Closing the Loop for Type 1 Diabetes: Finally!!

Stuart A Weinzimer, MD
Professor of Pediatrics
Yale University School of Medicine
Objectives

1. Recognize the rationale for closed-loop insulin delivery for optimal care of persons with type 1 diabetes

2. Understand the pathways and spectrum of approaches that have been undertaken to automate insulin delivery

3. Review the important clinical studies demonstrating progress towards a commercial closed-loop system
• Medtronic  Consultant
  Speaker
  Grant support (to Yale)

• Insulet  Consultant
  Speaker

• Sanofi-Aventis  Consultant
A Note on Nomenclature

- Automated insulin delivery
- “Closed-loop” insulin delivery
- “Artificial pancreas”
- “Bionic pancreas”
1. Present methods of diabetes treatments are largely unsuccessful in helping patients meet glycemic targets

2. Intensive management schemes are very burdensome and negatively impact quality of life for PWD and their loved ones
Type 1 Diabetes Exchange

Miller, Diab Care 2015
Anatomy of a closed-loop system

UVA DiAS System

Medtronic 670G HCL
Spectrum of closed-loop systems

- Full OL SAP
- Auto-Suspend
  - Threshold
  - Predictive
- Hybrid CL
  - Manual Meal
- Full CL Multi-H

Programmed Basal Suspend

Adaptive Basal
Example of Threshold Suspend Cycle

Insulin Suspends for 2 hours / Resumes for 4 hours

- Insulin infusion stops
- Suspend time maximum = 2 hrs
- Basal insulin infusion will resume even if glucose is below Thresh Suspend limit
Example of Predictive Suspend Cycle

Insulin suspends for up to two hours but resumes automatically

- Insulin infusion stops
- Basal insulin infusion resumes to prevent excessive rebound

Suspend time variable
Predictive Low Glucose Suspend reduced nocturnal hypoglycemia

Maahs, *Diab Care* 2014

N=45, 42 nights

Control

- BG Levels < 50 mg/dL: 19%
- BG Levels < 60 mg/dL: 14%
- BG Levels < 70 mg/dL: 12%

Intervention

- BG Levels < 50 mg/dL: 10%
- BG Levels < 60 mg/dL: 11%
- BG Levels < 70 mg/dL: 11%

Buckingham, *Diab Care* 2015

N=45

- BG Levels < 70 mg/dL: 11-14

N=36

- BG Levels < 70 mg/dL: 4-10
PLGM “in-clinic” induced hypoglycemia

N=69

<table>
<thead>
<tr>
<th>Definition of Hypoglycemia</th>
<th>Prevention rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 65 mg/dL</td>
<td>60%</td>
</tr>
<tr>
<td>≤ 60 mg/dL</td>
<td>68%</td>
</tr>
<tr>
<td>≤ 55 mg/dL</td>
<td>81%</td>
</tr>
</tbody>
</table>

Buckingham, Diabetes Technol Ther 2017
# Predictive Suspend Systems Challenged with Insulin or Exercise

<table>
<thead>
<tr>
<th>Insulin Challenge</th>
<th>Insulin Bolus</th>
<th>Basal Escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PLGM off</td>
<td>PLGM on</td>
</tr>
<tr>
<td>Hypo</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>No Hypo</td>
<td>4</td>
<td>23</td>
</tr>
</tbody>
</table>

Abraham, *Diabetes Technol Ther 18(7)*, 2016

<table>
<thead>
<tr>
<th>Exercise Challenge</th>
<th>Threshold 70 mg/dL</th>
<th>Threshold 80 mg/dL</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>PLGM off</td>
<td>PLGM on</td>
</tr>
<tr>
<td>Hypo</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>No Hypo</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

Abraham, *Diabetes Technol Ther 18(9)*, 2016
Predictive Suspend Systems: Outpatient Study

- Decreased time spent in all measures of hypoglycemia
- Increased time spent > 140 mg/dL (but not > 180)

Battelino, Diab Care 2017
Auto-Suspend pumps

- Threshold suspend pumps shown to reduce hypoglycemia without causing rebound highs or ketosis

- Predictive suspend pumps will likely be better at hypoglycemia avoidance but may predispose to hyperglycemia

- Neither will respond to HYPERglycemia!
Early closed-loop studies demonstrate benefit of “Hybrid” approach to meal control

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Daytime</th>
<th>Peak PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full CL</td>
<td>147 ± 58</td>
<td>154 ± 60</td>
<td>219 ± 54</td>
</tr>
</tbody>
</table>

Weinzimer SA. Diabetes Care 2008; 31:934-939.
Pharmacokinetic and pharmacodynamic properties of rapid-acting insulin bolus

Swan KL. Diabetes Care 2008; 31: 44-46
Closed-Loop Glucose and Plasma Insulin Levels

- **Reference BG**
- **Sensor Glucose**
- **Setpoint**
- **Meals**

**Glucose (mg/dl)**

- 6A
- 8A
- 10A
- Noon
- 2P
- 4P
- 6P

**Plasma Insulin (uU/mL)**

**Insulin Delivery Rate (U/hr)**

- 6A
- 8A
- 10A
- Noon
- 2P
- 4P
- 6P
MD-Logic overnight CL in home setting

Phillip, NEJM 2013, Nimri, Pediatr Diab 2014, Nimri Diabetes Care 2014
Overnight CL Camp Study

- N=20, 5-6 nights

Ly, Diab Care 2014
Night & Day CL Camp Study

Mean Glucose (mg/dL)

<table>
<thead>
<tr>
<th>Mean SG</th>
<th>SAP</th>
<th>CLC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Time in Range (%)

<table>
<thead>
<tr>
<th>Range</th>
<th>SAP</th>
<th>CLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-180</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 180</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ly, Diab Care 2016
Outpatient Hybrid CL improved average BG levels and time in target in adolescents

N=15
5 days/4 nights

Ly, Pediatr Diabetes 2017
Research Letter
October 4, 2016

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

Richard M. Bergenstal, MD\textsuperscript{1}; Satish Garg, MD\textsuperscript{2}; Stuart A. Weinzimer, MD\textsuperscript{3}; et al

News From the Food and Drug Administration
November 15, 2016

“Artificial Pancreas” Is Approved
10 sites (9 US, 1 Israel)

- Type 1 diabetes > 2yrs
  - A1C <10%
  - Adolescent: 14-21 yrs.
  - Adult: 22-75 yrs.

- Pump ≥6 months, +/-CGM
- Run-in: OL (Manual Mode) 2w
- Study: CL (Auto Mode) 3m
  - 6-day / 5-night hotel stay

### Characteristic

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adolescent (n=30)</th>
<th>Adult (n=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>16F / 14M</td>
<td>53F / 41M</td>
</tr>
<tr>
<td>Age (years)</td>
<td>16.5 ± 2.3</td>
<td>44.6 ± 12.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.4 ± 13.0</td>
<td>79.9 ± 18.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.7 ± 3.8</td>
<td>27.1 ± 5.4</td>
</tr>
<tr>
<td>Duration of diabetes (yrs)</td>
<td>7.7 ± 4.2</td>
<td>26.4 ± 12.4</td>
</tr>
<tr>
<td>Total daily dose of insulin (u/kg/day)</td>
<td>0.8 ± 0.2</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>A1C screening (%)</td>
<td>7.7 ± 0.8</td>
<td>7.3 ± 0.9</td>
</tr>
</tbody>
</table>

RUN-IN PERIOD:
Pump + CGM
2 weeks

Day 1: HCL Training
(Auto Mode)

Day 7: Auto Mode turned ON

STUDY PERIOD: Auto Mode*
3 months

670G Pivotal Trial: Change in A1c

- **All:** $7.4 \pm 0.9\%$ to $6.9 \pm 0.6\%$
- **Adults:** $7.3 \pm 0.9\%$ to $6.8 \pm 0.6\%$
- **Adolescents:** $7.7 \pm 0.8\%$ to $7.1 \pm 0.6\%$
- **No DKA or Severe Hypo**

HCL Utilization (% time): All Subjects = 87.2%, Adolescents = 75.8%, Adults = 88.0%
Study results confirmed in real-world setting

<table>
<thead>
<tr>
<th>Pivotal Trial Data</th>
<th>Manual Mode</th>
<th>Auto Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in Range (71-180 mg/dL/3.9-10 mmol/l)</td>
<td>66.7%</td>
<td>72.2%</td>
</tr>
<tr>
<td>Time in Auto Mode (%)*</td>
<td>N/A</td>
<td>87.2%</td>
</tr>
<tr>
<td>Sensor Wear*</td>
<td>---</td>
<td>95%</td>
</tr>
<tr>
<td>Time &lt; 50 mg/dL</td>
<td>1.0%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Time &lt; 70 mg/dL</td>
<td>5.9%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Time &gt; 180 mg/dL</td>
<td>27.4%</td>
<td>24.5%</td>
</tr>
<tr>
<td>Time &gt; 300 mg/dL</td>
<td>2.3%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Mean SG ± SD</td>
<td>150±23</td>
<td>151±14</td>
</tr>
</tbody>
</table>

Real World Data

<table>
<thead>
<tr>
<th>Manual Mode</th>
<th>Auto Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>63.1%</td>
<td>73.3%</td>
</tr>
</tbody>
</table>

12,389 patient days of data, 123 patients (three-month study)

>105,000 patient days of data;
>65,000 patient days in Auto Mode;
>3030 patients
Data as of 8/15/2017

Florence Closed-loop System c. 2015

- Insulin Pump
- Controller
- CGM Transmitter
- CGM Receiver
12 week in-home Day and Night Hybrid CL Control

A Adults (n=33)

Thabit, NEJM 2015
3 week in-home Day & Night CL Control

(n=12) Adolescents

Tauschmann, *Diabetes Care* 2016
Beyond HCL

1. Bi-hormonal systems
2. Alternate sites of insulin delivery
3. Additional system inputs
4. Way Beyond….
Dual-Hormone Delivery System with Insulin And Glucagon – “Bionic Pancreas”
Bi-hormonal AP in home setting

- Mean CGM glucose concentration (mmol/L)
  - Comparator
  - Bionic pancreas

- Cumulative CGM glucose concentration
  - 1% < 3.3 mmol/L
  - 5% < 3.3 mmol/L
  - 10% > 10 mmol/L
  - 50% > 10 mmol/L

- Cumulative night-time CGM glucose concentration

Fully-integrated bi-hormonal AP system

Inreda
Netherlands

- Bi-hormonal
  - insulin
  - glucagon
- Fully closed loop
  - no meal dosing

Fully-integrated bi-hormonal AP system

Pramlintide

- Analog of human amylin
  - Co-secreted with insulin in response to meals
  - Consistent 15:1 ratio

- Used as adjunct to insulin in T1D to reduce post-prandial glycemic excursions
  - Delay gastric emptying
  - Suppress endogenous glucagon
  - Promotes satiety
Full Closed-Loop – multiple hormone (pramlintide) without meal bolus

Fixed-ratio dosing of Pramlintide with Regular Insulin

Intra-peritoneal insulin delivery with the DiaPort
Intra-peritoneal insulin delivery in CL

**IP Delivery**

|% 80-140 mg/dl| 40 ± 8 | 26 ± 13 | p = 0.03 |
|Mean Glucose | 151 ± 11 | 190 ± 31 | p = 0.004 |
|% 70-180 mg/dl| 66 ± 9 | 44 ± 15 | p = 0.004 |
|% >180 mg/dl| 32 ± 9 | 54 ± 17 | p = 0.014 |
|% > 250 mg/dl| 6 ± 6 | 23± 11 | p = 0.0004 |

**SC Delivery**

Dassau E, Diabetes Obes Metab 2017, epub May 5.
Changes in BG levels following unannounced exercise
Heart rate as additional input signal for CL

- Cycle ergometer
- 15 min x 3
- Target HR = 140
Dual-hormone AP incorporating exercise detection with HR and accelerometry

- Treadmill ergometer
- 45 min @ 60% HR_{max}

Open APS

- > 100 users
- > 250,000 pt-hours

1. A1c: 7.1 to 6.2%
2. Time in Target (70-180): 58 to 81%
3. 95% improved sleep

Lewis D, J Diabetes Sci Technol 2017
The human side of the machine…

- Adoption
- Education
- Role of Clinician
C. A. R. E.: a conceptual model for the application of AID to clinical care

- Calculate - how does the system calculate insulin delivery?
- Adjust – what are the adjustable components?
- Revert – when should control be returned to user?
- Educate – where does user go for help?

Messer L, Pediatr Diabetes 2017, in press
Calculate: How does 670G calculate insulin delivery?

- **HYBRID Closed-Loop**
  - **Basal rates** system-determined by a PID algorithm
    - Dynamically adjusts basal rates every 5 min
    - Fixed “target” glucose 120 mg/dL (6.7 mmol/l)
    - “Temp” target for exercise 150 mg/dL (8.3 mmol/l)
  - **Boluses** requires user input for:
    - Meals (carbs) -- user enters through linked BGM
    - Corrections (BG) – determined by system
      - [“target” BG for correction is 150 mg/dL (8.3 mmol/l)]
**Adjust:**

What are the adjustable vs fixed parameters?

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adjustable</th>
<th>Not Adjustable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal rates</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Insulin-Carb Ratio</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Sensitivity Factor</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>BG Target *</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Active Insulin Time</td>
<td>●</td>
<td></td>
</tr>
</tbody>
</table>

* Temporary BG Target 150 mg/dL (8.3 mmol/l)
Using Pivotal Trial data to guide clinical care decisions for patients on 670G

- Collected insulin dosing data from 31 pediatric and young adult subjects in 670G Pivotal Study
  - Age 14-26y
  - Three clinical sites (Stanford, BDC, Yale)

- Baseline open-loop data were compared with HCL use at several time points:
  - 1 week
  - 1 month
  - 2 months
  - 3 months

Messer L et al, 2017
Using Pivotal Trial data to guide clinical care decisions for patients on 670G

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>3 Month</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakfast ICR</td>
<td>7.9 ± 2.7</td>
<td>6.8 ± 2.8 *</td>
<td>0.00002</td>
</tr>
<tr>
<td>Lunch ICR</td>
<td>8.9 ± 3.3</td>
<td>7.6 ± 3.1 *</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Dinner ICR</td>
<td>8.7 ± 3.4</td>
<td>7.2 ± 2.6 *</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Insulin Action (min)</td>
<td>174 ± 52</td>
<td>168 ± 47</td>
<td>0.08</td>
</tr>
</tbody>
</table>

- TDD, basal dose, bolus dose, basal/bolus ratio were not significantly different

Messer L et al, 2017
Revert:

When does system return to open-loop mode?

1. Missed calibrations
2. Prolonged high SG
   - ≥ 250 for 3 hr
   - ≥ 300 for 1 hr
3. Sensor accuracy concerns
4. Max or Min delivery time exceeded
   - Max > 4 hr
   - Min > 2.5 hr

“Safe Basal” Mode

Direct to Manual Mode
“Safe Basal” Mode

- **Fixed** basal rate temporarily used by system in certain clinical situations to address a problem
- Determined by algorithm from last 2-6 days of sensor values
- Not adjusted by current SG values
- Operates for up to 90 minutes
  - Situation resolves, will return to Auto Mode
  - Situation persists, will “Exit” to Manual Mode
Educate:
Where does the user go for help?

“Doctor and physician are outdated terms. I’m your biological tech support specialist.”
“Human Factors” Aspects of Automated Insulin Delivery

- Patient Selection
- Education
- Expectations
- Trust
- Negative Aspects?
  - “De-skilling”
  - Parent-Child Interactions
  - Unintended consequences?