Continuous Glucose Monitoring (CGM)
Assessing Glycemic Control: Hemoglobin A1C

- Hemoglobin A1C (A1C) indirectly measures average blood glucose levels over a 3-month period
- Has advantages over fasting plasma glucose or oral glucose tolerance tests, providing a longer-term average of glucose levels
- Widely used and accepted metric of glycemic control with strong predictive value for diabetic complications

Blood glucose (mg/dL) measurements were taken four times per day (fasting or pre-breakfast, pre-lunch, pre-dinner, and bedtime).

The straight black line shows an A1C measurement of 7.0 percent. The blue line shows an example of how blood glucose test results might look from self-monitoring four times a day over a 4-day period.


Image: https://www.niddk.nih.gov/health-information/diabetes/overview/tests-diagnosis/a1c-test#diagnose

Monitoring Glycemic Control: Hemoglobin A1C

- A1C targets to prevent microvascular complications are based on prior outcomes trials in both type 1 diabetes (T1D) and type 2 diabetes (T2D).
- Long-term follow-up showed the importance of **early, tight glucose control (A1C <7%) results in fewer microvascular complications** (diabetic kidney disease, neuropathy, and retinopathy) in T1D and T2D.

**DCCT:**

- Investigated the correlation between A1C and microvascular complications in patients with T1D.
- **Results:** tighter glycemic control can reduce the development and progression of microvascular complications by up to 76%.

**UKPDS:***

- Investigated effect of tight glycemic control on microvascular and macrovascular complications in patients with T2D.
- **Results:** tight glycemic control reduced the risk of microvascular complications, but not of macrovascular disease.

Legend: A1C, hemoglobin A1C; DCCT, Diabetes Control and Complications Trial; UKPDS, United Kingdom Prospective Diabetes Study.
This figure represents a broad framework to guide clinical decisions for patients with T1D and T2D. ADA recommends glycemic targets be individualized based on key patient/disease features. Life expectancy and burden of disease are important variables in determining stringency of glycemic control targets.
Limitations of A1C for Assessment of Glycemic Control

- Variability in the measurement of A1C
- Conditions that affect red blood cell turnover cause A1C discrepancies:
  - Hemolytic and other anemias
  - Glucose-6 phosphate dehydrogenase deficiency
  - Erythropoietic drugs
  - Recent blood transfusion
  - End-stage renal disease
  - Pregnancy
- Unreliable results in the presence of hemoglobinopathies
- Racial differences in A1C

Glycemic Variability

- A1C is easy to measure but provides limited insight into glucose control patterns
- Wide range of mean glucose variability can correspond to the same 3 month A1C measurement
- Short-term glycemic variability or hypoglycemic events can be missed
- CGM metrics can give a better picture of glycemic variability

Monitoring Glycemic Control: Continuous Glucose Monitoring (CGM)

- A1C cannot capture glycemic variability or glucose excursions, including hypoglycemic events\(^1\)
- With CGM, a small sensor is placed under the skin, to measure the interstitial glucose levels in intervals of 5 to 15 minutes\(^1\)
- CGM provides a more comprehensive assessment of glycemic control
- CGM can inform patients of impending glucose excursions using glucose trend arrows and influence treatment decisions\(^2\)
- CGM devices continue to become easier to use, more accurate, and more accessible to patients\(^2\)

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Current Commercially-Available CGM systems
# Key Features of Current CGM Devices

<table>
<thead>
<tr>
<th>CGM Category</th>
<th>rt-CGM</th>
<th>Personal</th>
<th>is-CGM</th>
<th>Professional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population Age (y)</td>
<td>≥2</td>
<td>≥2</td>
<td>≥16</td>
<td>≥18</td>
</tr>
<tr>
<td>Pregnancy Approval</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Warm-up time (h)</td>
<td>2</td>
<td>2</td>
<td>24</td>
<td>10-12</td>
</tr>
<tr>
<td>Sensor wear (d)</td>
<td>10</td>
<td>7</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Calibrations</td>
<td>None</td>
<td>2/d</td>
<td>2-4/d</td>
<td>2/d</td>
</tr>
<tr>
<td>Nonadjunctive Use</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Audible Alerts/Alarms</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Trend Arrows</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

# Key Features of Current CGM Devices cont.

<table>
<thead>
<tr>
<th>CGM Category</th>
<th>rt-CGM</th>
<th>is-CGM</th>
<th>Professional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Share features</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>Pump integration</td>
<td>Tandem t:slim X2, with Basal IQ</td>
<td>Tandem t:slim X2</td>
<td>None</td>
</tr>
<tr>
<td>Software Compatibility</td>
<td>Dexcom CLARITY Gloko Tidepool</td>
<td>Dexcom CLARITY Gloko Tidepool</td>
<td>LibreView</td>
</tr>
<tr>
<td>Acetaminophen Interference</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MARD (%)</td>
<td>9</td>
<td>10.6±9.6</td>
<td>13.6</td>
</tr>
<tr>
<td>Radiograph/MRI Compatible</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: is-CGM, intermittent scanned CGM; NA, not available; rt-CGM, real-time CGM.

Indications for CGM Therapy

**International Consensus:**
- All patients with T1D
- T2D treated with intensive insulin therapy, not meeting glycemic goals
- Those with problematic hypoglycemia

**AACE:**
- T1D with hypoglycemia/unawareness or not meeting glycemic goals
- T2D on intensive insulin therapy, high risk for hypoglycemia, or unappreciated hyperglycemia

**American Diabetes Association:**
- T1D not meeting glycemic goals (consider in T2D)
- Hypoglycemia/unawareness
- Sensor-augmented pump therapy
- Consider in pregnancy

Evidence for CGM Therapy: Hemoglobin A1C
CGM and Intensive Treatment of T1D

- Randomized, multicenter clinical trial that assessed the efficacy and safety of CGM in adults and children with T1D
- **Population:** Age ≥8 years, T1D diagnosis for ≥1 year, insulin pump use or ≥3 insulin injections daily, A1C 7-10%, no CGM use prior 6 months
- **Primary outcome:** Mean change in A1C from baseline to 26 weeks
- **Results:** Mean change in A1C in adults (age ≥25 years) at 26 weeks with use of CGM were significant (-0.53%, \(P<0.001\)). Results were not significant for those age 15-24 (0.08, \(P=0.52\)) or age 8-14 (-0.013, \(P=0.29\))

Legend: A1C, hemoglobin A1C; CGM, continuous glucose monitoring; T1D, type 1 diabetes.

Greater A1C Reduction in Patients Who Look at CGM Display

Comparison of Bottom and Top Quartiles of CGM Attention and A1C Reduction at 12 Weeks

<table>
<thead>
<tr>
<th></th>
<th>Bottom Quartile (n=32)</th>
<th>Top Quartile (n=31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-h trend screen views per day</td>
<td>9.8 ± 2.7</td>
<td>37.7 ± 11.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A1C change at 12 weeks (%)</td>
<td>-0.11 ± 0.61</td>
<td>-0.61 ± 0.76</td>
<td>0.008</td>
</tr>
<tr>
<td>3-h trend screen views per day</td>
<td>1.4 ± 0.7</td>
<td>5.8 ± 3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A1C change at 12 weeks (%)</td>
<td>-0.23 ± 0.66</td>
<td>-0.84 ± 0.93</td>
<td>0.006</td>
</tr>
<tr>
<td>9-h trend screen views per day</td>
<td>0.9 ± 0.4</td>
<td>3.7 ± 2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A1C change at 12 weeks (%)</td>
<td>-0.19 ± 0.49</td>
<td>-0.78 ± 0.94</td>
<td>0.004</td>
</tr>
<tr>
<td>All trend screen views per daya</td>
<td>12.2 ± 3.3</td>
<td>47.2 ± 13.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A1C change at 12 weeks (%)</td>
<td>-0.08 ± 0.58</td>
<td>-0.61 ± 0.75</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Data are mean ± SD values

*aCombined number of trend screen views (1-, 3-, and 9-h) per day

Legend: A1C, hemoglobin A1C; CGM, continuous glucose monitoring; SD, standard deviation.

Bailey et al. Diabetes Technol Ther 2007;9(3)
CGM vs Conventional Therapy in T1D: The GOLD Trial

- An open-label, randomized crossover trial in adults with T1D comparing the effect of CGM vs. conventional therapy (SMBG) on glycemic control
- **Population:** ≥18 years, T1D for ≥1 year on MDI, with A1C >7.5%
- 1:1 randomization CGM vs SMBG
- **Primary outcome:** Difference in A1C between CGM and conventional therapy at weeks 26 and 69.
- **Results:** Mean difference in A1C of -0.43% (P<0.001) during CGM vs conventional therapy after 26 weeks

Legend: A1C, hemoglobin A1C; CGM, continuous glucose monitoring; GOLD, Glycemic control & Optimization of Life quality in type 1 Diabetes; MDI, multiple daily injections; SMBG, self-monitoring of blood glucose; T1D, type 1 diabetes.

Lind et al. JAMA. 2017;317:379-387
CGM vs SMBG in T1D: The DIAMOND Trial

- Prospective RCT in adults with T1D comparing the effect of CGM to SMBG on glycemic control
- Primary outcome: Change in A1C from baseline to 24 weeks
- Results: At 24 weeks, mean A1C reduction from baseline of 1.0% in CGM group (from 8.6% to 7.7%) vs 0.4% in SMBG group ($P<0.001$). A1C decreased from 8.6% to 7.7% in CGM group. Time spent in hypoglycemia <70 mg/dL was 43 min/day with CGM vs 80 min/day with SMBG ($P=0.002$)

Legend: DIAMOND, Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes; RCT, randomized controlled trial; SMBG, self-monitoring of blood glucose
Prospective RCT in adults with T2D comparing the effect of CGM to SMBG on glycemic control

Enrollment criteria: Age ≥25 years, T2D on MDI ≥1 year, A1C 7.5%-10.0%, stable medication regimen and weight over past 3 months, SMBG ≥2 per day, without significant renal dysfunction

Primary outcome: A1C reduction at 24 weeks. Secondary outcomes: hypoglycemia, QOL, and CGM satisfaction

Results: Mean adjusted change in A1C of -1.0% from baseline to 24 weeks in CGM group compared with control group change of -0.6% ($P=0.005$) with adjusted difference of -0.3% ($P=0.022$)

No difference in hypoglycemia or QOL; high CGM satisfaction scores

Mean A1C change from baseline, %

<table>
<thead>
<tr>
<th></th>
<th>CGM Group (n=79)</th>
<th>Control Group (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 weeks</td>
<td>-1</td>
<td>-0.8</td>
</tr>
<tr>
<td>24 weeks</td>
<td>-0.6</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

Mean A1C, %

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 Weeks</th>
<th>24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGM Group</td>
<td>8.5</td>
<td>7.5</td>
<td>7.7</td>
</tr>
<tr>
<td>Control Group</td>
<td>8.5</td>
<td>7.9</td>
<td>8.0</td>
</tr>
</tbody>
</table>
CGM vs SMBG in T1D: COMISAIR Study 3-Year Outcomes

- A 3-year prospective, nonrandomized, real-world study comparing CGM with SMBG in patients receiving MDI or CSII
- Patients were divided into 4 groups: CGM+MDI, CGM+CSII (SAP), SMBG+MDI, and SMBG+CSII
- Primary outcome: Between-group difference in A1C at 3 years
- Results: At 3 years, both CGM groups had a mean A1C of 7%, a significant difference from both SMBG+CSII (7.7%) and SMBG+MDI (7.7% and 8.0%, respectively; \(P<0.0001\) for both)

Legend: COMISAIR, Comparison of Different Treatment Modalities for Type 1 Diabetes Including Sensor-Augmented Insulin Regimens; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; rt, real-time; SAP, sensor-augmented pump; SMBG, self-monitoring of blood glucose; T1D, type 1 diabetes.
Evidence for CGM Therapy: Time in Range
Meta-analysis of CGM trials in T1D and T2D

Change in Hemoglobin A1C

Time in Target Glucose Range

Continuous Glucose Monitoring Metrics
Continuous Glucose Monitoring Metrics

**Standardized CGM Metrics for Clinical Care: 2019**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Number of days CGM worn (recommend 14 days)</td>
<td></td>
</tr>
<tr>
<td>2. Percentage of time CGM is active (recommend 70% of data from 14 days)</td>
<td></td>
</tr>
<tr>
<td>3. Mean glucose</td>
<td></td>
</tr>
<tr>
<td>4. Glucose management indicator</td>
<td></td>
</tr>
<tr>
<td>5. Glycemic variability: Coefficient of Variation (%CV) target ≤36%*</td>
<td></td>
</tr>
<tr>
<td>6. Time above range: % of readings and time &gt;250 mg/dL (&gt;13.9 mmol/L)</td>
<td>Level 2</td>
</tr>
<tr>
<td>7. Time above range: % of readings and time 181-250 mg/dL (10.1-13.9 mmol/L)</td>
<td>Level 1</td>
</tr>
<tr>
<td>8. Time in range: % of readings and time 70-180 mg/dL (3.9-10.0 mmol/L)</td>
<td>In range</td>
</tr>
<tr>
<td>9. Time below range: % of readings and time 54-69 mg/dL (3.0-3.8 mmol/L)</td>
<td>Level 1</td>
</tr>
<tr>
<td>10. Time below range: % of readings and time &lt;54 mg/dL (&lt;3.0 mmol/L)</td>
<td>Level 2</td>
</tr>
</tbody>
</table>

- 2019 International Consensus Group streamlined 14 core metrics to 10 most applicable to clinical practice
- Provide more data for assessment of glycemic control compared with A1C

*Some studies suggest that lower %CV targets (<33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas.*

Glycemic Variability and Hypoglycemia

- Measures of Glycemic Variability
  - Standard Deviation (SD)
  - Coefficient of Variation (CV)
  - MAGE
- Stable glucose levels: CV<36%
- Glycemic variability is a consistent predictor of hypoglycemia
- **Figure:** highest rates of hypoglycemia in those with high variability (SD) and a lower mean glucose value (rectangle)

Legend: A1C, hemoglobin A1C; CV, coefficient of variation; MAGE, mean amplitude of glycemic excursion; OAD, oral antidiabetic drugs; SD, standard deviation; T1D, type 1 diabetes; T2D, type 2 diabetes.
Electronic AGP Report with Key CGM Metrics

**AGP Report**

<table>
<thead>
<tr>
<th>GLUCOSE STATISTICS AND TARGETS</th>
<th>TIME IN RANGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 Feb 2019 - 10 Mar 2019</td>
<td>13 days</td>
</tr>
<tr>
<td>% Time CGM is Active</td>
<td>99.8%</td>
</tr>
</tbody>
</table>

**Glucose Ranges**

- **Target** Range 70-180 mg/dL
- **Greater than** 70% (16h-48min)
- Below 70 mg/dL ...............Less than 4% (58min)
- Below 54 mg/dL ...............Less than 1% (14min)
- Above 250 mg/dL ...............Less than 5% (1h 12min)

Each 1% increase in time in range (70-180 mg/dL) is clinically beneficial.

**Average Glucose** 173 mg/dL

**Glucose Management Indicator (GMI)** 7.6%

**Glucose Variability** 49.5%

*Defined as percent coefficient of variation (%CV); target ≤36%*

**AMBULATORY GLUCOSE PROFILE (AGP)**

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.

**DAILY GLUCOSE PROFILES**

Each daily profile represents a midnight to midnight period.
CGM Data: Glucose Management Indicator (GMI)

- Using 10-14 days of data, CGM-derived mean glucose values can be used to find an “estimated A1C” (eA1C)\(^1\)

- GMI has been proposed as a new term to replace eA1C, as this better conveys the use of this metric
  - GMI helps inform or guide diabetes treatment decisions, but is not necessarily a perfect match with A1C levels\(^1\)


Image: https://professional.medtronicdiabetes.com/ipro2-professional-cgm.
Accessed on January 9, 2020
Individualizing Glycemic Control Goals Using CGM Metrics

Type 1* & Type 2 Diabetes

Target: <5%

>250 mg/dL (13.9 mmol/L)
>180 mg/dL (10.0 mmol/L)

Target Range: 70–180 mg/dL (3.9–10.0 mmol/L)
<70 mg/dL (3.9 mmol/L)
<54 mg/dL (3.0 mmol/L)

Older/High-Risk: Type 1 & Type 2 Diabetes

Target: <10%

>250 mg/dL (13.9 mmol/L)
>180 mg/dL (10.0 mmol/L)

Target Range: 70–180 mg/dL (3.9–10.0 mmol/L)
<70 mg/dL (3.9 mmol/L)
<54 mg/dL (3.0 mmol/L)

Pregnancy: Type 1 Diabetes†

Target: <25%

>140 mg/dL (7.8 mmol/L)
>100 mg/dL (5.6 mmol/L)

Target Range: 63–140 mg/dL (3.5–7.8 mmol/L)
<63 mg/dL (3.5 mmol/L)
<54 mg/dL (3.0 mmol/L)

Pregnancy: Gestational & Type 2 Diabetes§

Target: <4%

>140 mg/dL (7.8 mmol/L)
>100 mg/dL (5.6 mmol/L)

Target Range: 63–140 mg/dL (3.5–7.8 mmol/L)
<63 mg/dL (3.5 mmol/L)
<54 mg/dL (3.0 mmol/L)
Contributors

AACE would like to thank the following endocrinologists for their contributions.

- Dr. Georgia Davis, MD
- Dr. Francisco Pasquel, MD, MPH
- Dr. Archana Sadhu, MD, FACE