Artificial Pancreas Technologies:
New Tools to Improve Diabetes Care Today and Tomorrow

Mark D. DeBoer, MD, MSc., MCR
University of Virginia
Center for Diabetes Technologies
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Learning Objectives

1) List the mechanical components of an artificial pancreas system.
2) List commercially-available systems with progressively added features of artificial pancreas technology.
3) Identify 3 sources of delay inherent to how an AP system responds to blood glucose excursions.

Disclosures

1) I have no relevant financial disclosures related to the content of this presentation.
2) Many of the Artificial Pancreas technologies presented are not currently approved by the FDA (outside of research protocols).

The landscape of Type 1 diabetes…

Real

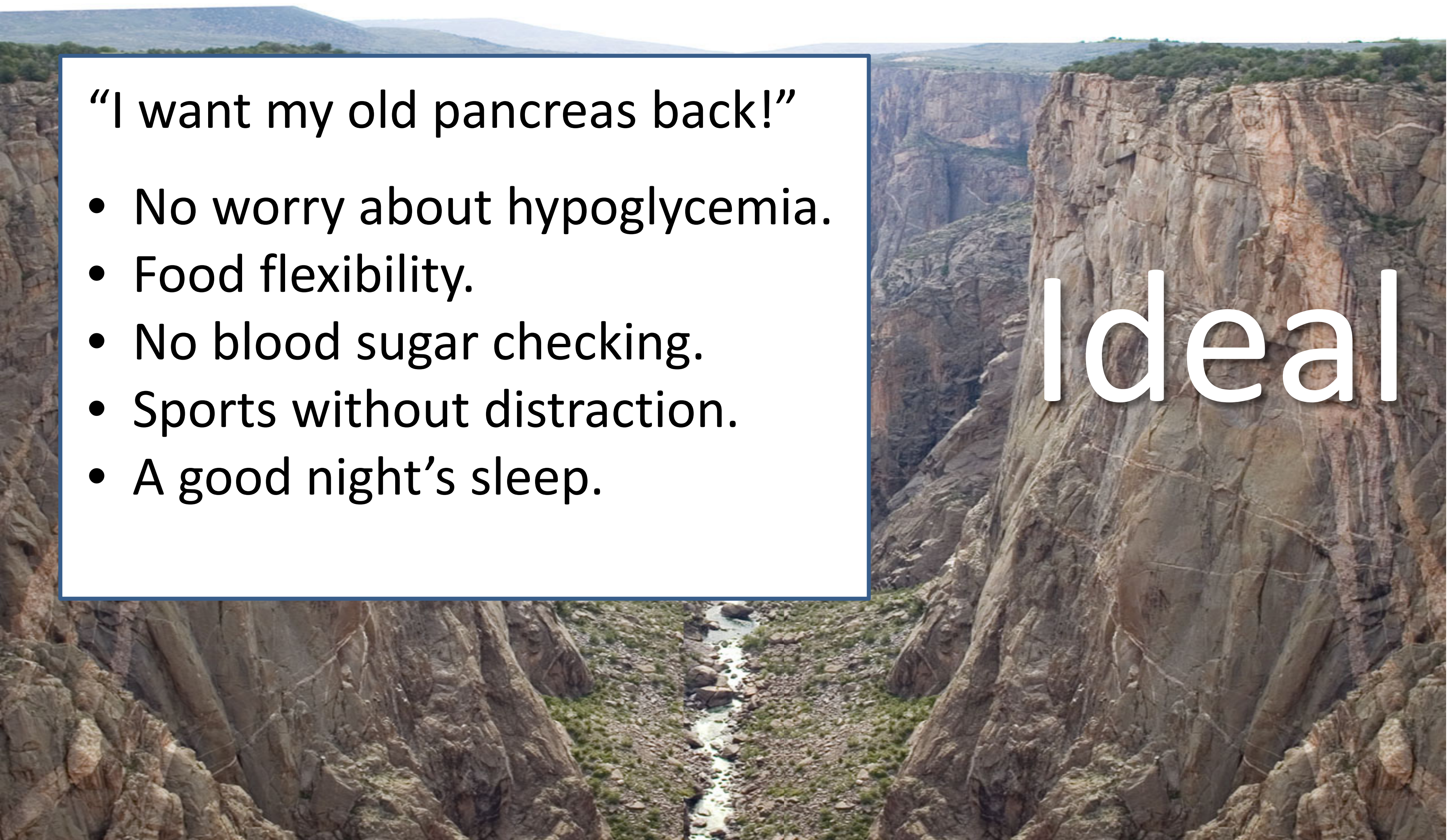
Ideal

The landscape of Type 1 diabetes…

The landscape of Type 1 diabetes…

“I want my old pancreas back!”

- No worry about hypoglycemia.
- Food flexibility.
- No blood sugar checking.
- Sports without distraction.
- A good night’s sleep.



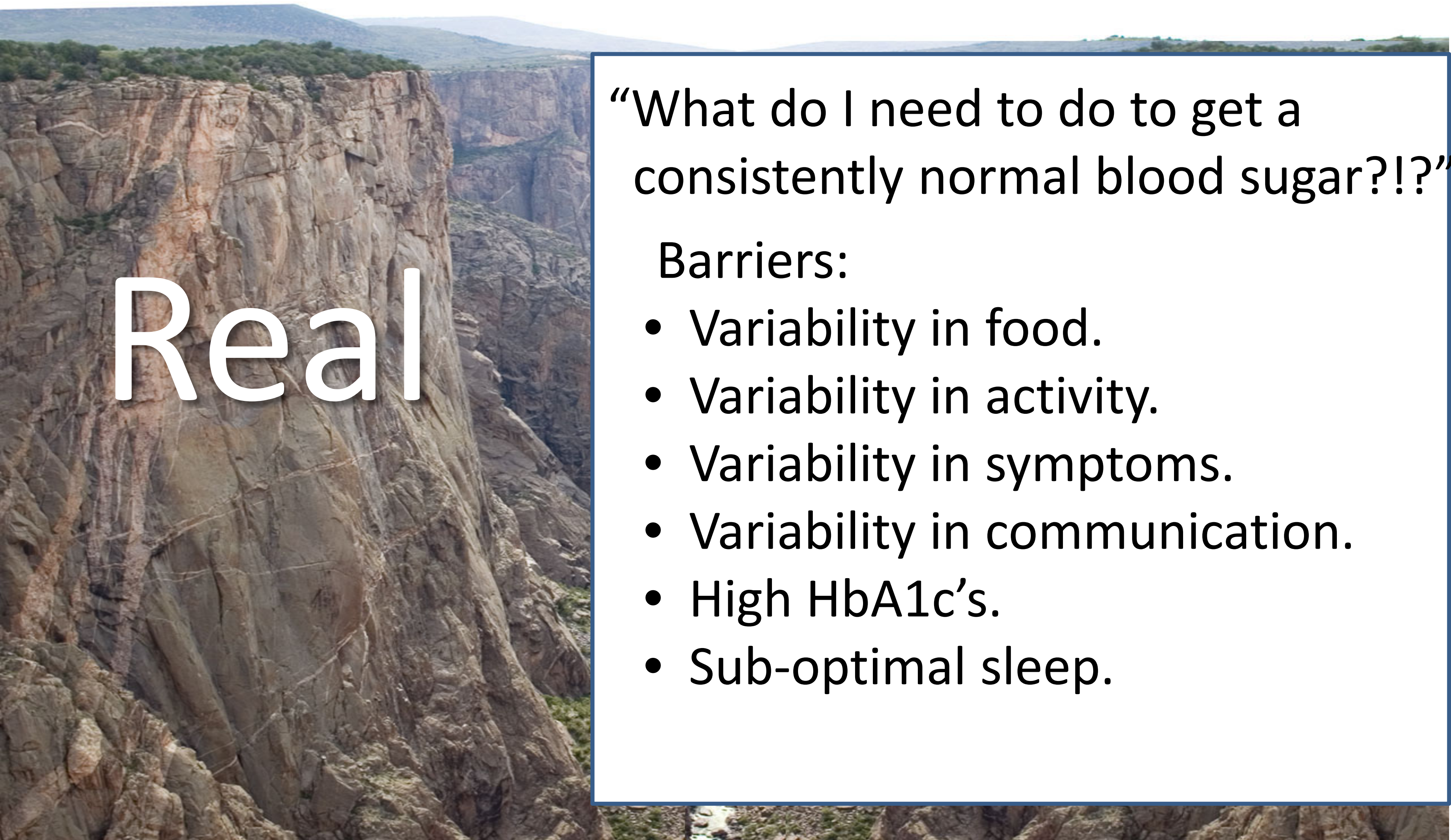
The landscape of Type 1 diabetes…

"What do I need to do to get a consistently normal blood sugar?!?"

Barriers:

- Variability in food.
- Variability in activity.
- Variability in symptoms.
- Variability in communication.
- High HbA1c's.
- Sub-optimal sleep.

The landscape of Type 1 diabetes…



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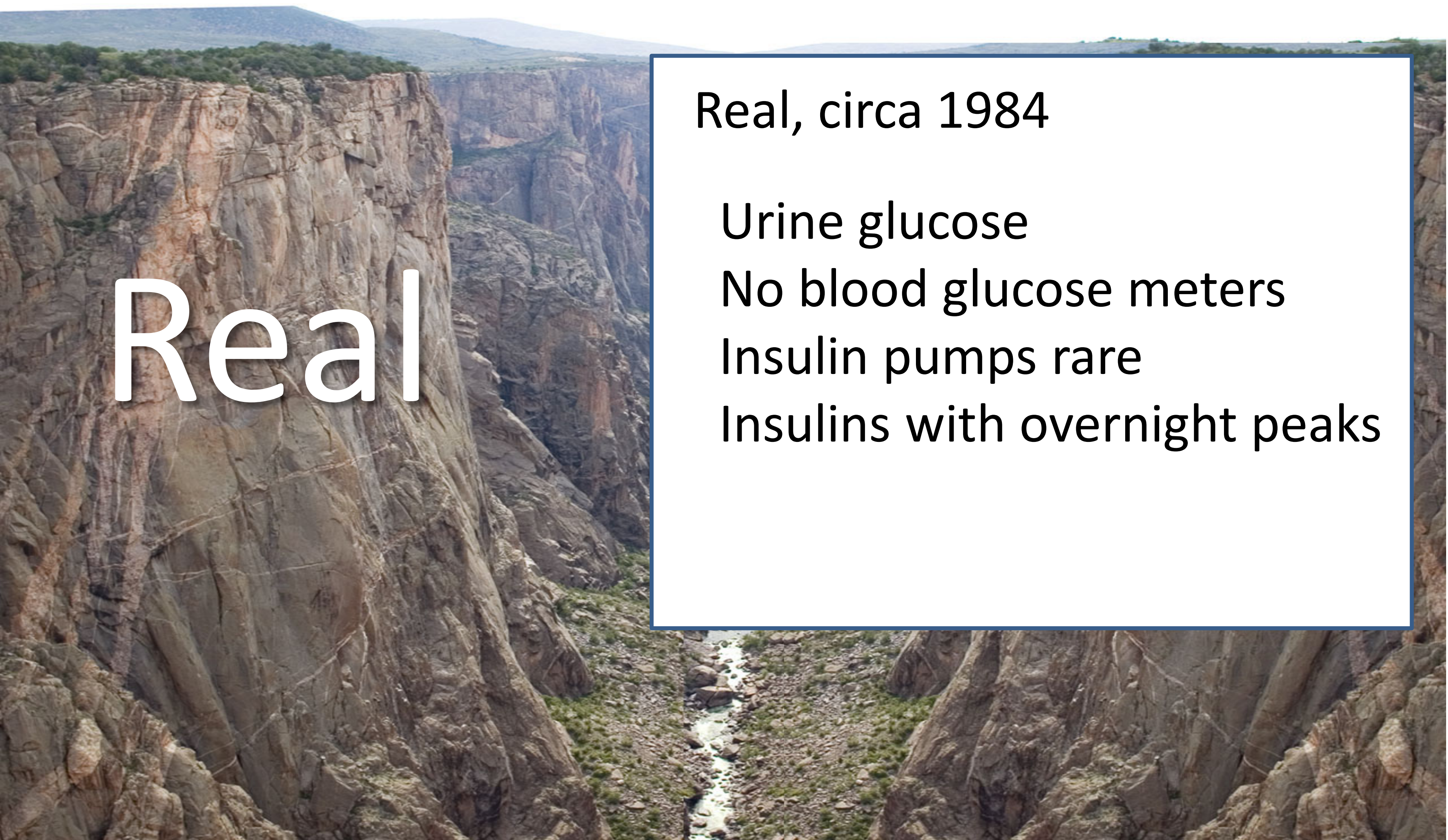
The landscape of Type 1 diabetes…



Real, circa 1984

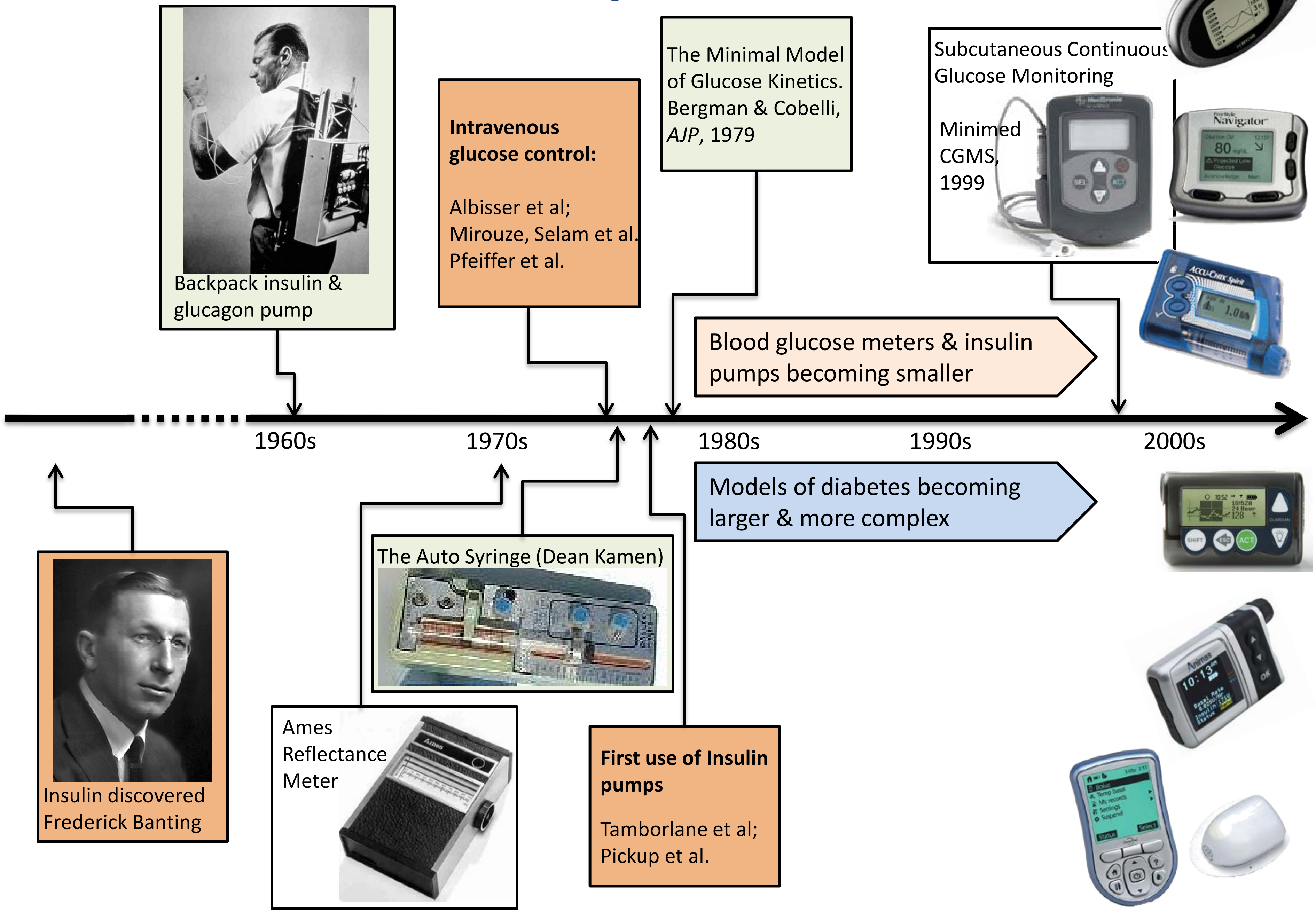
- Urine glucose
- No blood glucose meters
- Insulin pumps rare
- Insulins with overnight peaks

The landscape of Type 1 diabetes…

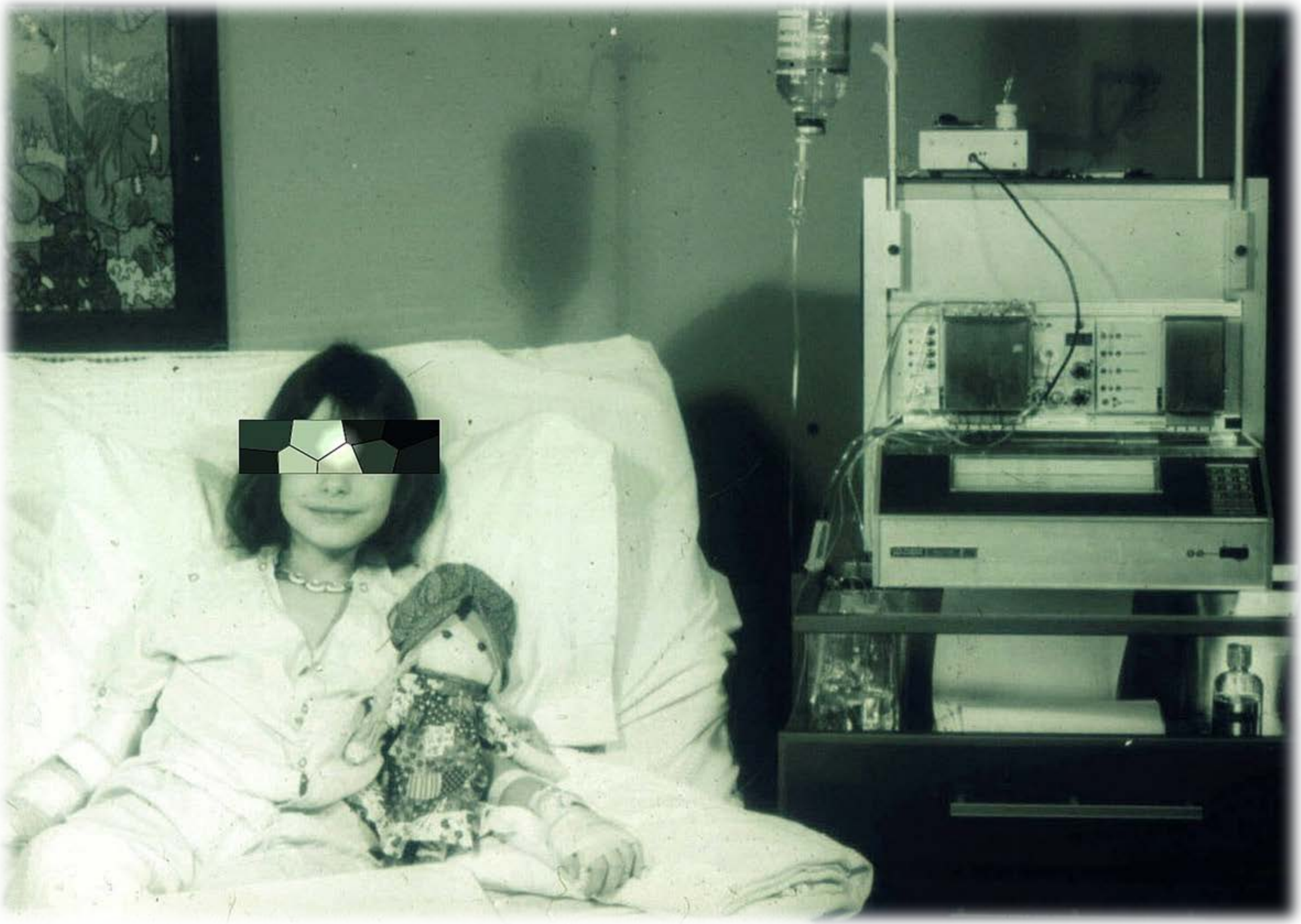
Real, circa 1960

Pig insulin
Follow symptoms only
No home glucose assessments

The Previous Century



The Artificial Pancreas 40 Years Ago



Trying to bridge the chasm…

Trying to bridge the chasm…

Insulin pumps:

Up-sides

- Variation of basal insulin delivery
- Painless delivery for smaller doses

Down-sides

- More things to go wrong
- Attached to hardware 24-7

Trying to bridge the chasm…

CGM:

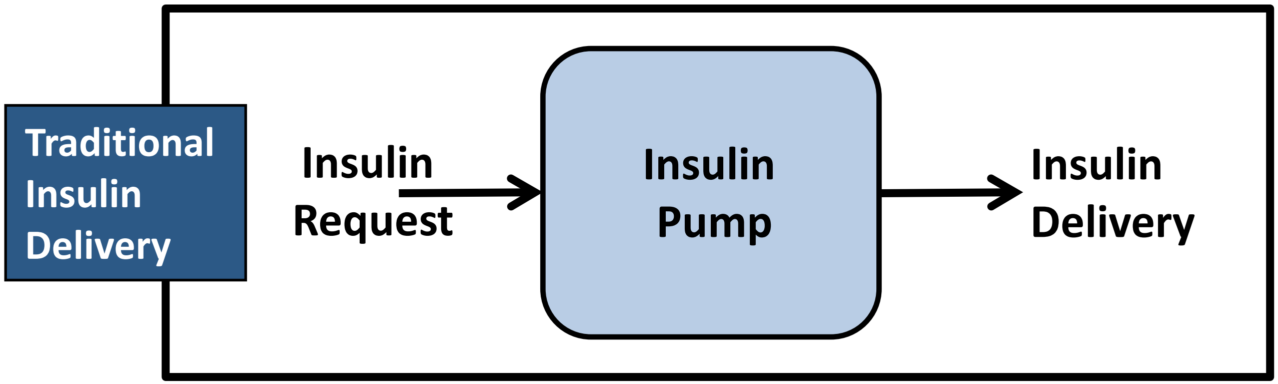
Up-sides

- View trends—predict lows/highs
- Alarm to wake for lows overnight

Down-sides

- Need to calibrate
- Delay in reading, not as accurate
- Teens: cost/benefit

Basic Design of AP Systems



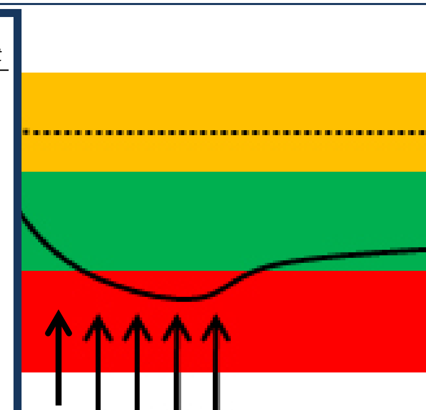
Basic Design of AP Systems

Glucose:
CGM

Insulin Paramete
basal rate, carb rat
correction factor, , t
daily insulin

Insulin-on-Boar

$$
\left\{
\begin{aligned}
\dot{G}_p &= -k_2.G_p + k_1.G_t - U_{ii} - E_t + k_{p1} - k_{p2}.G_p - k_{p3}.I_d + \frac{f.k_{abs}.Q_{gut}}{BW} \\
\dot{G}_t &= -k_1.G_t + k_2.G_p - \frac{\left(V_{m0} + V_{mX}.X\right)G_t}{K_{m0} + G_t} \\
\dot{G}_{sc} &= -k_{sc}\left(G_{sc} - \frac{G_p}{V_g}\right) \\
\dot{I}_p &= -\left(m_2 + m_4\right).I_p + m_1.I_l + k_{a1}.I_{sc1} + k_{a2}.I_{sc2} \\
\dot{I}_l &= -\left(m_1 + m_3\right).I_l + m_2.I_p \\
\dot{I}_1 &= -k_i\left(I_1 - \frac{I_p}{V_i}\right) \\
\dot{I}_d &= -k_i\left(I_d - I_1\right) \\
\dot{X} &= -p_{2u}\left(X - \left(\frac{I_p}{V_i} - I_b\right)\right) \\
\dot{I}_{sc1} &= -k_d.I_{sc1} - k_{a1}.I_{sc1} + \frac{J(t)}{BW} \\
\dot{I}_{sc1} &= k_d.I_{sc1} - k_{a2}.I_{sc2} \\
\dot{Q}_{sto1} &= -k_{gri}.Q_{sto1} + M(t) \\
\dot{Q}_{sto2} &= -k_{empt}.Q_{sto2} + k_{gri}.Q_{sto1} \\
\dot{Q}_{gut} &= k_{abs}.Q_{gut} + k_{empt}.Q_{sto2}
\end{aligned}
\right.
$$



Insulin
Decision

Basic Design of AP Systems

Glucose:
CGM

Insulin Paramete
basal rate, carb rat
correction factor, , t
daily insulin

Insulin-on-Boar

$$\dot{G}_p = -k_2.G_p + k_1.G$$

$$\dot{G}_t = -k_1.G_t + k_2.G$$

$$\dot{G}_{sc} = -k_{sc}\left(G_{sc} - \frac{G}{V}\right.$$

$$\dot{I}_p = -(m_2 + m_4).$$

$$\dot{I}_l = -(m_1 + m_3).$$

$$\dot{I}_1 = -k_i\left(I_1 - \frac{I_p}{V_i}\right)$$

$$\dot{I}_d = -k_i\left(I_d - I_1\right)$$

$$\dot{X} = -p_{2u}\left(X - \left(\frac{I_p}{V_i} - I_b\right)\right)$$

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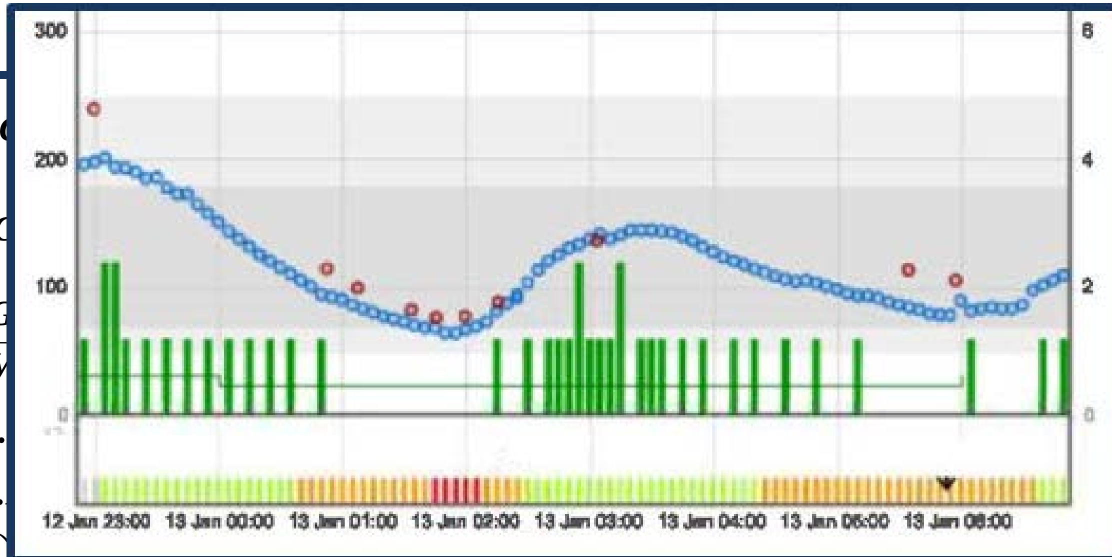
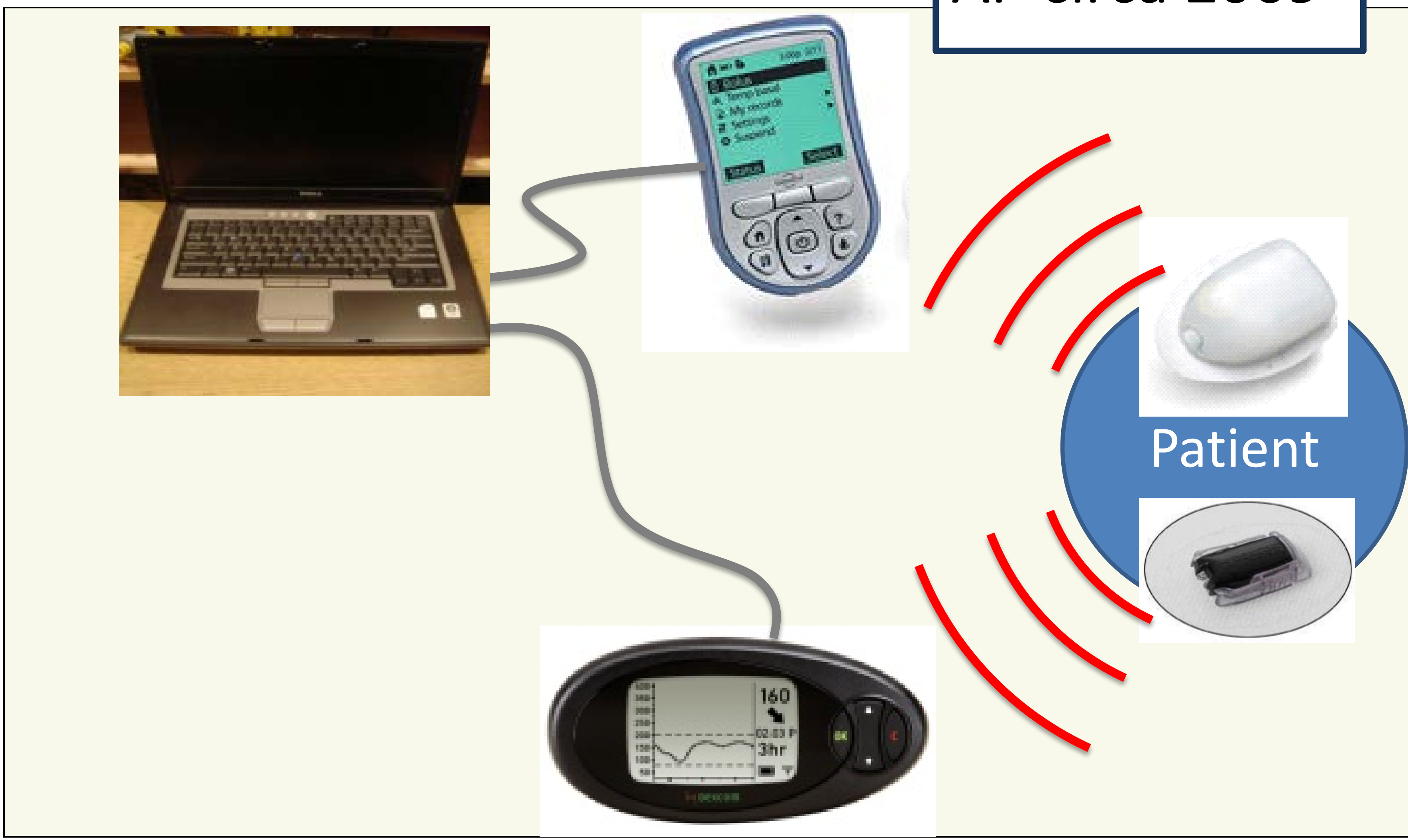


Insulin
Decision

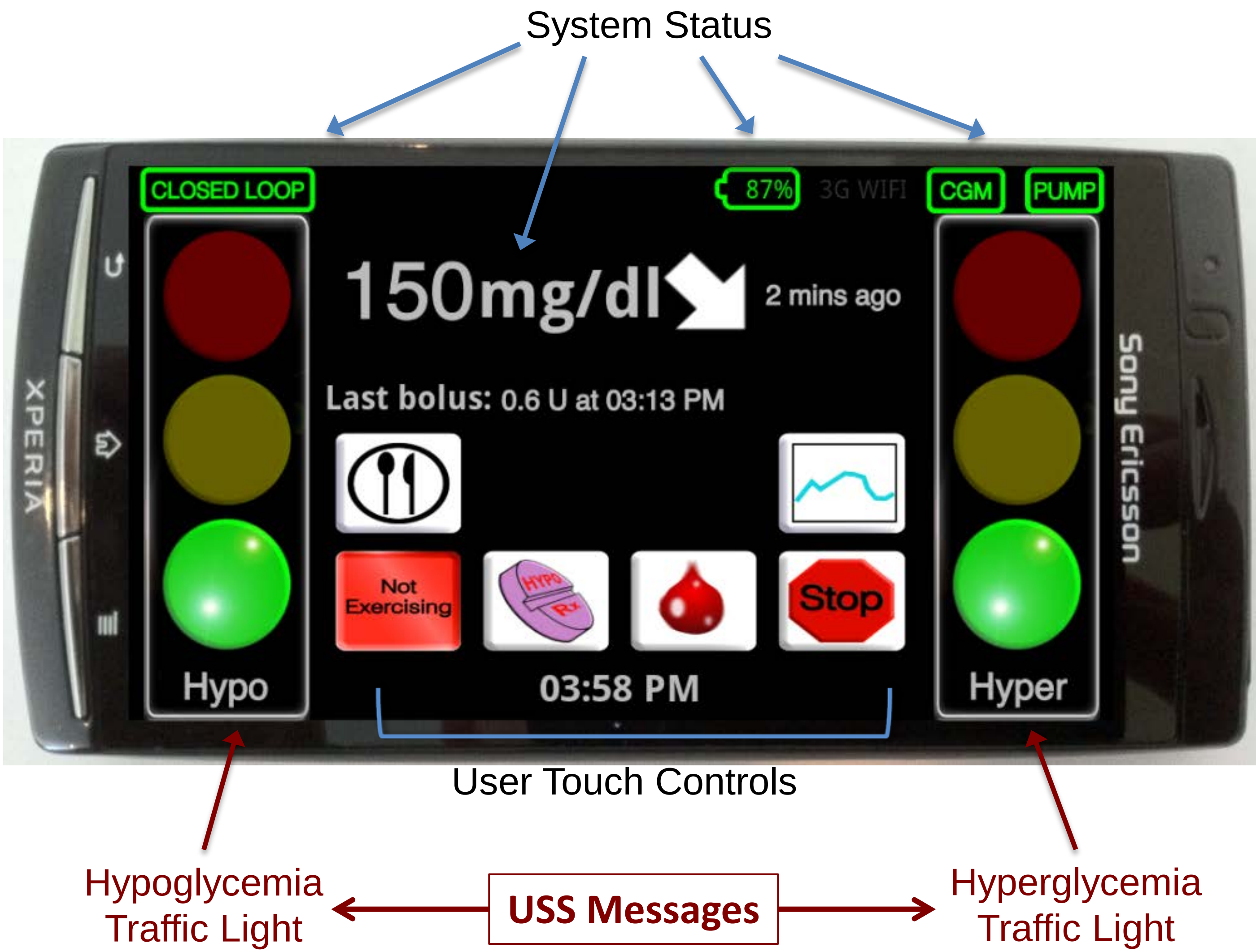
Basic Design of AP Systems

- “Closed Loop” Control

AP circa 2009



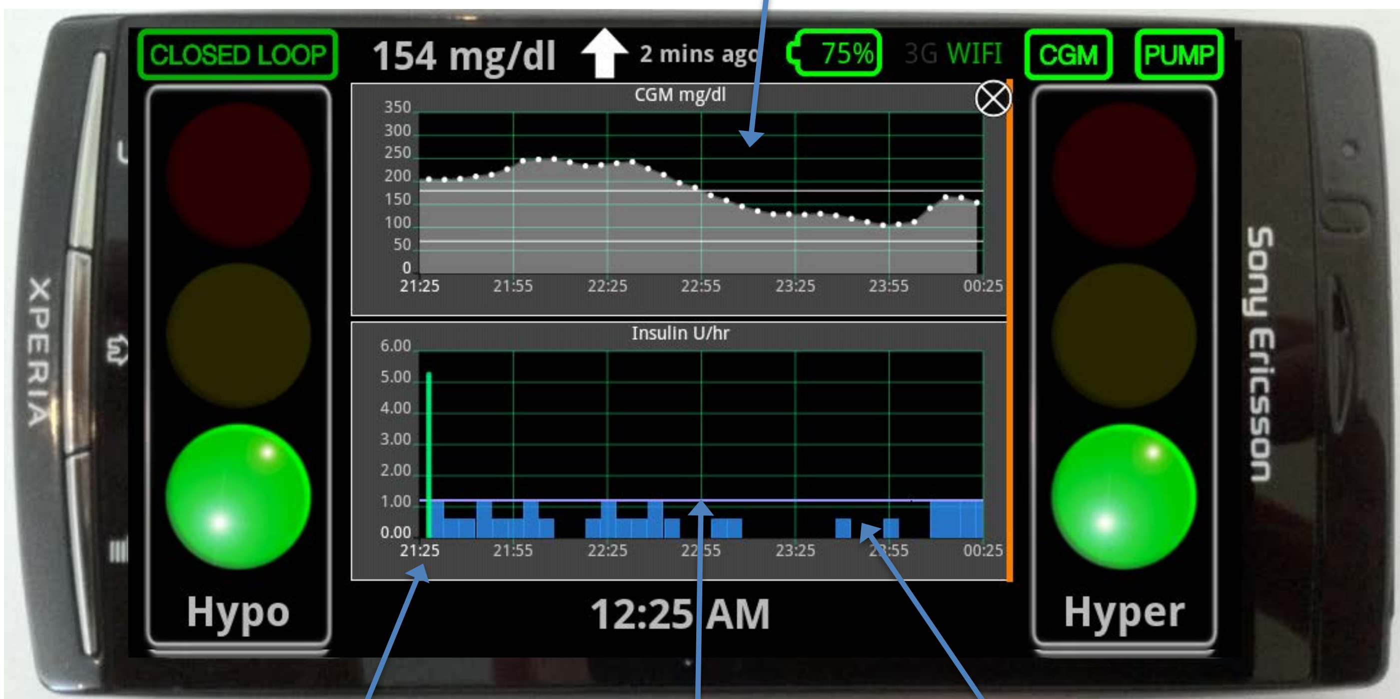
UVa's DiAs: the Diabetes Assistant



UVa's DiAs: the Diabetes Assistant

Plot screen

CGM trace



Bolus marker

Basal profile

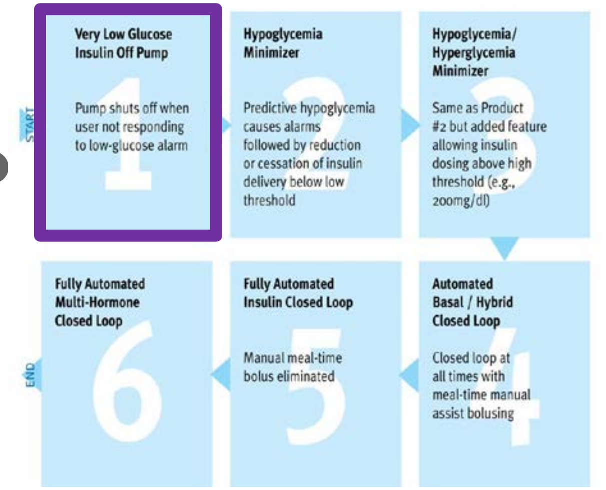
Basal delivery

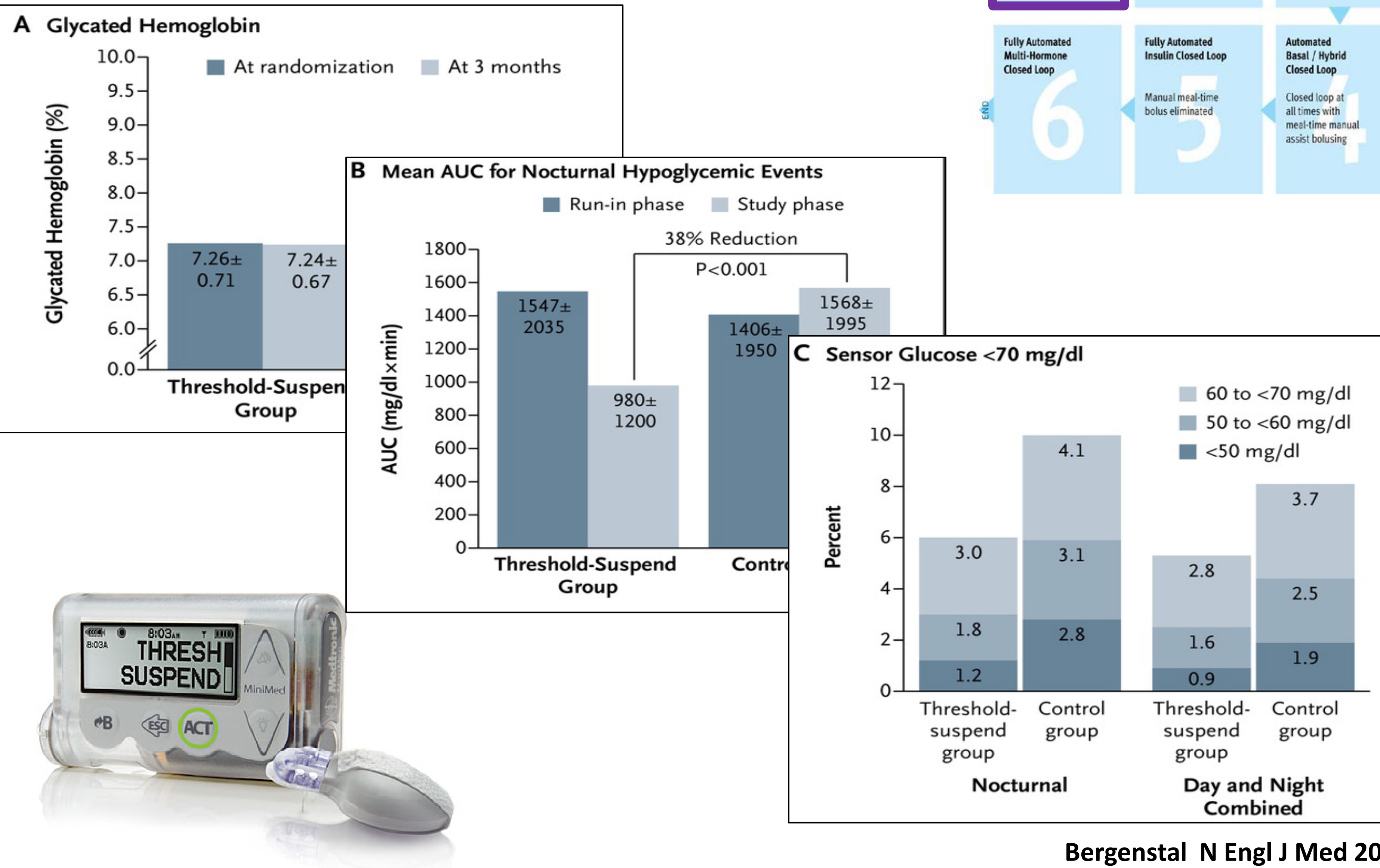
UVa's DiAs: the Diabetes Assistant

AP Strategy-Iterative: Increases in Automation

Kowalski AJ. Can we really close the loop and how soon? Accelerating the availability of an artificial pancreas: A roadmap to better diabetes outcomes. *Diabetes Technol Ther*, 11:S113-S119, 2009

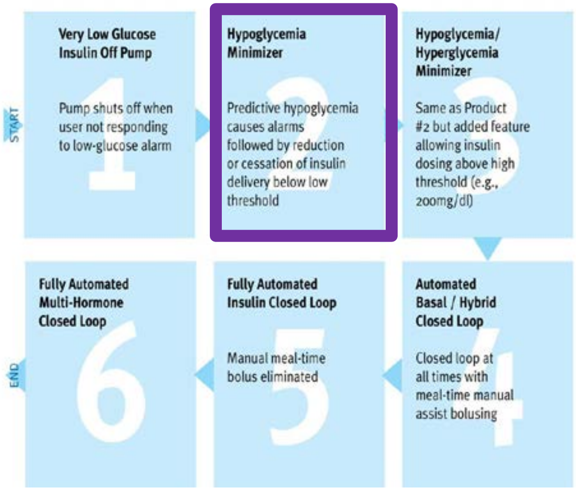
Threshold suspend: Medtronic

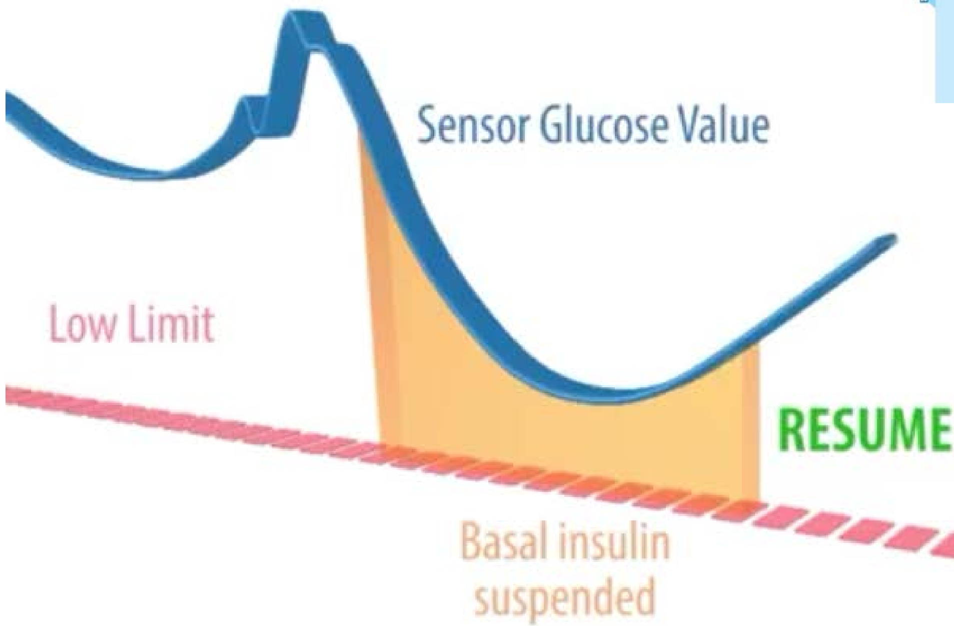




Bergenstal N Engl J Med 2013

Predictive suspend: Medtronic

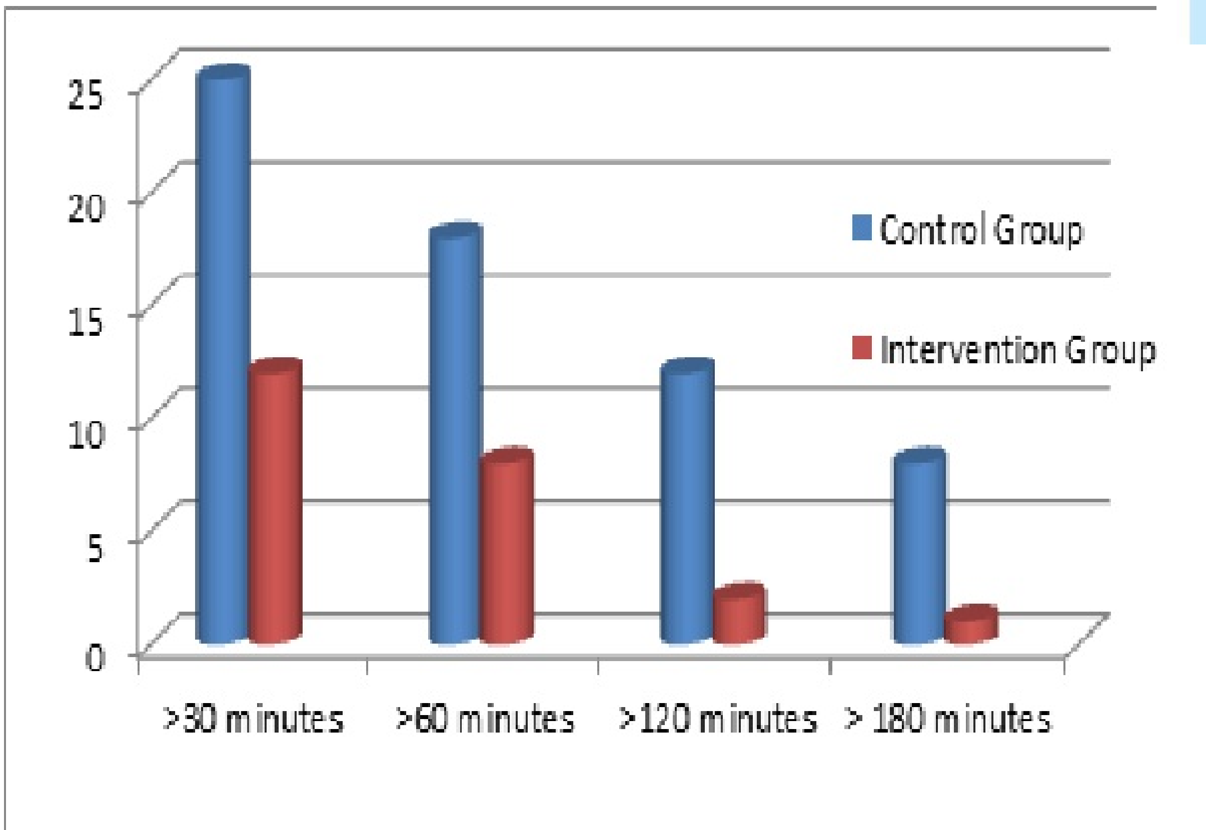


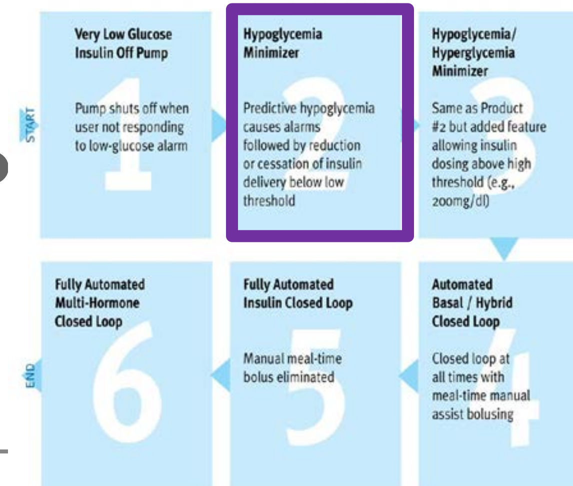


MiniMed 640G

Predictive suspend: Medtronic

Low BG's: 21% nights pLGS
33% control



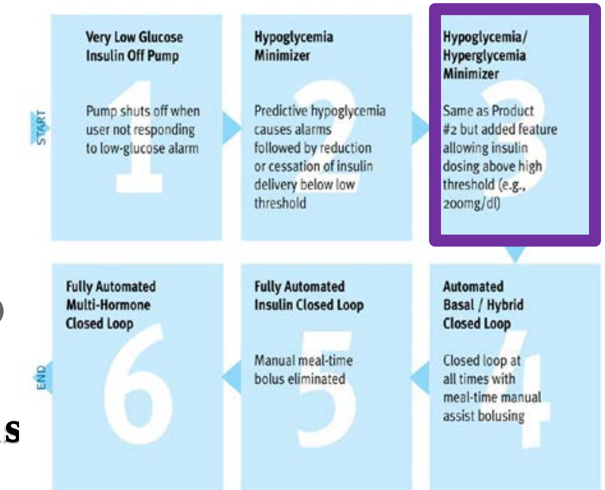


MiniMed 640G

Maahs Diab Care 2014

Bedside AP: UVa

UVA (Sue Brown, Stacey Anderson, Marc Breton, Boris Kovatchev);
Padova, Italy (Daniella Bruttomesso, Simone Del Favero, Claudio Cobelli)



Randomized cross-over design; two 5-day sessions

Control condition: CGM + pump (usual control)

Experimental condition: Daytime – CGM + pump;
Nighttime – closed-loop control (11PM-7AM);

No meal restrictions; Alcohol permitted; No intensive exercise;
Driving restricted to 25 miles during the day;

Primary Outcome: Time within target range
80-150 mg/dl at wakeup (7AM);

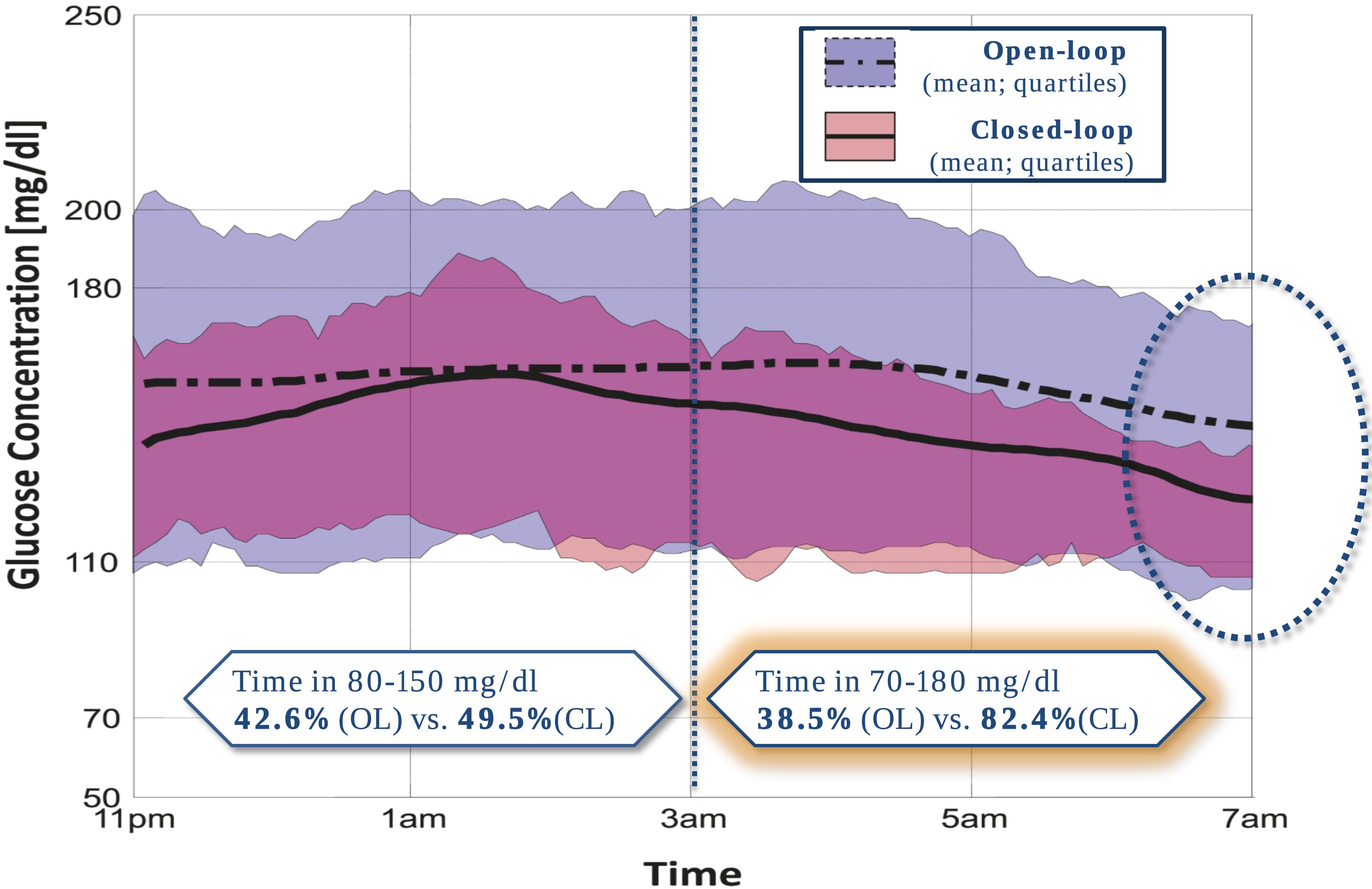
Control Algorithm: USS Virginia with nightly
"system (person) reset" to target of 120mg/dl at 7AM

N=40 participants

Brown JCEM 2017

Bedside AP: Nighttime glucose control

Overnight: Average glucose was **reduced by ~30 mg/dl**; Percent time in target **increased by 25%**. No adverse events.



Bedside AP: Outcomes

40 participants closed-loop vs. sensor-augmented pump therapy

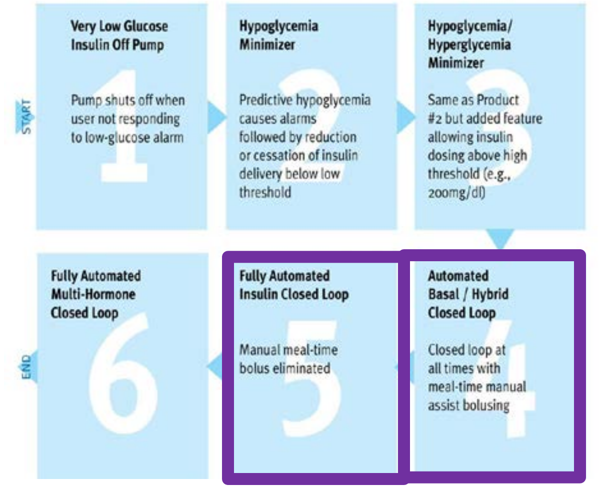
	Sensor-Augmented Pump	Closed-Loop Control	P-value
Average Blood Glucose at 7AM	145.3	123.7	<0.001
Average Blood Glucose overall (mg/dl)	147.0	142.0	NS
Percent time within 80-140mg/dl	42.9%	51.7%	0.001
Percent time below 70mg/dl	4.3%	2.5%	0.002

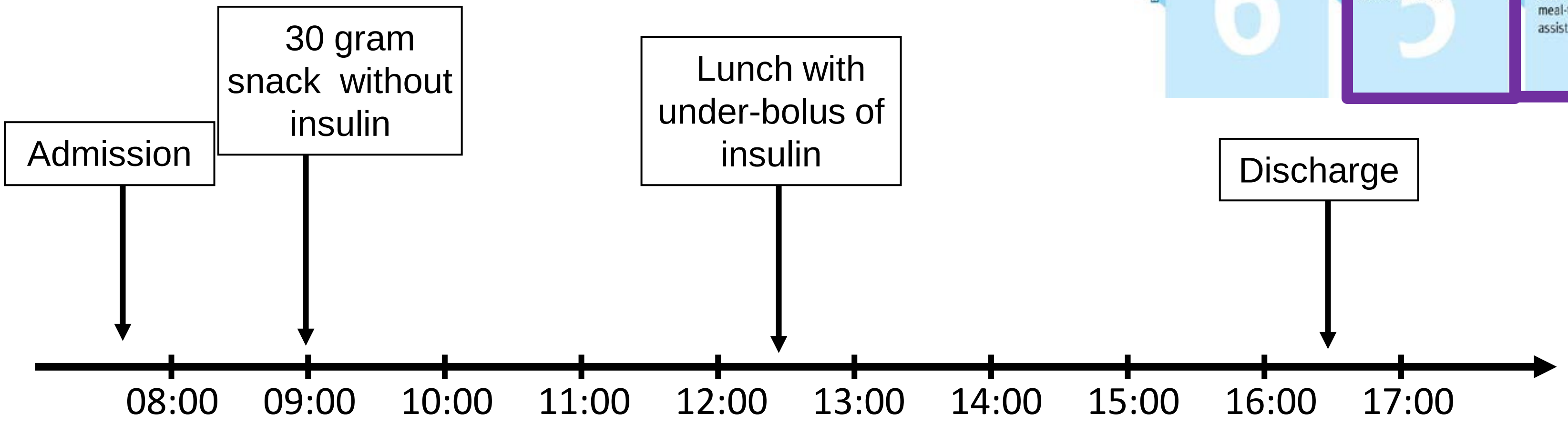
Overnight Control Correlated with Control the Next Day (r=0.4, p=0.008):

Challenges: Missed meal/snack

UVA (Danny Cherñavvsky, Mark DeBoer, Marc Breton, Boris Kovatchev)

Adolescents age 12-17 years





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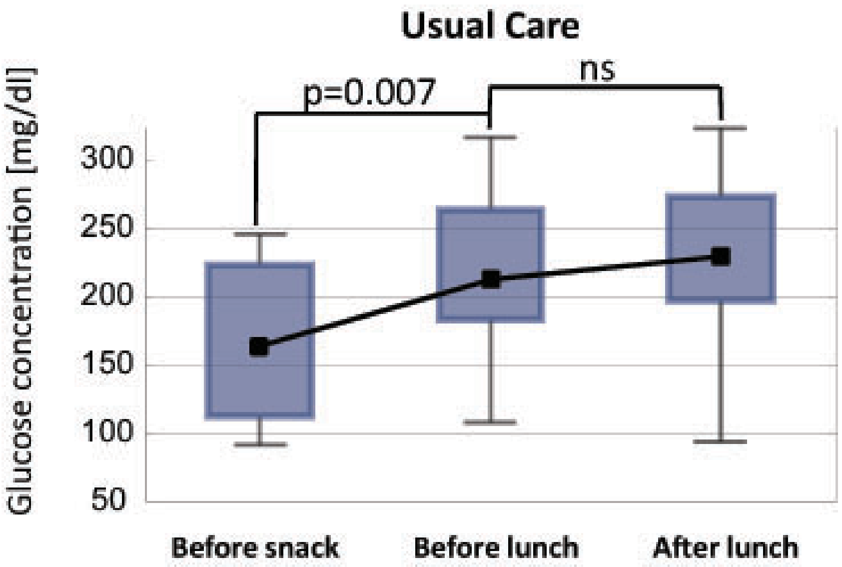

Cherñavvsky, DeBoer et al. Ped Diab 2014

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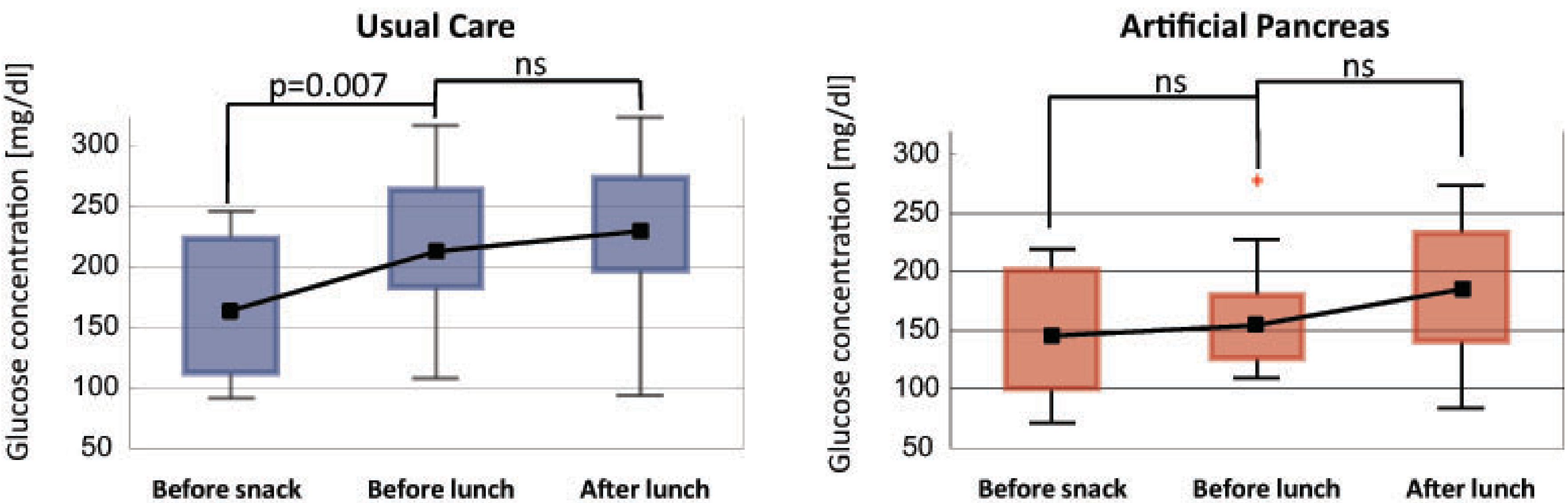
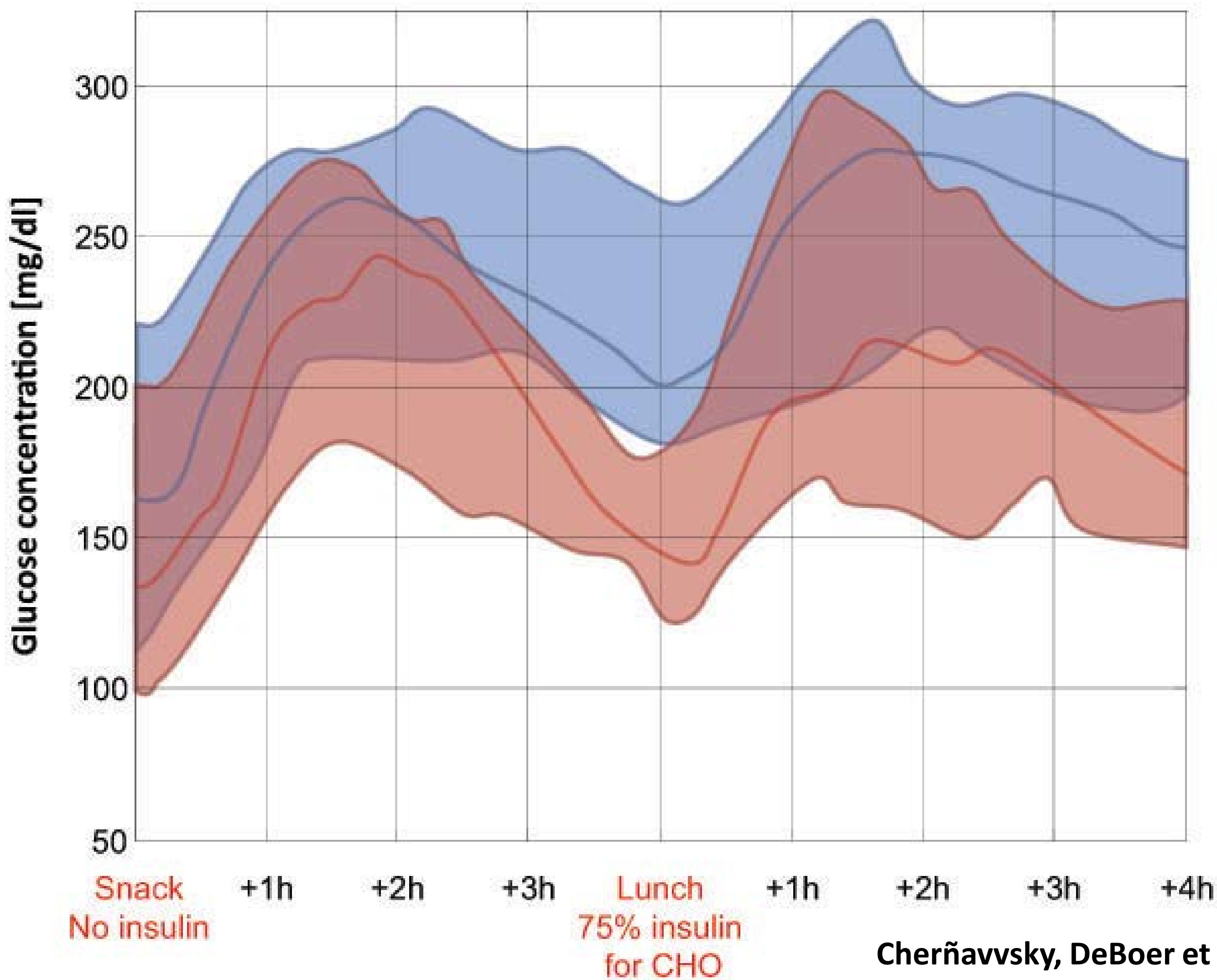


Cherñavvsky, DeBoer et al. Ped Diab 2014

Challenges: Missed meal/snack

Median and Quartile Glucose Traces for AP (red) and Usual Care (Blue)



Cherñavvsky, DeBoer et al. Ped Diab 2014

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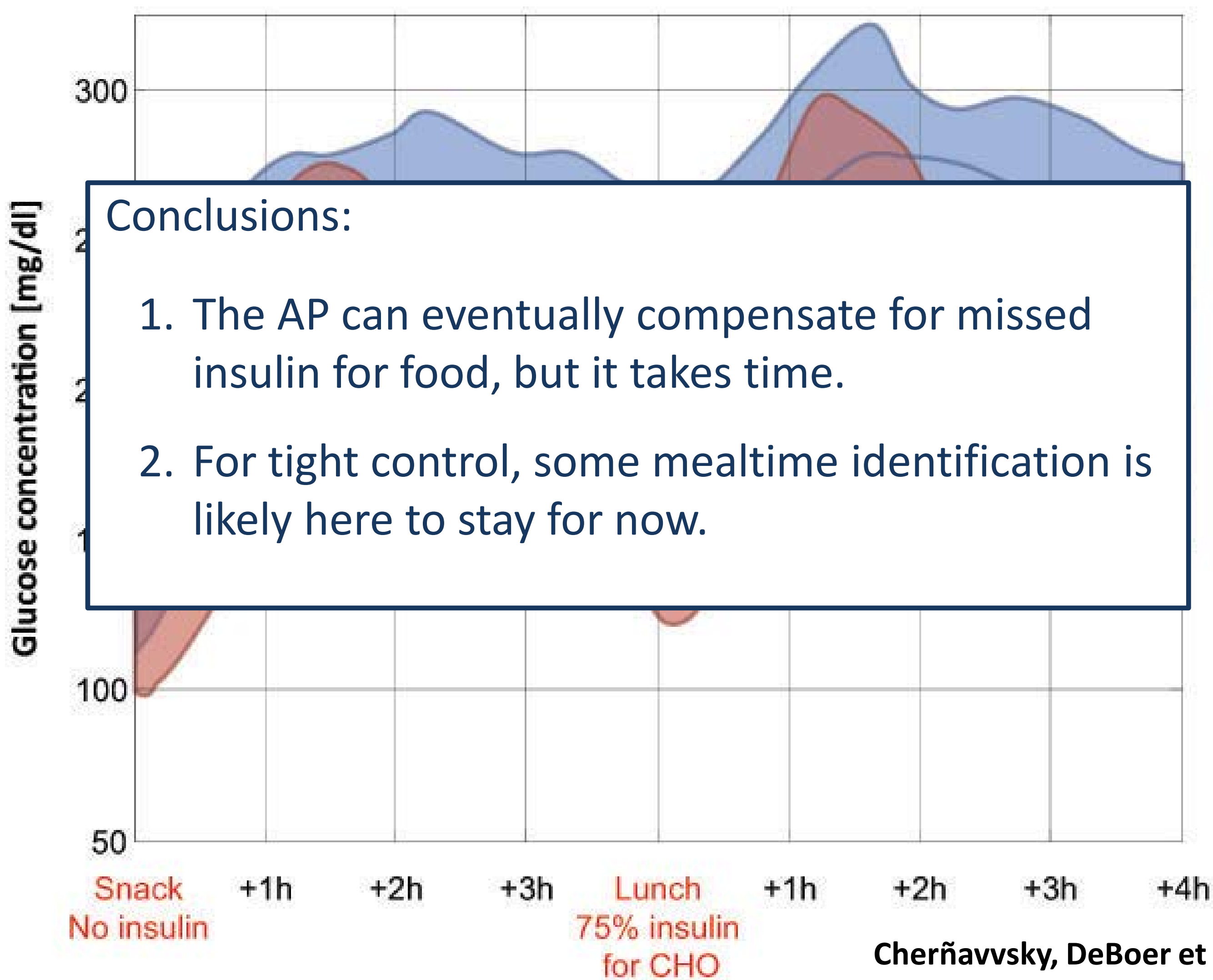


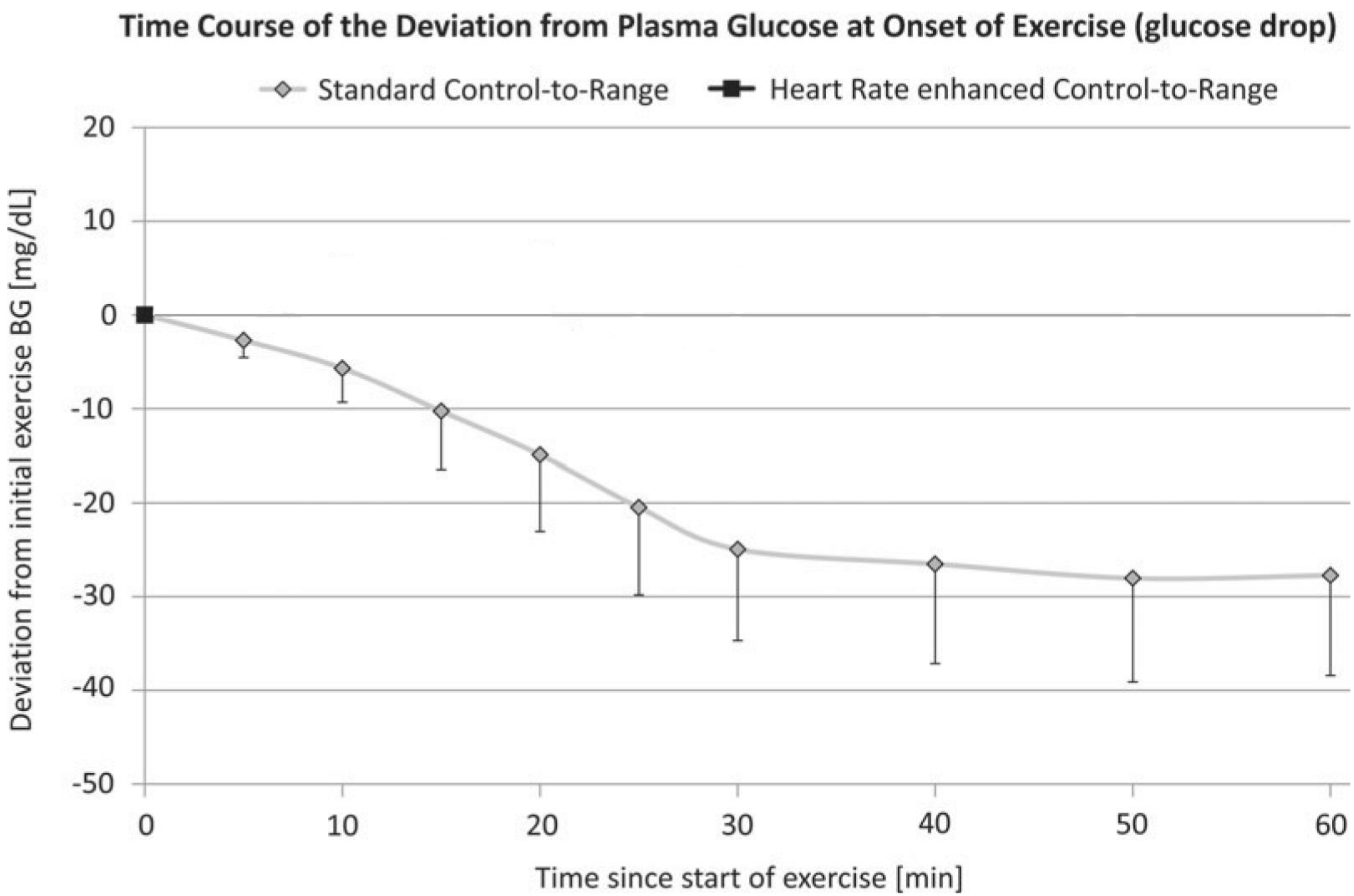
Conclusions:

1. The AP can eventually compensate for missed insulin for food, but it takes time.
2. For tight control, some mealtime identification is likely here to stay for now.

Cherñavvsky, DeBoer et al. Ped Diab 2014

Challenges: Exercise

UVA (Marc Breton, Sue Brown, Stacey Anderson, Boris Kovatchev)

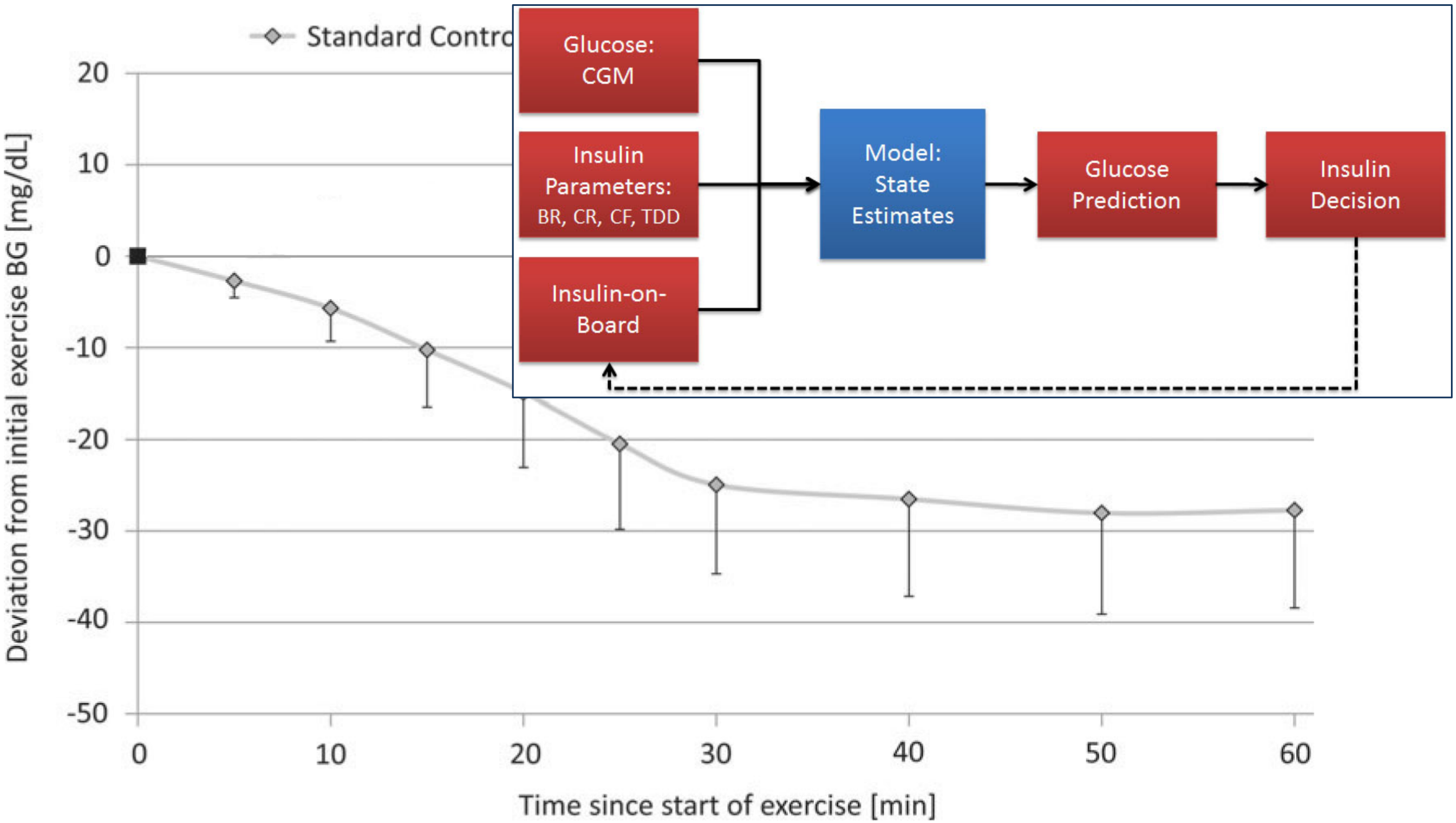


Breton Diab Tech Ther 2014

Challenges: Exercise

UVA (Marc Breton, Sue Brown, Stacey Anderson, Boris Kovatchev)

Time Course of the Deviation from Plasma Glucose at Onset of Exercise (glucose drop)



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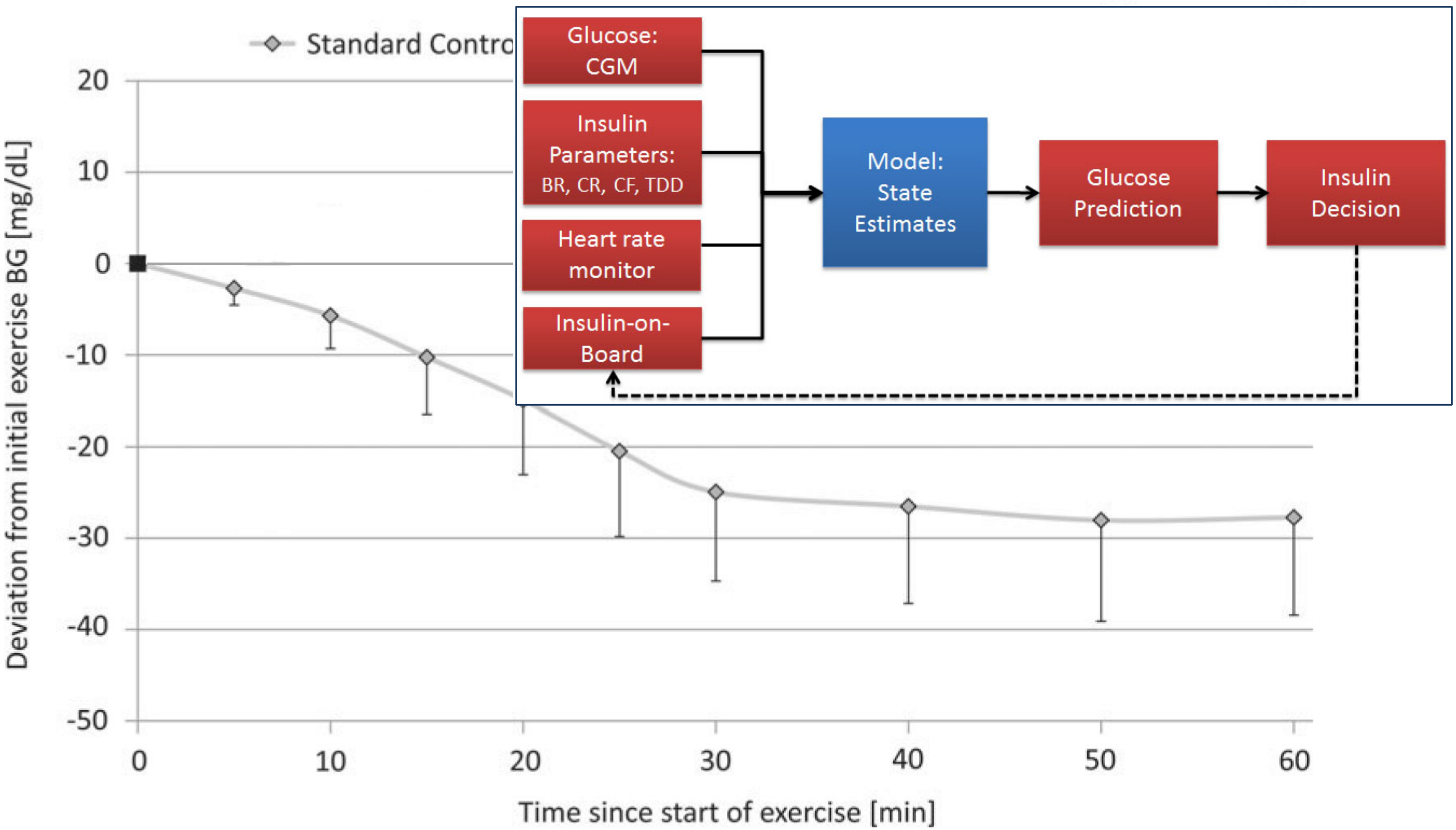

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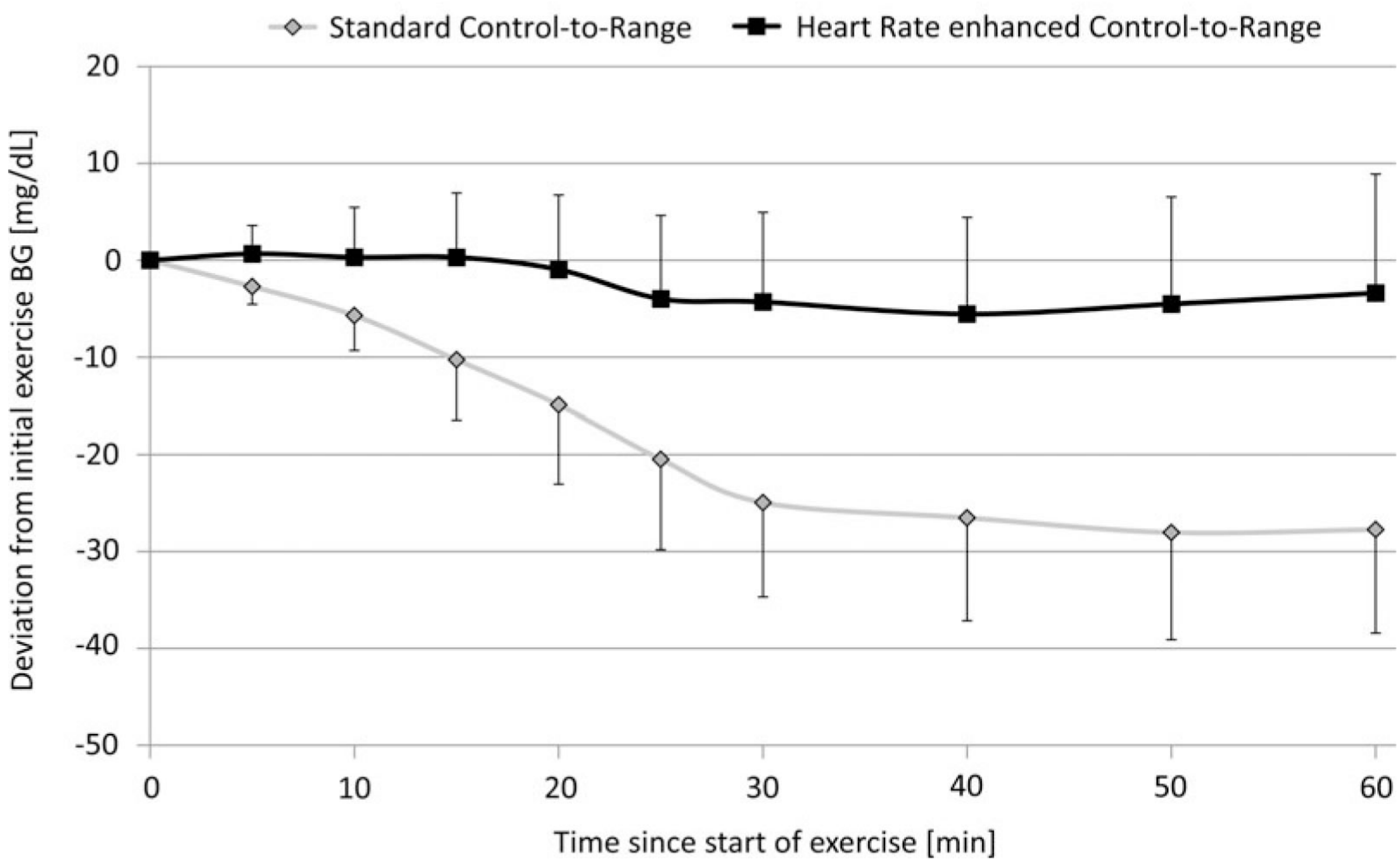
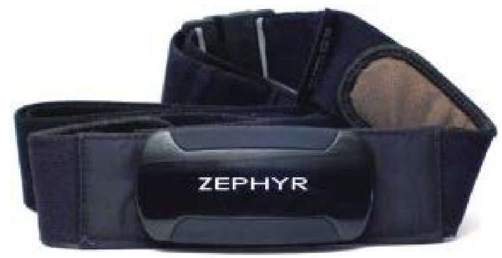


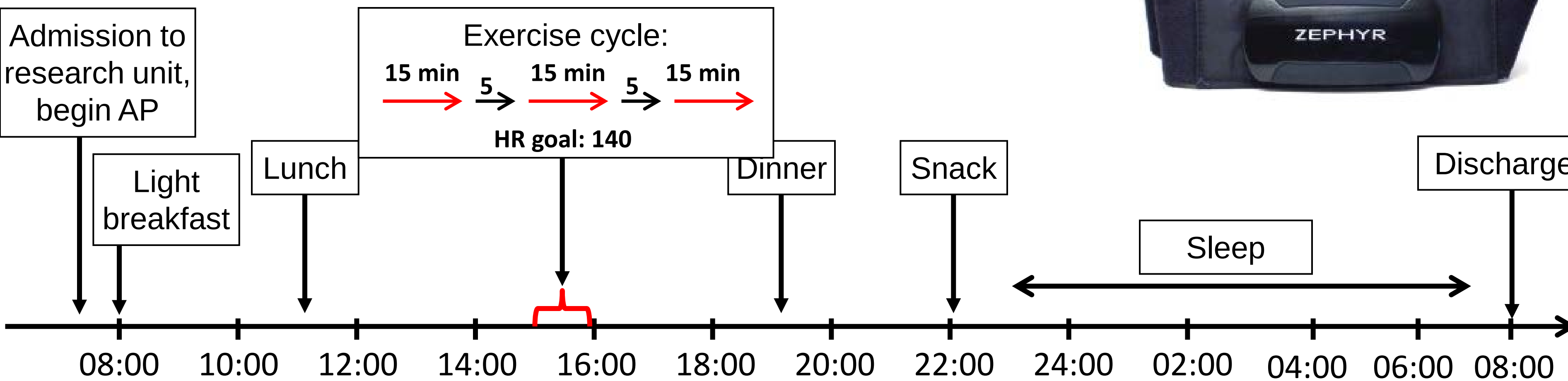
Breton Diab Tech Ther 2014

AP Challenges: Exercise

UVA, VCU (Mark DeBoer, Gary Francis, Marc Breton); **Funding** JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

Adolescents age 12-17 years, randomized cross-over:
AP and exercise with & without heart rate monitor input

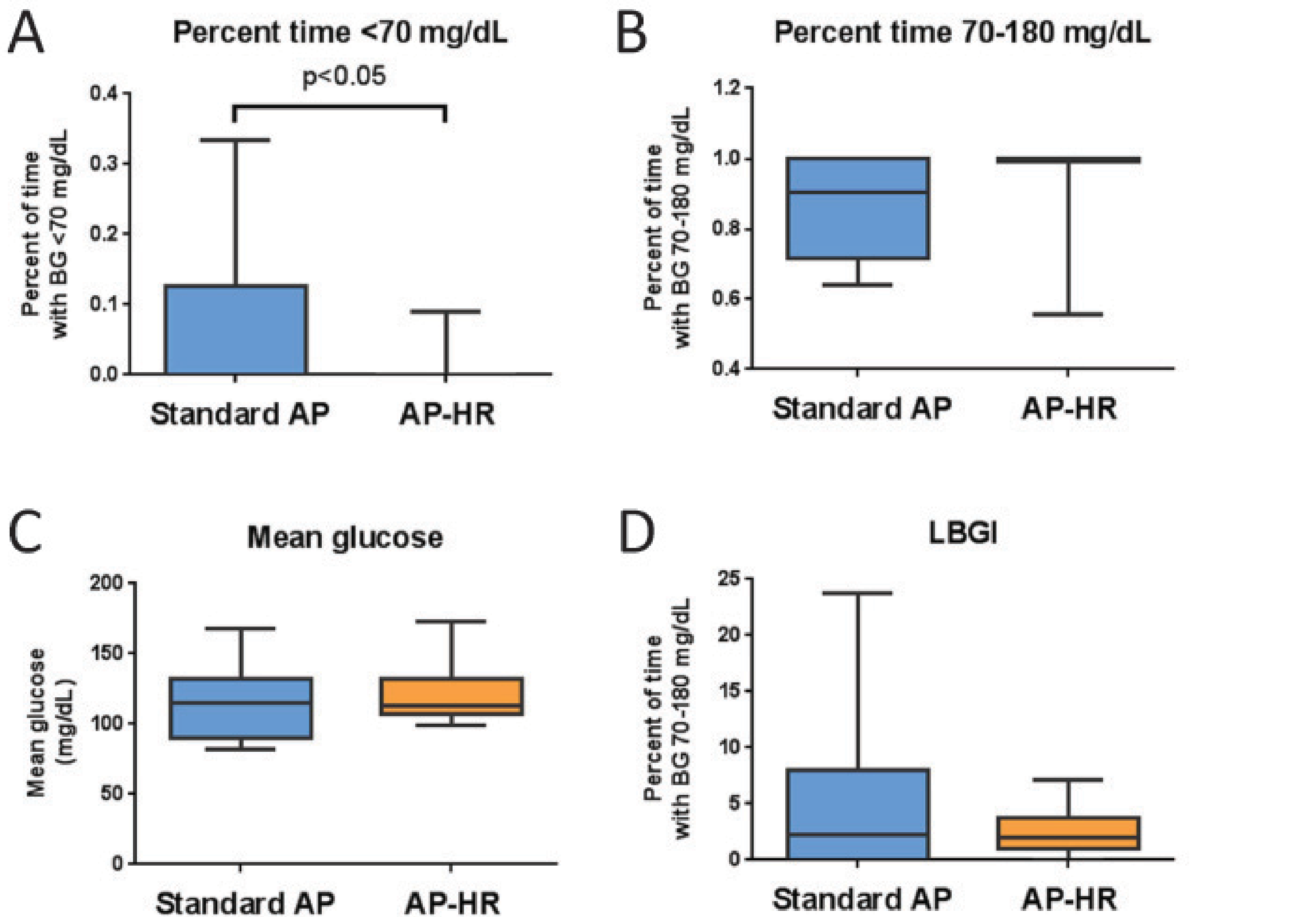




DeBoer Ped Diab 2016

Challenge: Exercise

UVa (Marc Breton, Mark DeBoer), **VCU** (Gary Francis)



DeBoer Ped Diab 2016

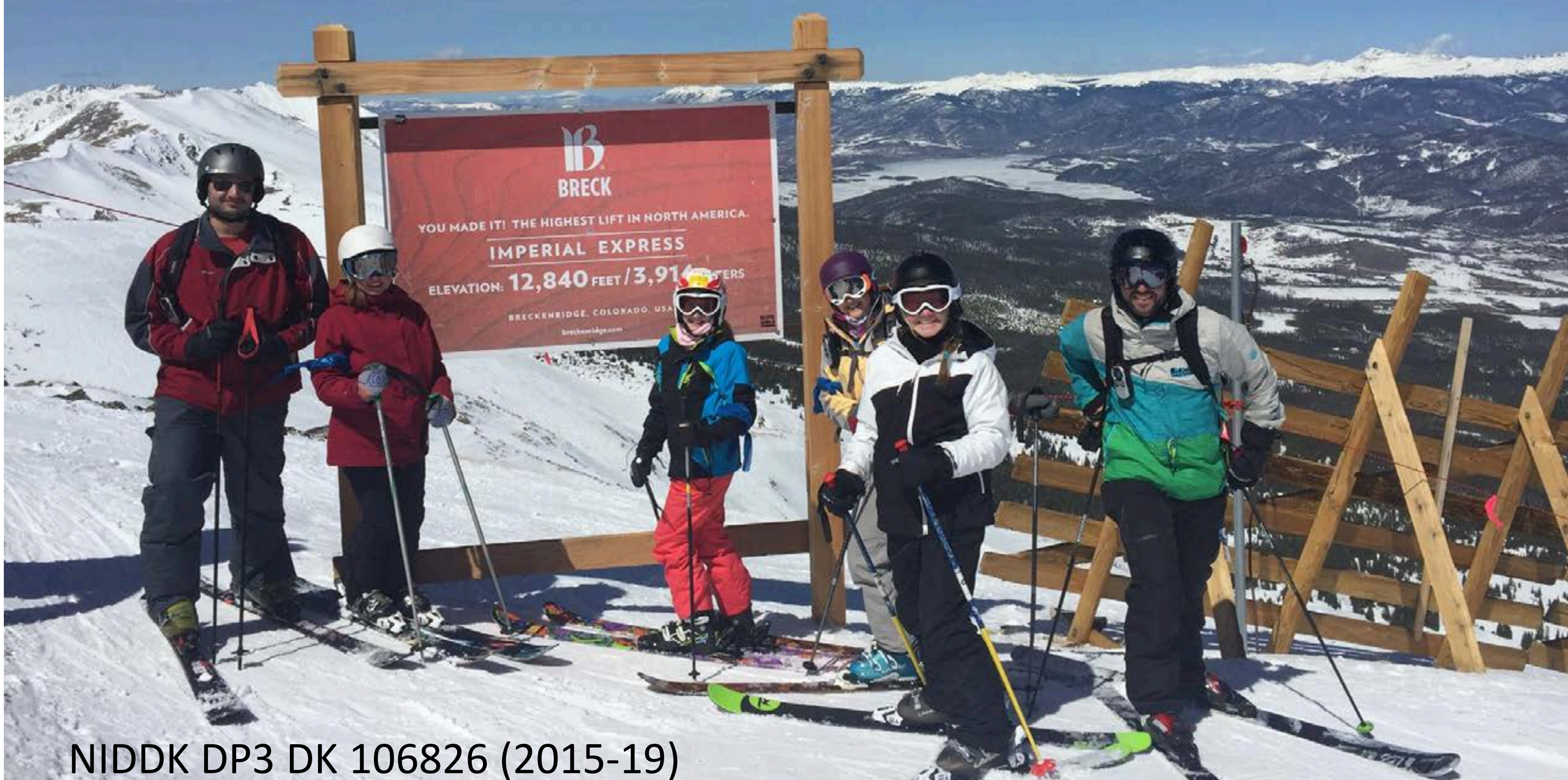
Challenge: Snow skiing

UVa (Marc Breton, Boris Kovatchev), **Barbara Davis** (David Maahs)

TO BOLDLY GO WHERE NO CLOSED LOOP HAS GONE BEFORE

<u>January 2016:</u> Five-Day Ski Camp on Closed-Loop Control
Wintergreen, Virginia, elevation 3,515’ (1,071 meters);

<u>April 2016:</u> Five-Day Ski Camp on Closed-Loop Control
Breckenridge, Colorado, elevation 12,840’ (3,914 meters)

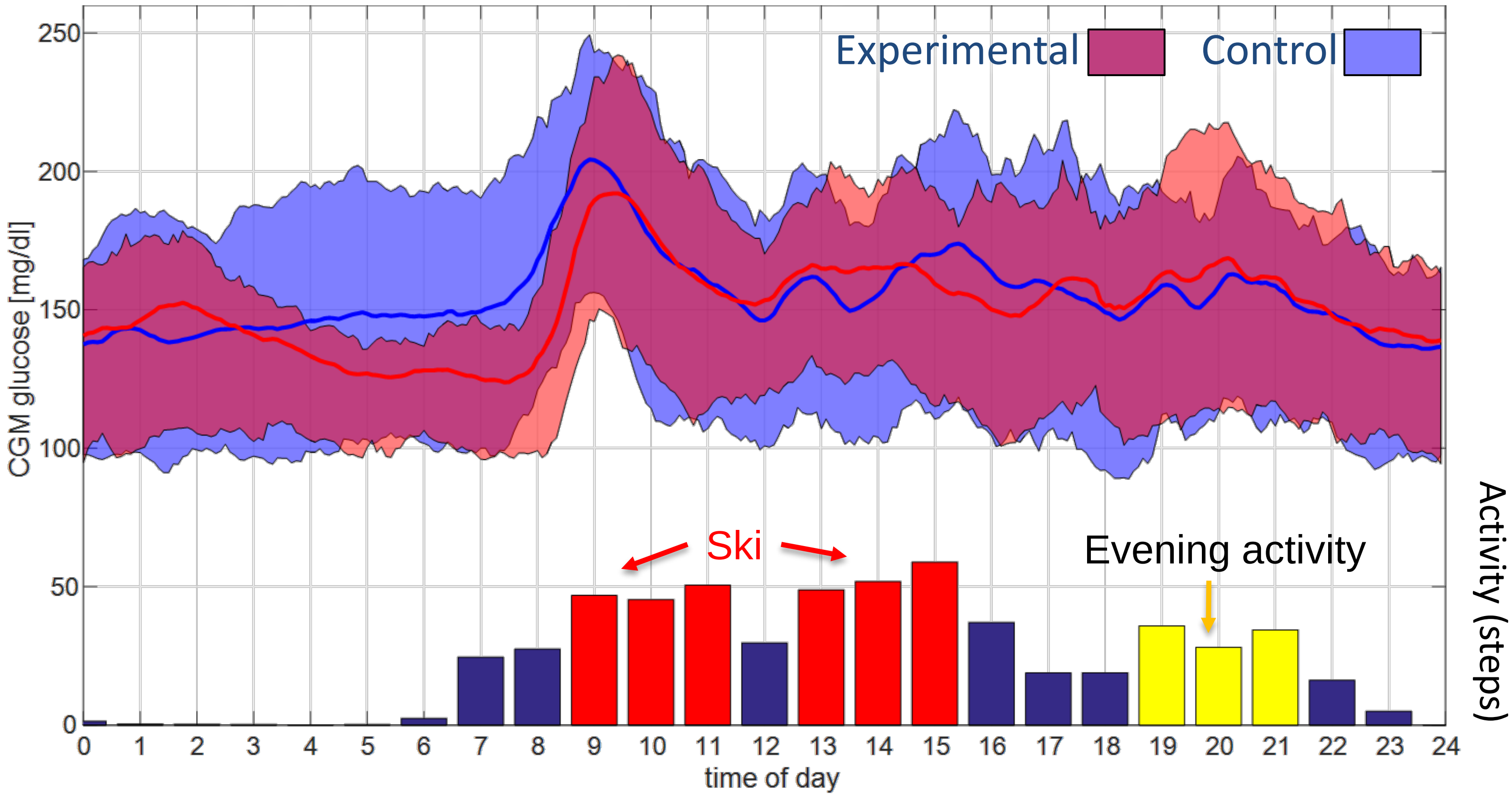


NIDDK DP3 DK 106826 (2015-19)

Challenge: Snow skiing

UVa (Marc Breton, Boris Kovatchev), **Barbara Davis** (David Maahs)

Average glucose and interquartile range:



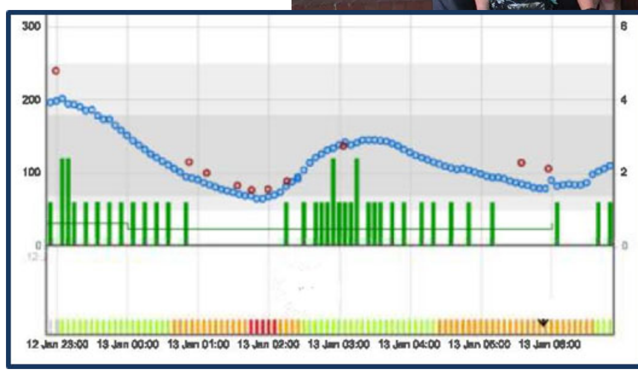
	Experimental	Control
Overall time in range (70-180mg/dl)	71.3%	64.7%
Time in range second half of night, 3-7AM	84.6%	66.2%
Time below 70 mg/dl	1.8%	3.2%

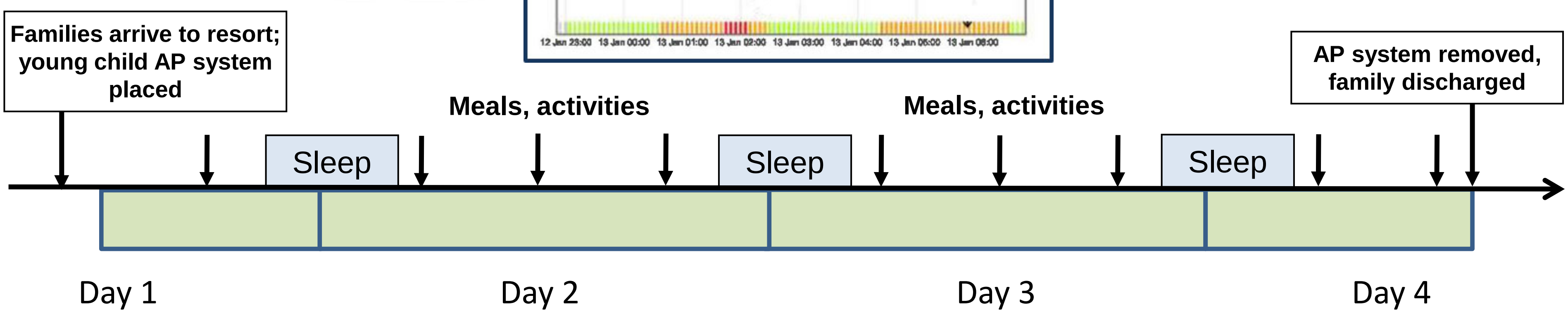
Breton
Diab Care 2017

Challenge: Young children

UVa (Mark DeBoer, Daniel Chernavvsky)

12 children age 5-8 years





DeBoer Diab Tech & Ther 2017

Challenge: Young children

UVa (Mark DeBoer, Daniel Chernavvsky)

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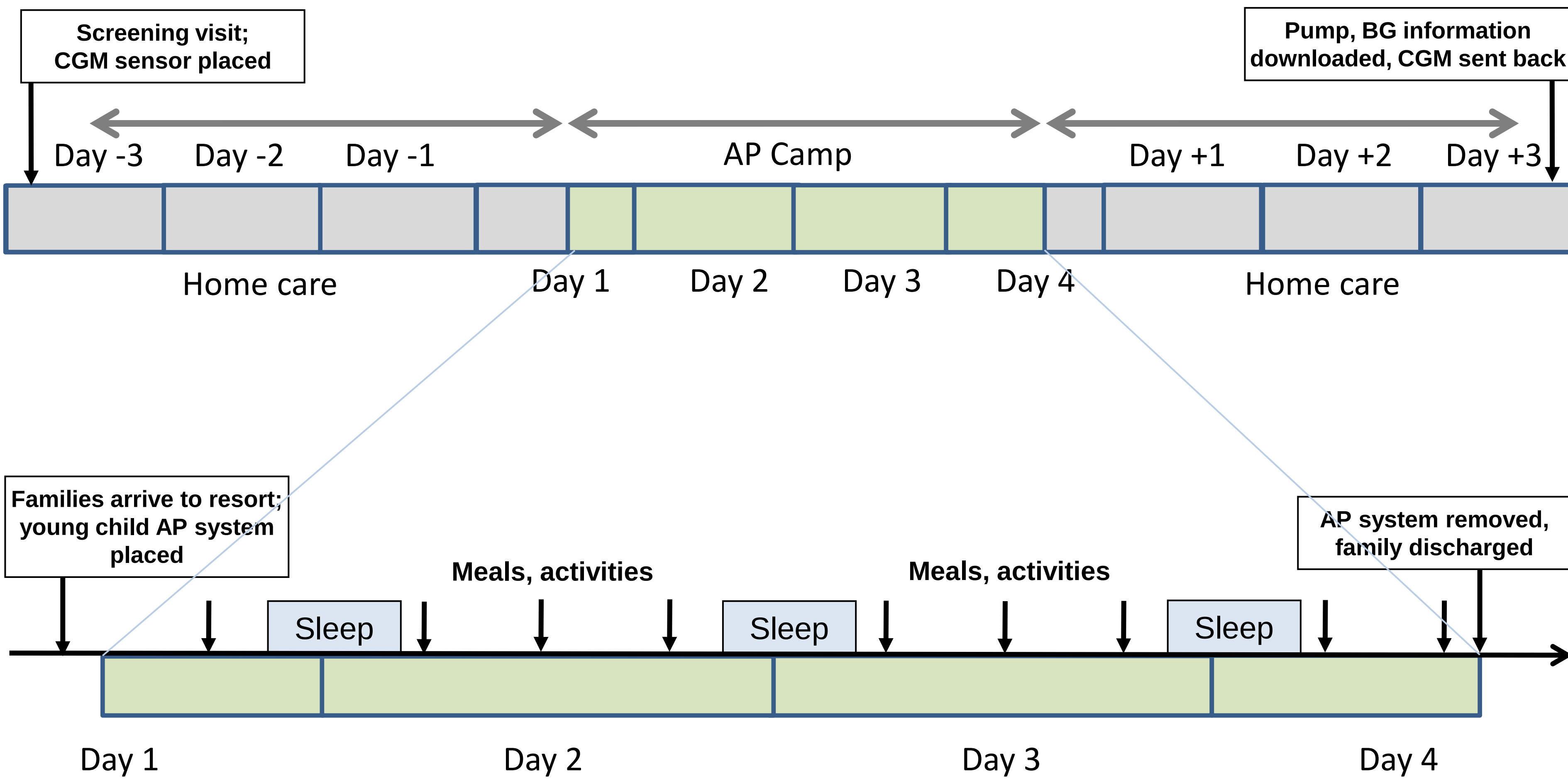

DeBoer Diab Tech & Ther 2017

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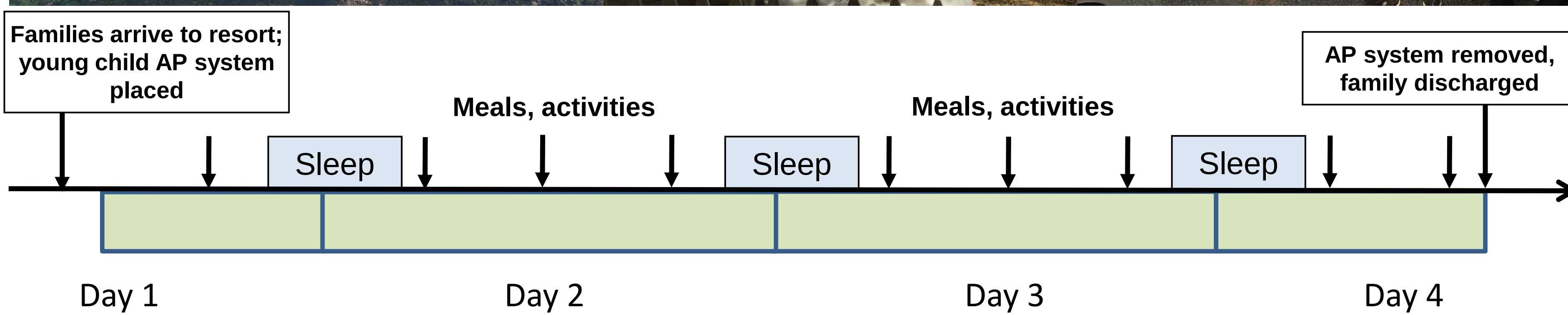

DeBoer Diab Tech & Ther 2017

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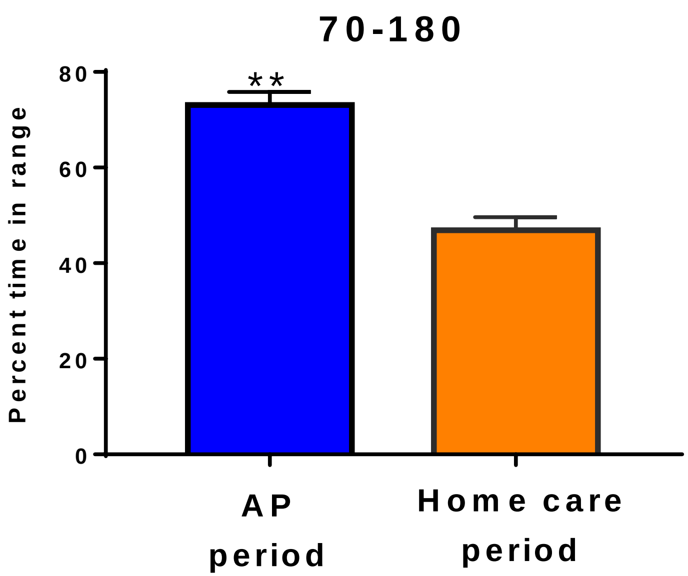
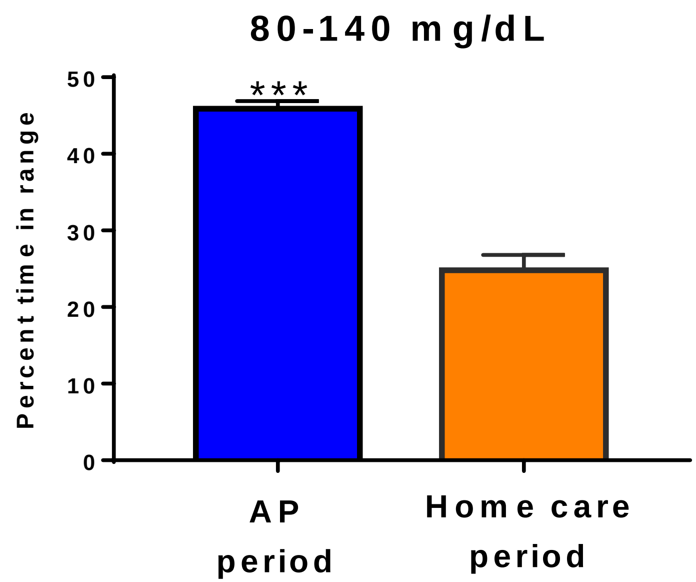


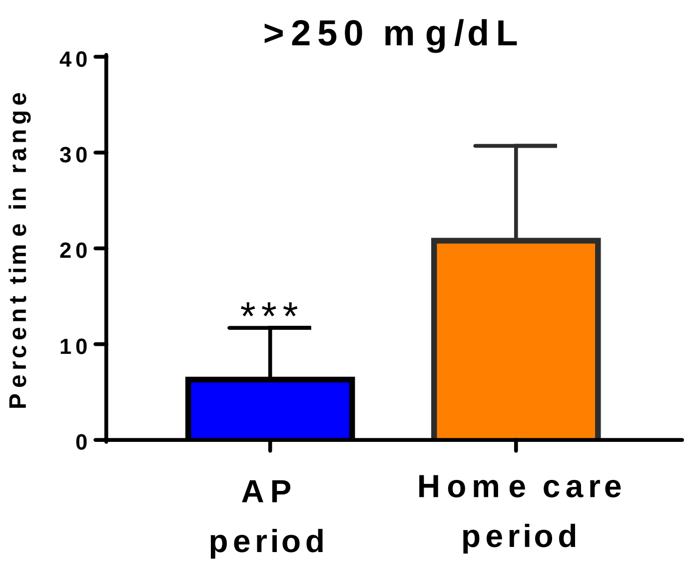


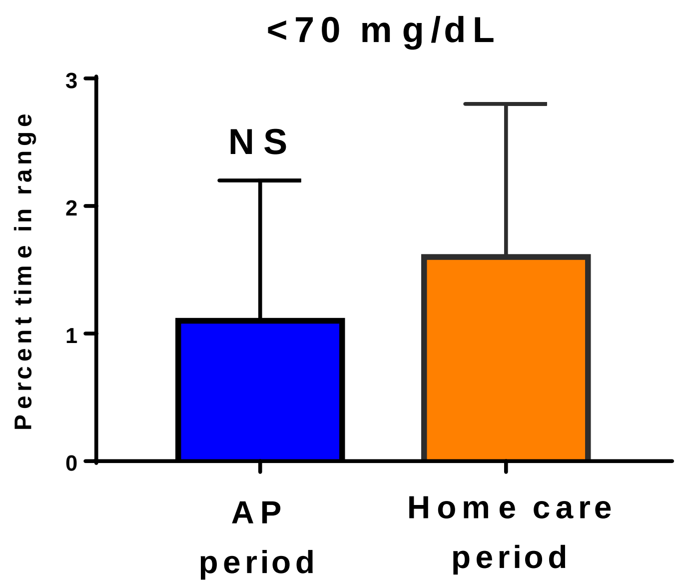
Differences adjusted for total steps:

** p<0.01

*** p<0.001

NS p>0.05





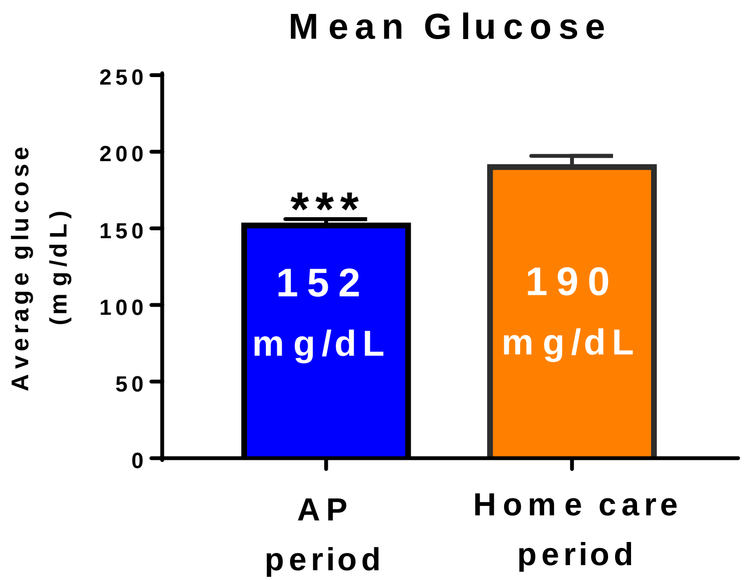
Total events <70 per participant:

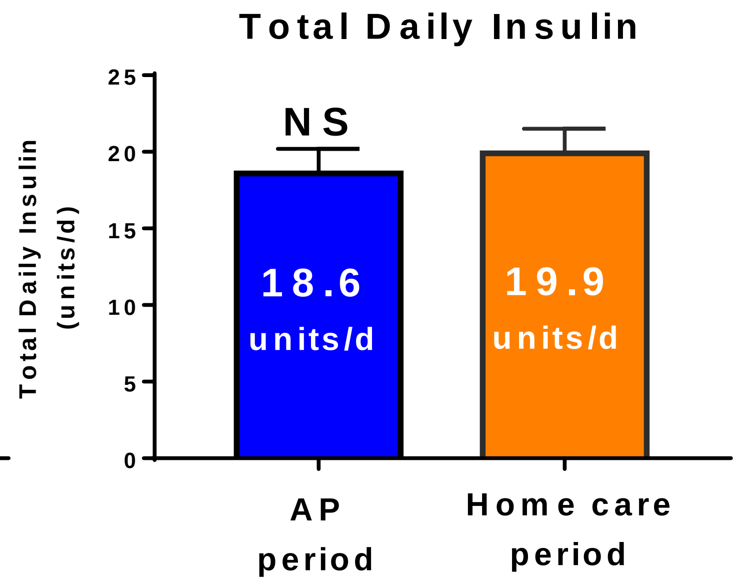
AP 3.3 ±1.0

Home 4 ±1.0

DeBoer DTT 2017

Results: Mean BG





DeBoer DTT 2017

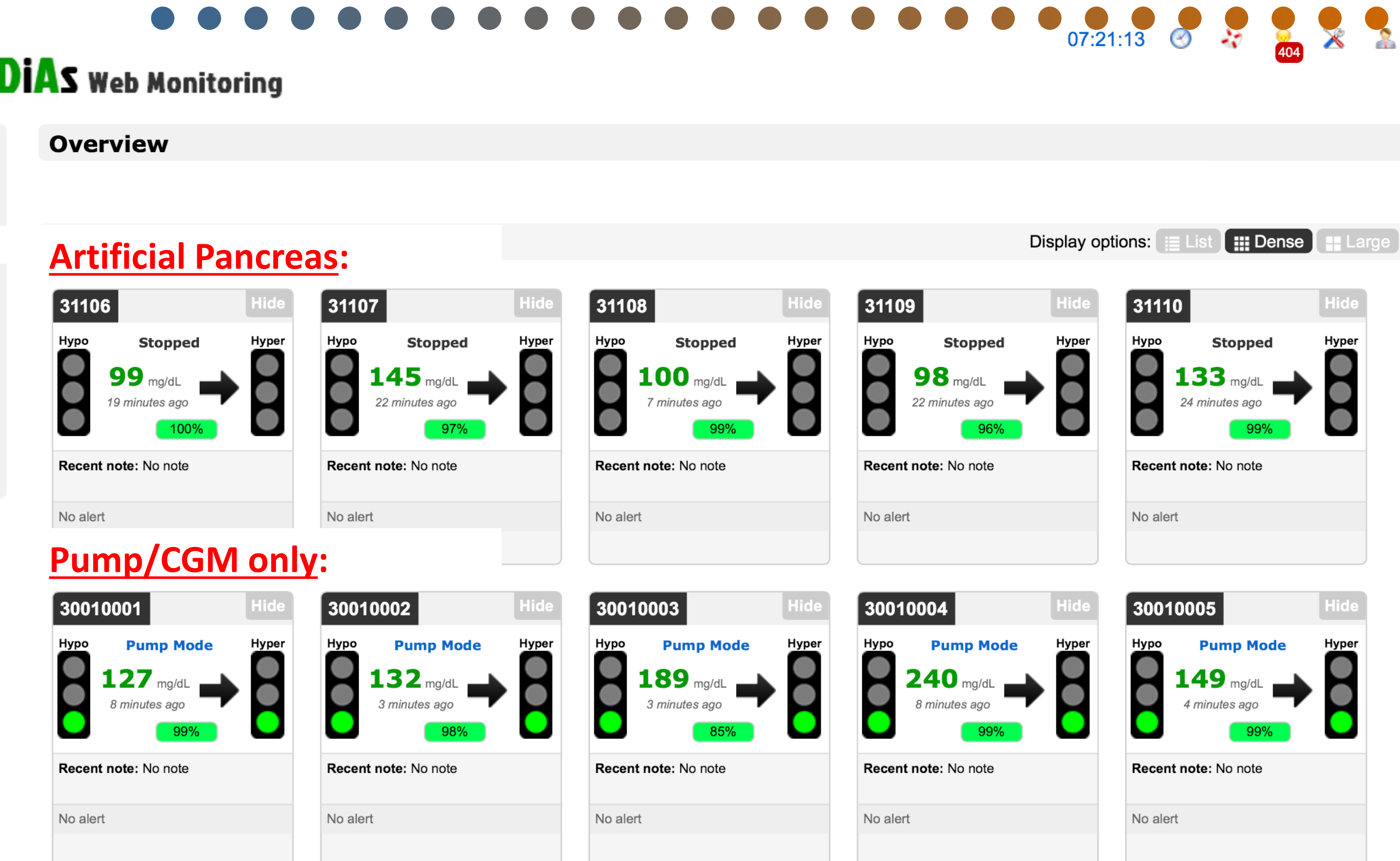
Results: Lock-out screens

- 0/12 parents reported that their child discovered the password or were found entering insulin doses or settings unsupervised.

DeBoer DTT 2017

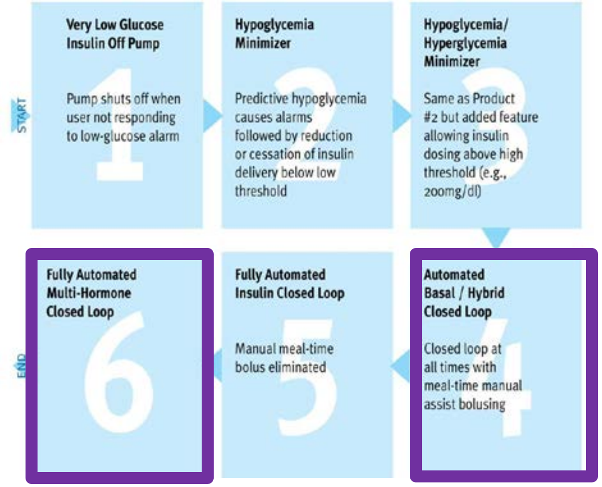

UVA
Montpellier
NIH
JDRF
Helmsley Charitable Trust
AP@Home
Padova
Santa Barbara

Bedside AP: *at home*

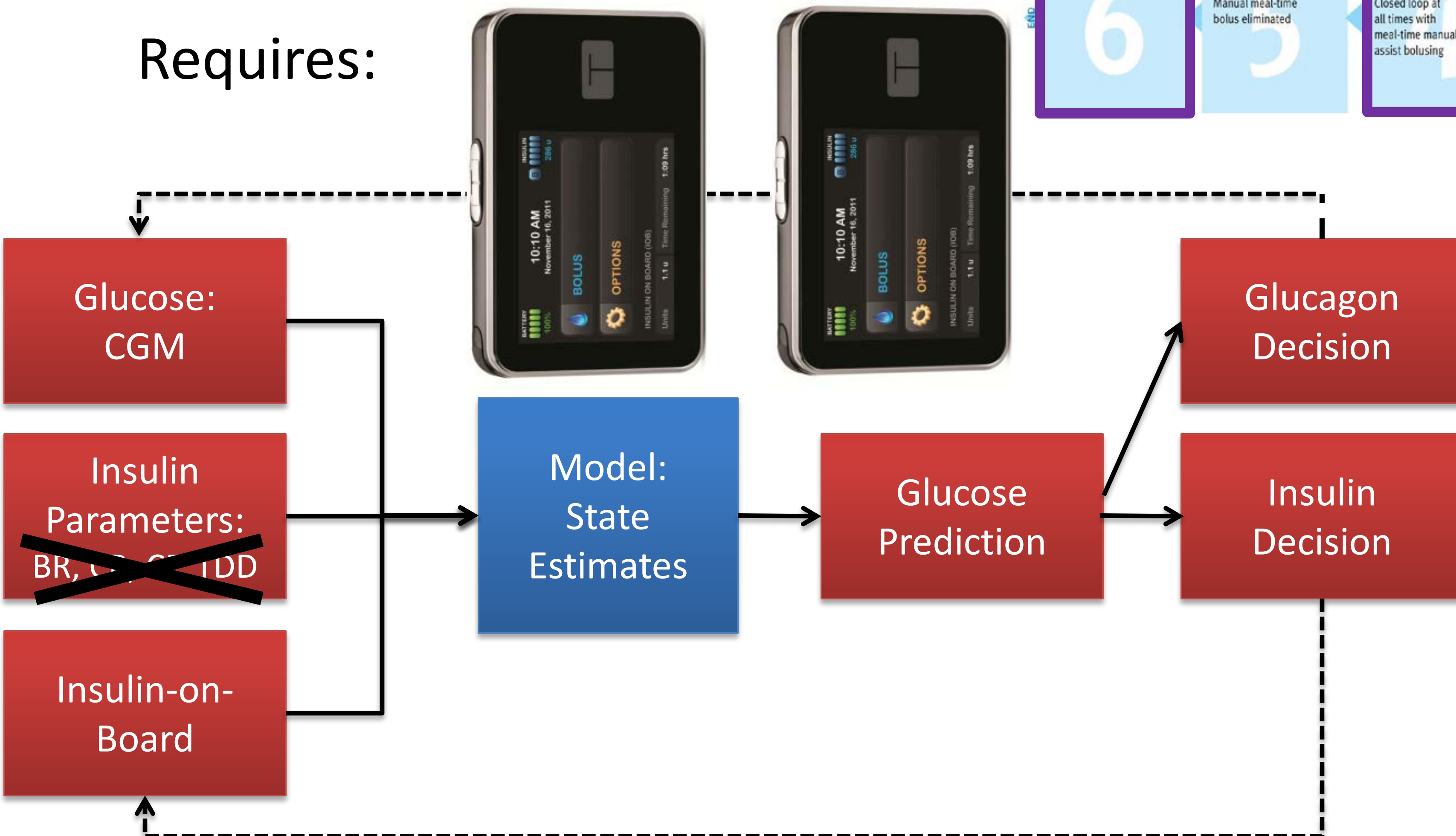


Dual-hormone system

Boston U: (El-Khatib, Russell, Magyar, Sinha, McKeon, Nathan, Damiano)



Requires:



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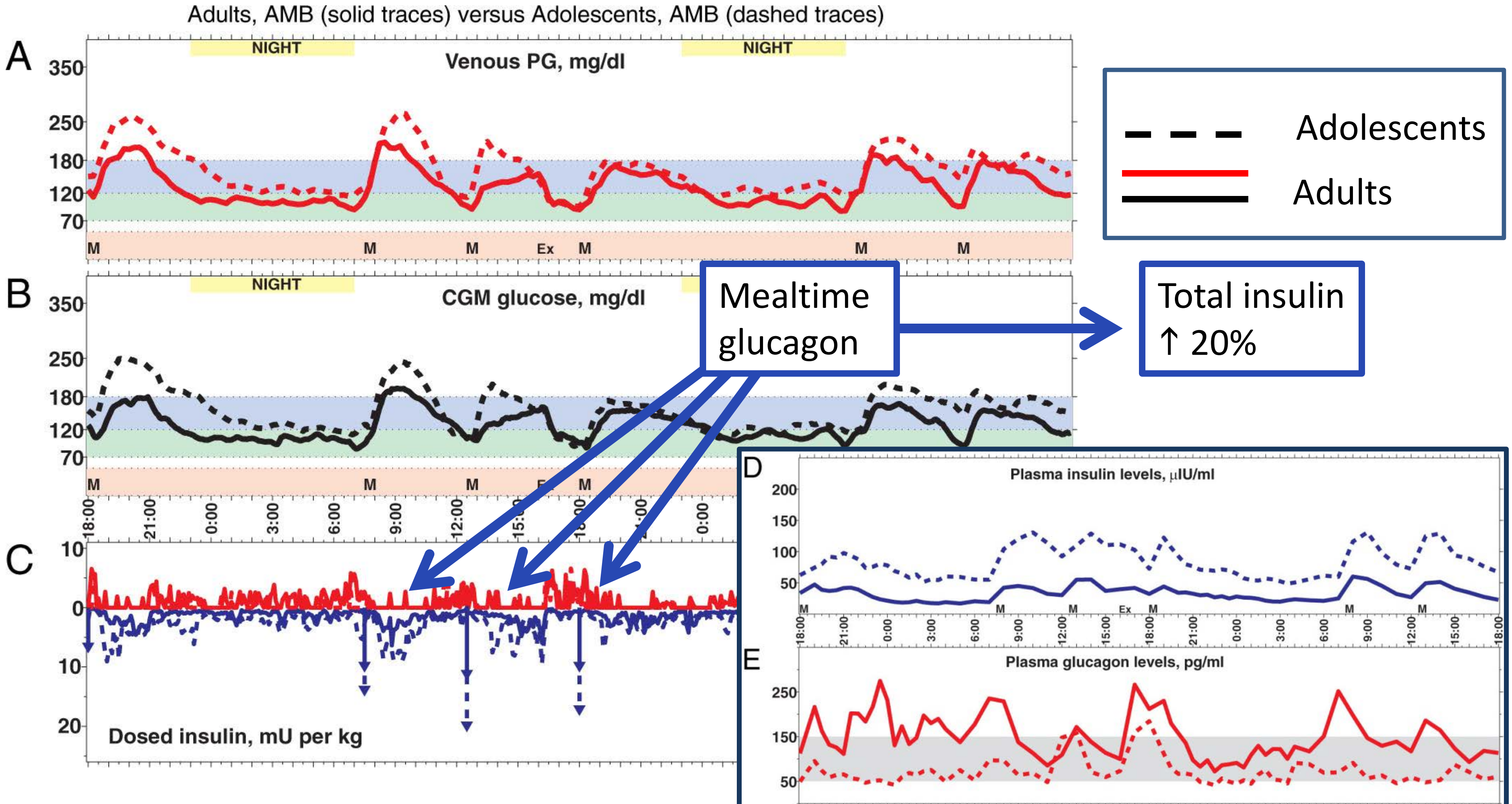

El-Khatib JCEM 2014

Recent Closed-Loop Studies at a Glance

Source of Data	Medtronic 670G safety trial [1]	JDRF Pilot trial of long-term closed-loop control [2,3]	Home use of bihormonal bionic pancreas [4]
Duration of Closed-Loop Control	3 months	6 months	11 days
Number of participants	124	30 (Phase 1) 14 (Phase 2)	39
Algorithm Automation	Basal Rate Only	Basal Rate and Correction Boluses	Insulin + Glucagon
Algorithm Description	PID with insulin feedback	Model-based sliding target	-
Sensor/Pump	Medtronic MiniMed 670G System	Dexcom G4 with Software 505 + Roche insulin pump	Dexcom G4 Platinum + two Tandem t:slim insulin pumps

[1] Bergenstal RM, Garg S, Weinzimer SA, et al.; Safety of a Hybrid Closed-Loop Insulin Delivery System in Patients With Type 1 Diabetes. *JAMA* 2016; 316:1407-1408.

[2] Anderson SM, Raghinaru D, Pinsker JE, et al.; Multinational Home Use of Closed-Loop Control Is Safe and Effective. *Diabetes Care* 2016; 39:1143-1150. (Phase 1)

[3] Kovatchev B, Cheng P, Anderson SM, et al.; Feasibility of Long-Term Closed-Loop Control: A Multicenter 6-Month Trial of 24/7 Automated Insulin Delivery. *Diabetes Technol Ther* 2017; 19:18-24. (Phase 2)

[4] El-Khatib FH, Balliro C, Hillard MA, et al.; Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicenter randomised crossover trial. *Lancet* 2017; 389:369–380.

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Insulin injection U/kg/day	0.66	0.57	0.66
Glucagon injection	none	none	0.51 mg/day
Time below 70 mg/dl	**2.9%** (**42** minutes/day)	**1.3%** (**19** minutes/day)	**1.8%** (**26** minutes/day)
Time below 60 mg/dl	-	0.3%	0.6%
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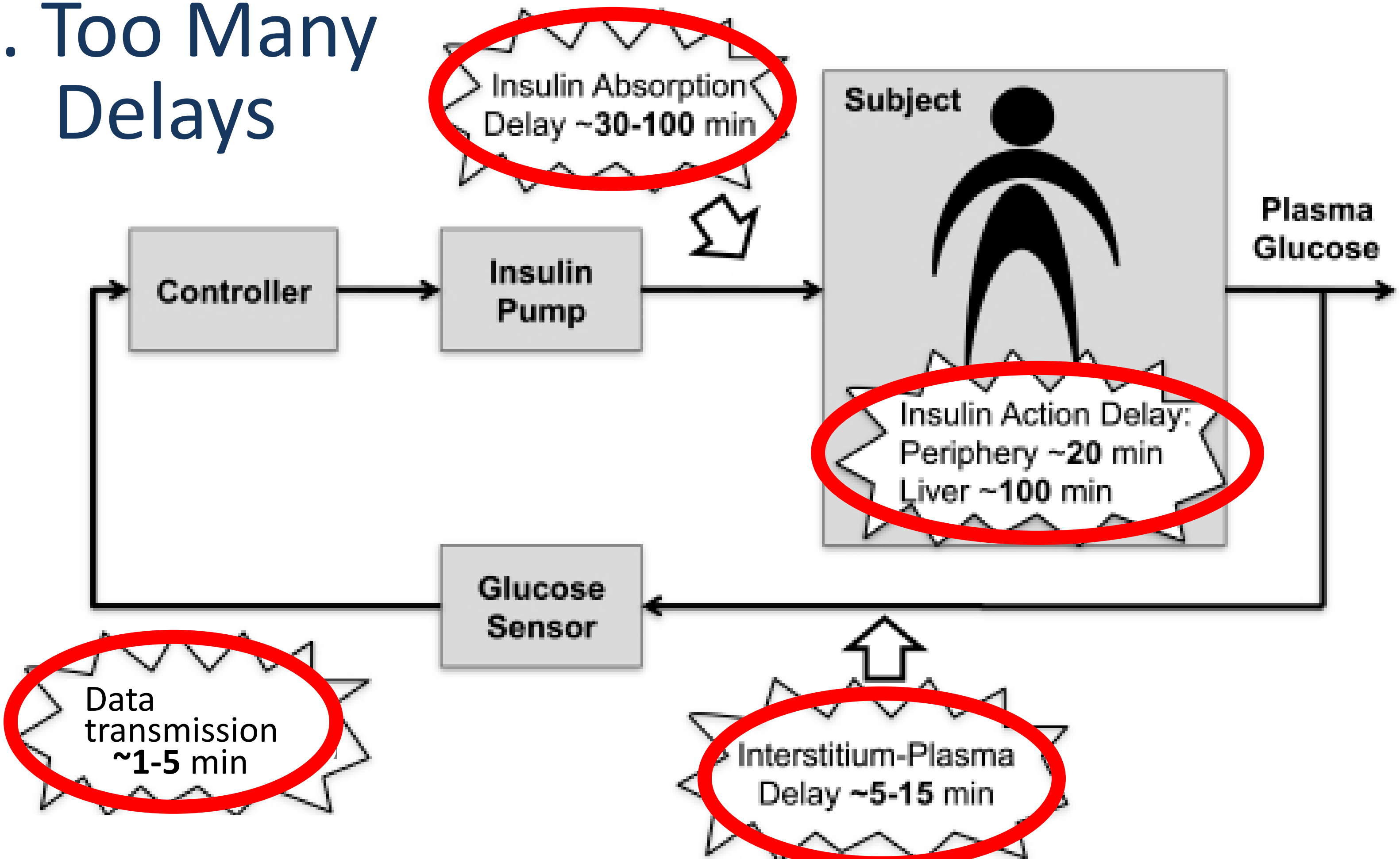
Overall AP Challenges

1. CGM accuracy (e.g. at extremes), failure
2. Too Many Delays



Cobelli et al, Diabetes 2011

Overall AP Challenges

1. CGM accuracy (e.g. at extremes), failure
2. Too Many Delays
3. Complexity/connectivity of devices

Algorithmic Solutions:

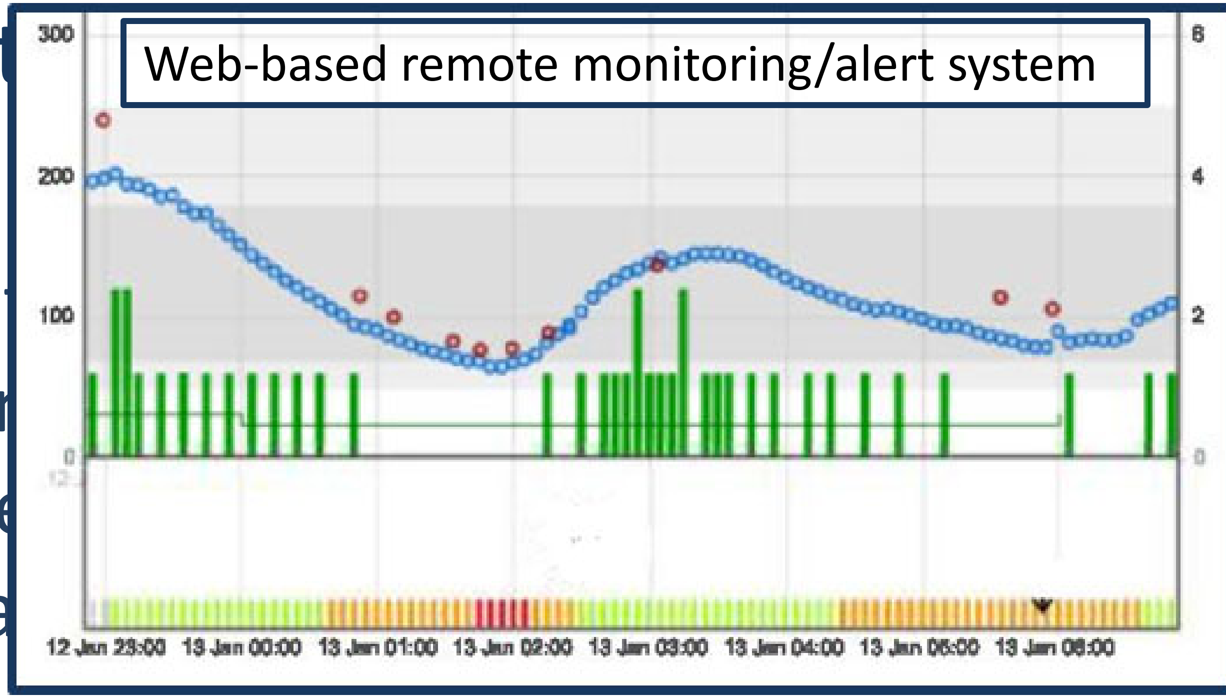
- Can be modeled into the algorithm
- Detection of sensor failures
- Revert to Open Loop mode with system failure

AP Timeline

"Within about

Steps:

- Definitive sa
- Establishmen
- Industry agre
- FDA approva



Speedier timing:

- European approval
- Approval of AP technologies besides closed-loop

Lingering Questions

Will adolescents be willing to increase their diabetes-related effort for the gain of automated insulin delivery?

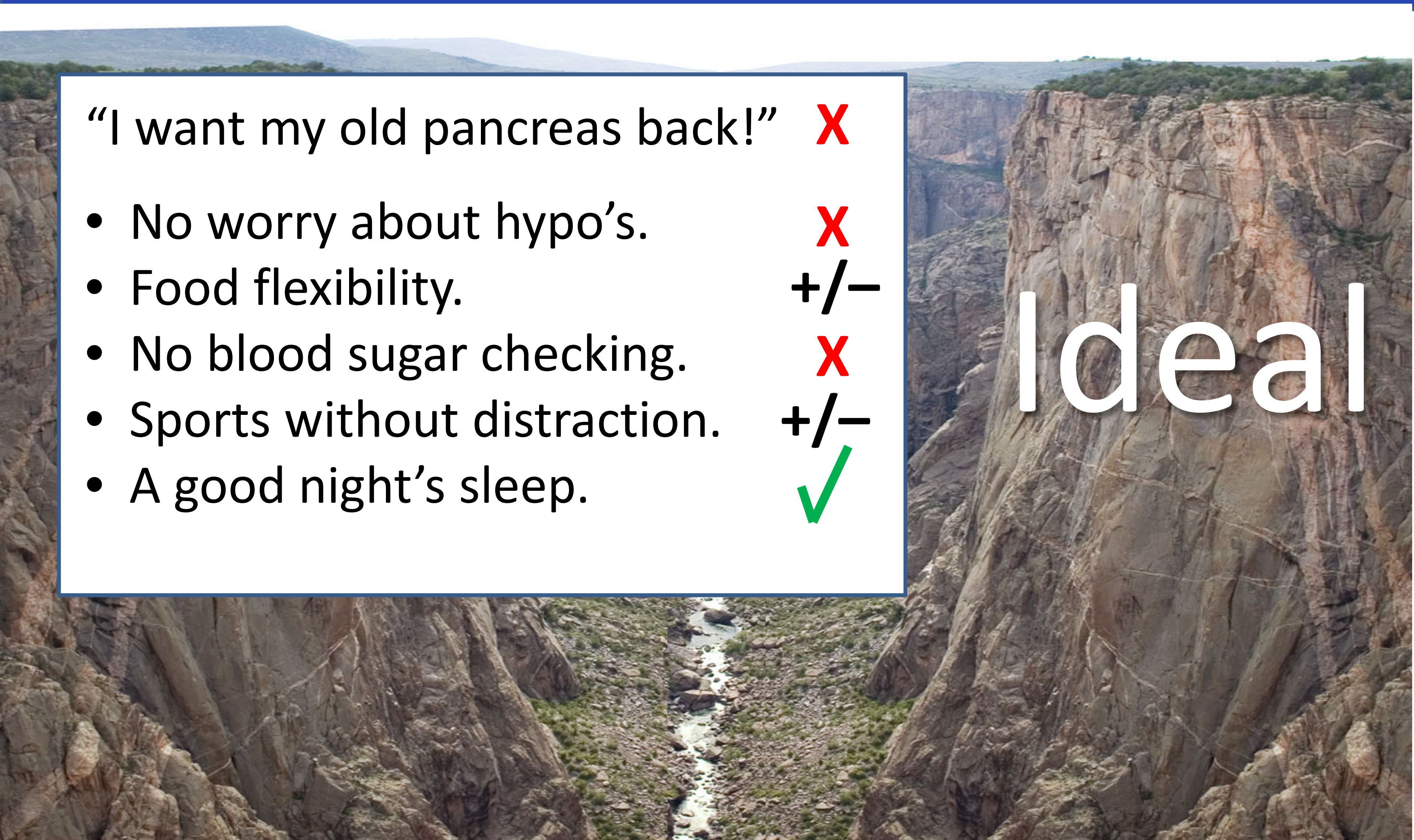
Will well-controlled individuals start unhealthy practices, expecting the system to compensate?

Bridging the canyon…

Bridging the canyon…

"I want my old pancreas back!" X

- No worry about hypo's. X
- Food flexibility. +/–
- No blood sugar checking. X
- Sports without distraction. +/–
- A good night's sleep. ✓



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