Improved clinical concordance of TIR and HbA1c by accounting for personal glycation factors

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	No, Nothing to disclose
X	Yes, please specify disclosures

Company / Name	Honoraria / Expense	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity Position	Employee	Other (Please specify)
Abbott						Yes	Yes	

BACKGROUND

ADA Standards of Care[1] recognizes A1C can represent a large range of average glucose levels

Table 6.1—Estimated average glucose (eAG)

A1C (%)	mg/dL*	mmol/L
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

95% Confidence Intervals

95% CI Range of Average Glucose (mg/dL)	95% CI Range of Average Glucose (mmol/L)
44	2.5
52	3.0
62	3.5
70	4.0
79	4.5
89	5.0
97	5.5
107	6.0

1. *Diabetes Care* 2023;46(Suppl. 1):S97–S110

ADA Standards of Care[1] describes limitations of A1C to reflect average glycemia due to variations in **red blood cell lifespan**, and reports[2] indicate variation in **overall glycation rate**

"...hemolytic and other anemias, glucose-6-phosphate dehydrogenase deficiency, recent blood transfusion, use of drugs that stimulate erythropoiesis, endstage kidney disease, and pregnancy... **may result in discrepancies between the A1C result and the patient's true mean glycemia**"

A1C has 3 major drivers:

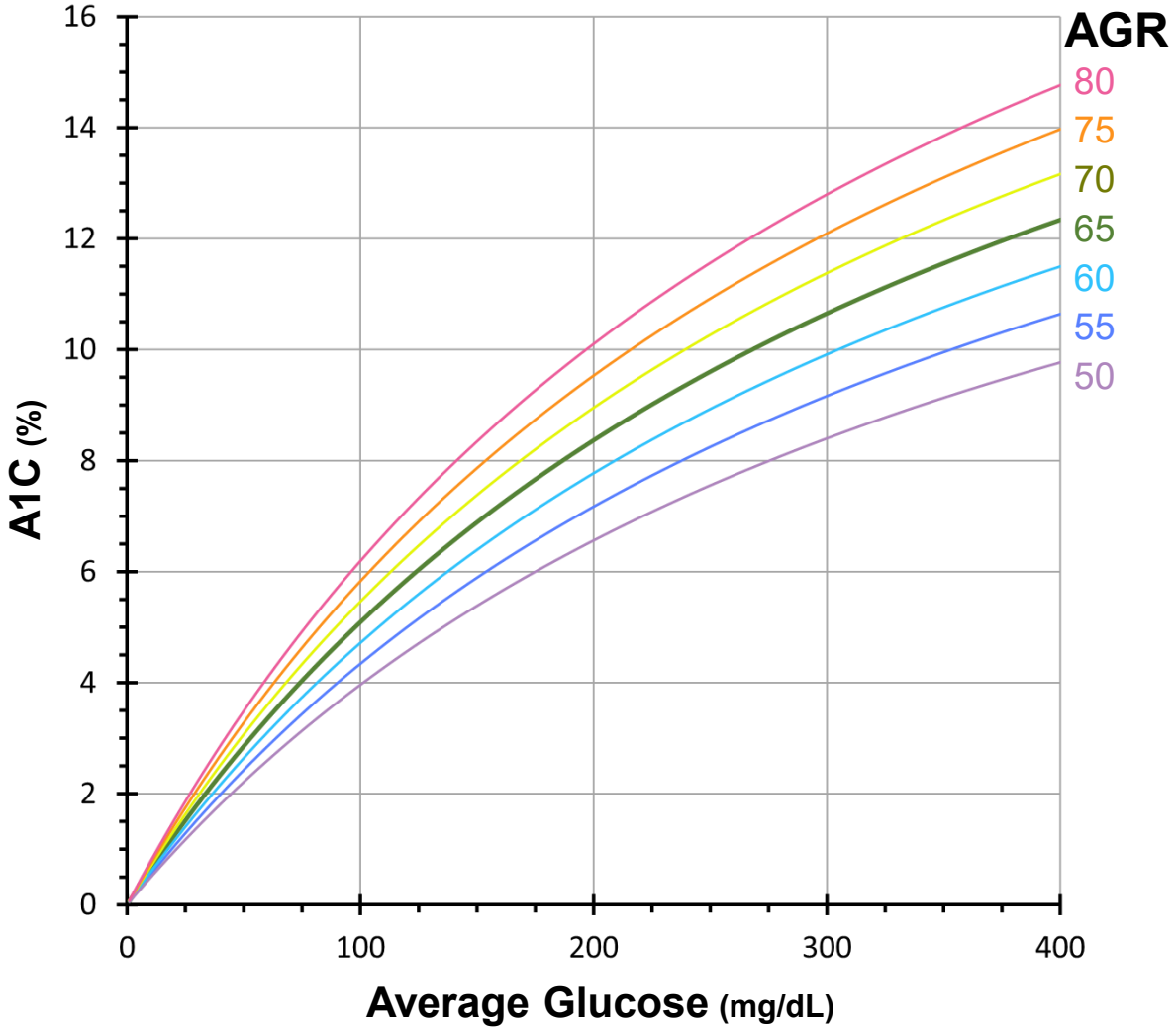
1. Average glucose
2. RBC lifespan
3. Overall Hb glycation

Combined, these can be considered as:
"Apparent Glycation Rate"

1. *Diabetes Care* 2023;46(Suppl. 1):S97–S110
2. Ladyzynski et al. *J Trans Med*. 2014; 12:328

BACKGROUND

Using a novel model[1-7] the AGR can be found with time-matched values of Average Glucose and A1C



$$\mathrm{AGR} = \frac{\frac{1}{\text{Average Glucose}} + \frac{1}{\mathrm{K_M}}}{\frac{1}{\mathrm{A1C}/100} - 1} * 10^5$$

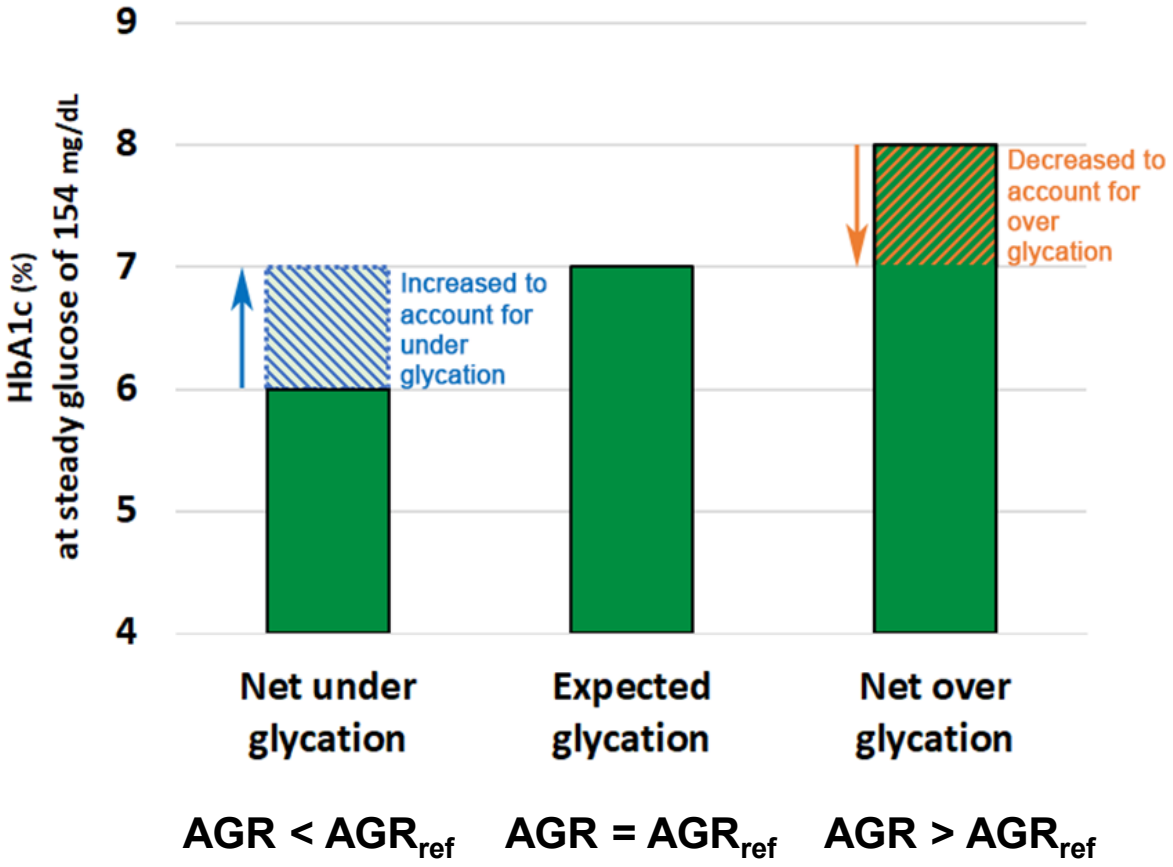
where:

$\mathrm{K_M} = 472$ mg/dL [8]

[1] Xu, et al. *J Diabetes Sci Technol*. 2021 Mar;15(2):294-302
[2] Xu, et al. *Diabetes Technol Ther*. 2021 Jun;23(6):452-459
[3] Xu, et al. *Diab Vasc Dis Res*. 2021 May-Jun;18(3)
[4] Xu, et al. *elife*. 2021 Sep 13;10:e69456
[5] Xu, et al. *Diabetes Obes Metab*. 2022 Sep;24(9):1779-1787
[6] Xu, et al. *Diabetes Obes Metab*. 2022 Dec;24(12):2383-2390
[7] Hirota, et al. *Diabetes Obes Metab*. 2023 Jan;25(1):319-322
[8] Nishimura, et al. *J Biol Chem*. 1993;268(12):8514-8520.

BACKGROUND

Our novel model[1-7] proposes a **Personalized A1C (pA1C)** adjusted to reflect average glucose levels in standard RBCs to match clinical trial findings



$$\text{Personalized A1C} = \text{pA1C} = \frac{100}{1 + \frac{AGR}{AGR_{ref}}\left(\frac{100}{A1C} - 1\right)}$$

where:

$AGR_{ref} = 65.1$ dL/mg

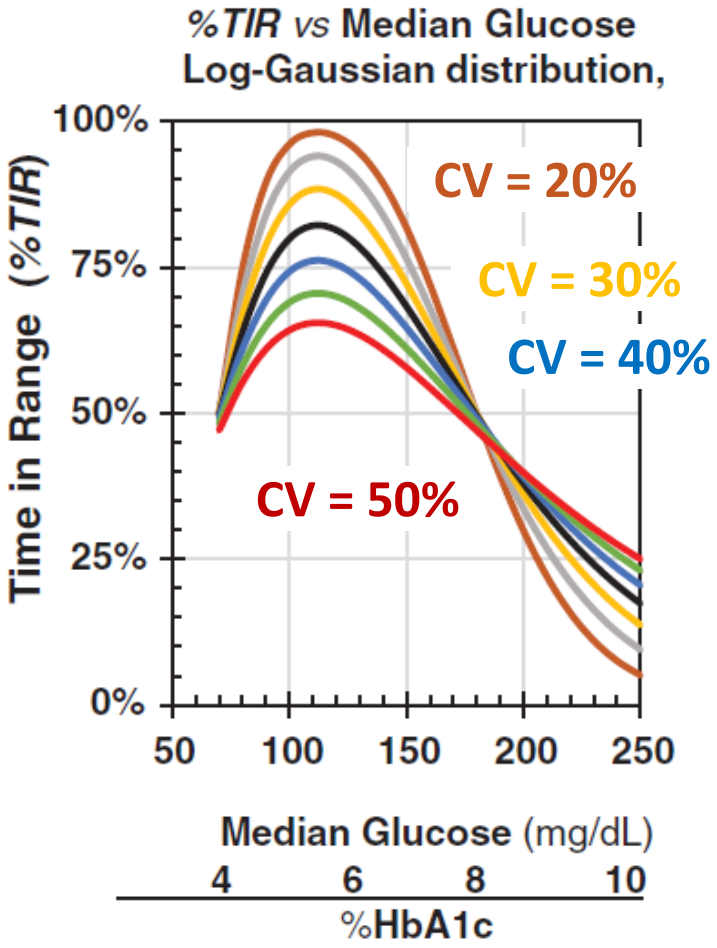
Standard RBC lifespan = 105 days [8]

Standard RBC glycation rate constant= 6.2 e-6 dL/mg/day [9]

[1] Xu, et al. *J Diabetes Sci Technol*. 2021 Mar;15(2):294-302
[2] Xu, et al. *Diabetes Technol Ther*. 2021 Jun;23(6):452-459
[3] Xu, et al. *Diab Vasc Dis Res*. 2021 May-Jun;18(3)
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[5] Xu, et al. *Diabetes Obes Metab*. 2022 Sep;24(9):1779-1787
[6] Xu, et al. *Diabetes Obes Metab*. 2022 Dec;24(12):2383-2390
[7] Hirota, et al. *Diabetes Obes Metab*. 2023 Jan;25(1):319-322
[8] Khera, et al. *Am J Hematol*. 2015; 90:50-55
[9] Ladyzynski et al. *J Trans Med*. 2014; 12:328

AIMS

- Evaluate improved A1C accuracy at reflecting in-range glucose exposure by adjusting for a personal RBC factor
- Investigate the effects of glycaemic variability on A1C accuracy.



- Previous work[1] has described the theoretical relationship between TIR and A1C given an underlying shape of the glucose distribution
- The TIR-A1C relationship should vary with glucose variability (CV)

1. Rodbard D. *Diabetes Technol Ther*. 2020 Jul;22(7):492-500

CGM and A1C data

- 3 months of CGM preceding A1C values
  - (n=1,636 periods, from 758 people in 7 clinical trials[1])
- All individuals had 2 to 5 repeated A1C-CGM periods to determine their AGR
- Calculated metrics:
  - TIR 70-180 mg/dL (90-day period)
  - Glucose CV (90-day period)
  - Personalized A1C

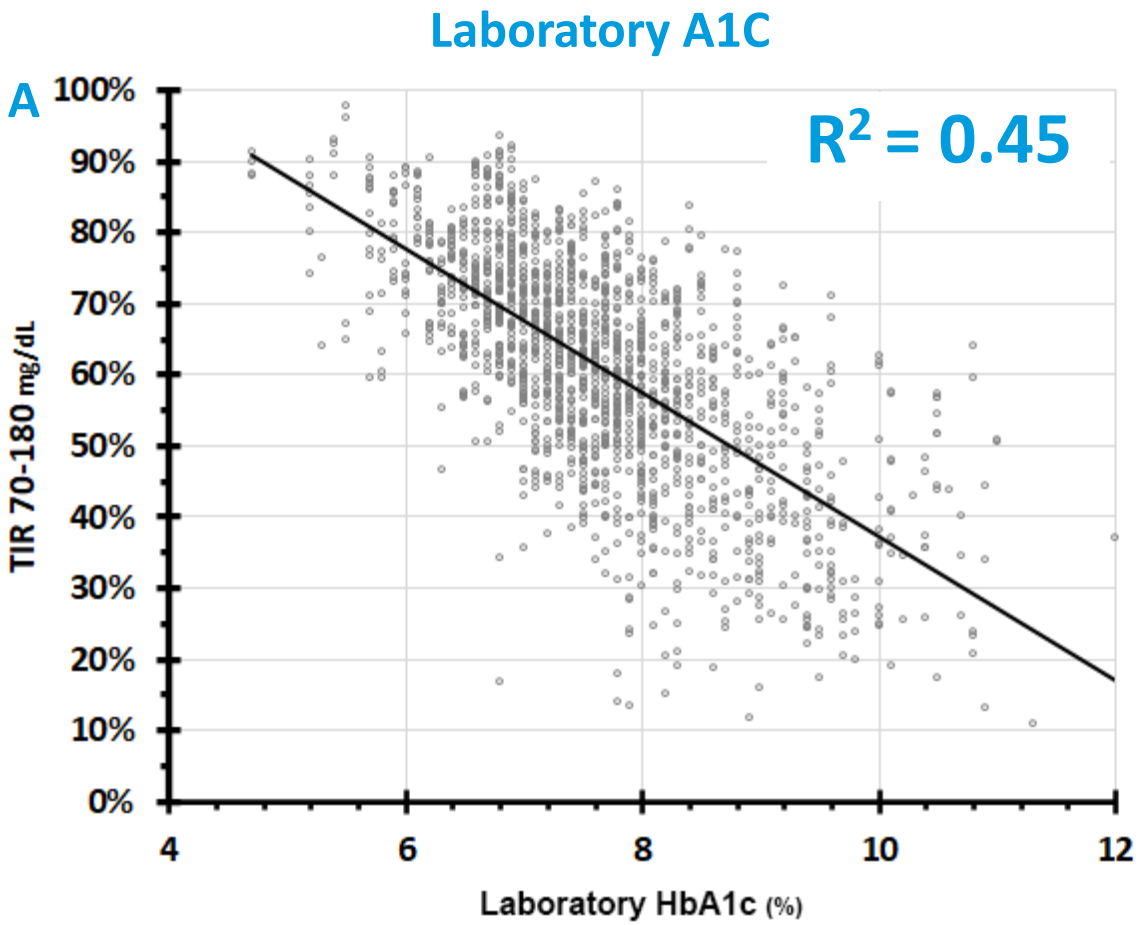
Statistical analysis

- Linear regression of TIR and A1C values
  - Overall
  - Subgroup by quartiles of glucose CV

1. Datasets available at Jaeb Center for Health Research https://www.jaeb.org/resources

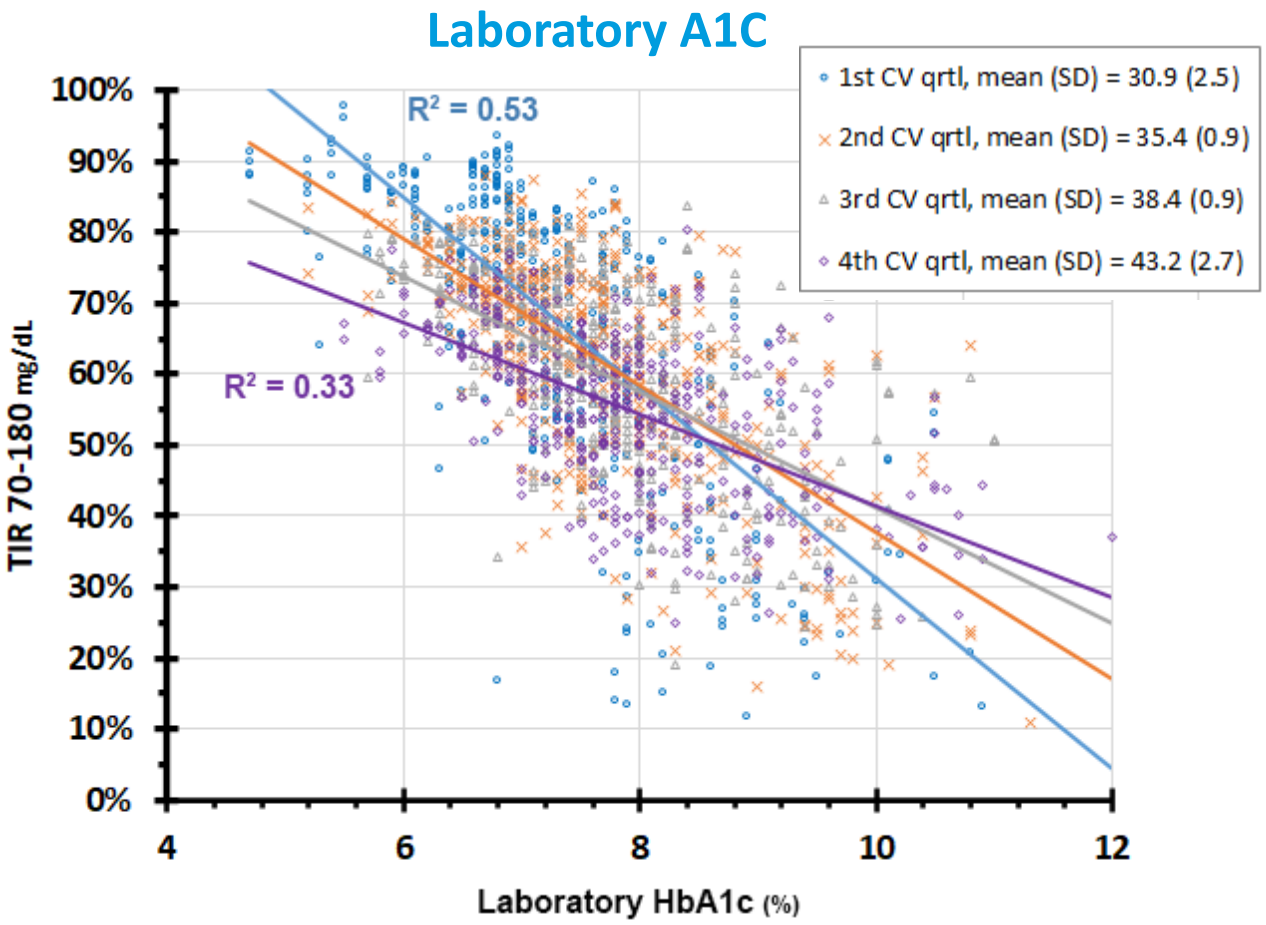
RESULTS 1 OF 2

Substantially better agreement between TIR and Personalized A1C



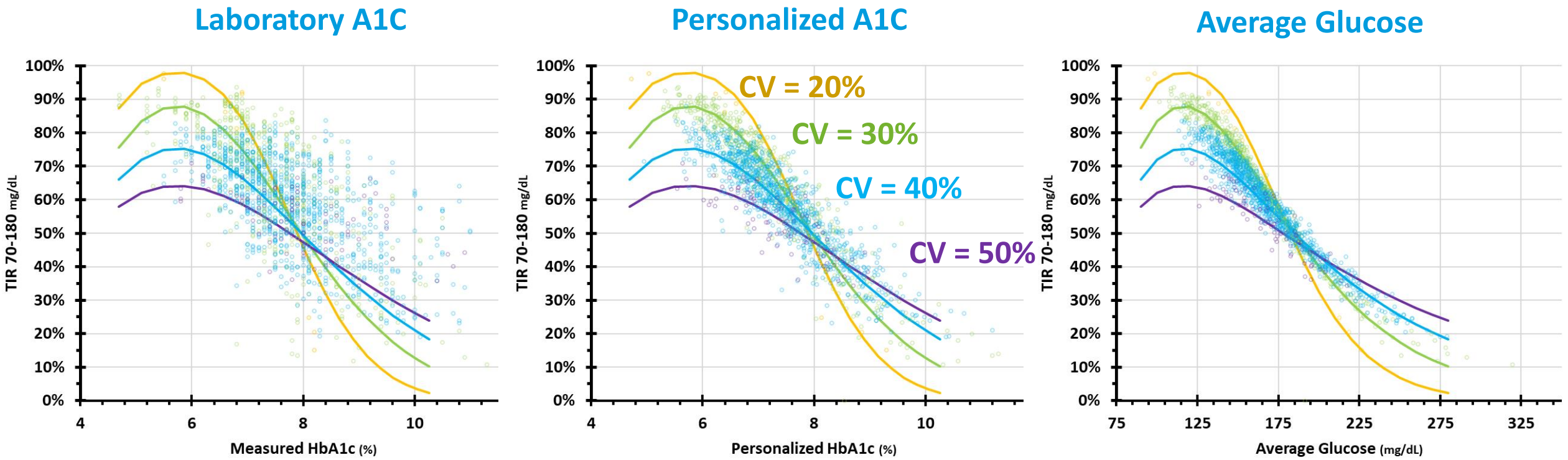
RESULTS 2 OF 2

Agreement between TIR and Personalized A1C maintained at high CV



DISCUSSION

Agreement with gamma-shaped underlying glucose distribution[1]



CV<25%	0.9%
25%<CV≤35%	34%
35%<CV≤45%	60%
45%<CV	5%

1. Xu, Y et al. Glucose Variability Alters the Relationship between Avearge Glucose and Time In Range: Implications for Clinical Practice. *ATTD*, 2023, E-Poster 320

Accounting for a personal glycation factor improves the accuracy of A1C at reflecting glucose exposure even in the presence of high GV

- Adjustment to standard RBC factor improves agreement between TIR at Personalized A1C
- Personalization of A1C supports consistent clinical decision-making when reviewing both A1C and CGM measures



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