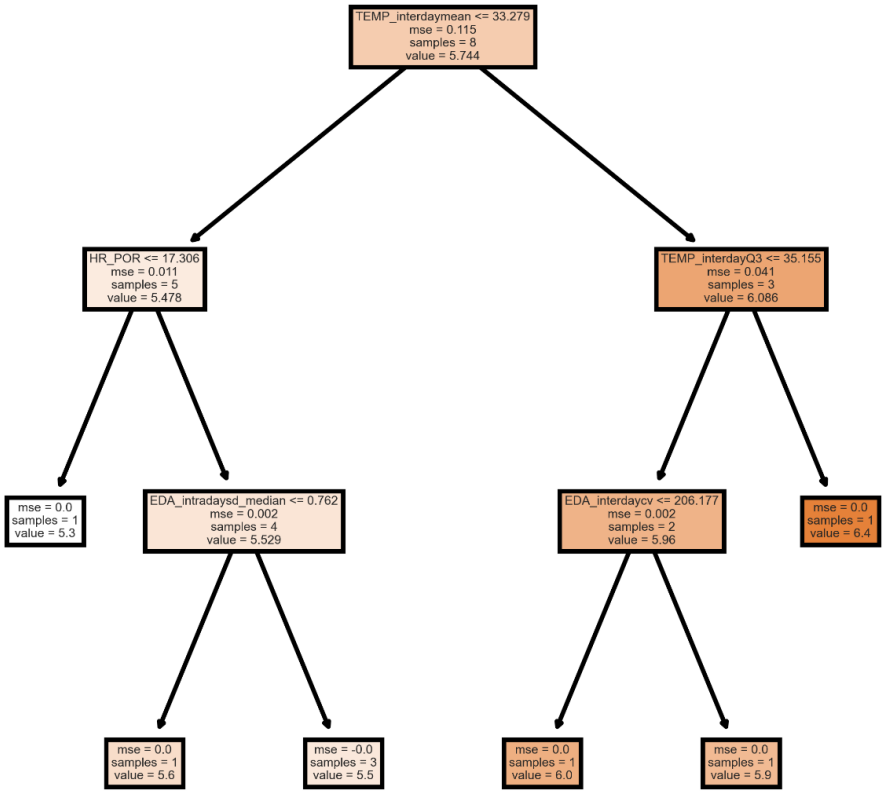
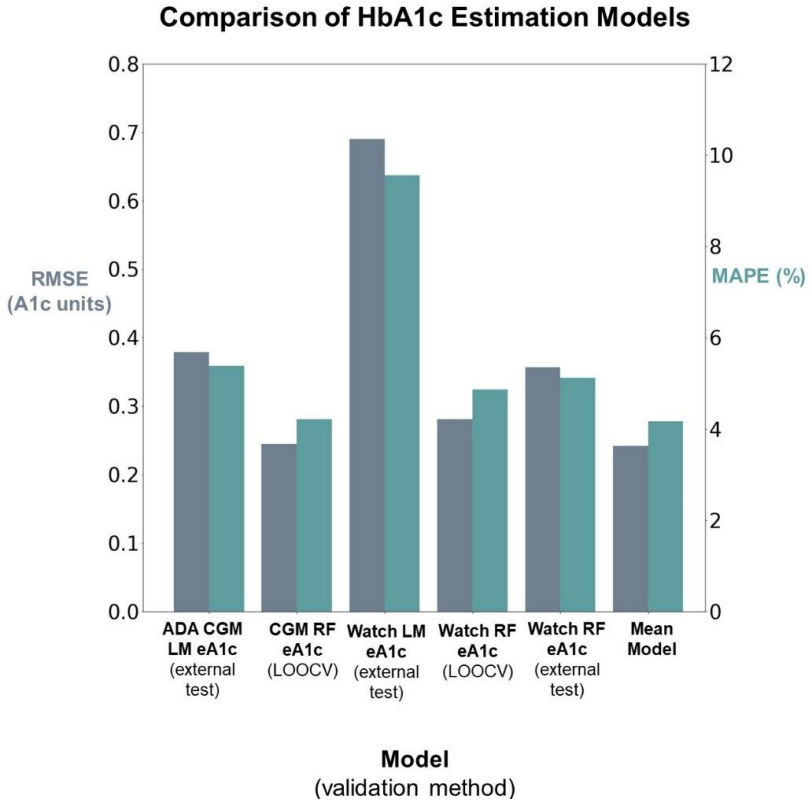
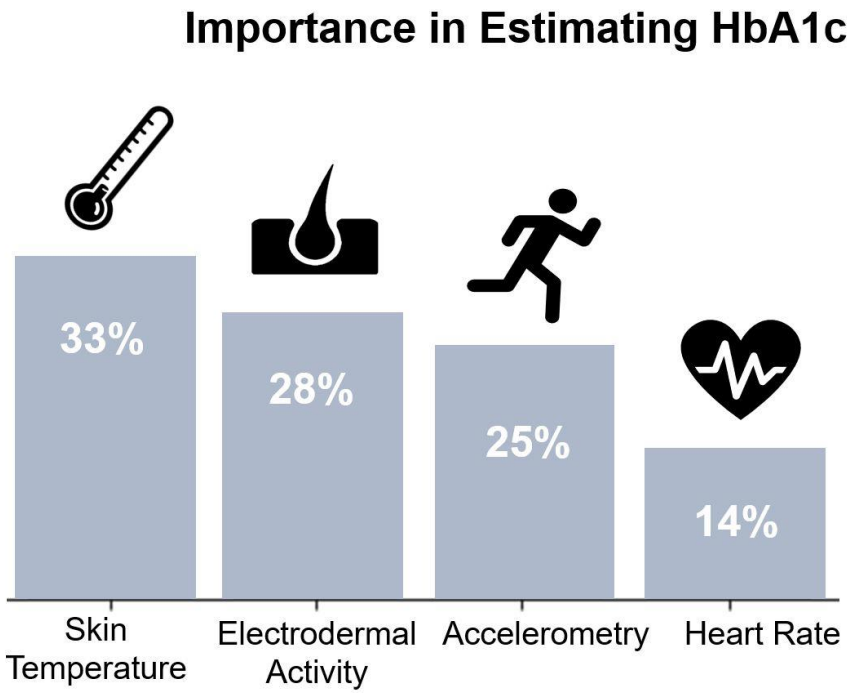
SUPPLEMENT



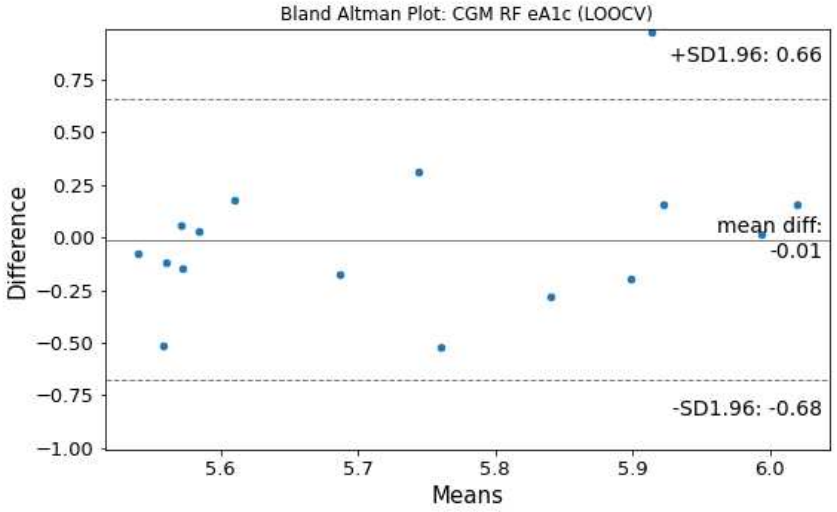
Supplementary Figure 1. An example of a decision tree used in the random forest model for HbA1c estimation with the *WatchRF* model. Please note that there are 1000 decision trees in each random forest and this is only one example, so the final model results may vary from the numbers and structure portrayed in this diagram. This is for explanatory purposes only.



Supplementary Figure 2. Comparison of A1c estimation models. Models: American Diabetes Association estimated A1c, our model estimating A1c using glucose metrics from CGM (LOOCV, tuned), our linear model using Watch data, our model using noninvasive wearable sensors (LOOCV, tuned), our model using noninvasive wearable sensors (tested on retrospective, external validation test set), and the mean model.



Supplementary Figure 3. The relative importance of wearable sensors in estimating clinical HbA1c in the *Watch RF (external validation test)* model.



Supplementary Figure 4. Bland Altman plots for the *CGM RF eA1c* model validated using LOOCV on the prospective cohort. The mean difference is shown with a solid line and limits of agreement are shown with dashed lines.

Supplementary Table 1. Glucose and Glucose Variability Metrics

Metric	Description	Equation
interdaySD[12,31]	Interday standard deviation of glucose	$\sigma_{interday} = \sqrt{\frac{\sum(G_i - \mu)^2}{N}}$ Where N = total days, G= glucose value
interdayCV[12]	Interday coefficient of variation of glucose	$CV_{interday} = \frac{\sigma_{interday}}{\mu}$
intradaySD Mean[12]	Intraday standard deviation of glucose (mean across all days)	$\sigma_{intraday_{mean}} = \sum_N \sigma_i$
intradayCV Mean[12]	Intraday coefficient of variation of glucose (mean across all days)	$CV_{intraday_{mean}} = \sum_N CV_i$
intradaySD Median[37]	Intraday standard deviation of glucose (median across all days)	$\sigma_{intraday_{median}} = median\ (\sigma_i)$
intradayCV Median[37]	Intraday coefficient of variation of glucose (median across all days)	$CV_{intraday_{median}} = median\ (CV_i)$
intradaySD Standard Deviation[37]	Intraday standard deviation of glucose (standard deviation across all days)	$\sigma_{intraday_{standard\ deviation}} = SD\ (\sigma_i)$
intradayCV Standard Deviation[37]	Intraday coefficient of variation of glucose (standard deviation across all days)	$CV_{intraday_{standard\ deviation}} = SD\ (CV_i)$
CONGA24[14,31]	Continuous overall net glycemic action over 24 hours	$CONGA24 = SD\ (\lvert G_t - G_{t-24hours} \rvert$
GMI[32,35]	Glucose management indicator	$GMI = 3.31 + (0.02392 * \mu\ (mg/dL))$
HBGI[12,31]	High Blood Glucose Index	$\sum \frac{r_l}{n}$ $r_l = 22.7 * \left(f(G_i)\right)^2\ if\ f(G_i) \leq 0, r_l = 0\ otherwise$ $f(G_i) = \ln(G_i)^{1.084} + 5.381$
LBGI[12,31]	Low Blood Glucose Index	$\sum \frac{r_h}{n}$ $r_h = 22.7 * \left(f(G_i)\right)^2\ if\ f(G_i) > 0, r_l = 0\ otherwise$ $f(G_i) = \ln(G_i)^{1.084} + 5.381$
ADRR[12]	Average Daily Risk Range, assessment of total daily glucose variations within risk space	$ADRR = \frac{\sum_{all\ days}(LR^j + HR^j)}{N\ days}$ $where\ LR^j = \max(r_l)\ and\ HR^j = \max(r_h)$
J-index[31,33]	Measure of both the mean level and variability of glycemia	$J = 0.001 * (\mu + \sigma)^2$
MGE[31]	Mean of glucose excursions (default = 1SD)	$\mu_{glucose\ outside\ \#\ SD\ of\ mean}$

		Where # is set, default is 1 SD
MGN	Mean amplitude of normal glucose (default = 1SD)	$\mu_{glucose\ inside\ \#\ SD\ of\ mean}$
MODD[12,14]	Mean of daily differences in glucose	$MODD = \frac{\sum\lvert G_t - G_{t-24hours}\rvert}{total\ matched\ observations}$
TIR[11]	Time spent in range (minutes), default = 1SD	$TIR = \sum_N time\ inside\ \#\ SD\ of\ mean$
TOR[11]	Time spent outside range (minutes), default = 1SD	$TOR = \sum_N time\ outside\ \#\ SD\ of\ mean$
POR[34]	Percent of time spent outside range, default = 1SD	$POR = \frac{TOR}{total\ time}\ x\ 100\%$
PIR[34]	Percent of time spent inside range, default = 1SD	$PIR = \frac{TIR}{total\ time}\ x\ 100\%$
eA1c[36]	Estimated A1c (according to American Diabetes Association)	$eA1c = \frac{(46.7 + \mu)}{28.7}$
meanG[14]	Mean glucose over all days	$\mu = \frac{\sum_N \bar{x_i}}{N}$
medianG[32,37]	Median glucose over all days	$\text{median}(Glucose)$
minG[34]	Minimum glucose over all days	$\min(Glucose)$
maxG[34]	Maximum glucose over all days	$\max(Glucose)$
Q1G[34]	First quartile glucose value over all days	$\text{first quartile}(Glucose)$
Q3G[34]	Third quartile glucose value over all days	$\text{third quartile}(Glucose)$

Supplementary Table 2. Wearable Sensor Variability Metrics (each metric in this table was calculated for each wearable sensor)

Metric	**Description**	**Equation**
interday SD	Interday standard deviation	$\sigma_{interday} = \sqrt{\frac{\sum(S_i - \mu)^2}{N}}$

		Where N = total days, S= sensor value
interday CV	Interday coefficient of variation	$CV_{interday} = \frac{\sigma_{interday}}{\mu}$
intradaySD Mean	Intraday standard deviation (mean across all days)	$\sigma_{intraday_{mean}} = \sum_N \sigma_i$
intradayCV Mean	Intraday coefficient of variation (mean across all days)	$CV_{intraday_{mean}} = \sum_N CV_i$
intradaySD Median	Intraday standard deviation (median across all days)	$\sigma_{intraday_{median}} = median\ (\sigma_i)$
intradayCV Median	Intraday coefficient of variation (median across all days)	$CV_{intraday_{median}} = median\ (CV_i)$
intradaySD Standard Deviation	Intraday standard deviation (standard deviation across all days)	$\sigma_{intraday_{standard\ deviation}} = SD\ (\sigma_i)$
intradayCV Standard Deviation	Intraday coefficient of variation (standard deviation across all days)	$CV_{intraday_{standard\ deviation}} = SD\ (CV_i)$
MASE	Mean amplitude of sensor excursions (default = 1SD)	$\mu_{glucose\ outside\ \#\ SD\ of\ mean}$ Where # is set, default is 1 SD
TIR	Time spent in range (minutes), default = 1SD	$TIR = \sum_N time\ inside\ \#\ SD\ of\ mean$
TOR	Time spent outside range (minutes), default = 1SD	$TOR = \sum_N time\ outside\ \#\ SD\ of\ mean$
POR	Percent of time spent outside range	$POR = \frac{TOR}{total\ time}\ x\ 100\%$
interday mean	Mean over all days	$\mu = \frac{\sum_N \bar{x}_i}{N}$
interday median	Median over all days	$\text{median}(Sensor)$
interday minimum	Minimum over all days	$\min(Sensor)$
interday maximum	Maximum over all days	$\max(Sensor)$
interday Q1	First quartile over all days	$\text{first quartile}(Sensor)$
interday Q3	Third quartile over all days	$\text{third quartile}(Sensor)$
Mean of intraday mean	Intraday Mean (mean across all days)	$\mu_{intraday_{mean}} = \sum_N \mu_i$
Median of intraday mean	Intraday Mean (median across all days)	$\mu_{intraday_{median}} = median\ (\mu_i)$
Standard deviation of intraday mean	Intraday Mean (standard deviation across all days)	$\mu_{intraday_{standard\ deviation}} = SD\ (\mu_i)$

Supplementary Table 3. Demographics of Study Participants

Characteristic		Number of Participants Prospective Cohort	Number of Participants Retrospective Cohort
Sex			
	Male	8	5
	Female	8	5
Age, years			
	0-34	0	0
	35-39	0	1
	40-49	1	2
	50-59	11	3
	60-69	4	4
	70+	0	0
Race			
	White/Caucasian	11	6
	Black/African American	4	4
	Biracial	1	0
	Other	0	0

Supplementary Table 4. Glucose Variability Mean and Median Model Performance Comparison. Higher performance indicates lower evaluation metrics (RMSE) than the mean and/or median model.

Model to Estimate:	**Outperformed mean model**	**Outperformed median model**
Glucose Management Indicator	N	N
Interday Mean Glucose	N	N
Interday Median Glucose	Y	Y
Interday Minimum Glucose	N	Y
Interday Maximum Glucose	N	N
Interday Quartile 1 Glucose	Y	Y
Interday Quartile 3 Glucose	N	Y
Mean Amplitude of Glucose Excursions	Y	Y
Interday Standard Deviation	N	N
Mean of Intraday Standard Deviation	N	N
Standard Deviation of Intraday Standard Deviation	N	N
Median of Intraday Standard Deviation	Y	Y
Interday Coefficient of Variation	N	N
Mean of Intraday Coefficient of Variation	N	N
Standard Deviation of Intraday Coefficient of Variation	N	N
Median of Intraday Coefficient of Variation	Y	Y
J-index	Y	Y
Mean of Daily Differences	Y	Y
Percent Outside Range +/- 1 SD	N	N
Percent Inside Range +/- 1 SD	Y	Y
Time Outside Range +/- 1 SD	Y	Y
Time Inside Range +/- 1 SD	Y	Y
Average Daily Risk Range	N	N
Continuous overall net glycemic action for 24 hours	N	N
Mean of Normal Glucose	N	Y
Low blood glucose index	N	N
High blood glucose index	N	N

Supplementary Table 5. R squared for Each Glucose Variability Model. For each of the glucose variability models, we present the variance explained the model, R^2

Model	**R^2 (%)**
Glucose Management Indicator	11.91%
Interday Mean Glucose	13.12%
Interday Median Glucose	0.25%
Interday Minimum Glucose	53.48%
Interday Maximum Glucose	17.49%
Interday Quartile 1 Glucose	0.84%
Interday Quartile 3 Glucose	14.18%
Mean of Glucose Excursions	4.20%
Interday Standard Deviation	31.51%
Mean of Intraday Standard Deviation	15.69%
Standard Deviation of Intraday Standard Deviation	2.45%
Median of Intraday Standard Deviation	0.37%
Interday Coefficient of Variation	25.30%
Mean of Intraday Coefficient of Variation	40.04%
Standard Deviation of Intraday Coefficient of Variation	1.62%
Median of Intraday Coefficient of Variation	47.50%
J-index	15.05%
Mean of Daily Differences	6.25%
Percent Outside Range +/- 1 SD	39.20%
Percent Inside Range +/- 1 SD	39.75%
Time Outside Range +/- 1 SD	8.36%
Time Inside Range +/- 1 SD	20.13%
Average Daily Risk Range	15.24%
Continuous overall net glycemic action for 24 hours	15.42%
Mean of Normal Glucose	10.25%
Low blood glucose index	0.52%
High blood glucose index	0.63%

Supplementary Table 6. Relative Importance of Wearable Sensors for Each Glucose Variability Model. For each of the glucose variability models, we present the importance of each of the four wearable sensors in predicting that metric.

Model to Estimate:	**Skin Temperature Importance (%)**	**Electrodermal Activity Importance (%)**	**Accelerometry Importance (%)**	**Heart Rate Importance (%)**
Glucose Management Indicator	18.5	33.4	18.1	29.8
Interday Mean Glucose	19.3	32.1	18.1	30.3
Interday Median Glucose	17.9	36.2	19.5	26.0
Interday Minimum Glucose	28.3	27.3	19.0	25.2
Interday Maximum Glucose	23.2	16.2	18.8	40.7
Interday Quartile 1 Glucose	17.0	35.7	23.6	24.1
Interday Quartile 3 Glucose	20.3	35.0	16.7	27.9
Mean of Glucose Excursions	13.2	24.7	10.0	52.0
Interday Standard Deviation	21.7	27.5	15.3	35.1
Mean of Intraday Standard Deviation	21.7	39.3	14.1	24.8
Standard Deviation of Intraday Standard Deviation	14.1	43.2	13.1	29.4
Median of Intraday Standard Deviation	29.3	28.2	12.0	29.6
Interday Coefficient of Variation	20.8	20.7	13.4	44.2
Mean of Intraday Coefficient of Variation	21.7	39.3	14.1	23.8
Standard Deviation of Intraday Coefficient of Variation	14.1	43.2	13.1	29.4
Median of Intraday Coefficient of Variation	29.3	28.9	12.0	29.6
J-index	19.3	23.0	11.3	46.4
Mean of Daily Differences	17.1	20.9	13.8	48.1
Percent Outside Range +/- 1 SD	31.8	37.3	11.0	19.7
Percent Inside Range +/- 1 SD	30.1	37.8	12.3	19.8
Time Outside Range +/- 1 SD	32.5	11.4	25.7	29.7
Time Inside Range +/- 1 SD	24.9	12.2	26.25	35.6
Average Daily Risk Range	23.0	27.8	9.1	39.8
Continuous overall net glycemic action for 24 hours	29.7	17.8	13.6	38.9
Mean of Normal Glucose	17.7	24.9	20.8	26.3
Low blood glucose index	11.2	47.2	16.1	25.4
High blood glucose index	19.2	20.2	9.4	51.1

Supplementary Table 7. T-tests of statistical differences between models. (* signifies significance by being less than the Bonferroni corrected p-value of 0.005.) This table shows which t-test type was used to compare each of the models. Additionally, it shows the p-values of each of the comparisons.

Model 1	**Model 2**	**T-test type**	**p-value**
ADA CGM LM eA1c (external validation test)	CGM RF Model (LOOCV)	Paired	0.225
ADA CGM LM eA1c (external validation test)	Watch RF eA1c (LOOCV)	Paired	0.580
CGM RF Model (LOOCV)	Watch RF eA1c (LOOCV)	Paired	0.454
Watch RF eA1c (external validation test)	ADA CGM LM eA1c (external validation test)	two-sided t-test for two independent samples	0.807
Watch RF eA1c (external validation test)	CGM RF Model (LOOCV)	two-sided t-test for two independent samples	0.640
Watch RF eA1c (external validation test)	Watch RF eA1c (LOOCV)	two-sided t-test for two independent samples	0.913
Watch LM eA1c (external validation test)	ADA CGM LM eA1c (external validation test)	two-sided t-test for two independent samples	0.112
Watch LM eA1c (external validation test)	CGM RF Model (LOOCV)	two-sided t-test for two independent samples	0.0472
Watch LM eA1c (external validation test)	Watch RF eA1c (LOOCV)	two-sided t-test for two independent samples	0.0598
Watch LM eA1c (external validation test)	Watch RF eA1c (external validation test)	Paired	0.0748

Supplementary Table 8. Results of Watch RF eA1c (external validation test) models built using only one sensor: accelerometry, heart rate, electrodermal activity, and skin temperature.

Sensor used in individual sensor model	RMSE on external validation cohort	MAPE on external validation cohort
Accelerometry	0.421	6.057%
Heart Rate	0.338	5.295%
Electrodermal Activity	0.387	5.557%
Skin Temperature	0.362	5.830%

Supplementary Equation 1.

$$Y_i = \propto_i + \ a + b + c + d + e + f + g + h + i + j + k + l + \ \varepsilon_i$$

Where the observation (Y) is HbA1c for each participant (i). ε_i accounts for the random noise. The random effect parameter α_i accounts for participant-specific differences. The features include ACC MASE (a), ACC Interday Standard Deviation (b), HR percent out of range (c) + HR median of intraday standard deviation (d), ACC standard deviation of intraday mean (e), EDA MASE (f), EDA interday CV (g), EDA median of intraday standard deviation (h), TEMP interday mean (i), TEMP interday minimum (j), TEMP interday quartile 1 (k), and TEMP interday quartile 3 (l).

Supplemental Information 1.

GitHub repository with tables of each WatchRF and WatcheGluVar model importances: https://github.com/Big-Ideas-Lab/PoC_prediabetes