

Development of new technologies to address the problem of diabetes in aviation

Prof. Felice Strollo

Vicepresident AIMAS - Secretary General ESAM

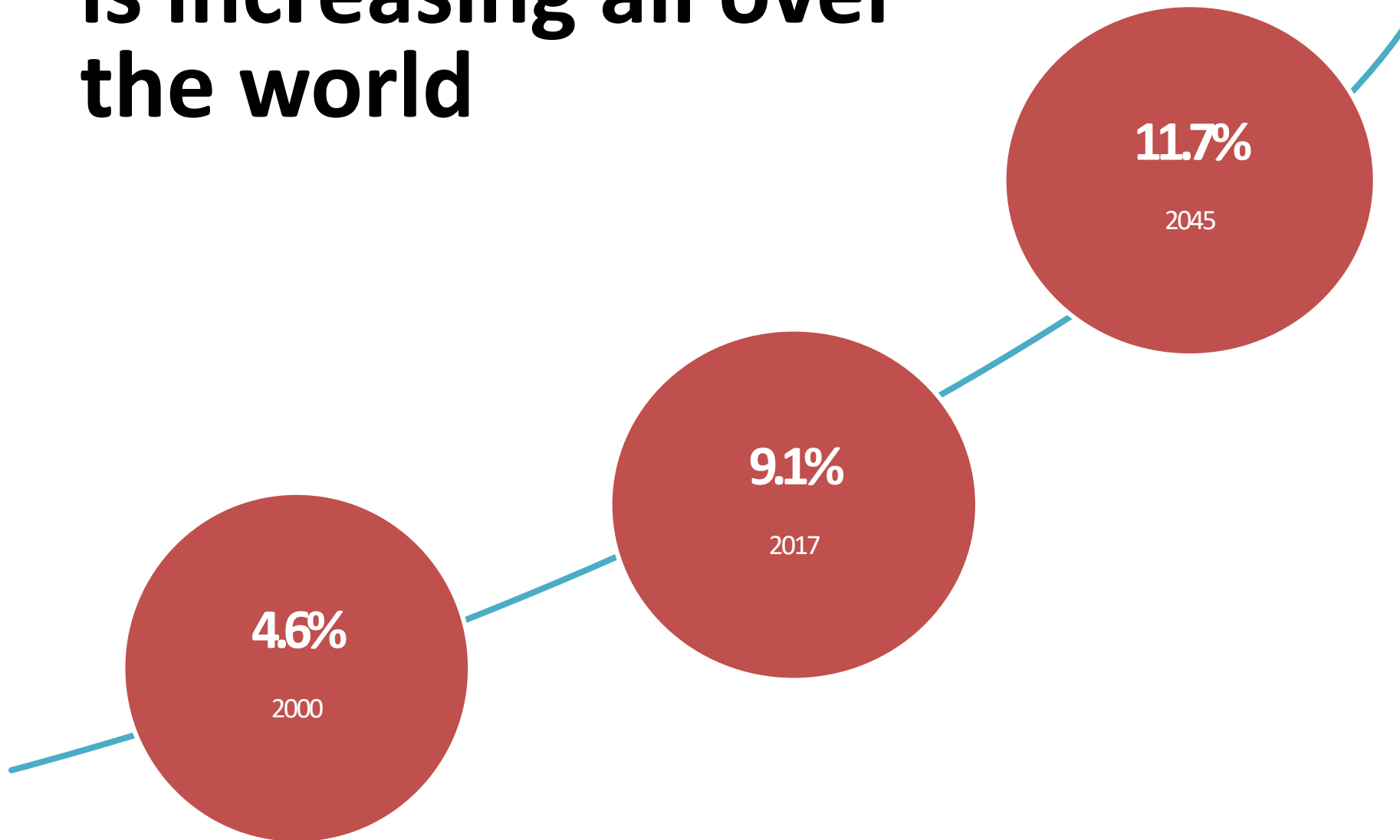
Lecturer at DISFEB, Milan University, Italy

1° AMDA Congress
Moscow 17-20 October 2018

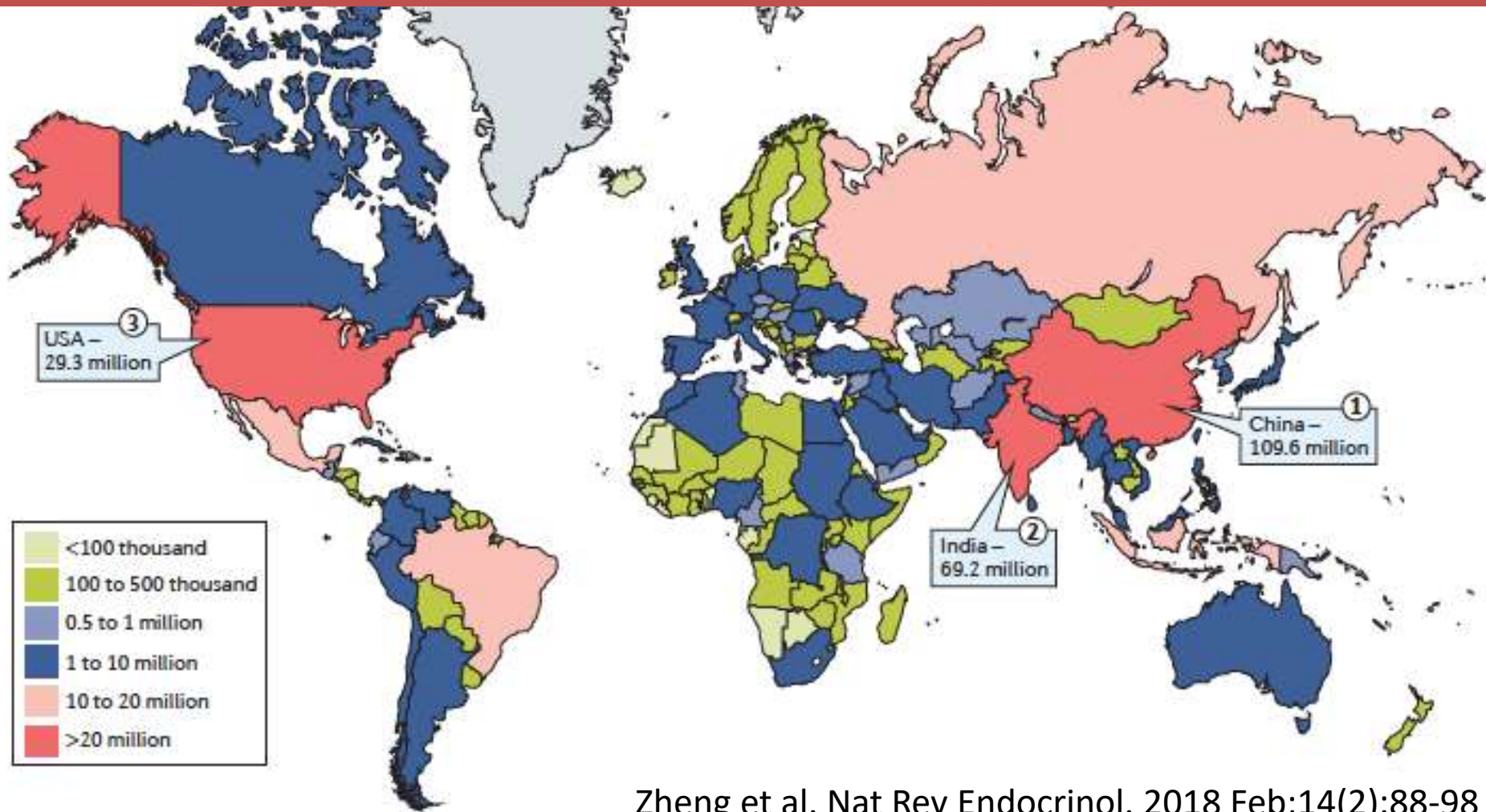
In memory of my father, Prof. Mario Strollo

- He was a 2nd world war MD prisoner and he loved Russian people as open and friendly
- as the first Italian Air Force psychologist he performed human factor studies for safety in aerospace medicine and had good Russian contacts during Gagarins' period
- flying on insulin is a real flight safety issue and has huge human factor implications
- a good compromise is needed among safety issues, longevity and life challenges including employment and self-confidence
- The Russian scientific long standing experience in the field and the deep humanistic culture of Russian people might strongly contribute to updating diabetes related AMC list

Diabetes prevalence is increasing all over the world



DM prevalence worldwide



NORTH AMERICA & CARIBBEAN

Half the global diabetes healthcare spending occurs in this region

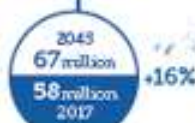
1 in 7 adults in this region is at risk of type 2 diabetes



EUROPE

USD 1 in every USD 4 of the global diabetes healthcare spending occurs in this region

1 in 6 live births is affected by hyperglycaemia in pregnancy



SOUTH AND CENTRAL AMERICA

2 out of 3 people with diabetes were undiagnosed

Only 4% of global healthcare expenditure for diabetes spent in this region



WORLD



MIDDLE EAST AND NORTH AFRICA

1 in 3 live births are affected by hyperglycaemia in pregnancy

1 out of 2 deaths due to diabetes were in people under the age of 60



AFRICA

2 out of 3 people with diabetes are undiagnosed

3 out of 4 deaths due to diabetes were in people under the age of 60



WESTERN PACIFIC

1 in 3 adults with diabetes lives in this region

1 in 3 deaths attributable to diabetes happen in this region



SOUTH-EAST ASIA

1 in 3 adults with diabetes lives in this region

1 in 4 live births is affected by hyperglycaemia in pregnancy

The trend is overwhelming!

In **2045...**

1 in 9
will have
DM

736
million
people

\$1
trillion

Acceptable Means of Compliance - **AMC**

European Aviation Safety Agency

**Acceptable Means of Compliance
and
Guidance Material to Part-MED¹**

Initial issue
15 December 2011

¹ Acceptable Means of Compliance and Guidance Material to Commission Regulation (EU) No 1178/2011 of 3 November 2011 laying down technical requirements and administrative procedures related to civil aviation aircrew pursuant to Regulation (EC) No 216/2008 of the European Parliament and of the Council.

PART – MED for:

- **1st Class Pilots**
- **2nd Class Pilots**
- **LAPL**
- **Cabin Crew**

MED.B.025 Metabolic and Endocrine Systems

AMC1-2 MED.B.025 – AMC5 MED.B.095

Diabetes mellitus Type 1: Class 1, Class 2, LAPL: UNFIT

Diabetes mellitus Type 2 - Non Hypoglycaemic Treatment

Biguanides

Glitazones

Gliptins

GLP-1 receptor agonists

Alfa glucosidase inhibitors (Acarbose)

Class 1: OML (deferral)
Class 2: FIT (consultation)
LAPL: FIT (no consultation)

Diabetes mellitus Type 2 treated with insulin:

Class 1, Class 2: UNFIT;

LAPL: FIT with limitations and specific surveillance protocols

Consequences of hypoglycaemia

Hypoglycemia

Hospitalization costs⁴

CV complications⁵

Weight gain by defensive eating⁶

Dizzy turn unconsciousness⁵

Seizures⁵

Car accident³

Increased risk of dementia¹

Coma⁵

Death²

1: Whitmer RA et al JAMA 2009, 301:1565-1572

2: Zammitt NN et al Diabetes Care 2005, 28:2948-2961

3 Canadian Diabetes Association's Clinical Practice Guidelines for Diabetes and Private and Commercial Driving. Canadian Journal Of Diabetes. 2003;27(2):128-140.

4:Jönsson L et al. Cost of Hypoglycemia in Patients with Type 2 Diabetes in Sweden. Value In Health. 2006; 9: 193-198

5: Barnett AH, CMRO 26, 1333-1342, 2010

6. Foley J & Jordan J, Vascular Health Risk Management, 2010 6:541-548

Diabetes drugs and hypoglycemia

High risk ^{1,2}	Low risk ^{1,2}
Insulin	Metformin
Sulphonylureas	α -glucosidase inhibitors
Glinides	Thiazolidinediones
	GLP-1 receptor agonists
	DPP-4 inhibitors

Solutions

(3) Applicants with diabetes mellitus Type 2 treated with insulin may be assessed as fit with limitations for revalidation if blood sugar control has been achieved and the process under (e) and (f) below is followed.

An OSL limitation is required.

A TML limitation for 12 months may be needed to ensure compliance with the follow-up requirements below. Licence privileges should be restricted to aeroplanes and sailplanes only.

SOLUTIONS (CONT'D 1)

(e) Aero-medical assessment by, or under the guidance of, the licensing authority:

- (1) A diabetology review at yearly intervals....
- (2) Ophthalmological review at yearly intervals....
- (3) Blood testing at 6-monthly intervals:
 - (i) HbA1c: target is 7,5–8,5 %;
 - (ii) renal profile;
 - (iii) liver profile;
 - (iv) lipid profile.

SOLUTIONS (CONT'D 2)

(f) Pilot responsibility

Blood sugar testing is carried out during non-operational and operational periods Pilots should prove to AME or AeMC or licencing authority that testing has been performed as indicated below and with which results.

(1) Testing during non-operational periods:

normally 3-4 times/day or as recommended by the treating physician, and or any awareness of hypoglycemia

SOLUTIONS (CONT'D 3)

(f) Pilot responsibility

(2) Testing frequency during operational periods:

- (i) 120 min. before departure;
- (ii) <30 min. before departure;
- (iii) 60 min. during flight;
- (iv) 30 min. before landing;

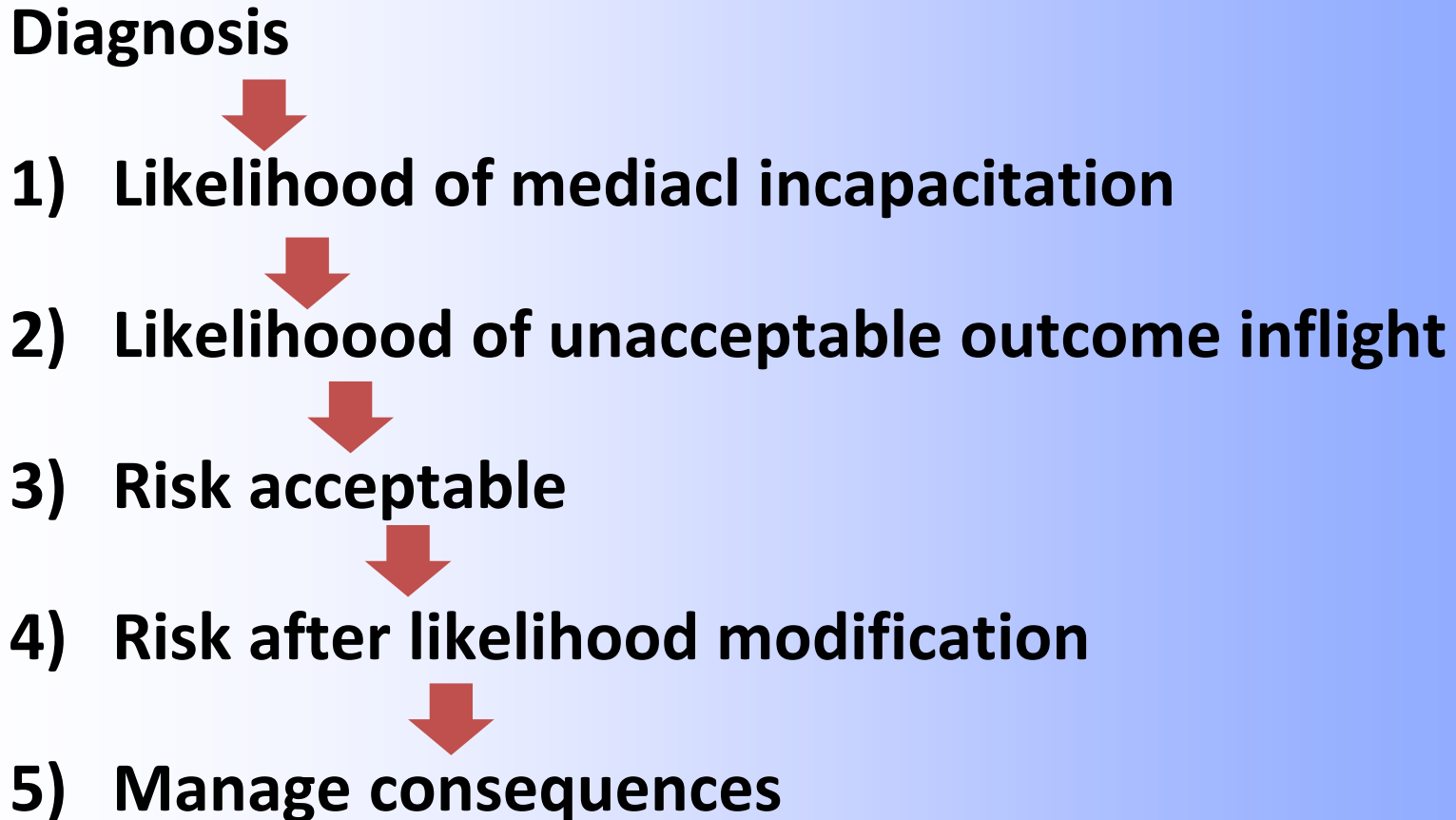
(3) Actions following glucose testing:

- (i) 120 min. before departure: if the test result is >15 mmol/l, piloting should not be commenced
- (ii) 10-15g of carbohydrate should be ingested and a re-test performed within 30 minutes if:
 - (A) any test result is <4,5 mmol/l
 - (B) the pre-landing test measurement is missed or a subsequent go-around/diversion is performed

**Is this the best
approach?**

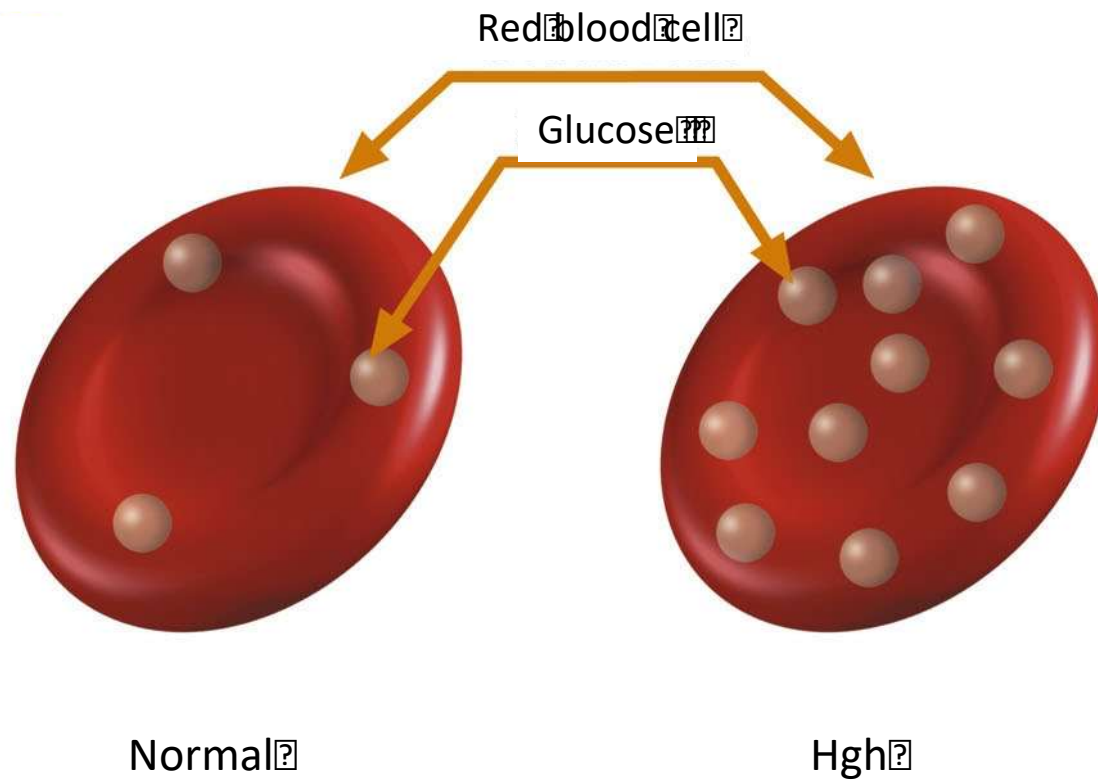
Dr. Punita-Masrani's Algorithm

Diagnosis

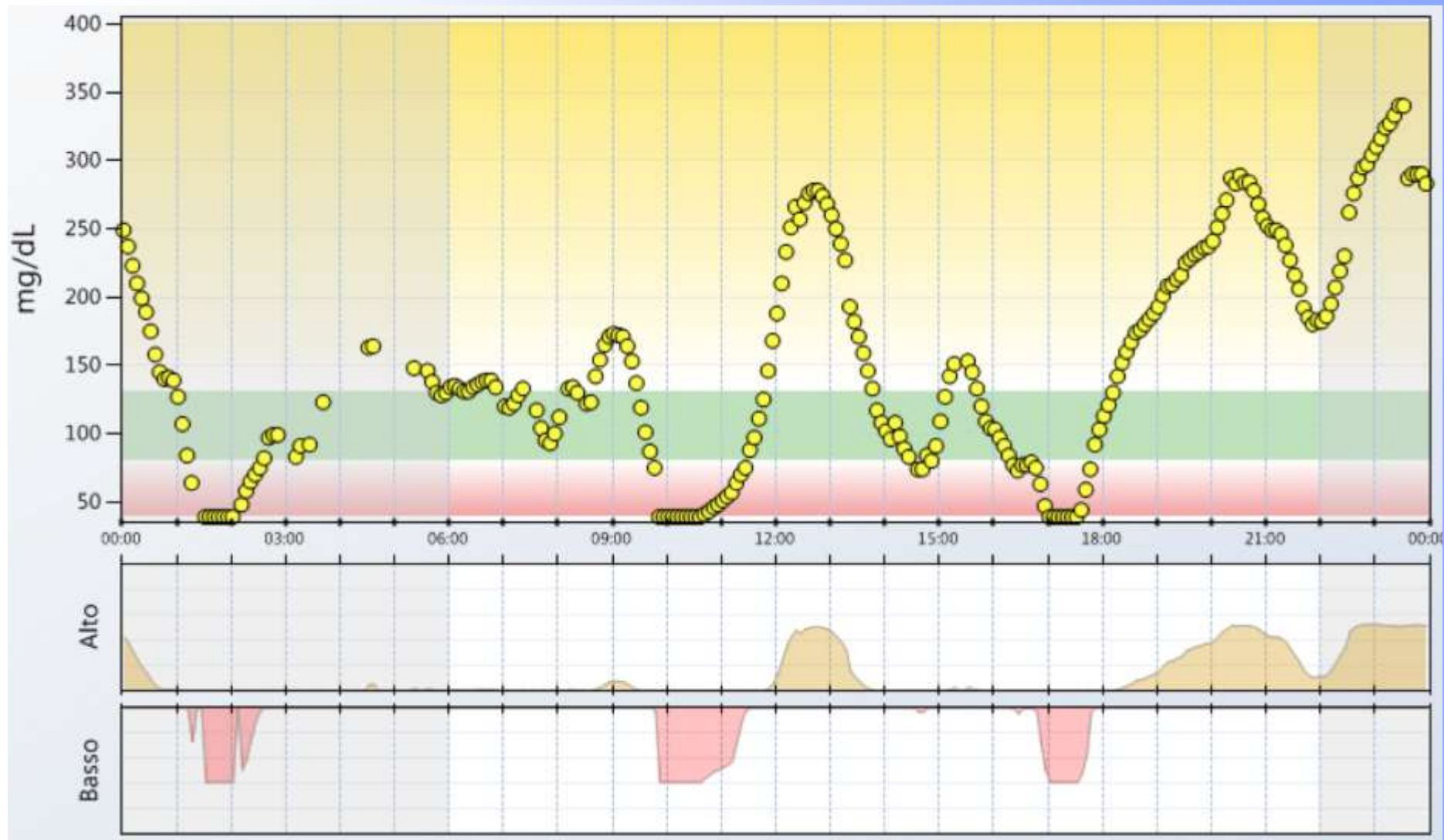
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- ```
graph TD; A[Diagnosis] --> B[1) Likelihood of medical incapacitation]; B --> C[2) Likelihood of unacceptable outcome in flight]; C --> D[3) Risk acceptable]; D --> E[4) Risk after likelihood modification]; E --> F[5) Manage consequences]; F --> G[Risk acceptable after consequence modification];
```
- 1) Likelihood of medical incapacitation
  - 2) Likelihood of unacceptable outcome in flight
  - 3) Risk acceptable
  - 4) Risk after likelihood modification
  - 5) Manage consequences

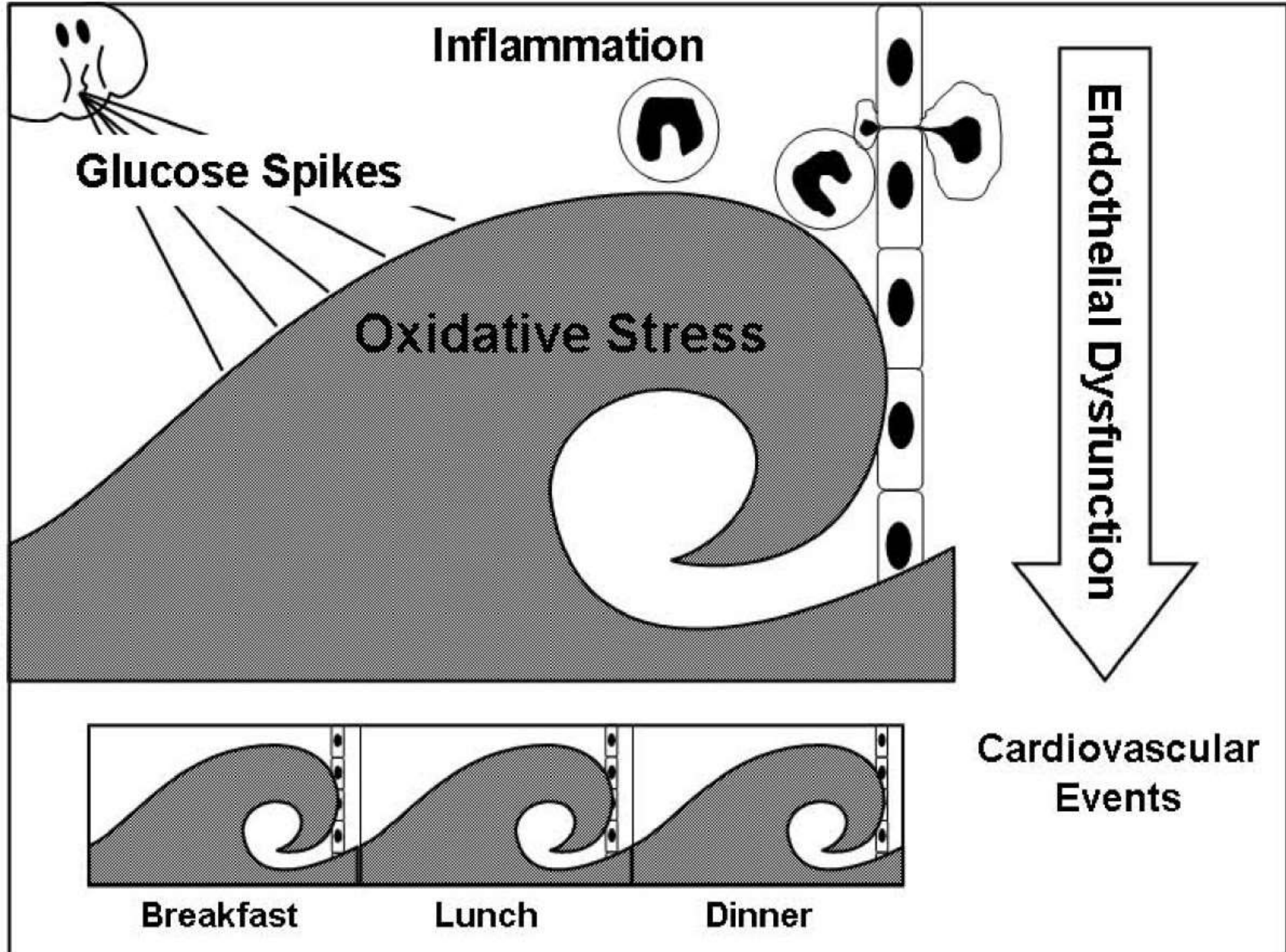
**Risk acceptable after consequence modification**

# HbA1c?



# A one glucose day profile









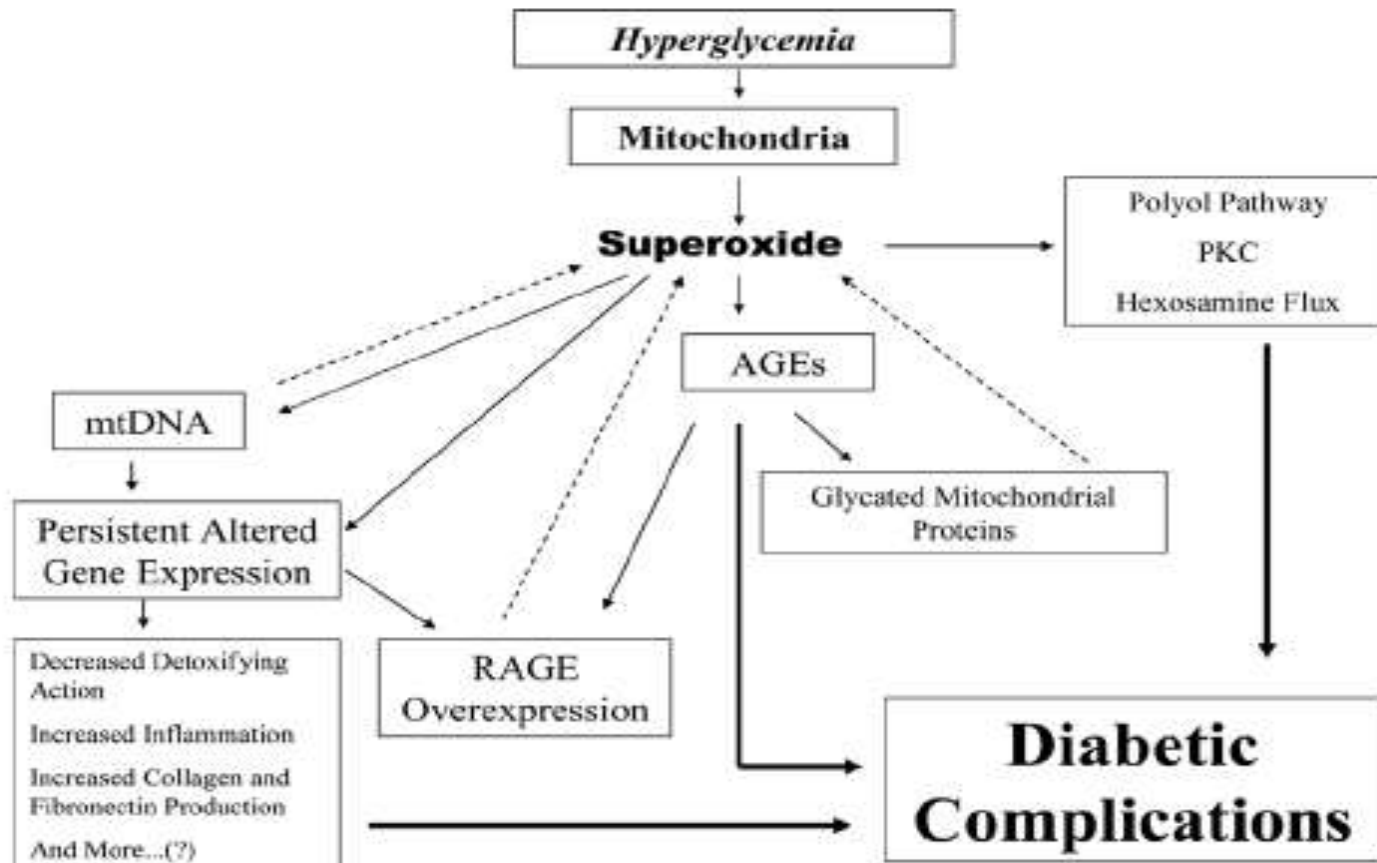
Contents lists available at ScienceDirect

Diabetes Research  
and Clinical Practicejournal homepage: [www.elsevier.com/locate/diabres](http://www.elsevier.com/locate/diabres)

## Hypothesis: the “metabolic memory”, the new challenge of diabetes

Antonio Ceriello\*

Chair of Endocrinology, University of Udine, Italy



# Various CGMS devices

Guardian REAL-  
Time



Dexcom SEVEN  
Plus



MiniMed  
Paradigm®

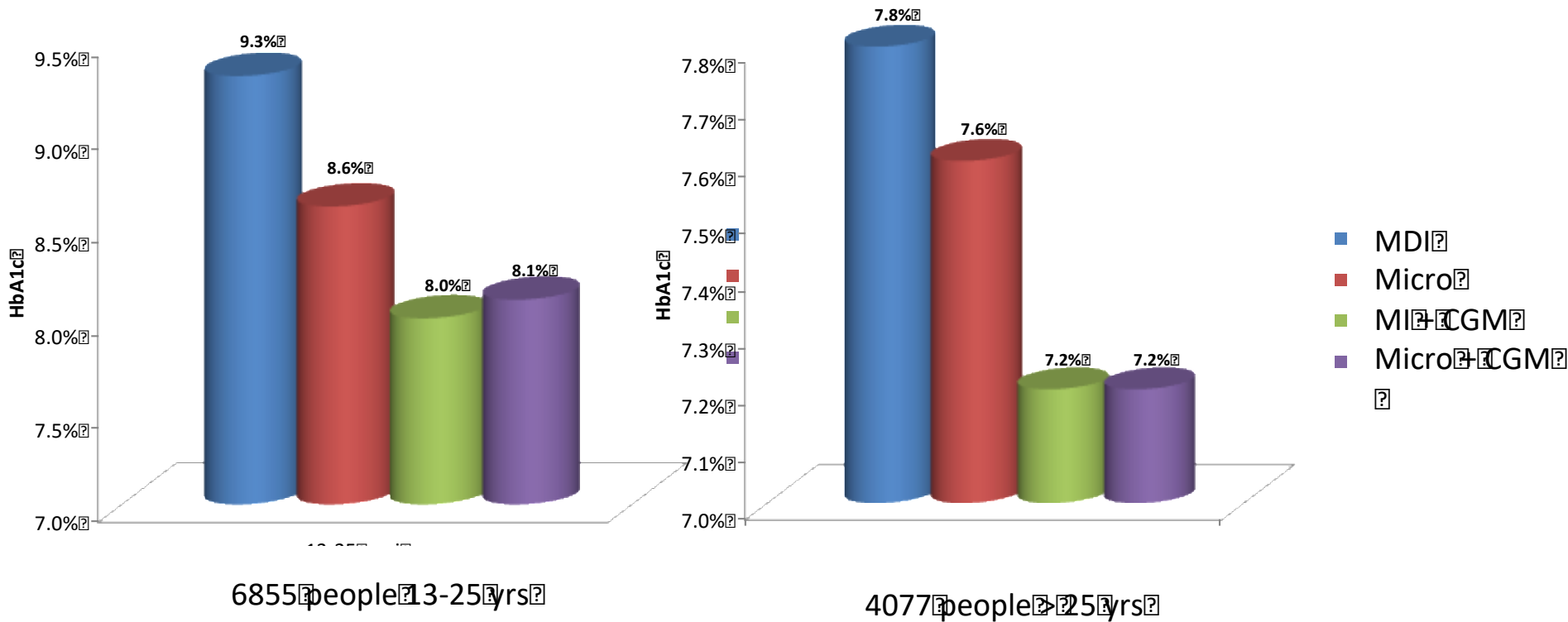


Abbott FreeStyle  
Navigator®



# CGM Benefits

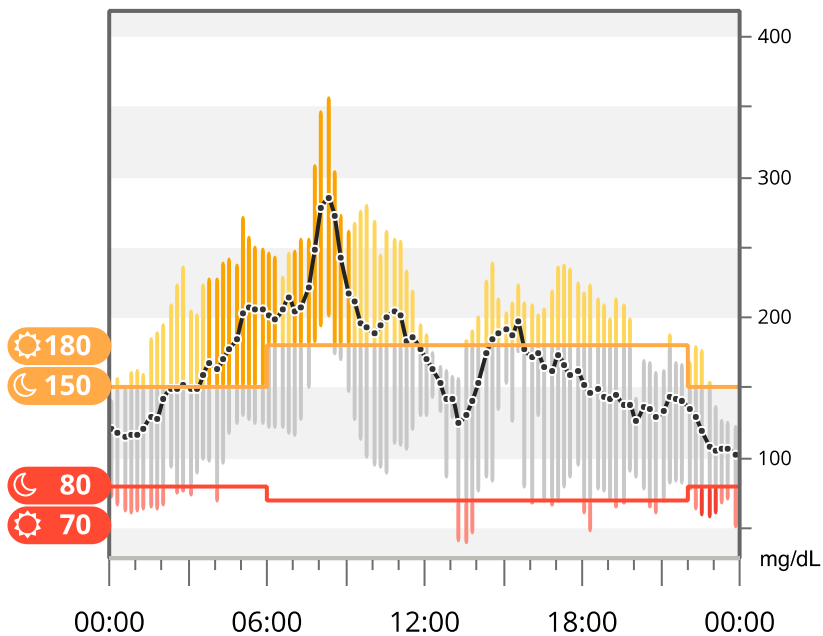
HbA1c decreases independently of age  
and insulin injection method



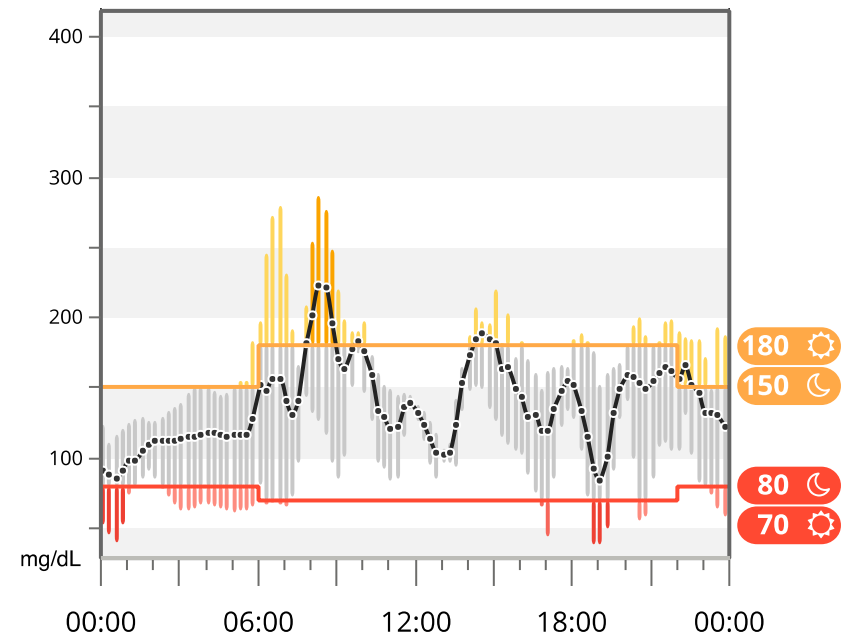


# Web based CGM data sharing for interpretation and decision making

7 day profile 1week 1



7 day profile 1week 2



# MAIN CHARACTERISTICS

## Components

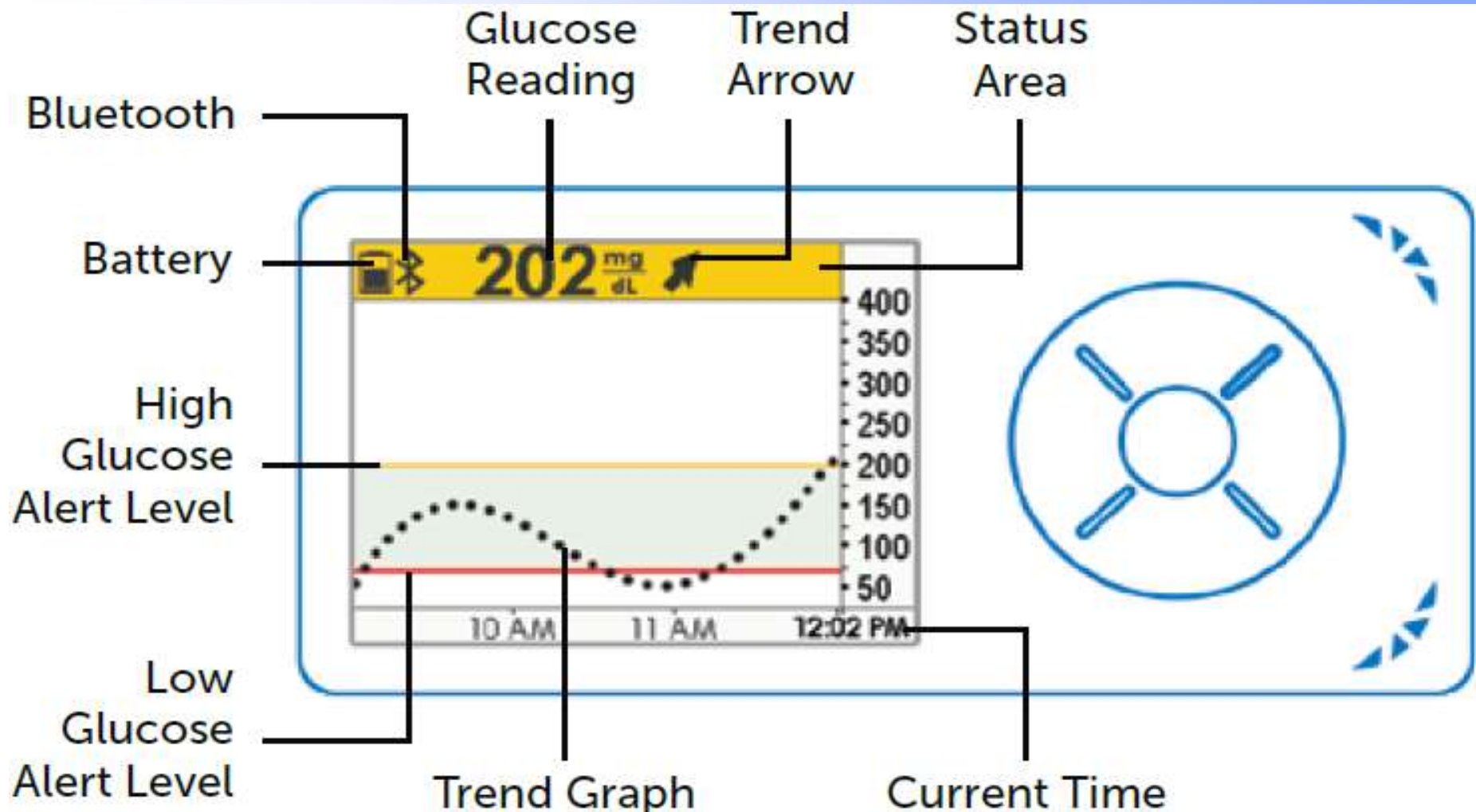
1. **Sensor:** electrohchemical
2. **Trasmitter:** via bluetooth to the app and / or receiver



3. **Display:**  
shows trends and sends out alarms



# Receiver



Original Article

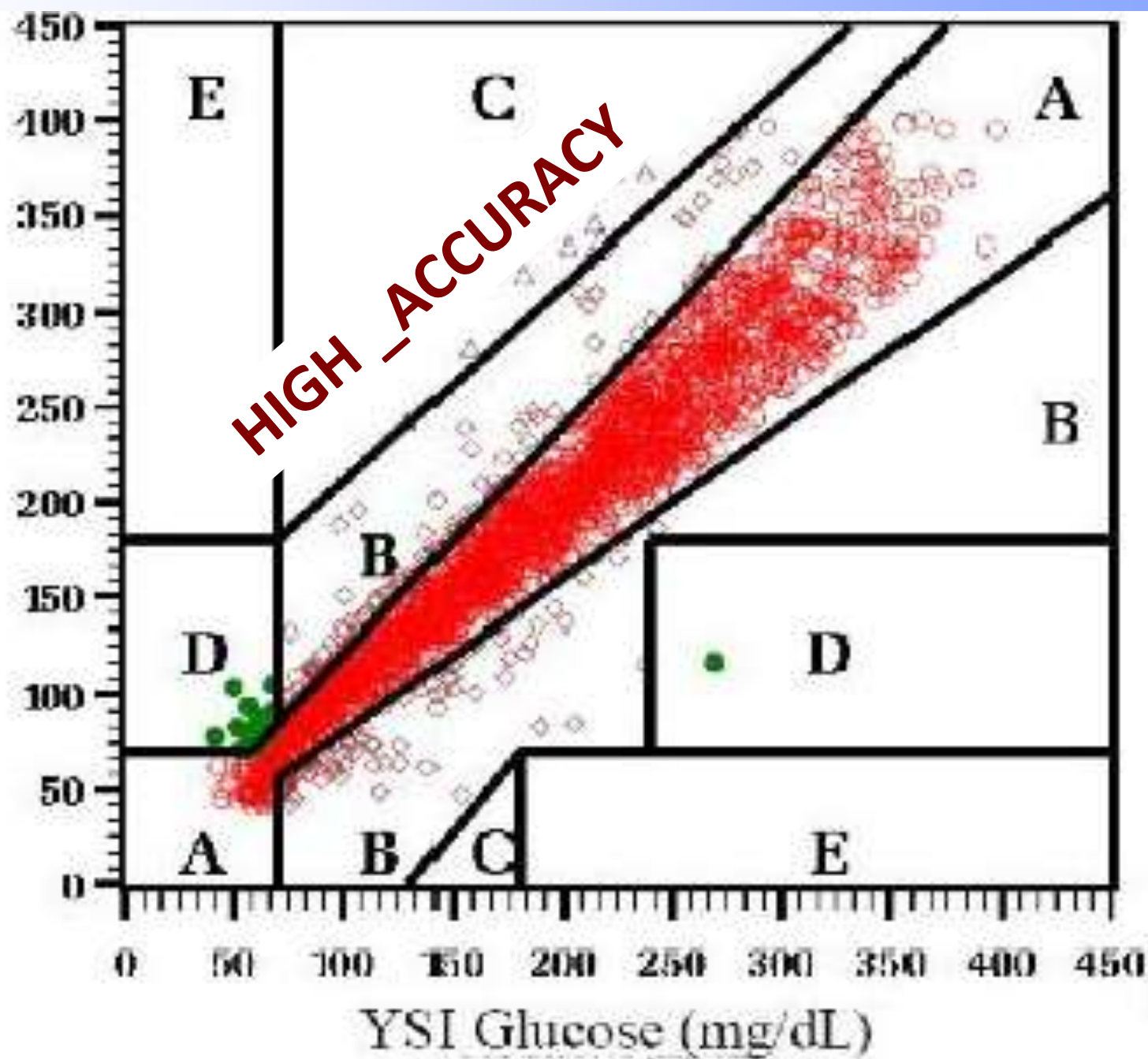
## Discrepancies Between Blood Glucose and Interstitial Glucose—Technological Artifacts or Physiology: Implications for Selection of the Appropriate Therapeutic Target



*Are ISFG (interstitial fluid glucose) and BG (blood glucose) interchangeable as for decision making?*

- ❑ Blood takes glucose everywhere in the body, ISF only to closer cells
- ❑ BG reflects overall available glucose amount, ISFG depends on local changes (blood to ISF transfer rate and tissue utilization rate)
- ❑ from a physiological point of view, tissue (and especially brain) glucose concentrations provide sounder information than circulating levels

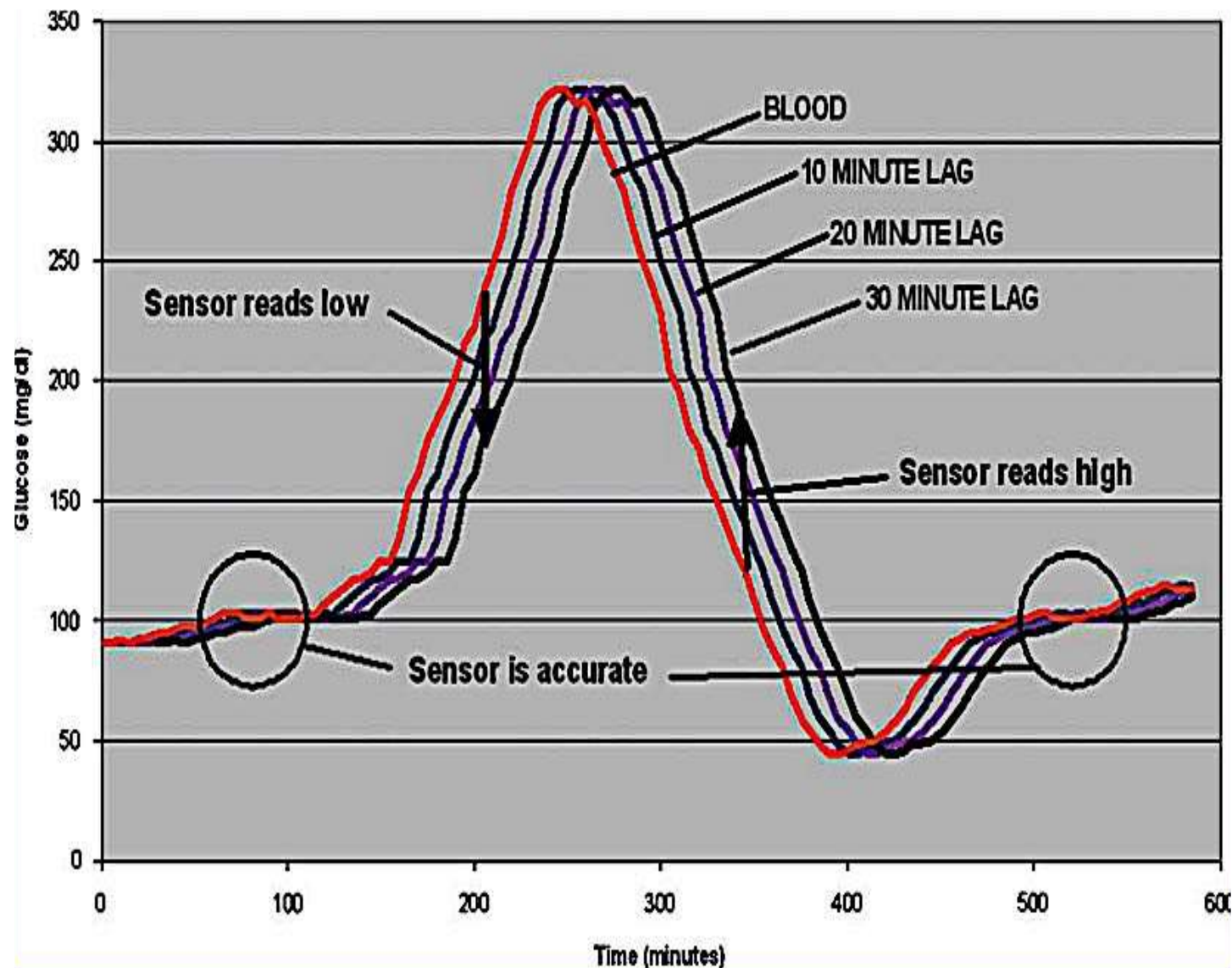
CGM Glucose (mg/dL)



# Average sensor time lag versus blood glucose

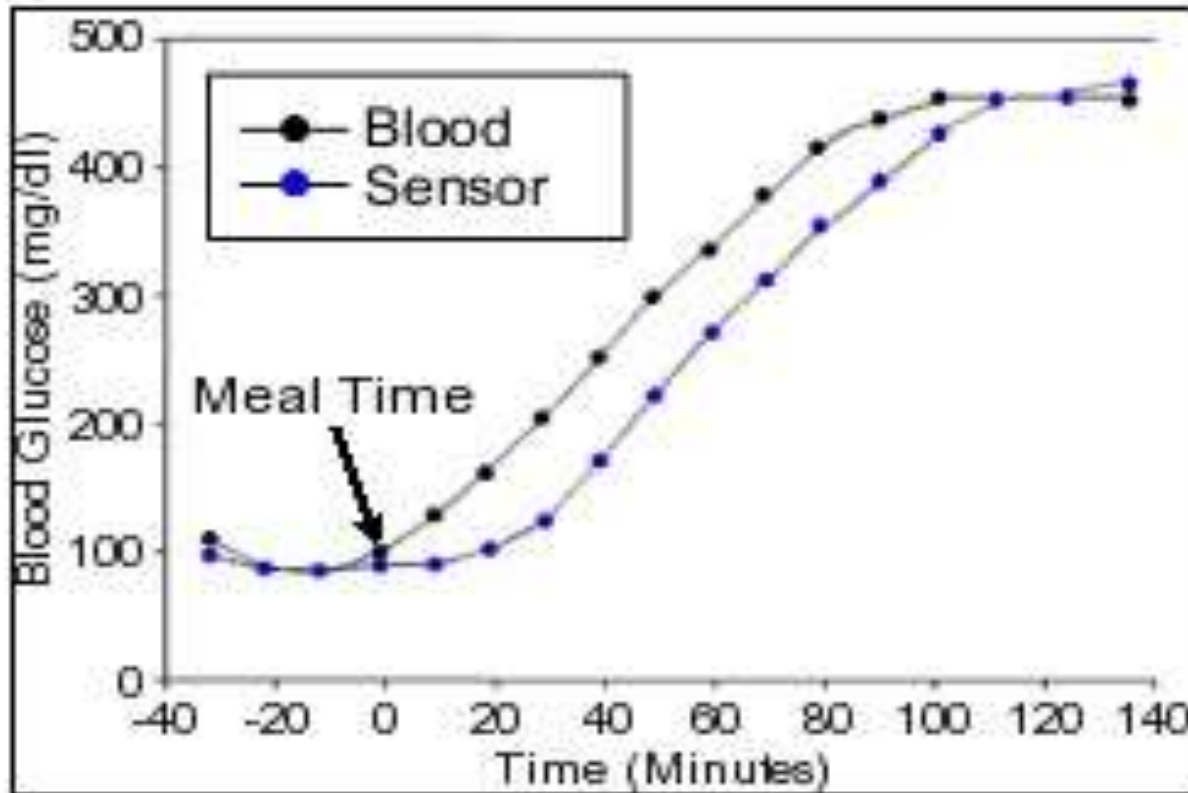
**LAG TIME**

Elevated when  
fast glucose  
changes occur  
(5-20 minutes)





# Lag Time



**Sensor glucose lags behind blood glucose after a meal**



# **Toward Calibration-Free Continuous Glucose Monitoring Sensors: Bayesian Calibration Approach Applied to Next-Generation Dexcom Technology**

DIABETES TECHNOLOGY & THERAPEUTICS  
Volume 20, Number 1, 2018  
© Mary Ann Liebert, Inc.  
DOI: 10.1089/dia.2017.0297

## **RESULTS:**

The one-per-day and one-every-two-days calibration scenarios in the next-generation CGM data have an accuracy of 8.5% MARD (vs. 11.59% of DG4P) and 8.4% MARD (vs. 11.63% of DG4P), respectively. Accuracy slightly worsens to 9.2% (vs. 11.62% of DG4P) when calibrations are reduced to one-every-four-days. The calibration-free scenario results in 9.3% MARD (vs. 12.97% of DG4P).

## **CONCLUSIONS:**

In next-generation Dexcom CGM sensor data, the use of an online calibration algorithm based on a multiple-day model of sensor time variability and Bayesian parameter estimation aids in the shift toward a calibration-free scenario with even better results than those obtained in present-generation sensors.

The extent of use as replacement for BGSM and exceptional situations in which the manufacturers of the two systems regard additional BGSM as necessary are described in the instructions for use (at least those used in Germany) as follows:

With the Dexcom G5 therapeutic decisions may only be made :

- if glucose values and warnings comply with symptoms and expectations
- if the instructions were followed and the system was calibrated 12 hours after the initial calibration
- on the basis of the tissue glucose value, trend arrow, trend diagram, and/or attainable warnings
- if at least three consecutive measurement results from the last 15 minutes are available

When using FreeStyle Libre, additional blood glucose measurements have to be performed:

- In phases of rapidly changing glucose values
- To confirm a sensor-reported hypoglycemia or impending hypoglycemia
- If symptoms do not comply with the glucose value displayed by the system

# use CGM non-adjunctively to adjust their insulin doses

- Today, although this procedure is not approved, many persons with diabetes use CGM non-adjunctively to adjust their insulin doses (Endocr Pract 2015;21: 613–620)
- FDA Advisory Panel Votes to Recommend Non-Adjunctive Use of Dexcom G5 Mobile CGM (DIABETES TECHNOLOGY & THERAPEUTICS Volume 18, Number 8, 2016):








# FDA Advisory Panel Votes to Recommend Non-Adjunctive Use of Dexcom G5 Mobile CGM

1. Is there reasonable assurance that the Dexcom G5 CGM is safe for the proposed indications for use? : **8 yes/2 no**
2. Is there reasonable assurance that the Dexcom G5 is effective for the proposed indications for use? : **9 yes/1 no**
3. Do the benefits of the Dexcom G5 CGM for the proposed indications for use outweigh the risks for the proposed indications for use? : **8 yes/2 no**




**The Advisory Committee concluded that the G5 is sufficiently safe and effective for non-adjunctive use to guide diabetes treatment decisions, and that the benefits of its use in this way outweigh the risks.**

The Dexcom G5 Mobile has EMEA (European) approval for non-adjunctive use

# **New Approach to Adjusting Insulin Doses Using Trend Arrows in Adults: Pre-meal and Corrections $\geq 4$ Hours Post-meal**

| Trend Arrows |                                                                                     | Correction Factor* (CF) | Insulin Dose Adjustment (U) |
|--------------|-------------------------------------------------------------------------------------|-------------------------|-----------------------------|
| Receiver     | App                                                                                 |                         |                             |
| ↑↑           |    | <25                     | +4.5                        |
|              |                                                                                     | 25–<50                  | +3.5                        |
|              |                                                                                     | 50–<75                  | +2.5                        |
|              |                                                                                     | $\geq 75$               | +1.5                        |
| ↑            |    | <25                     | +3.5                        |
|              |                                                                                     | 25–<50                  | +2.5                        |
|              |                                                                                     | 50–<75                  | +1.5                        |
|              |                                                                                     | $\geq 75$               | +1.0                        |
| ↗            |    | <25                     | +2.5                        |
|              |                                                                                     | 25–<50                  | +1.5                        |
|              |                                                                                     | 50–<75                  | +1.0                        |
|              |                                                                                     | $\geq 75$               | +0.5                        |
| →            |    | <25                     | No adjustment               |
|              |                                                                                     | 25–<50                  | No adjustment               |
|              |                                                                                     | 50–<75                  | No adjustment               |
|              |                                                                                     | $\geq 75$               | No adjustment               |
| ↘            |    | <25                     | -2.5                        |
|              |                                                                                     | 25–<50                  | -1.5                        |
|              |                                                                                     | 50–<75                  | -1.0                        |
|              |                                                                                     | $\geq 75$               | -0.5                        |
| ↓            |   | <25                     | -3.5                        |
|              |                                                                                     | 25–<50                  | -2.5                        |
|              |                                                                                     | 50–<75                  | -1.5                        |
|              |                                                                                     | $\geq 75$               | -1.0                        |
| ↓↓           |  | <25                     | -4.5                        |
|              |                                                                                     | 25–<50                  | -3.5                        |
|              |                                                                                     | 50–<75                  | -2.5                        |
|              |                                                                                     | $\geq 75$               | -1.5                        |

Insulin adjustments using trend arrows do not replace standard calculations using ICR and CF. Adjustments are increases or decreases of rapid-acting insulin in addition to calculations using ICR and CF. Adjustments using trend arrows are an additional step to standard care.

| Trend Arrows |                                                                                     | Correction Factor* (CF) | Insulin Dose Adjustment (U) |
|--------------|-------------------------------------------------------------------------------------|-------------------------|-----------------------------|
| Receiver     | App                                                                                 |                         |                             |
| ↑↑           |  | <25                     | +4.5                        |
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|              |                                                                                     | $\geq 75$               | +1.0                        |
| ↗            |  | <25                     | +2.5                        |
|              |                                                                                     | 25–<50                  | +1.5                        |
|              |                                                                                     | 50–<75                  | +1.0                        |
|              |                                                                                     | $\geq 75$               | +0.5                        |



treatment efficacy  
assessment

structured education

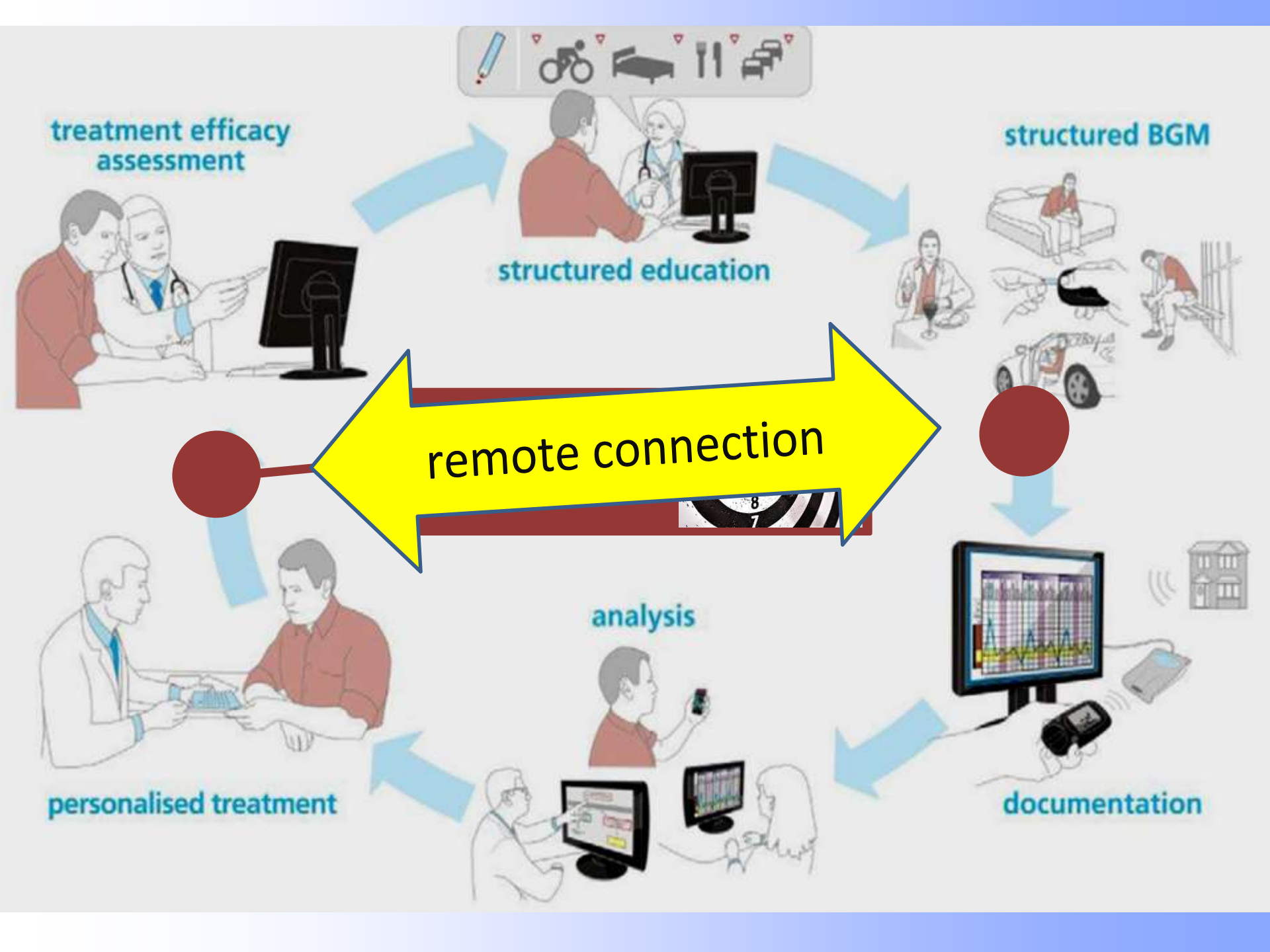
structured BGM

remote connection

analysis

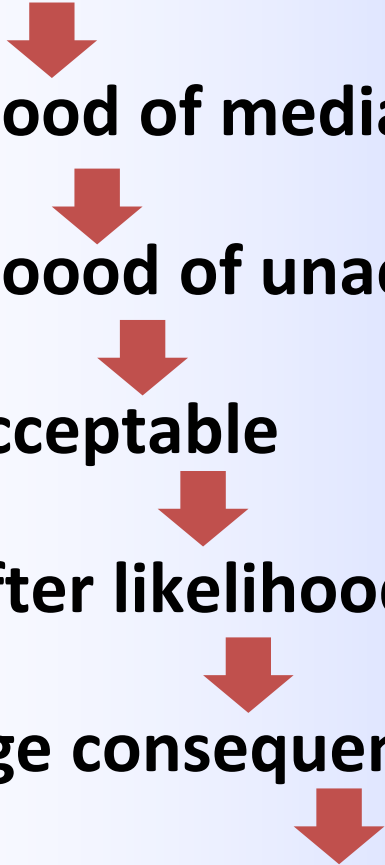
personalised treatment

documentation



# Dr. Punita-Masrani's Algorithm

## Diagnosis

- 
- ```
graph TD; A[Diagnosis] --> B[1) Likelihood of mediocl incapacitation]; B --> C[2) Likelihood of unacceptable outcome inflight]; C --> D[3) Risk acceptable]; D --> E[4) Risk after likelihood modification]; E --> F[5) Manage consequences]; F --> G[RISK ACCEPTABLE AFTER CONSEQUENCE MODIFICATION];
```
- 1) Likelihood of mediocl incapacitation
 - 2) Likelihood of unacceptable outcome inflight
 - 3) Risk acceptable
 - 4) Risk after likelihood modification
 - 5) Manage consequences

RISK ACCEPTABLE AFTER CONSEQUENCE MODIFICATION

PILOTS ON INSULIN



Let's try to build up confidence and trust