
Representing Glucometric Data

• Mean, median, and %CV metrics describe overall glycemia
  – Average glucose level may represent the mean or median
  – The SD of glucose is highly correlated with mean glucose
    • %CV is usually the best method to characterize variability
    1-6

• Other methods describe actionable patterns to help clinicians optimize diabetes therapy
  – In graphical presentation, “standard day,” “modal day,”7,8 or AGP displays individual glucose measurements (pooled over multiple days) by time of day on a single 24-hour scale

AGP = ambulatory glucose profile; CV = coefficient of variation; SD = standard deviation.

Standard or Modal Day

- The “Standard Day” or “Modal Day” graph indicates both glucose values and times of day when monitoring occurs
  - Facilitates detection of consistent patterns in glucose excursions
  - Provides assessment of glucose monitoring adequacy
  - Generally shows glucose values by time of day but can show them in relation to meals

Glucose Profile by Time of Day

Glucose in Relation to Meals

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Ambulatory Glucose Profile

• To generate AGP:
  – Blood glucose levels are measured via BGM or CGM
  – All glucose data pooled and analyzed as if it had been collected during a single 24-hour period
  – Result is a standardized software report that can be displayed graphically

• AGP provides an excellent starting point for a standardized computerized display of BGM and/or CGM data by time of day\textsuperscript{1-3}

AGP = ambulatory glucose profile; BGM = blood glucose monitor; CGM = continuous glucose monitor; T1DM = type 1 diabetes mellitus

• The solid curve in the middle represents the smoothed median glucose (50th percentile) values for a 24-hour period.
• The striped, shaded area shows the presumptive target range (70-180 mg/dL or 3.9-10 mmol/l).

AGP = ambulatory glucose profile; CGM = continuous glucose monitor; IQR = interquartile range; T2DM = type 2 diabetes mellitus.

Other Graphical Displays of Glucometric Data

- Other ways that graphic data related to glucose changes over time can be displayed
  - Pie graphs
  - Simple bar charts
  - Box plots
  - Scattergrams
  - Stacked bar charts
  - Histograms

- The purpose of these displays is to help clinicians identify and prioritize clinical problems and educate and motivate the patient to achieve improved glycemic control.
Recommendations

• Patients should be educated to interpret and use GM data to:
  – Enhance their ability to self-adjust therapy
  – Decide when to seek medical assistance

• To assess glucometrics, physicians should first examine:
  – Overall statistics (mean, SD, %CV)
  – Distribution of glucose values
  – Glucose by date, by time of day and in relationship to meals, and by day of the week

• The most helpful glucometric graphical displays show:
  – Graphs of glucose by date
  – AGP
  – Stacked bar charts and/or box plots by time of day, in relation to meals, and by day of the week

AGP = ambulatory glucose profile; CV = coefficient of variation; GM = glucose monitoring; SD = standard deviation.
Glucose Monitoring, Looking Forward

• Improvements:
  – Accuracy
  – Data-sharing via the Internet and mobile phone is possible
  – Usability & greater patient acceptance

• Mobile health apps for patients are proliferating

• Comprehensive and standardized integration of multiple data inputs is needed

• Assistive interpretive technology is needed (for people with diabetes AND clinicians)

• CGM technology advances may broaden the appeal and applicability of CGM in T1DM and T2DM

CGM = continuous glucose monitoring; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.