Continuous Glucose Monitoring Systems

Bruce Buckingham, MD
Objectives:

• Review of CGM technology.
  – Benefits and limitations.
• CGM patient selection and education.
• CGM Research
• Algorithms and tools for using CGM data.
Diabetes Management Evolution

**Glucose Monitoring**

- **1977** Blood Glucose Meter
- **1978** First Minimed Pump 502
- **1983** First Minimed Pump 502 (Pump 502)

**Insulin Delivery**

- **2000** First CGM system
- **2005-2007** Real-time CGM
- **2006** Paradigm REAL-Time, combining Insulin Pump and CGM
Daily Patient Log

- **Fingerstick Measurement**
- **Insulin Bolus**

### Glucose (mg/dl)

**Target Range**

- **Breakfast**: 8:30 am
- **Lunch**: 12:00 noon
- **Dinner**: 6:00 p.m.
- **Bedtime**: 10:30 p.m.
Daily Patient Log and Sensor Data

- **Glucose (mg/dl)**
  - Breakfast: 8:30 a.m.
  - Lunch: 12:00 noon
  - Dinner: 6:00 p.m.
  - Bedtime: 10:30 p.m.

- **Sensor Measurement**
- **Fingerstick Measurement**
- **Insulin Bolus**

- **Target Range**

The graph shows the glucose levels throughout the day with markers for breakfast, lunch, dinner, and bedtime. The target range is indicated on the graph.
MiniMed CGMS
Sensor Lag

- Blood Glucose (mg/dl)
  - 0
  - 100
  - 200
  - 300
  - 400
  - 500

- Time (minutes) (0 = start if meal)
  - -40
  - -20
  - 0
  - 20
  - 40
  - 60
  - 80
  - 100
  - 120
  - 140

- Freestyle
- Sensor
Issues with Lag Time

- Occurs with all subcutaneous sensors
- Will delay alarm for hypoglycemia
- Recovery from hypoglycemia may not be apparent on sensor
- Will affect calibration of sensor
  - Calibration should not be done when glucose values are changing rapidly
Moral of the Story....

- More Frequent Calibration is NOT always Better.
- It is better to selectively calibrate when BG is relatively stable.
- BG and CGM will not always agree this is NORMAL and EXPECTED.
The Devices

- Paradigm® 722 System
- Guardian® RT
- Dexcom® STS
- Navigator
Abbott FreeStyle Navigator Sensor

Sensor Delivery Unit

Sensor

Transmitter

Receiver

Sensor
DexCom STS Sensor
Side View Showing Needle Sensors

CGMS - 722  Navigator  Dexcom
## Device Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Paradigm 722</th>
<th>DexCom</th>
<th>Navigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of change arrows</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Programmable Threshold Alarm</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Projected low alarm</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Days of wear</td>
<td>3</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Ability to download</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ability to integrate with pump</td>
<td>Yes (MiniMed)</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Trend Arrows

 Navigator

 - Updated every minute

 Paradigm

 - Updated every 5 minutes

- >2 (mg/dL)/min

- 1 to 2 (mg/dL)/min

- -1 to 1 (mg/dL)/min

- -1 to -2 (mg/dL)/min

- < -2 (mg/dL)/min
Projected Glucose Levels in 20 Minutes with Arrows
Using Rate of Change Arrows

- If you are projected to be low in 20 minutes, take 10 grams of CHO to prevent the low
  - Example: Hypoglycemic alarm goes off, actual meter glucose is 85 mg/dL, but there is a down arrow
- Adjust insulin dose based on arrows
  - For 1 arrow or 45° arrow, change by 10%
  - For 2 arrows or 90° arrow, change by 20%

# Accuracy of Sensors

Kovatchev, electronic preprint, Diabetes Care, 2008

<table>
<thead>
<tr>
<th></th>
<th>Guardian</th>
<th>Dexcom</th>
<th>Navigator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accuracy 70-180 mg/dl</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median ARD%</td>
<td>15</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>% within 20%</td>
<td>73</td>
<td>52</td>
<td>72</td>
</tr>
<tr>
<td><strong>Accuracy &lt; 70 mg/dl</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median ARD%</td>
<td>14</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>% within 15 mg/dl</td>
<td>77</td>
<td>53</td>
<td>79</td>
</tr>
</tbody>
</table>
Possible Candidates

- Are not at goal despite adequate BG testing.
- Have a fear of hypoglycemia
- Have a history of hypoglycemia unawareness or severe hypoglycemia
- Pregnancy/ Preconception
- Gastroparesis
- Athletes
- Patients on medications like pramlintide and exenatide.
- May wear the sensor intermittently to better understand their own diabetes
PATIENCE is Important

Insulin Delivery

Carbohydrates and Exercise

Summary

<table>
<thead>
<tr>
<th>Glucose BG/SG</th>
<th>Insulin</th>
<th>Carbs</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average (mg/dL)</td>
<td>Total (U) 46.4</td>
<td>Total Carbs (grams) 334</td>
<td>Total Minutes -</td>
</tr>
<tr>
<td>High (mg/dL)</td>
<td>Basal (U) 10.9 23%</td>
<td>Average Carbs (grams) 57</td>
<td>Average Minutes -</td>
</tr>
<tr>
<td>Low (mg/dL)</td>
<td>Bolus (U) 35.5 77%</td>
<td># of Meals 5</td>
<td># of Episodes -</td>
</tr>
<tr>
<td># of Readings</td>
<td>Normal (U) 32.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td># of BG Hyps</td>
<td>Normal (U) 3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td># Hypo Excursions</td>
<td>Suspended Minutes 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Temp Basal Minutes 189</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Online Teaching Tool

• Teaches how and when to calibrate each sensor
• Issues with interstitial lag time
• How to use a sensor in real time
• Set hyper and hypoglycemic alarms
• Adjust insulin doses in real time
• Use downloaded reports for retrospective analysis
WELCOME to the original online Continuous Glucose Monitoring School!

This school is designed to help anyone who wants to learn more about continuous glucose monitoring:

- Parents
- Adults
- Teens
- Anyone currently using a CGM
- Anyone interested in a CGM
- Anyone with diabetes
- Health care providers with patients on a CGM

How to use the site:
1. Read through the introduction on CGM by clicking the 'Introduction' link in the navigation bar at the top of the page.
2. Click the 'Change' button above to select the CGM, insulin delivery method, and topic you want to learn about next.
3. Learn key guidelines for using the selected device by clicking the 'Guidelines' link in the navigation bar at the top of the page.
4. Test Yourself! Click 'Case Studies' in the navigation bar above to practice your new skills.
• [https://studies.jaeb.org/ndocs/extapps/CGMTTeaching](https://studies.jaeb.org/ndocs/extapps/CGMTTeaching)
Fifteen minutes ago you treated a meter confirmed low blood glucose of 62 mg/dl. Your blood glucose is now 97 mg/dl. Should you calibrate your sensor?

A - Yes, your blood glucose is within range which means it is always a good time to calibrate

B - No, your blood glucose could still be rising since you just treated a low

C - No, your blood glucose should be higher before calibrating
Fifteen minutes ago you treated a meter confirmed low blood glucose of 62 mg/dl. Your blood glucose is now 97 mg/dl. Should you calibrate your sensor?

- Yes, your blood glucose is within range which means it is always a good time to calibrate.
- No, your blood glucose could still be rising since you just treated a low.
- No, your blood glucose should be higher before calibrating.
Question 11a

It is bedtime and you have just given yourself a correction bolus for your high glucose of 250 mg/dl. Your Paradigm sensor is alarming continuously because you are high. What do you do?

A - Change the "high snooze" to 1 hour

B - Place device in a drawer in the kitchen so you can't hear the alarm

C - Put device on vibrate so you can sleep through it
JDRF CGM Study Group
Primary Cohort
Six Month Outcome Data

NEJM and 44th EASD Annual Meeting Rome, Italy
September 8, 2008
JDRF CGM STUDY SITES

- U. Washington
- Nemours
- Atlanta Diabetes Assoc.
- Joslin x 2
- U. Iowa
- Kaiser
- Stanford
- Yale
- Atlanta Diabetes Assoc.
- NORDC/U. Chicago
- Nemours
Major Eligibility Criteria

- **Inclusion**
  - Clinical diagnosis of type 1 diabetes for at least one year duration
  - Age $\geq$ 8 years
  - HbA1c 7.0% to 10.0%
  - Using insulin pump or $\geq$ 3 insulin injections per day
Sample Size Estimates

- ~110 subjects with type 1 diabetes in each of three pre-defined age groups:
  - >25 years, 15-24 years, and 8-14 years
- This gives 90% power to detect a true mean difference of 0.5 in HbA1c even if 15% dropout or are noncompliant with protocol.
Fix or delete animation
jmlawrence, 8/29/2008
Follow-up Over 26 Weeks

- Clinic visits at weeks 1, 4, 8, 13, 19, and 26
- One scheduled phone call between each visit
- Subjects downloaded devices weekly at home (if able)
- Control group uses blinded RT-CGM at weeks 13 and 26
- HbA1c measured locally at each visit
- HbA1c measured by central laboratory (University of Minnesota) at 0, 13 and 26 weeks
HbA1c at enrollment by Age Group

Mean baseline HbA1c: 7.8%
Other Baseline Characteristics

**Gender**
- Female: 56%
- Male: 44%

**Race/Ethnicity**
- Non-Hispanic White: 92%
- Non-White: 8%
I messed up this slide. Needs to have white background on both or neither slide. If blue background remains, need to use another color for female and NHW so the legend does not blend with the background.

jmlawrence, 8/29/2008
Other Baseline Characteristics

**Insulin Modality**
- 80% MDI (Multiple Daily Injections)
- 20% Pump

**Severe Hypoglycemia in the last 6 Months**
- 93% None
- 7% ≥ 1 episode
Study Completion

- Visit completion rate ranged from 95% to 100%.

- Protocol-specified phone contacts completion rate ranged from 93% to 98%.

- 26-week outcome visit completion rate was 162 of 165 in CGM group and 155 of 157 in the Control Group.

- Two control group patients (both 8-14 years old) initiated CGM use before the 26-week visit.
Study Outcomes

Efficacy

Primary Outcome
– Difference in the change in A1c from baseline to 26 weeks

Secondary Outcomes:
% of subjects in each group with
– A1c < 7.0%
– 10% relative drop
– 0.5% absolute reduction

Safety
– Severe Hypoglycemia (requiring assistance)
Changes in A1c in \( \geq 25 \) yr olds

*Error bars stand for 95% CI.*
Changes in A1c in ≥ 25 yr olds

Difference: -0.53%
P-value < 0.001
Secondary A1c Outcomes in ≥ 25 yr olds

- RT-CGM
- Control

P = 0.003
P < 0.001
P = 0.005
P = 0.003
Percent Values > 10.0 mmol/L
(180 mg/dL) Age ≥ 25 years, RT-CGM Group

Percent

Overall  MN-6am  6am-Noon  Noon-6pm  6pm-MN

Baseline 26 Weeks
Percent Values > 10.0 mmol/L (180 mg/dL) Age ≥ 25 years, Control Group

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>26 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td>MN-6am</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>6am-Noon</td>
<td>37</td>
<td>33</td>
</tr>
<tr>
<td>Noon-6pm</td>
<td>36</td>
<td>35</td>
</tr>
<tr>
<td>6pm-MN</td>
<td>40</td>
<td>36</td>
</tr>
</tbody>
</table>
Percent Values $\leq 3.9$ mmol/L (70 mg/dL) Age $\geq 25$ years, RT-CGM Group

Baseline 26 Weeks

- Overall: 4.2, 3.9
- MN-6am: 6.2, 5.8
- 6am-Noon: 4.6, 4.2
- Noon-6pm: 5.2, 3.3
- 6pm-MN: 6.2, 3.9
Percent Values ≤ 3.9 mmol/L (70 mg/dL) Age ≥ 25 years, Control Group

Baseline 26 Weeks

Overall MN-6am 6am-Noon Noon-6pm 6pm-MN

Percent

5.6 5.8 5.1 5.2 5.0 5.0

6.6 6.6 5.7 5.0 6.2
Percent Values ≤ 2.8 mmol/L (50 mg/dL) Age ≥ 25 years, RT-CGM Group

Baseline vs 26 Weeks

<table>
<thead>
<tr>
<th>Time</th>
<th>Overall</th>
<th>MN-6am</th>
<th>6am-Noon</th>
<th>Noon-6pm</th>
<th>6pm-MN</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 Weeks</td>
<td>2.2</td>
<td>3.1</td>
<td>1.6</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.8</td>
<td>0.9</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Overall 26 Weeks compared to Baseline.
Percent Values $\leq 2.8$ mmol/L (50 mg/dL) Age $\geq 25$ years, Control Group

![Graph showing percent values at different times](chart.png)
Changes in A1c in 8-14 yr olds

P-value = 0.29

RT-CGM: -0.37
Control: -0.22

P-value = 0.29
Secondary A1c Outcomes in 8-14 yr olds

- RT-CGM
- Control

- P=0.01
- P=0.04
- P=0.009

- <7.0
- >10% drop
- drop ≥0.5
Changes in A1c in 15-24 yr olds

P-value = 0.52

RT-CGM: -0.18
Control: -0.21

P-value = 0.52
Mean Hours of CGM Use by Age Group

- Age ≥ 25
- Age 8-14
- Age 15-24

<table>
<thead>
<tr>
<th>Week 1-4</th>
<th>5-8</th>
<th>9-13</th>
<th>14-17</th>
<th>18-21</th>
<th>22-26</th>
</tr>
</thead>
<tbody>
<tr>
<td>140</td>
<td>120</td>
<td>110</td>
<td>100</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>120</td>
<td>110</td>
<td>100</td>
<td>90</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>100</td>
<td>90</td>
<td>80</td>
<td>70</td>
<td>60</td>
<td>50</td>
</tr>
</tbody>
</table>
The Teen Brain

- Myelination increases through childhood
- Axonal pruning increases coherent white matter bundles and cognitive function
- Prefontal cortex does not reach adult levels until 21-25 years of age
Relationship Between Change in A1c and Frequency of CGM Use

![Graph showing the relationship between change in glycated hemoglobin and CGM use frequency across different age groups.](image)
Sensor Wear and A1c Outcome by Subject Age

<table>
<thead>
<tr>
<th>Age</th>
<th>% using sensor 6 or more days/week at study end</th>
<th>Change in A1c at study end</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-&lt;11</td>
<td>Above 0 X 100 = % wearing 6 days/week, Below 0 = change in A1c at study end</td>
<td></td>
</tr>
<tr>
<td>11-&lt;15</td>
<td>-0.8</td>
<td></td>
</tr>
<tr>
<td>15-&lt;18</td>
<td>-0.6</td>
<td></td>
</tr>
<tr>
<td>18-&lt;21</td>
<td>-0.4</td>
<td></td>
</tr>
<tr>
<td>21-&lt;25</td>
<td>-0.2</td>
<td></td>
</tr>
<tr>
<td>25-&lt;40</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>40-&lt;50</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>&gt;50</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

Age
## Baseline Factors for 8-24 year olds by CGM Use

(N=113)

<table>
<thead>
<tr>
<th></th>
<th>CGM &lt;4 days/week (n=18)</th>
<th>CGM 4-&lt;6 days/week (n=50)</th>
<th>CGM ≥6 days/week (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>61%</td>
<td>52%</td>
<td>44%</td>
</tr>
<tr>
<td>Injection Rx</td>
<td>39%</td>
<td>28%</td>
<td>16%</td>
</tr>
<tr>
<td>Daily SMBG</td>
<td>4.8 ± 1.4</td>
<td>5.9 ± 2.1</td>
<td>7.0 ± 2.0</td>
</tr>
</tbody>
</table>
# Severe Hypoglycemic Events

<table>
<thead>
<tr>
<th></th>
<th>CGM (N=165)</th>
<th>Control (N=157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects with ≥1 severe event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-14 yrs</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>15-24 yrs</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>≥25 yrs</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>
Impact of RT-CGM on Rate of Severe Hypoglycemia Compared to DCCT* 

*not including the one patient with 6 episodes

NEJM 1993;329:977
A1c <7.0 and No Severe Hypoglycemia
Effect of RT-CGM on Glycemic Variability

Mean Amplitude of Glycemic Excursion (MAGE) did not change in any of the three age groups.

Absolute rate of change of glucose declined from $0.041 \pm 0.01$ to $0.037 \pm 0.008$ mmol/L/min ($0.73 \pm 0.18$ to $0.66 \pm 0.15$ mg/dL/min) in the adult group ($P = 0.07$).
Summary

- As anticipated, there was a significant interaction between treatment group and age group in the change in A1c with CGM use ($p = 0.003$).
- In the >25 year olds, CGM substantially improved all A1c measures of glycemic control.
- No change was observed in 15-24 yr olds.
- In 8 to 14 year olds, although there was no difference in the change in A1c, a greater percentage of CGM subjects had a relative 10% or more reduction in HbA1c and a greater percentage achieved a HbA1c level <7.0%.
- Near-daily CGM use was associated with similar benefit on HbA1c at all ages.
- Hypoglycemia did not increase even in the adult group who lowered A1c values.
Requirements for Success

• Good understanding of “basics” of intensive insulin therapy
• Patient attitude and perspective
  – Motivation
  – Little fear of new technologies
  – Ability to react to trends and not specific numbers
  – Ability to accept previous perceptions regarding own diabetes may be incorrect (response to certain foods, lag times)
• Willingness to wear device most of the time, ideally 24/7
Requirements for Success

• **Provider** attitude and perspective
  – Ideally working with a team of clinicians expert in diabetes and insulin management
  – Ability to accept pre-conceived notions about insulin treatment may be incorrect
  – Ability to appreciate that successful insulin therapies can be extremely variable from patient to patient
  – Appreciation that there is a significant time commitment both for initial training and on-going follow-up
Implications of RT-CGM

• Like all modern-day diabetes therapies, “success” is still patient-dependent and CGM is simply another tool to assist in improving diabetes control

• Patients who do best with this technology are those who change their behaviors based on real-time and retrospective review of their data

• Successful use of RT-CGM requires more, not less attention to diabetes management
At Study Onset A1c = 8.2
And Persistent Postprandial Hyperglycemia, Especially After Breakfast
At 3 Month Visit A1c = 6.2 And Has Eliminated Carbohydrates At Breakfast And Gives A Pre-bolus Before Lunch And Dinner
Drill Bit Through Thumb
Drill Bit Through Thumb

**Glucose (mg/dL)**

- Paradigm BG
- Meter BG
- Sensor
- Sensor Alarm
- Target Range
- Hypo

**Insulin Delivery**

- Pump Alarm
- Bolus
- Square Bolus
- Basal
- Temp Basal
- Suspend

Graphs showing glucose levels and insulin delivery over time.
JDRF CGM Study Group Secondary Cohort Randomized Clinical Trial

Efficacy and Safety of Continuous Glucose Monitoring in Patients with Type 1 Diabetes with A1c Levels <7.0% on entry into the study
Major Eligibility Criteria

➢ Inclusion
  • Clinical diagnosis of type 1 diabetes for at least one years duration
  • Age ≥8 years
  • HbA1c < 7.0 %
  • Using insulin pump or ≥ 3 insulin injections per day

➢ Exclusion
  • Significant psychiatric or medical disorder
  • Home use of RT-CGM in past 6 months
  • Pregnant or planning to become pregnant in next year
Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CGM</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>67</td>
<td>62</td>
</tr>
<tr>
<td>Age (yrs) mean ± SD</td>
<td>29.3 ± 16.3</td>
<td>32 ± 17.7</td>
</tr>
<tr>
<td>Duration DM (yrs) mean ± SD</td>
<td>16.3 ± 15.5</td>
<td>18.4 ± 14.7</td>
</tr>
<tr>
<td>Pump Rx N (%)</td>
<td>62 (93%)</td>
<td>49 (79%)</td>
</tr>
<tr>
<td>MDI Rx N (%)</td>
<td>5 (7%)</td>
<td>13 (21%)</td>
</tr>
<tr>
<td>Insulin dose (U/kg/day) mean ± SD</td>
<td>0.6 ± 0.2</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>Meter tests per day mean ± SD</td>
<td>7.3 ± 2.4</td>
<td>6.8 ± 2.4</td>
</tr>
</tbody>
</table>
Change in the Frequency of Sensor Glucose Levels <70 mg/dL

<table>
<thead>
<tr>
<th></th>
<th>Median minutes/day</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline RT-CGM</td>
<td>91</td>
<td>0.002</td>
</tr>
<tr>
<td>26 Wks RT-CGM</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Baseline Control</td>
<td>96</td>
<td>0.43</td>
</tr>
<tr>
<td>26 Wks Control</td>
<td>91</td>
<td></td>
</tr>
</tbody>
</table>

P = 0.16
Changes in A1c From Baseline to 26 Weeks

*Error bars stand for 95% CI.
Compound Hypoglycemia and A1c Outcomes

HbA1c ↓ or ↑ = ≥0.3%
Glucose <70 ↓ or ↑ = >42 min

A = HbA1c ↓ & no severe hypo, p<0.001
B = HbA1c ↓ & glucose <70 not ↑, p=0.007
C = Glucose <70 ↓ & HbA1c not ↑, P=0.005
D = Either ‘B’ or ‘C’, P=0.003
Conclusion of Results from JDRF Randomized Control Trial for Subjects with an A1c ≤ 7%

Although the frequency of hypoglycemic glucose levels ≤70 mg/dL did not significantly differ between treatment groups, the weight of evidence suggests that continuous glucose monitoring is beneficial for individuals with T1DM who have already achieved HbA1c <7.0% in maintaining exquisite control of diabetes.
The Human Interface

• The real estate of skin
  – All want to wear just one device (as sensor and pump)

• Wearing/carrying controllers/receivers
  – Want a single device to control pump and receive sensor signal
    • Cell phone
    • PDA
    • MP3
    • Games
Pumps and Sensors Communicate to a Shared Platform
Nocturnal Severe Hypoglycemia (SH)

Incidence:
- 55% of SH in DCCT (Diabetes Care 18,1415,1995)
- 75% of SH in children (Davis, Diabetes Care 20:22,1997)

Causes:
- No decrease in insulin
- Attenuated glucagon and epinephrine responses
  a. Particularly at night
  b. Particularly with antecedent hypoglycemia or prior exercise
  c. Reduced cognition: 71% of youth failing to respond to nocturnal alarms (Buckingham, Chase et al. DT&T, 7,440,2005)
Hypoglycemic Predictive Algorithms

- **SP**: Statistical linear prediction: multiple empirical, statistical models are used to estimate future blood glucose values and their error bounds.
- **KF**: Kalman filter to estimate glucose and its rate-of-change (ROC), which are then used to predict future glucose levels.
- **HIIR**: Hybrid Infinite Impulse Response filter that generates glucose predictions using previous CGM data.
- **NLA**: Numerical logical algorithm that predicts by numerical estimation of the ROC and a set of logical expressions.
- **LP**: Linear projection based on a short term linear extrapolation of the glucose trend.
Results – Hypoglycemia Prediction

(2/5) ~50 min, ~115 mg/dL
(3/5) ~45 min, ~108 mg/dL
(5/5) ~35 min, ~100 mg/dL

Dassau et al. 68th ADA meeting San Francisco CA, 06.08.08
CL2-MW 9/3/08
3 Alarm, Threshold 80 mg/dl, Horizon 35 min

ROC = -.36 mg/dl-min
# Results Of Using Two Algorithms to Trigger Pump Shut-Off

<table>
<thead>
<tr>
<th></th>
<th>Success</th>
<th>Failure</th>
<th>% Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Subject</td>
<td>12</td>
<td>4</td>
<td>75%</td>
</tr>
<tr>
<td>Per Event</td>
<td>21</td>
<td>4</td>
<td>84%</td>
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</table>
Metabolic Control

Effect of Metabolic Control At Onset of Diabetes on Progression of Type 1 Diabetes
• Specific Aim: To determine if early and sustained restoration of metabolic control will improve C-peptide compared to routine diabetes management

• Secondary Aims:
  1. To determine if improved metabolic control will have an impact on the underlying autoimmune process
  2. To assess changes in metabolic control
     - Hemoglobin A1c levels
     - Blood glucose levels
Probability of maintaining C-peptide secretion (stimulated C-peptide level $\geq 0$)

![Graph showing the probability of maintaining C-peptide secretion over time for intensive and conventional treatment groups.]

Number of patients in each treatment group who were evaluated

<table>
<thead>
<tr>
<th>Year</th>
<th>Intensive</th>
<th>Conventional</th>
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</thead>
<tbody>
<tr>
<td>Eligibility</td>
<td>138</td>
<td>165</td>
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<tr>
<td>Year 1</td>
<td>131</td>
<td>150</td>
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<tr>
<td>Year 2</td>
<td>80</td>
<td>63</td>
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<td>Year 3</td>
<td>53</td>
<td>32</td>
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<td>Year 4</td>
<td>32</td>
<td>22</td>
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<tr>
<td>Year 5</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Year 6</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>


Annals of Internal Medicine
The Effect of C-Peptide Response on Long-Term Complications and Hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>Intensive Treatment Group</th>
<th>Conventional Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responders</td>
<td>Non responders</td>
</tr>
<tr>
<td>Retinopathy*</td>
<td>2.0</td>
<td>4.7</td>
</tr>
<tr>
<td>Nephropathy*</td>
<td>1.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Severe Hypoglycemia*</td>
<td>6.6</td>
<td>17.3</td>
</tr>
</tbody>
</table>

* Rate per 100 patient-years
Metabolic Control Protocol

• 2 year study, subjects on treatment for 2 years

• 72 new onset type 1 subjects
  – Age range 3 – 45 years (10-45 initially)
  – 2/3rds to treatment arm, 1/3 to standard treatment arm
  – Intent is to randomize at time of diagnosis
    • Window up to 1 week post diagnosis

• 4 sites initially: Stanford, Yale, Barbara Davis Center, LA Children’s
Intensive Metabolic Control Group

1) With a SQ sensor/SQ insulin closed-loop for 4 days when beginning oral meals (CRC)
2) With a sensor augmented SQ pump for 2 years (Home)
Standard Care Group

• Intensive management by the medical staff at the participating institution
• 5 day “retrospective” CGMS data collected at onset and for 5 days preceding each clinic visit (every 3 months)
• Subjects would be allowed to see downloaded results of CGMS data
Eligibility Criteria

• Participants must meet all of the following criteria:
  – Have been diagnosed with Type 1 Diabetes within the last 7 days.
  – 10 to less than 46 years of age
  – If female not pregnant and agree to avoid pregnancy.
  – Willing to be randomized to either group.
  – Able to send data electronically every month.
To Learn More:

• Visit any of the following websites:
  – TrialNet:
    • http://www.diabetestrialnet.org/patientinfo/studies.htm
  – DirecNet:
    • http://public.direc.net/general/currentStudies.htm
  – Stanford University Department of Pediatric Endocrinology:
    • http://dped.stanford.edu/research/

• Contact: Bruce Buckingham
  – buckingham@stanford.edu