ANTICIPATING THE AVAILABILITY OF ARTIFICIAL PANCREAS SYSTEMS: WHAT TO EXPECT IN THE CLINIC

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JDRF Chief Mission Officer & VP of Research

Disclosures:
• No conflict of interests/disclosures

AP Systems are Coming...
• MDT: Hybrid CL: April 2017
• Bigfoot Biomedical: Hybrid CL 2018
• Insulet 2018
• Tandem 2017 PLGM 2019 HHM
• Beta Bionics 2017 Insulin, 2019 Insulin+Glucagon
• Animas HHM
• Roche
• Type Zero: Hybrid CL

What to EXPECT?

“The Sensor-augmented pumps without automation will be obsolete soon”
Dr. Steven Russell at the JDRF-NIH Artificial Pancreas Meeting @ADA New Orleans 2016

The Future?
The Future?

A Glimpse into the Future?

Why Artificial Pancreas Systems: The Need for Better Diabetes Treatment Options Still Exists

A Snapshot of Care of Individuals with T1D Today

T1D Exchange

Clinic Registry
Biobank
Patient Website
Glu

• >70 sites in USA
• Reporting on ~ 26,000 individuals

Average Current HbA1c by Age

*All years old and still years old are pooled

Predictive Low Glucose Suspend in Children

JDRF Launched Artificial Pancreas Project in 2006 Focused on CGM and Artificial Pancreas

The JDRF Artificial Pancreas Project (APP)

Project Goals – Artificial Pancreas

- Accelerate the availability of a first generation artificial pancreas
- Ensure the artificial pancreas and its components are widely available
- Ensure devices from multiple companies are approved and reimbursed, encouraging investment in next generation technologies

Continuous Glucose Sensor Trial

- Purpose: To collect clinical data to independently assess and advance health plan coverage and clinical adoption of continuous glucose sensors
- Goal-oriented, fast-track process:
  - Designed trial structure — large, year-long, multi-site trial focused on HbA1c and hypoglycemia
  - Research review — 9 sites recommended and approved for funding — approximately $4 million/yr for 2 years
  - Accelerated process to appoint coordinating center, study co-chairs, and finalize protocol to be used at all sites
  - Enrollment to begin in fall

JDRF Continuous Glucose Monitor Trial

Validating A Key APP Component

The New England Journal of Medicine
Continous Glucose Monitoring and Intensive Treatment of Type 1 Diabetes

Background
The value of continuous glucose monitoring in the management of type 1 diabetes mellitus has not been determined.

Conclusions
Continuous glucose monitoring can be associated with improved glycemic control in children with type 1 diabetes. Further work is needed to identify barriers to effective- ness of continuous monitoring in children and adolescents. (ClinicalTrials.gov num-

Artificial Pancreas Consortium

Barbara Davis Center for Childhood Diabetes
Dans ses écrits, un sage Italien
 Dit que le mieux est l'ennemi du bien.

In his writings, a wise Italian
 says that the best is the enemy of good.

La Bécqueule,
Voltaire 1772
Low-glucose Suspend:
Pump suspends insulin below a certain glucose number (i.e. 70) for up to two hours

ASPIRE – LGS Reduced Nocturnal Hypoglycemia without increasing HbA1c

- 32% reduction in nocturnal hypo
- 38% reduction in hypo exposure (AUC)
- No seizure or coma in SAP-LGS but 4 in SAP (severe hypoglycemia)

Predictive Low-glucose Suspend:
Pump suspends insulin before glucose reaches a low number

Predictive Low Glucose Suspend in Children

<table>
<thead>
<tr>
<th>11 - 14 Year Olds</th>
<th>p</th>
<th>4 – 10 Year Olds</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>941</td>
<td>955</td>
<td></td>
</tr>
<tr>
<td>System Active</td>
<td>755</td>
<td>769</td>
<td></td>
</tr>
<tr>
<td>% nights &lt;60 for 120 min</td>
<td>8%</td>
<td>3% &lt; 0.001</td>
<td>5%</td>
</tr>
<tr>
<td>Mean Overnight Glucose (mg/dl)</td>
<td>144 ± 10</td>
<td>152 ± 19 &lt; 0.001</td>
<td>153 ± 14</td>
</tr>
</tbody>
</table>

Buckingham et al. Diabetes Care 2015;38:1197–1204

Outpatient Randomized Trial
Ages 15 - 45 years
% of nights with glucose level ≤60 mg/dl
Means, Buckingham Diabetes Care, 2014

<table>
<thead>
<tr>
<th></th>
<th>Control N=45 Participants</th>
<th>Intervention N=45 Participants</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td># Nights</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30 min</td>
<td>24%</td>
<td>12%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 60 min</td>
<td>18%</td>
<td>8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 120 min</td>
<td>11%</td>
<td>3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 180 min</td>
<td>8%</td>
<td>1%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Buckingham et al. Diabetes Care 2015;38:1197–1204
Treat-to-Range:
Pump automatically increases insulin delivery if blood sugar is going too high/reduces if going too low

Cambridge & colleagues
Free living unsupervised home use (over 10 years experience)
Featured publication: NEJM 2015

Three 24/7 home studies underway

Medtronic: 670G

The “Extreme-Sport” Closed Loop:
5-Day Ski Camps in Virginia and Colorado

Medtronic Pivotal Trial Data

Pivotal 670G - 3 months
n=124, 72.2% in range 70-180 mg/dL, A1C 7.4% to 6.9% (All)

Medtronic Pivotal Trial Data

Pivotal 670G - Adults
n=90, 73.8% in range 70-180 mg/dL, A1C 7.8% to 6.8%
Medtronic Pivotal Trial Data

Pivotal 670G - Adolescents
n=34, 67.2% in range 70-180 mg/dL, A1C 7.7% to 7.1%

Day and Night Outpatient Hybrid Closed-Loop Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Type of Closed-loop</th>
<th>n</th>
<th>Duration</th>
<th>Mean Age</th>
<th>Mean BG</th>
<th>Mean Control</th>
<th>Control % &lt;70</th>
<th>Closed-loop % &lt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russell</td>
<td>Lancet</td>
<td>Bihormonal BP</td>
<td>19</td>
<td>5 days</td>
<td>9.8</td>
<td>167</td>
<td>137</td>
<td>6.1</td>
<td>2.9</td>
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<tr>
<td>Russell</td>
<td>NEJM</td>
<td>Bihormonal BP</td>
<td>32</td>
<td>5</td>
<td>16</td>
<td>158</td>
<td>142</td>
<td>4.9</td>
<td>3.1</td>
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<tr>
<td>Russell</td>
<td>NEJM</td>
<td>Bihormonal BP</td>
<td>20</td>
<td>5</td>
<td>16</td>
<td>159</td>
<td>133</td>
<td>7.3</td>
<td>4.1</td>
</tr>
<tr>
<td>Ly</td>
<td>DC</td>
<td>Insulin-670G</td>
<td>21</td>
<td>9 days</td>
<td>19</td>
<td>147</td>
<td>157</td>
<td>2.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Lastaranta</td>
<td>DC</td>
<td>Insulin-MP</td>
<td>17</td>
<td>4 days</td>
<td>34</td>
<td>158</td>
<td>146</td>
<td>5</td>
<td>3.7</td>
</tr>
<tr>
<td>Thabit</td>
<td>NEJM</td>
<td>Insulin-MP</td>
<td>33</td>
<td>3 month</td>
<td>40</td>
<td>168</td>
<td>157</td>
<td>4</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AVERAGE</td>
<td>160</td>
</tr>
</tbody>
</table>

#OPENAPS ADA Poster Data

While using OpenAPS, self-reported outcome measures showed median HbA1c dropped from 7.1% (SD 0.8%) to 6.2% (SD 0.5%), and median percent time in range (80-180 mg/dL) increased from 58% (SD 14%) to 81% (SD 8%). All but one respondent reported some improvement in sleep quality, and 56% reported a large improvement.

Multi-Hormone:
Insulin plus other hormones (glucagon or amylin) to more closely restore all hormones that are lost or imbalanced in type 1 diabetes

Insulin + Glucagon – Great control, with Caveat…

I love you, #DIYPS closed loop!
pic.twitter.com/BjJhTP3FMj
06:10 PM - 14 Jan 15

#OpenAPS @DanaMLewis
What will the Challenges in Introducing AP Systems Be? It Depends on Who you Ask?

The Value Proposition of AP Systems Varies By Stakeholder

AP Systems will impact different stakeholders in different ways

- Scorekeepers:
  - People with diabetes (& their loved ones)
  - Clinicians
  - Payers
- Categories:
  - Glycemic
  - “Burden”
  - Value

Value will be judged beyond A1c results

Unrealistic Expectations

- Artificial Pancreas/Automated Insulin Delivery Systems are not a diabetes cure
- AP/AIDs will not restore euglycemia
- AP/AIDs will still require two sites
- AP/AIDs will still require bolusing for maximum benefit
- Infusion sets and sensors will still require changing
- Fingersticks will still be needed for calibration
- Deskilling

We can learn from CGM evolution

Device Size: Smaller is better

Miniturization is an opportunity

Introducing Infusion Set Innovations

Current Insulins Work too Slowly and Last too Long

Faster on and Faster off insulin will drive more time in target

Liver-targeted may be more physiologic
Amylin – The Second β cell Hormone Missing in people with type 1 diabetes

- Pramlintide (Symlin™):
  - delays gastric emptying, causes weight loss
  - suppresses glucagon, augments actions of insulin
- Dosing strategy has been an issue in adoption by the diabetes community

(Courtesy: ECHequette, Amylin Pharmaceuticals; Miller et al., Disk Care 2003; Better Health Data Web 2004)

Morning Dashboard

Amylin delivered in a more physiologic manner may improve efficacy of AP systems

What if diabetes devices were less “medical”

Challenges: HCPs
New areas of focus in the clinic

- Shifting paradigm – increased focus on meal-time
- Potential large increase in number of pumpers
- Lack of reimbursement
- Increased time per patient? Initially?
- Patient selection?
- Special populations

Easier Access to Data

Tidepool Uploader

Our goal is auto-pushing data to the clinic with decision support

Free, open source, multi-device

Blip

The hub of your diabetes data.

- Designed in partnership with UCSF
- Device validation
- Currently in use for T1D Exchange / Joslin Center "RepealBG" study

“Let me start by saying that Blip is 100 times better than what is currently out there…”
- Ed, Beta Participant

Challenges: Payers
New and Potentially more Costly Diabetes Tool

- Lack of large efficacy trial
- Lack of appreciation of value of outcomes beyond A1c
- Lack of definition of appropriate patient populations
- Value proposition not clearly defined

Dr. Kaufman also shared that Medtronic is planning a major 1,000-patient, six-month post-approval outcomes study for the 670G. This study would be the largest in Medtronic Diabetes’ history, and would compare the 670G in a real-world setting to an insulin pump with CGM (no automation) or a pump by itself. That study will more definitively show how much automated insulin delivery can improve hypoglycemia and average blood glucose (A1c) – we expect improvements on both counts.

**The Definitive Study**

**Diabetes Program Overview**

- **Steering Committee (SC)**
- **Advisory Committees (AC)**
- **Researchers**
- **People with T1D**
- **Industry**

**Outcomes:**
- HbA1c
- Incidence of hypoglycemia

**Objectives:**
- Establish closed-loop control as a viable treatment for type 1 diabetes;
- Generate safety and efficacy data satisfying requirements by regulatory agencies;
- Demonstrate clinical effectiveness to facilitate reimbursement.

**Design:**
- 17 weeks RCT closed loop vs SAP
- Adolescent, overnight, three-centre (n=25)
- Mean glucose ↓89 mg/dl
- HbA1c ↓2/5
- Time in target ↑21%

**Free living unsupervised home use (over 10 years experience):**
- Adolescents, overnight, three-centre (n=25)
- Time in target ↑21%
- Mean glucose ↓89 mg/dl
- HbA1c ↓2/5

- Adults, 24/7 three-centre, 3 months (n=33)
- Time in target ↑11%
- Mean glucose ↓11 mg/dl
- HbA1c ↓0.5%

- Adults, 24/7 home studies underway
- n = 180
- 5 yrs - adults, UK & US, 3 months
- Adults, 3 wks
- Pregnancy, 3 wks

**Three 24/7 home studies underway:**
- n = 130
- 6 yrs - adults, UK & US, 3 months
- Adults, 3 wks
- Pregnancy, 3 wks

**People with T1D:**

- American Association of Clinical Endocrinologists (AACE)
- American Association of Diabetes Educators (AACE)
- American Diabetes Association (ADA)
- Endocrine Society
- Helmsley-Charitable Trust
- Pediatric Endocrine Society (PES)
- T1D Exchange
Summary

- Challenges and Barriers will exist as artificial pancreas/automated insulin delivery systems reach the clinic
- The challenges may vary depending on the stakeholder
- JDRF and Others are working aggressively to better understand and break down these barriers to ensure new technologies are available and people with diabetes derive the maximum benefit from them

Acknowledgments:

JDRF Team