Dexcom G5 Mobile Continuous Glucose Monitoring (CGM) System for Non-Adjunctive Management of Diabetes

July 21, 2016

Dexcom, Inc.

Clinical Chemistry and Clinical Toxicology Devices Panel

Introduction

Andrew Balo

Executive Vice President

Clinical, Regulatory & Global Access

Dexcom, Inc.

Current Dexcom G5 CGM Indication: Adjunctive Use

- For detecting and tracking glucose trends and patterns in persons with diabetes
- For use as an **adjunctive device to complement, not replace,** information obtained from standard home glucose monitoring devices (SMBG)

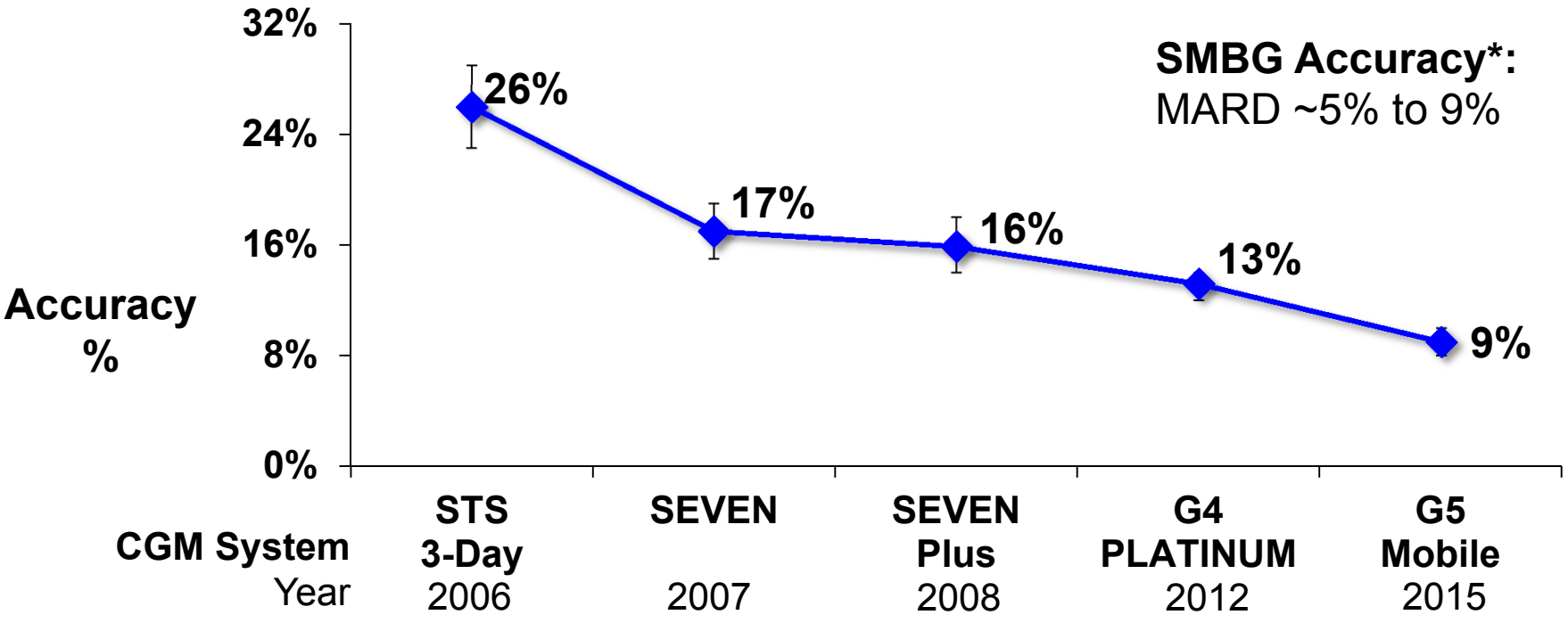
SMBG: Self-monitoring of blood glucose

Proposed Dexcom G5 CGM Indication: Non-Adjunctive Use

- For management of diabetes
- Designed to **replace fingerstick** glucose testing for diabetes **treatment decisions**
- Fingerstick calibration every 12 hours
- Instructions for use to include information on CGM use for treatment decisions

Public Health Rationale for Indication Change

1. Improvements over decades of use have made data highly reliable



* Tack et al., (2012); Zueger et al., (2012); Kuo et al., (2011)
MARD: Mean Absolute Relative Difference; Error Bar = 95% Bootstrapped CIs

Public Health Rationale for Indication Change

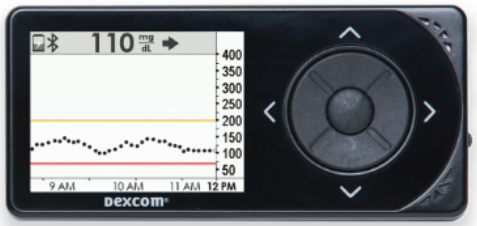
1. Improvements over decades of use have made data highly reliable
2. Many existing patients currently use Dexcom CGM for making treatment decisions
   - Ability to educate on proper use is vital
3. Broader label will
   - Decrease fingerstick requirement
   - Increase access to CGM

Dexcom G5 System: FDA-Approved Continuous Glucose Monitor (CGM)

Mobile App

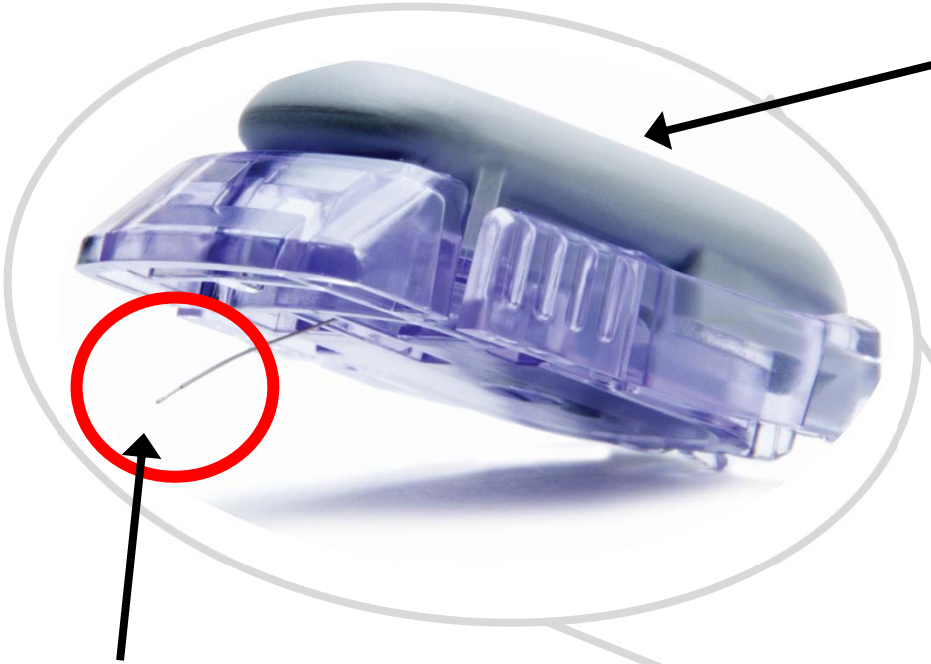
Sensor
(in applicator)

Receiver



Transmitter

Dexcom G5 CGM System: Sensor and Transmitter

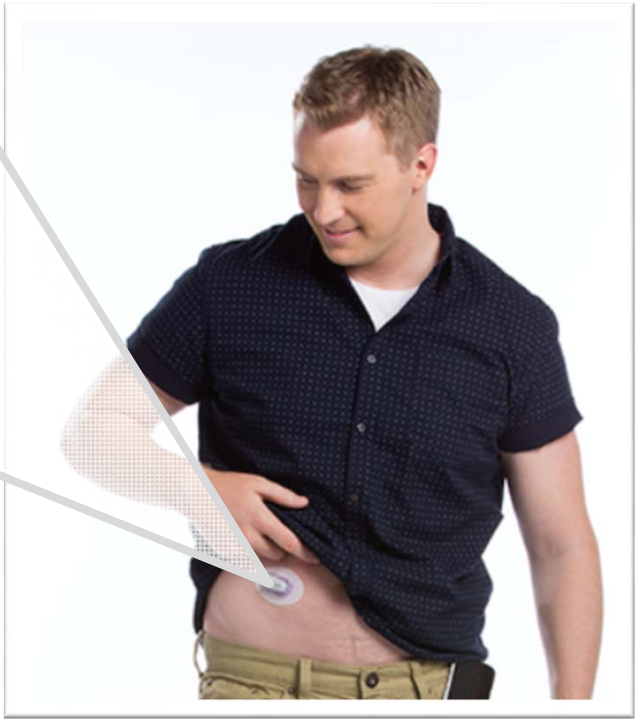


Transmitter

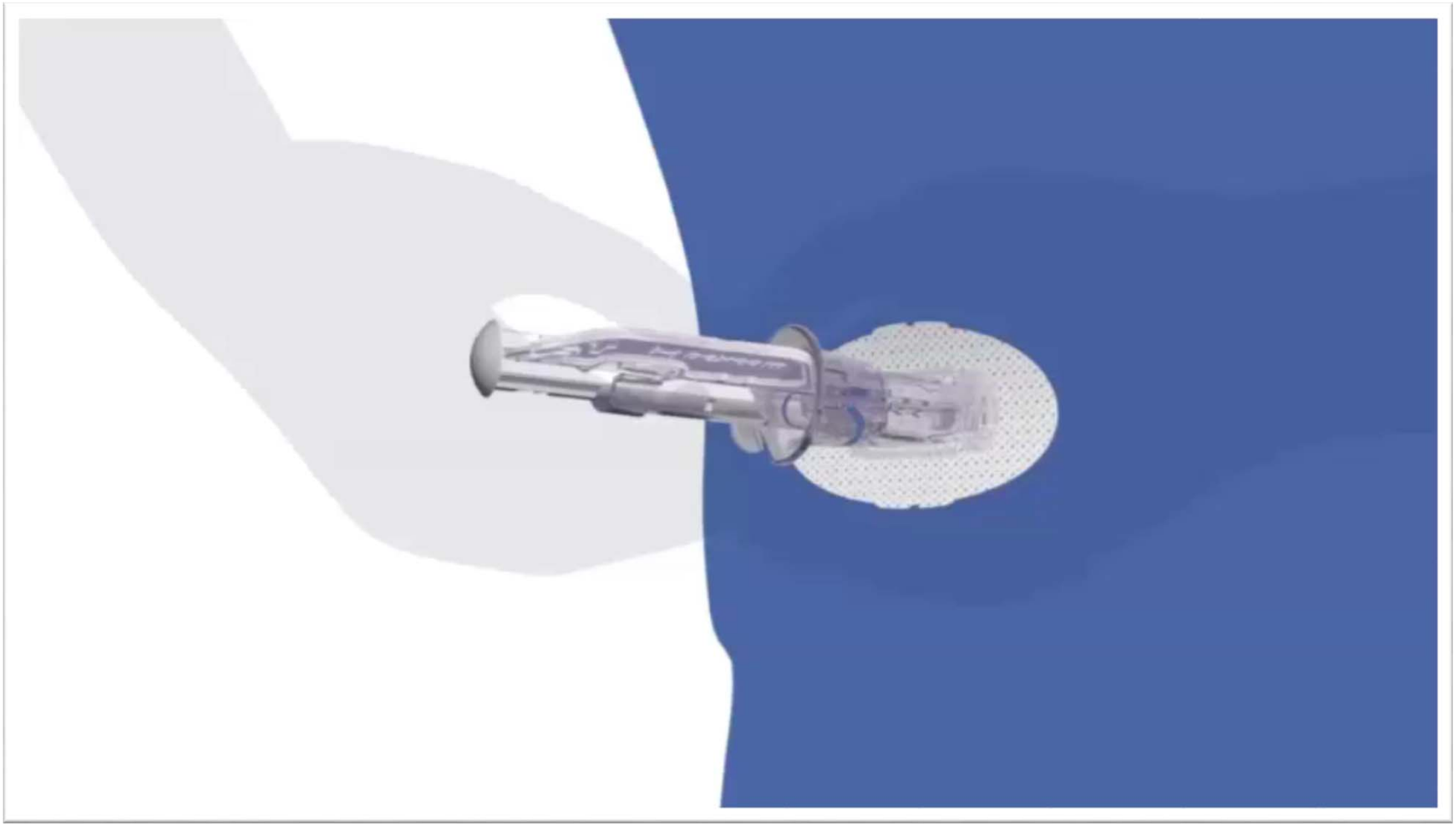
- Converts sensor data into glucose readings (Software 505)
- Glucose data broadcast via Bluetooth to display device

Sensor

- Tiny wire inserted
- Converts glucose into electrical current
- Glucose range: 40-400 mg/dL
- Every 5 minutes, up to 7 days



Simple Sensor Insertion



Display Devices: Mobile App or Receiver

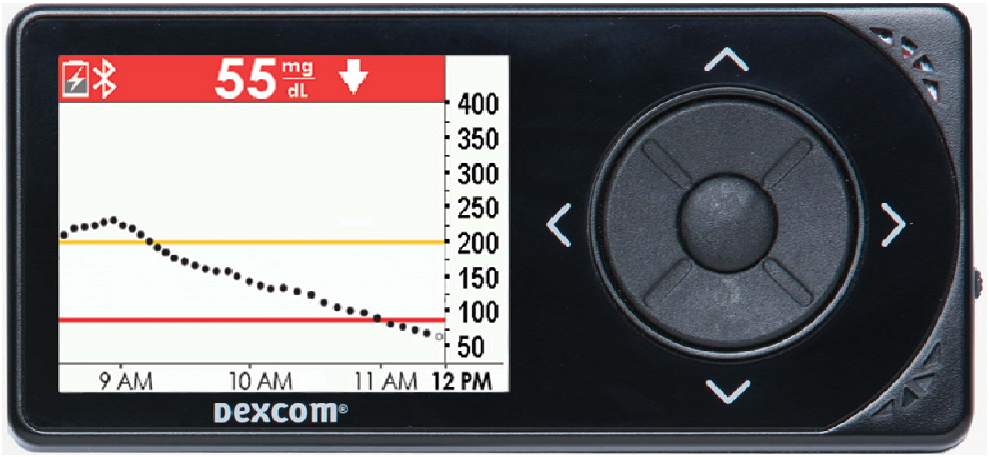
Mobile App

Receiver

Devices display:

- Current glucose reading
- Arrows indicate direction and rate of change
- Tracing of last 3 hours
- Configurable alerts

Fixed Low Glucose Alarm at 55 mg/dL



Devices display:

- Fixed, non-configurable alarm set to 55 mg/dL
- Audible and vibratory alarm
- Repeats every 5 minutes until acknowledged or glucose level rises above 55 mg/dL

Dexcom CGM Provides More Information than SMBG

- Up to 288 readings per day
- Readily available
- Glucose trends/rate of change
- Alerts and alarms
- Improve time to treatment
- Remote monitoring (“sharing”)

Regulatory Discussions

- Testing strategy
- Mitigations for new risks
- Clinical data
- Human Factors
- Computer simulations
  - Provide additional data related to risks at physiological, sensor and meter extremes
  - Demonstrate safety and effectiveness

Agenda

Clinical Utility of CGM-Based Treatment	**Bruce Buckingham, MD** Stanford University
Simulation Studies	**David Price, MD** Dexcom, Inc.
Planned Training and Human Factors Study	**Claudia Graham, PhD** Dexcom, Inc.
Benefit-Risk Conclusion	**Steven Edelman, MD** University of California at San Diego

Additional Experts

- **Claudio Cobelli, PhD**
  Professor of Biomedical Engineering
  Dept. of Information Engineering
  University of Padova
  Padova, Italy

- **Andrea Facchinetti, PhD**
  Asst. Professor of Biomedical Engineering
  Dept. of Information Engineering
  University of Padova
  Padova, Italy

- **Jake Leach**
  Senior Vice President
  Research & Development
  Dexcom, Inc.

Clinical Utility of CGM-Based Treatment Decisions

Bruce Buckingham, MD

Professor of Pediatrics (Endocrinology)

The Lucile Salter Packard Children's Hospital

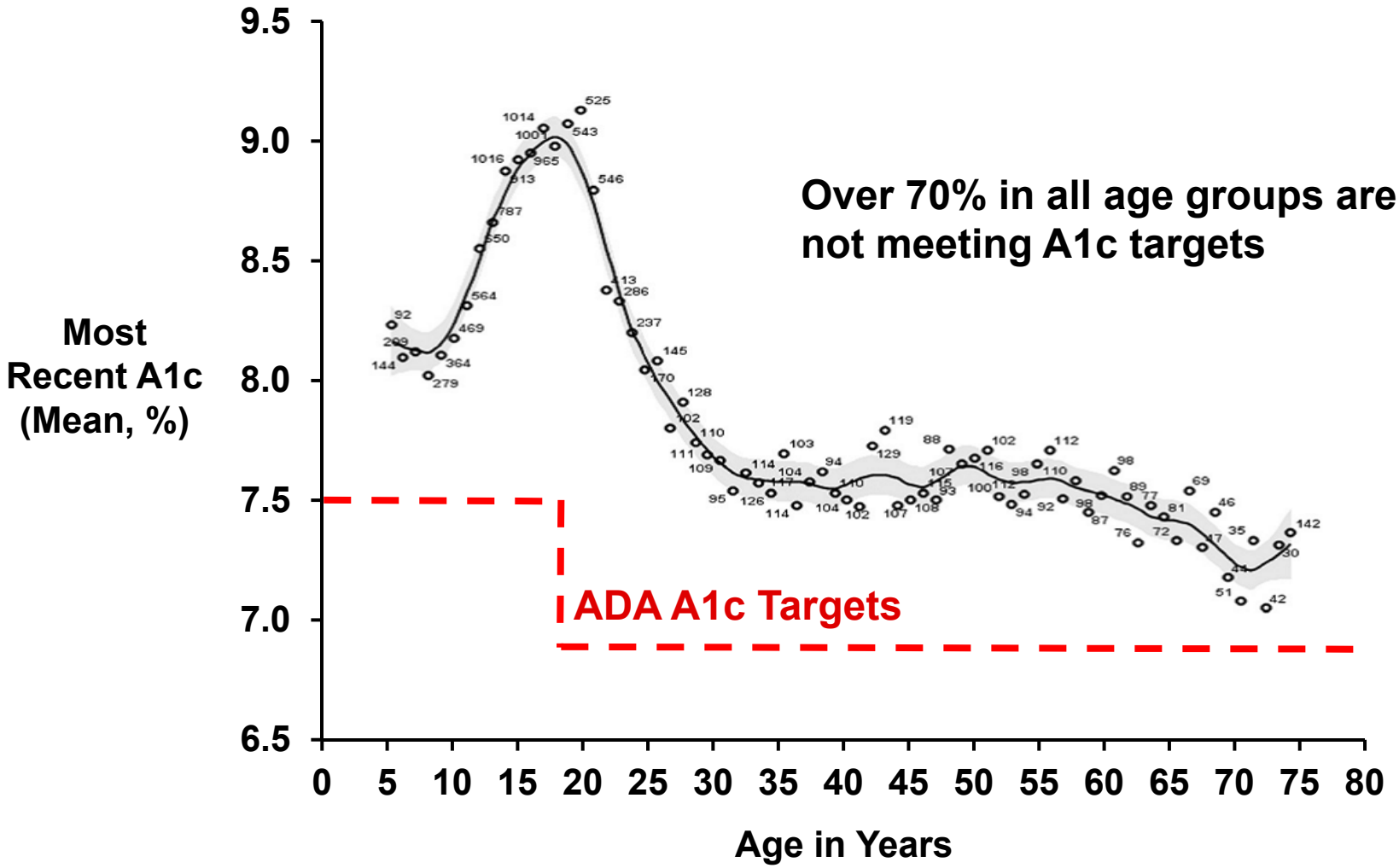
Stanford University

Patients Using Insulin Are at Risk for Hypoglycemia and Chronic Complications

- 3-4 million people with diabetes require insulin[1]
- Higher risk of hypoglycemia
- >10% of adults have severe hypoglycemia event annually[2]
  - Most severe hypoglycemia events occur at night or during sleep
  - SMBG testing is inadequate to prevent severe hypoglycemia

1. CDC (2012); 2. Miller et al., (2015)

Diabetes Remains Poorly Controlled



Miller et al., (2015)

Managing a Complex Disease with Imperfect Glucose Data

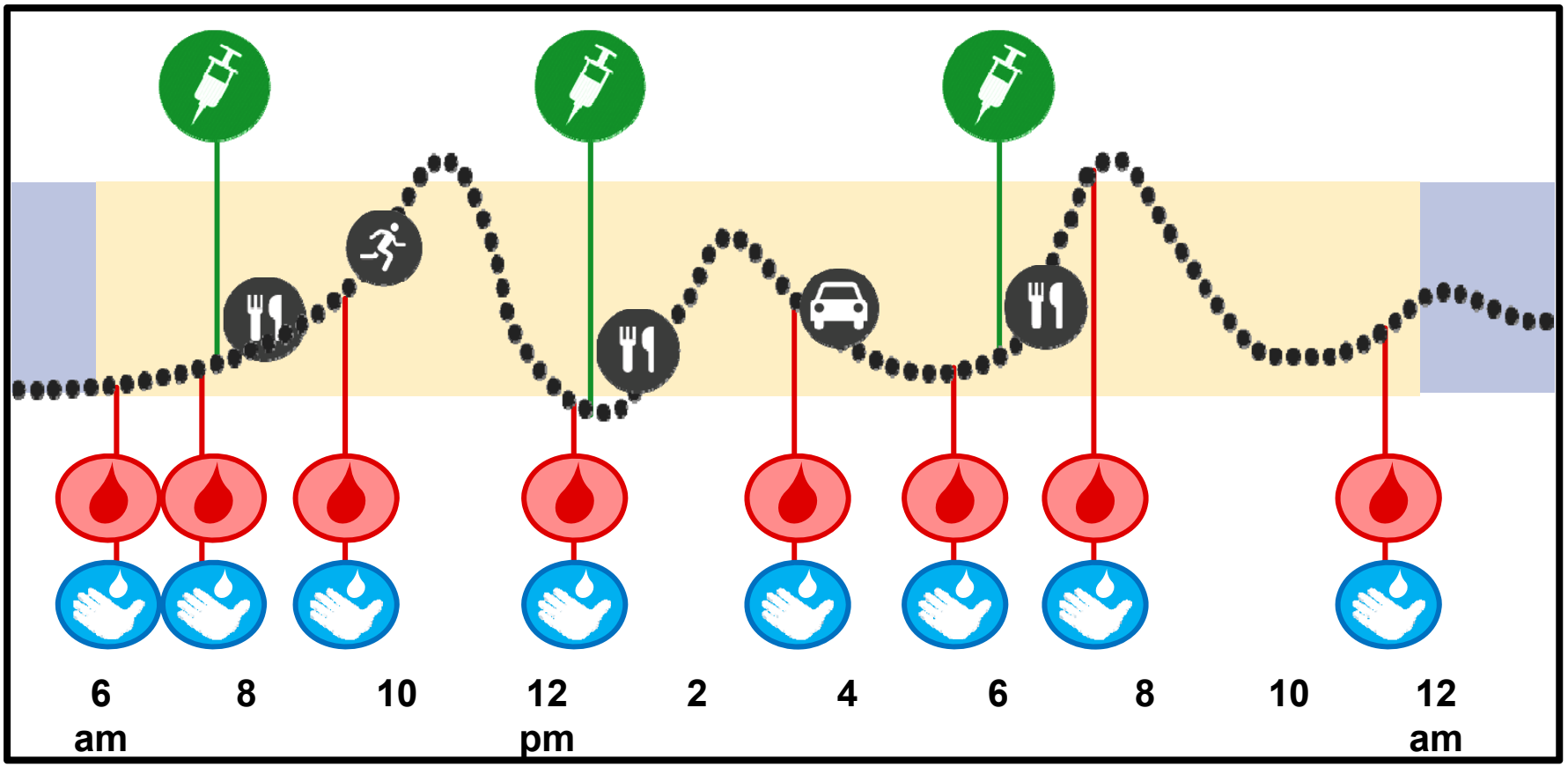
- SMBG may not always be accurate
- SMBG does not provide trend, rate of change or alert information
  - Particularly beneficial for ~20-25% with hypoglycemia unawareness

Freckmann et al., (2012); Geddes et al., (2008); Graveling et al., (2014)

Need to Increase Access to CGM

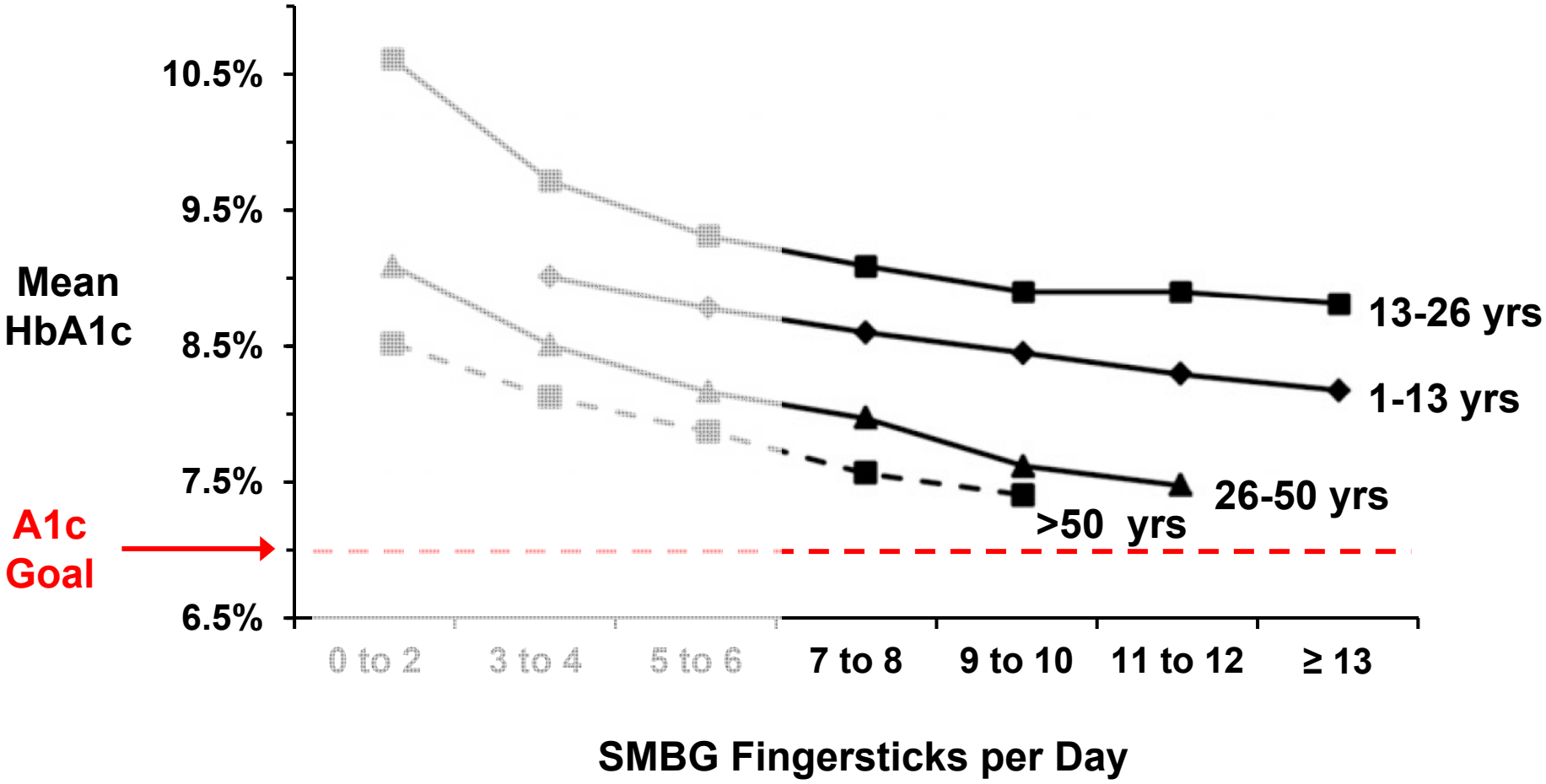
- CGM use improves treatment decisions
- CGM can reduce burden associated with fingersticks
  - Pain
  - Inconvenience
- CGM reduces inaccuracies associated with SMBG
- Many patients already using CGM for treatment decisions
- Changing label will improve access and allow for proper education and training

Clinical Decisions in Typical Day for SMBG Insulin User



- Before eating 3-6 times a day
- Before bedtime
- Before driving
- Before, during, and after exercise
- Feeling shaky, sweating or suspicious of hypoglycemia
- When sick

Even High Frequency Fingerstick Testing Does Not Lead to Sufficient HbA1c Control



Miller et al., (2013)

Many Patients Do Not Test as Recommended

Daily SMBG Tests	T1D Exchange N=16,061
0 to 3	34%
4 to 6	45%
7 to 9	15%
>9	5%

Miller et al., (2015)

Top 3 Reasons Patients Do Not Perform SMBG Test

Reason	Frequency N=932
Too painful	27%
Testing is slow and too much of a hassle	42%
Attracts too much attention from other people	18%

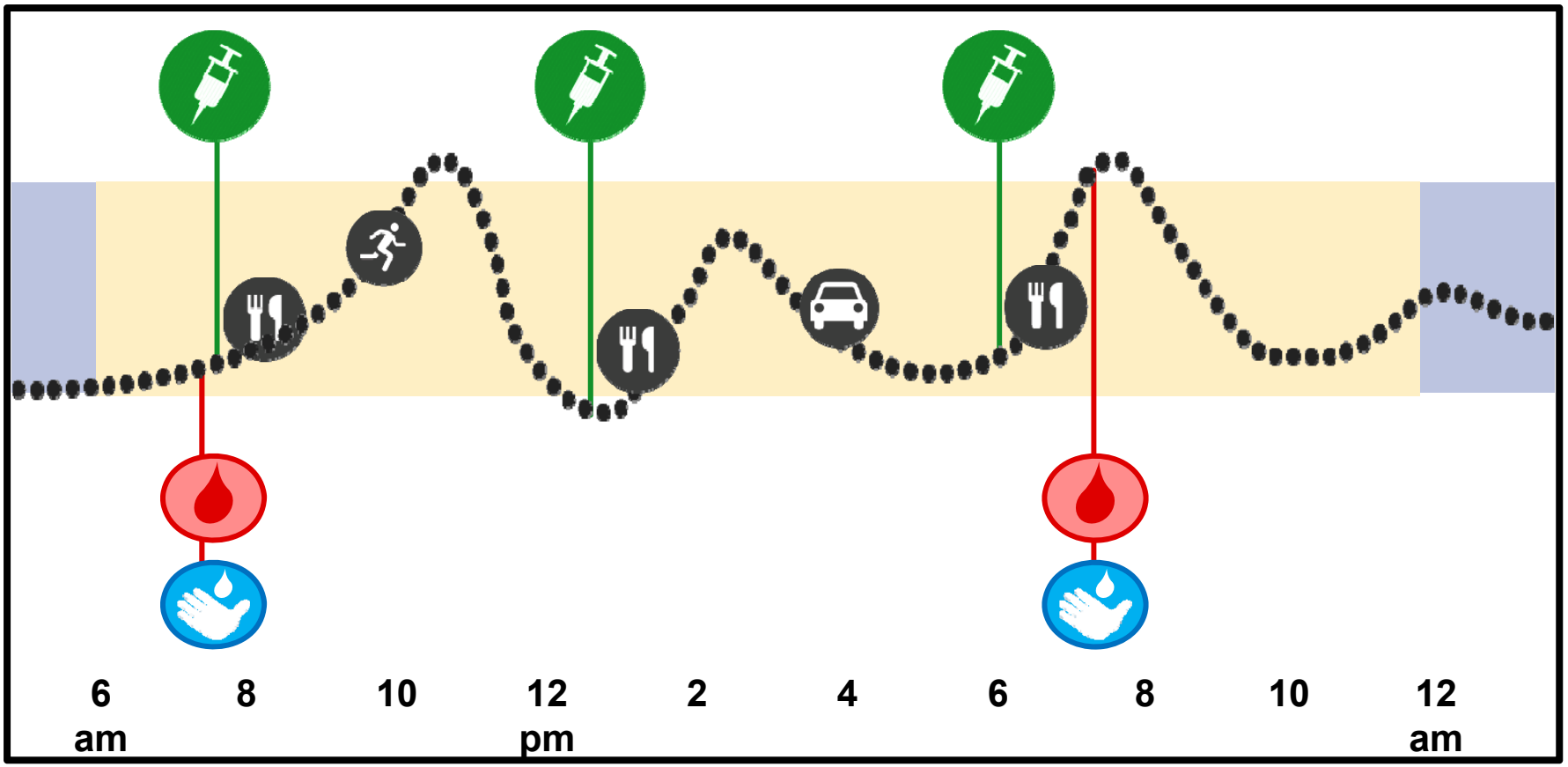
Data extrapolated from dQ&A (2014)

Skin Contaminants Reduce Meter Accuracy

Exposure	Washed Hands (median)	Exposed Finger No Washing (median)
Peeling an orange	98 mg/dL	171 mg/dL
Peeling a grape	93 mg/dL	360 mg/dL

Hirose et al., (2011)

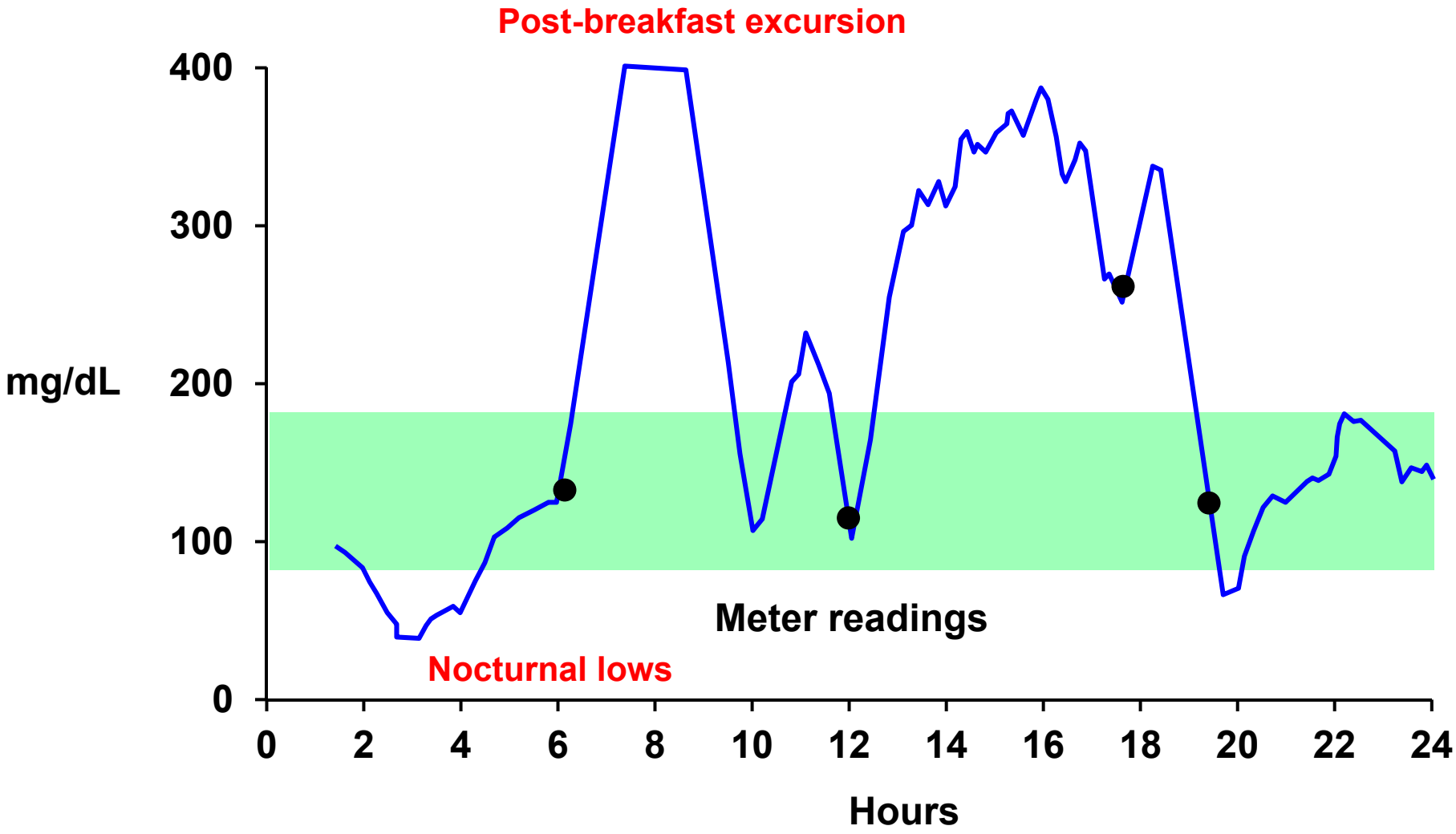
Significant Reduction in Fingersticks With CGM-Based Treatment Decisions



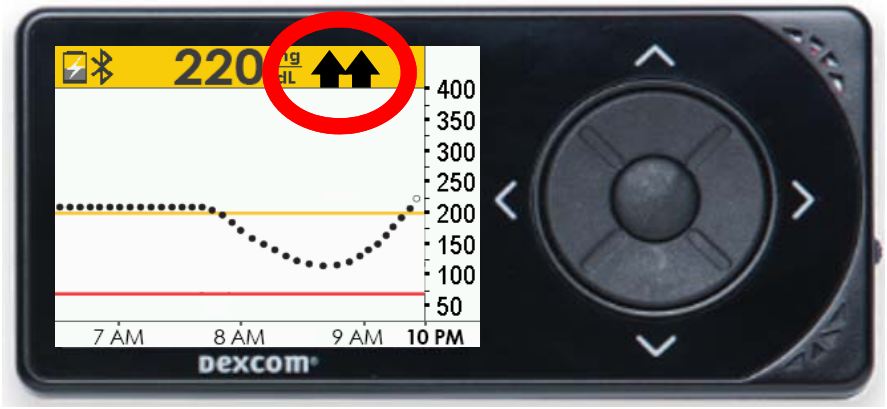
- Fingerstick to calibrate or when symptoms don't match CGM readings
- Patients look at their CGM display ~30 times/day*

*** New et al., (2015); Nakamura et al., ADA (2016)**

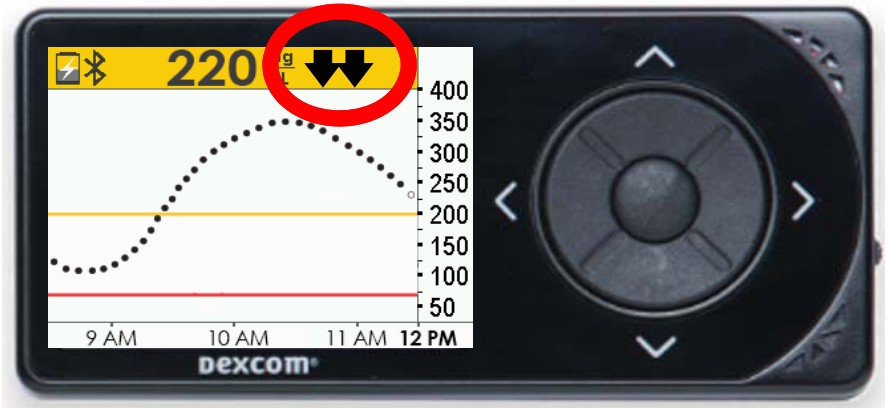
Intermittent Monitoring is Not Enough



CGM Allows Better Informed Treatment Decisions



Take a larger than usual dose



No insulin and maybe eat carbs

Pettus et al., (2015)

Use of Trend Arrows to Prevent Hypoglycemia

- About to begin 40 minute drive home
- In 30 minutes, glucose could be 18 mg/dL
  - Eat food to treat

Clinical Studies Using G5 Software: System Performance and Accuracy

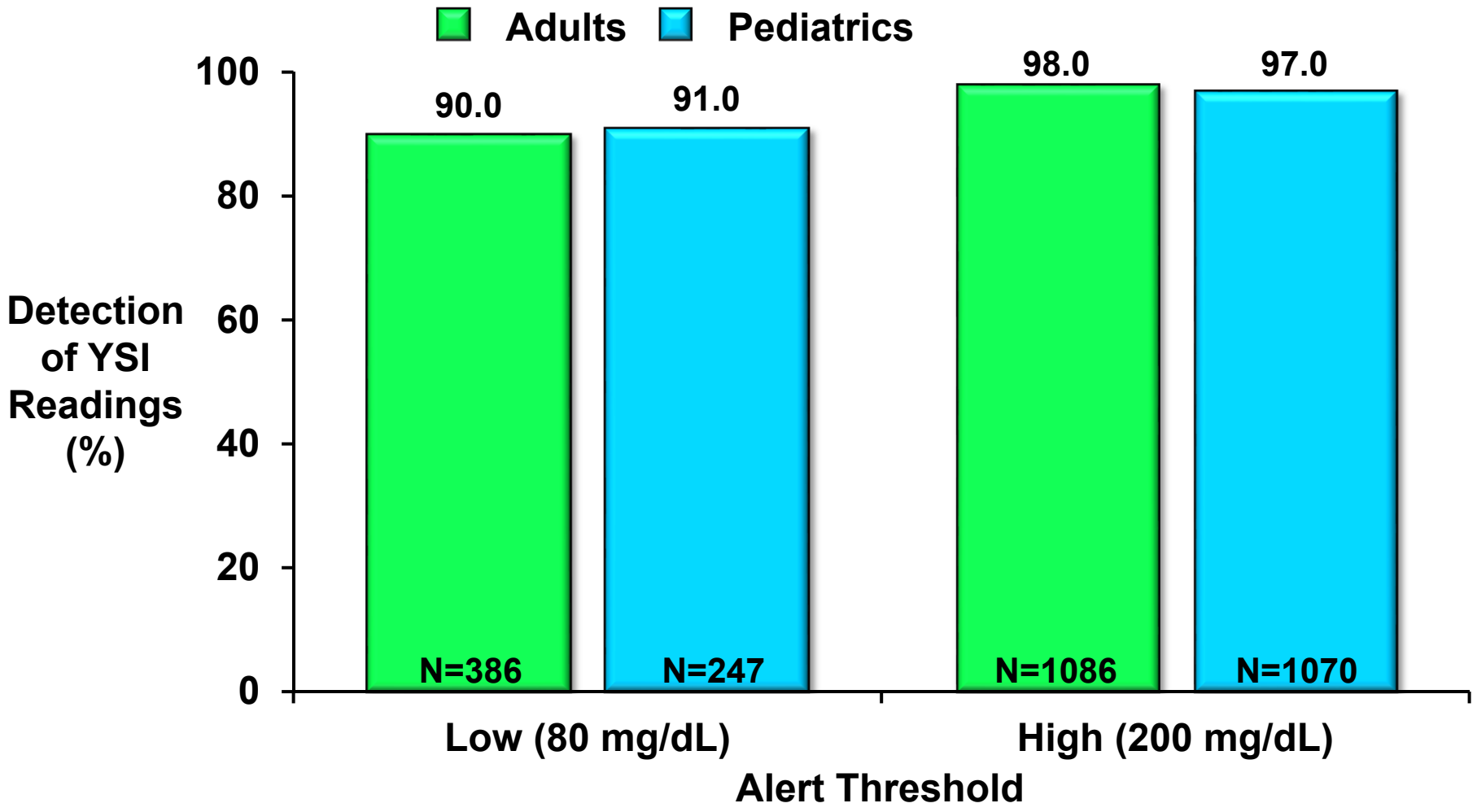
- Two studies:
  - Adults: ≥ 18 years
  - Pediatrics: 2 to 17 years
- Each subject wore 1 sensor
- Clinic glucose tracking study

Accuracy Similar between Adult and Pediatric Patients

Performance Parameters	Adults CGM vs. YSI N=50	Pediatrics CGM vs. YSI N=59
Temporally matched pairs	2,263	2,262
MARD %	9%	10%
%20/20	93%	91%
MAD (mg/dL) in hypoglycemia range (≤ 70 mg/dL)	6.4	10.7

YSI = laboratory glucose reference standard (YSI Incorporated, Yellow Springs, OH)
Laffel et al., (2016); Bailey et al., (2015)

Effective Alert Performance: Within 15 Minutes of YSI ≤ 80 or ≥ 200 mg/dL



Percentage of true YSI events captured by sensor

Benefits of CGM Use Demonstrated in Randomized Controlled Trials

- RCTs compared CGM with SMBG
- CGM use improves outcomes
  - Reduction of A1C
  - Reduction or no increase in hypoglycemia
- CGM informs better decisions
- Studies performed in diverse populations

JDRF, (2008, 2009); Hermanides et al., (2011); Berganstal et al., (2011); Vigersky et al., (2012); Battelino et al., (2012)

DiaMonD Study Further Demonstrates CGM Improves Outcomes

- Randomized controlled trial comparing adjunctive CGM to SMBG alone (n=157)
- CGM use:
  - Reduced HbA1c from 8.6% to 7.7%
  - Reduced hypoglycemia from 76 to 53 min/day
  - Reduced fingersticks from 5.1 to 3.6 tests/day

Results presented at ADA 2016

Updated Label Would Support Increased Access

- Currently, 16% of patients with T1D use CGM
- Elderly patients have high risk for hypoglycemia
- CGM not eligible for coverage due to adjunctive label
- Non-adjunctive label may make CGM eligible for coverage in vulnerable population

Summary

- State of diabetes care in US is suboptimal
- Dexcom CGM is accurate
- CGM use improves treatment decisions
- Many patients already using CGM for treatment decisions
- Changing label will improve access and allow for proper education and training

Simulation Studies

David Price, MD

Vice President

Medical Affairs

Dexcom, Inc.

Benefits of Simulations

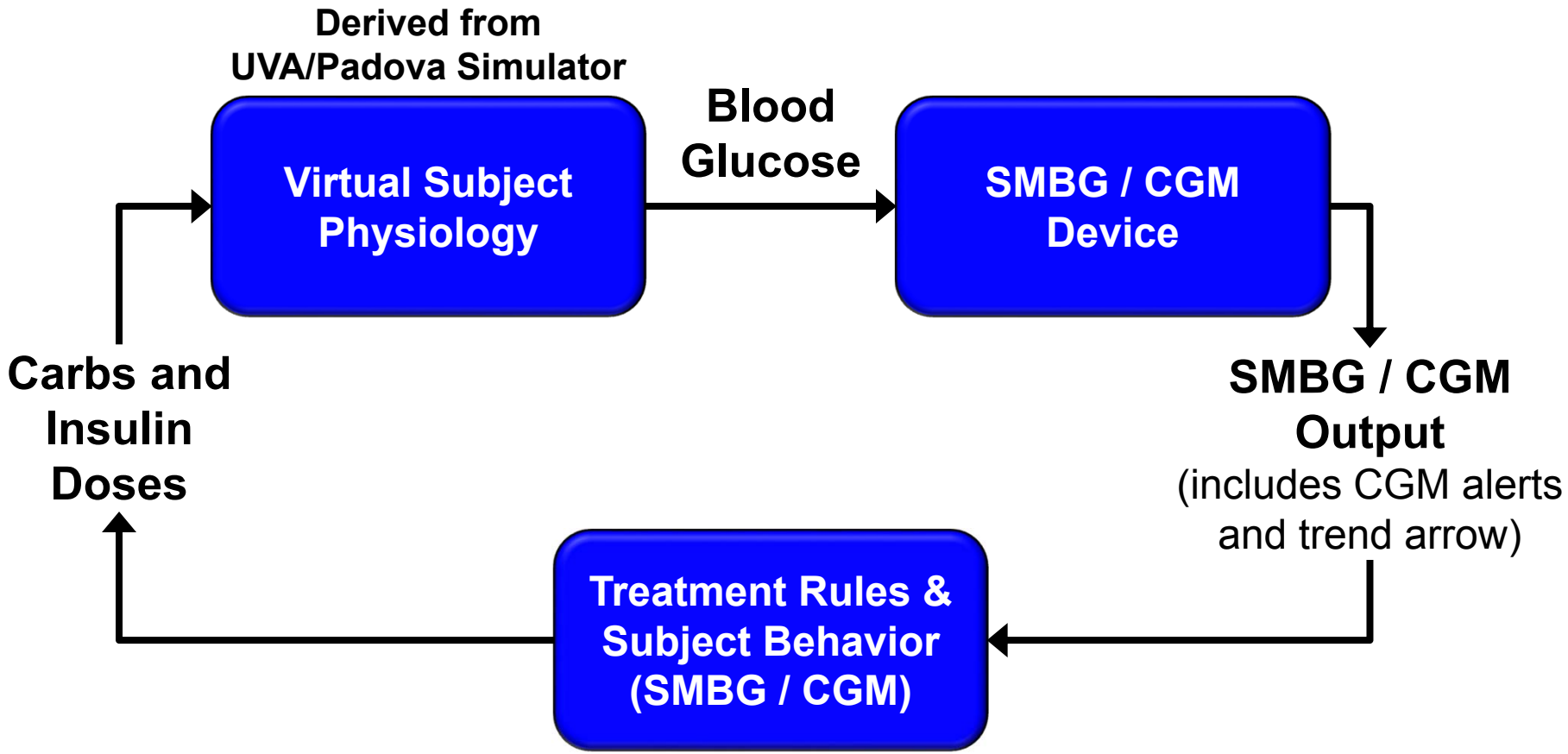
- Virtual subjects act as their own control
- Allow isolation and evaluation of key variables that may influence risk
  - Can test variable extremes
- Virtual subjects can be treated more aggressively
- High risk populations can be simulated
- Allow clear separation between CGM- and SMBG-based decisions

Two Simulations Using Different Models Were Conducted

1. **Two-Week Simulation Study**
   - Uses validated physiological model
   - Evaluates typical conditions
2. **Meal Dosing Simulation Study**
   - Single-meal dose simulation
   - Isolating individual conditions and behaviors
   - Evaluates more extreme conditions

Two-Week Simulation Study

Simulation Components

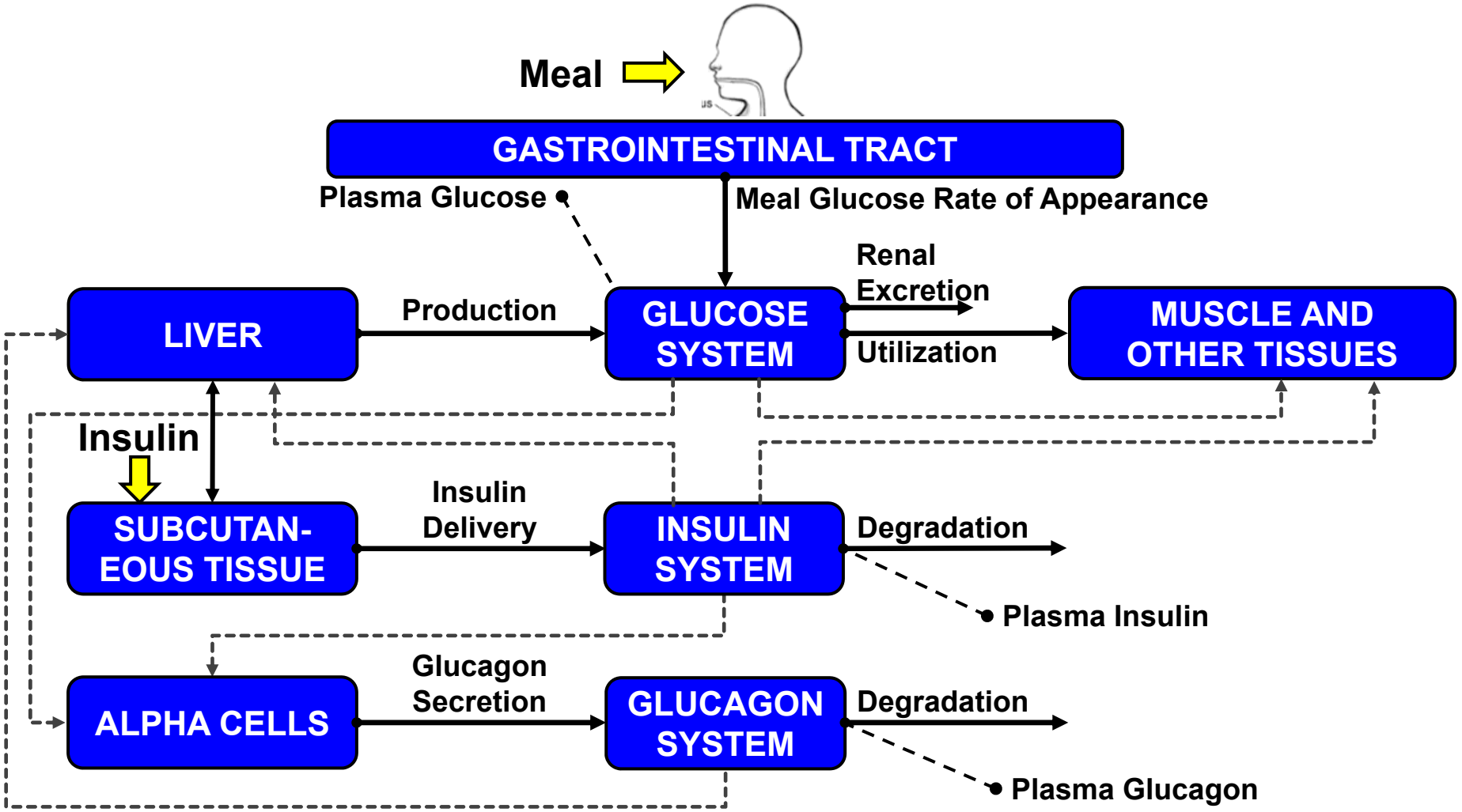


UVA/Padova T1D Simulator

- Developed and validated using clinical data on meal response
  - Development: healthy subjects (N=204)
  - Validation: Type 1 subjects (N=71)
- First accepted by FDA in 2008 (updated in 2013)
  - As substitute to preclinical trials
- Adopted by JDRF Artificial Pancreas Consortium
- Supported 18 IDE approvals
- Cited in 1,030 publications
- Used by 32 academic research groups

Basu et al., (2006); Kovatchev et al., (2009); Visentin et al., (2014, 2015 and 2016); Dalla Man et al., (2007 and 2013); Hinshaw et al., (2013)

UVA/Padova Type 1 Diabetes Simulator



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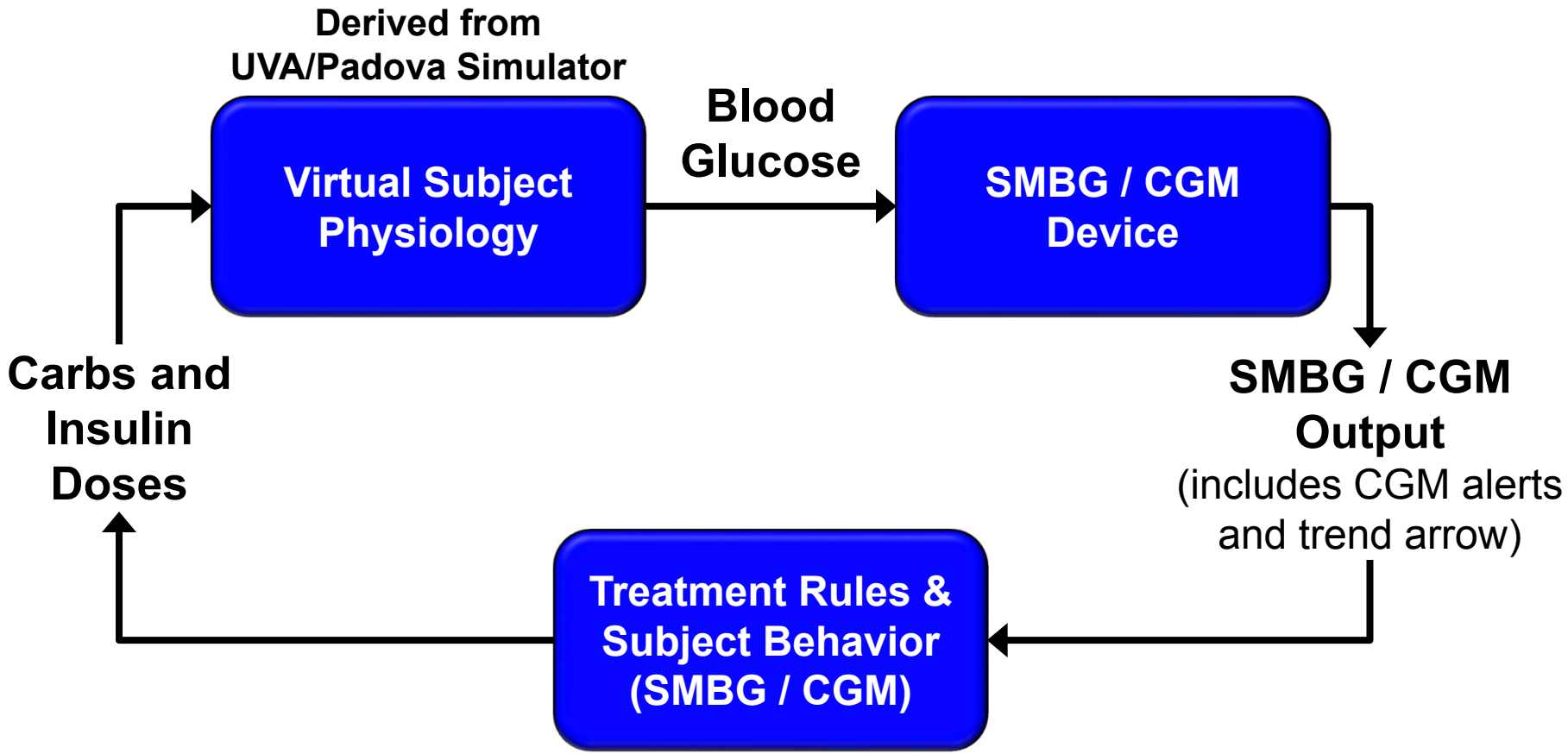


Facchinetti et al., (2014); Vettoretti et al., (2015)

Treatment Rules

SMBG-based Treatment	CGM-based Treatment
• Standard meal dose • Correction bolus if routine check reveals hyperglycemia • Hypotreatments in response to symptoms or if routine check reveals low glucose	• Standard meal dose • Correction bolus in response to high alerts • Hypotreatments in response to low alerts/alarms and symptoms • All doses are corrected for CGM trend arrow according to published guideline*

Assumptions:

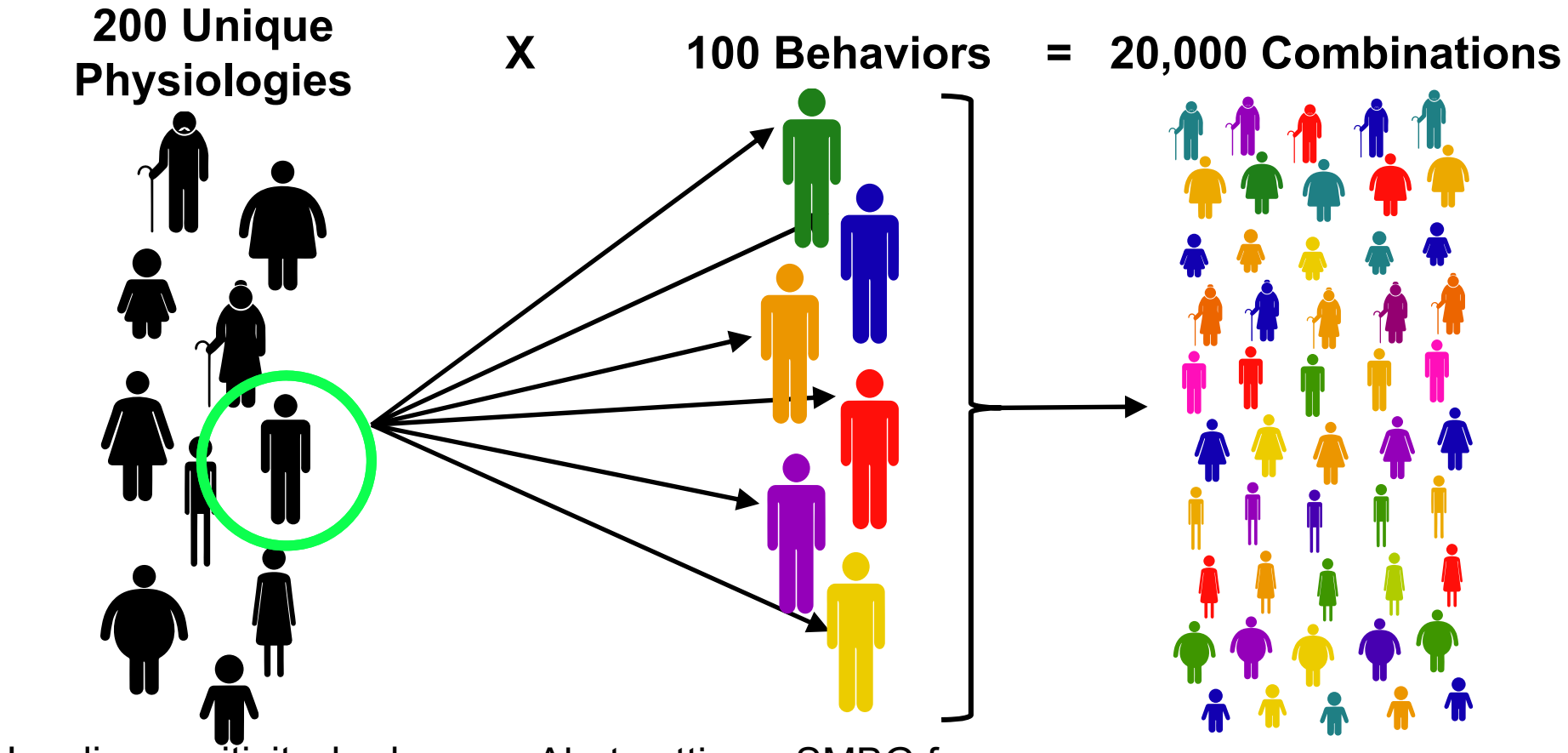
- No insulin boluses within 2 hours since last bolus
- No delay in response to hypoglycemia symptoms or alerts

* Scheiner, (2015)

Simulation Parameters

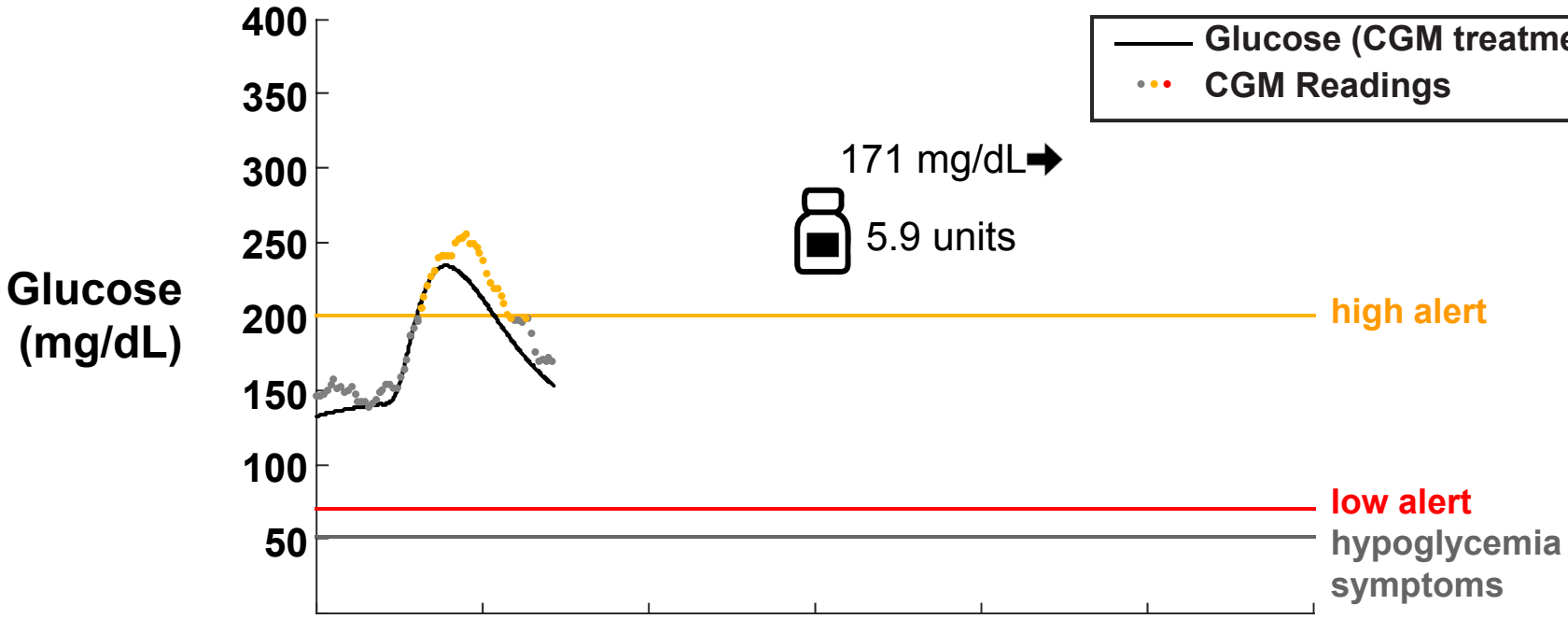
Physiology	Subject Behavior
36 physiological parameters, including: • Body weight • Insulin sensitivity • Basal glucose • Time constant of plasma-interstitial glucose kinetics Derived therapy parameters: • Insulin-to-carbohydrate ratio • Correction factor	• Frequency of SMBG testing • CGM low alert setting • CGM high alert setting • Threshold of hypoglycemia recognition • Carbohydrate counting errors • Meal sizes and times

40,000 Unique Adult and Pediatric Combinations Generated



Additional 20,000 for impaired hypoawareness

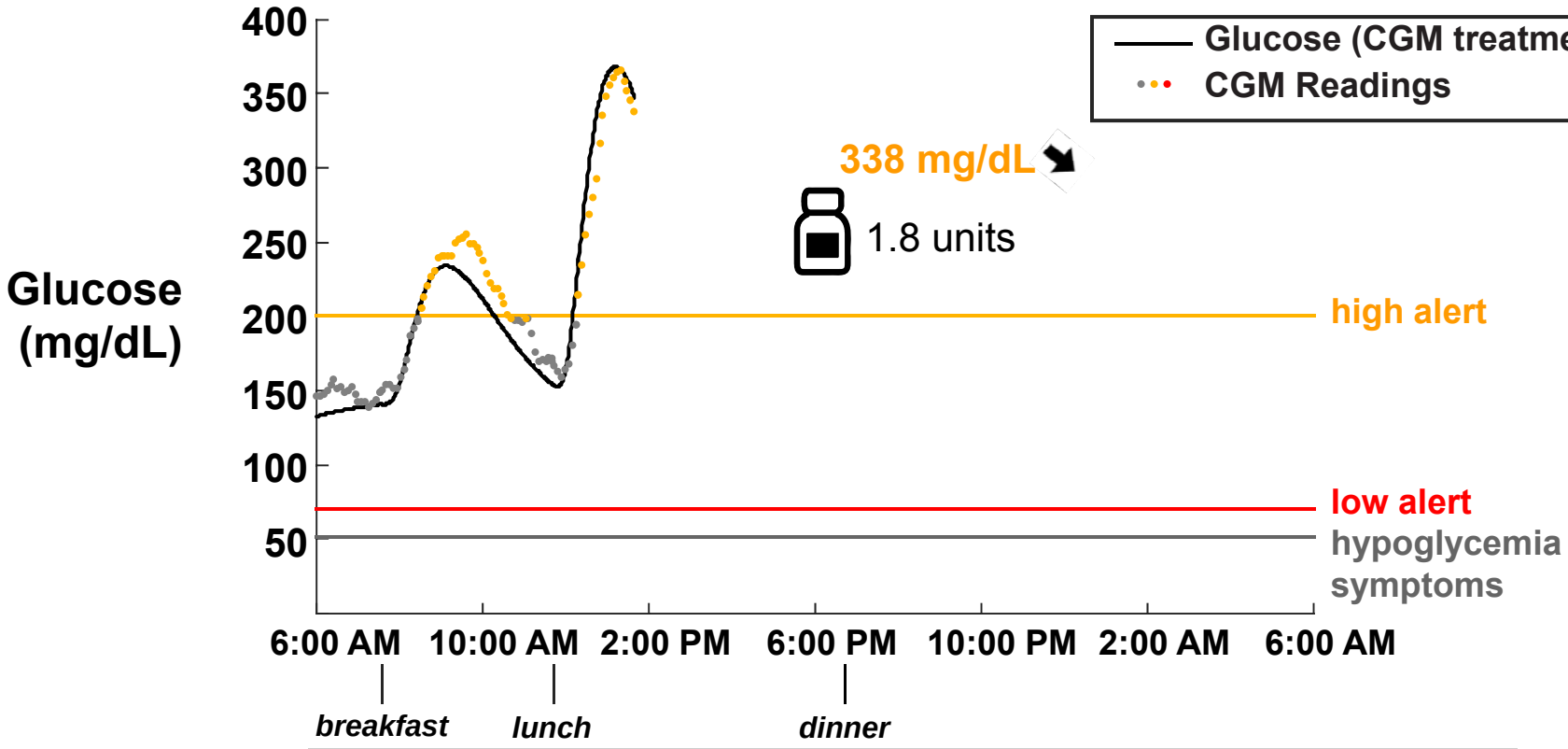
Simulated Day of CGM-Based Treatment



breakfast	*lunch*	*dinner*	
7:34 AM	11:41 AM	6:43 PM	meal time
40 grams	100 grams	99 grams	actual carbohydrate content
46 grams	88 grams	137 grams	estimated carbohydrate content

Insulin sensitivity factor: 55 mg/dL/unit; **Insulin-to-carb. ratio:** 15 grams/unit; **Hypoglycemia symptom threshold:** 51 mg/dL

Simulated Day of CGM-Based Treatment



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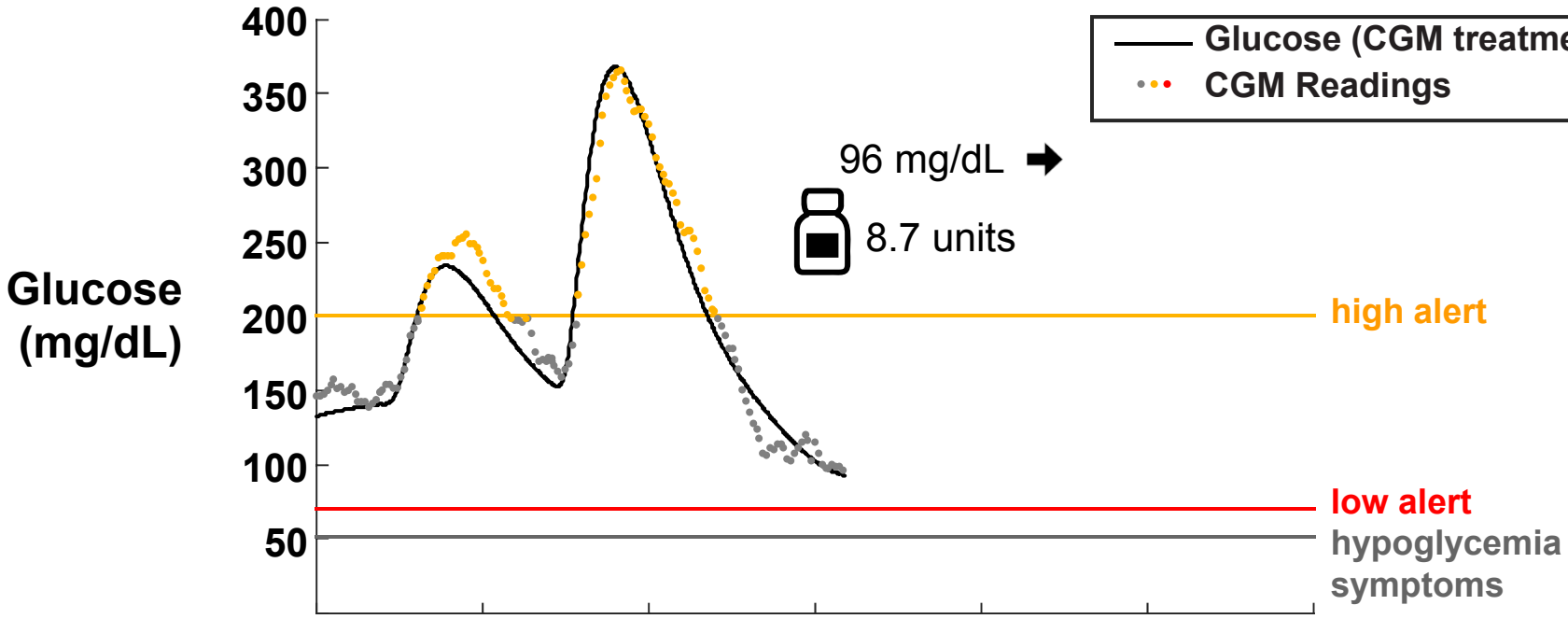

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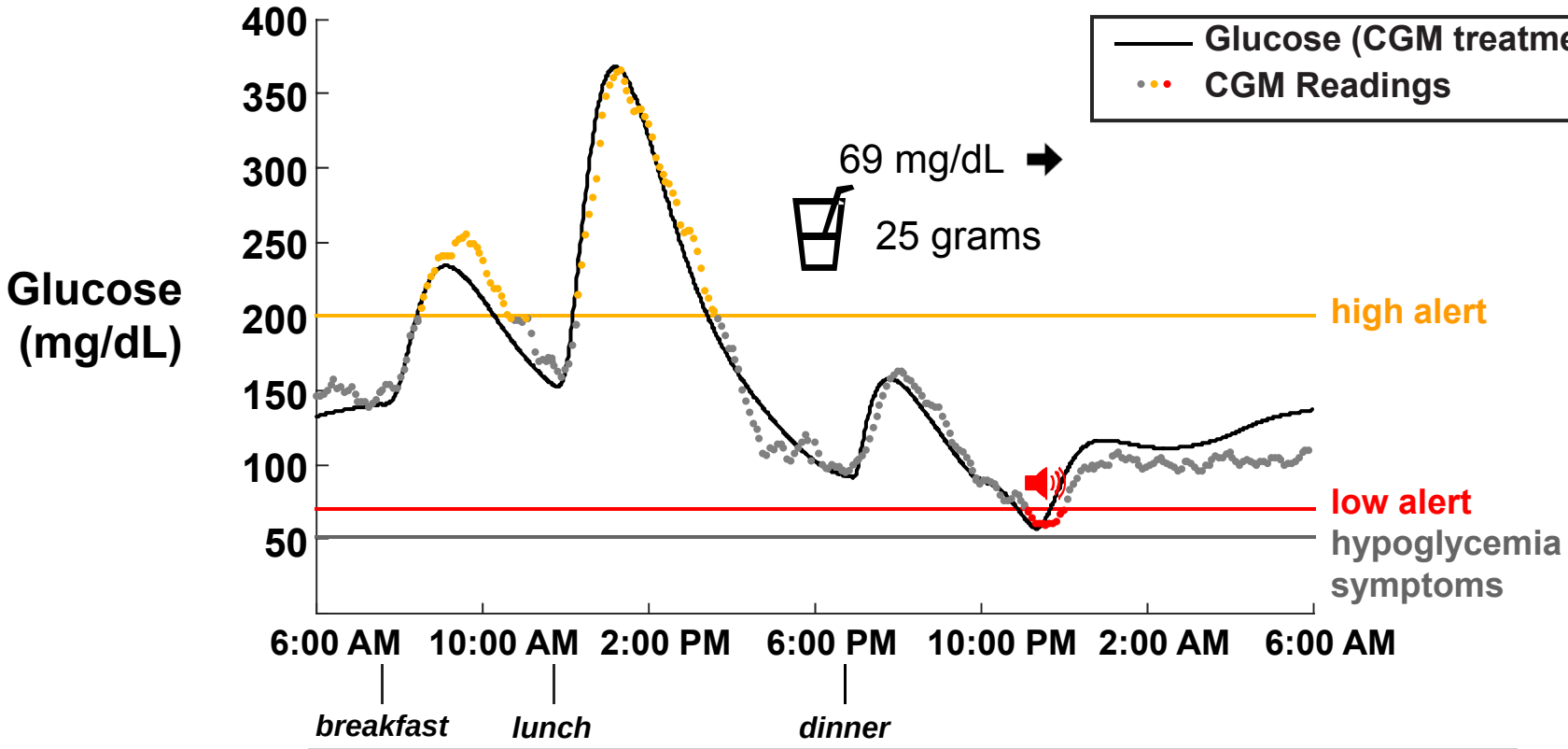

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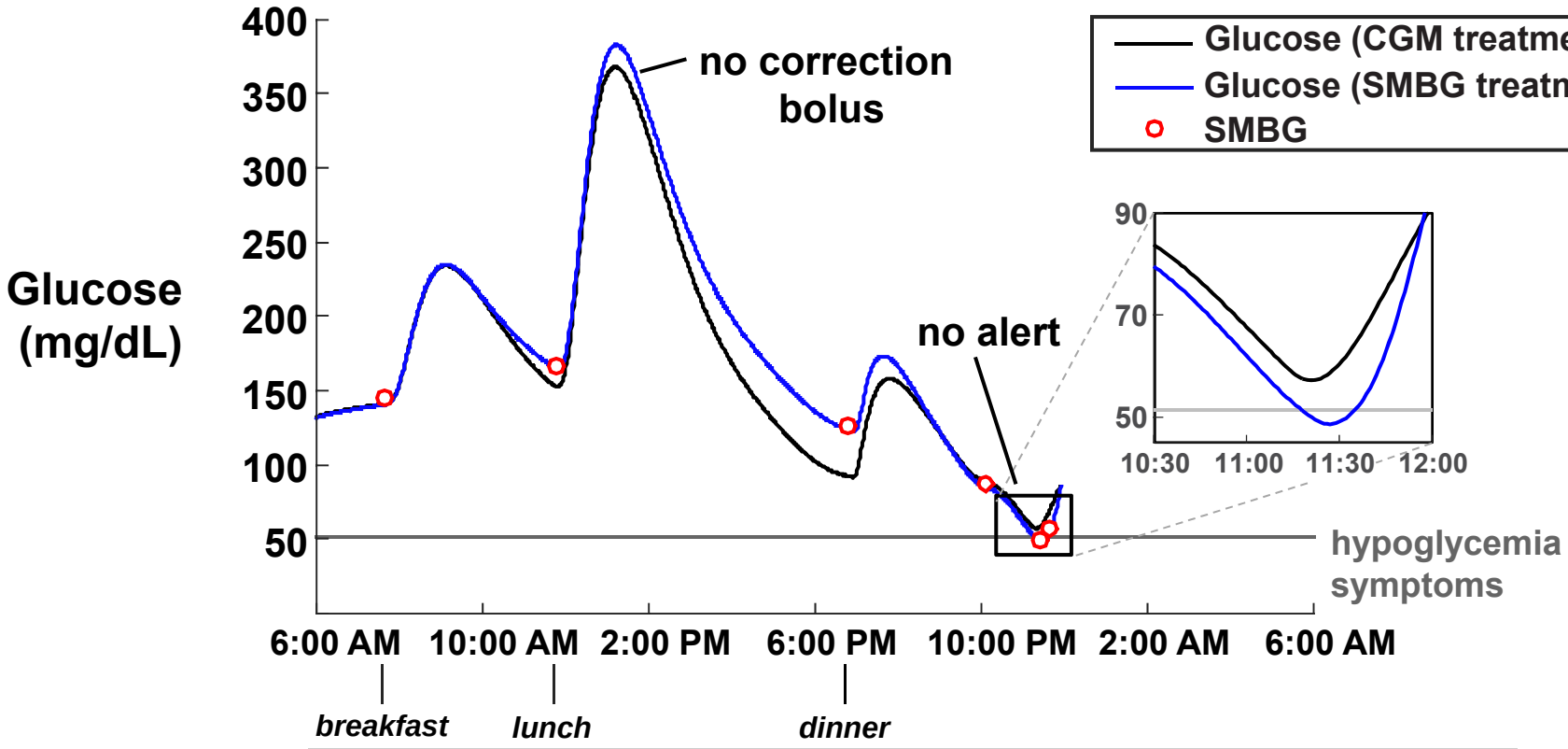
Simulated Day of SMBG-Based Treatment



7:34 AM	11:41 AM	6:43 PM	meal time
40 grams	100 grams	99 grams	actual carbohydrate content
46 grams	88 grams	137 grams	estimated carbohydrate content

A Priori Research Question

Are glycemic metrics obtained when basing treatment decisions on CGM **equivalent to** or **better than** metrics obtained when basing treatment decisions on SMBG?

Pre-specified endpoints:

- Daily time below 50 mg/dL
- Daily time above 250 mg/dL

Derived endpoints:

- Event rate and average duration of low glucose events (below 50 mg/dL)

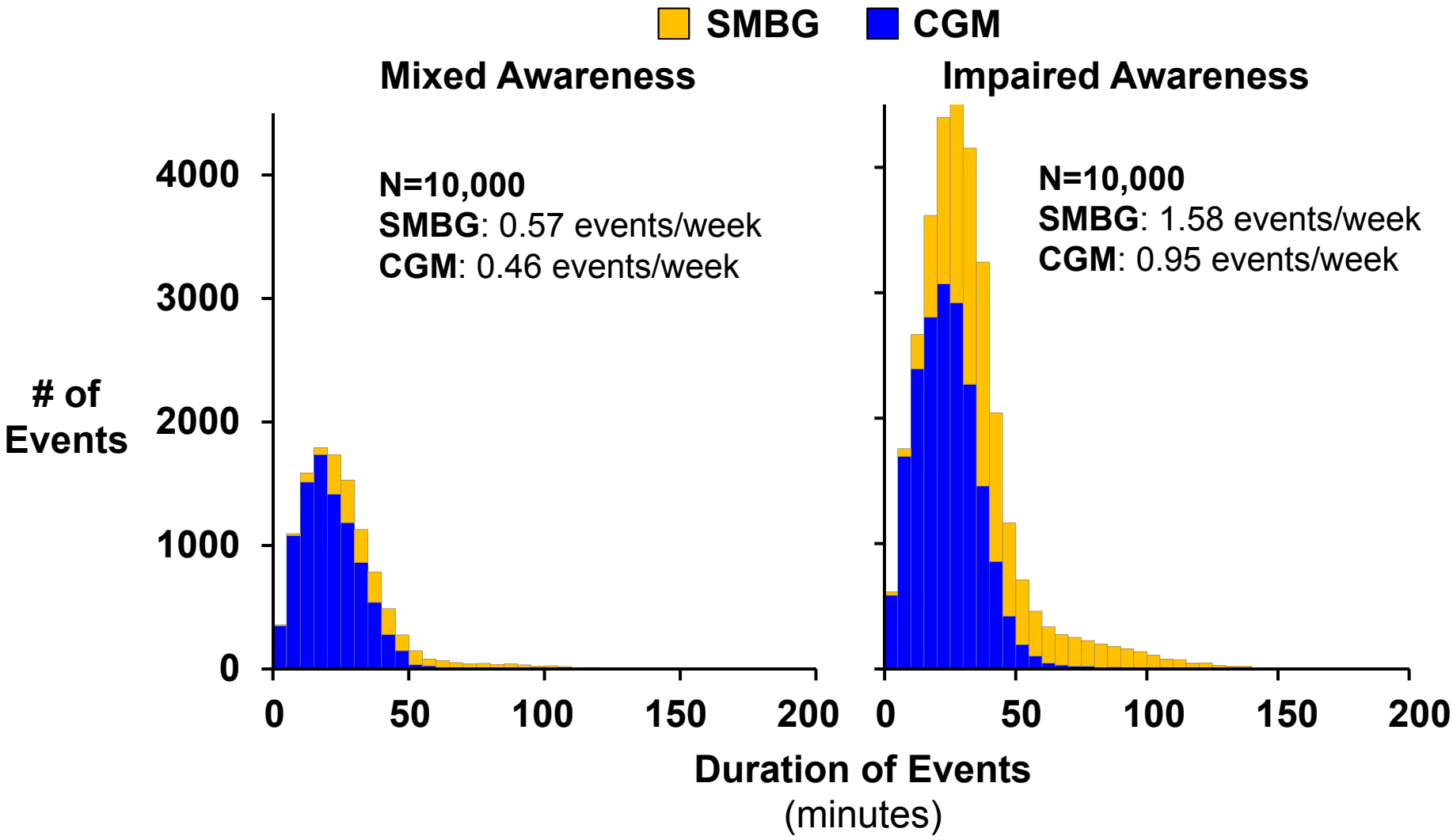
Results in Adults

Metric [min/day]	SMBG Median [1Q, 3Q]	CGM Median [1Q, 3Q]	Difference (CGM - SMBG)
Mixed Hypoglycemia Awareness			
Time below 50 mg/dl	**0.0** [0.0-1.8]	**0.0** [0.0-1.4]	**0.0**
Time above 250 mg/dl	**125.6** [62.6-211.8]	**119.1** [59.7-197.9]	**-6.5**
Impaired Hypoglycemia Awareness			
Time below 50 mg/dl	**3.9** [0.0-10.3]	**1.4** [0.0-4.6]	**-2.5**
Time above 250 mg/dl	**125.2** [62.3 – 212.1]	**118.2** [59.7 – 198.2]	**-7.0**

Results in Pediatrics

Metric [min/day]	SMBG Median [1Q, 3Q]	CGM Median [1Q, 3Q]	Difference (CGM - SMBG)
Mixed Hypoglycemia Awareness			
Time below 50 mg/dl	**0.0** [0.0-0.0]	**0.0** [0.0-0.3]	**0.00**
Time above 250 mg/dl	**212.6** [116.9-330.8]	**200.2** [112.4-309.6]	**-12.4**
Impaired Hypoglycemia Awareness			
Time below 50 mg/dl	**1.4** [0.0-4.9]	**0.0** [0.0-2.1]	**-1.4**
Time above 250 mg/dl	**212.1** [116.3-329.6]	**200.6** [112.7-409.3]	**-11.5**

Number and Duration of Events Below 50 mg/dL Reduced by CGM (Adults)



Meal Dose Simulations

Single-Meal Dosing Simulation Method

- Simulated 50,000 subjects with hypoglycemia unawareness, one meal per subject
- Inputs included meal size, insulin sensitivity and insulin-to-carbohydrate ratio
- Basic model of physiology, focused on meal dosing and post-meal glucose
- Rising and falling pre-meal glucose were modeled
- Same meal modeled with SMBG- and CGM-based doses (with alerts)
- **Endpoint**: % of meals with hypoglycemia defined as glucose below 70 mg/dL

Meal-Time Simulation Assumptions

- Doses determined from standard bolus equation (with trend adjustment for CGM)
- Dose error causes proportional deviation from target glucose, based on device measurement errors, carb-counting errors, and insulin sensitivity
- No spontaneous post-meal glucose values
- No high glucose alerts
- No hypoglycemia awareness
- CGM and SMBG performance derived from clinical data

DirecNet Study Group, (2008)

Factors Evaluated in Meal Dosing Simulation

Category	Factor
Patient Physiology	• Insulin sensitivity (ISF and ICR) • Relationship between ISF and ICR • Errors in insulin sensitivity estimation
User Behavior	• Carbohydrate-counting error • Alert threshold • Erroneous compensation for pre-meal rate of change • Target glucose • Meal size • Calibration frequency
SMBG Performance	• SMBG precision • Systematic SMBG bias • Inaccurate calibration of CGM
Miscellaneous	• Adult vs. pediatric CGM performance • Pre-meal glucose level • Day of CGM wear

ISF: Insulin sensitivity factor
ICR: Insulin-to-carbohydrate ratio

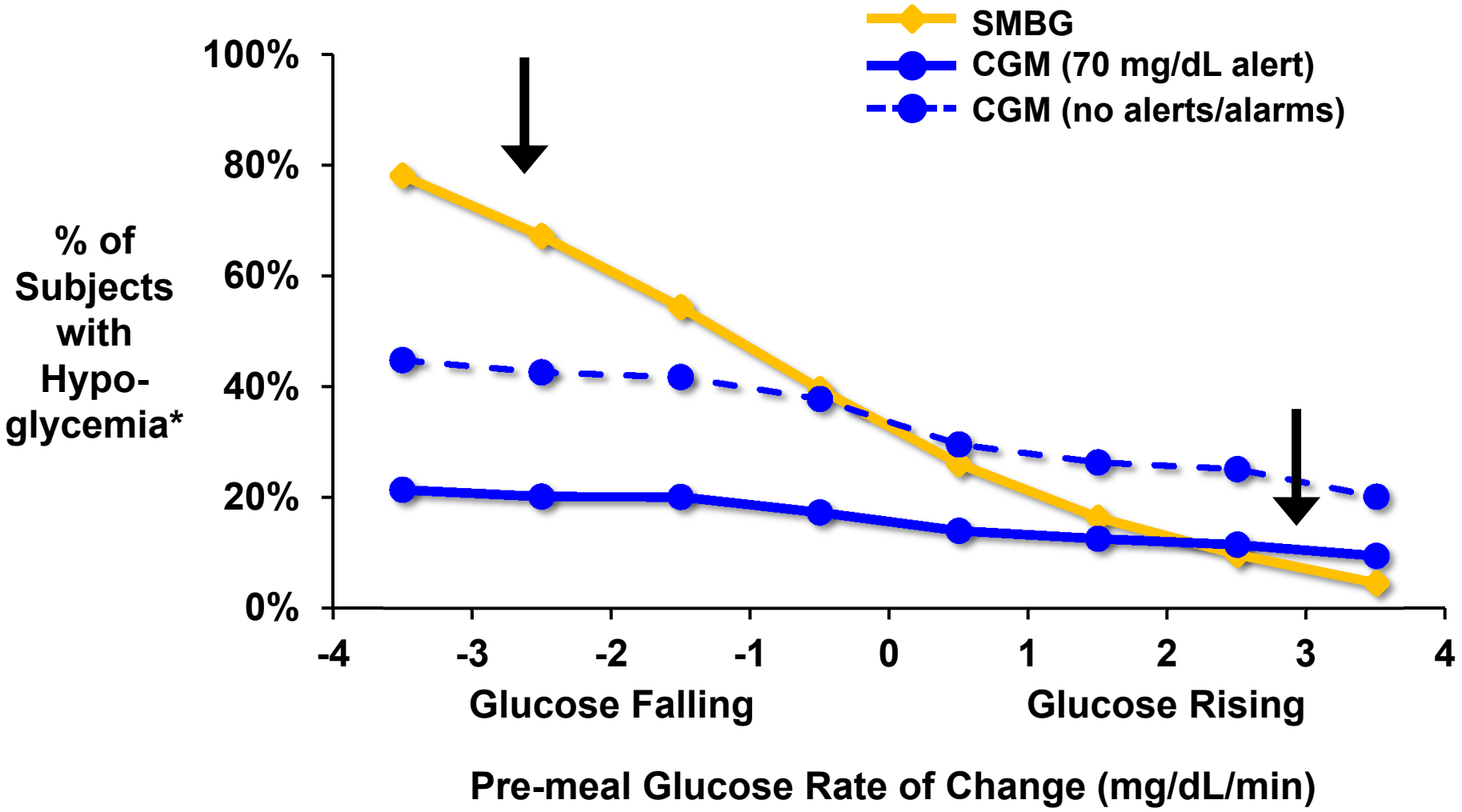
Examples of Tested Conditions

- Hypoglycemia alert setting
  - 55 mg/dL vs. 80 mg/dL
- Target glucose
  - 80 mg/dL vs. 120 mg/dL
- Calibration frequency
  - 4 times/day vs. once every two days
- Trend adjustments
  - No adjustment vs. over-adjustment
- Carb counting error
  - No error vs. large error

Overview: Meal Dosing Simulation Results

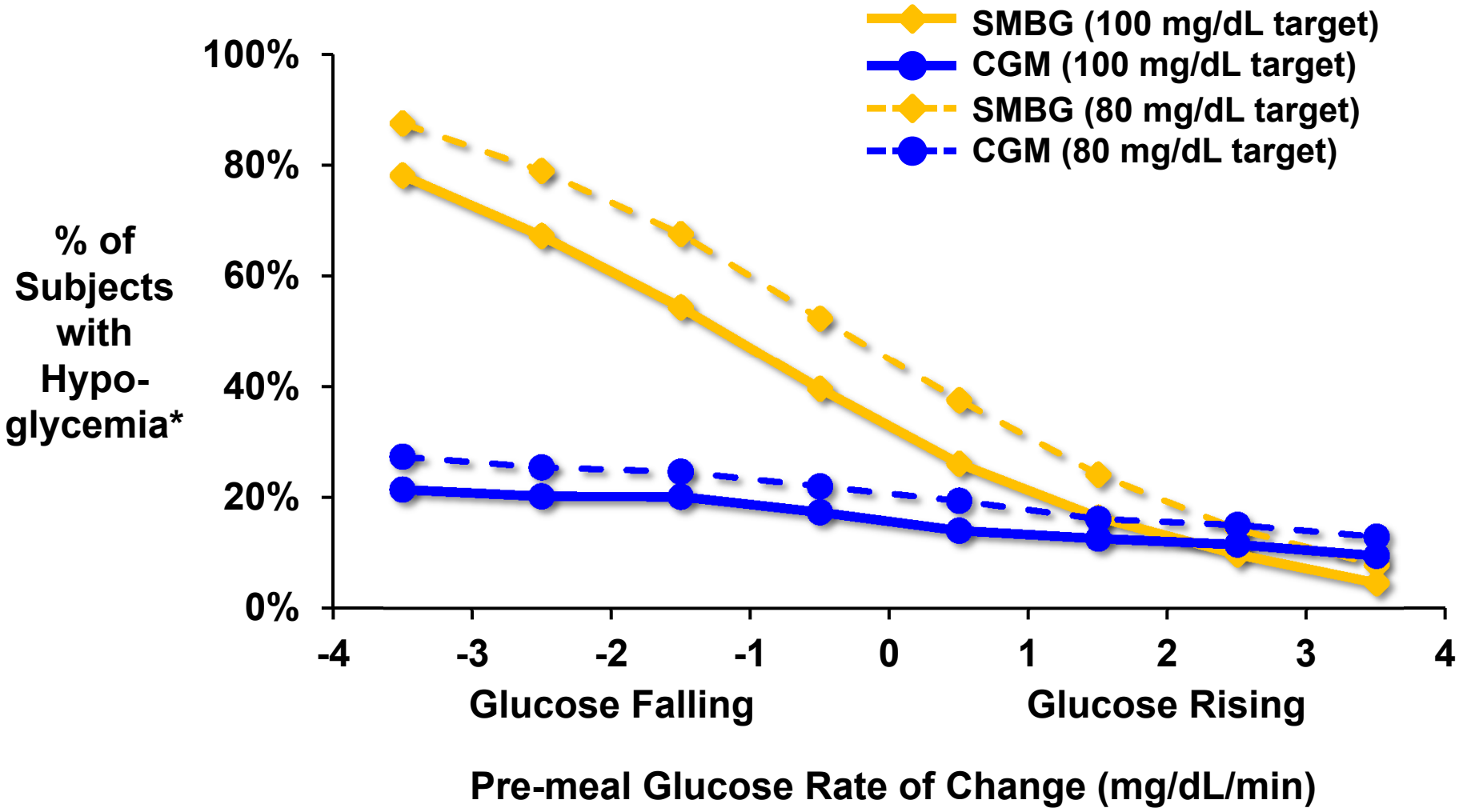
- Most factors did not elevate risk or increased risk similarly with CGM vs. SMBG
  - Lower target glucose
  - Higher errors in estimating
    - Carbohydrates
    - Insulin sensitivity
- 3 factors increased risk with CGM dosing
  - Setting excessively low alert threshold
  - Making inappropriate trend adjustments
  - Calibrating less than once a day

Risk of Hypoglycemia with CGM-Based vs. SMBG-Based Dosing



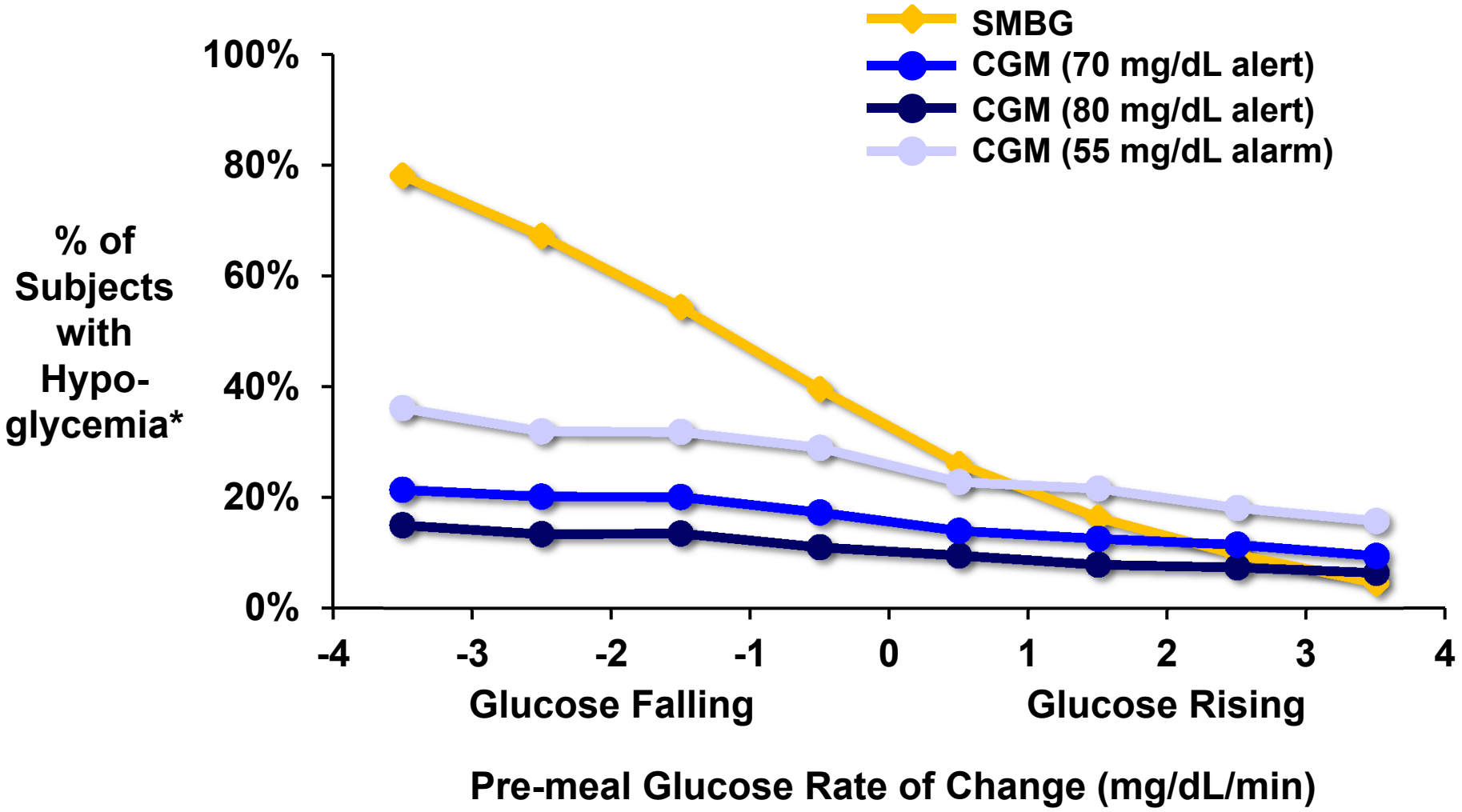
* Glucose below 70 mg/dL

Lowering Target Glucose Results in Comparable Increase in Risk



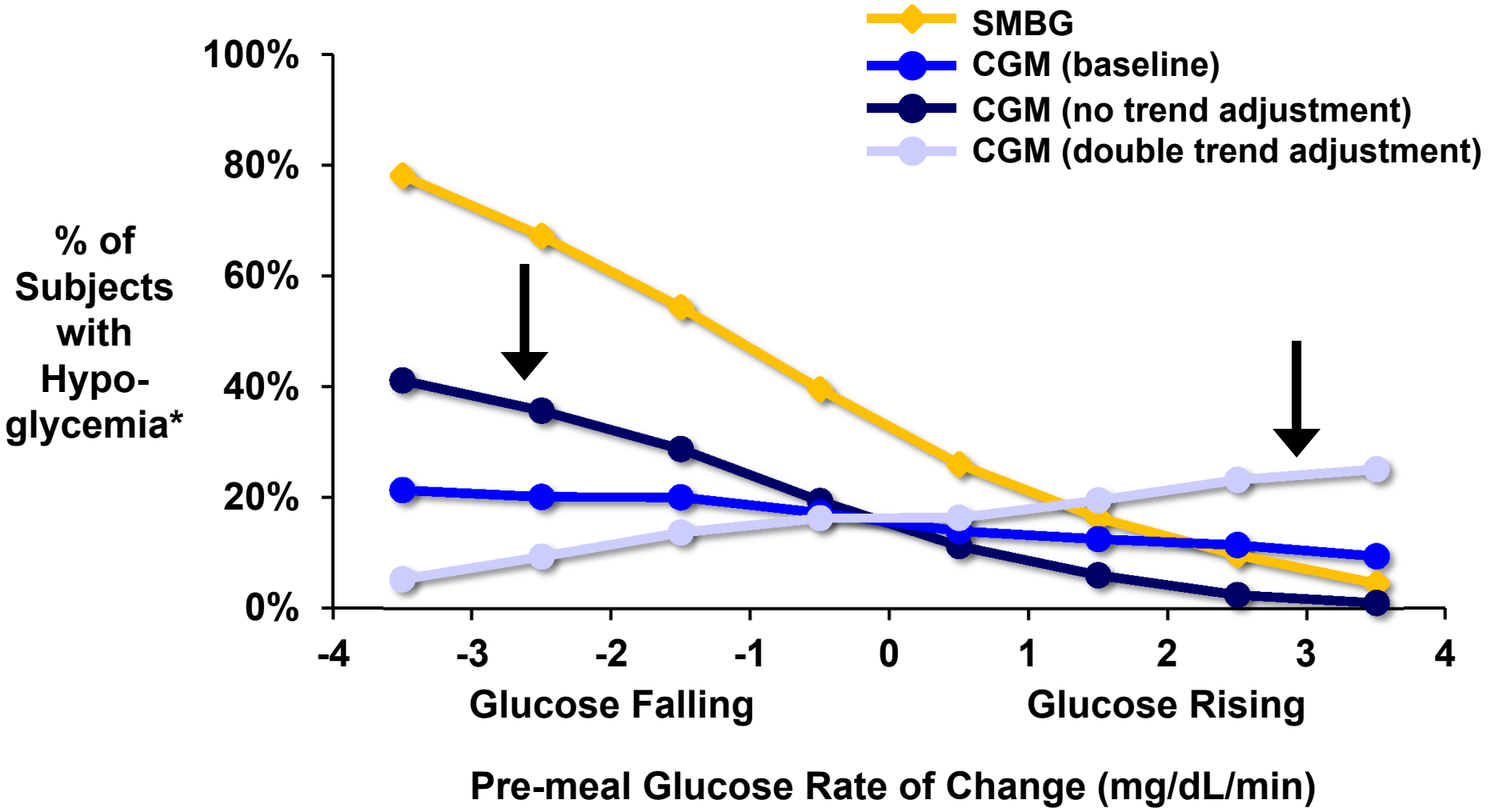
* Glucose below 70 mg/dL

Higher Alert Setting (80 vs. 55 mg/dL) Reduces Hypoglycemia Risk



* Glucose below 70 mg/dL

Changing Use of Trend Adjustment Impacts Risk



* Glucose below 70 mg/dL

Summary of Simulation Studies

- Compared glycemic metrics for CGM- and SMBG-based treatment in two simulations
- CGM-based decisions did NOT increase risk under most conditions
- Increased CGM risk with inadequate calibration, large errors in trend adjustment, inappropriate alert settings
- Greatest benefit of CGM
  - Treatment decisions made with falling glucose
  - Impaired hypoglycemia awareness

Planned Training and Human Factors Study

Claudia Graham, PhD, MPH

Senior Vice President

Global Access

Dexcom, Inc.

CGM Training vs. Medical Management

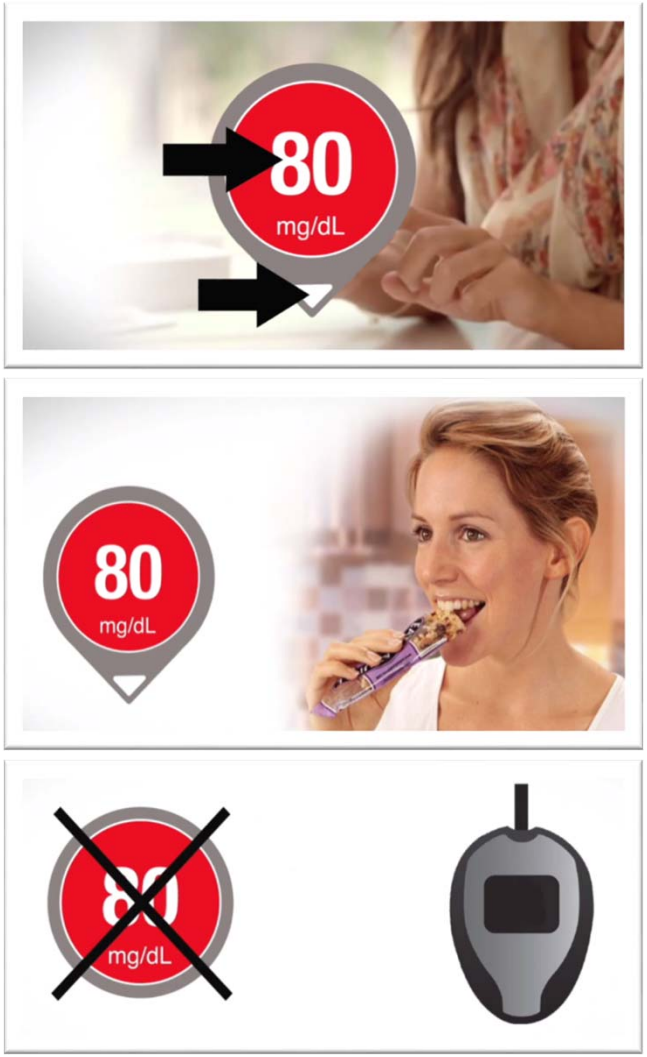
- Device training encompasses how to set up and use CGM device
- Medical management is individualized treatment regimen determined between clinician and patient
- Dexcom Human Factors tested device usability and efficacy of training

Training Focus: How to Use CGM for Treatment and Dosing Decisions

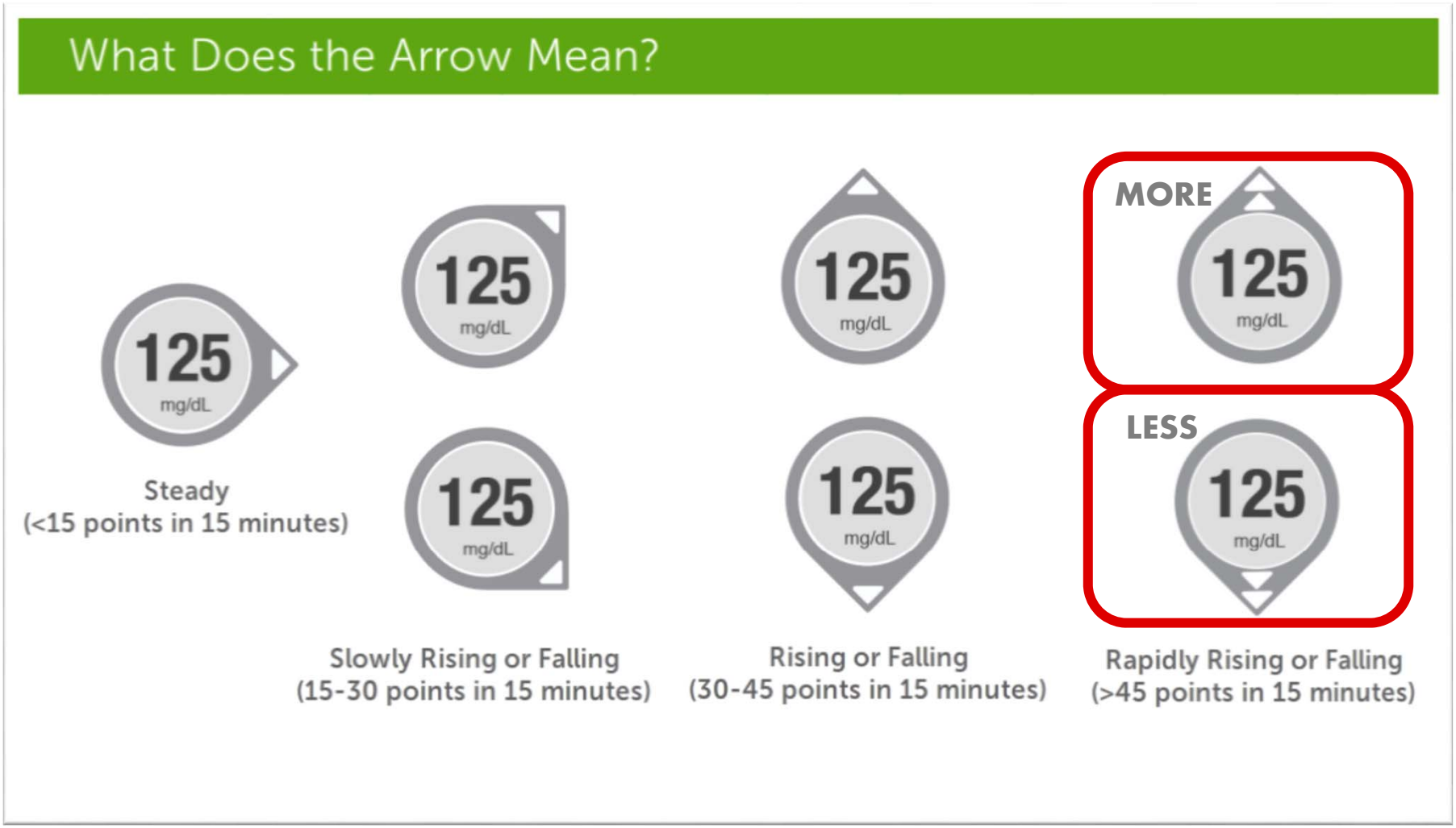
- When SMBG tests are necessary
  - Calibration
  - No CGM reading or arrow
  - Symptoms don’t match CGM reading
  - Acetaminophen
- Use CGM to make treatment and dosing decisions
  - Set proper alerts and alarms
  - Use CGM reading and trend arrow
- Educate about risks of stacking insulin
  - Too much insulin too close in time

Tutorial Examples of When SMBG Tests Are Necessary

- Reading and arrow are needed for CGM-based treatment decisions
- If you have both, you may treat based on CGM number
- If you are missing either, use SMBG for treatment decisions

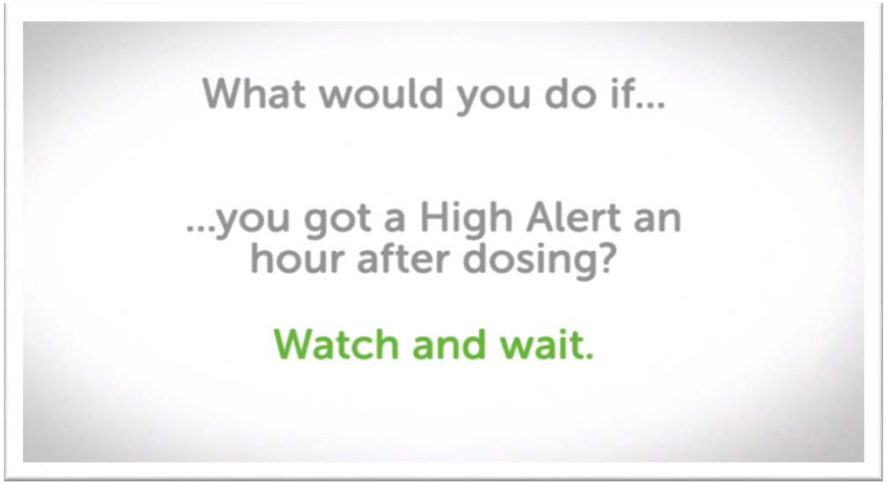


Training Materials: Using CGM to Make Treatment Decisions



Tutorial Example: Educate About Risks of Stacking Insulin

- If glucose level is rising an hour after taking insulin, watch and wait

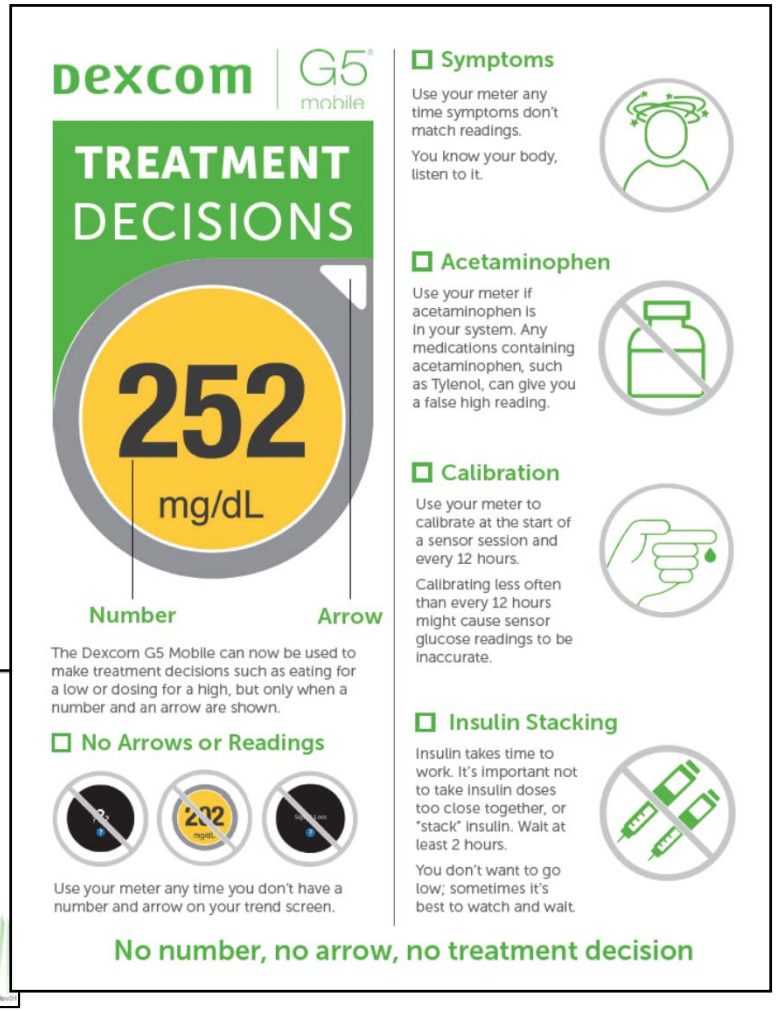


Training via 5 Methods

Method	Content
Product Instructions for Use	• Getting Started Guide • Interactive tutorial • User Guide • Brief package inserts in sensor and receiver kits
In-app Training	• Users required to view screens during initial setup of Dexcom G5 Mobile App
Dexcom Patient Care Team	• 1-on-1 and group patient training • Phone, email, text communications • Webinars
Additional Web-Based Materials	• Case-based examples
Education for Healthcare Professionals	• Account training • Printed materials • Online materials

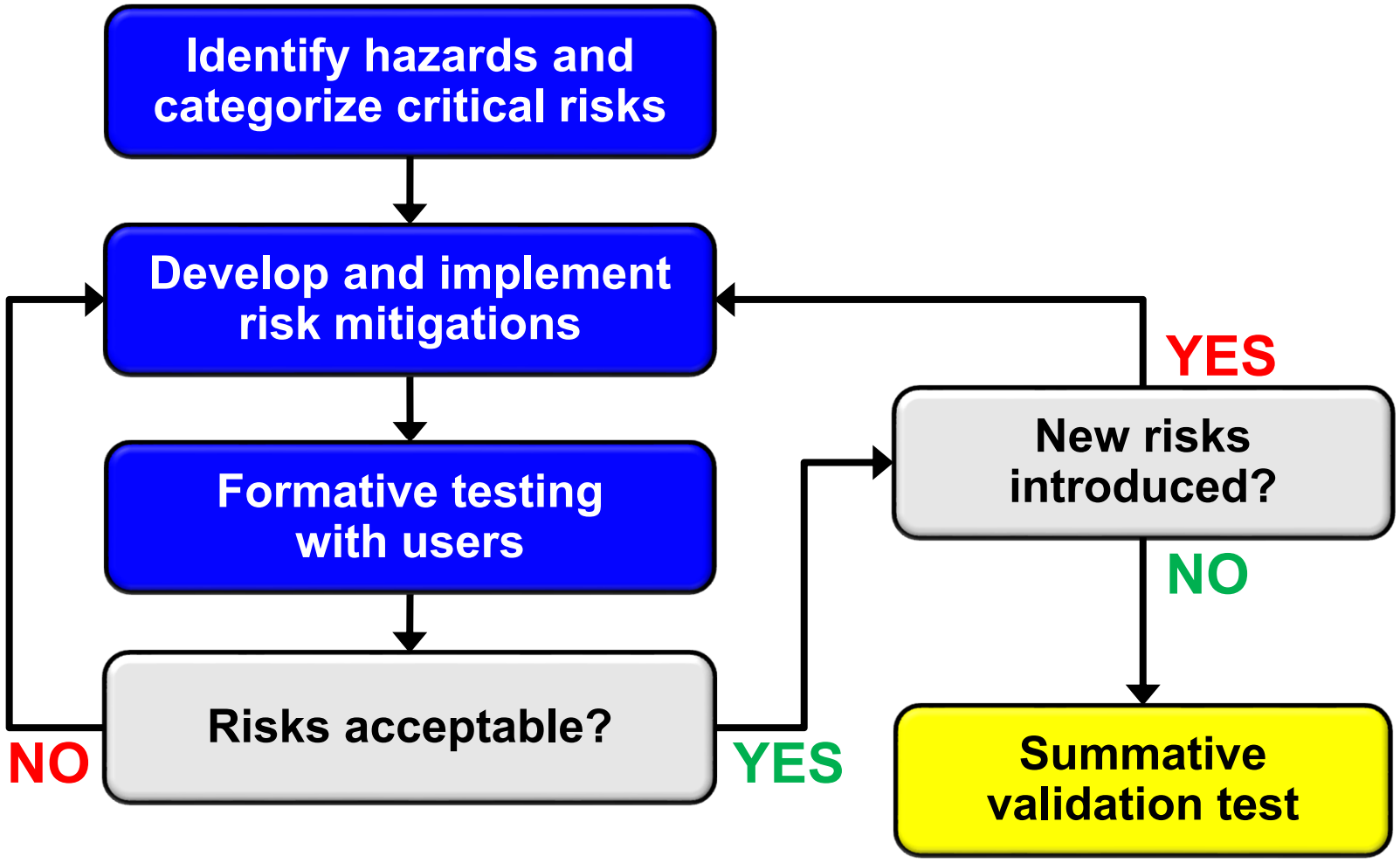
Healthcare Professional Education for CGM-Based Treatment Decisions

1. One page conversation guide around non-adjunctive use
2. Web-based education program
3. Clinic Account Training
4. Conferences and local education



Human Factors Usability Study

Robust Human Factors Process to Identify Risks



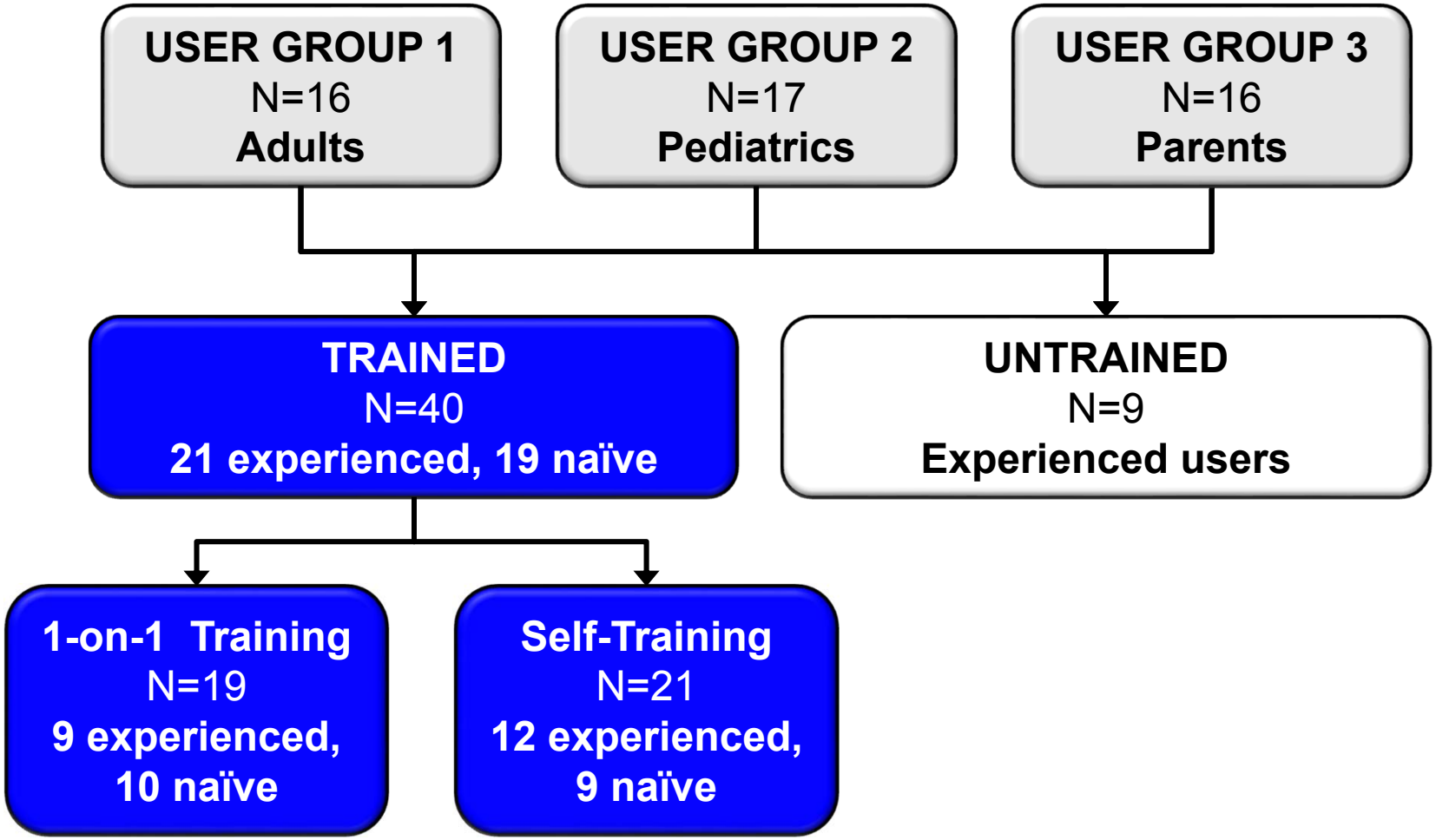
Human Factors Testing

Study	N
Formative 1	15
Formative 2	9
INITIAL Summative	47
Significant edit to training materials	
Formative 3	16
FINAL Summative	49
TOTAL	136

Final Summative Study: Risks of Non-Adjunctive CGM Use

1. Using CGM for treatment decisions without number and arrow
   - 3 distinct scenarios
2. Using CGM for treatment decisions when symptoms do not match CGM reading
   - 1 scenario
3. Insulin stacking
   - 2 scenarios

Final Summative Study Design (N=49)



Results for Trained Users (n=40)

- 99% overall pass rate for CGM-based scenarios
- 100% pass rate:
  - Pediatric users (n=13)
  - Users who self-trained with tutorial (n=21)
  - CGM naïve users (n=19)
- 1 failure observed
  - Adult with CGM experience
  - 1:1 training
  - Scenario: missing arrow

Results for Untrained Users (n=9)

- Total of 4 failures observed
  - All occurred in participants currently using CGM non-adjunctively (off-label)

n / User Group	Scenario(s) Failed
1 Adult **1 Parent**	• CGM did not have an arrow
1 Pediatric	• CGM did not have an arrow • Symptoms did not match CGM readings

Demonstrates need for indication to allow training

Training Materials and Instructions for Use are Effective

- Risks of CGM-based decisions largely mitigated through training
- Small residual risk for untrained patients
- Supports need for indication change to properly train

Benefit-Risk Conclusion

Steven Edelman, MD

Professor of Medicine

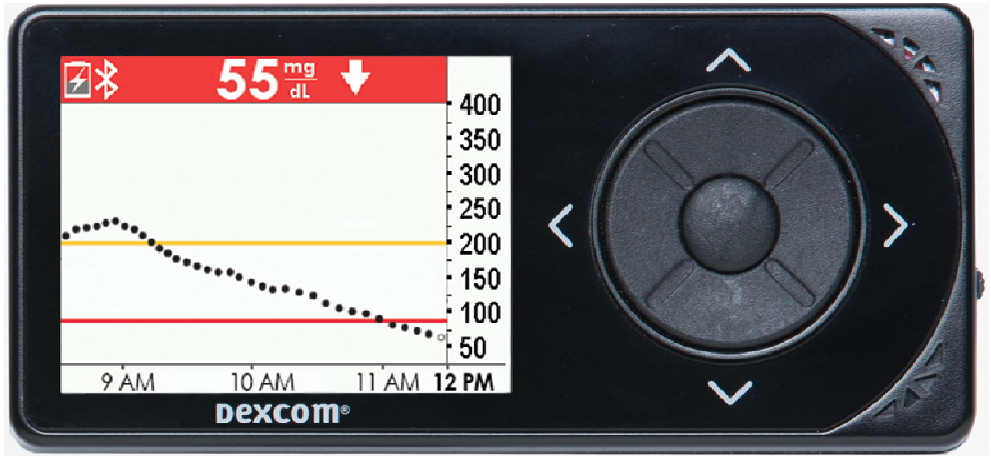
Endocrinology, Diabetes & Metabolism

University of California at San Diego (UCSD)

Problem: Majority of Patients Do Not Achieve Glycemic Goals

- Excessive episodes of hypoglycemia lead to morbidity and mortality
- Frustration, poor quality of life, economic costs and human suffering for user and entire family
- Not enough data throughout day and night
- SMBG is burdensome
  - "Pricking" 6 to 10 times a day leaves wide gaps of time with no information
  - Most people test far fewer

CGM Offers Glucose Value With Added Benefit of Trend and Alerts



- Alerts are active when patient is not monitoring
  - Work, school, driving, or sleeping

Possible Risk: Inaccurate Sensor Values

- Possible causes:
  - Calibrating to erroneous meter error
  - Infrequent calibration
- Mitigated by:
  - Device reminders
  - Training
  - Perform confirmatory fingersticks

Possible Risk: Inappropriate Dosing Decisions

- Possible causes:
  - Over-adjusting dose based on Trend Arrows
  - Insulin Stacking
- Mitigated by:
  - Use of alerts and alarms
  - Consultation with healthcare professional
  - Education

Alerts Provide Additional Layer of Protection

- Greatest benefit observed in people with impaired hypoglycemic awareness
  - Highest risk for severe hypoglycemia → severe medical consequences
- Even people who have normal hypoglycemia awareness commonly have periods of diminished awareness
  - Sleeping
  - Distracted: work, driving, caring for children

Many Patients Have Already Made Transition to CGM-Based Decisions

- Trust in Dexcom CGM has increased
- CGM-based decision making is common among Dexcom users
- Established CGM users make treatment decisions without confirmatory fingersticks
  - Lower rate of hypoglycemia after initiating CGM
  - Making adjustments to insulin dose and timing based on trend information

Edelman et al., (2015)

Benefits of Dexcom G5 CGM-Based Treatment Decisions Outweigh Risks

- Overall risk of CGM-based treatment decisions is lower than with SMBG
- Added benefits of trends arrows, alerts, and sharing ability improves decision making
- Simulations and accuracy support safe and effective use
- Human Factors study validate training is effective

Dexcom G5 Mobile Continuous Glucose Monitoring (CGM) System for Non-Adjunctive Management of Diabetes

July 21, 2016

Dexcom, Inc.

Clinical Chemistry and Clinical Toxicology Devices Panel

BACKUP SLIDES SHOWN

Human Factors Sample Size Is Sufficient to Detect User Errors

- Followed FDA guidance on sample size for summative study
  - Considerations for Determining Sample Sizes for Human Factors Validation Testing, Appendix B
- Research by Faulkner (2003)
  - Sample size of 15 per user group detects a minimum of 90% and an average of 97% of all usability issues.

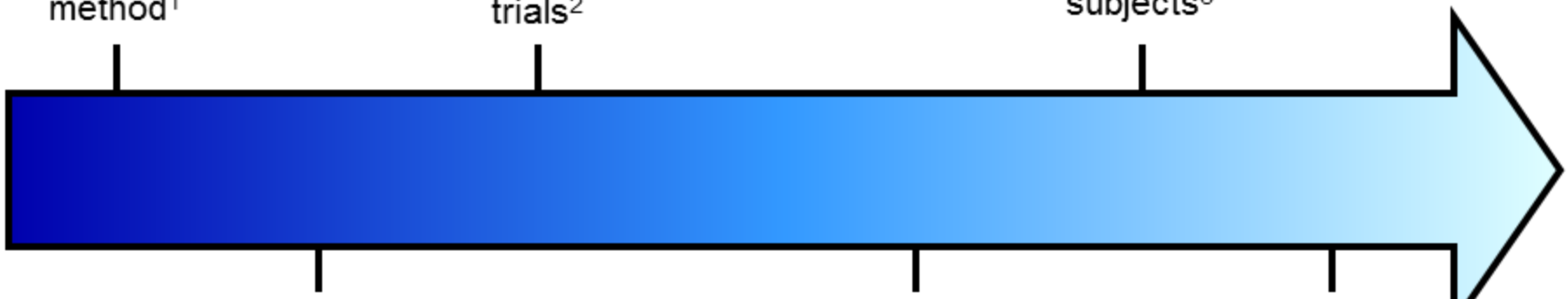
Percentage of Total Known Usability Problems Found in 100 Analysis Samples				
# Users	Min. % Found	Mean % Found	SD	SE
5	55	85.55	9.2957	.9295
10	82	94.69	3.2187	.3218
15	90	97.05	2.1207	.2121
20	95	98.4	1.6080	.1608
30	97	99.0	1.1343	.1051

Faulkner, 2003

Why Is Hypoglycemia Predicted In Silico Less Than That Clinically Observed?

- Factors increasing the risk of hypoglycemia in real life that were not considered in simulations:
  - Physical exercise
  - Stress
  - Errors in the time of meal insulin dose administration
- However:
  - these factors were not considered in both SMBG and CGM treatment scenario
  - sufficiently large number of hypos on 40,000 virtual subject (total # of events below 50 mg/dl: 64,519 with SMBG; 42,161 with CGM)

UVA/Padova T1D Simulator: Development



2006:
204 non-diabetic subjects studied by triple-tracer method[1]

2007:
non-diabetic simulator[4]

2008:
Non-diabetic simulator adapted to T1D and **accepted by FDA** to perform pre-clinical trials[2]

2013:
New version of T1D simulator with improved model of hypoglycemia and glucagon, **accepted by FDA**[5]

2014:
1st validation of T1D simulator on 24 T1D subjects[3]

2015-2016:
Incorporation of circadian insulin sensitivity & 2nd validation of T1D simulator on 47 T1D subjects[6]

[1] Basu et al., 2006
[2] Kovatchev et al., 2009
[3] Visentin et al., 2014
[4] Dalla Man et al., 2007
[5] Dalla Man et al., 2013
[6] Hinshaw et al., 2013; Visentin et al., 2015; Visentin et al.,2016

UVA/Padova T1D Simulator: Validation

Comparison on 24 T1D subjects

	Data	Simulation
Mean (BG) mg/dl	156.9 ± 41.3	157.3 ± 43.3 (n.s.)
% Values in Hypo	6.47 ± 10.19	7.98 ± 13.21 (n.s)
% Values in Hyper	28.87 ± 24.75	27.64 ± 24.93 (n.s)
% Time in Hypo	4.04 ± 7.93	6.22 ± 11.81 (0.006)
% Time in Hyper	33.90 ± 29.02	33.44 ± 30.99 (n.s)
Nr. Hypo Events	37	32
Nr. Hyper Events	72	67

Visentin et al., 2014

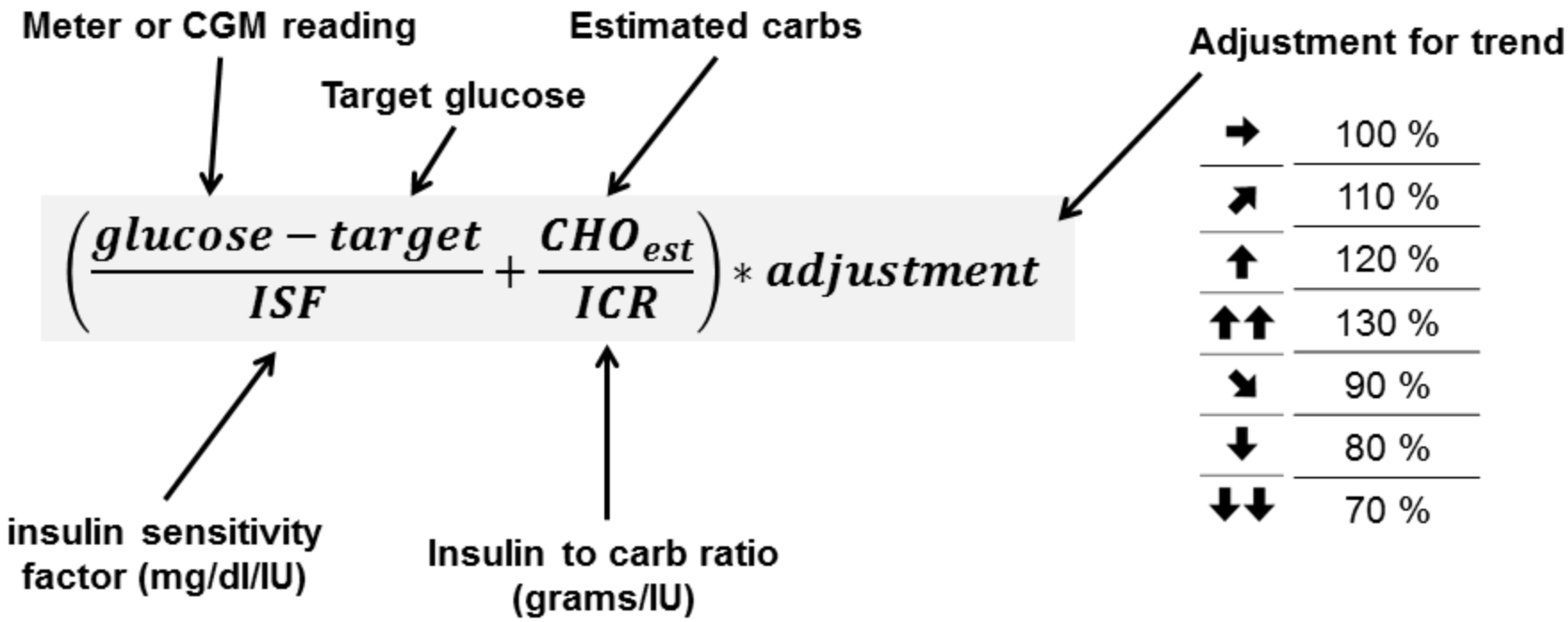
UVA/Padova T1D Simulator: Validation

- Data: 141 glucose traces, collected in 47 T1D subjects recruited for the AP@home FP7-EU project
- The physiological model implemented in the simulator was identified by Bayesian estimation
  - The distribution of parameters identified from data was statistically compared to the distribution of parameters of the simulator
  - No statistically significant differences were found except for the rate of intestinal absorption at breakfast (p-value=0.03)

Visentin et al., 2016

Dose Determination (Meal simulations)

Standard bolus equation, with adjustments for glucose trend based on guidelines in published literature*



* DirecNet Study Group 2008

Mealtime Dose Determination (Two Week Simulation)

- Standard bolus equation, with adjustment for glucose trend as recommended in published literature*

Current Meter or CGM reading

Target glucose

estimated carbohydrates In meal

$$\left(\frac{glucose + trend\ adjustment - target}{ISF} + \frac{CHO_{est}}{ICR}\right)$$

insulin sensitivity factor (mg/dl/IU)

Insulin to carbohydrate ratio (grams/IU)

Trend	Adjustment
→	0
↗	+25 mg/dL
↑	+50 mg/dL
↑↑	+50 mg/dL
↘	-25 mg/dL
↓	-50 mg/dL
↓↓	-50 mg/dL

* "Practical CGM" by Gary Scheiner, 2015

Post-Market Follow-Up EU for Non-Adjunctive Use of G5 CGM

- Dexcom G5 Mobile users surveyed in Germany and Sweden (in progress)
- 200 surveys sent
  - 62 completed in Germany
  - 23 completed in Sweden
- Population
  - 53% Pediatric
  - 47% adult
- Diabetes type
  - 98% Type 1
  - 2% Type 2