Is A1C Out?
Is Time in Range In?

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Speaker Disclosure – Lori Berard RN CDE

- Advisor/Consultant/Speaker Bureau:
  - Eli Lilly; Sanofi; Novo Nordisk;Lifescan; Abbott; BD; MontMed; Merck; Bayer; Ascencia; Janssen; AstraZeneca; Boehringer Ingelheim
- Research Funding
  - MontMed
- Contract Employment
  - Quanta

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- Financial support from the ABBOTT Diabetes Care in the form of an educational grant to the organizers

Potential for conflict of interest:

- The faculty member has received honoraria from Langs for the presentation
- ABBOTT Diabetes Care may benefit from the sale of products that may be discussed in this program

Mitigation of Potential Bias

- The speaker is responsible for complete creation of the content and format of this program.
- The speaker was solely and fully responsible for developing all content and was involved at all stages of CME development to achieve scientific integrity, objectivity and balance. ABBOTT Diabetes Care was not involved in any aspect of the program development process.
- Any discussion of products outside of their indications represents the personal opinion of the presenter and unsolicited questions should be directed to the presenter.

Session objectives

- Review measures of glycemia that help guide decision making
- Discuss advantages and disadvantages of tools to guide diabetes care
- Introduce the concept of time in range
- Debate – A1C versus Time in Range

Temperature Check – Time in Range (TIR)

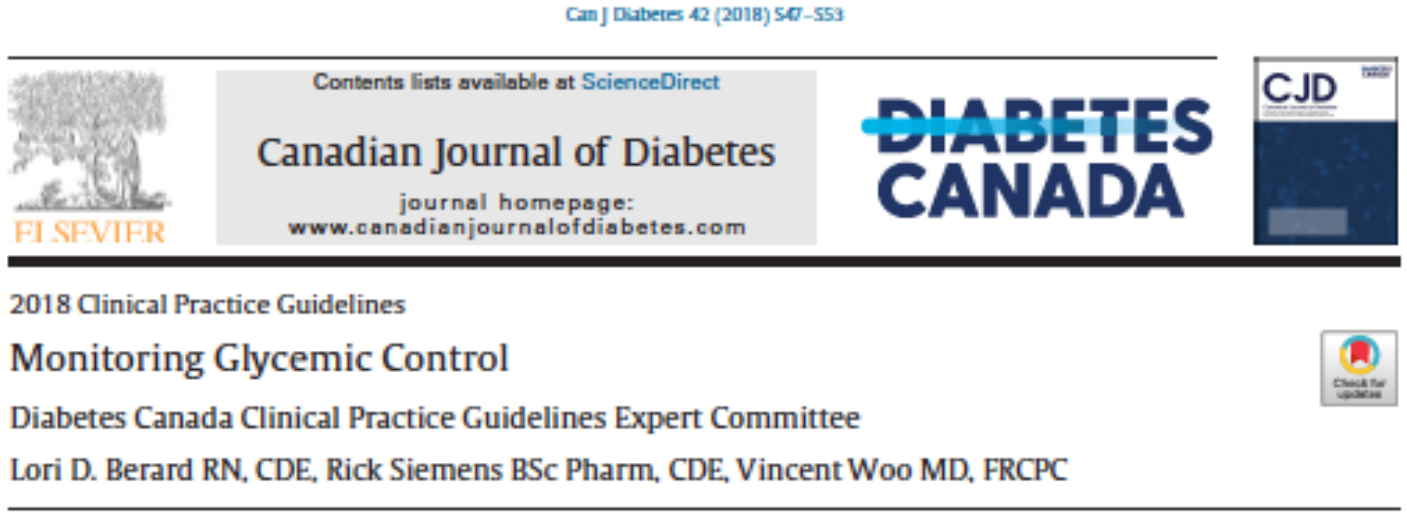
A. Never heard of TIR

B. Thinking about TIR

C. Using TIR consistently

D. Think TIR is a “gimic”

As a reminder 2018 Clinical Practice Guidelines



Can J Diabetes 42 (2018) S47–S53

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Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

2018 Clinical Practice Guidelines

Monitoring Glycemic Control

Diabetes Canada Clinical Practice Guidelines Expert Committee

Lori D. Berard RN, CDE, Rick Siemens BSc Pharm, CDE, Vincent Woo MD, FRCPC

Key messages

Awareness of all measures of glycemia - self-monitored blood glucose results including SMBG, flash glucose monitoring, continuous glucose monitoring and A1C - provides the best information to assess glycemic control

SMBG, self-monitoring of blood glucose

Berard LD, Siemens R, Woo V. Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada: monitoring glycemic control. *Can J Diabetes* 2018;42(Suppl 1):S47-S53

A Quick Review – What is the Evidence?

- A1C - “outcomes” predictor of risk of complications
- SMBG – “clinical decision making”
- Continuous glucose monitoring – A1C and hypoglycemia (CSII and MDI)
- Flash glucose monitoring - Hypoglycemia

Glucose Targets – Traditional with SMBG

Recommended blood sugar targets for most people with diabetes*

Your target may not be the same as the examples in this blood sugar levels chart. Yours should be specific to you.

	A1C**	Fasting blood glucose (sugar) / blood sugar before meals (mmol/L)	Blood sugar two hours after eating (mmol/L)
Target for most people with diabetes	7.0% or less	4.0 to 7.0	5.0 to 10.0 (5.0 – 8.0 if A1C** targets not being met)

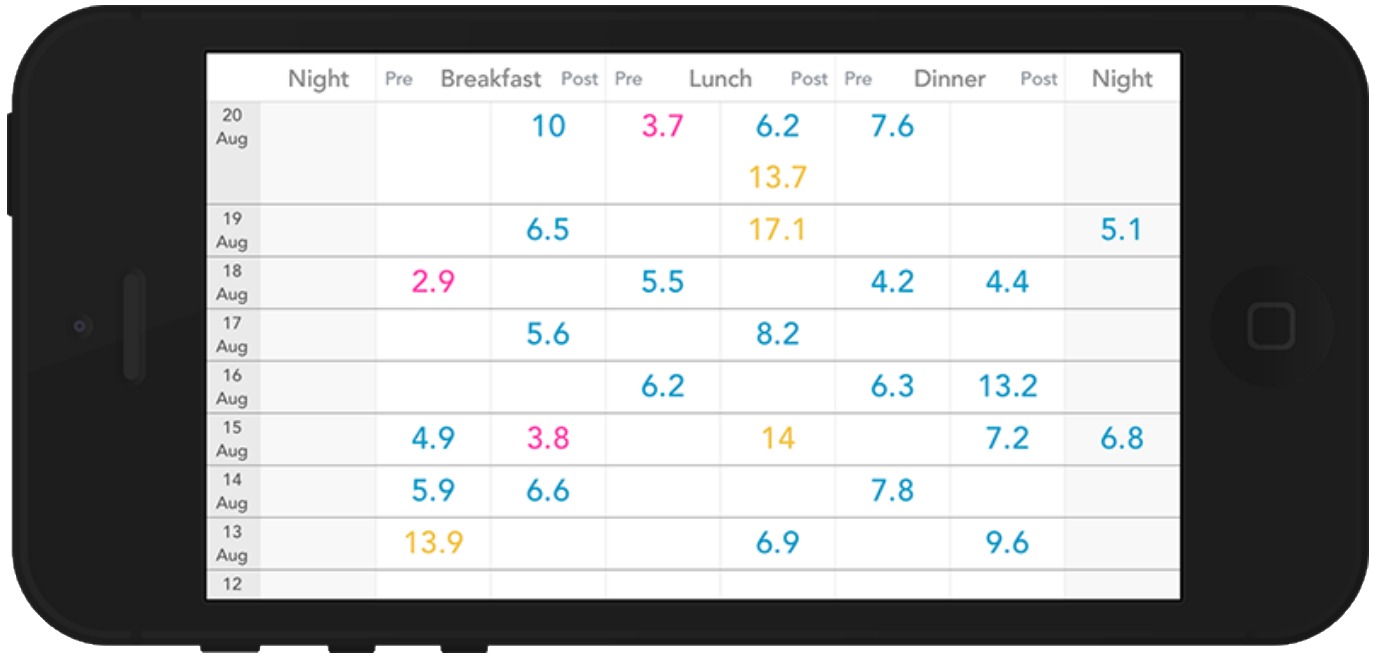
* This information is based on the Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada and is a guide.

** A1C is a measurement of your average blood sugar control for the last 2 – 3 months and approximately 50% of the value comes from the last 30 days.

A fingerstick represents one second of one minute of one hour of one day

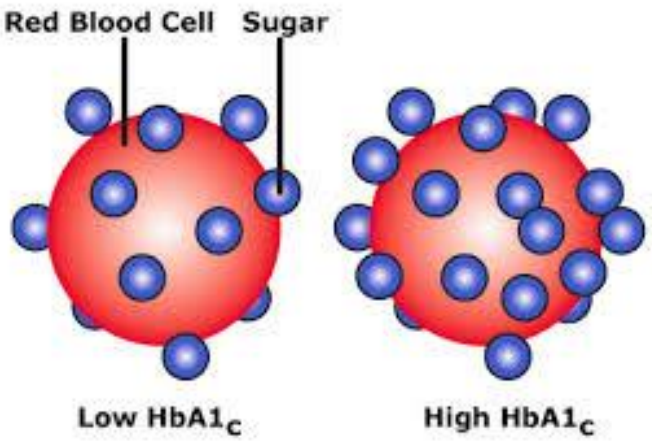
Various recommendations for testing

It is a snapshot of what is happening – a polaroid picture



	Night	Pre	Breakfast	Post	Pre	Lunch	Post	Pre	Dinner	Post	Night
20 Aug			10		3.7	6.2 13.7		7.6			
19 Aug			6.5			17.1					5.1
18 Aug		2.9			5.5			4.2	4.4		
17 Aug			5.6			8.2					
16 Aug					6.2			6.3	13.2		
15 Aug		4.9	3.8			14			7.2		6.8
14 Aug		5.9	6.6					7.8			
13 Aug		13.9				6.9			9.6		
12											

A1C – The “GOLD” STANDARD



Which of the following is not correct regarding A1C measurements

A. Is not affected by blood transfusions or donations

B. Can be reduced in people with chronic kidney disease.

C. Can be inaccurate in people of different ethnic backgrounds.

D. Is a reliable estimate of glucose levels over the previous 8 to 12 weeks.

E. 30 days immediately preceding the blood sampling contributes 50% of the result and the prior 90 to 120 days contributes 10%

“In uncommon circumstances, where the rate of red blood cell turnover is significantly shortened or extended, or the structure of hemoglobin is altered, A1C may not accurately reflect glycemic status”

Factors that can affect A1C

Factor	Increased A1C	Decreased A1C	Variable change in A1C
Erythropoiesis	Iron deficiency B12 deficiency Decreased erythropoiesis	Use of erythropoietin, iron or B12 Reticulocytosis Chronic liver disease	
Altered hemoglobin			Fetal hemoglobin Hemoglobinopathies Methemoglobin Genetic determinants
Altered glycation	Alcoholism Chronic renal failure Decreased erythrocyte pH	Ingestion of aspirin, vitamin C or vitamin E Hemoglobinopathies Increased erythrocyte pH	
Erythrocyte destruction			
Assays	Increased erythrocyte lifespan: • Splenectomy	Decreased erythrocyte lifespan: • Chronic renal failure • Hemoglobinopathies • Splenomegaly • Rheumatoid arthritis • Antiretrovirals • Ribavirin • Dapsone	

Berard LD, Siemens R, Woo V. Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada: monitoring glycemic control. *Can J Diabetes* 2018;42(Suppl 1):S47-S53

Evidence for A1C ≤ 7.0%

The New England
Journal of Medicine

Volume 329 SEPTEMBER 30, 1993 Number 14

THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG-TERM COMPLICATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP*

THE LANCET

CORRESPONDENCE | VOLUME 352, ISSUE 9144, P1932, DECEMBER 12, 1998

The UK Prospective Diabetes study

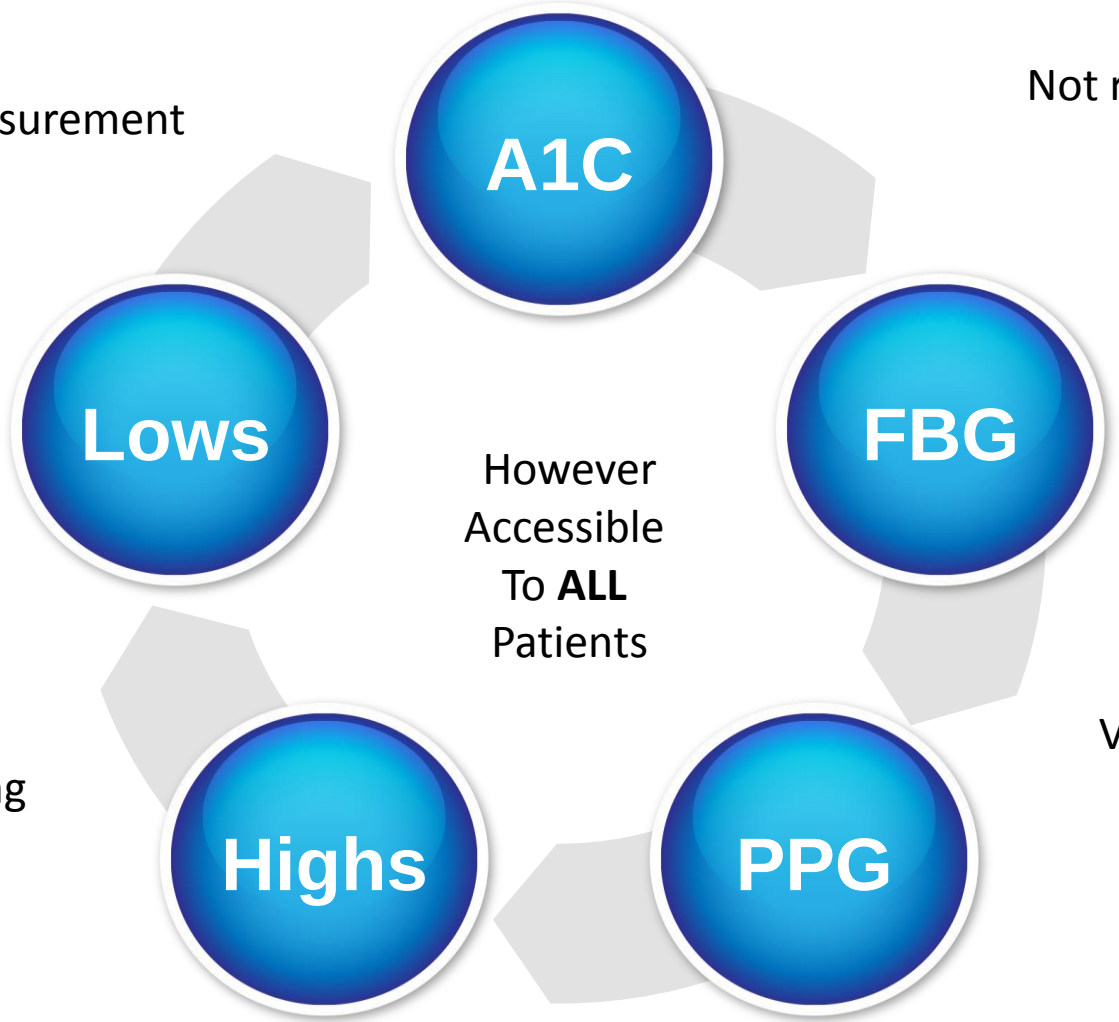
Clifford J Bailey • Peter J Grant

Published: December 12, 1998 • DOI: https://doi.org/10.1016/S0140-6736(98)00090-7

SMBG and A1C
The Complete Picture?

Long term measurement

Not reliable in all patients



Variable patient adherence

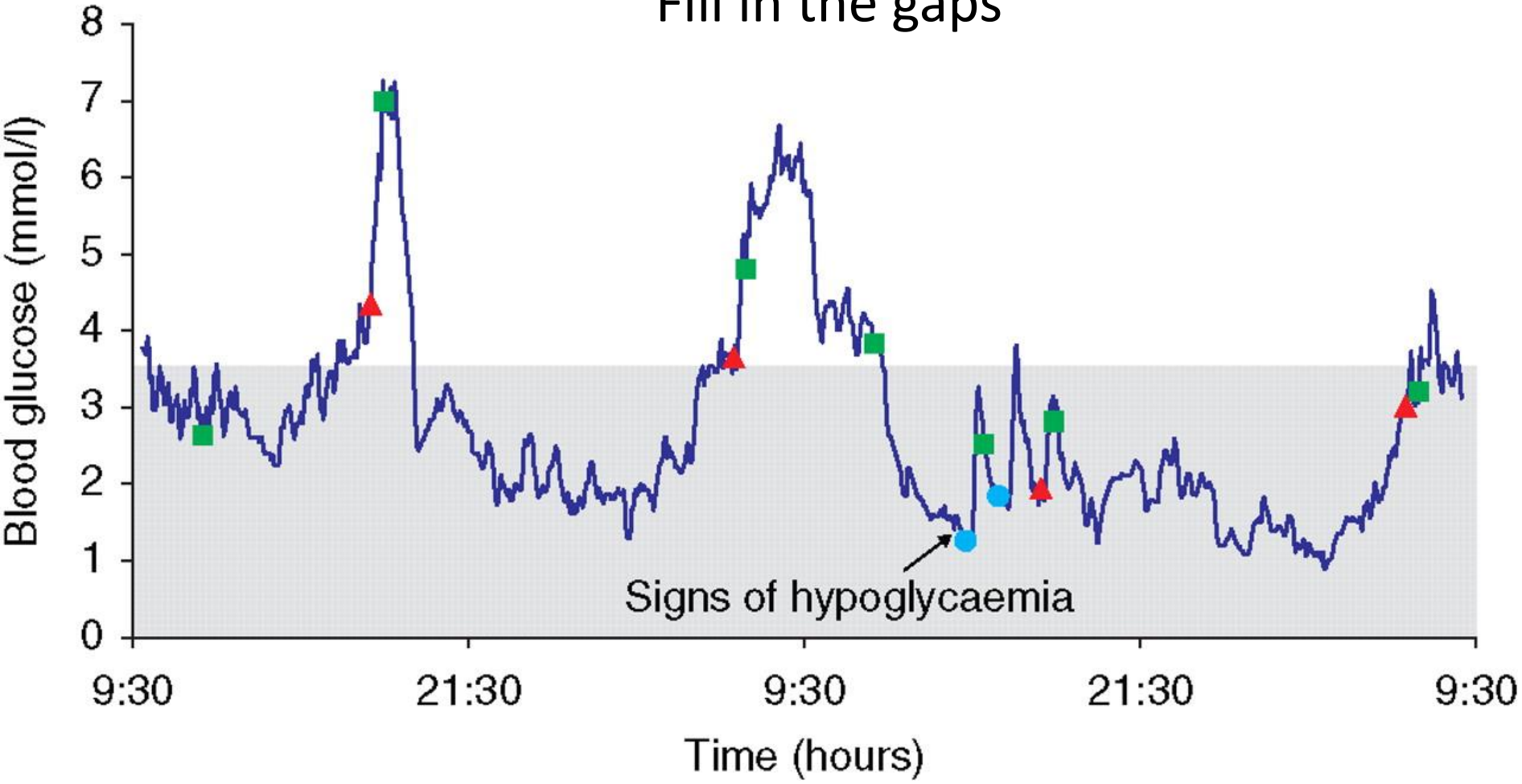
Often miss capturing

“Self Monitored Glucose”

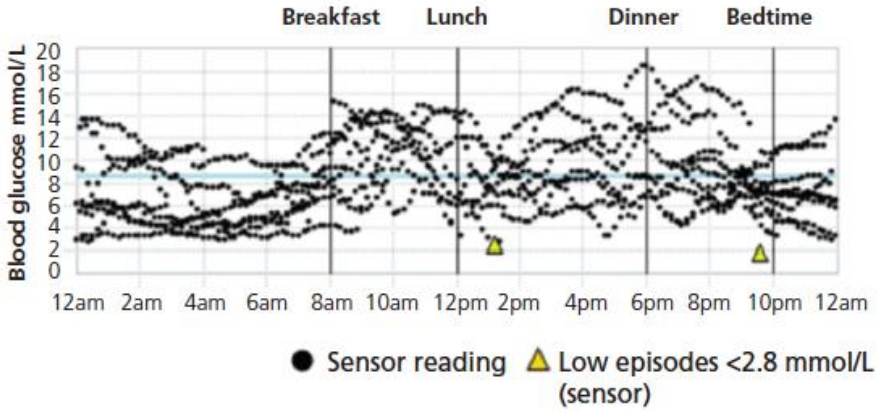
What is the role of interstitial fluid glucose monitoring?

“Continuous Glucose Monitoring
Flash glucose Monitoring

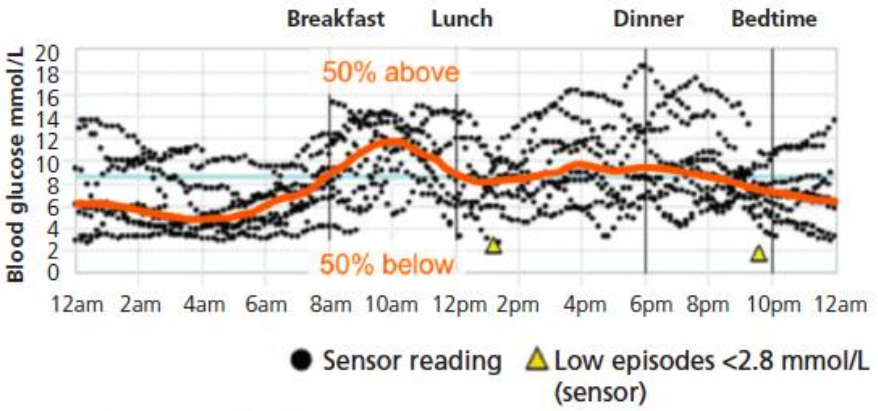
Fill in the gaps”



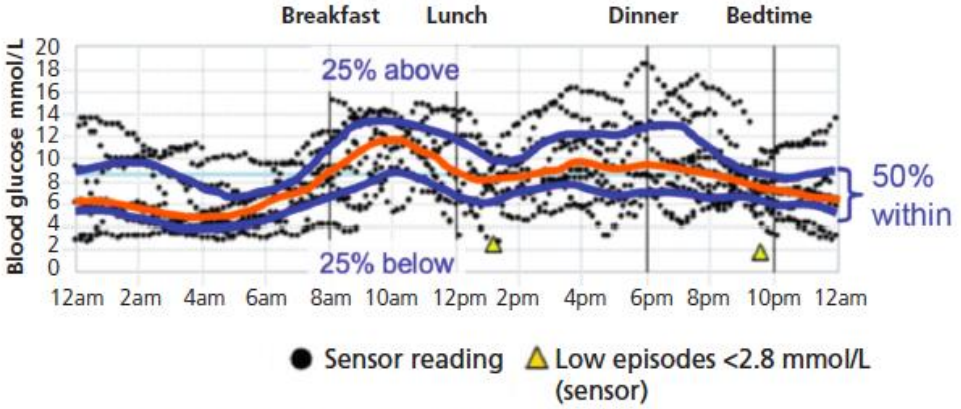
MORE IS NOT ALWAYS BETTER…



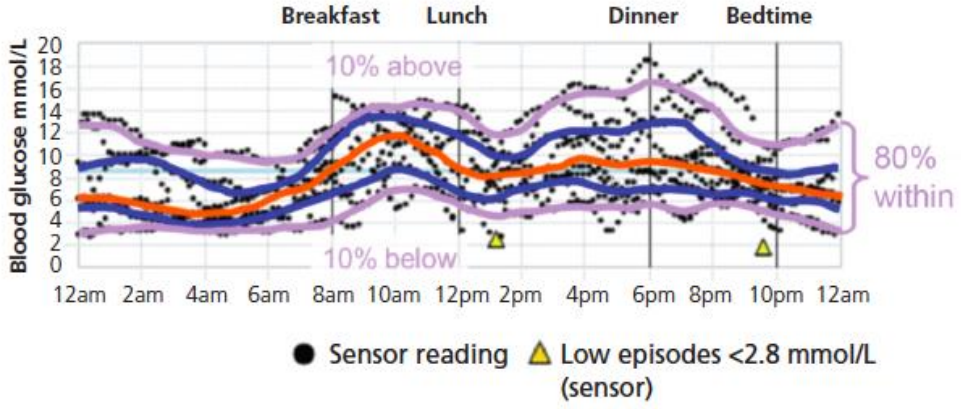
1. Modal day displaying all blood glucose readings obtained



2. Hourly median line is added



3. Hourly quartile lines are added



4. Hourly decile lines are added to complete the AGP

In Your Practice – For Patients using CGM or Flash Glucose Monitoring – You …

A. Download the devices at every visit and spend an hour looking at all those graphs
B. Ask the patients to send in their reports prior to appointment

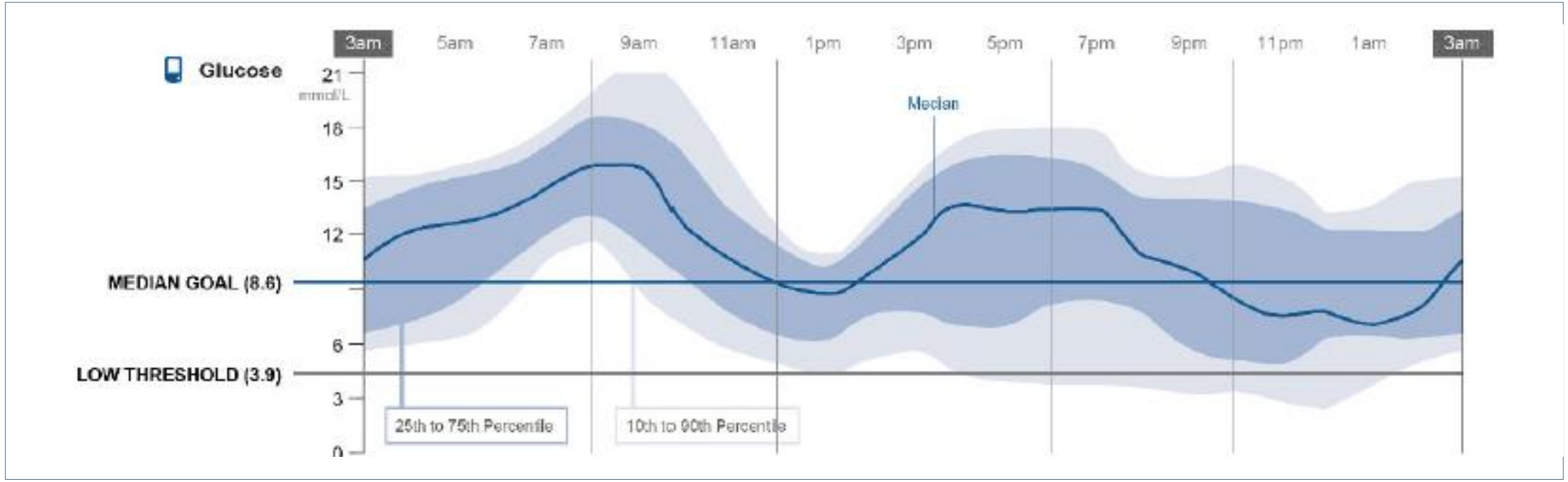
C. Use the devices to access the patient data

D. We have no time to look at this information – we use A1C

E. We do not feel confident looking at all this data

Managing the Data Tsunami….

THE AGP: 14-DAY PROFILE

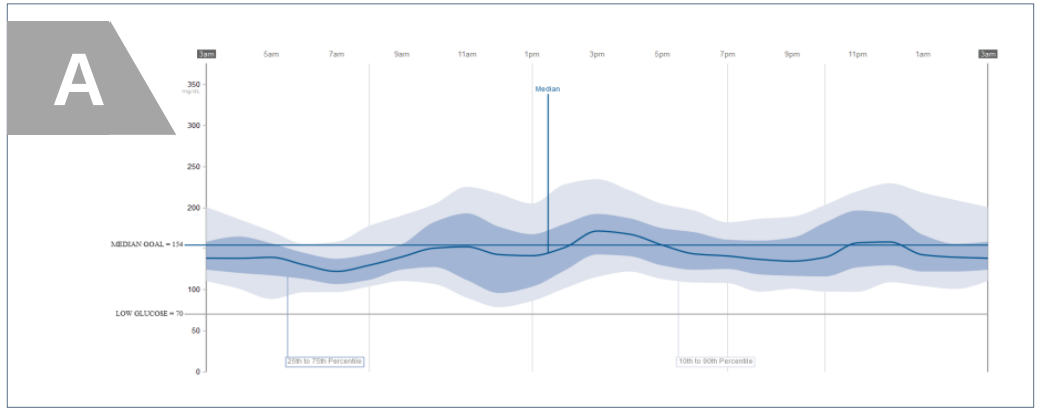


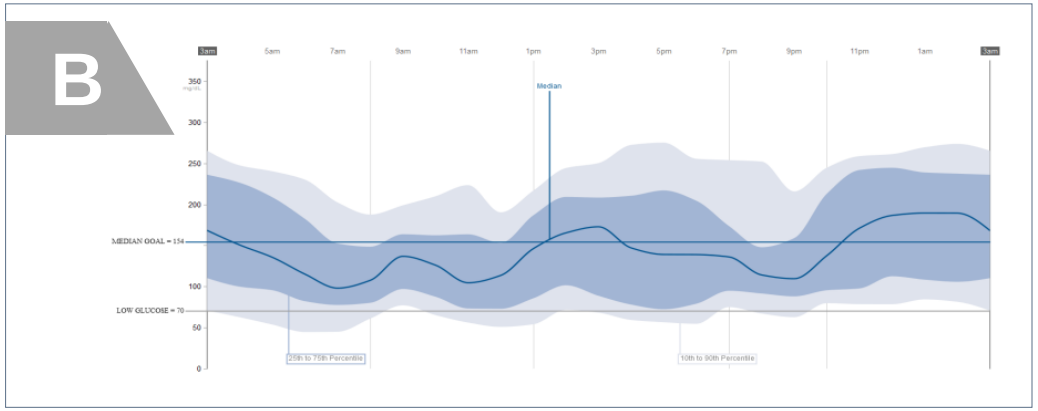
- Provides enough information to **identify daily glucose patterns and assess the efficacy of treatment**[1]

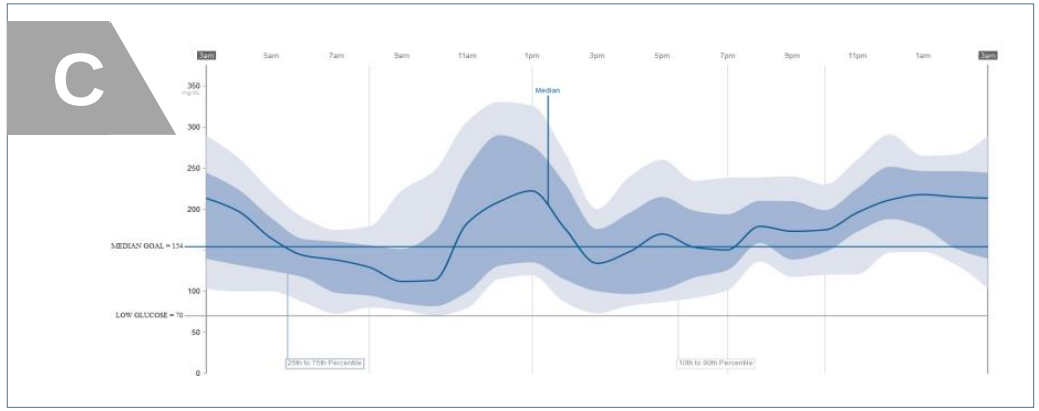
1. Dunn Timothy C., Crouther Nathan. Assessment of the variance of Ambulatory Glucose Profile over 3 to 30 days of continuous glucose monitoring. 46th European Association for the Study of Diabetes Annual Meeting, Stockholm. September 2010.
2. Mazze R.S., *et al.* (2001). Chapter 3: Characterizations of Glucose Metabolism. In Mazze R.S., Strock E.S., *et al* (eds). Staged Diabetes Management. 3rd edn. Wiley-Blackwell, Oxford.

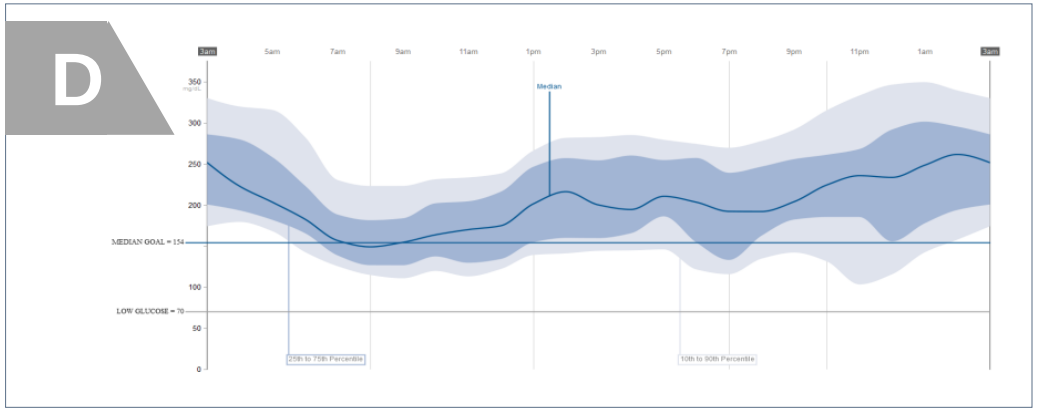
NOT ALL A1C'S ARE CREATED EQUAL

Four women with T1D, A1C = 7.6 to 7.7%









1. Dunn TC, Hayter GA, Doniger KJ, Wolpert HA. *J Diabetes Science and Tech* 2014;8(4).

Integrating Ambulatory Glucose Profile Into Clinical Practice

?Evidence?
?Experience?
?Easy?

WHAT IS TIME IN RANGE?

- An approach to glucose management with continuous interstitial fluid glucose monitoring – either CGM or Flash Glucose Monitoring
- Refers to the percentage of time that glucose concentrations are within, above and below targets[1].

1. Lang, Beck RW, Bergenstal RM, *et al.*, Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials." *Diabetes Care*, 2018, doi: 10.2337/dc18-144

DIABETES CARE

PUBLISH AHEAD OF PRINT, PUBLISHED ONLINE JUNE 8, 2019

Diabetes Care

Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range

https://doi.org/10.2337/dci19-0028

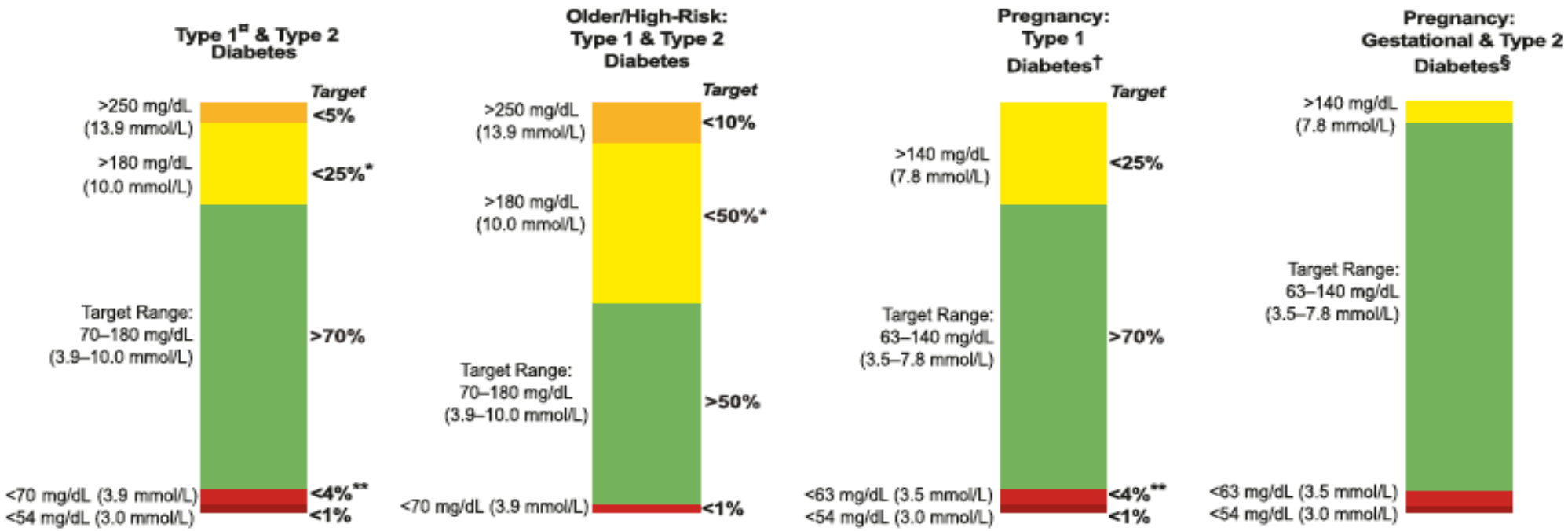
Table 2—Standardized CGM metrics for clinical care: 2019

1. Number of days CGM worn (recommend 14 days) (42,43)	
2. Percentage of time CGM is active (recommend 70% of data from 14 days) (41,42)	
3. Mean glucose	
4. Glucose management indicator (GMI) (75)	
5. Glycemic variability (%CV) target ≤36% (90)*	
6. Time above range (TAR): % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2
7. Time above range (TAR): % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1
8. Time in range (TIR): % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range
9. Time below range (TBR): % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1
10. Time below range (TBR): % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2
Use of Ambulatory Glucose Profile (AGP) for CGM report	

CV, coefficient of variation. *Some studies suggest that lower %CV targets (<33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas (45,90,91).

CGM-BASED TARGETS

FOR DIFFERENT DIABETES POPULATIONS[1]



¤ For age <25 yr., if the A1C goal is 7.5%, then set TIR target to approximately 60%. (See *Clinical Applications of Time in Ranges* section in the text for additional information regarding target goal setting in pediatric management.)

† Percentages of time in ranges are based on limited evidence. More research is needed.

§ Percentages of time in ranges have not been included because there is very limited evidence in this area. More research is needed. Please see *Pregnancy* section in text for more considerations on targets for these groups.

* Includes percentage of values >250 mg/dL (13.9 mmol/L).

** Includes percentage of values <54 mg/dL (3.0 mmol/L).

1. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range, Diabetes Care 2019 Aug; 42(8): 1593-1603.

UNDERSTANDING TIME IN RANGE

- Easy to assess risk related to hypoglycemia – less red
- Reflective of 'daily' diabetes management vs. A1c which is a measure of long-term risk[1]
- Recognized by patients as an important outcome - Highest ranked outcome to have a "big impact" on daily life for individuals with type 1 and type 2 diabetes[1]
- Improved time in range helps to reduce glycemic variability – less red and yellow - more green
- It is a "tool" – another way to analyze glucose measurements

1. Runge AS *et al.* Does time-in-range matter? Perspectives from people with diabetes on the success of current therapies and the drivers of improved outcomes. *Clin Diabetes* 2018; 36: 112-119.

Perspective

Table 5—Estimate of A1C for a given TIR level based on type 1 diabetes and type 2 diabetes studies

Beck et al. (26) (n = 545 participants with type 1 diabetes)			Vigersky and McMahon (27) (n = 1,137 participants with type 1 or type 2 diabetes)	
TIR 70–180 mg/dL (3.9–10.0 mmol/L)	A1C, % (mmol/mol)	95% CI for predicted A1C values, %	TIR 70–180 mg/dL (3.9–10.0 mmol/L)	A1C, % (mmol/mol)
20%	9.4 (79)	(8.0, 10.7)	20%	10.6 (92)
30%	8.9 (74)	(7.6, 10.2)	30%	9.8 (84)
40%	8.4 (68)	(7.1, 9.7)	40%	9.0 (75)
50%	7.9 (63)	(6.6, 9.2)	50%	8.3 (67)
60%	7.4 (57)	(6.1, 8.8)	60%	7.5 (59)
70%	7.0 (53)	(5.6, 8.3)	70%	6.7 (50)
80%	6.5 (48)	(5.2, 7.8)	80%	5.9 (42)
90%	6.0 (42)	(4.7, 7.3)	90%	5.1 (32)
Every 10% increase in TIR = ~0.5% (5.5 mmol/mol) A1C reduction			Every 10% increase in TIR = ~0.8% (8.7 mmol/mol) A1C reduction	

The difference between findings from the two studies likely stems from differences in number of studies analyzed and subjects included (RCTs with subjects with type 1 diabetes vs. RCTs with subjects with type 1 or type 2 diabetes with CGM and SMBG).

1. Runge AS *et al.* Does time-in-range matter? Perspectives from people with diabetes on the success of current therapies and the drivers of improved outcomes. *Clin Diabetes* 2018; 36: 112-119.

Time in Range - Reducing Hypoglycemia

- “Effective goals should utilize CGM data to identify specific instances for the patient to take measurable action to prevent hypoglycemia.”

- “When applying the CGM metrics in clinical practice, it may be more meaningful and motivating to communicate to people living with diabetes the importance of working to reduce the time spent ,70 mg/dL (,3.9 mmol/L) to less than 1 h per day and time spent , 54 mg/dL (,3.0 mmol/L) to less than 15 min per day, rather than using, 4% and ,1%, respectively, as the goal.”

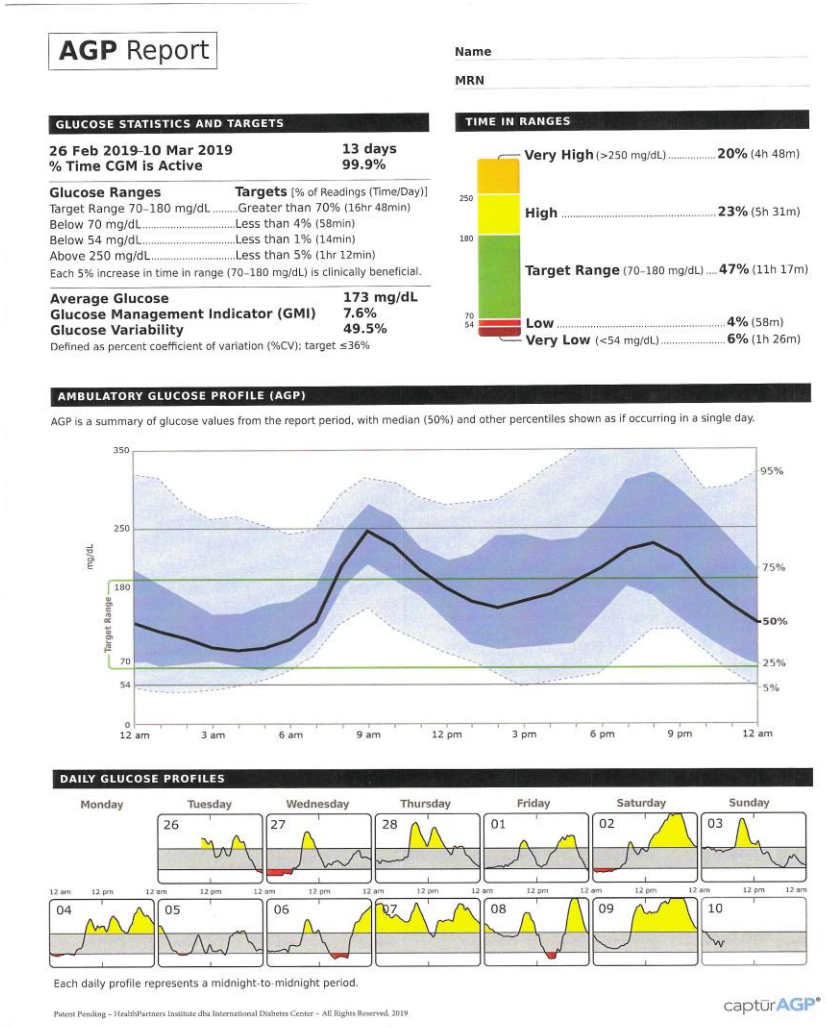
1. Runge AS *et al.* Does time-in-range matter? Perspectives from people with diabetes on the success of current therapies and the drivers of improved outcomes. *Clin Diabetes* 2018; 36: 112-119.

WHY IS ADDRESSING GLYCEMIC VARIABILITY (GV) IMPORTANT?

- Increasing GV is correlated with more frequent episodes of hypoglycemia[1-3]
- GV has been associated with increased ~~is~~ risk of diabetic retinopathy[4,5] and nephropathy[5]
- Emerging evidence of the relationship between GV and increased risk of severe hypoglycemia and cardiovascular outcomes[6]
- Patients experiencing severe hypoglycemia have an increased risk of cardiovascular outcomes and death, therefore reducing hypoglycemia is important[7]

1. *Diabetes* Monnier L, *et al. Diabetes Technol Ther* 2011;13:813-18.
2. Qu Y, *et al. Diabetes Technol Ther* 2012;14:1008-12.
3. Gorst, *et al. Diabetes Care.* 2015;38:2354-69.
4. Lu *et al Diabetes Care.* 2018;41:2370–2376
5. Lachin *et al Diabetes Care.* 2017 Jun;40(6):777-783. doi: 10.2337/dc16-2426. Epub 2017 Apr 12.
6. Zinman et al *Diabetologia.* 2018; 61: 48-57
7. Zinman *et al Diabetes Care.* 2018 Aug;41(8):1783-1791

Is it Ambulatory Glucose Profile or Time in Range?



AGP Report

Name

MRN

GLUCOSE STATISTICS AND TARGETS

26 Feb 2019-10 Mar 2019	**13 days**
% Time CGM is Active	**99.9%**

Glucose Ranges	**Targets** [% of Readings (Time/Day)]
Target Range 70–180 mg/dL	Greater than 70% (16hr 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 250 mg/dL	Less than 5% (1hr 12min)

Each 5% increase in time in range (70–180 mg/dL) is clinically beneficial.

Average Glucose	**173 mg/dL**
Glucose Management Indicator (GMI)	**7.6%**
Glucose Variability	**49.5%**

Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES

250
180
70
54

Very High (>250 mg/dL) **20%** (4h 48m)
High **23%** (5h 31m)
Target Range (70–180 mg/dL) ... **47%** (11h 17m)
Low **4%** (58m)
Very Low (<54 mg/dL) **6%** (1h 26m)

AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.

mg/dL
Target Range
350
250
180
70
54
0
95%
75%
50%
25%
5%
12 am
3 am
6 am
9 am
12 pm
3 pm
6 pm
9 pm
12 am

DAILY GLUCOSE PROFILES

Monday Tuesday Wednesday Thursday Friday Saturday Sunday

26 27 28 01 02 03
04 05 06 07 08 09 10

Each daily profile represents a midnight-to-midnight period.

captürAGP®

Glucose Statistics

"Monitoring "

(Accountability Metrics)

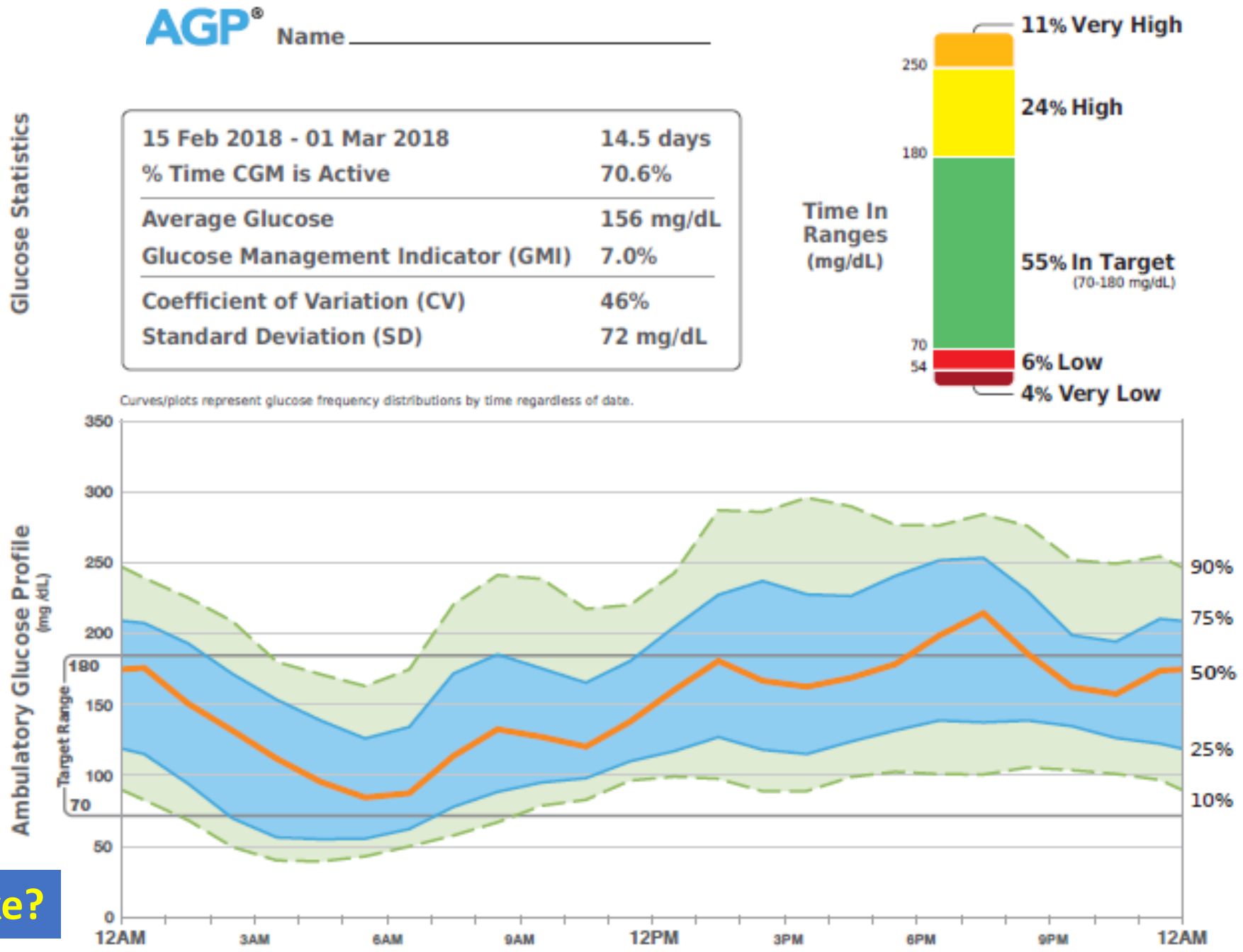
Do I need to take action?

AGP –

"Patterns Management"

(Therapy Adjustment)

What action do I need to take?



www.AGPreport.org

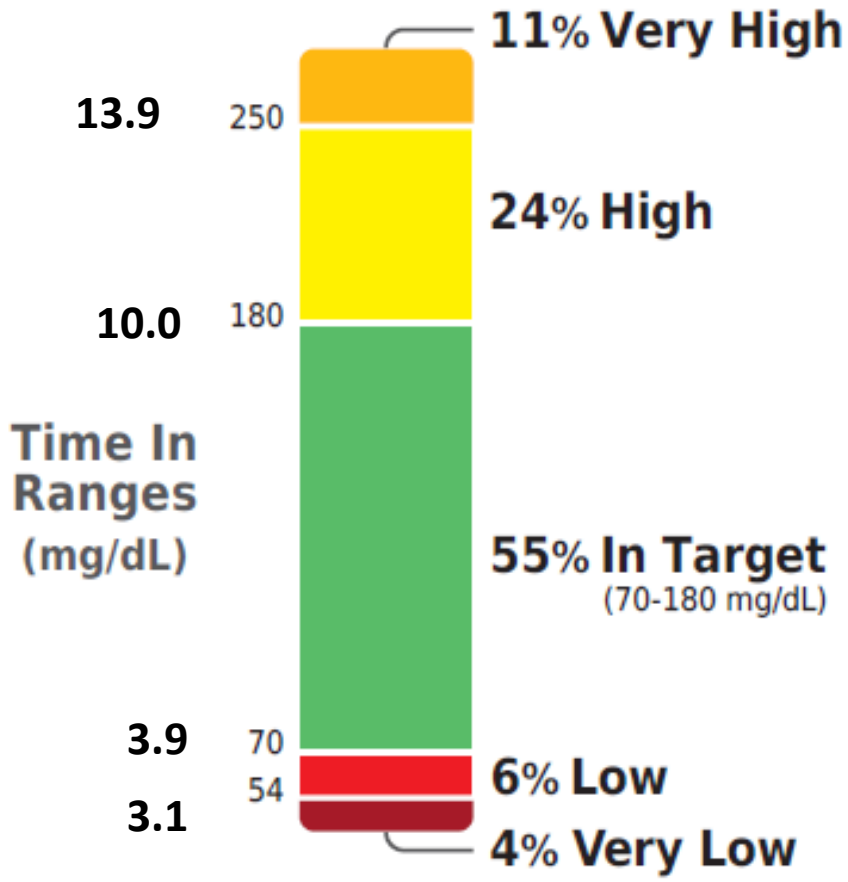
Population Health Metric

A1C

7.8 %

Personalized Care Metrics

TIR (CGM)



Reference. Richard Bergenstal DC Conference Oct 2019

Final Slide

- Reviewed measures of glycemia that help guide decisions making
- Discussed advantages and disadvantages of tools to guide diabetes care
- Introduced the concept of time in range
- Debate – A1C versus Time in Range???

Which of the following statements is NOT correct?

A. Time in range is going to replace A1C.

B. Time in range give us information about lows, highs, glycemic variability and quality of A1C.

C. For some people Time in Range may be more accurate than A1C.

D. Time in Range provide real time feedback on diabetes self care changes.