Emerging Automated Insulin Delivery Systems

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International Diabetes Center
Park Nicollet & HealthPartners
Minneapolis, MN
Richard M. Bergenstal (RMB) has participated in clinical research, a scientific advisory board or served as a consultant for:

- Eli Lilly
- Novo Nordisk
- Sanofi
- Hygieia
- Abbott Diabetes Care
- DexCom
- Medtronic Diabetes
- Johnson and Johnson
- Roche Diabetes Care

RMB owed Merck stock in the past year (no longer does) and is a volunteer for ADA & JDRF & receives NIH funding for HCL work.

RMB’s employer, non-profit HealthPartners Institute, contracts for his services and he receives no personal income from these activities.
I hope Emmett can afford his life-saving insulin!

I hope to see an artificial pancreas come to market during my career!
Average Current A1C by Age

20% had SH (seizure coma) in last 12 months

Type 1 Diabetes by A1c

A1c 5.7
A1c 6.1
A1c 6.1
A1c 6.7
A1c 6.7
A1c 6.7
A1c 7.7
A1c 7.8
A1c 7.8
A1c 9.2
A1c 9.7
A1c 9.9
### Type 1 Diabetes by A1c

<table>
<thead>
<tr>
<th>A1C %</th>
<th>% TIR 70-180</th>
<th>% Time Hypo (&lt;70)</th>
<th>CV %</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.7</td>
<td>83</td>
<td>1% 15 min/d</td>
<td>26</td>
<td>HCL (670G)</td>
</tr>
<tr>
<td>6.7</td>
<td>69</td>
<td>6% 90 min/d</td>
<td>42</td>
<td>CSII</td>
</tr>
<tr>
<td>6.7</td>
<td>51</td>
<td>9% 135 min/d</td>
<td>53</td>
<td>MDI</td>
</tr>
</tbody>
</table>
What is the first question - you always ask - when you try to sort out a pattern?

Is it Laurel?  or  Is it Yanny?
## Ambulatory Glucose Profile – AGP

**First Name** | **Last Name** | **15 Feb 2016 - 01 Mar 2016 (14.6 days)**
--- | --- | ---

**CGM Metrics**

<table>
<thead>
<tr>
<th>Glucose Statistics</th>
<th>Avg Glucose mg/dL</th>
<th>GMI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>98 - 115 mg/dL</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
<td>156</td>
<td>7.0%</td>
</tr>
<tr>
<td><strong>&lt; 6 mg/dL</strong></td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
<td><strong>Level 1</strong></td>
<td><strong>In Target Range</strong></td>
</tr>
<tr>
<td><strong>Below 54 mg/dL</strong></td>
<td><strong>Below 70 mg/dL</strong></td>
<td><strong>70 - 180 mg/dL</strong></td>
</tr>
</tbody>
</table>

**TIR**

<table>
<thead>
<tr>
<th>Measured TIR</th>
<th>HbA1c</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>40%</strong></td>
<td>8.1%</td>
<td>7.1-9.1%</td>
</tr>
<tr>
<td><strong>50%</strong></td>
<td>7.7%</td>
<td>6.7-8.7%</td>
</tr>
<tr>
<td><strong>60%</strong></td>
<td>7.3%</td>
<td>6.3-8.3%</td>
</tr>
<tr>
<td><strong>70%</strong></td>
<td>6.9%</td>
<td>5.9-7.9%</td>
</tr>
<tr>
<td><strong>80%</strong></td>
<td>6.5%</td>
<td>5.5-7.5%</td>
</tr>
</tbody>
</table>

**Personal communication; secondary analysis on data set from Fallacy of A1c, Beck, Bergenstal et al. D Care 2017**

**A1C**

670G Pivotal Trial
JAMA 2016

<table>
<thead>
<tr>
<th>Value</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;250</td>
<td>5%</td>
<td>5.6%</td>
</tr>
<tr>
<td>181-250</td>
<td>20%</td>
<td>19%</td>
</tr>
<tr>
<td>70-180</td>
<td>72%</td>
<td>72.4%</td>
</tr>
<tr>
<td>54-69</td>
<td>2%</td>
<td>2.2%</td>
</tr>
<tr>
<td>&lt;54</td>
<td>1%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>
CGM Glucose Pattern Summary
March 11, 2016 – March 25, 2016 (15 days)

CGM Device: FreeStyle Libre Pro  XX% Compliant w/Calibration  XX% Time Worn

Summary

<table>
<thead>
<tr>
<th>Average Glucose</th>
<th>Glucose Management Index (SMI)*</th>
<th>Time In Range</th>
<th>Coefficient of Variation (CV)</th>
<th>Standard Deviation (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>214 mg/dL</td>
<td>9.1%</td>
<td>56.6%</td>
<td>49.3%</td>
<td>105 mg/dL</td>
</tr>
<tr>
<td>88-116*</td>
<td>&lt;6*</td>
<td>-</td>
<td>19-25*</td>
<td>10-26*</td>
</tr>
<tr>
<td>Above 180 mg/dL</td>
<td>(above 250 mg/dL: 38.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In Target Range</td>
<td>(70-180 mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below 70 mg/dL</td>
<td>(below 54 mg/dL: 3.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Formerly known as Estimated A1c (eA1C)  *Reference ranges calculated from population without diabetes.

Ambulatory Glucose Profile
Curves/plots represent glucose frequency distributions by time regardless of date.

[Graph showing glucose levels over time]
Technology For Diabetes Management Has Come A Long Way

Auto Syringe
First Commercialized Insulin Pump in the US
1979

MiniMed™ 670G System
First Commercialized Hybrid Closed Loop system in the US
April 2017
Artificial pancreas treatment for outpatients with type 1 diabetes: systematic review and meta-analysis

Eleni Bekiari,1 Konstantinos Kitsios,2 Hood Thabit,3 Martin Tauschmann,3 Eleni Athanasiadou,1 Thomas Karagiannis,1 Anna-Bettina Haidich,4 Roman Hovorka,3 Apostolos Tsapas1,5

OPEN ACCESS  BMJ 2018;361:k1310 2 March 2018

AP vs Control

- Increased TIR (70=180) 2 hr. 20 min. ≈ 10%
- Decreased TIIHyper (>180) 2 hr. ≈ 8.3%
- Decreased TIIHypo (<70) 20 min ≈ 1.4%

- Studies Short
- Often look at Feasibly or Safety – not long term Effectiveness
- Variation in metrics assessed
- Need common repository clinical trial data
- Broaden inclusion criteria including ethnic minorities
2016

Research Letter | September 15, 2016

Safety of a Hybrid Closed-Loop Insulin Delivery System in Patients With Type 1 Diabetes

2017

Glucose Outcomes with the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults with Type 1 Diabetes
Pivotal Trial MiniMed™ 670G System (JAMA online Sept. 15, 2016) Single-arm, Non-randomized Study (FDA approved Sept. 28, 2016)

- **10 sites** (9 US, 1 Israel) N=124
- **Type 1 diabetes > 2yrs**
  - A1C <10%
  - Adolescent: 14-21 yrs.
  - Adult: 22-75 yrs.
- Pump ≥6 months, +/-CGM
- Run-in: Open loop (Manual Mode) 2wks.
- Study: Closed loop (Auto Mode) 3 mos.
  - 6-day / 5-night hotel stay
  - 24 hour FST (reference i-STAT)

**A1C STUDY RESULTS**

- **A1C**
  - Baseline = 7.4±0.9%
  - Study End = 6.9±0.6%
- Safety in Study Phase
  - 0 Severe Hypoglycemia
  - 0 DKA


Moving Beyond A1C
Time in Range: Time in Hypoglycemia and Hyperglycemia

**Day and Night (p<0.001)**

<table>
<thead>
<tr>
<th>Sensor Glucose</th>
<th>Run-in % Time in Range</th>
<th>Study % Time in Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 300 mg/dL</td>
<td>2.3</td>
<td>1.7</td>
</tr>
<tr>
<td>&gt; 180 mg/dL</td>
<td>27.4</td>
<td>24.5</td>
</tr>
<tr>
<td>71 – 180 mg/dL</td>
<td>66.7</td>
<td>72.2</td>
</tr>
<tr>
<td>≤ 70 mg/dL</td>
<td>5.9</td>
<td>3.3</td>
</tr>
<tr>
<td>≤ 50 mg/dL</td>
<td>1.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Within-day SD</td>
<td>2.8</td>
<td>2.6</td>
</tr>
</tbody>
</table>

**Night Time Only (data on file)**

<table>
<thead>
<tr>
<th>Sensor Glucose</th>
<th>Run-in % Time in Range</th>
<th>Study % Time in Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 300 mg/dL*</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td>&gt; 180 mg/dL</td>
<td>26.8</td>
<td>21.6</td>
</tr>
<tr>
<td>71 – 180 mg/dL</td>
<td>66.8</td>
<td>75.3</td>
</tr>
<tr>
<td>≤ 70 mg/dL</td>
<td>6.4</td>
<td>3.1</td>
</tr>
<tr>
<td>≤ 50 mg/dL*</td>
<td>1.1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*Medtronic data on file
**MiniMed™ 670G System**
**Before And After Safety Trial**

**Median and Interquartile SG Values / Day & Night**

**A** All Patients  
**B** Adults  
**C** Adolescents *

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**HCL Utilization (% time):**

All Subjects = 87.2%, Adolescents = 75.8%, Adults = 88.0%

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*For type 1 patients 14 and over. WARNING: May not be safe for children under 7 or those requiring less than less 8 units of insulin per day.
Overnight (2200-0700) Range for SG Values

Tighter Glucose range overnight

Overnight (2200-0700) Range for Insulin Dosing

Wider Insulin delivery range overnight

Most patients program in multiple basal rates
- Alternate Basal Rates
Dawn Phenomenon – Unpredictable
Programming for Dawn Phenomenon is ineffective and may be hazardous

- Almost every patient had Dawn phenomenon at some point
- Those with DAWN – had it 56% of the nights (median) rate

Is this really a problem with CSII / SAP therapy today?
Can closed loop therapy help address this problem?

48-year-old male with T1D 30 yrs.

Overnight glucose control
Good

- Multiple basal rates
- A programmed increase from 1-3 AM (0.9-2.0 u/hr)

Conclusion:
Alternate basal rate overnight just right
48-year-old male with T1D 30 yrs.

Overnight glucose control - Hyperglycemic

Conclusion: Alternate basal rate overnight needs to be increased
48-year-old male with T1D 30 yrs.

Overnight glucose control - Hypoglycemic

Conclusion: Alternate basal rate overnight needs to be decreased
48-year-old male with T1D 30 yrs.

First night closed loop.
Overnight glucose control
Good

Second week closed loop
Overnight glucose control
Good
Presented ATTD 2018 Poster

EXPLORATORY ANALYSIS FOR SELECTED PATIENTS WITH DAWN PHENOMENON DURING THE MINIMED™ 670G HYBRID CLOSED-LOOP PIVOTAL TRIAL

Bergenstal RM, MD;¹ Chen X, PhD;² Liu M, BS;² Shin L;² Cordero TL, PhD;² Shin J, MBA, PhD;² Kaufman FR, MD²

¹International Diabetes Center-Park Nicollet, Minneapolis, MN, USA; ²Medtronic, Northridge, CA, USA

During Pivotal trial – 2 week run in:

• **66% of Pivotal trial 670G users had Dawn Phenomenon** at least 25% of the time
  o Rise in glucose (10 mg/dL) or basal rate (>10%) from 3AM to 6 AM

<table>
<thead>
<tr>
<th>Table 1. Glycemic metrics and basal insulin delivery, in patients meeting DP criteria, during the baseline run-in (Manual Mode) and study (Auto Mode-enabled) phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of SG across ranges, mg/dL (mmol/L)</td>
</tr>
<tr>
<td>Run-in</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>≤70 (≤3.9)</td>
</tr>
<tr>
<td>71-180 (&gt;3.9-10)</td>
</tr>
<tr>
<td>&gt;180 (&gt;10)</td>
</tr>
</tbody>
</table>

Presented ATTD 2018 Poster
In Patients with Dawn Phenomenon using 670G:

- Improved TIR from 67.9% to 77.3%
- Reduced TlHyper
- Reduced TlHypo

- 40%
- 52%
“As much as we don’t want to admit it, [the device is] smarter than we are.”
Dr. Amy Criego, pediatric endocrinologist, on the pump’s accuracy

16 & 17 yr. old high school friends (and their parents!!)

First-of-its-kind pump rolls out
16-year-old, Type 1 Diabetes

Blood sugar **before** Artificial Pancreas started

Normal blood sugar

Twice every night, for years, her father has checked her blood sugar and given her juice or insulin if needed!

**Blood Sugar after** Artificial Pancreas started - Day 1!
Closed Loop Algorithms

• PID (proportional-integral-derivative)
• MPC (model predictive control)
• Fuzzy Logic control
Hybrid Closed Loop in an Adolescent (24 hrs) (Manual meal boluses)

Hovorka R. et al.  Cambridge


Minimed 670G System: 3 Components

- MiniMed 670G pump
- Guardian 3 CGM
- Ascensia Contour Next Link 2.4 meter
• Small insulin boluses every 5 minutes based on sensor glucose
• Target BG of 120 mg/dl (can set Temp Target of 150 mg/dl)
• Must still carb count and bolus for meal
• Pump requires 48 hours of Manual Mode (starting at 12AM) for the algorithm to learn that patient’s insulin delivery patterns
• In Auto Mode, the only settings you can change are carbohydrate ratios and active insulin time
• Accurate Manual Mode settings will remain important
Minimed 670G Carelink Reports

- Assessment & Progress
- Weekly Review
- Adherence
- Logbook
- Device Settings
- Meal Bolus Wizard
Auto Mode vs manual mode on Minimed 670G system

Statistics

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto Mode (per week)</td>
<td>72% (5d 01hrs)</td>
<td>0% (0hrs)</td>
</tr>
<tr>
<td>Manual Mode (per week)</td>
<td>28% (1d 23hrs)</td>
<td>100% (7d 00hrs)</td>
</tr>
<tr>
<td>Sensor Wear (per week)</td>
<td>92% (6d 10hrs)</td>
<td>88% (6d 04hrs)</td>
</tr>
<tr>
<td>Average SG ± SD</td>
<td>151 ± 46 mg/dL</td>
<td>224 ± 68 mg/dL</td>
</tr>
<tr>
<td>Estimated A1C</td>
<td>6.9%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Average BG</td>
<td>167 ± 61 mg/dL</td>
<td>261 ± 68 mg/dL</td>
</tr>
<tr>
<td>BG / Calibration (per day)</td>
<td>6.6 / 3.1</td>
<td>5.0 / 1.2</td>
</tr>
<tr>
<td>Total daily dose (per day)</td>
<td>59 units</td>
<td>54 units</td>
</tr>
<tr>
<td>Bolus amount (per day)</td>
<td>33U (56%)</td>
<td>20U (37%)</td>
</tr>
<tr>
<td>Auto Basal / Basal amount (per day)</td>
<td>26U (44%)</td>
<td>34U (63%)</td>
</tr>
<tr>
<td>Set Change</td>
<td>Never</td>
<td>Never</td>
</tr>
<tr>
<td>Reservoir Change</td>
<td>Every 3.0 days</td>
<td>Every 2.0 days</td>
</tr>
<tr>
<td>Meal (per day)</td>
<td>5.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Carbs entered (per day)</td>
<td>143 ± 43g</td>
<td>166 ± 69g</td>
</tr>
<tr>
<td>Active Insulin time</td>
<td>2:30 hrs</td>
<td>3:00 hrs</td>
</tr>
</tbody>
</table>
Step 5: Review Exit Reason Details and time periods.

Step 6: Review bolus patterns and AIT sails.

Step 7: Review Auto-Basal and Basal rates.

Step 8: Note time change, temp targets, etc.
Case #1

• 38 year old with type 1 diabetes since age 14
• Mild retinopathy, did well on pump for years but now has 2 young children and not as focused on his care
• Has been on MiniMed™ 530G system for years; A1C in 7-7.5% range
• Mostly aware of hypoglycemia, but tends to run glucose high overnight just to be safe (even when he has CGM on – out of habit)
Manual Mode

Graph showing percentile comparison and time in range.

Hypoglycemic patterns:
- 1: 1:45 AM - 2:35 AM (1 occurrence)

Hyperglycemic patterns:
- 2: 1:00 PM - 2:30 PM
- 3: 5:00 PM - 11:40 PM
- 4: 9:35 AM - 10:35 AM

Statistics:
- Auto Mode (per week): 0% (0)
- Manual Mode (per week): 100% (70/70)
- Sensor Wear (per week): 87% (66/72)
- Average SG ± SD: 173 ± 51 mg/dL
- Estimated A1C: 7.2%
- Average BG: 166 ± 43 mg/dL
- DS / Calibration (per day): 0.0 ± 0.0
- Total daily dose (per day): 63 units
- Basal amount (per day): 31U (42%)
- Auto basal / basal amount (per day): 32U (31%)
- Insulin Change: 4
- Reservoir Change: 6
- Meal (per day): 1.8
- Carbs entered (per day): 137 ± 28g
- Active insulin time: 4.86 hrs

* red and yellow pump settings are displayed; ** only highest priority shown.
### Meal Bolus Wizard

#### 6/9/17 - 6/17/17 (15 Days)

**Data Sources:** Medtronic

**Generated:** 10/17/17, 2:54 PM

**Page 1 of 11**

#### Manual Mode

<table>
<thead>
<tr>
<th>Time</th>
<th>Bolus Count</th>
<th>Carb Ratio (g/L)</th>
<th>Avg. Glucose (g)</th>
<th>Avg. Bolus (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>morning</td>
<td>6</td>
<td>5.0</td>
<td>27 ± 6</td>
<td>5.4 ± 1.5</td>
</tr>
<tr>
<td>lunch</td>
<td>8</td>
<td>4.6</td>
<td>12 ± 5</td>
<td>115 ± 1.5</td>
</tr>
<tr>
<td>dinner</td>
<td>1</td>
<td>5.0</td>
<td>13 ± 7</td>
<td>137 ± 1.4</td>
</tr>
<tr>
<td>overnight</td>
<td>5</td>
<td>5.0, 5.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Breakfast - Analyzed Meals**

- Observations

**Lunch - Analyzed Meals**

- Observations

**Dinner - Analyzed Meals**

- Observations

**Overnight - Analyzed Meals**

- Observations
<table>
<thead>
<tr>
<th>Statistics</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto Mode (per week)</td>
<td>0% (0h)</td>
<td></td>
</tr>
<tr>
<td>Manual Mode (per week)</td>
<td>100% (7d 00h)</td>
<td></td>
</tr>
<tr>
<td>Sensor Wear (per week)</td>
<td>87% (6d 02h)</td>
<td></td>
</tr>
<tr>
<td>Average SG ± SD</td>
<td>173 ± 51 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Estimated A1C</td>
<td>7.7%</td>
<td></td>
</tr>
<tr>
<td>Average BG</td>
<td>166 ± 49 mg/dL</td>
<td></td>
</tr>
<tr>
<td>BG / Calibration (per day)</td>
<td>4.0 / 4.0</td>
<td></td>
</tr>
<tr>
<td>Total daily dose (per day)</td>
<td>63 units</td>
<td></td>
</tr>
<tr>
<td>Bolus amount (per day)</td>
<td>31U (49%)</td>
<td></td>
</tr>
<tr>
<td>Auto Basal / Basal amount (per day)</td>
<td>32U (51%)</td>
<td></td>
</tr>
<tr>
<td>Set Change</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Reservoir Change</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Meal (per day)</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Carbs entered (per day)</td>
<td>137 ± 28g</td>
<td></td>
</tr>
<tr>
<td>Active Insulin time</td>
<td>4:00 hrs</td>
<td></td>
</tr>
</tbody>
</table>
Going into Auto Mode:

**Basal rates:**
- 12AM 1.05 units/hr.
- 4AM 1.60 units/hr.
- 12PM 1.40 units/hr.
- 6PM 1.70 units/hr.
- 10PM 1.00 units/hr.

**Carb ratios:**
- 12AM 5
- 11AM 4.5
- 4PM 5

**Sensitivity:** 12AM 40, 4PM 36

**Active Insulin Time (AIT):** 4:00hrs

**Changes made before Auto Mode:**
- 10% reduction in basal rates
- Change ICR from 4.5 to 4 at lunch
- Change AIT to 3 hours
<table>
<thead>
<tr>
<th>Statistics</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto Mode (per week)</td>
<td>86% (6d 00h)</td>
<td>0% (0h)</td>
</tr>
<tr>
<td>Manual Mode (per week)</td>
<td>14% (1d 00h)</td>
<td>100% (7d 00h)</td>
</tr>
<tr>
<td>Sensor Wear (per week)</td>
<td>94% (6d 14h)</td>
<td>87% (6d 02h)</td>
</tr>
<tr>
<td>Average SG ± SD</td>
<td>160 ± 57 mg/dL</td>
<td>173 ± 51 mg/dL</td>
</tr>
<tr>
<td>Estimated A1C</td>
<td>7.2%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Average BG</td>
<td>176 ± 65 mg/dL</td>
<td>166 ± 49 mg/dL</td>
</tr>
<tr>
<td>BG / Calibration (per day)</td>
<td>8.2 / 4.3</td>
<td>4.3 / 4.0</td>
</tr>
<tr>
<td>Total daily dose (per day)</td>
<td>72 units</td>
<td>63 units</td>
</tr>
<tr>
<td>Bolus amount (per day)</td>
<td>35U (49%)</td>
<td>31U (49%)</td>
</tr>
<tr>
<td>Auto Basal / Basal amount (per day)</td>
<td>37U (51%)</td>
<td>32U (51%)</td>
</tr>
<tr>
<td>Set Change</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Reservoir Change</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Meal (per day)</td>
<td>3.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Carbs entered (per day)</td>
<td>149 ± 27g</td>
<td>137 ± 28g</td>
</tr>
<tr>
<td>Active Insulin time</td>
<td>3:00 hrs</td>
<td>4:00 hrs</td>
</tr>
</tbody>
</table>

Hypoglycemic patterns(2):
1. 3:59 AM- 5:19 AM (1 occurrences)
2. 2:03 AM (1 occurrences)
One Week Later...

Still:
- Spiking after dinner
- High most nights
- Strengthened dinner carb ratio from 4.5 to 4.0
One Month Later…
• Not well studied but often encountered
Exercise and AID

• Limited data, “no one-size fits all” solution

Closed-Loop Control During Intense Prolonged Outdoor Exercise in Adolescents with T1 Diabetes

• 32 adolescents with T1D randomized to remotely-monitored Sensor Augmented Pump (SAP) vs. the University of VA Closed Loop system (CLC)
• 5 day ski camp, skiing about 5 hrs. per day
• Evaluated for time in range (based on skiing ability)

Cgm values during the day for both SAP and Closed Loop

TIR (70-180 mg/dL) improved
- 71.3% CLC
- 64.7% SAP

Time <70 mg/dL
- halved in both groups
- most pronounced in the beginners

Exercise: example starting point

**Use Temp Target** (150 mg/dL)
- Start Temp Target 1 – 2 hours before
- Stop Temp Target 1-2 hours after
- May need longer Temp Target if exercise is extensive (possibly needed overnight)
- Should consider carbs during if activity is long or intense

**If hypoglycemia occurs using this method:**
- Re-assess the use of uncovered carbs *before* exercise as resulting glucose rise may increase Auto Basal delivery
- Consider having patient suspend for at least some of the exercise time
Considerations for AID During Illness

• Initially, continue in Auto Mode
• Continue to recommend usual “sick day” diabetes rules: frequent glucose checks, monitoring for ketones (preferably plasma), adequate fluid replacement, and replace (or carefully check) infusion site, etc.
• If intake and glucose trending low: may need Temp Target (150 mg/dL)
• If glucose trending high and intake is adequate: do frequent glucose checks to receive additional boluses from algorithm.
• If having frequent exits to Manual Mode, or if more insulin is needed than is being delivered by the system -- stay in Manual Mode with Suspend before low turned on
• If still high consider insulin by injection by syringe, replace infusion set (again), call medical team

WARNING: Do not use Auto Mode for a period of time after giving a manual injection of insulin by syringe or pen. Manual injections are not accounted for in Auto Mode. Therefore, Auto Mode could deliver too much insulin. Too much insulin may cause hypoglycemia. Consult with your healthcare professional for how long you need to wait after a manual injection of insulin before you resume Auto Mode.
AID in Gastroparesis

- MiniMed™ 670G system not studied in gastroparesis
- When going into Auto Mode, establish what has worked for the patient in the past, and if they’re willing to try working to find a similar method while in Auto Mode
  - If using Dual Wave™ bolus (in Manual Mode) or split bolus, consider having them divide their carb amount (e.g. bolus for ½ the carbs upfront, and the other ¼ to ½ after 1-2 hours – can possibly give less to allow the auto basal to respond)
- Avoid quick bolus
What improvements in the Hybrid Closed Loop System would have the most impact?

- **Continued good diabetes management education**
- Sensor improvements (accuracy and size)
- Faster acting insulin
- Algorithm adjustments (more aggressive insulin increase & decrease)
- Infusion Set improvements (less occlusion, longer duration, 2 in 1)
- Improvements in data reports and integration with EMR, RT reports
- More HCL systems available - enhanced innovation & competition
- Trials or experience with more subgroups of patient types
- Multi-hormone system?
### 22 Factors That Affect Blood Glucose

#### FOOD
- **↑ 1. Carbohydrates**
- **↑ 2. Fat**
- **↑ 3. Protein**
- **↑ 4. Caffeine**
- **↓ 5. Alcohol**

#### BIOLOGICAL
- **↑ 11. Dawn phenomenon**
- **↑ 12. Infusion set issues**
- **↑ 13. Scar tissue and lipodystrophy**
- **↑ 14. Insufficient sleep**
- **↑ 15. Stress and illness**
- **↑ 16. Allergies**
- **↑ 17. A higher glucose level**
- **↓ 18. Periods (menstruation)**
- **↓ 19. Smoking**

#### MEDICATION
- **↓ 6. Medication dose**
- **↑ 7. Medication timing**
- **↓ 8. Medication interactions**

#### ACTIVITY
- **↓ 9. Light exercise**
- **↑ 10. High-intensity and moderate exercise**

#### ENVIRONMENTAL
- **↑ 20. Insulin that has gone bad**
- **↑ 21. An accurate blood glucose reading**
- **? 22. Altitude**

---

**Bright Spots & Landmines**

*The Diabetes Guide I Wish Someone Had Handed Me*  
**By Adam Brown**
# Factors That Affect BG

<table>
<thead>
<tr>
<th>Food</th>
<th>Biological</th>
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</thead>
<tbody>
<tr>
<td>↑↑ 1. Carbohydrate quantity</td>
<td>↑ 20. Insufficient sleep</td>
</tr>
<tr>
<td>↑↑ 2. Carbohydrate type</td>
<td>↑ 21. Stress and illness</td>
</tr>
<tr>
<td>↑↑ 3. Fat</td>
<td>↓ 22. Recent hypoglycemia</td>
</tr>
<tr>
<td>↑↑ 4. Protein</td>
<td>↑ 23. During-sleep blood sugars</td>
</tr>
<tr>
<td>↑↑ 5. Caffeine</td>
<td>↑ 24. Dawn phenomenon</td>
</tr>
<tr>
<td>↓↓ 6. Alcohol</td>
<td>↑ 25. Infusion set issues</td>
</tr>
<tr>
<td>↑↑ 7. Meal timing</td>
<td>↑ 26. Scar tissue and lipodystrophy</td>
</tr>
<tr>
<td>↑↑ 8. Dehydration</td>
<td>↓↓ 27. Intramuscular insulin delivery</td>
</tr>
<tr>
<td></td>
<td>↑ 29. A higher glucose level</td>
</tr>
<tr>
<td></td>
<td>↑ 30. Periods (menstruation)</td>
</tr>
<tr>
<td></td>
<td>↑ 31. Puberty</td>
</tr>
<tr>
<td></td>
<td>↑ 32. Celiac disease</td>
</tr>
<tr>
<td></td>
<td>↑ 33. Smoking</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication</th>
<th>Environmental</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓↑ 10. Medication dose</td>
<td>↑ 34. Expired insulin</td>
</tr>
<tr>
<td>↓↑ 11. Medication timing</td>
<td>↑ 35. Inaccurate BG reading</td>
</tr>
<tr>
<td>↓↑ 12. Medication interactions</td>
<td>↓↓ 36. Outside temperature</td>
</tr>
<tr>
<td>↑↑ 13. Steroid administration</td>
<td>↑ 37. Sunburn</td>
</tr>
<tr>
<td>↑↑ 14. Niacin (Vitamin B3)</td>
<td>↑ 38. Altitude</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Activity</th>
<th>Behavioral &amp; Decision Making</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑↓ 15. Light exercise</td>
<td>↓ 39. Frequency of glucose checks</td>
</tr>
<tr>
<td>↑↑ 16. High-intensity and moderate exercise</td>
<td>↑↑ 40. Default options and choices</td>
</tr>
<tr>
<td>↓↓ 17. Level of fitness/training</td>
<td>↑↑ 41. Decision-making biases</td>
</tr>
<tr>
<td>↑↓ 18. Time of day</td>
<td>↓↓ 42. Family relationships and social pressures</td>
</tr>
<tr>
<td>↓↓ 19. Food and insulin timing</td>
<td></td>
</tr>
</tbody>
</table>
What improvements in the Hybrid Closed Loop System would have most impact?

- Continued good diabetes management education
- **Sensor improvements (accuracy and size)**
- Faster acting insulin
- Algorithm adjustments (more aggressive insulin increase & decrease)
- Infusion Set improvements (less occlusion, longer duration, 2 in 1)
- Improvements in data reports and integration with EMR, RT reports
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- Trials or experience with more subgroups of patient types
- Multi-hormone system?
What improvements in the Hybrid Closed Loop System would have the most impact?

- Continued good diabetes management education
- Sensor improvements (accuracy and size)
- Faster acting insulin Fiasp -- Faster Acting Aspart Mealtime Insulin approved in US, 09/29/2017
- Algorithm adjustments (more aggressive auto-basal and automatic boluses)
- Infusion Set improvements (fewer occlusions, longer duration, 2 in 1)
- Improvements in data reports and integration with EMR
- Trials with more subgroups of patient types
- Multi-hormone system?
- More HCL systems available -enhanced innovation & competition
Fast-Acting Insulin Aspart Improves Glycemic Control in Basal-Bolus Treatment for Type 1 Diabetes: Results of a 26-Week Multicenter, Active-Controlled, Treat-to-Target, Randomized, Parallel-Group Trial (onset 1)
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AP Systems in Development

- **Tandem Diabetes Care**
- **TypeZero**
- **Insulet Corporation**
  - Horizon AP System

- **Beta Bionics**
- **iLet**
- **Bigfoot Biomedical**

- **Lilly**
  - Smart Pen, Automated Insulin Delivery System
Omnipod® Horizon™ Automated Glucose Control System

Hand-held controller
Pod
CGM
MPC Algorithm Integrated into Pod

Cloud Server
Data Analytics
Caregiver Follow Mobile App
User Secondary Display Mobile App

Investigational device. Limited by Federal (or United States) law to investigational use. Not for sale in the United States.
Safety and Feasibility of the OmniPod Hybrid Closed-Loop System in Adult, Adolescent, and Pediatric Patients with Type 1 Diabetes Using a Personalized Model Predictive Control Algorithm

Bruce A. Buckingham, MD¹  Gregory P. Forlenza, MD²  Jordan E. Pinsker, MD³  Mark P. Christiansen, MD⁴  R. Paul Wadwa, MD²  Jennifer Schneider, MD⁵  Thomas A. Peyser, PhD⁵  Eyal Dassau, PhD⁶  Joon Bok Lee, PhD⁷  Jason O’Connor, BS⁷  Jennifer E. Layne, PhD⁷  and Trang T. Ly, MBBS, FRACP, PhD⁷
## Glycemic Outcomes During

### 7-Day Open-Loop Phase  
### 36-H Hybrid Closed-Loop Phase  

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adults(^b) (n = 10)</th>
<th>Adults (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean sensor glucose, mg/dL</td>
<td>146.9 (16.4)</td>
<td>155.0 (14.8)</td>
</tr>
<tr>
<td>Standard deviation, mg/dL</td>
<td>56.3</td>
<td>46.2</td>
</tr>
<tr>
<td>Coefficient of variation, %</td>
<td>38.5</td>
<td>29.8</td>
</tr>
<tr>
<td>Percentage time in glucose range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 mg/dL</td>
<td>5.4 (3.3)</td>
<td>0.7 (2.1)</td>
</tr>
<tr>
<td>70 to 180 mg/dL</td>
<td>69.0 (11.5)</td>
<td><strong>73.0 (15.0)</strong></td>
</tr>
<tr>
<td>&gt;180 mg/dL</td>
<td>25.6 (11.1)</td>
<td>26.3 (14.4)</td>
</tr>
<tr>
<td>≥250 mg/dL</td>
<td>6.0 (6.5)</td>
<td>3.6 (3.7)</td>
</tr>
</tbody>
</table>
Fully Closed-Loop Multiple Model Probabilistic Predictive Controller Artificial Pancreas Performance in Adolescents and Adults in a Supervised Hotel Setting

Gregory P. Forlenza, MD, Faye M. Cameron, PhD, Trang T. Ly, MBBS, FRACP, PhD et al.

MMPPC FCL

4 hr. Postprandial CGM response

Unannounced meal (N=60)

Announced meal (N=30)

Hygoglycemia treatments
What improvements in the Hybrid Closed Loop System would have most impact?

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Is (Hybrid) Closed Loop Therapy for Most with T1D?

- Those not at goal (too high or too low) who are willing and able to use the technology & can afford it.
- Those with overnight alternate basal rates programmed to prevent dawn phenomenon

- Need further study of:
  - Young and old
  - Hypoglycemia unaware (should help)
  - Pregnancy
  - Gastroparesis
  - Inpatient use
  - Long term outcome studies
  - Cost-effectiveness studies
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BU/MGH Bionic Pancreas (insulin + glucagon)
## Sensor Glucose Distribution - MiniMed™ 670G System

### National Data

<table>
<thead>
<tr>
<th>U.S. MiniMed™ System Dataset* - CareLink™ Personal Data</th>
<th>Parameter Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>40,824 Users</td>
<td>Ages: All Ages</td>
</tr>
<tr>
<td>Time in Auto Mode: 76.4%</td>
<td>Dates: All Dates</td>
</tr>
<tr>
<td>Est. A1C**: 7.1%</td>
<td>Day / Night: 24-Hrs</td>
</tr>
<tr>
<td>Time in Range (Auto Mode): 72.1%</td>
<td></td>
</tr>
</tbody>
</table>

### HCP Group Data: Park Nicollet Adult

<table>
<thead>
<tr>
<th>U.S. MiniMed™ System Dataset* - CareLink™ Personal Data</th>
<th>Parameter Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>138 Users</td>
<td>Ages: All Ages</td>
</tr>
<tr>
<td>Time in Auto Mode: 78.0%</td>
<td>Dates: All Dates</td>
</tr>
<tr>
<td>Est. A1C**: 6.9%</td>
<td>Day / Night: 24-Hrs</td>
</tr>
<tr>
<td>Time in Range (Auto Mode): 75.0%</td>
<td></td>
</tr>
</tbody>
</table>

### Graphs

- **SmartGuard™ Auto Mode**
  - Time in Range: 72.1%
  - Time Range:
    - 0.3%: 4.1%
    - 1.6%: 1.7%
    - 61.7%: 6.8%
    - 3.4%: 20.3%

- **SmartGuard™ OFF**
  - Time in Range: 61.7%
  - Time Range:
    - 0.3%: 4.1%
    - 1.6%: 1.7%
    - 61.7%: 6.8%
    - 3.4%: 20.3%
Thank You!

Thanks to IDC Team & Endocrine Clinic Teams

- Anders Carlson, MD
- Amy Criego, MD
- Tom Martens, MD
- Beth Olson, RN, CDE
- Shannon Beasley, NP, CDE
- Jamie Hyatt, RN, CDE
- Diane Whipple, RN, CDE
- Kathy McCann, RN, CDE
- Mary Johnson, RN, CDE
- Janet Davidson, RN, CDE
- Gregg Simonson, PhD
- Gregg Damberg, MD, David Tridgell, MD, Rebecca Moxness, MD and colleagues Adult Endo Park Nicollet

Questions?