Closing the Loop: Building an Artificial Pancreas

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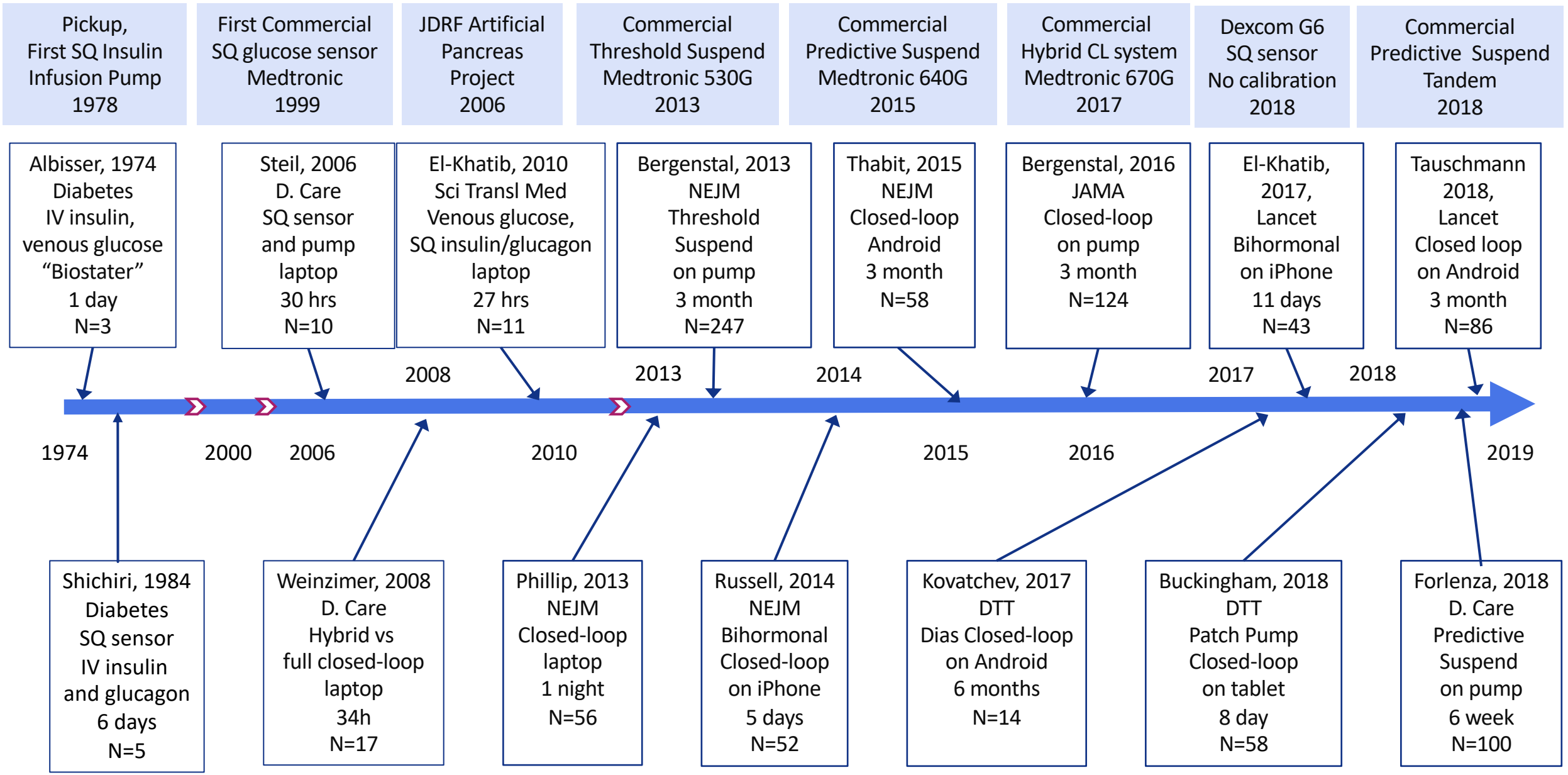
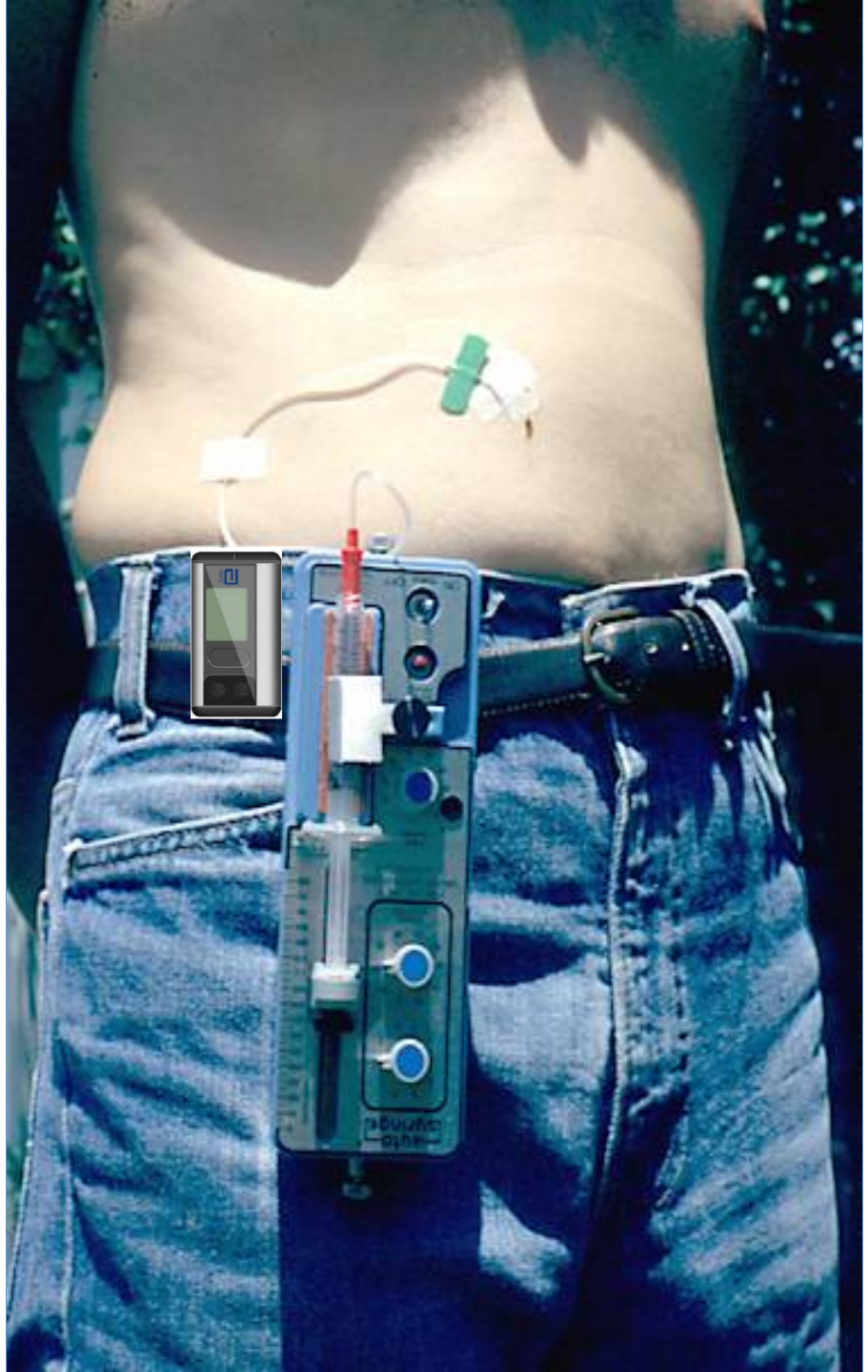
Basics to Building a Closed-loop

- Pump
- Sensor
- Algorithm

Timeline of Selected Closed-Loop Advances





Pump Therapy 1979

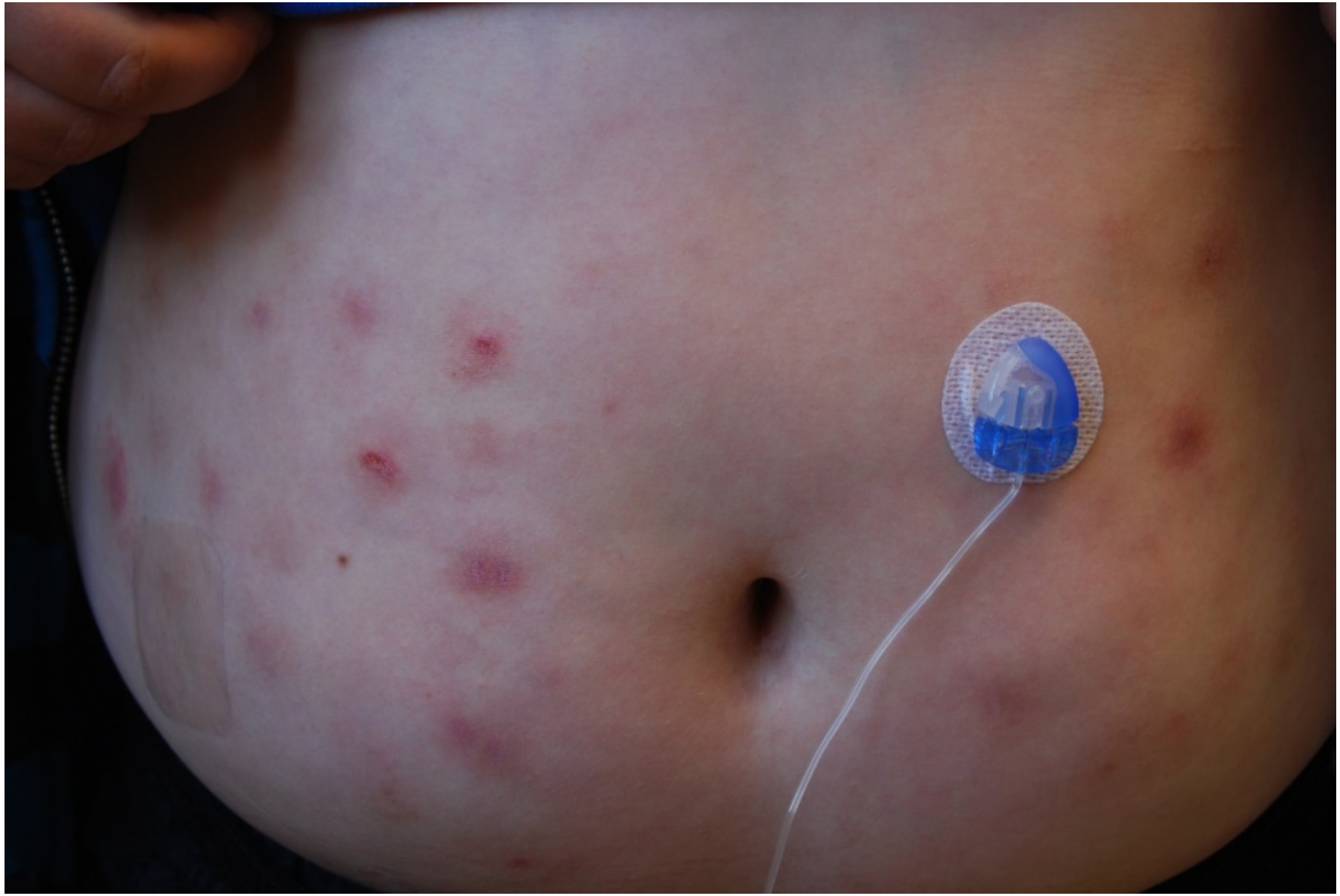

MiniMed
ACT
PARADIGM

Patch Pumps

Infusion Sets

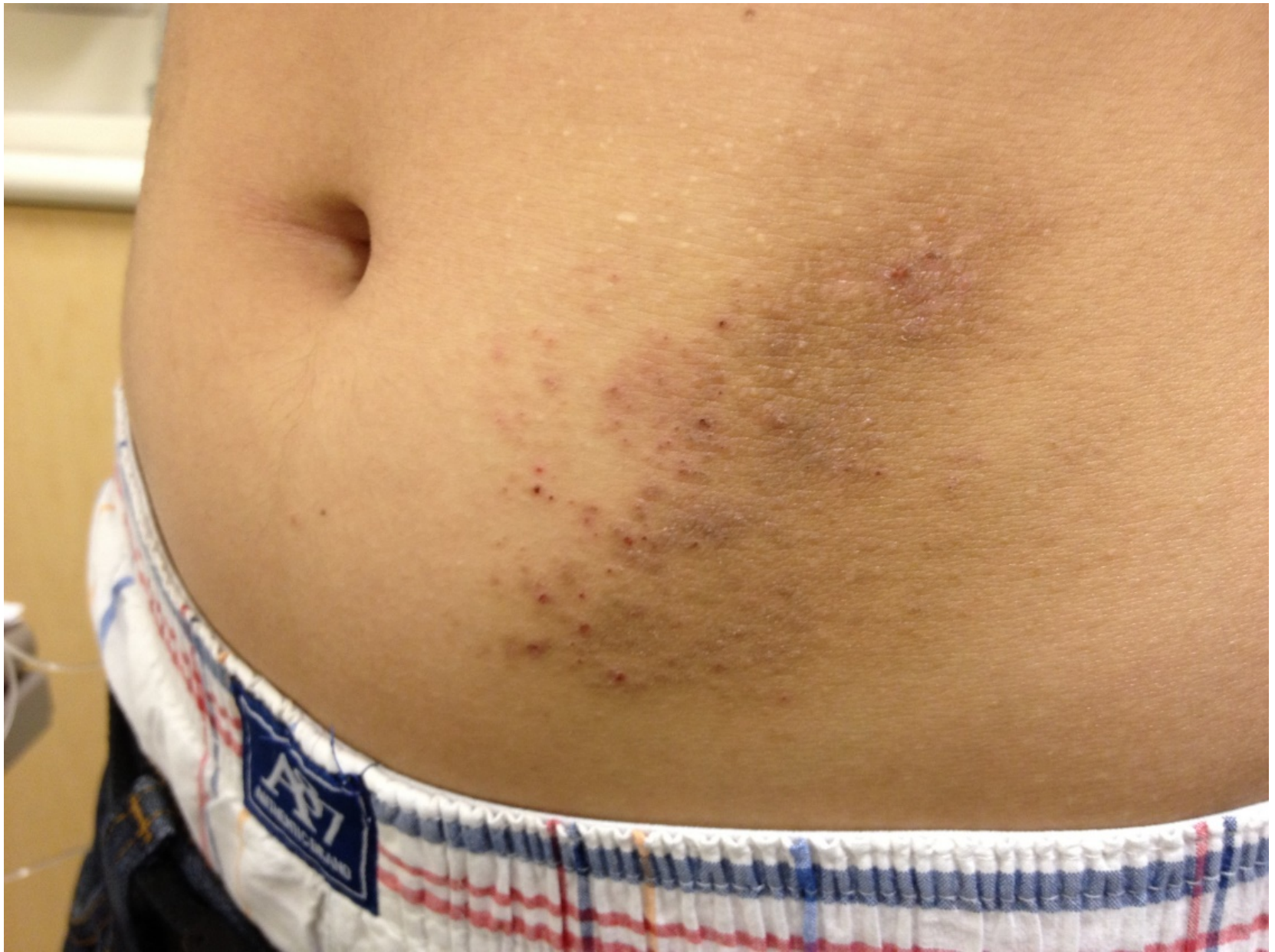
- The weak link in insulin pump delivery

Acute Infusion site Reactions



Scarring and Hyperpigmentation

Acute and Chronic Changes – Tape reaction

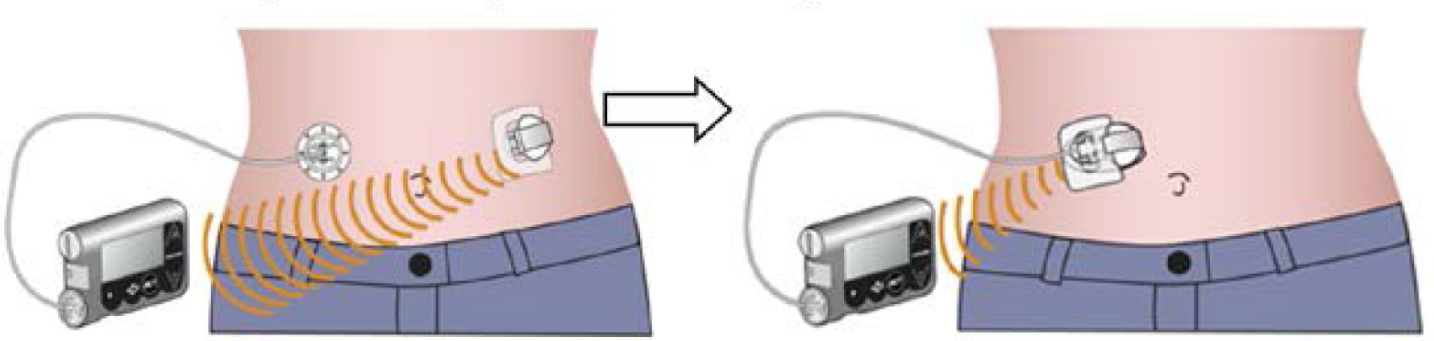


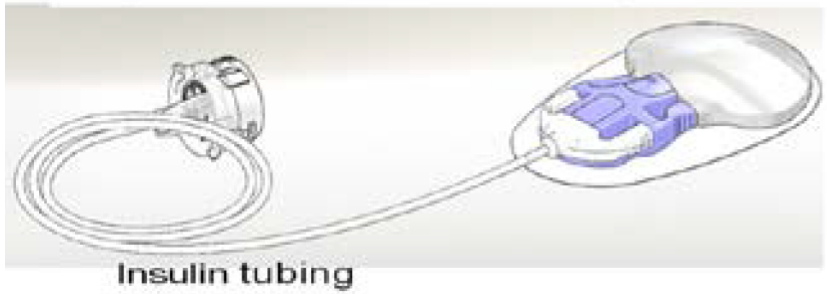
Slight Desquamation at Infusion Set and Tape Reaction 3/31

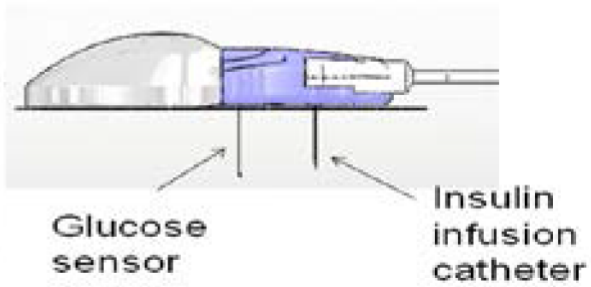
Infusion Set Infection

Lipohypertrophy

Integrated Sensor and Infusion Set





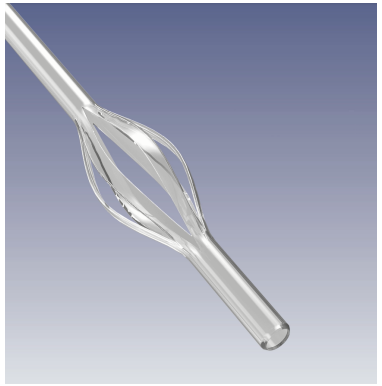


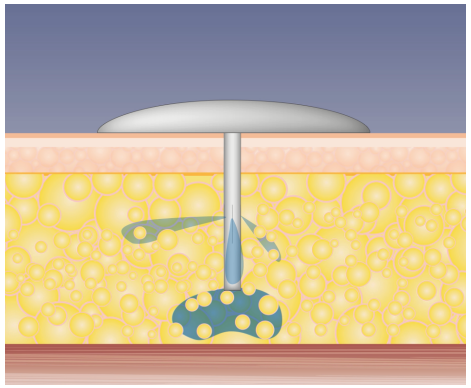
Summary of 353 Weeks of Testing for 7 days of Infusion Set Wear

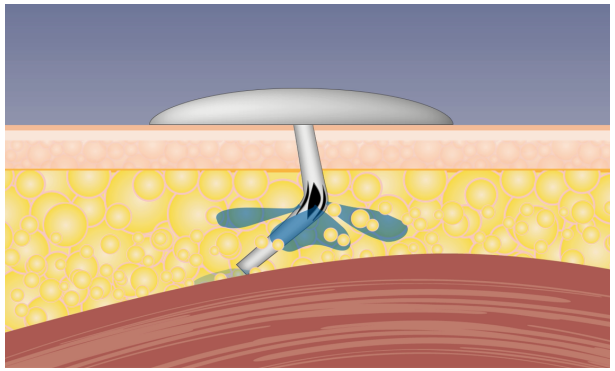
Mean Duration of Wear	5.0 ± 1.8 days
Percent Lasting 7 days	40%
Removal for unexplained hyperglycemia	26%
Removal for pain, infection or erythema	17%
Removal for other – eg. pulled out adhesive failure, unknown	20%

“Lantern” Infusion Set

16 subjects have completed study to date for 10 day wear;
90% wore set for 7 days

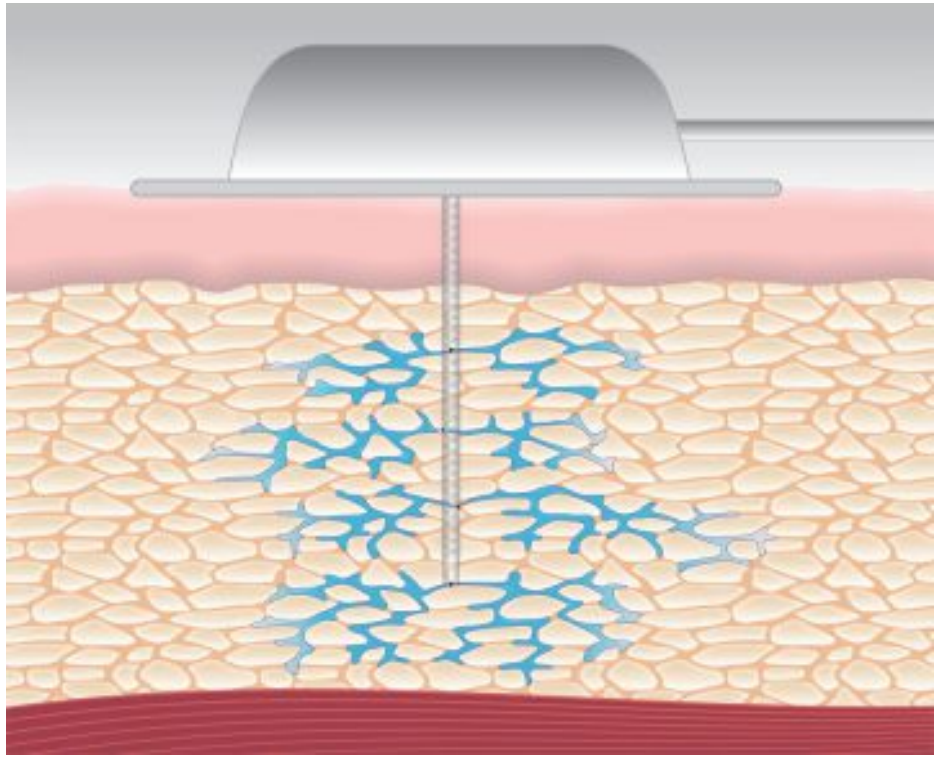






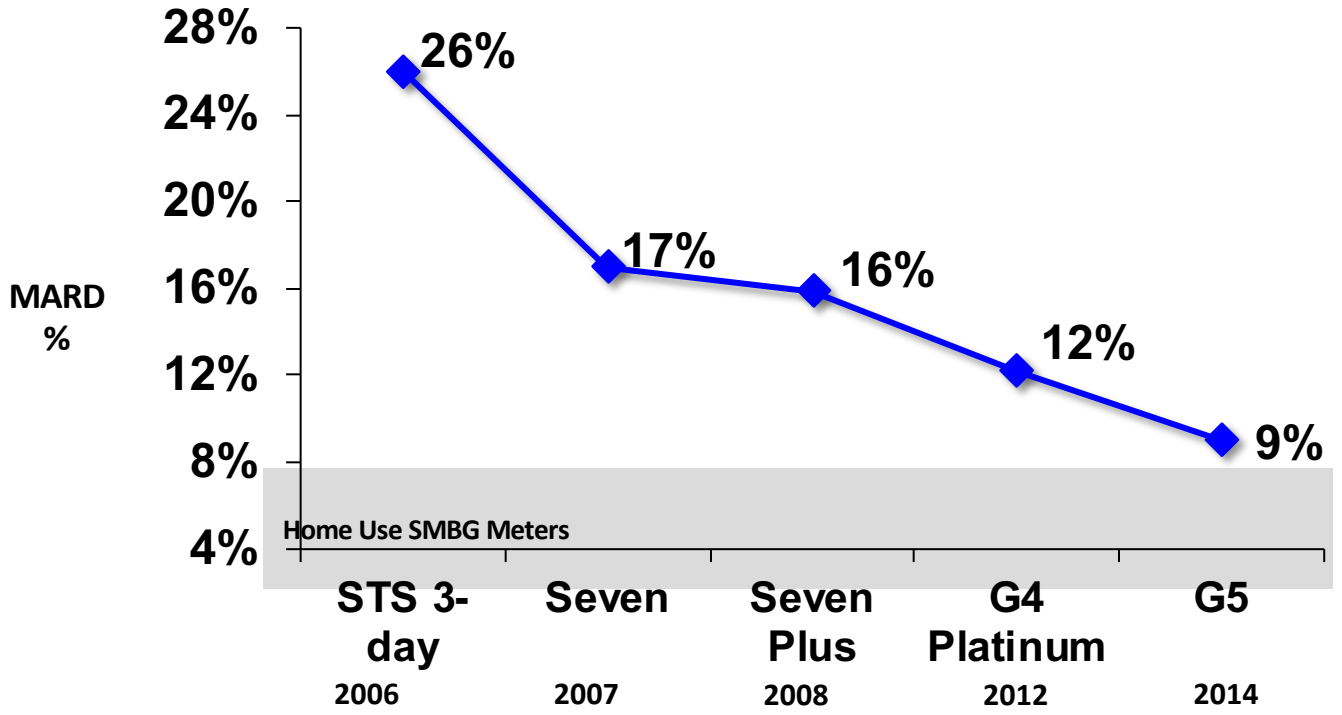
Steadiset

Capillary Biomedical



- Does not Kink
- Multiple holes distribute insulin over a larger area
- Consistent absorption

Evolution of Dexcom CGM Accuracy



Dexcom G6

- MARD 9% (% error)
- Approved down to age 2
- No calibration
- 10 Day Wear
- New Inserter –One button
- No acetaminophen cross-reactivity
- iCGM

The Eversense System

Sensor

Smart Transmitter

Mobile App

Sensor that lasts up to 180 days
No weekly sensor insertion
No open wound

Removable and rechargeable
On-body vibe alerts
Gentle-on-skin adhesive

No extra device to carry
iOS and Android platform
Alarm settings & reports

Sensor Performance Comparison

	Matched Pairs	Percent of System Readings Within 15/15% of Reference	Percent of System Readings Within 20/20% of Reference	MARD (%)
Eversense PRECISE II Trial	15,753	87%	94%	8.5
PRECISION Trial	15,170	85%	93%	9.6
Dexcom G5*	2,263	86%	93%	9.0
Dexcom G6**	25,101		92%	9.8
Libre*	5,772	82%	91%	9.7
Medtronic Enlite 3* 3-4 Cal / Day	12,090	83%	91%	9.6

* Summary of Safety and Effectiveness Data (SSED) Medical Device Databases – http://www.fda.gov,
**Dexcom G6 User Manual – accessed 6.24.18

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Closed-loop systems

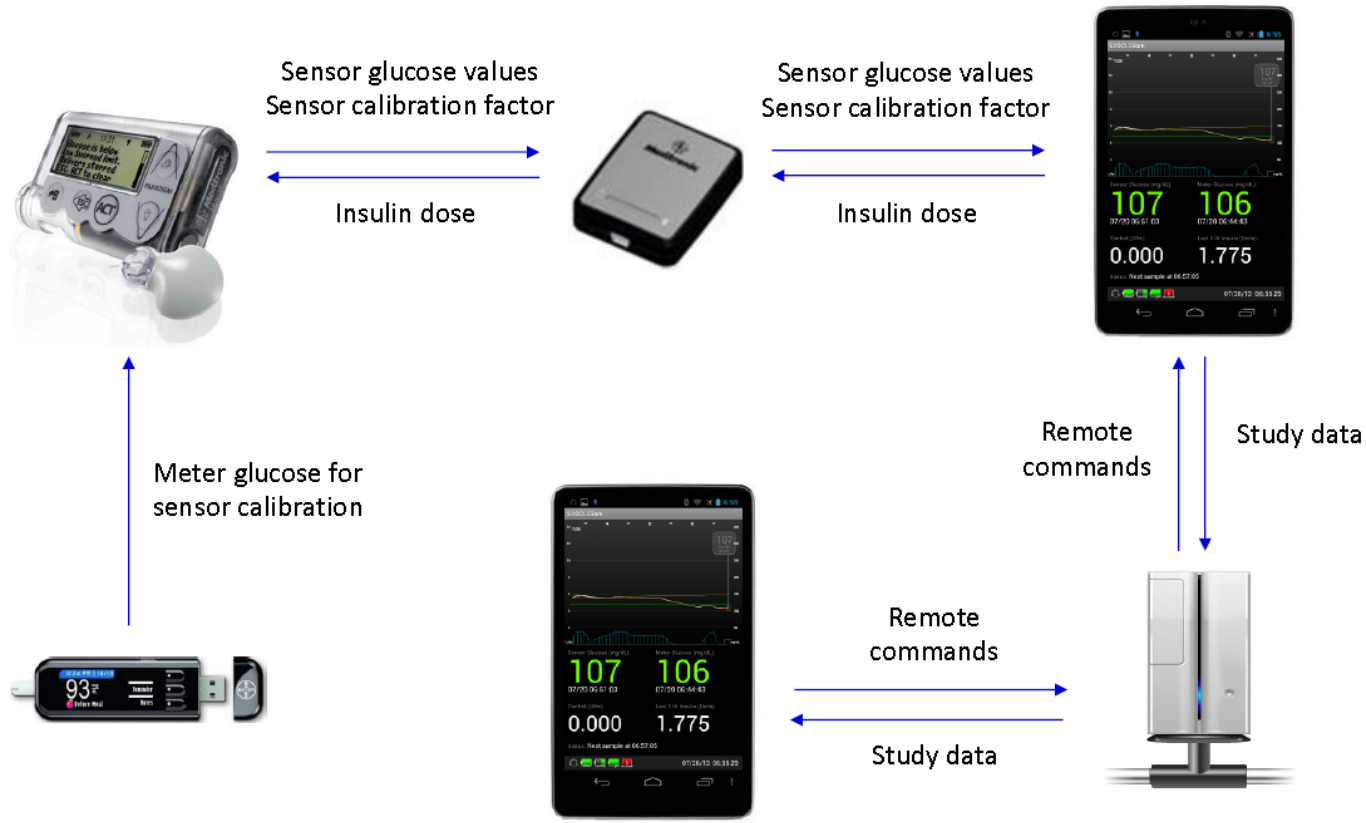
Dr. Arnold Kadish

Am J Med Electronics 3:82-86, 1964

- 1964
- Measured Venous blood every 15 seconds with 7 min lag time
- Delivered insulin at 0.1 U/min if >150 mg/dl (8.3 mmol/L)
- Delivered glucagon at 0.05 mg/min if < 50 mg/dl (2.8 mmol/L)

Medtronic Inpatient Studies - 2009

Medtronic Android-based PID-IFB System **2013 - 2014**



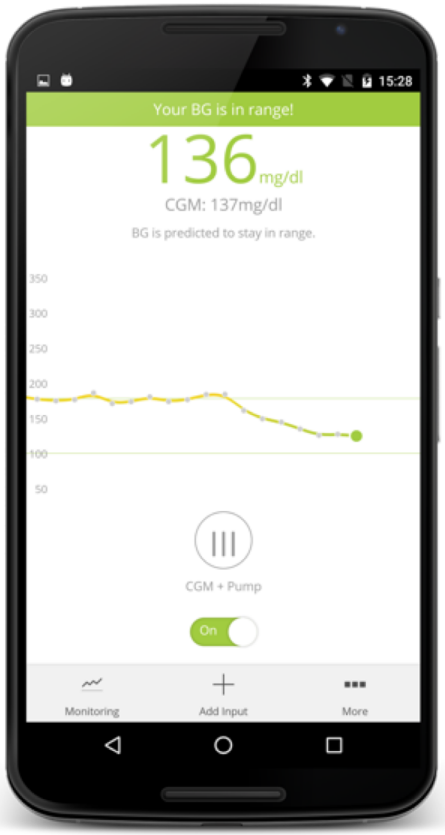
Medtronic 670G

Glucometer

Enlite 3 sensor

DiAs (UVA) System - 2014

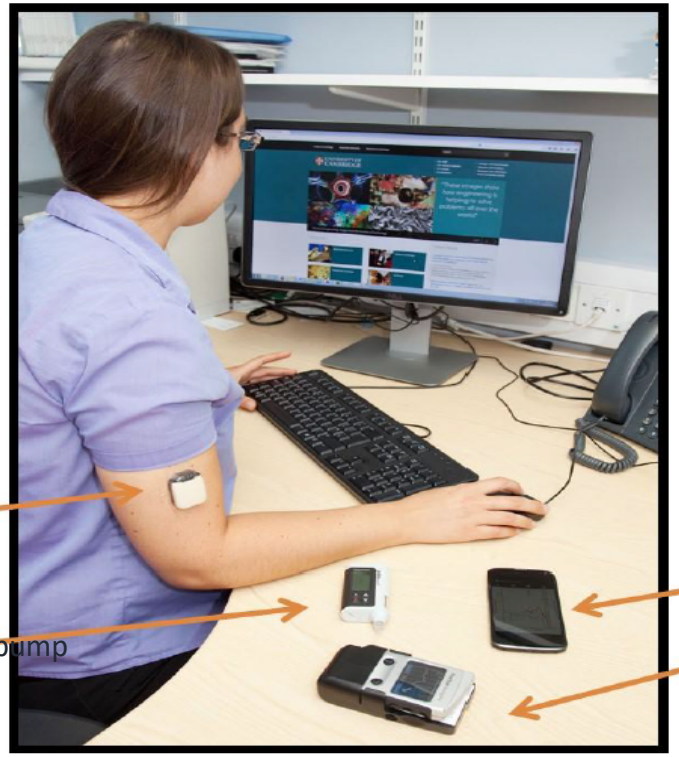
Type 0
InControl



Tandem Control IQ

FlorenceD2A closed-loop system

Adults

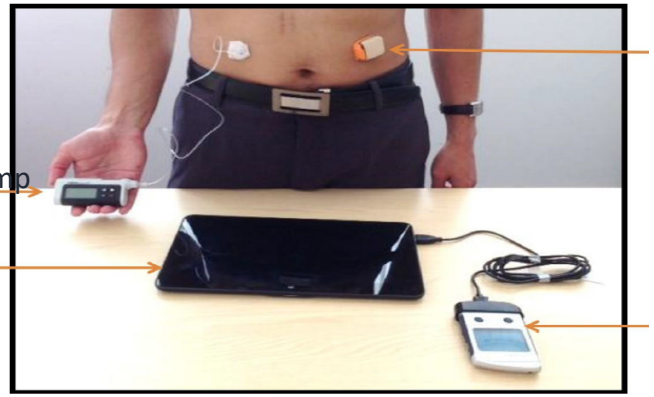


DANA-R pump

Nexus 4 LG smartphone

Nav 2 CGM receiver and translator

Children and adolescents



DANA-R pump

Dell Latitude tablet

Thabit, Tauschmann, Hovorka et. al. on behalf of APCam consortium and AP@home consortium, NEJM Sep 2015

Automated Closed-Loop System for Hovorka Studies

Android phone with enclosure

640G pump

Enlite 3
sensor

Bionic Pancreas - 2014

The iLet -2018 Gen3

Gen 4 iLet – 2019

57% smaller than Gen 3

Bigfoot Biomedical

Insulet

Omnipod Platform for Algorithm Development

Omnipod Hybrid Closed – Loop System

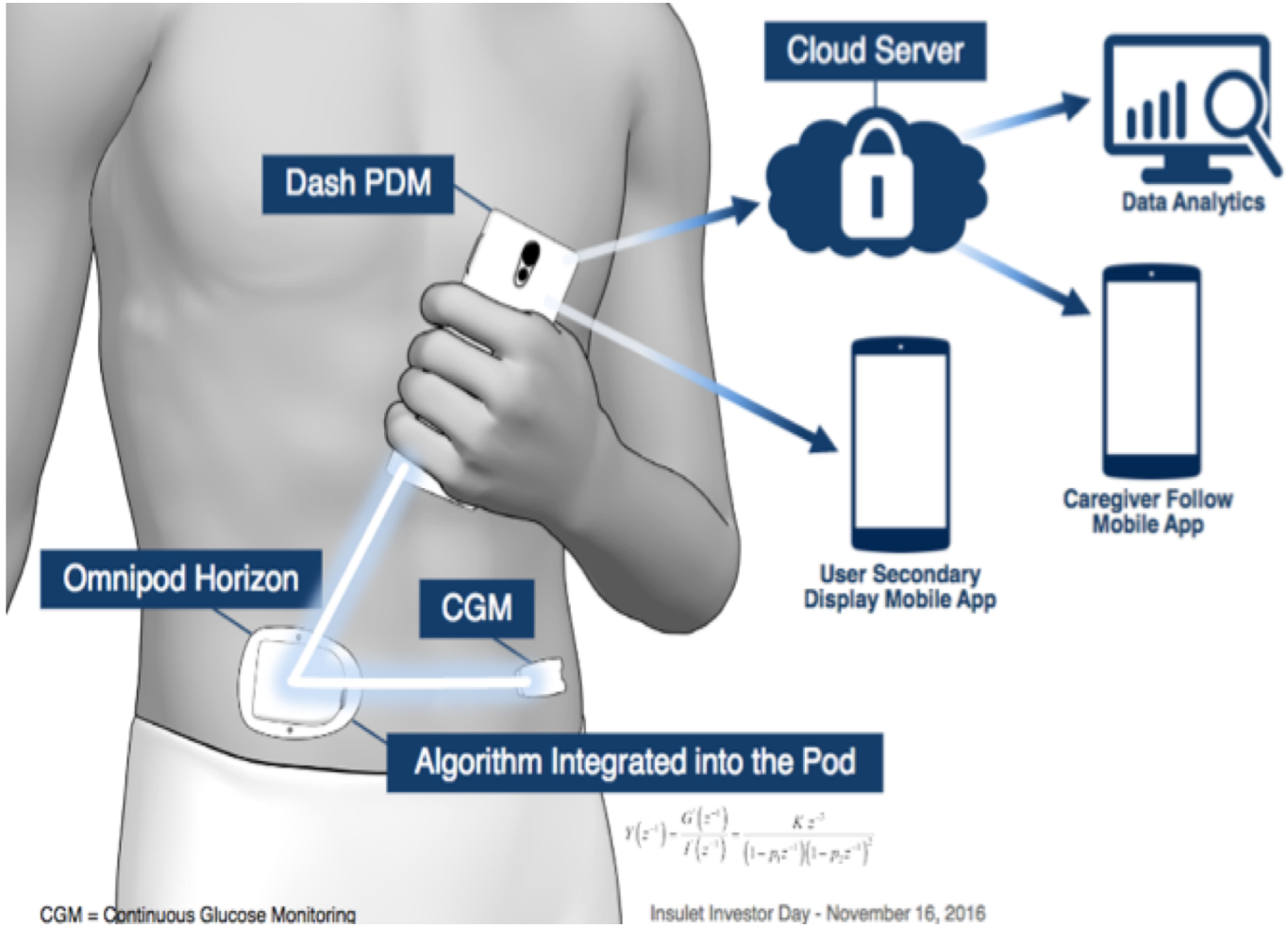
Modified Omnipod insulin pump BLE relay

MPC algorithm running on pAPS platform

Dexcom G4 (505) sensor with Share receiver

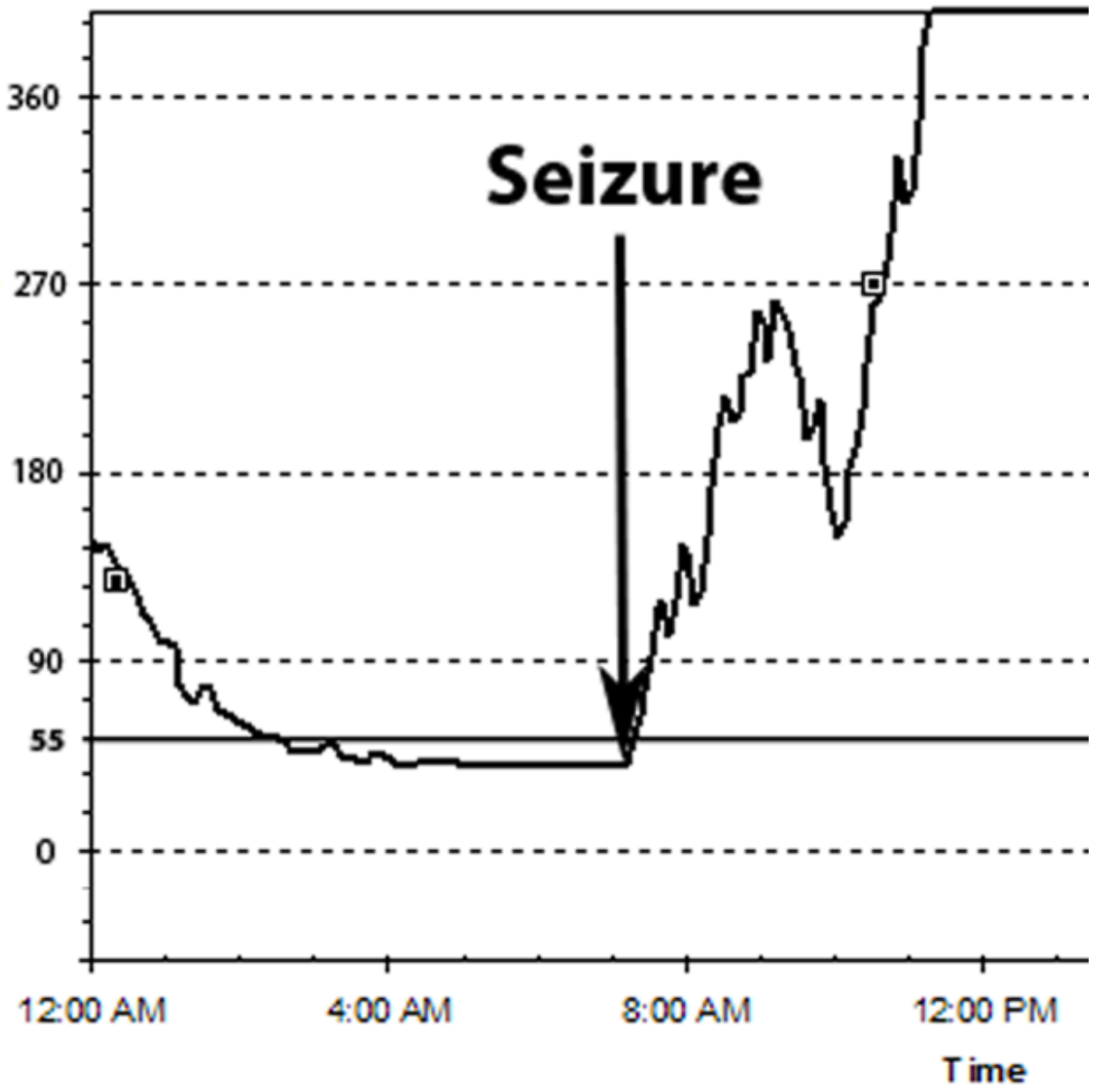
Reference - Dassau E, Zisser H, Palerm CC, Buckingham BA, Jovanovič L, Doyle III FJ. Modular Artificial β-Cell System: A Prototype for Clinical Research J Diabetes Sci Technol. 2008;2(5):863-72.
NOTE - Investigational Device. Limited by Federal (or United States) law to investigational use.

Insulet Horizon



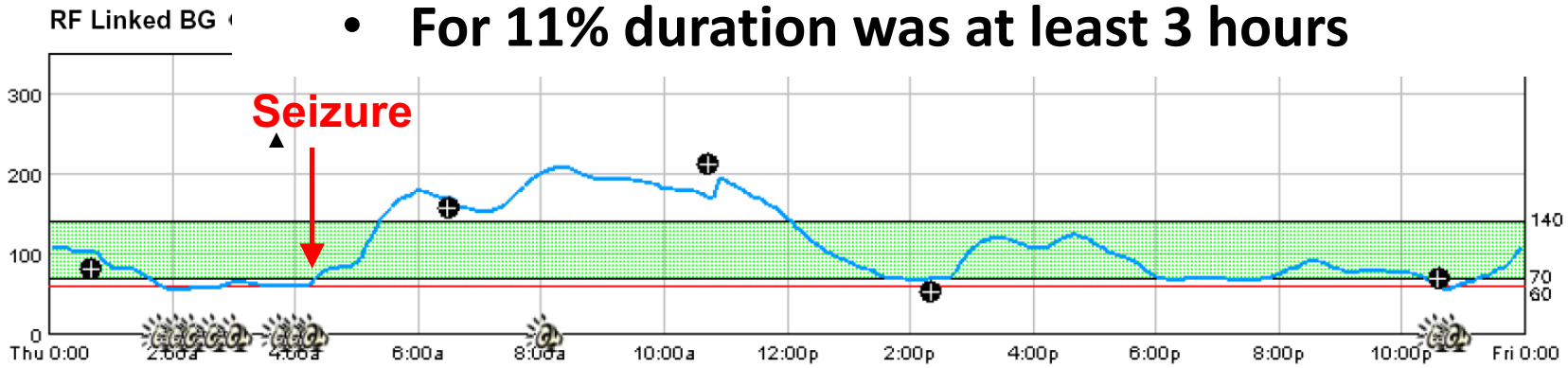
Suspending Insulin Delivery to Prevent Hypoglycemia

Australian Patient

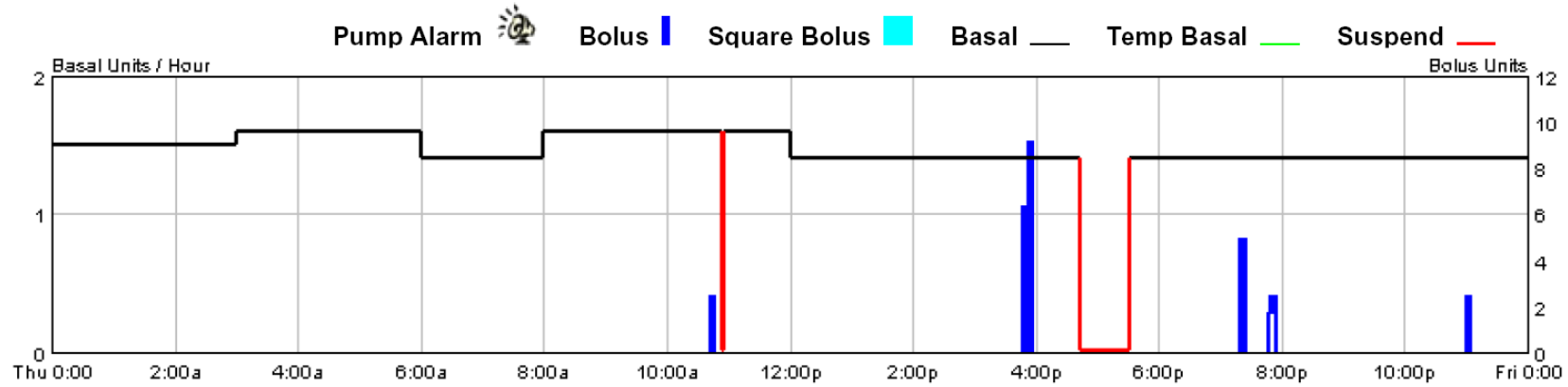


- 36,000 nights in JDRF RCT, 176 subjects
- Hypoglycemia occurred 8.5% of nights
  - (2 consecutive CGM readings < 60 mg/dl)
- Mean duration 81 minutes
  - For 23% duration was at least 2 hours
  - For 11% duration was at least 3 hours

Glucose (mg/dL)

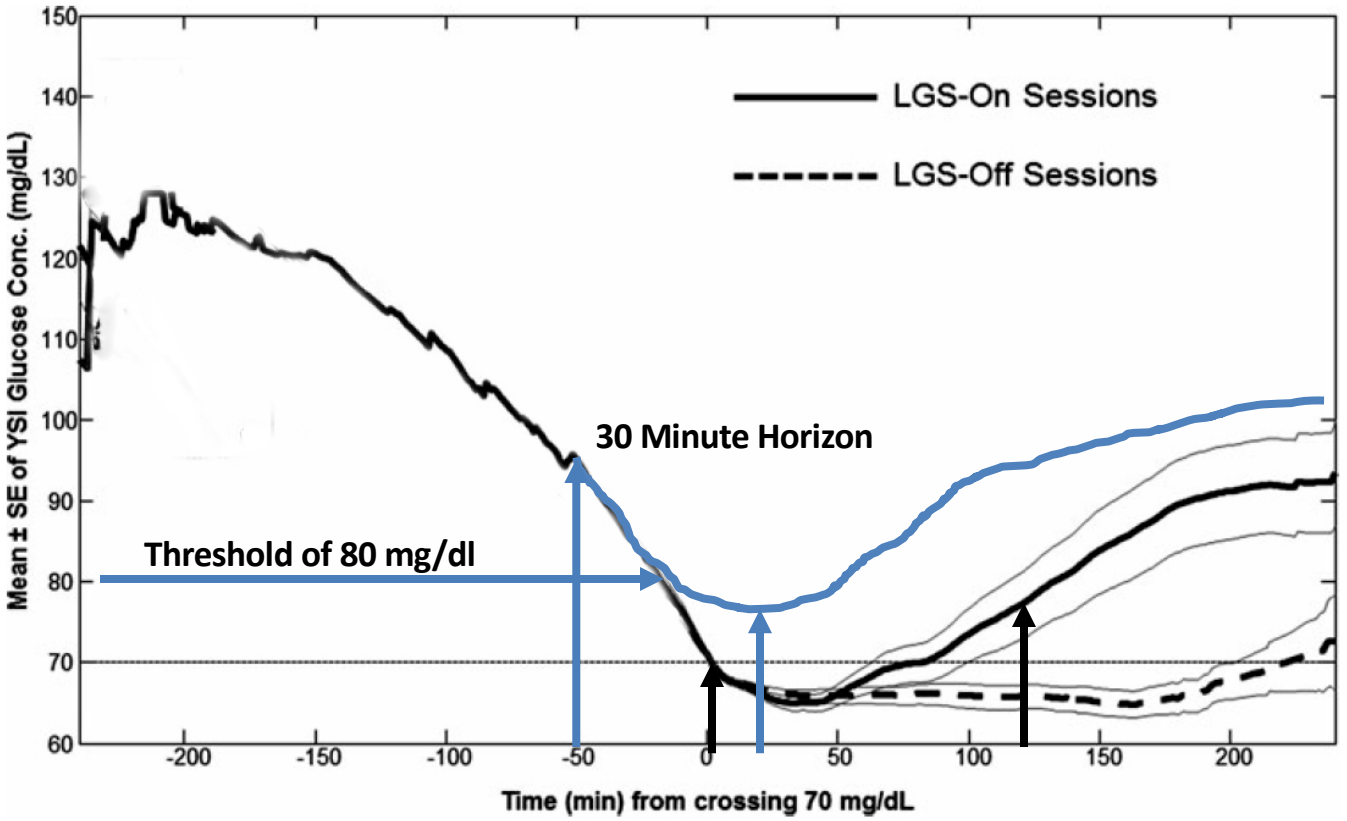


Insulin Delivery



Low Glucose Suspend with Exercise Induced Hypoglycemia (50 subjects)

DTT (2012) 14:205



Predictive Low Glucose Suspend

(5,332 randomized nights of testing)

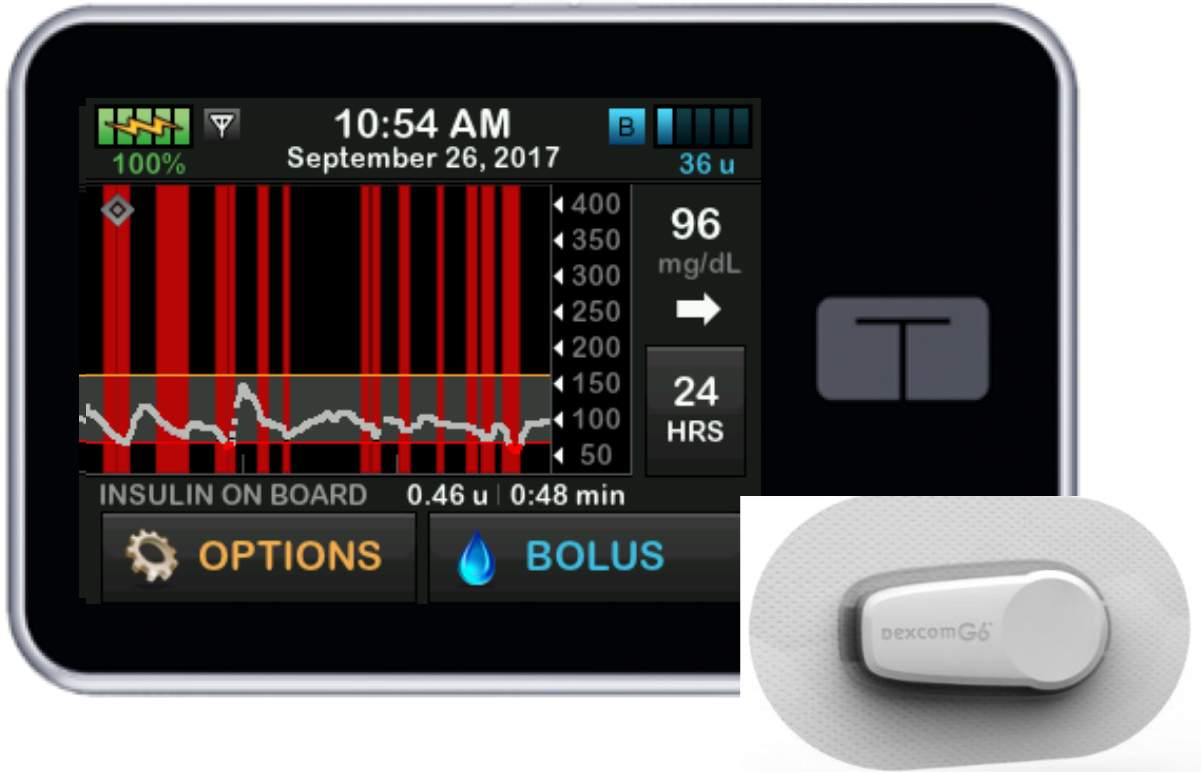
	4 – 10 Year Olds		p	11 -14 Year Olds		p	15-45 Year Olds		p
	Control	System Active		Control	System Active		Control	System Active	
# nights	755	769		941	955		970	942	
% nights <60 mg/dl for 120 min	5%	1%	<0.001	8%	3%	< 0.001	11%	3%	<0.001

- Maahs, Diabetes Care 2014; 37:1885-1891
- Buckingham, Diabetes Care 2015; 38: 1197-1204

Tandem Predictive Low Glucose Suspend System

- Tandem t:slim X2 pump with Basal-IQ
- Integrated with Dexcom G6 sensor and PLGS algorithm
- No Alarms with suspensions

- Released 8/17/18
- Free download to Tandem t:slim X2 pump users



DiAs (UVA) System - 2014

Type Zero


Glucometer
Dexcom Gen4 Receiver
Roche Accu-Chek Insulin Pump
Remote Monitor

Ski Camp Study: April 2018
Stanford at Lake Tahoe, Kirkwood

- 12 kids tested the UVA artificial pancreas system in extremes of exercise, weather, and altitude.
- Participants are randomized 1:1 to wear either their own pump with a real-time continuous glucose monitor or the experimental artificial pancreas system

Tandem Control IQ

- For start up:
  - Basal rates, Correction Factors, Carb ratios, Target BG
  - Weight and Total Daily Insulin
- Sleep Start and Stop times
  - Can have patterns for different days of the week

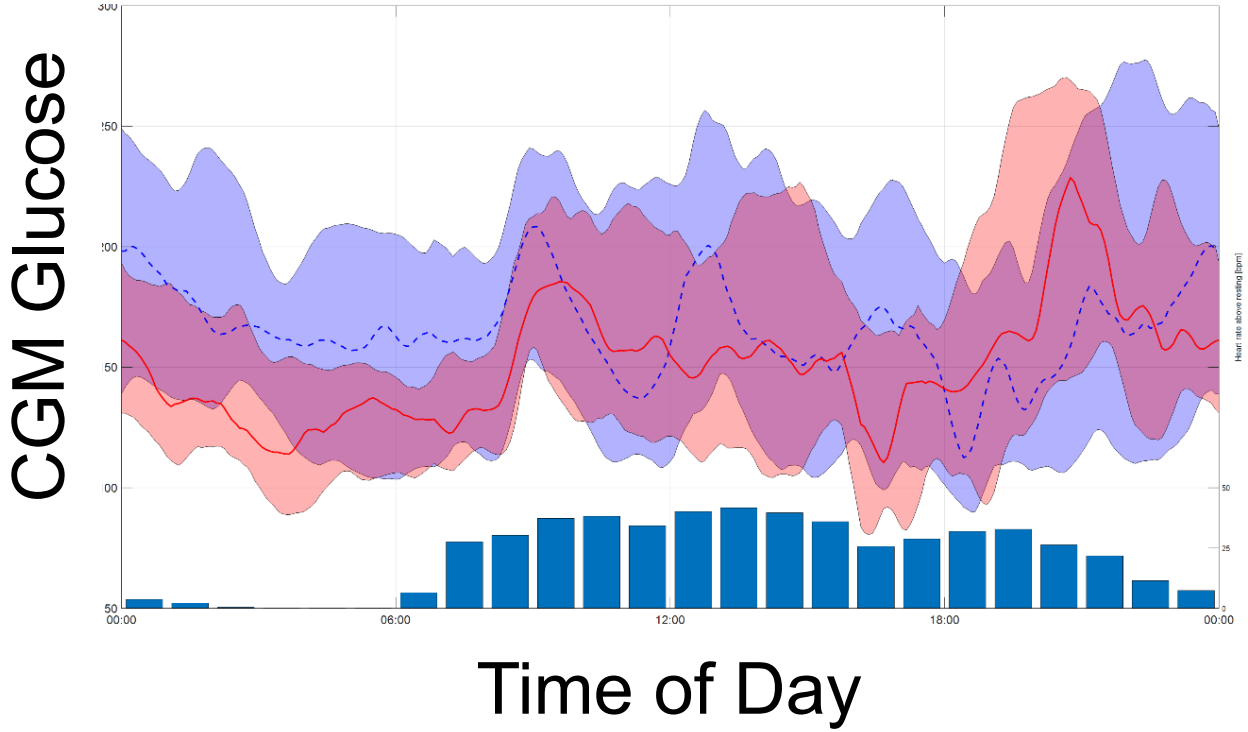
Control IQ Algorithm – Targets

- Wake – 112.6 to 160 mg/dl
- Sleep – gradually lowers target to 112.5 to 120 mg/dl
  - Should be reached in 5 hours
  - Does not give automatic correction doses during sleep mode
- Uses 30 minute prediction to adjust basal delivery
  - Decreases if prediction is <112.5
  - Stops if prediction is <70 mg/dl
  - Increases if prediction is >160 mg/dl

Control IQ Algorithm – Auto Correction

- Occurs hourly
- When 30 minute predicted CGM is >180 mg/dl
- Delivers 60% of correction dose to target of 110 mg/dl

24-hour glycemic control at ski camp

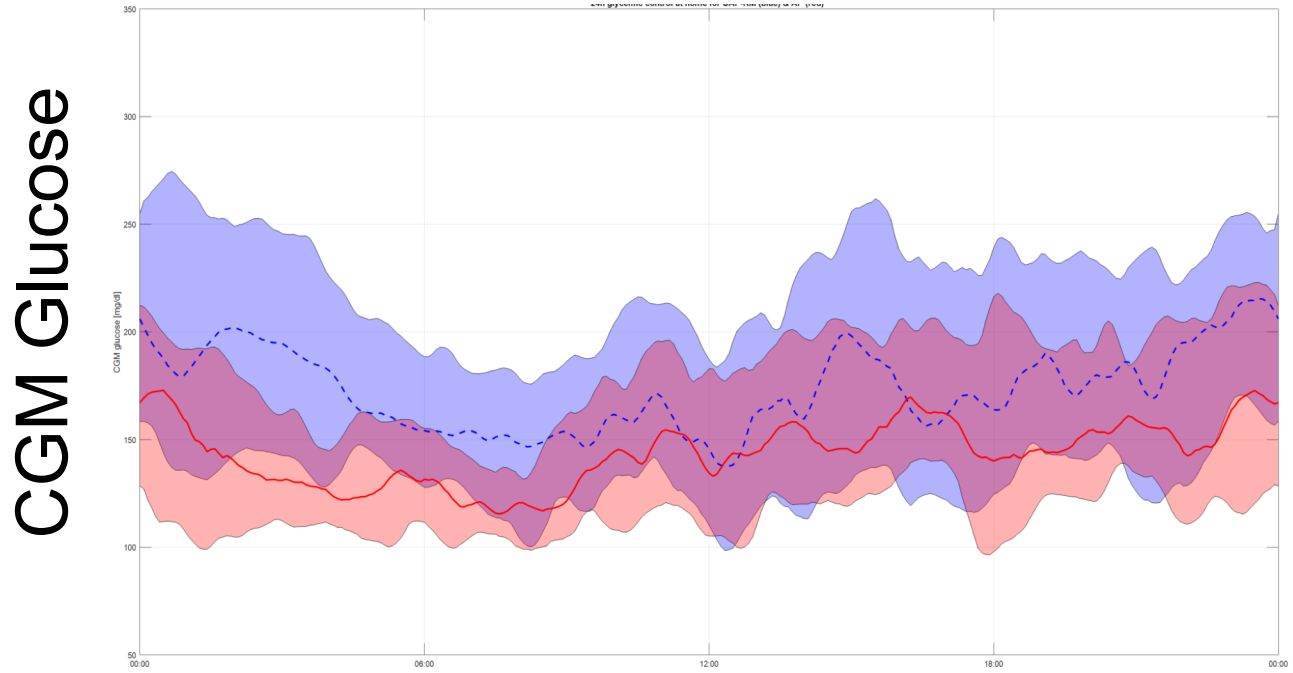


RED: AP

BLUE: Control

ACTIVITY LEVEL

24-hour glycemic control during home use



RED: AP

BLUE: Control

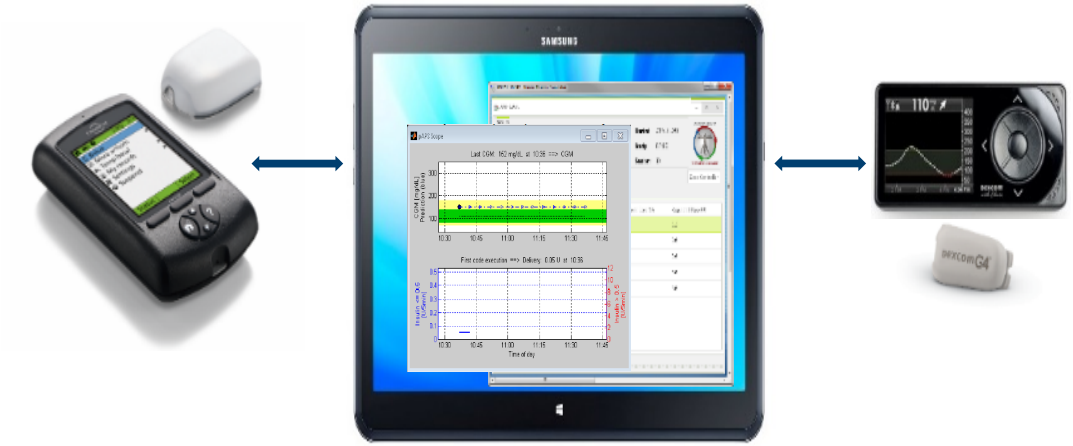
Stanford Ski Camp Tandem Control IQ

International Diabetes Closed-Loop Trial (iDCL)

- 7 centers
- t:slim X2 with Control-IQ and Dexcom G6 system
- A randomized (2:1) controlled trial
- 6 month at home with a 3 month extension phase
- Ages 14-75
- 168 subjects

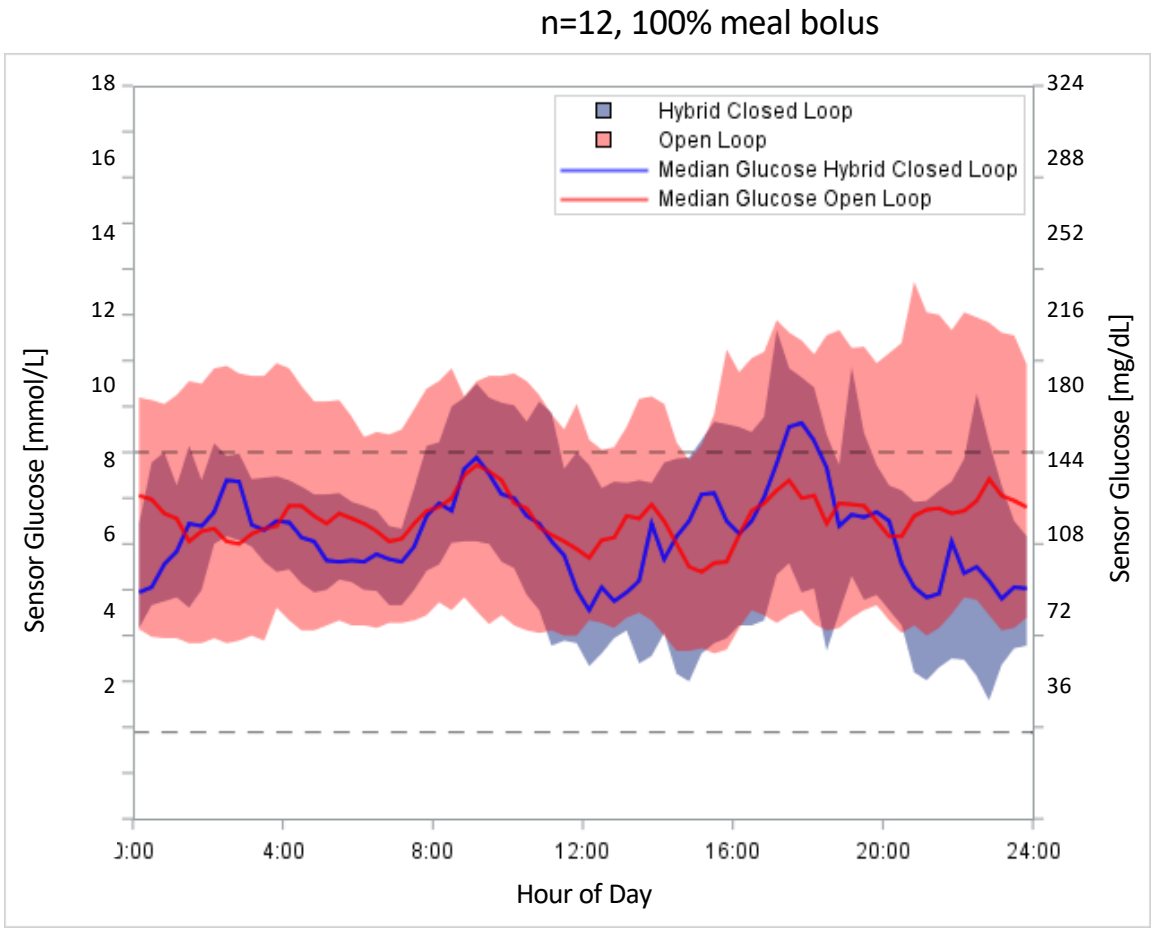
Omnipod Platform for Algorithm Development

- Feasibility studies in patients with type 1 diabetes have been completed to assess the Omnipod Horizon™ personalized Model Predictive Control (MPC) algorithm
  - 36-hour inpatient study in adults, adolescent and pediatrics
  - 54-hour meal bolus challenges reflective of real life conditions
  - 5 day / 4 night study across age groups including MDI patients



Investigational Device. Limited by Federal (or United States) law to investigational use.

Adolescents - Sensor Glucose over 24 hours



Buckingham B et al. *Diabetes Technol & Thera.* 2018; in press.

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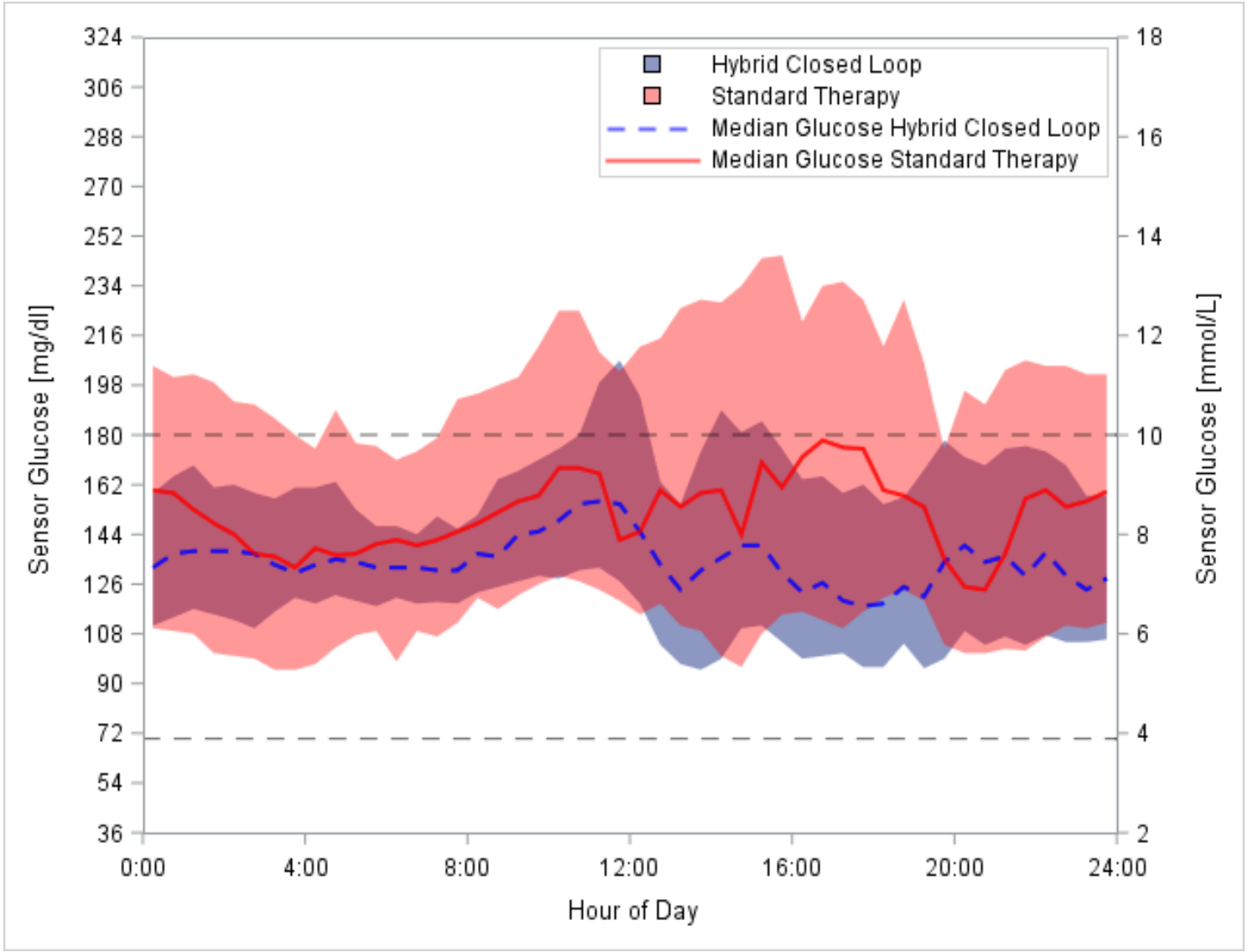
Children - Sensor Glucose over 24 hours



Glycemic Outcomes in Adolescents

Glycemic Outcomes	Overall (36 h)	Overnight 23:00-07:00
Mean glucose (mg/dL)	153.4 ± 21.6	149.3 ± 24.4
Time in range, %		
<70 mg/dL	2.0 ± 2.4	0.2 ± 0.6
70-180 mg/dL	72.6 ± 15.5	84.7 ± 25.1
≥250 mg/dL	4.9 ± 6.3	1.5 ± 4.9

N=12; 100% meal bolus

Data are mean±SD

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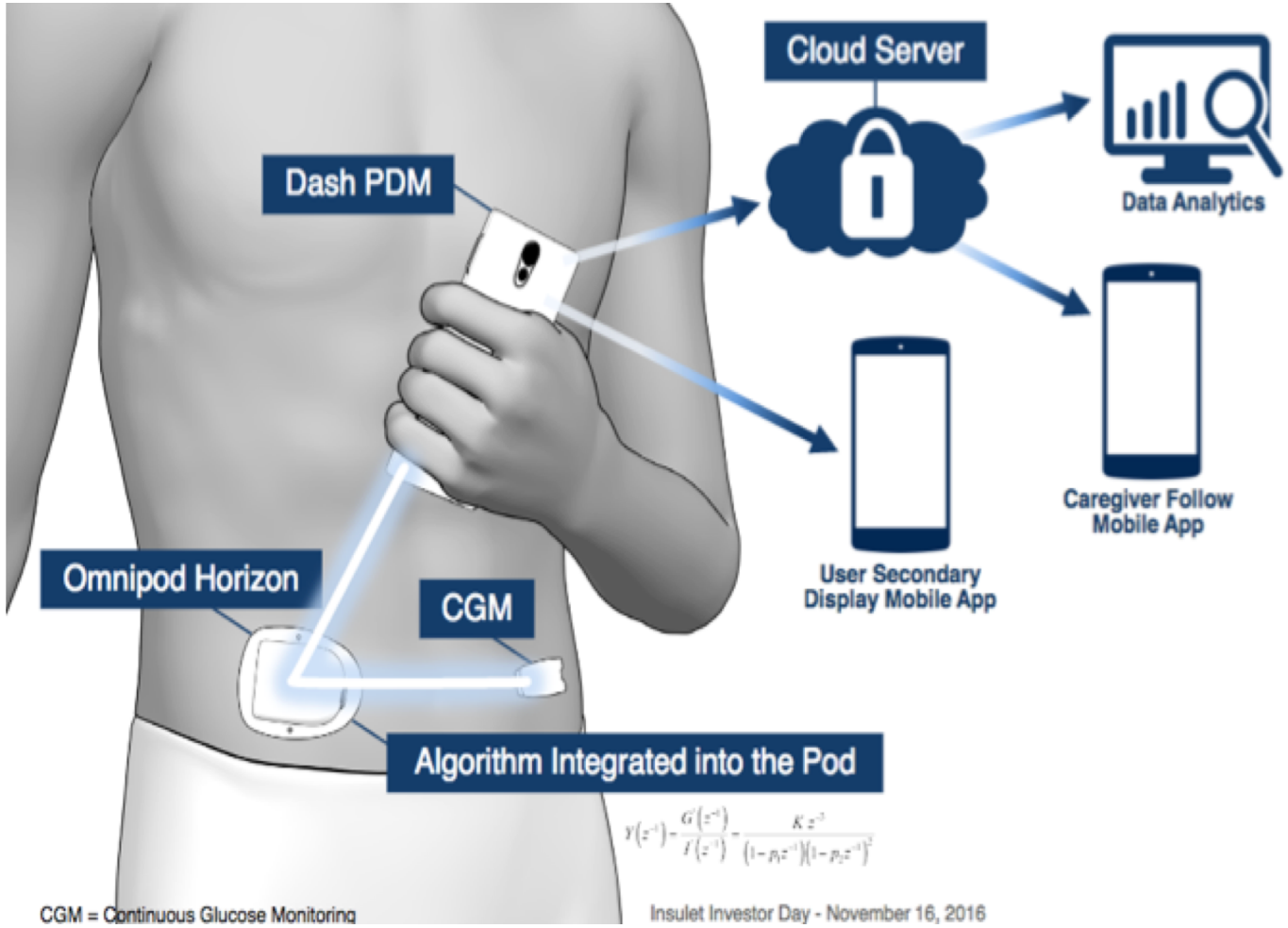
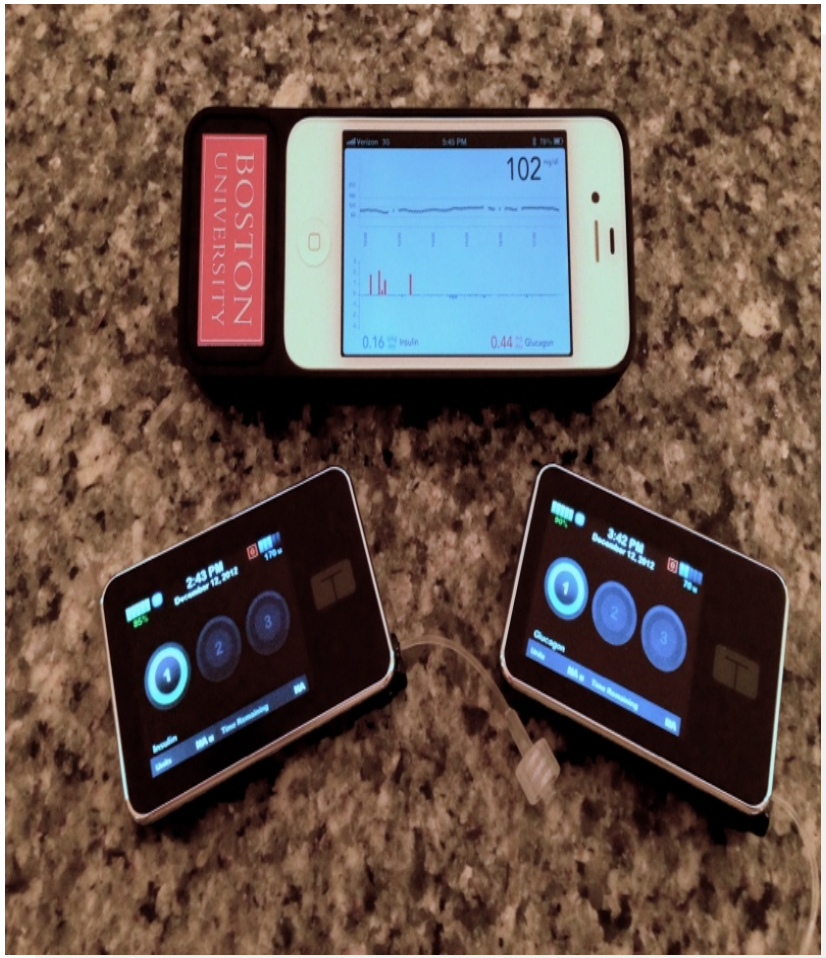
Insulet Toddler Studies 2018

Insulet Horizon



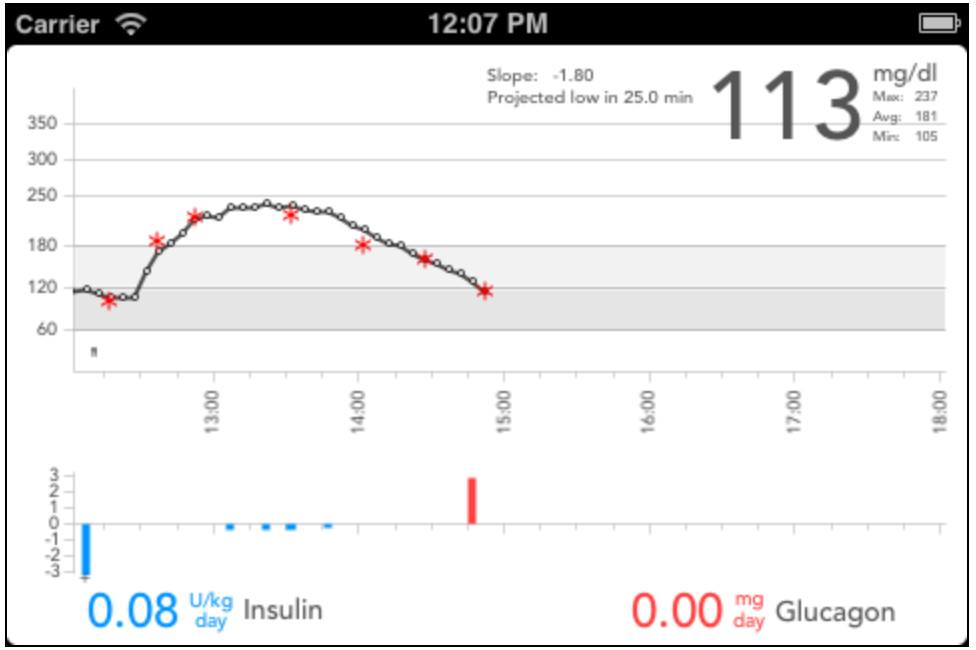
Bionic Pancreas
The Iphone Based System



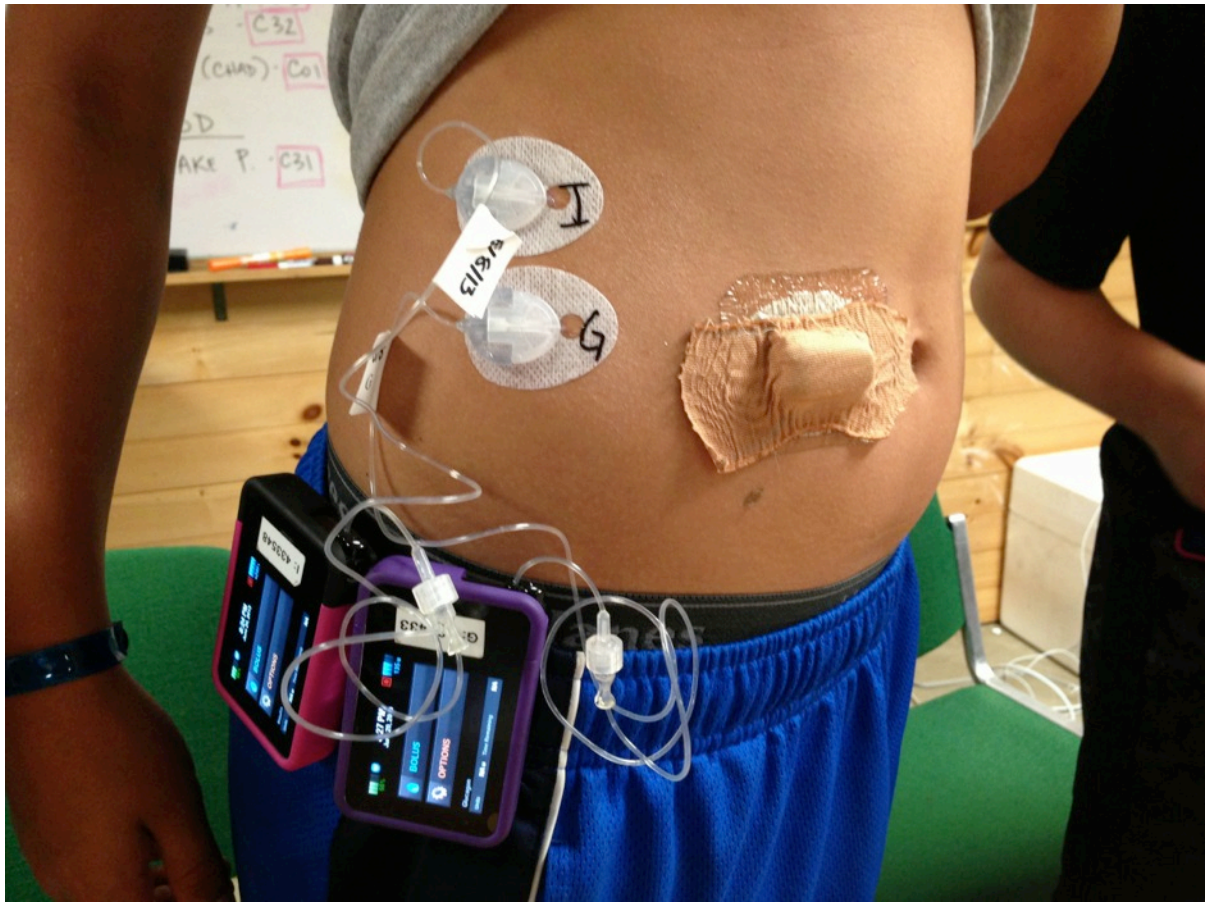
Bionic Pancreas Control Algorithm

- Only patient weight for initialization
- Operation solely based on glucose
- Adapts to individual insulin needs over ~18 hours
- Predicts pending insulin action with model for absorption and clearance to avoid stacking (MPC controller)
- Glucagon dosing: A proportional-derivative control algorithm

User Interface



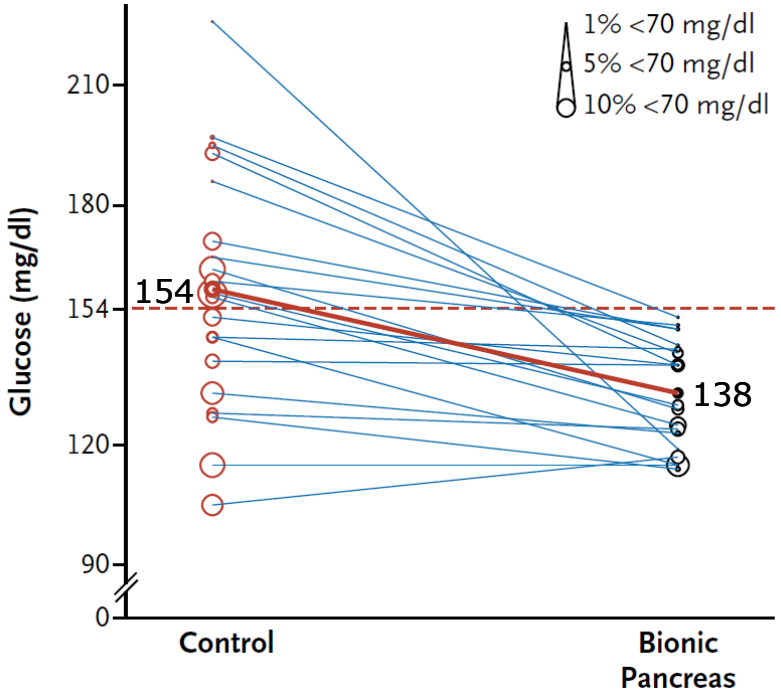
Bionic Pancreas Clinical Studies



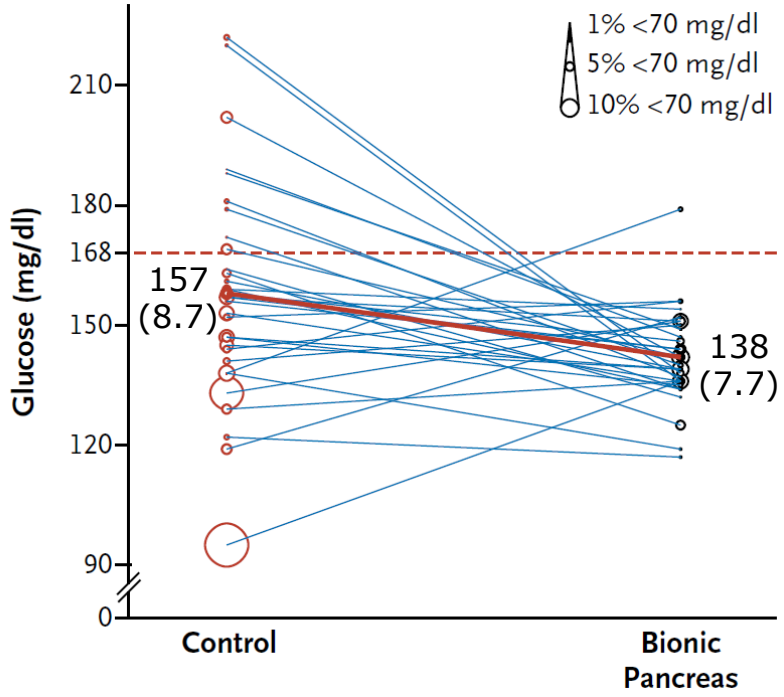
Outpatient bionic pancreas – 5 day randomized cross-over of 20 adults and 32 adolescents

Russell SJ et al. *N Engl J Med* 371:313-25, 2014

Mean glucose levels in adults



Mean glucose levels in adolescents



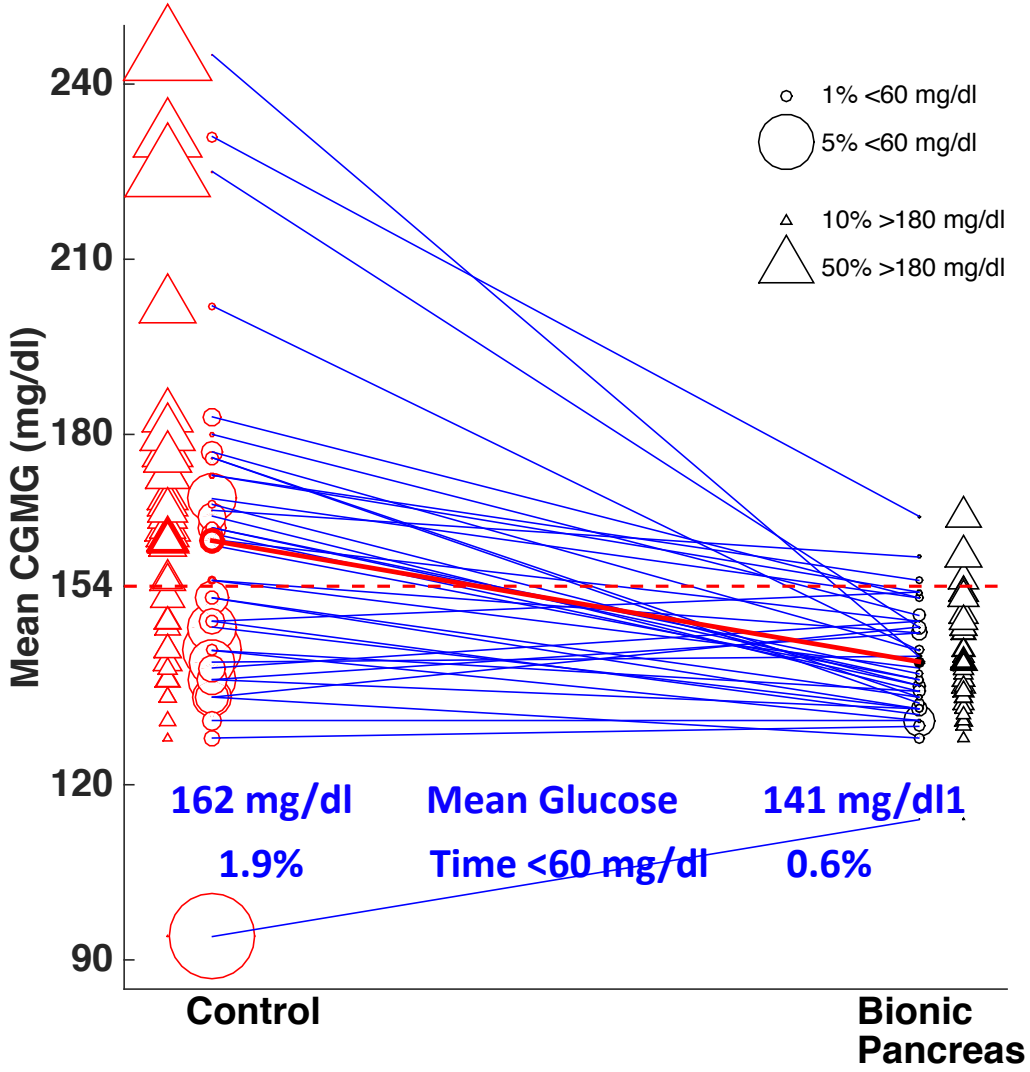
THE LANCET

Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised crossover trial

Forty three Adults (>18) with type 1 diabetes

- Random order cross-over
- bionic pancreas vs. usual care
- Patients who were lived/worked near on one of four campuses
  - MGH, UNC Chapel Hill, **Stanford**, UMass Medical Center

Bionic Pancreas vs. Usual Care



162 mg/dl	Mean Glucose	141 mg/dl1	p<0.0001
1.9%	Time <60 mg/dl	0.6%	p<0.0001
0.66 u/kg	Insulin TDD	0.63 u/kg	P= 0.01
	Glucagon TDD	0.51 mg/day	

El-Khatib-FH, Lancet, 2017

Bionic Pancreas Bihormonal Features Translatable to an Insulin Only (BPIO) System

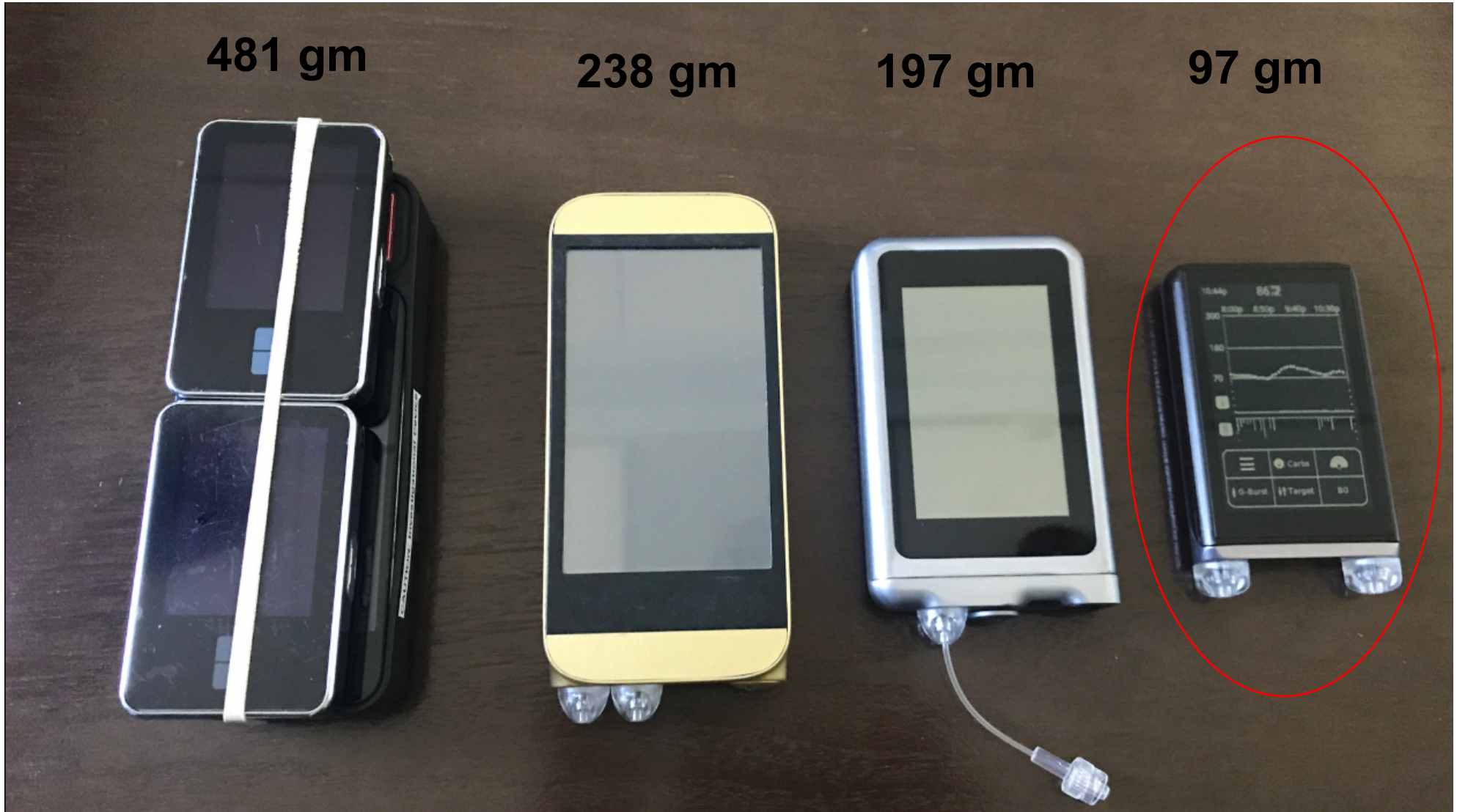
- Initialize with weight only – no prior insulin or glucose data
- Rapid adaptation to insulin requirements
- No Carbohydrate counting
- Meal Adaptation

ILet Gen 3

iLet studies – Insulin Only 2018


GO
BIONIC

Future studies with iLet Gen 4



Bigfoot Biomedical

Medtronic 670G – 2014

Glucometer

Tunable parameters

- Carbohydrate to insulin ratios
  - Can have multiple ratios throughout the day
- Duration of insulin action
- Insulin Bolus Speed

Controller Adaptability

- The controller gain (how aggressive it is), maximum basal insulin delivery limit, insulin sensitivity factor, and “safe basal” rates are adapted daily
  - Based on glucose levels overnight and total daily insulin dose

Correction Bolus with 670G

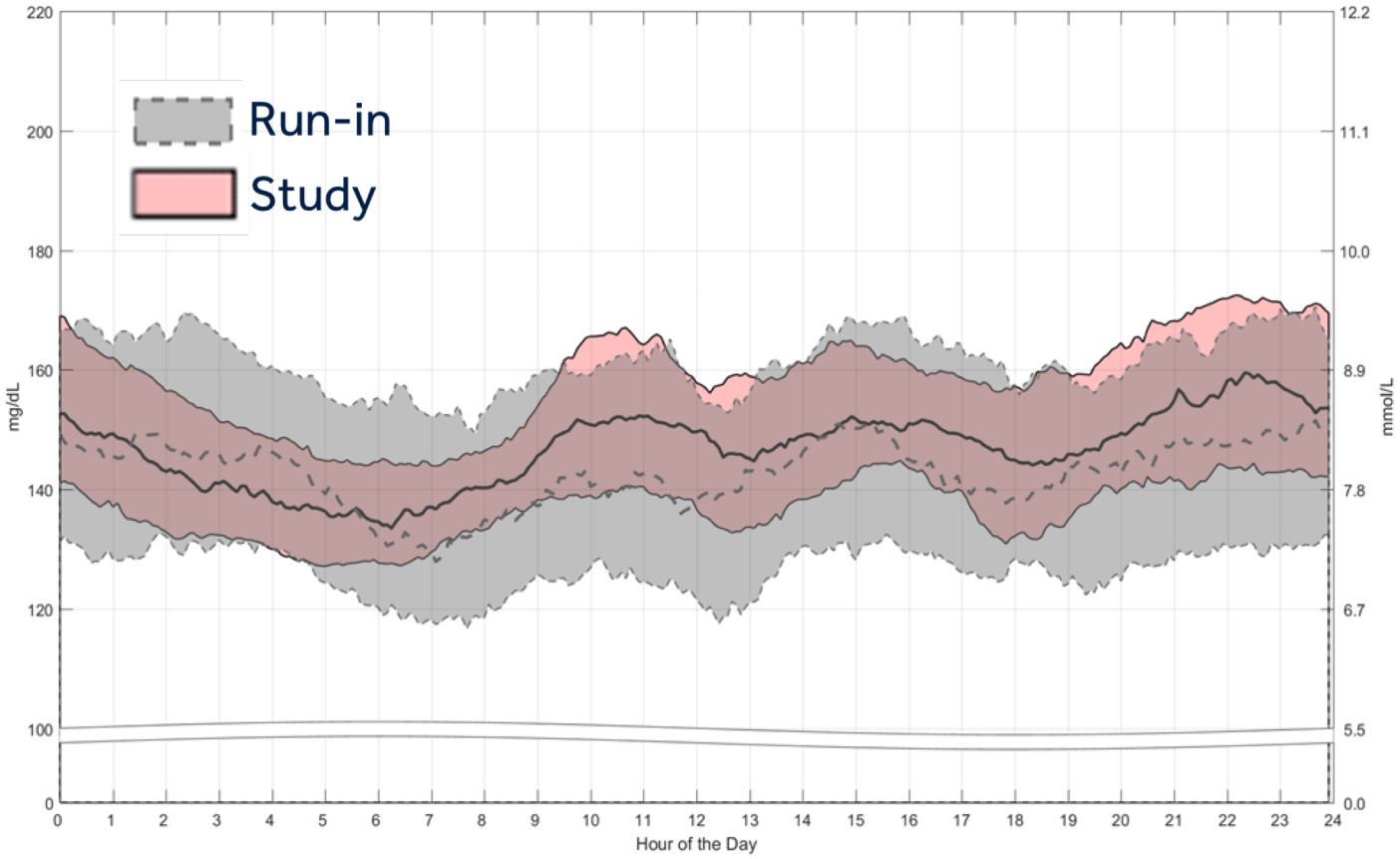
- If meter BG is >150 mg/dl

Reasons for transitioning from Auto Mode to Safe Basal

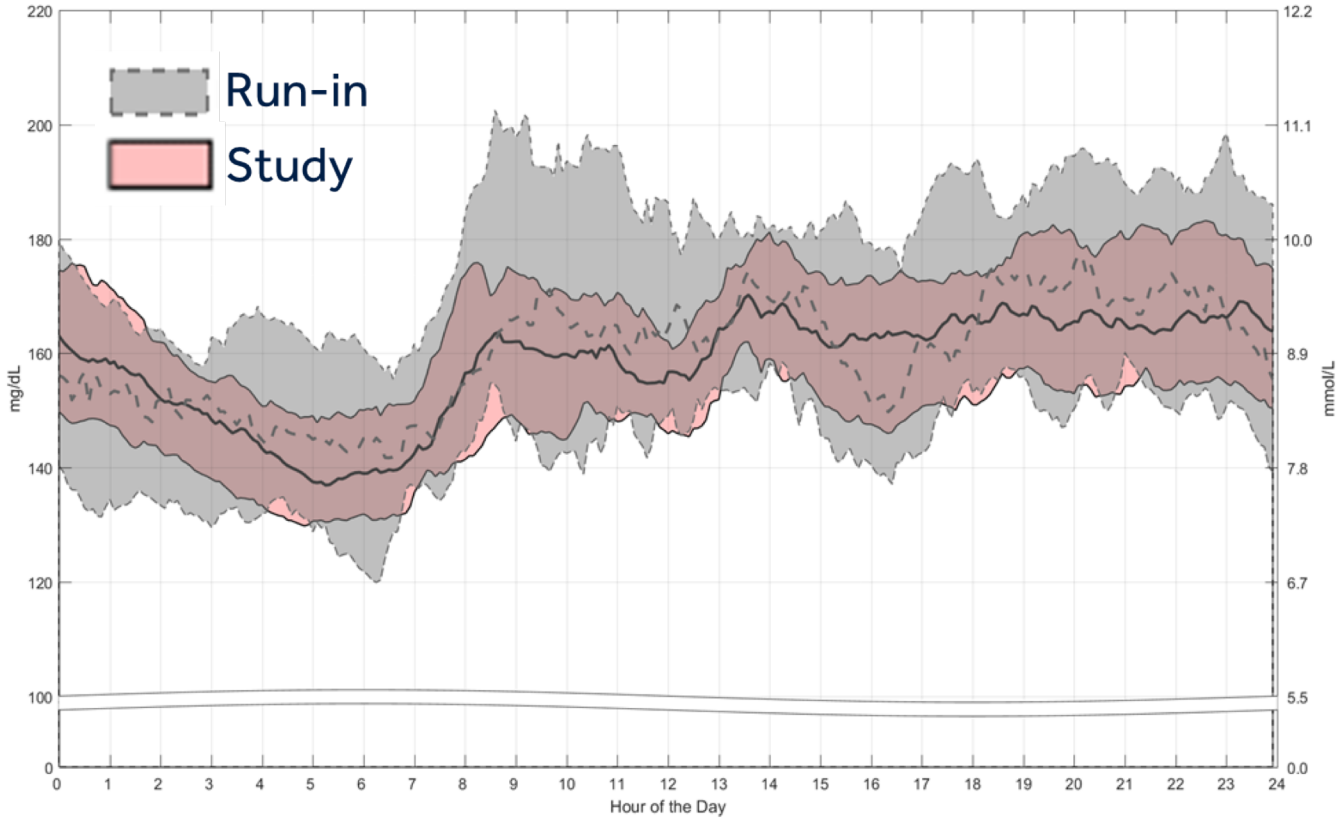
- Minimal insulin deliver for 2 ½ hours
  - Concern for sensor failure
- Maximum insulin for 4 hours
  - Concern for infusion set failure
- Sensor glucose of >300 for 1 hour, or >250 for 2 hours,
  - Concern for infusion set failure
- Lost sensor

13 y.o. male, A1c=8.8, Daily Summary

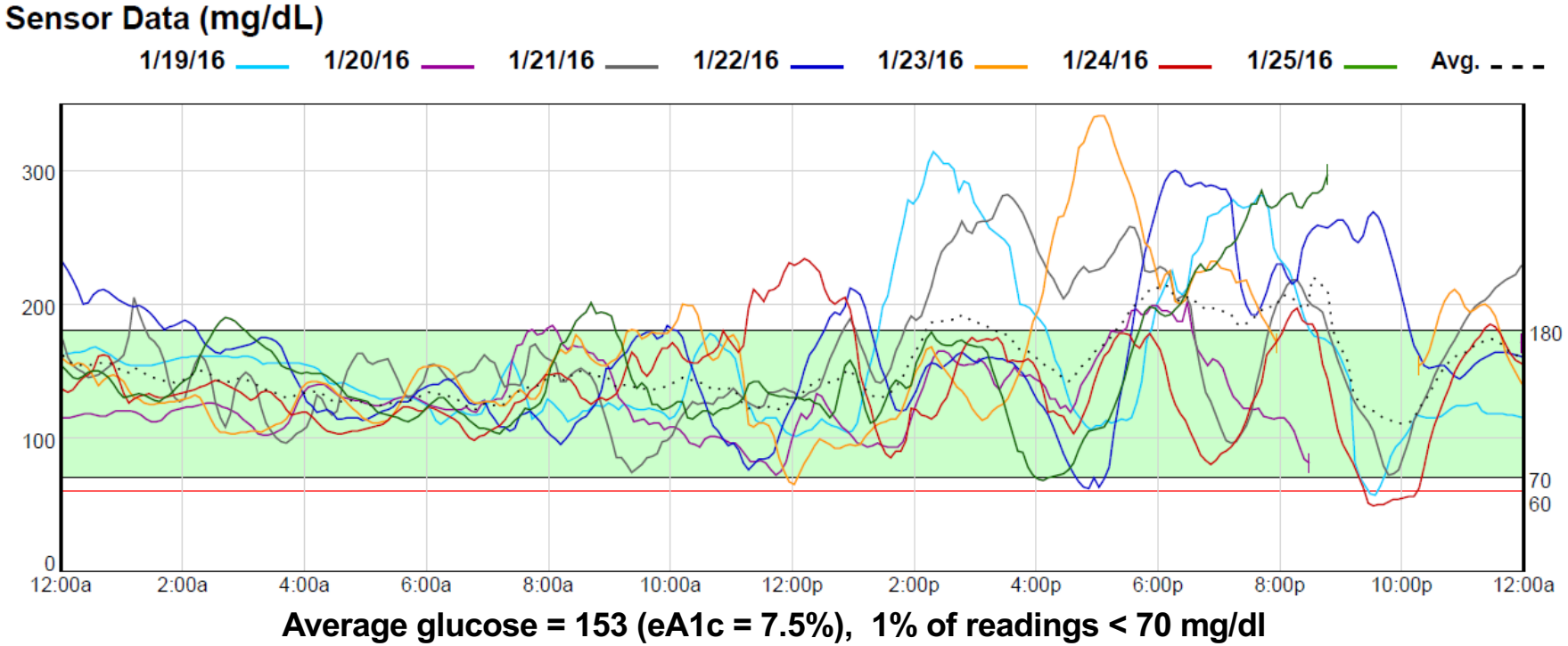
Adults: 22-75 years old, N=94



Adolescents: 14-21 years old
N=30

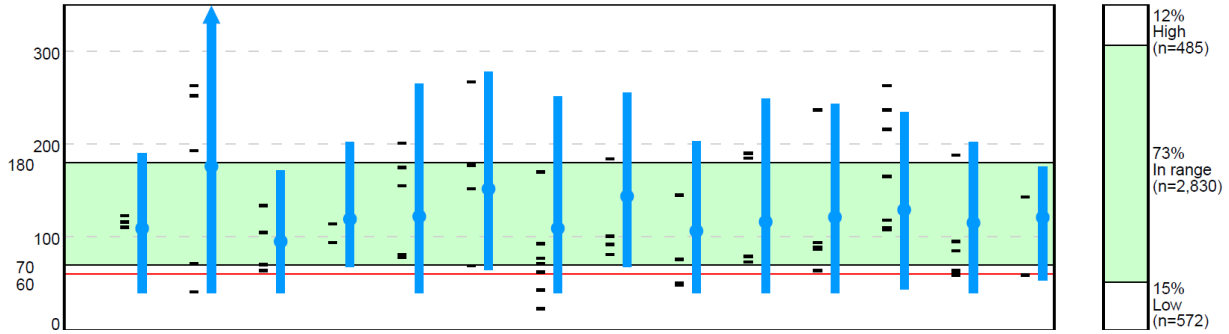


670G Study Subject Download



Average glucose = 153 (eA1c = 7.5%), 1% of readings < 70 mg/dl

Adolescent male, 78 kg

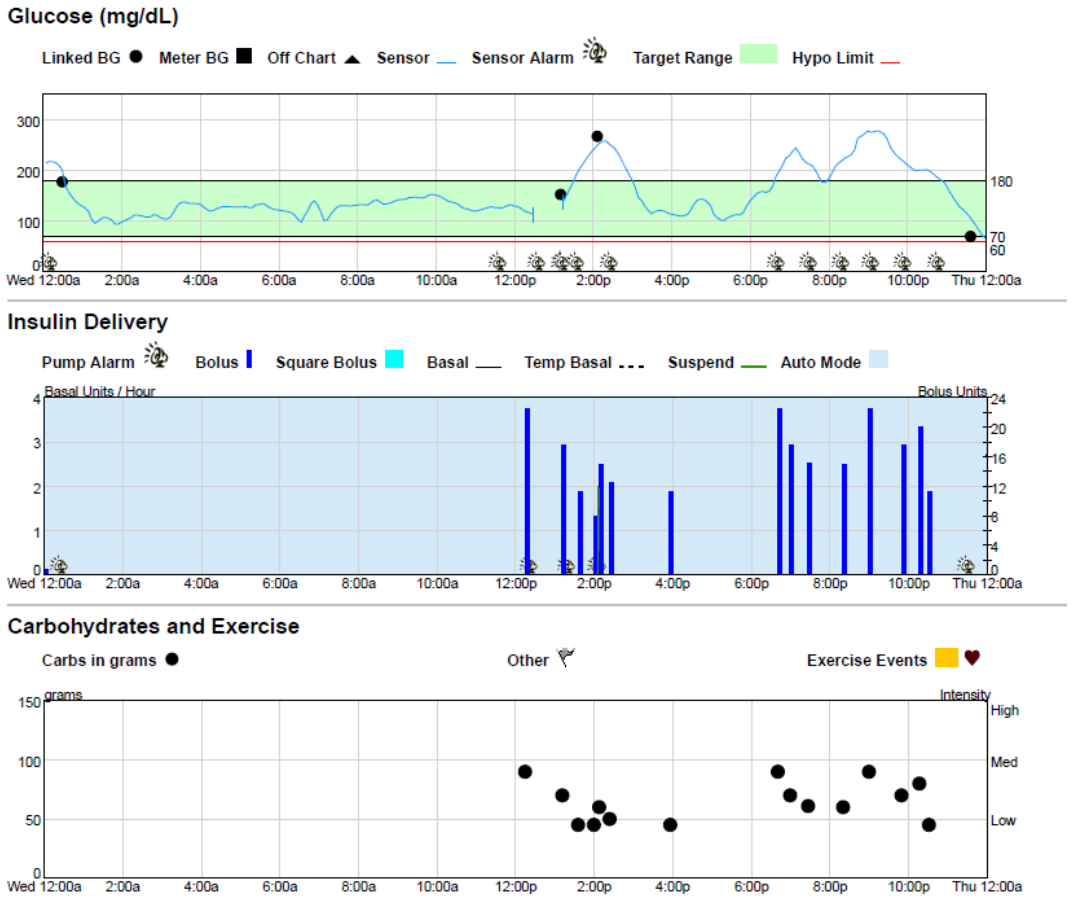


Carbohydrates vary from 160 to 971 grams a day

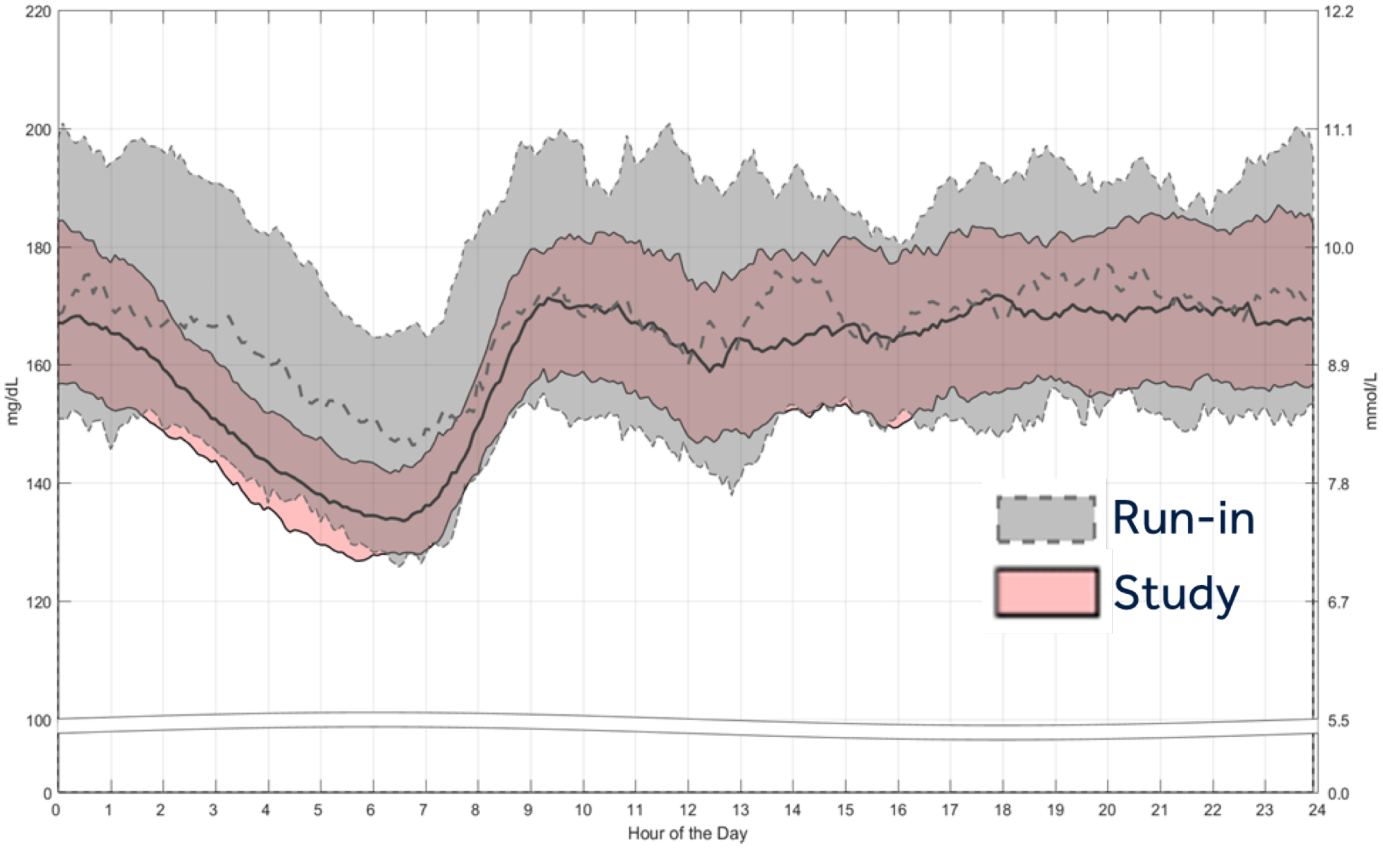
Insulin varies from 73 to 267 units a day

Mean Glucose = 124 ± 52 mg/dl

Day of 971 grams of CHO



Pediatrics: 7-13 years old, N=105



Statistics for All Subjects in 670G
94 Adults, 30 Adolescents

	Run In (Baseline)	3 month Data	p
HbA1c	7.4 ± 0.9	6.9 ± 0.6	<0.001
% <70 mg/dl	6.4 ± 5.3	3.3 ± 2.0	<0.001
% 71-180	66.7 ± 12.2	72.2 ± 8.8	< 0.001
TDI	47 ± 22	51 ± 27	< 0.001

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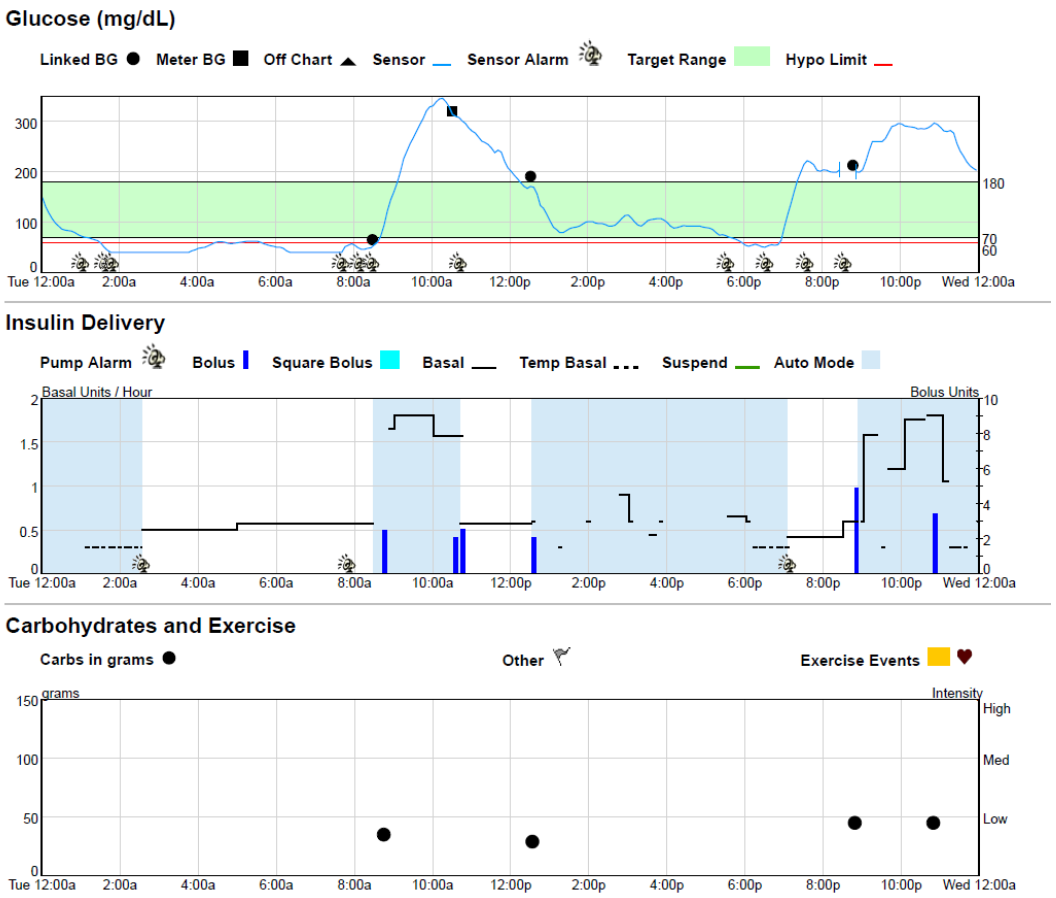
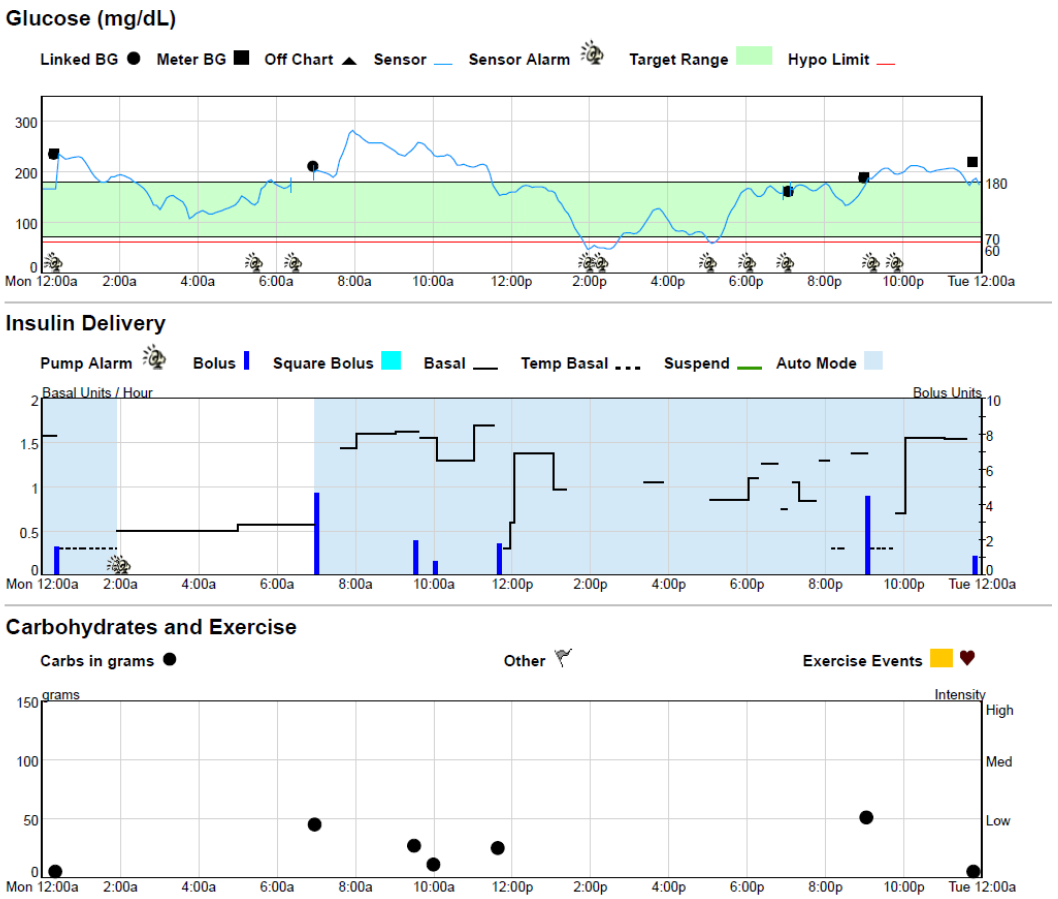
670G and Severe Hypoglycemia

- 65,000 days and nights of 670G wear
- This represents 178 patient years
- From T1D Exchange data there should have been at least 12 severe hypoglycemic events with seizure or loss of consciousness
- Actual number of severe hypoglycemic events = 0

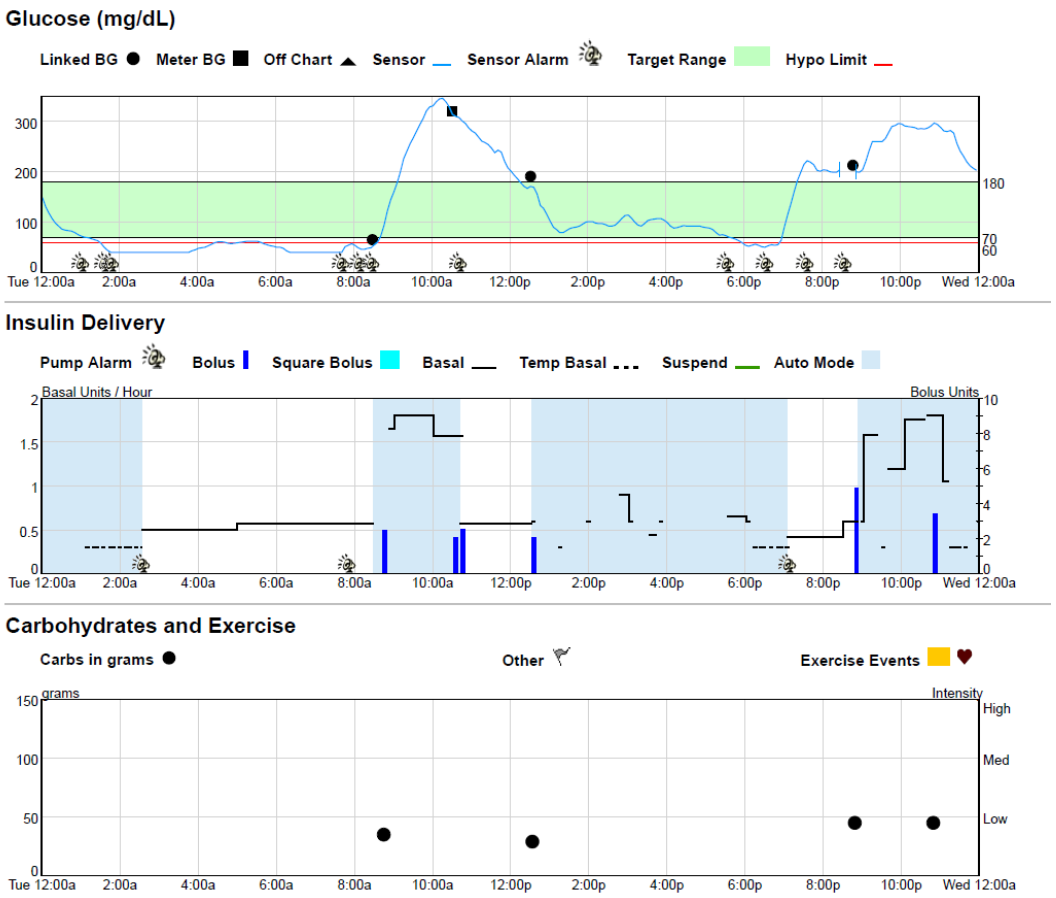
7 Hours of Nocturnal Hypoglycemia



The Night Before

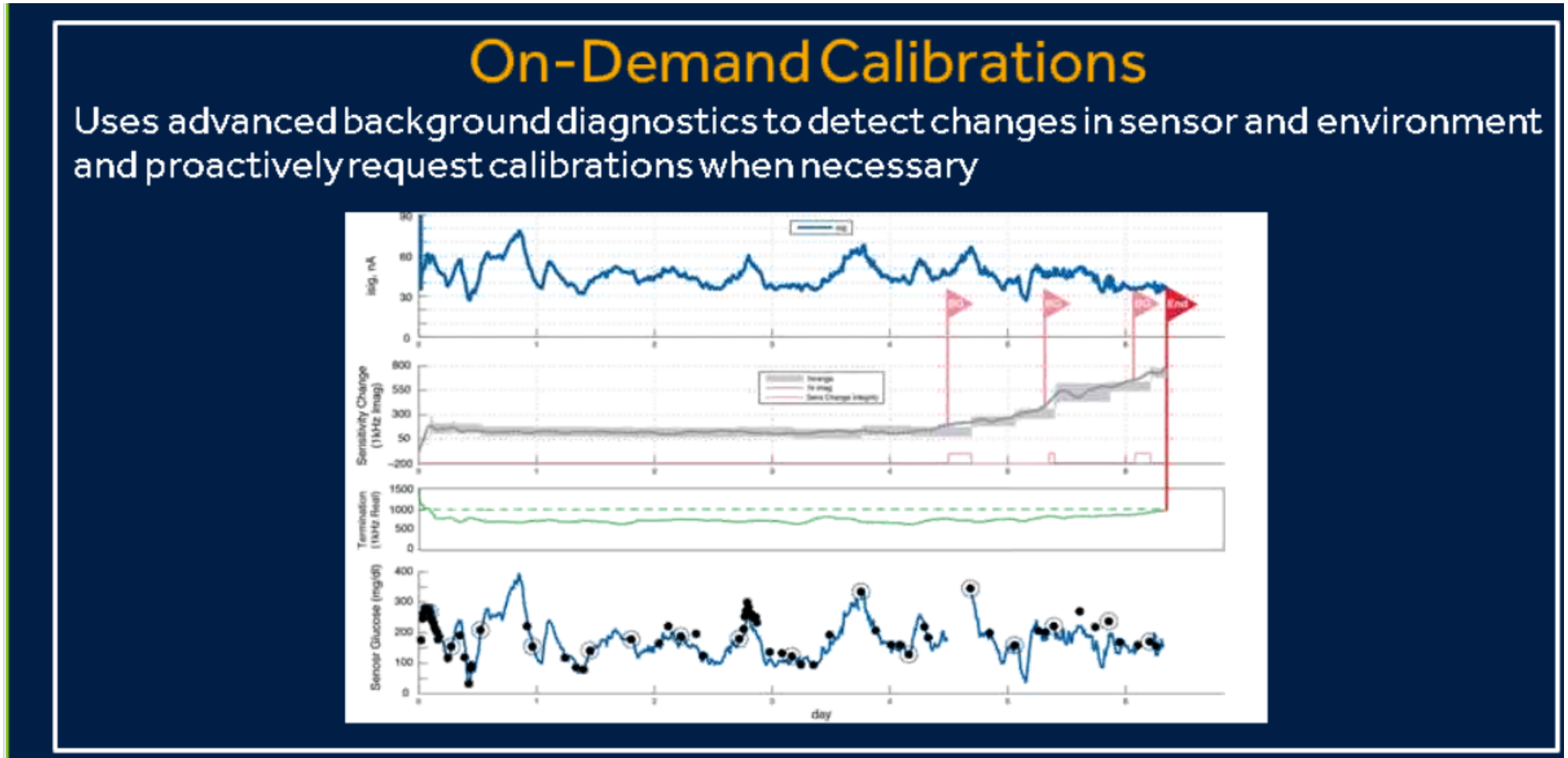


7 Hours of Nocturnal Hypoglycemia

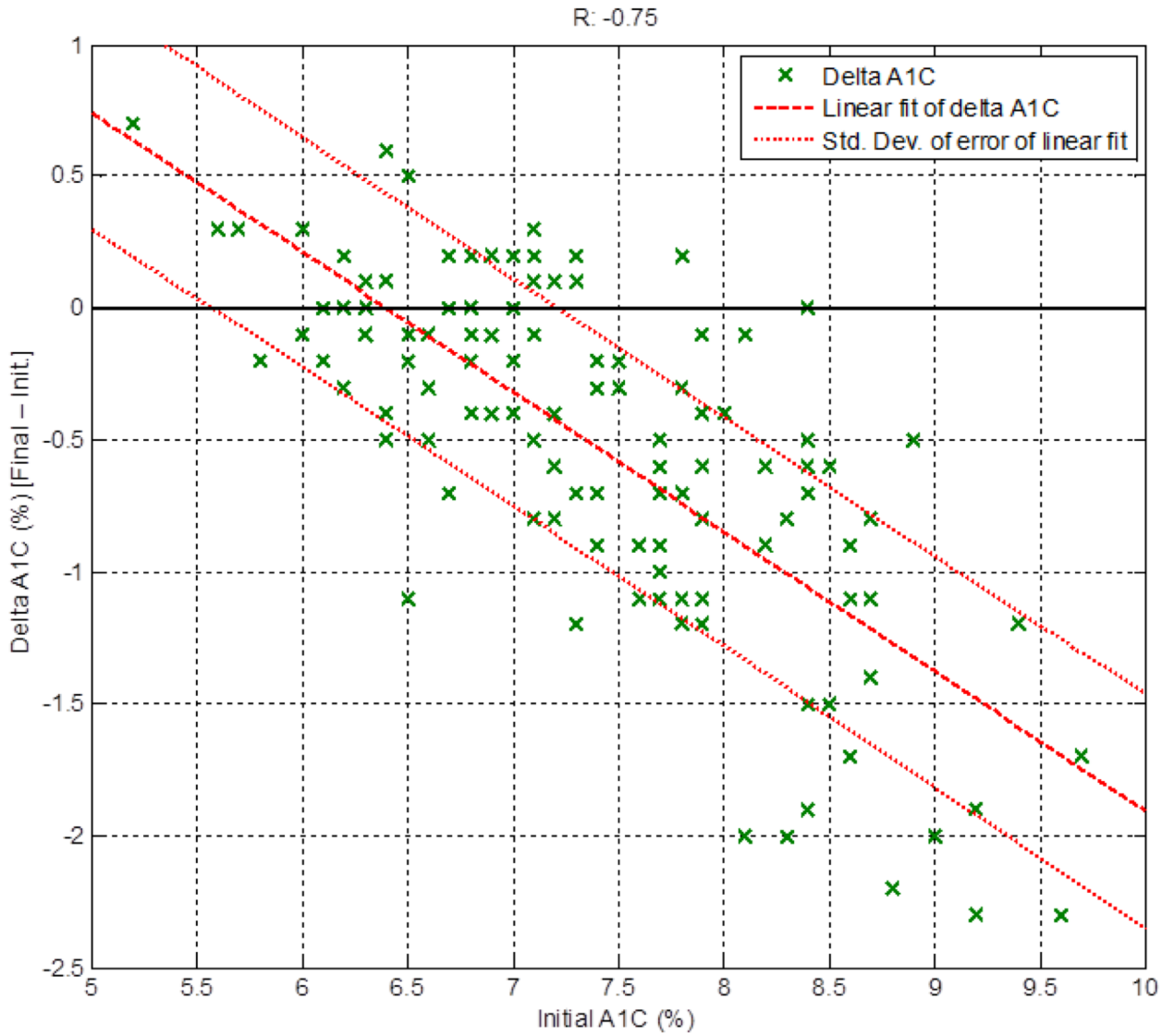


Sensor Alerts to Recalibrate

- Wait at least ½ hour before recalibrating



Does A1c determine who is a good candidate?



670G

- Greatly improves overnight control
- Start the day with a good glucose
- Improved sensor MARD 10.3%
- Need to optimize meal coverage - insulin:carbohydrate ratio
- Understand the fail-safe modes – limits on insulin delivery, glucose extremes, and sensor performance

670G Toddler Studies 2018

670G Toddler Study 2018

DIY Closed Loop

OpenAPS – Pump Hardware

x12

x15

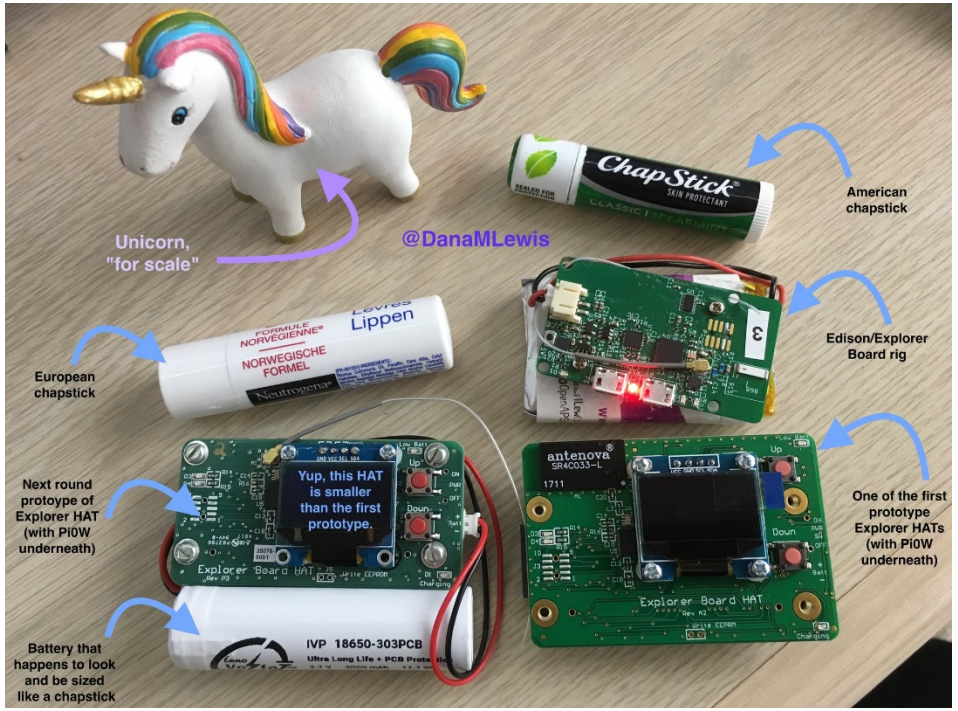
x22

x23 (FW ≤ 2.4A)

x54 - European (FW ≤ 2.6A)

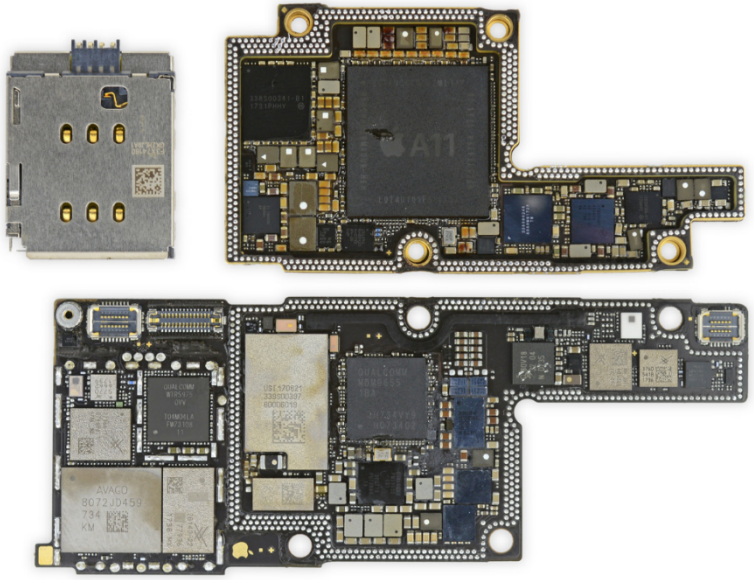
x54 – Canadian (FW ≤ 2.7A)

OpenAPS – Hardware Controller

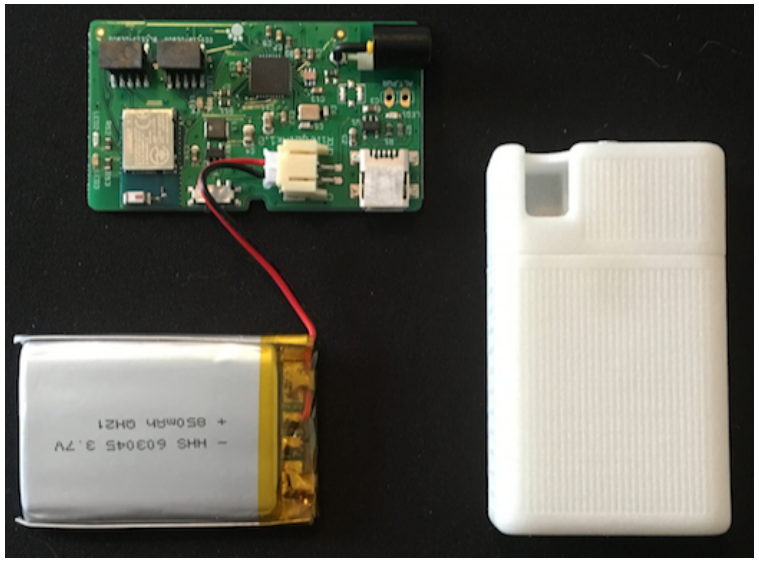


Microcontroller (Edison or Pi) + 900MHz Explorer Board ± Display

Loop – iOS with Bluetooth + RileyLink



Microcontroller (iPhone)
(RileyLink)



Bluetooth -> 900MHz bridge

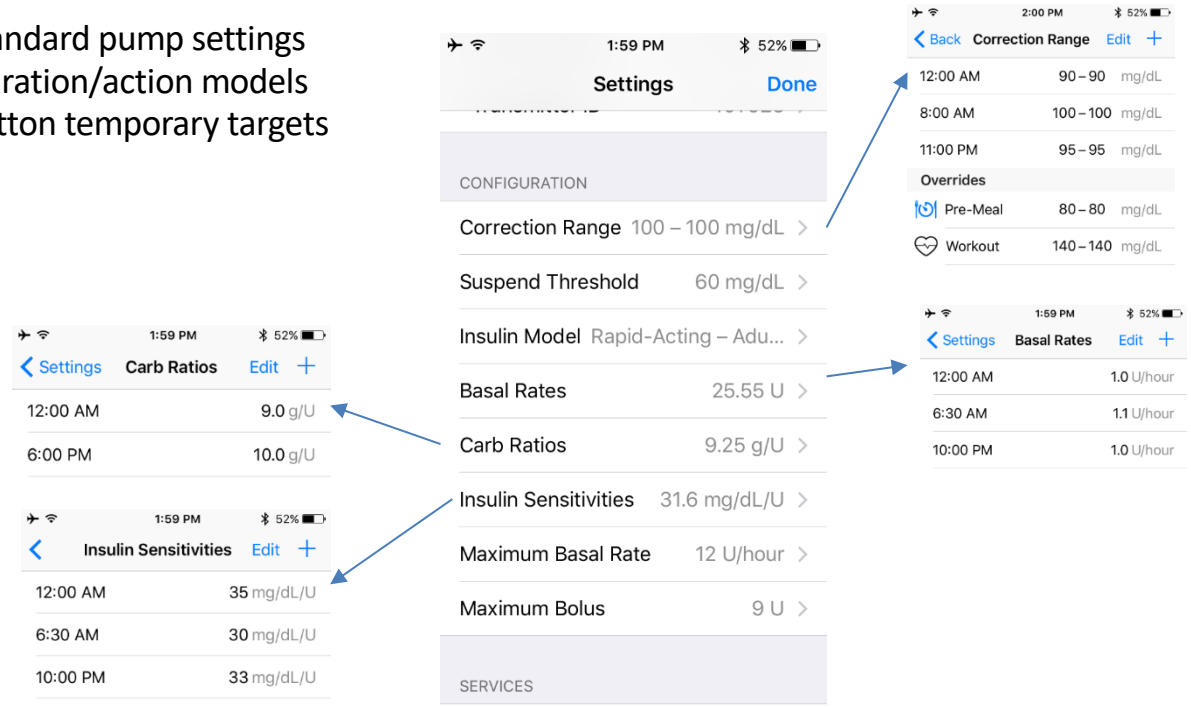
Loop – Pump Hardware


Carbs
Bolus


Cancel
15
GRAMS
Add Carbs

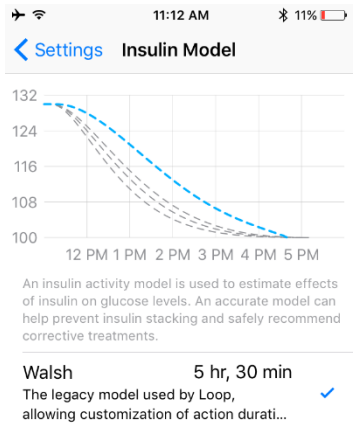
Customizable Settings

- All the standard pump settings
- Insulin duration/action models
- Easy 1 button temporary targets

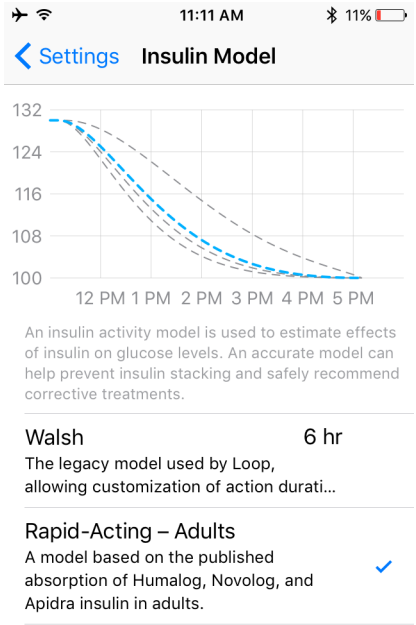


Insulin Models

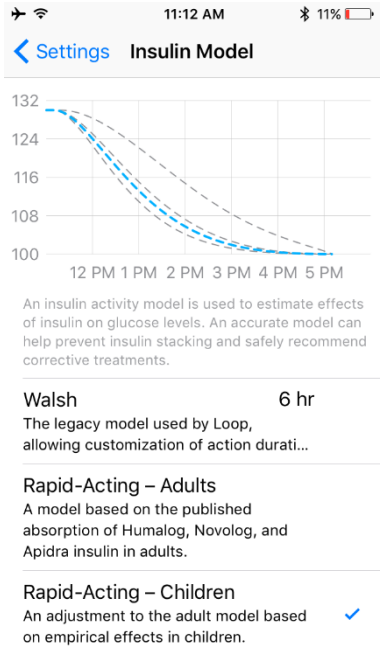
screenshots taken approximately on the hour to show duration of insulin action by model



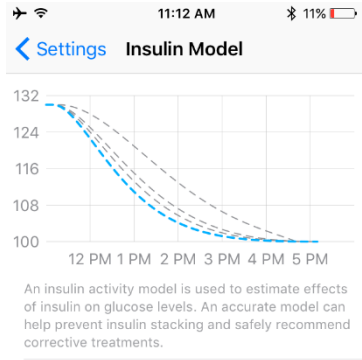
- Used by Loop until mid 2017
- Only model with an adjustable duration of insulin action time
- Most users set the model to 3.5-4 hours



- New model introduced mid 2017
- Standardized insulin curve (not adjustable)
- Most common model in use in adults



- New model introduced mid 2017
- Standardized insulin curve (not adjustable)
- Most common model in use in children



- Fiasp model, based upon published data and not adjustable

Nightscout reporting

Day to day | Daily Stats | Distribution | Hourly stats | Percentile Chart | Weekly success | Calibrations | Treatments

From: 2017-02-21 To: 2017-03-06 Today Last 2 days Last 3 days Last week Last 2 weeks Last month Last 3 months

Notes contain:

Event Type:

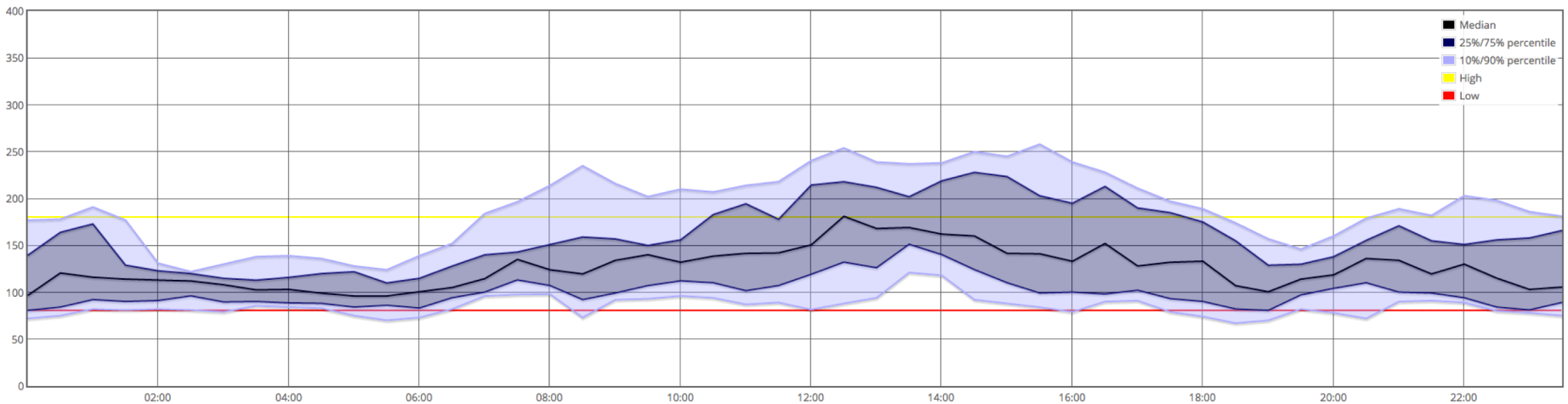
Mo Tu We Th Fr Sa Su

Target bg range bottom: 80 top: 180

Order: oldest on top newest on top

Show

Glucose Percentile report

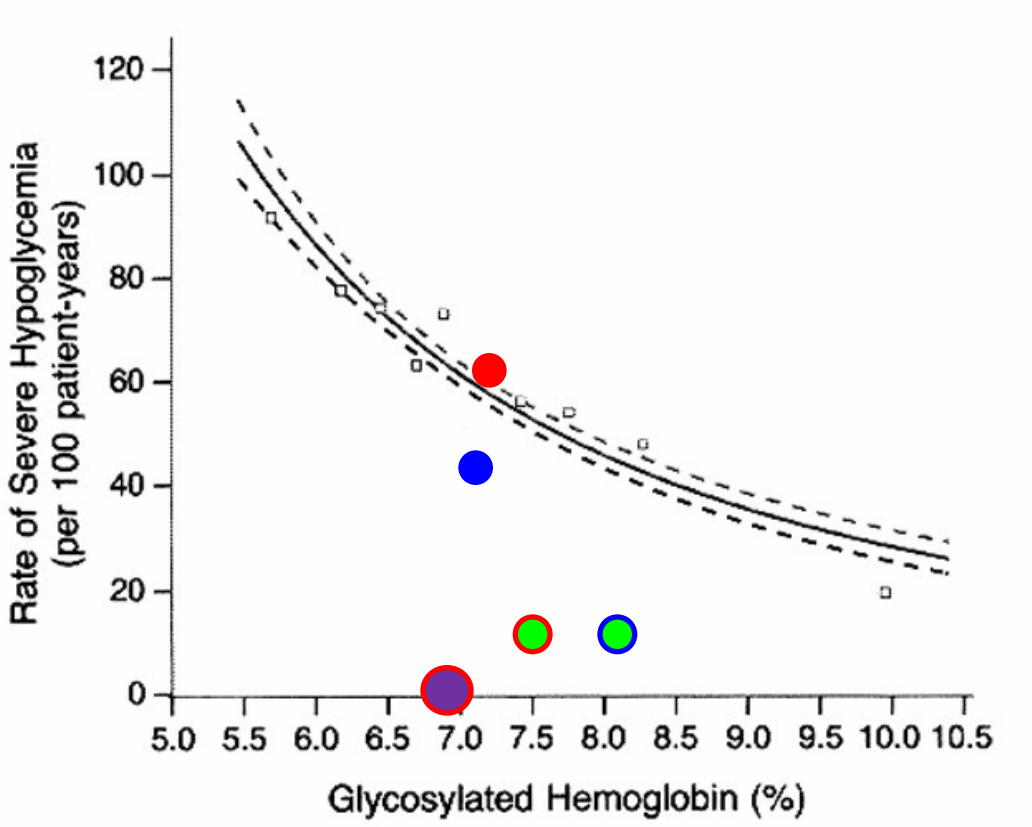


Authentication status:
Not authorized (Authenticate)

We are not waiting – Do It Yourself

- At the cutting edge
- User interfaces designed by users

Severe Hypoglycemia and A1C:
DCCT[15] (1993), JDRF[2] (2008), and STAR 3[16] (2010) Studies
670G (2017)



DCCT (intensive therapy):
62 per 100 pt-yrs,
A1C(6.5 yr): 9.0% → 7.2%

JDRF CGM (adults, 1 subject excluded):
20.0 per 100 pt-yrs;
A1C (6 mo): 7.5% → 7.1%

STAR 3 MDI (all ages):
13.5 per 100 pt-yrs;
A1C (1 yr): 8.3% → 8.1%

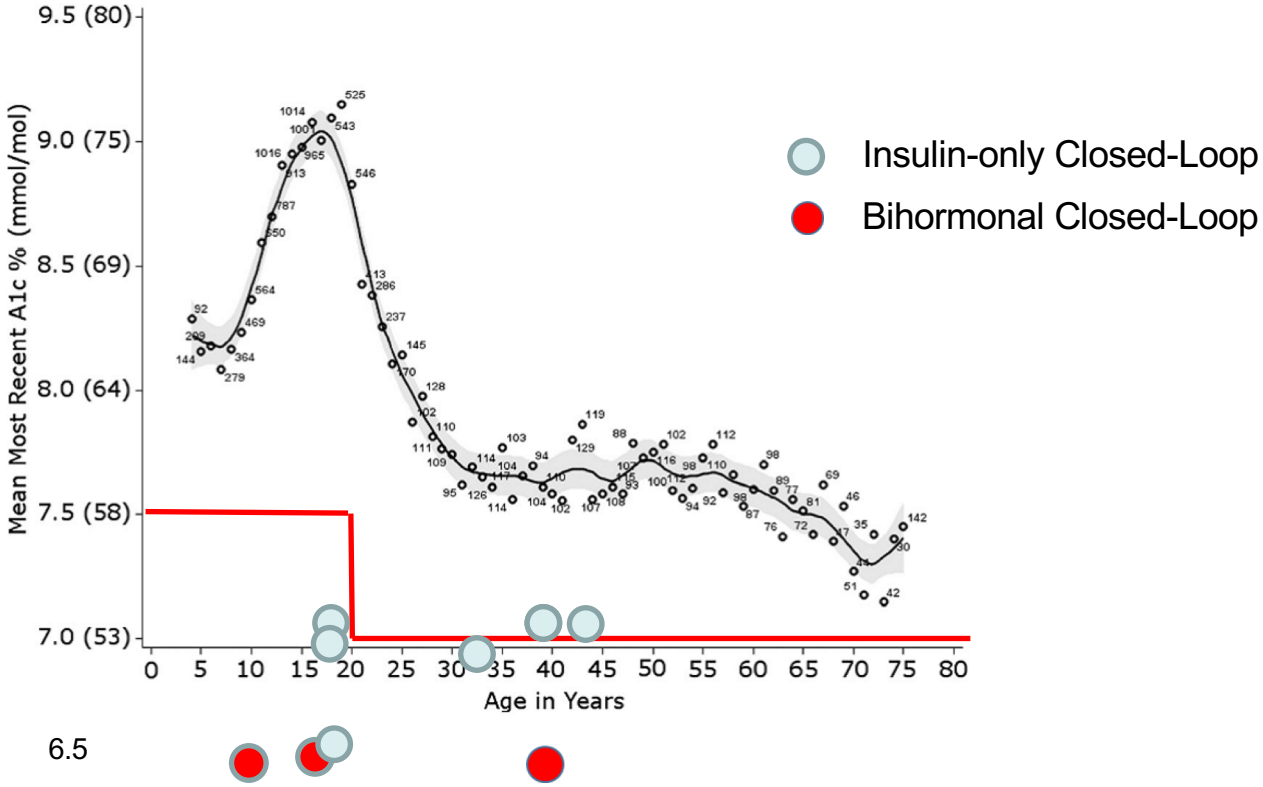
STAR 3 SAP (all ages):
13.3 per 100 pt-yrs;
A1C (1 yr): 8.3% → 7.5%

670G Pivotal and Extension
A1c 6.9% No Severe Hypo

15. Adapted from Figure 5B of: DCCT. *N Engl J Med*. 1993;329:977-986.
2. JDRF data from: JDRF CGM Study Group. *N Engl J Med.* 2008;359:1465-1476.
16. Bergenstal RM, Tamborlane WV, Ahmann A, et al. [published online ahead of print June 29, 2010]. *N Engl J Med*. doi: 10.1056/NEJMoa1002853.

Current State of Type 1 Diabetes
Updated T1D Exchange - 2015

K. Miller , Diabetes Care 38: 971

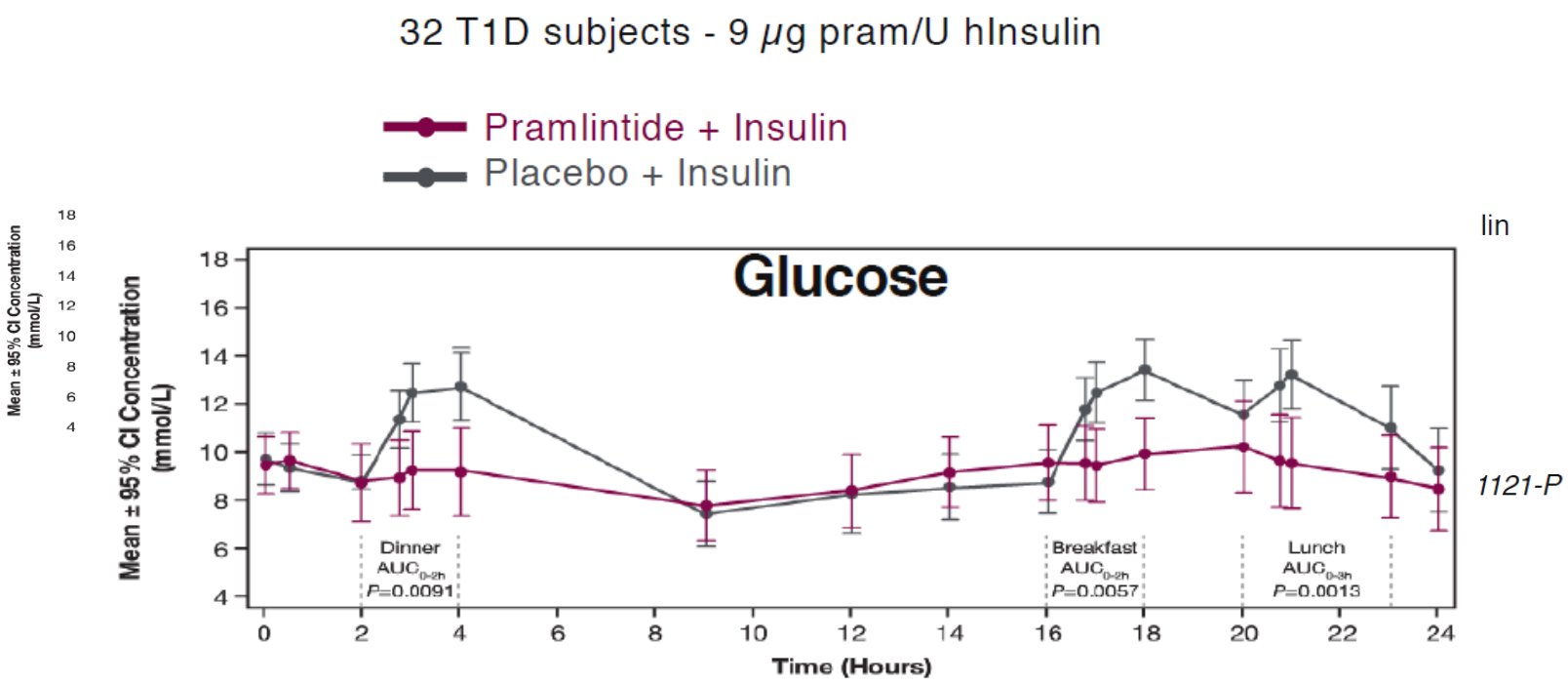


Full Closed Loop
(no meal or correction boluses)

- Faster acting insulins
- Co-formulations with insulin and amylin (pramlintide)
- Insulin and GlP-1 agonists
- Automated early detection of eating
- Automated detection of meal composition (high fat meals)

24 Hour Co-Infusion of Pramlintide and Human Insulin

Haider, et.al. ADA 2017 Poster 1121



lin

1121-P

Klue

1

Open Loop

Bolus Reminders

2

Hybrid Closed Loop

Prompted Meal Announcements

3

Meal-aware Closed Loop

Fully Automated Insulin Delivery

KLUE

Bolus Reminder App Demo

KLUE

Living with Type 1?
Get mealtime insulin reminders

Living with Type 1?
Get mealtime insulin reminders

Snooze to get a second reminder


Living with Type 1?
Get mealtime insulin reminders
Snooze to get a second reminder
Track hypoglycemic events
6:35
KLUE
Eating?
Yes, bolused
Snooze
Hypo
No carbs
Dismiss

Living with Type 1?

Get mealtime insulin reminders

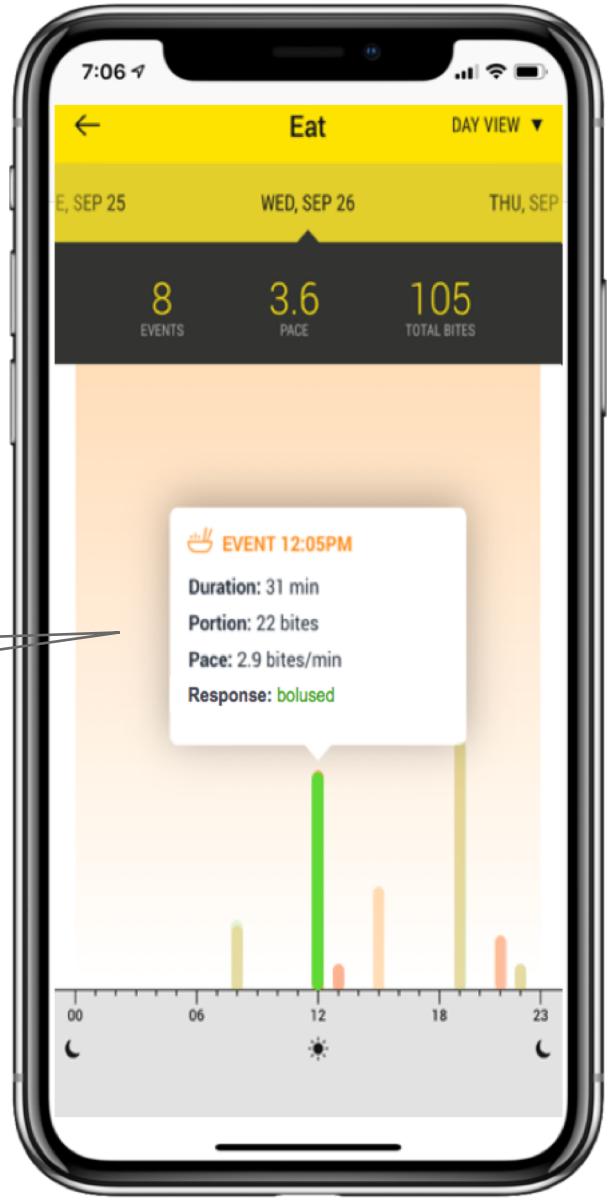
Snooze to get a second reminder

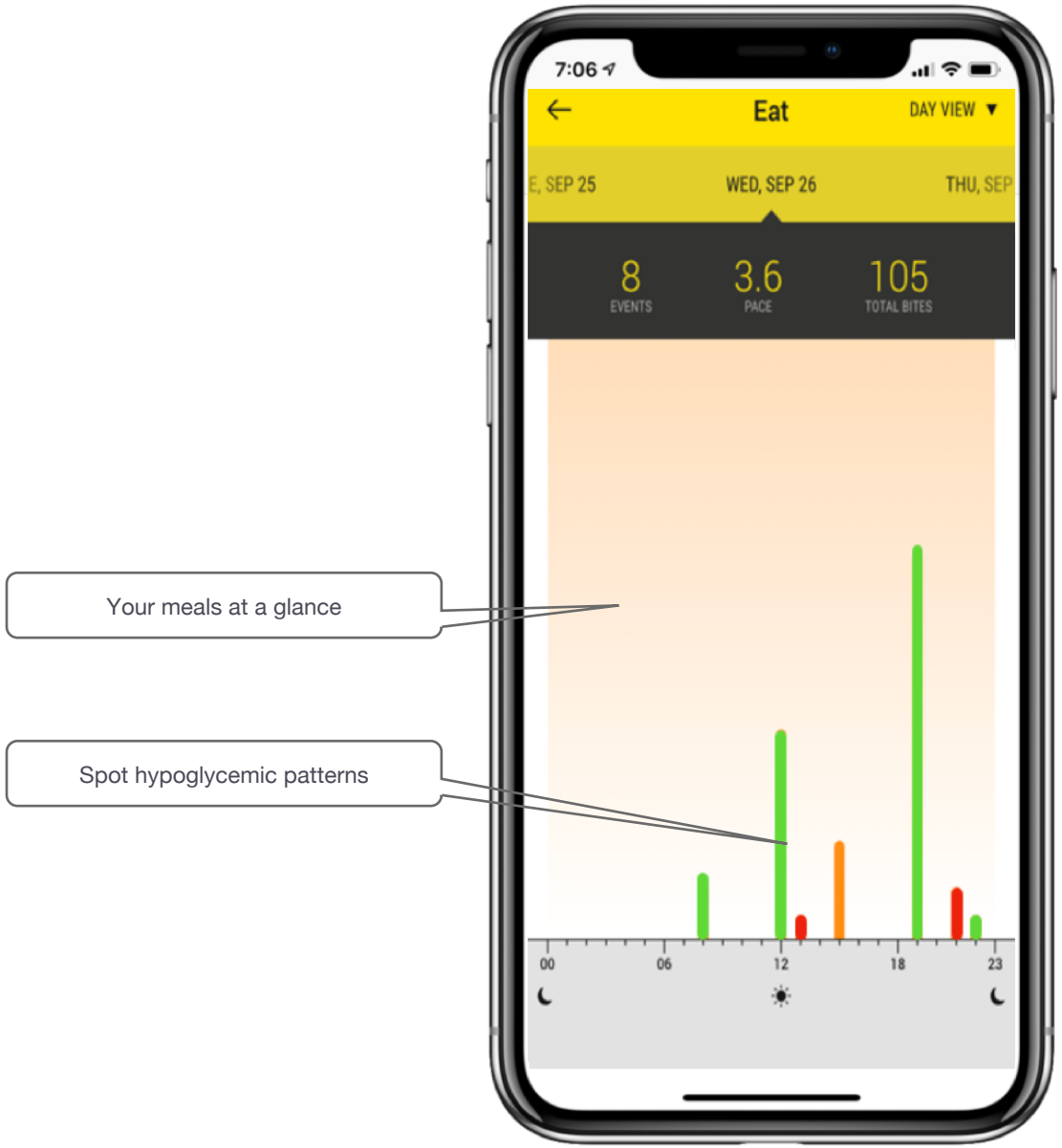
Track hypoglycemic events

Caring for a loved one?

Find peace of mind with automatic text messaging

Your meals at a glance




Your meals at a glance
Spot hypoglycemic patterns
7:06
Eat
DAY VIEW
E, SEP 25
WED, SEP 26
THU, SEP
8
EVENTS
3.6
PACE
105
TOTAL BITES
00
06
12
18
23

REALLY helpful.”

Intrigued and would like to give it a try?

Join our pilot program for free today!

goklue.com/t1d

KLUE

The Future

- Adaptability
  - Basal requirements
  - Meal requirements
  - Weekday/weekend patterns
  - Corrections
  - Exercise
- Adaptable to how you want to manage your diabetes
  - To the amount of control you want to give over to automated insulin delivery
  - It will do much better at night

The Future

- Use of Accelerometers and Heart Rate Monitors
  - Detect and adjust automatically for activity
  - Allows detection of sleep to modify algorithm
- Integration into Consumer Devices
  - Apple/Apple Watch
  - Google Android

The Future

- Improved infusion sets
  - Longer duration of wear
  - Combined with sensors
- Improved Sensors
  - MARD less than 10%
  - Duration of wear 2 weeks
  - Factory Calibration

The Future

- Full Closed-Loop
- No CHO counting, no premeal bolus
- Less than perfect, but may be good enough

Irl Hirsch – 2017
Stanford = 30, Washington = 22

Thank you

Stanford Closed-loop Team

Thank You

Bruce Buckingham, MD

buckingham@Stanford.edu

Exercise Adjustment with 670G

- Set Temp Target
- 150 mg/dl
- Duration 30 min to 12 hours

Tandem Control IQ – Exercise Mode

- Manually Start and Stop

Exercise adjustment with Tandem Control IQ

- Target is 140-160 mg/dl based on 30 minute horizon
- Basal rate set to “0” if prediction is <80 mg/dl
- Maximum insulin delivery limits are unchanged during exercise
- Corrections are less aggressive than during usual Wake
- If exercise is on when sleep mode is scheduled to begin, Sleep does not start

Adjusting for Exercise with Loop

- https://www.youtube.com/watch?v=GCYPTHVQERs