**Evidence Table**

**Clinical Area:** Real-time continuous glucose monitors  

**Study Type:** Comparison of diagnostic tests  
**Study Aim:** Access the accuracy of the FreeStyle Navigator (Abbott Diabetes Care) in adults, at the time an investigational device under review by the FDA.

**Outcomes**  
- **Primary:** Reliability, accuracy

**Design**  
- **Number of subjects:** N=58
- **Description of study population:** Age 18-64 years old (mean age=40 years); 62% male; 81% white; mean length of time since DM diagnosis=22 years.
- **Inclusion and exclusion criteria:**
- **Procedure:** Participants were admitted to an in-patient research facility for 5 days. Two glucose sensors were inserted into each participant by trained personnel. One was worn on the upper arm, and other on the abdomen. Calibration of the devices occurred at different times of day, and both per- and post-prandially. Venous blood samples were taken every 15 minutes over 50 hours of inpatient admission in 2-3 separate sessions. During the 5 day stay, patients were given an insulin challenge or 75-g oral glucose load to obtain data during deliberately induced periods of rapidly falling or rising blood glucose levels.

**Validity**  
- **Independent blind comparison with a gold standard or follow-up of those not receiving the gold standard test?** Yes, venous blood samples.  
- **Was “normal” defined?** Yes.  
- **Appropriate spectrum of disease?** Yes.  
- **Methods described in enough detail to enable you to replicate the test?** Yes.  
- **Reproducible results?** Yes.  
- **Conclusions regarding validity of methods:** Valid methods, and Clarke error grid analysis is generally accepted.

**Results**

N=58: Total of 20,362 paired points with both venous samples and interstitial fluid glucose measurements.

Reliability: Performance of the arm and abdominal sensors were comparable over all glucose ranges and over time.
Clinical accuracy: 81.7% of points were in the clinically accurate A zone, 16.7% were in the benign error B zone and 1.7% were outside of the A and B zones.

<table>
<thead>
<tr>
<th>Absolute rate of change</th>
<th>% of paired points in Clarke error grid</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt;1 mg<em>dl⁻¹</em> min⁻¹)</td>
<td></td>
</tr>
<tr>
<td>&lt; -2</td>
<td>54.6</td>
</tr>
<tr>
<td>-2 to -1</td>
<td>71.7</td>
</tr>
<tr>
<td>-1 to 1</td>
<td>84.9</td>
</tr>
<tr>
<td>1 to 2</td>
<td>79.8</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>63.5</td>
</tr>
</tbody>
</table>

Hypoglycemia = (M70 mg/dl) was detected either by the threshold or projected alarms in 79.8% of the instances within 30 minutes of the reference measurements. The false alarm rate for the hypoglycemic threshold alarm was 7.2%.

**Authors’ Conclusions**
“Measurements with the FreeStyle Navigator system were found to be consistent and accurate with venous measurements made using a laboratory reference method over 5 days of sensor wear (82.5% in the A zone on day one and 80.9% on day 5).

**Reviewer’s Conclusions**
The FreeStyle Navigator system was found to be reasonable accurate in adults, when compared with venous blood samples, and used under controlled conditions.
Evidence Table

Clinical Area: Real-time continuous glucose monitors

Study Type: Comparison of diagnostic tests
Study Aim: Access the accuracy of the FreeStyle Navigator (Abbott Diabetes Care) in children, at the time an investigational device under review by the FDA.

Outcomes
• Primary: Reliability, accuracy

Design
• Number of subjects: N=30
• Description of study population: Mean age=11.2 ± 4.1 years; 40% female; 93% white; mean duration of diabetes=5.8 ± 3 years.
• Inclusion and exclusion criteria: 3-18 years old; type 1 diabetes ≥ 1 year.
• Procedure: One week of blinded Navigator use at home. Inpatient admission for 24 hours in a clinical research center. Venous blood samples were taken every 30 minutes. Additional samples were taken during exercise sessions, and post-prandially.

Validity
• Independent blind comparison with a gold standard or follow-up of those not receiving the gold standard test? Yes.
• Was “normal” defined? Yes.
• Appropriate spectrum of disease? Yes.
• Methods described in enough detail to enable you to replicate the test? Yes.
• Reproducible results? Yes.
• Conclusions regarding validity of methods: Reasonably valid, although the sample size was relatively small.

Results

Median number of paired samples per participant=66.

Median absolute difference (AD)=17 mg/dl.; 74% of sensor values met ISO home glucose meter criteria.

Accuracy measures improved slightly when incorporating a 10-minutes sensor lag.

Exercise: median fall in reference glucose=91 mg/dl; median absolute difference in the fall between the Navigator and reference=16 mg/dl.
Navigator values lagged behind the reference values, causing the Navigator to underestimate the rate of change, particularly in participants with a rapid fall in glucose during exercise. The median time to the nadir=100 min for the Navigator and 78 min for the reference.

**Authors’ Conclusions**
“The Navigator’s accuracy does not yet approach the accuracy of current-generation home glucose meters, but it is sufficient to believe that the device has the potential to be an important adjunct to treatment of youth with type 1 diabetes.”

**Reviewer’s Conclusions**
The primary accuracy limitation identified was the lag time required for the Navigator to detect a rapid fall in glucose during exercise. The study was too short and had too small a sample size to draw definitive conclusions about accuracy, or to evaluate the accuracy of the Navigator for detecting episodes of hypoglycemia.
Evidence Table

Clinical Area: Real-time continuous glucose monitors

Study Type: Randomized controlled trial.
Study Aim: To evaluate the effect of a real-time glucose monitor on glycemic control in patients with poorly controlled type 1 diabetes.

Outcomes
- **Primary**: A1C
- **Secondary**: Insulin dose, hypoglycemia.

Design
- **Number of subjects**: N=162
- **Description of study population**: Mean age of children=14.4 years; mean age of adults=39.1 years.
- **Eligibility criteria**: Type 1 diabetes; adherent to intensified insulin treatment; HbA1C ≥8%.
- **Intervention**: Patients were randomized to one of three groups: 1) Medtronic Minimed Guardian RT continuously; 2) Medtronic Minimed Guardian RT for three days every 2 weeks; 3) conventional self-monitoring of blood glucose (SMBG). Treatment adjustments were by physicians and patients based on SMBG profiles in control patients and on real-time glucose profiles in the Guardian RT groups. Patients assigned to receive a continuous glucose monitor were instructed to perform confirmatory SMBG measurements before changes to therapy were made if symptoms occurred or hypo- or hyperglycemic alarms were triggered. Alert thresholds were set at 50-80 mg/dl for hypoglycemic and 170-250 mg/dl for hyperglycemia. The upper alarm was lowered to 200 mg/dl after the first 10 days, and settings could be adjusted during the study.
- **Source of outcome data**: Glucose measurements.
- **Length of follow-up**: 3 months.

Validity
- **Blinding?** Not mentioned.
- **Appropriate randomization procedures?** Yes, stratified by age group.
- **Appropriate comparison intervention?** Yes.
- **Treatment/control groups comparable at baseline?** Not known—did not report baseline characteristics other than age.
- **Other than intervention, was care/follow-up similar in each group?** Yes.
- **Adequate compliance with intervention?** Yes.
- **Sufficient statistical power?** Not reported.
• **Intention to treat analysis?** Yes.
• **Completeness of follow-up:** 156/162 (96%) completed the study.
• **Industry funding?** Yes, study was funded by Medtronic and several authors had financial links (eg. travel expenses, consulting fees, honoraria) with Medtronic.
• **Conclusions regarding validity of methods:** Possible limitations include lack of blinding of outcome assessment, no reporting of statistical power and no reporting of baseline characteristics other than age. There may have been differences between groups that affected outcomes. In addition, industry sponsorship could have led to bias in design or reporting.

**Results**

Group 1: Continuous use of Guardian RT; Group 2: Guardian RT 3 days every 2 weeks; Group 3: Managed without CGMS.

**HbA1C (mean % ± SD)**

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>9.5 ± 1.1</td>
<td>9.6 ± 1.2</td>
<td>9.7 ± 1.3</td>
</tr>
<tr>
<td>Reduction at 1 month</td>
<td>0.6 ± 0.8</td>
<td>0.4 ± 0.9</td>
<td>0.2 ± 0.8</td>
</tr>
<tr>
<td>Reduction at 3 months</td>
<td>1.0 ± 1.1</td>
<td>0.7 ± 1.3</td>
<td>0.4 ± 0.9</td>
</tr>
</tbody>
</table>

p-values (difference in reduction in HbA1C)
Group 1 vs. control, 1 month, p=0.008
Group 1 vs. control, 3 months, p=0.003
There was no significant difference between Group 2 and control, or Group 2 and Group 1 at either time point.

**Changes in insulin or diet/lifestyle**

At 3 months, 95% of patients in the Guardian RT groups reported making dietary or lifestyle change using the real-time information. Details were not provided.

At 3 months, total insulin dose per day was not significantly different from baseline in the three groups.

**Hypoglycemia**

Severe hypoglycemia occurred in 1 patient in group 1 and 1 patient in group 2. (The patient in group 2 was not wearing the CGMS at the time).

**Authors’ Conclusions**

“This is the first randomized controlled trial to demonstrate a clinically meaningful reduction in A1C using real-time CGM in type 1 diabetic patients.”

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Reviewer’s Conclusions

In this RCT sponsored by Medtronic, there was a significantly greater reduction in HbA1C at 1 and 3 months in a group that continuously wore the Guardian RT compared to a control group that used conventional self-monitoring of blood glucose. There was no significant difference in HbA1c reduction between the control group and patients who used the Guardian RT intermittently (3 days every 2 weeks). Severe hypoglycemia occurred in 2 patients—this number of events was too small to determine whether glucose monitoring impacted the occurrence of hypoglycemic events. Study limitations include industry sponsorship, unknown baseline differences, and minimal information on how Guardian RT data were used to adjust insulin dose or affect lifestyle changes.
Evidence Table

Clinical Area: Real-time continuous glucose monitors

Study Type: Case Series
Study Aim: To evaluate change in HbA1c over 12 weeks in adults with diabetes who used a real-time continuous glucose monitor (the DexCom STS).

Outcomes
• **Primary**: Change in HbA1c.
• **Secondary**:

Design
• **Number of subjects**: N=140
• **Description of study population**: Multicenter study conducted in the US. 78% type 1 diabetes; baseline HbA1C: 33% <7%; 56% 7-9%; 11% >9%.
• **Inclusion criteria**: Age 18 and over; type 1 or type 2 diabetes.
• **Exclusion criteria**: Pregnant or lactating.
• **Consecutive patients?** Not specified.
• **Intervention**: Participants used the DexCom STS system at home for 12 weeks. On Day 1, patients received the device and were trained in its use. They were instructed to use data from the monitor as an adjunct to self-monitoring of blood glucose. Patients were allowed to modify the high glucose alert (range 140-400 mg/dL, or no high alert) and low glucose alert (60-90 mg/dL, or no alert). A non-modifiable hypoglycemia alarm was set at glucose levels ≤ 55 mg/dL.
• **Source of outcome data**: Clinic-based HbA1C.
• **Length of follow-up**: 12 weeks. Follow-up visits every 3 weeks.

Validity
• **Was population homogenous?** Possibly, there were few eligibility criteria.
• **Potential selection biases**: “Healthy user” bias: patients willing to use the glucose monitor may have been more motivated to control their glucose level.
• **Were intervention/ care/follow-up similar in each group?** Yes.
• **Did an objective observer assess outcomes?** Yes.
• **Completeness of follow-up**: Appears to be 100% follow-up.
• **Industry funding**? Yes, sponsored by DexCom
• **Conclusions regarding validity of methods**: This is a case series and is subject to selection and observational biases. For example, participation bias (patients in the study were asked to pay close attention to their blood glucose levels) and “healthy user” bias. The study was sponsored by the manufacturer of the glucose monitor, which could have introduced biases in study design and/or reporting.
Results

HbA1C, mean % ± SE

<table>
<thead>
<tr>
<th>Value</th>
<th>Change from baseline</th>
<th>p-value (change from baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>7.6 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>Week 6</td>
<td>7.2 ± 0.9</td>
<td>-0.4 ± 0.5</td>
</tr>
<tr>
<td>Week 12</td>
<td>7.2 ± 1.0</td>
<td>-0.4 ± 0.5</td>
</tr>
</tbody>
</table>

HbA1C, stratified by baseline value, mean % ± SE

<table>
<thead>
<tr>
<th>Value</th>
<th>Change from baseline</th>
<th>p-value (change from baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7.0% (n=46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.4 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>6.4 ± 0.5</td>
<td>-0.05 ± 0.06</td>
</tr>
<tr>
<td>7-9% (n=78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.8 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>7.3 ± 0.7</td>
<td>-0.5 ± 0.06</td>
</tr>
<tr>
<td>&gt;9% (n=15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>10.0 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>8.6 ± 1.6</td>
<td>-1.4 ± 0.4</td>
</tr>
</tbody>
</table>

Hypoglycemia

4 patients experienced 5 hypoglycemic events requiring third-party assistance. In 4/5, the monitor provided the user with a low glucose alert and alarm.

Authors’ Conclusions

“This observational study showed that home use of real-time CGM was safe and well tolerated and associated with a clinically and statistically significant reduction in HbA1C. Large-scale randomized, controlled outcome studies of CGM are indicated.”

Reviewer’s Conclusions

There was a significant reduction in HbA1c level after 12 weeks of continuous glucose monitoring with the DexCom STS. There was no comparison group, so it is not known whether the HbA1C would have decreased with usual care. Moreover, increased attention to glycemic control due to study participation could have affect HbA1c values. As the authors state, this study is hypothesis-generated and randomized controlled trials are need to determine effectiveness.
## Combined Evidence Table

Case studies on feasibility and short-term efficacy of FreeStyle Navigator

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Study Population, baseline differences</th>
<th>Results</th>
<th>Validity Concerns/Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>DirecNet Study Group, 20071</td>
<td>1 week run-in period: Navigator data blinded to collect baseline data</td>
<td>Inclusion: 3-18 years old; type 1 diabetes of ≥1 year duration; home computer; stable insulin regimen with pump ≥6 months</td>
<td>Usage: - Weeks 1-4 unblinded sensor use, the sensor was worn an average of 149 ± 22 hours per week (out of a maximum of 168 hrs/wk). - Weeks 9-13, the sensor was worn an average of 134 ± 37 hours/week - 5% of participants averaged ≥6 days of Navigator use per week HbA1C Mean value at baseline= 7.1% ± 0.6% Mean value at 13 weeks= 6.8% ± 0.7% p-value=0.02 Hypoglycemia No patients reported a severe episode during the 6 months prior to the study No cases of severe hypoglycemia were reported during the study Adverse effects 2 patients had severe skin reactions due to adhesive tape</td>
<td>No control group. Selection bias likely. Possibility of study participation bias (lowering of HbA1C due to close monitoring as part of study participation). Financial disclosures not included in publication.</td>
</tr>
<tr>
<td>Follow-up: 13 weeks</td>
<td>24 hour inpatient stay to determine accuracy (published separately), and instruct families on use</td>
<td>Baseline characteristics: Mean age=11.2 ± 4 years; 40% female; mean duration of diabetes=5.8 ± 3.0 years.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcomes: Feasibility, short-term efficacy (unspecified)</td>
<td>Home use of Navigator for 3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial N: 33</td>
<td>Final N: 28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weinzimer et al., 20082</td>
<td>1 week run-in period: Navigator data blinded to collect baseline data</td>
<td>Inclusion: 3-17 years old; type 1 diabetes of ≥1 year duration; home computer; glargine-based multiple daily injection (MDI) insulin therapy</td>
<td>Usage: - Weeks 1-4 unblinded sensor use, the sensor was worn an average of 107 ± 52 hours per week (out of a maximum of 168 hrs/wk). - Weeks 9-13, the sensor was worn an average of 107 ± 44 hours/week HbA1C Mean value at baseline= 7.9% ± 1.0% Mean value at 13 weeks= 7.3% ± 0.9% p-value=0.0004 Hypoglycemia (Severe episodes prior to study not reported) No cases of severe hypoglycemia were reported during the study</td>
<td>Similar study design, except patients treated with glargine-based therapy rather than pumps. No control group. Selection bias likely. Possibility of study participation bias (lowering of HbA1C due to close monitoring as part of study participation). Abbott health care provided monitors and supplies, but not study funding.</td>
</tr>
<tr>
<td>Follow-up: 13 weeks</td>
<td>24 hour inpatient stay to determine accuracy (published separately), and instruct families on use</td>
<td>Baseline characteristics: Mean age=11.0 ± 4 years; 40% female; mean duration of diabetes=3.4 years.</td>
<td></td>
<td></td>
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<tr>
<td>Primary outcomes: Feasibility, short-term efficacy (unspecified)</td>
<td>Home use of Navigator for 3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial N: 27</td>
<td>Final N: 23</td>
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