HbA1c, OGTT & CGM in defining stage 2 and 3 T1D

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CHILDHOOD DIABETES PREVENTION SYMPOSIUM

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Presenter Disclosure

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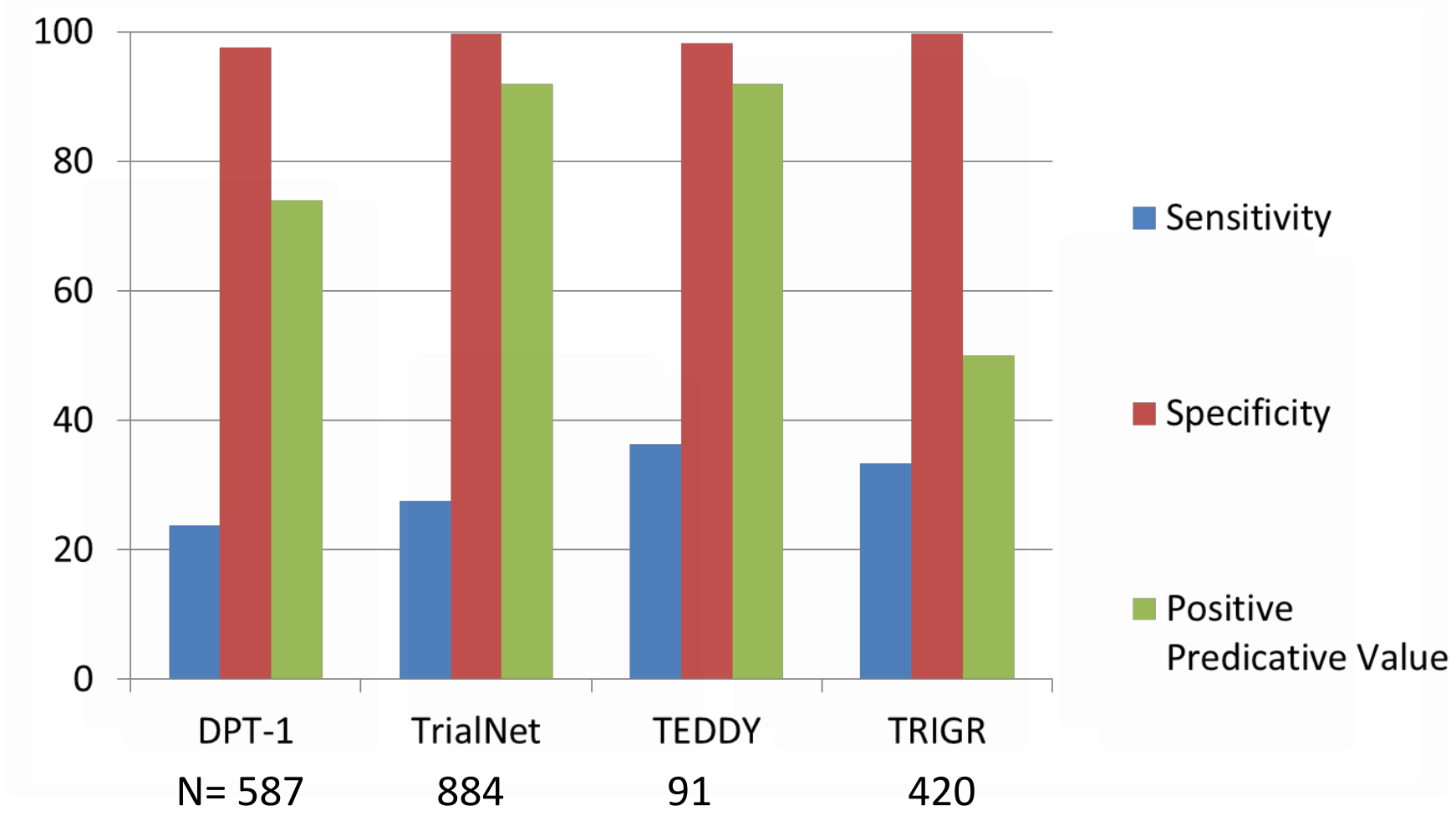
Monitoring in Early-Stage T1D

- Prevents presentation in DKA
- Improves long-term outcomes
- Allows for intervention & disease modulation
- Available tools for monitoring: HbA1c, Self-Monitoring of Blood Glucose (SMBG), Oral Glucose Tolerance Test (OGTT), Continuous Glucose Monitoring (CGM)

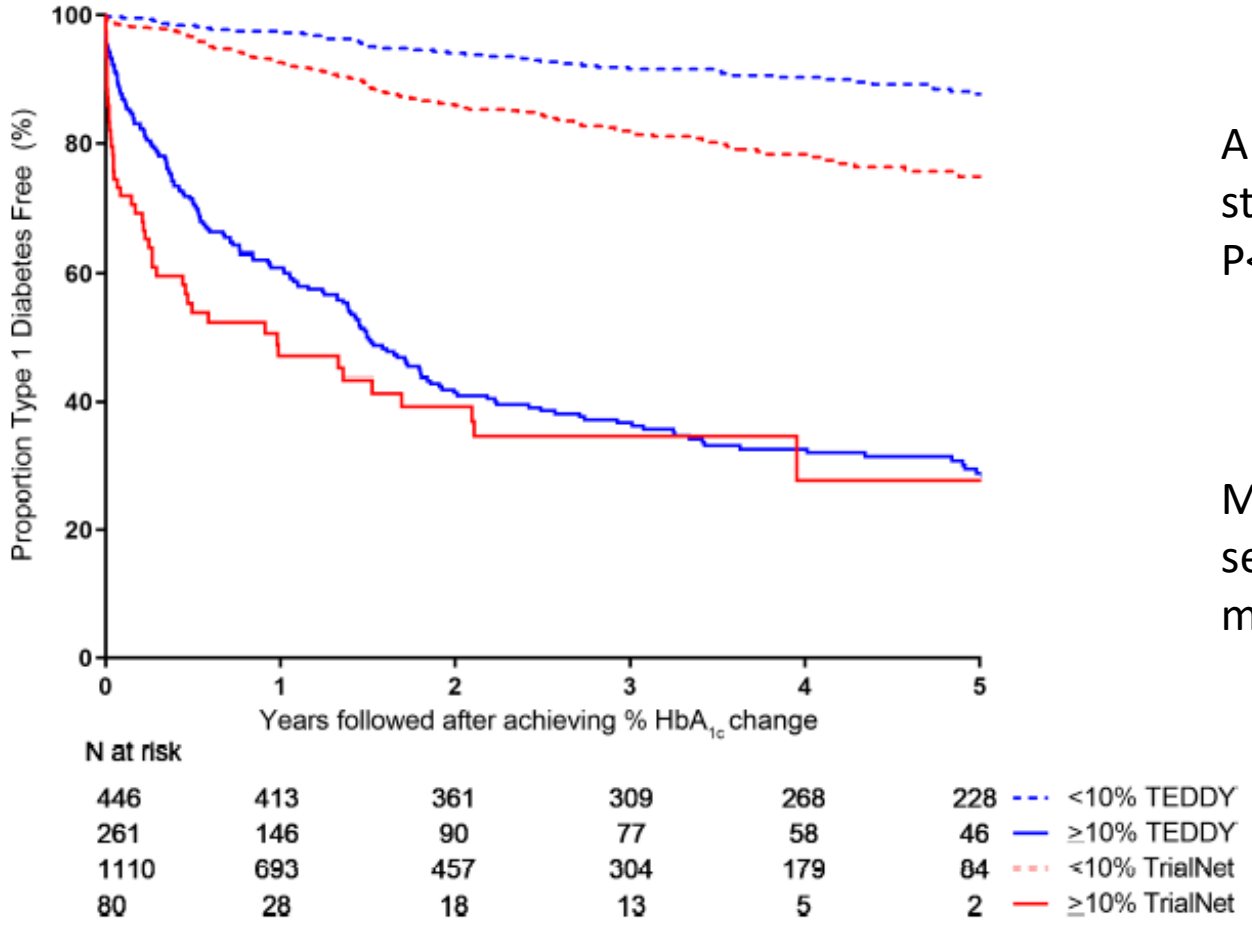
HbA1c is a specific but not sensitive indicator for stage 3 in children



HbA1c ≥6.5%:
low sensitivity (24-34%)
high specificity (98-99%)

Vehik, Diabetes Care 2012

≥10% A1c increase in TEDDY & TrialNet on progression to stage 3

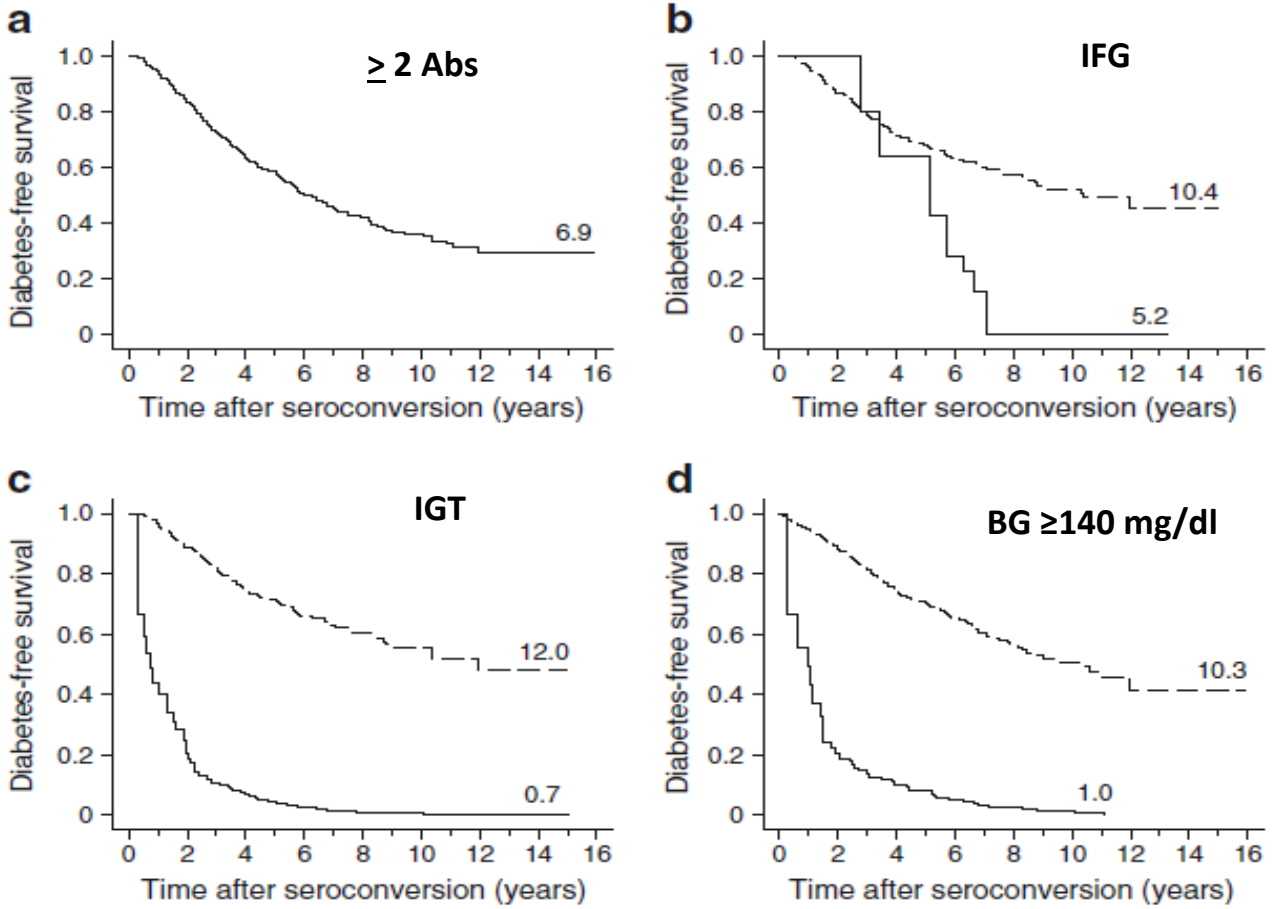


A ≥10% increase in HbA1c increases risk to stage 3 T1D in both TEDDY (HR 12.7, P<.0001) and TrialNet (HR 5.1, P<.0001)

Multivariate Cox PH model adjusted for age, sex, number of Abs, baseline HbA1c and maximum rate of change from baseline

Vehik et al, Diabetes Care 2022

OGTT or BG as predictors to stage 3 in multiple Ab+ children (DIPP)



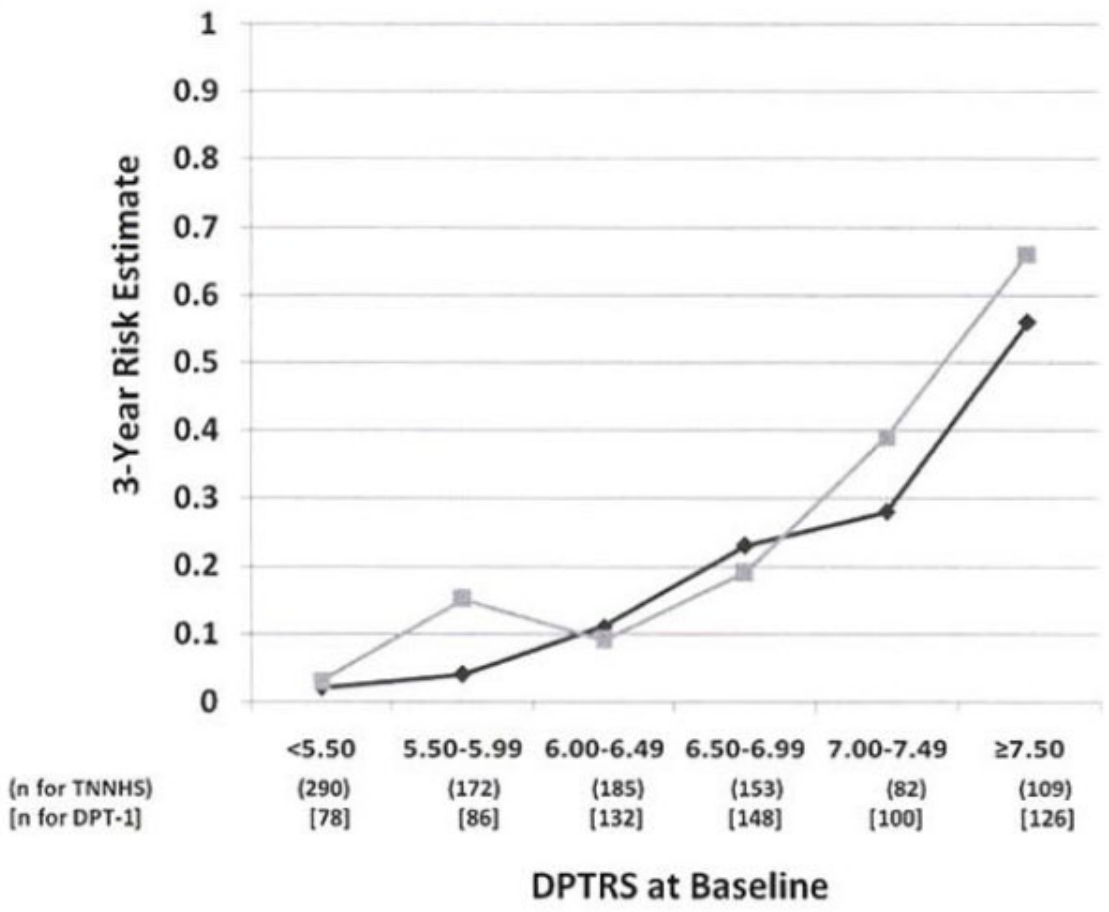
Median diabetes free survival time indicated for each curve

OGTT group: 209/403 (52%) progressed to T1D
Random BG group: 204/505 (40%) progressors

(a) ≥ 2 islet autoantibodies
(b) IFG in OGTT (solid line) or not (dashed line)
(c) IGT in OGTT (solid line) or not (dashed line)
(d) random BG≥140 mg/dl (solid) or not (dashed)

Helminen et al, Diabetologia 2015

DPTRS: Diabetes Prevention Trial-Type 1 Risk Score



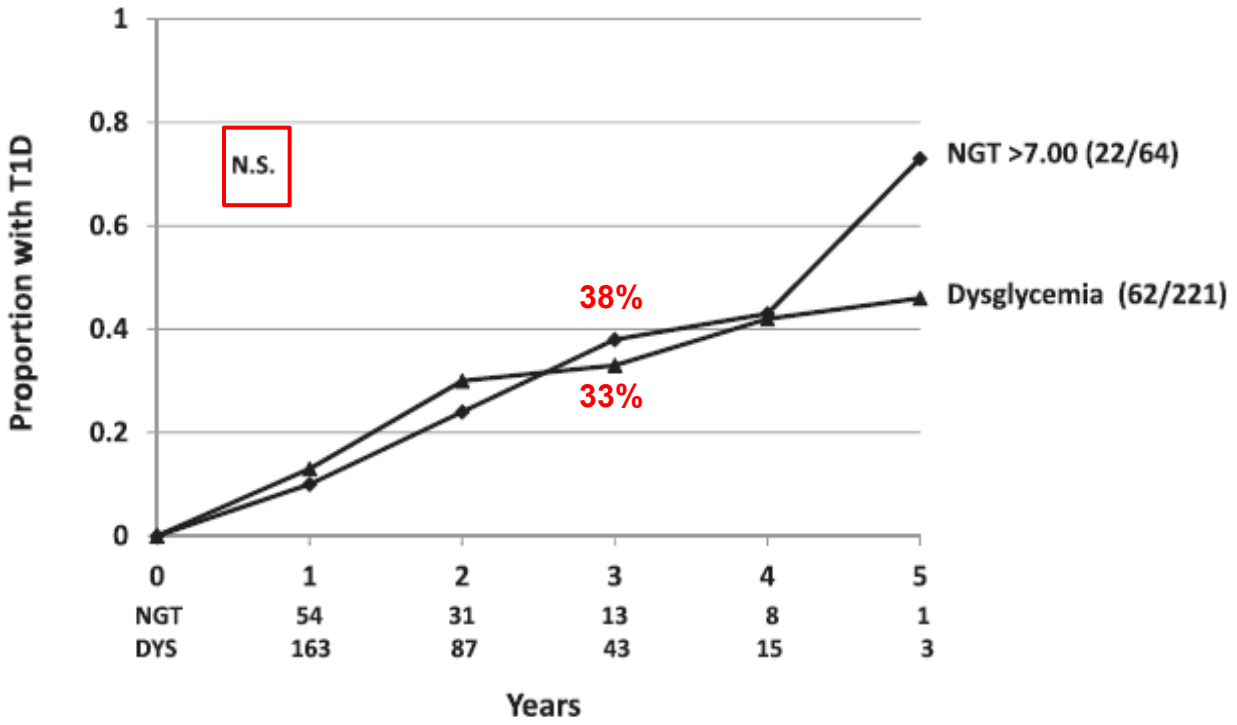
DPTRS <6.5: low risk (< 20%)
DPTRS ≥7.5: high risk (> 50%)

The DPTRS includes the glucose and C-peptide sums of 30-, 60-, 90-, and 120-min values, fasting C-peptide, BMI, and age

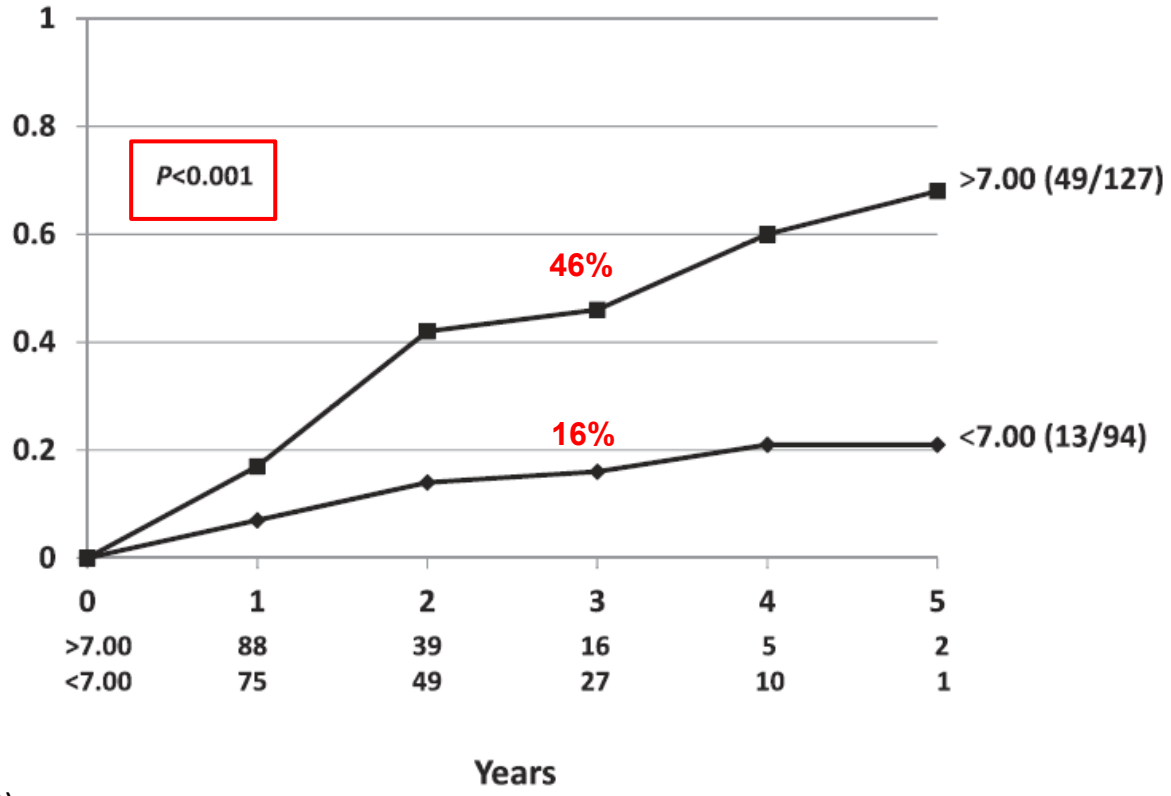
Sosenko et al, Diabetes Care 2011

Cumulative incidence curves to stage 3 T1D (TrialNet)

NGT and DPTRS>7 vs dysglycemia



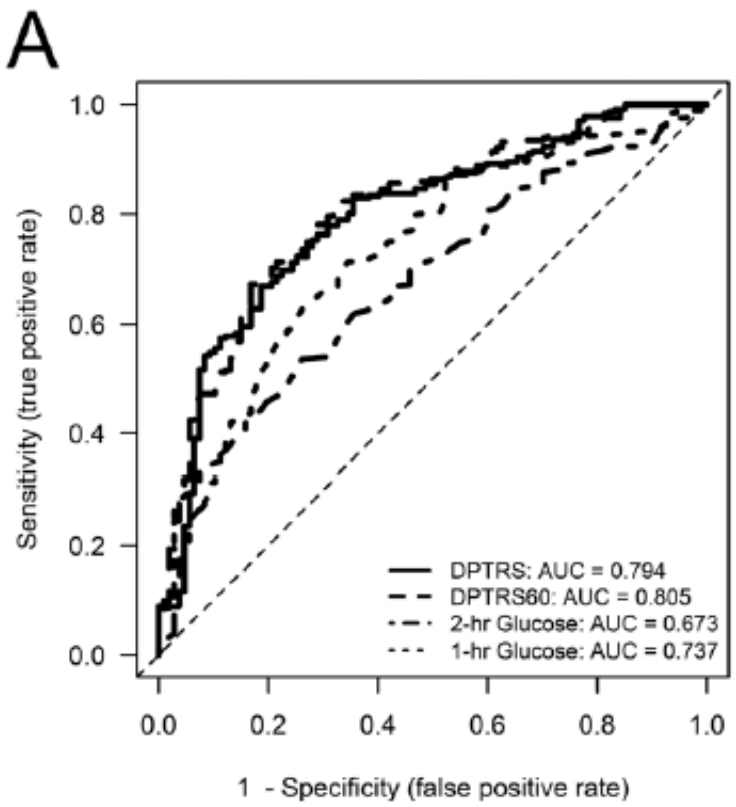
Dysglycemia by DPTRS >7 vs <7



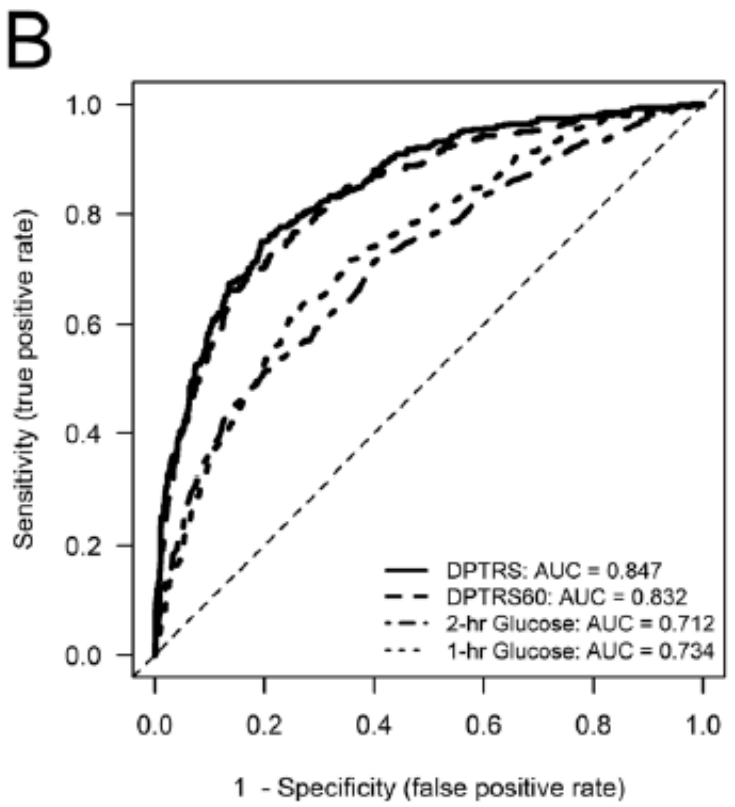
Dysglycemia defined by: - fasting BG between 110 and 125 mg/dL (IFG)
- 30-, 60-, and/or 90-min value ≥200 mg/dL (indeterminate)
- 2-h value between 140 and 199 mg/dL (IGT)

Sosenko et al, Diabetes Care 2014

ROC curves for T1D prediction 5 years from baseline (DPT-1 & TrialNet)



A: DPT-1 (N = 654)



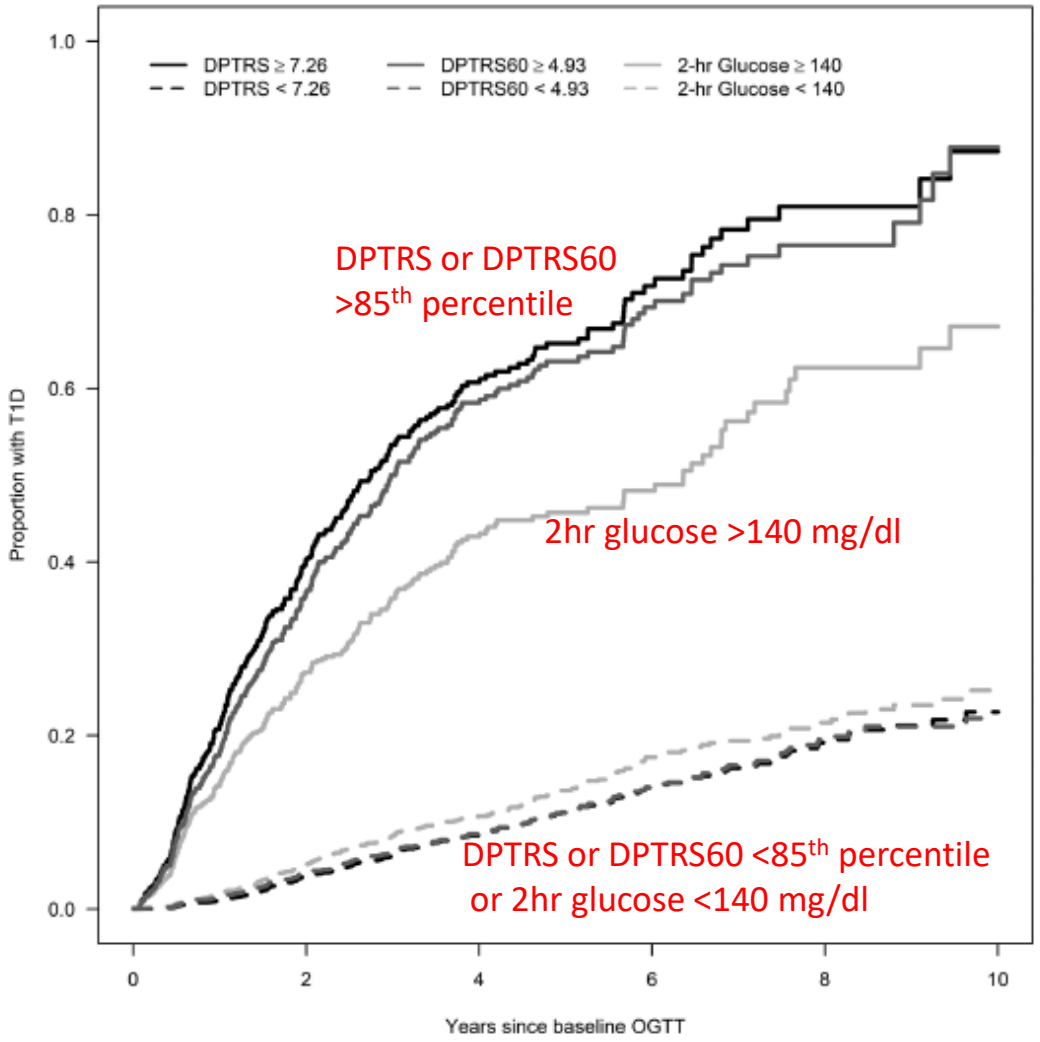
B: TrialNet (N = 4610)

DPTRS60 includes:

- log fasting C-peptide, age, log BMI
- 1-hour glucose and C-peptide values

Simmons et al, JCEM 2020

Cumulative Incidence for stage 3 T1D (TrialNet)



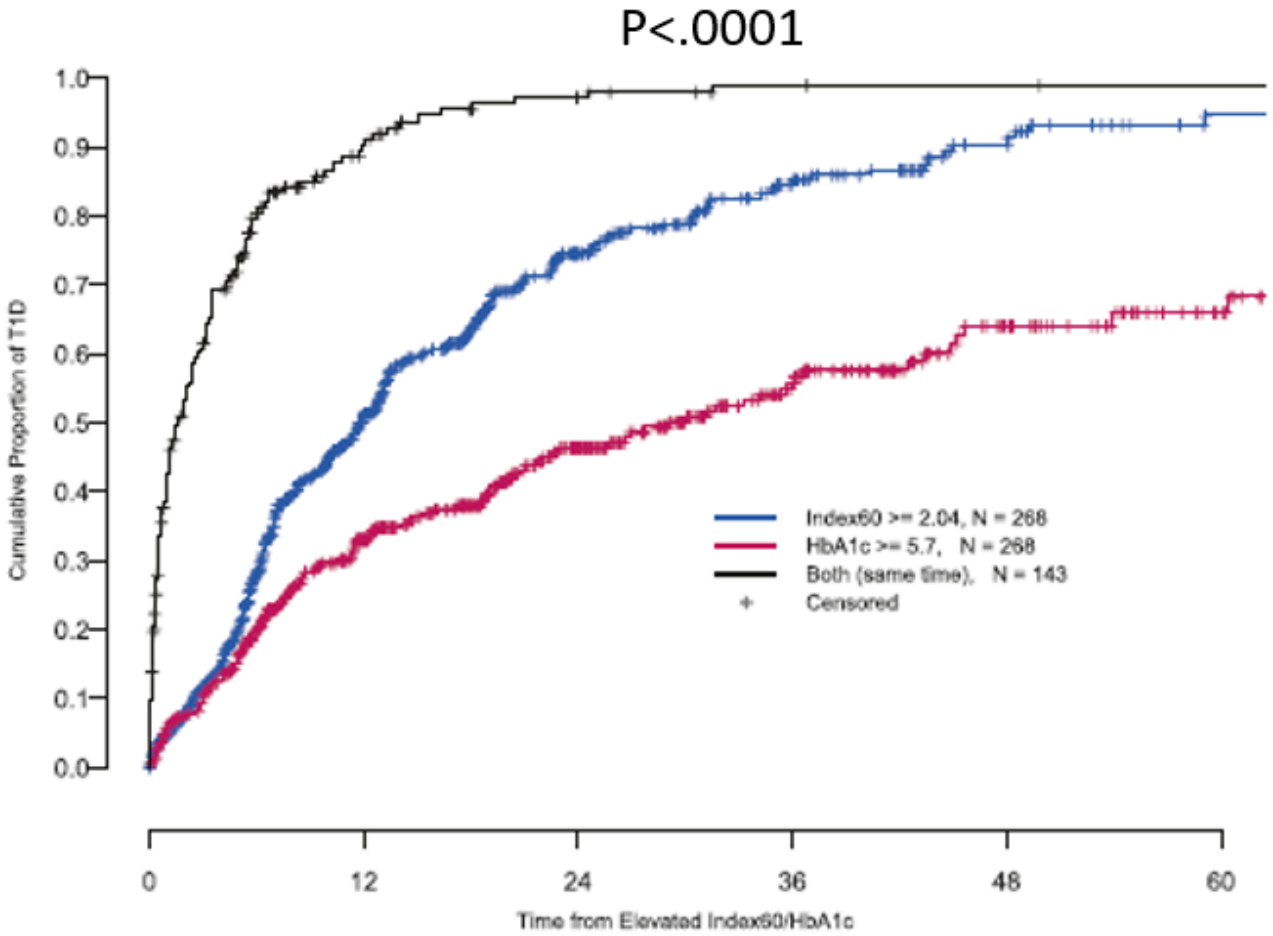
2-hr glucose threshold of 140 mg/dL (IGT) and 85th percentile thresholds for DPTRS and DPTRS60

Greater differential at 5-year for DPTRS60 (63%) and DPTRS (65%) compared to 2hr PG (46%)

DPTRS estimates similar to those of DPTRS60

Simmons et al, JCEM 2020

Cumulative incidence of stage 3 over 5 years (TrialNet)



top 18% of Index60 (≥ 2.04) vs
top 18% of HbA1c(≥ 5.7%) vs both

5 year stage 3 risk: 66% for HbA1c, 95% for Index60 and 99% for both

Index60: log fasting C-peptide, 60-minute glucose and C-peptide

Jacobsen et al, JCEM 2022

Different CGM metrics for T1D prediction (DAISY)

23 Ab+ subjects, 8 progressed to stage 3 T1D at a median age of 14 yrs

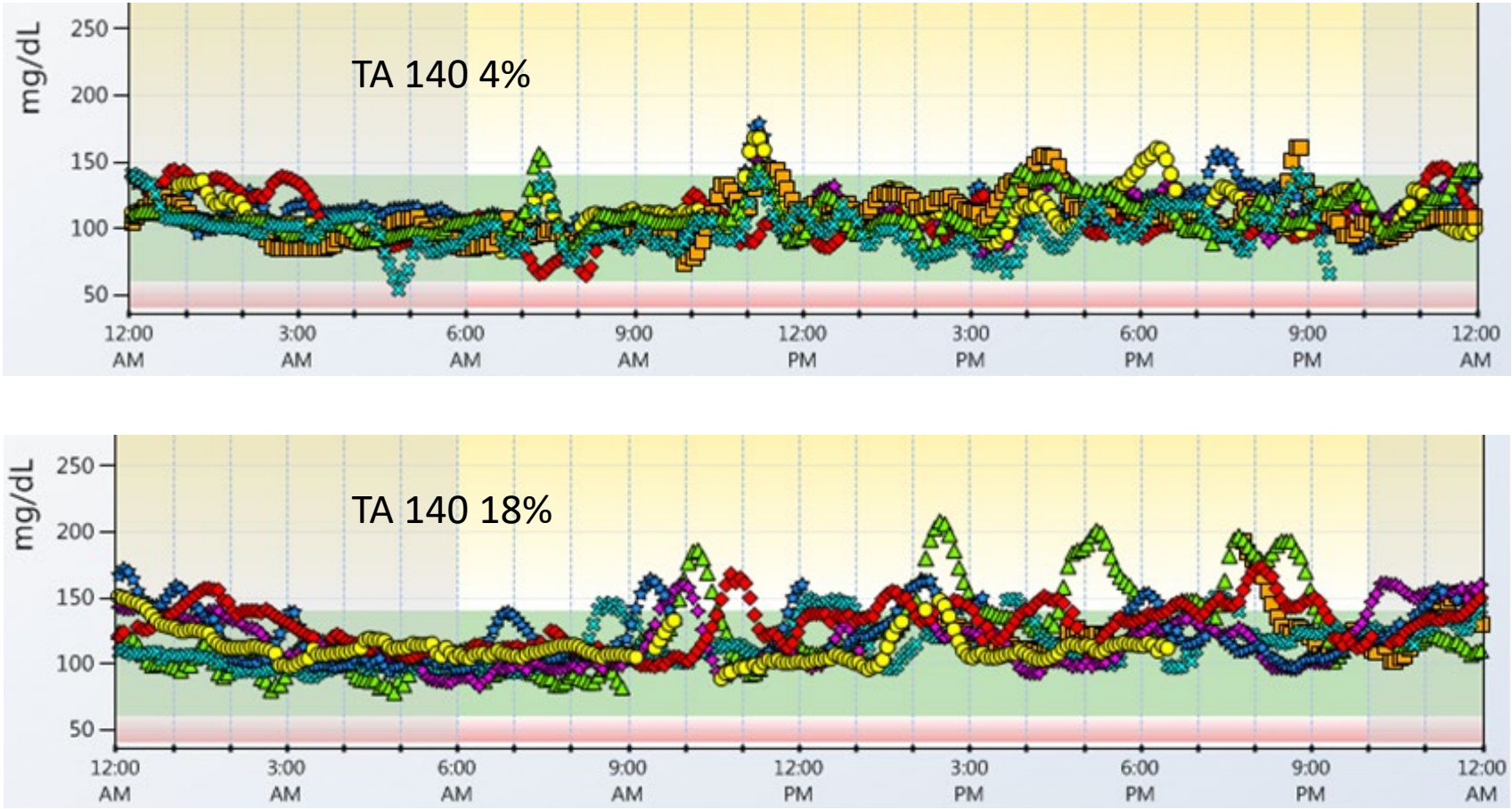
Index	AUC (95% CI)	P value
% time > 120	0.80 (0.57-1.00)	0.009
% time > 140	0.85 (0.62-1.00)	0.003
% time > 160	0.85 (0.63-1.00)	0.002
% time > 180	0.79 (0.58-1.00)	0.008
% time > 200	0.70 (0.46-0.93)	0.10

ROC curves were generated to compare area under the curve (AUC) for T1D prediction

Index	cutoff	PPV	NPV	Sensitivity	Specificity
% time > 120	36%	0.714	0.812	0.625	0.867
% time > 140	18%	1.000	0.883	0.750	1.000
% time > 160	6%	0.833	0.824	0.625	0.933
% time > 180	2%	0.714	0.813	0.625	0.867
% time > 200	0.2%	0.546	0.813	0.750	0.667

The Youden Index was used to select the optimal cutoff point for each variable

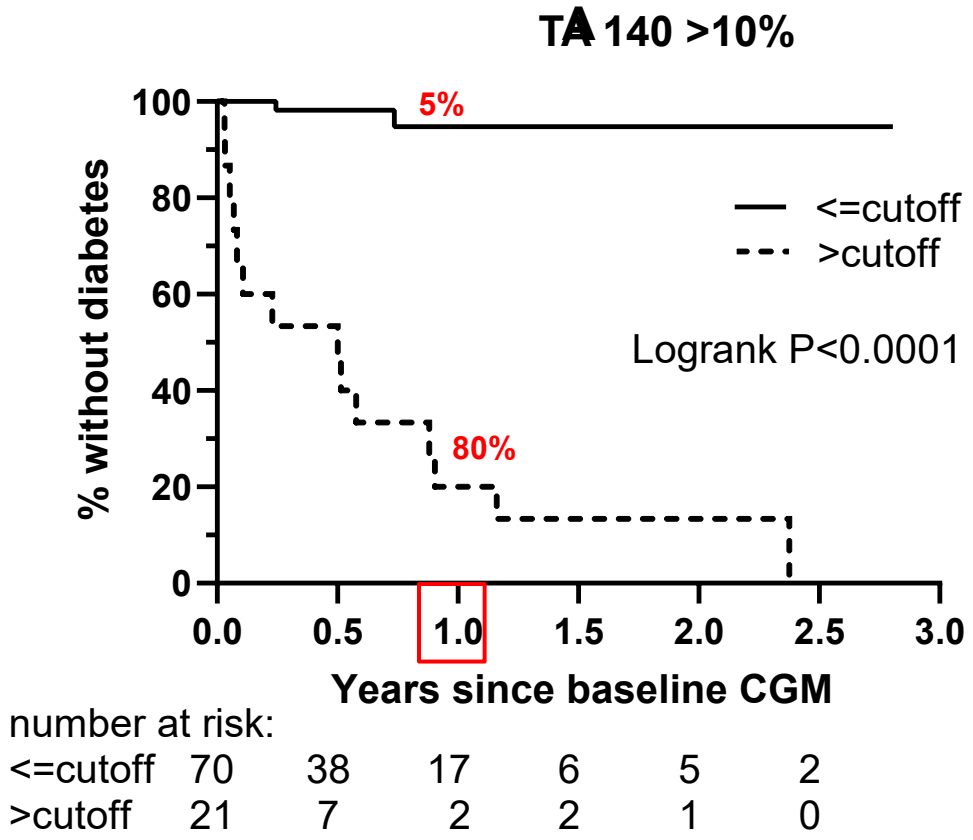
CGM profiles of DAISY subjects with TA140 <10% and >10%



Steck et al, JCEM 2019

CGM Ab+ ASK participants (N=91)

- 91 children persistently islet Ab+ (median age 11.5 y, 48% non- Hispanic White, 57% female) with a baseline CGM
- Of these, 16 (18%) progressed to clinical diabetes
- Progressors were more likely to be multiple Ab+ (81 vs 69%, p=0.048)
- Baseline HbA1c was higher in progressors versus non-progressors 5.6 vs 5.2% (p=0.005)



ROC AUC analyses for prediction of T1D

Variables	AUC (95% CI)	P value
HbA1c	0.75 (0.57-0.93)	0.006
% time > 120 mg/dL (6.7 mmol/l)	0.81 (0.66-0.96)	<0.0001
% time > 140 mg/dL (7.8 mmol/l)	0.89 (0.75-1.00)	<0.0001
% time > 160 mg/dL (8.9 mmol/l)	0.88 (0.74-1.00)	<0.0001
% time > 180 mg/dL (10 mmol/l)	0.88 (0.76-0.99)	<0.0001
% time > 200 mg/dL (11.1 mmol/l)	0.81 (0.68-0.94)	<0.0001
SD	0.89 (0.79-0.98)	<0.0001
CV	0.84 (0.74-0.93)	<0.0001
MAGE	0.90 (0.82-0.99)	<0.0001
MODD	0.86 (0.75-0.97)	<0.0001

MAGE: mean amplitude of glycemic excursions

MODD: mean of daily differences

Steck et al, Diabetes Care 2022

Sensitivity, Specificity, PPV and NPV (CGM metrics vs HbA1c)

Model Source	Cut-offs	Sensitivity	Specificity	PPV	NPV
HbA1c	5.5 %	43.8%	89.3%	46.7%	88.2%
% time > 120 mg/dL (6.7 mmol/l)	37.3%	68.8%	94.7%	73.3%	93.4%
% time > 140 mg/dL (7.8 mmol/l)	10%	87.5%	90.7%	66.7%	97.1%
% time > 140 mg/dL (7.8 mmol/l)	15%	68.8%	98.7%	91.7%	93.7%
% time > 160 mg/dL (8.9 mmol/l)	3.5%	81.3%	90.7%	65.0%	95.8%
% time > 180 mg/dL (10 mmol/l)	1.9%	68.8%	96.0%	78.6%	93.5%
% time > 200 mg/dL (11.1 mmol/l)	0.3%	62.5%	94.7%	71.4%	92.2%
SD	20	81.3%	81.3%	48.2%	95.3%
CV	16	81.3%	65.3%	33.3%	94.2%
MAGE	37	68.8%	90.7%	61.1%	93.2%
MODD	19	75.0%	80.0%	44.4%	93.8%

The Youden Index was used to select the optimal cutoff point for each variable

Steck et al, Diabetes Care 2022

TrialNet CGM Metrics by Stages

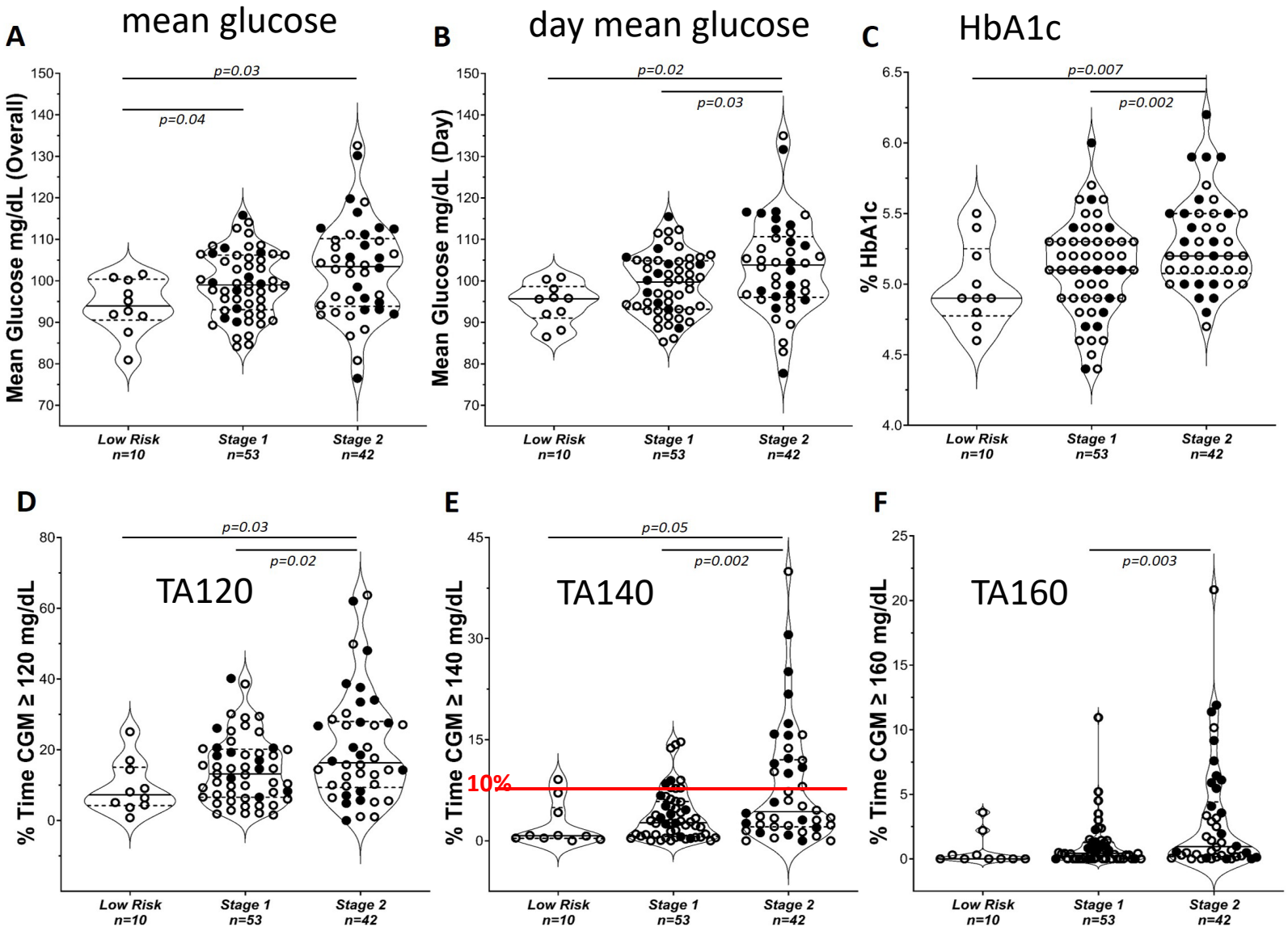
Variables	Low Risk n=10	Stage 1 n=53	Stage 2 n=42	*P* Value
Mean glucose, mg/dL	93.9 ± 6.5	99.3 ± 7.8	102.8 ± 11.8	***0.02***
SD, mg/dL	18.4 ± 6.4	19.3 ± 6.9	21.0 ± 5.8	0.33
CV, mg/dL	19.6 ± 6.7	19.4 ± 6.4	20.3 ± 4.3	0.77
Mean †day glucose, mg/dL	94.6 ± 4.8	99.3 ± 7.3	103.5 ± 11.5	***0.01***
Mean night glucose, mg/dL	91.9 ± 12.4	99.3 ± 13.0	100.9 ± 14.4	0.18
Maximum CGM glucose, mg/dL	165.8 ± 36.0	179.6 ± 47.9	183.7 ± 32.8	0.47
Minimum CGM glucose, mg/dL	45.4 ± 14.6	54.5 ± 12.2	57.0 ± 12.3	***0.03***
Mean Glucose Range, mg/dL	120.4 ± 43.1	125.2 ± 52.9	126.7 ± 33.0	0.92
Maximum †day glucose value, mg/dL	165.1 ± 36.5	171.9 ± 37.3	181.7 ± 32.4	0.26
Maximum night glucose value, mg/dL	136.6 ± 20.3	155.5 ± 47.8	152.2 ± 32.6	0.40
% Time CGM ≥ 120 mg/dL	9.4 ± 7.4	14.4 ± 9.4	20.8 ± 15.6	***0.008***
% Time CGM ≥ 140 mg/dL	2.4 ± 3.3	3.8 ± 3.7	8.1 ± 8.8	***0.002***
% Time CGM ≥ 160 mg/dL	0.6 ± 1.2	1.0 ± 1.8	3.0 ± 4.4	***0.004***
CONGA	18.2 ± 6.6	18.5 ± 5.5	20.5 ± 4.9	0.17
DySF	2.8 ± 2.4	2.5 ± 2.0	3.8 ± 2.8	***0.04***
MAGE	35.5 ± 10.7	38.9 ± 15.1	41.6 ± 10.3	0.35
MODD	18.2 ± 6.2	18.5 ± 6.1	20.6 ± 5.8	0.19
HbA1c, %	5.0 ± 0.3	5.1 ± 0.3	5.3 ± 0.3	***0.006***

95 relatives with Stage 1 or 2 T1D
29 progressed to Stage 3 T1D at a mean of 17.9 years

Glucose variability measures: SD, CV, MAGE, MODD, DySF (Dynamic Stress Factor), CONGA (continuous overall net glycemic action)

Wilson, Diabetes Care 2023

Low Risk, Stage 1 and Stage 2 participants



Dot-plot charts

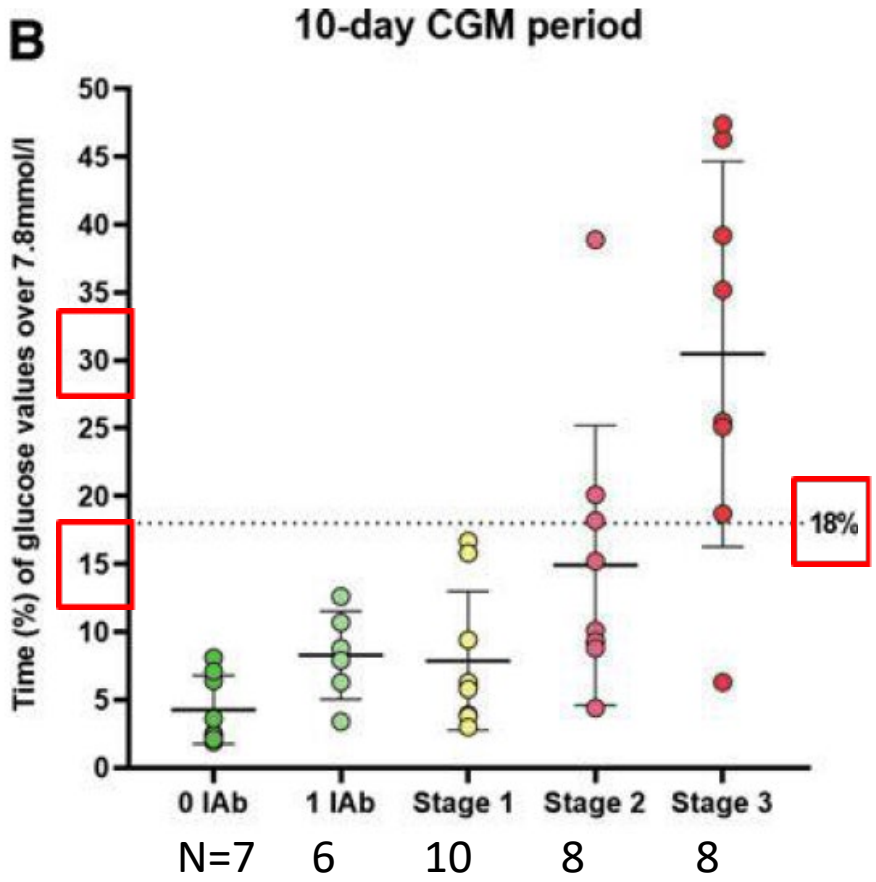
A: Overall mean glucose
B: Day mean glucose
C: HbA1c (%)

D: time spent >120mg/dl
E: time spent >140mg/dl
F: time spent > 160mg/dl

Wilson, Diabetes Care 2023

CGM in subjects with 0 Ab, 1 Ab and at stages 1–3 T1D (DIPP)

CGM TA140

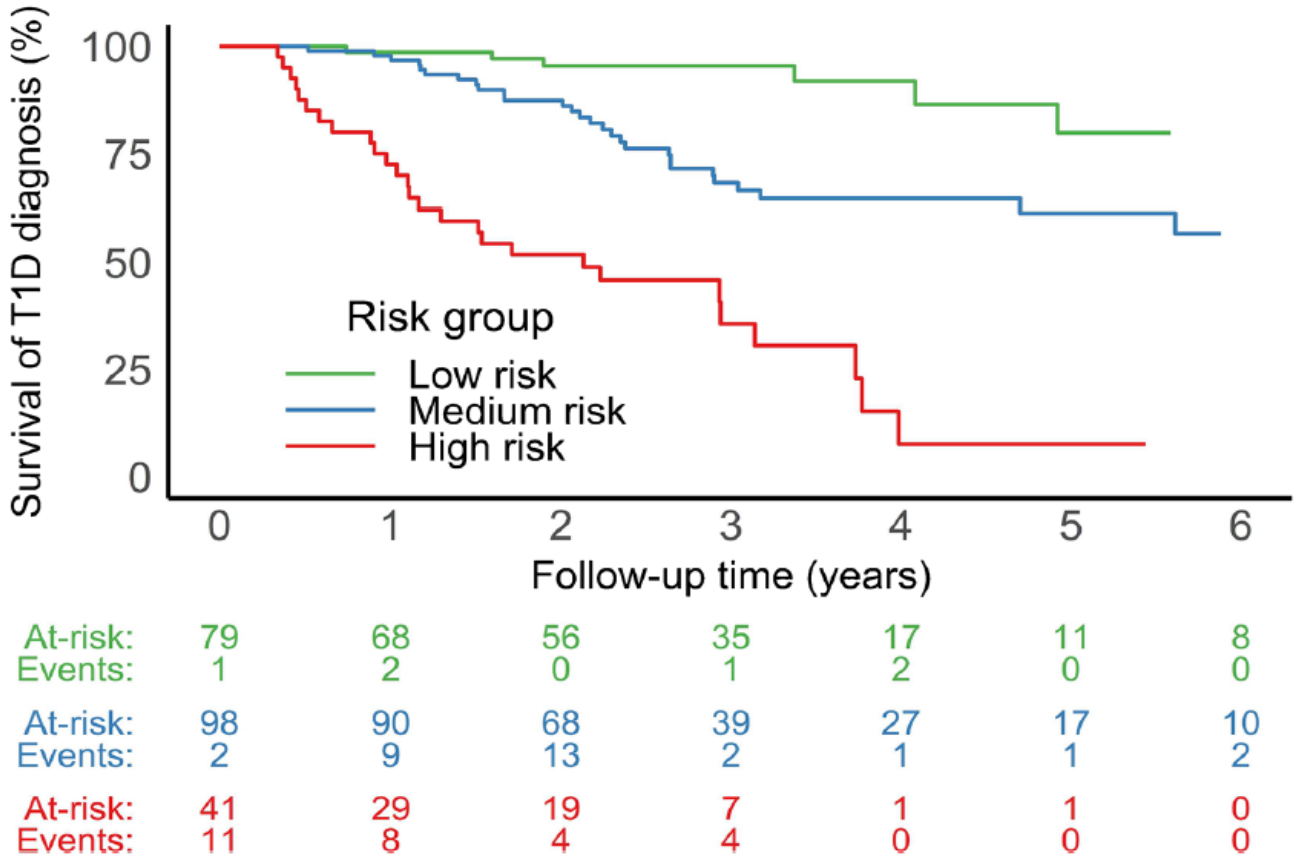


39 DIPP participants who had an OGTT and a 10-day Dexcom G6 CGM wear

Staging done at baseline visit based on IAbs and OGTT

Kontola et al, DTT 2022

CGM Metrics from 5 Studies Identify Participants at Risk of Stage 3 T1D



Predictor[a]	Low risk[b], *n*=79	Medium risk[b], *n*=98	High risk[b], *n*=41
Percentage of time >7.8 mmol/l	2.1 (0.6, 3.9)	2.9 (1.1, 6.9)	10.4 (6.9, 17.3)
HbA_{1c} (mmol/mol)	32±4	34±3	37±4
HbA_{1c} (%)	5.1±2.6	5.3±2.4	5.5±2.5
Female sex	52 (66)	53 (54)	12 (29)
First-degree relative	34 (43)	70 (71)	29 (71)
IA-2 AAb positivity	7 (9)	79 (81)	39 (95)
GAD AAb positivity	74 (94)	91 (93)	35 (85)

218 subjects, median follow-up 2.6 yrs,
76% multiple (≥2) islet Ab positive,
64 (29%) progressed to stage 3 T1D

T1D risk prediction better with combined baseline CGM model (including CGM TA140, HbA1c, FDR, sex, IA2A & GADA status)

Risk of T1D by 2 years was 5%, 13%, and 48% in the low, medium, and high-risk groups

Calhoun et al, Diabetologia 2025

Repeated OGTT vs CGM for Stage 3 T1D Prediction

Design & Endpoint

BDR

AAb screening for FDRs of T1D probands

n=34 multiple AAb-positive participants
Baseline stage 2 T1D: n=2
Baseline age: 17 (13-23) years

Repeated metabolic monitoring with OGTT, HbA_{1c} and 5-day CGM 2x/year

Follow-up: 3.5 (2.0-7.5) years

n=17 progressors to stage 3 T1D

n=17 non-progressors (n=2: stage 2 T1D)

Analysis

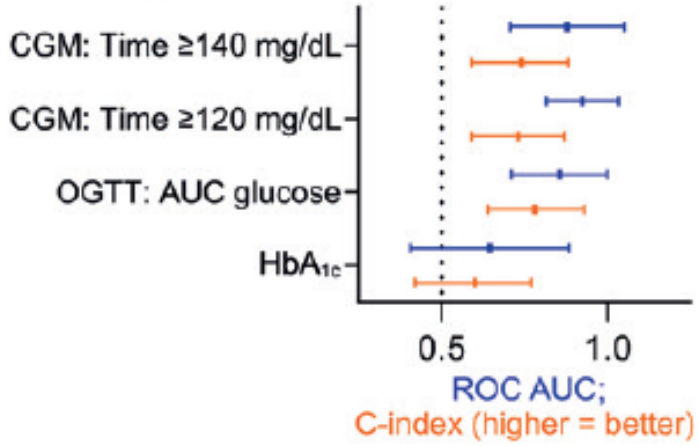
Statistics

Results

Conclusion

BASELINE PREDICTIONS

ROC AUC; diagnostic efficiency
Kaplan Meier
Cox PH regression: hazard ratio, C-index

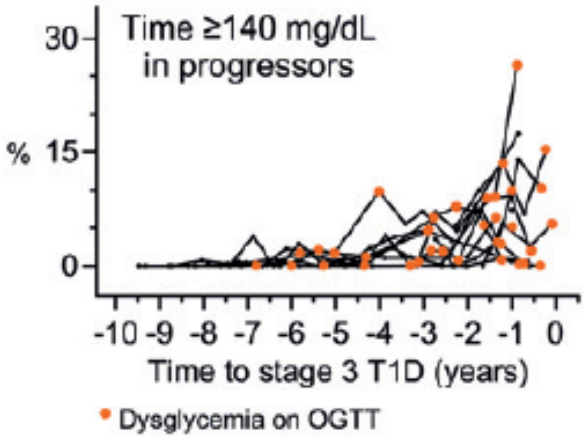


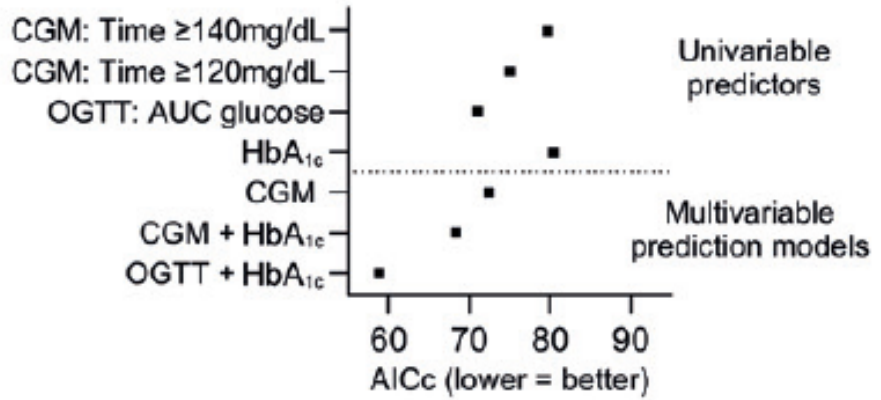
CGM and OGTT perform similarly

HbA_{1c} less informative

LONGITUDINAL PATTERNS & PREDICTIONS BY MULTIPLE RECORDS (n=197)

Spaghetti plots
Extended Cox PH regression, adjusted for intra-individual correlations: hazard ratio, AICc





OGTT ≥ CGM; CGM + HbA_{1c}: alternative to repeat OGTT for clinical monitoring

Important intra-individual variability in OGTT and CGM

Desouter et al, Diabetes Care 2025

CGM in healthy participants

	All Participants	Age Group					1-6 years
		6 to <12 y	12 to <18 y	18 to <25 y	25 to <60 y	≥60 y	
n	153	27	30	29	41	26	N=39
CGM use, h (mean ± SD) [range]	192 ± 31 [84–245]	180 ± 35 [84–233]	181 ± 28 [111–233]	192 ± 28 [92–223]	207 ± 25 [136–245]	195 ± 33 [124–236]	205.6 ± 68.6 79.5 to 425.1
Overall glucose distribution and variability							
Mean, mg/dL (mean ± SD)	99 ± 7	99 ± 7	98 ± 6	98 ± 6	99 ± 6	104 ± 9	103 ± 8
SD, mg/dL (mean ± SD)	17 ± 3	16 ± 3	15 ± 2	18 ± 3	16 ± 3	18 ± 5	17 ± 3
CV, % (mean ± SD)	17 ± 3	16 ± 3	15 ± 2	18 ± 3	16 ± 3	17 ± 4	17% ± 3%
Percentage of glucose sensor values, median (IQR)							
>180 mg/dL	0.0 (0.0–0.2)	0.0 (0.0–0.1)	0.0 (0.0–0.0)	0.0 (0.0–0.4)	0.0 (0.0–0.2)	0.1 (0.0–0.5)	0.14 (0.00 - 0.49)
>160 mg/dL	0.3 (0.1–0.9)	0.2 (0.1–0.8)	0.2 (0.0–0.2)	0.4 (0.2–1.1)	0.4 (0.2–0.9)	0.6 (0.1–2.9)	0.79 (0.40 - 1.79)
>140 mg/dL	2.1 (0.9–3.9)	1.7 (0.8–2.9)	1.2 (0.3–2.0)	2.4 (1.3–4.4)	2.1 (1.1–3.1)	4.1 (1.3–8.6)	3.35 (2.20 - 6.15)
70–140 mg/dL	96 (93–98)	97 (94–97)	97 (95–98)	95 (91–97)	97 (94–98)	93 (89–96)	96 (92 - 97)
70–120 mg/dL	89 (82–92)	90 (83–92)	92 (86–93)	87 (82–90)	89 (86–91)	81 (71–86)	86 (75 - 89)
<70 mg/dL	1.1 (0.3–2.9)	1.1 (0.3–3.3)	1.7 (0.6–2.6)	1.3 (0.5–3.6)	1.0 (0.3–2.3)	1.4 (0.2–3.4)	0.44 (0.13 - 1.02)
<60 mg/dL	0.2 (0.0–0.6)	0.2 (0.0–0.3)	0.2 (0.0–0.8)	0.2 (0.0–0.7)	0.2 (0.0–0.4)	0.3 (0.0–0.7)	0.10 (0.00 - 0.22)
<54 mg/dL	0.0 (0.0–0.2)	0.0 (0.0–0.2)	0.0 (0.0–0.4)	0.1 (0.0–0.4)	0.0 (0.0–0.2)	0.1 (0.0–0.2)	0.02 (0.00 - 0.15)
Percentage of participants with ≥1 hypoglycemic event[a]	28	19	27	41	24	31	23%
Duration of hypoglycemic events for participants with ≥1 hypoglycemic event (min)[a,b]							
n	70	9	10	23	17	11	N=13
Median (IQR)	58 (40–100)	60 (35–165)	53 (40–85)	50 (40–75)	65 (40–100)	80 (50–120)	45 (35, 50)

Shah et al, JCEM 2019
DuBose et al, JES 2022

Current T1D Staging

Table 2.4—Staging of type 1 diabetes

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• Autoimmunity • Overt hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple islet autoantibodies • No IGT or IFG, normal A1C	• Islet autoantibodies (usually multiple) • Dysglycemia: ◦ IFG: FPG 100–125 mg/dL (5.6–6.9 mmol/L) or ◦ IGT: 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) or ◦ A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Autoantibodies may become absent • Diabetes by standard criteria

Adapted from Skyler et al. (38). FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose. Alternative additional stage 2 diagnostic criteria of 30-, 60-, or 90-min plasma glucose on oral glucose tolerance test ≥200 mg/dL (≥11.1 mmol/L) and confirmatory testing in those aged ≥18 years have been used in clinical trials (84). Dysglycemia can be defined by one or more criteria as outlined in the table.

Stage of T1D	Islet autoantibody status	Glycemic status
At-risk (pre-stage 1 T1D)	Single autoantibody or transient single autoantibody	• Normoglycemia • FPG <5.6 mmol/L (<100 mg/dL) • 120-min OGTT <7.8 mmol/L (<140 mg/dL) • HbA_{1c} <39 mmol/mol (<5.7%)
Stage 1 T1D (also referred to as early-stage T1D or presymptomatic T1D)	≥2 autoantibodies	• Normoglycemia • FPG <5.6 mmol/L (<100 mg/dL) • 120-min OGTT <7.8 mmol/L (<140 mg/dL) • HbA_{1c} <39 mmol/mol (<5.7%)
Stage 2 T1D (also referred to as early-stage T1D or presymptomatic T1D)	≥2 autoantibodies*	Glucose intolerance or dysglycemia not meeting diagnostic criteria for stage 3 T1D, with at least two of the following, or meeting the same single criteria at two time points within 12 months: • FPG 5.6–6.9 mmol/L (100–125 mg/dL) • 120-min OGTT 7.8–11.0 mmol/L (140–199 mg/dL) • OGTT values ≥11.1 mmol/L (≥200 mg/dL) at 30, 60, and 90 min • HbA_{1c} 39–47 mmol/mol (5.7–6.4%) or longitudinal ≥10% increase in HbA_{1c} (66,67) from the first measurement with stage 2 T1D • CGM values >7.8 mmol/L (>140 mg/dL) for 10% of time over 10 days' continuous wear (73)† and confirmed by at least one other non-CGM glucose measurement test listed

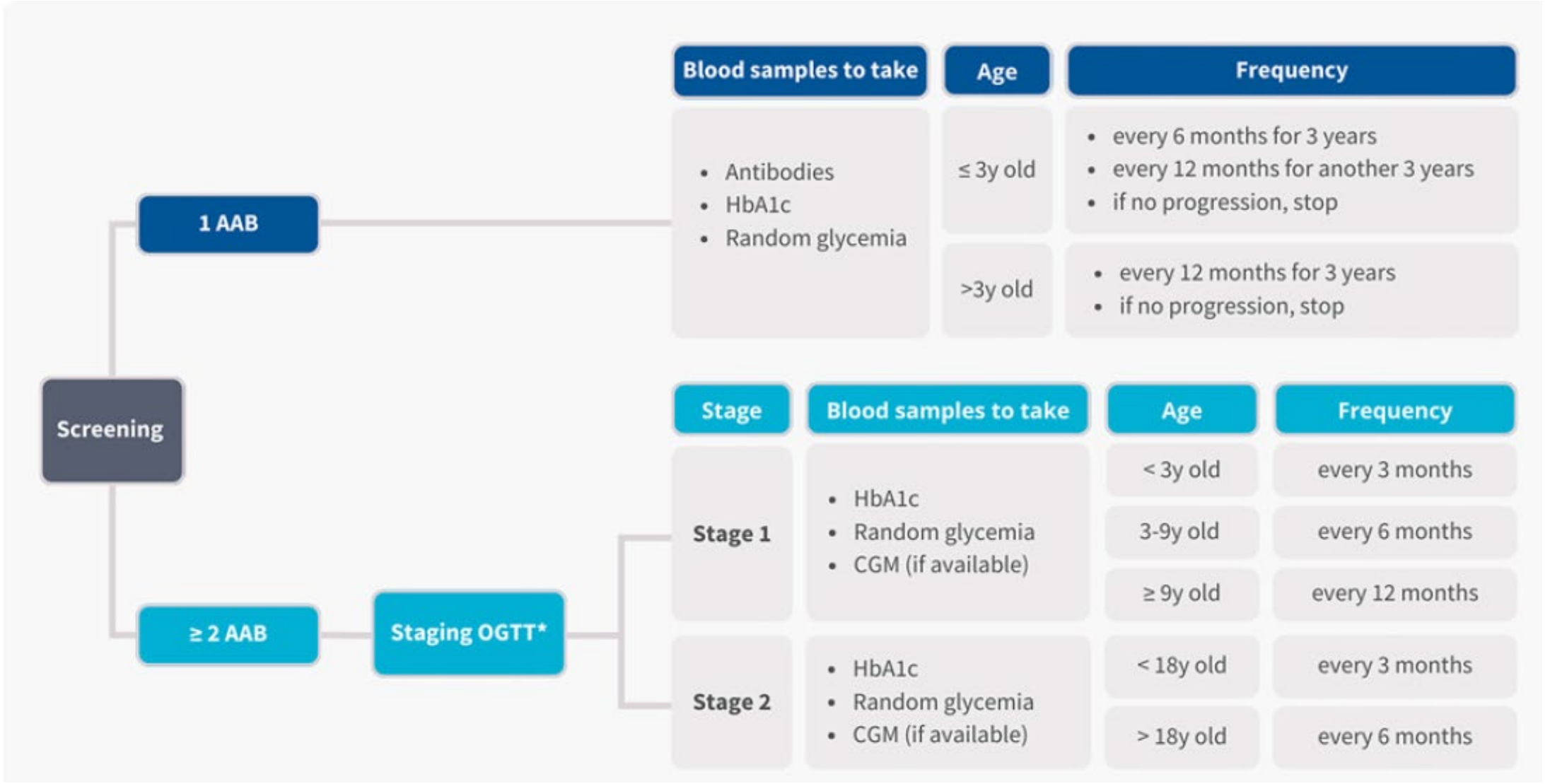
Staging criteria for Ab-positive individuals in early stages of T1D

Consensus Guidance for Monitoring Individuals With Early Stage T1D

Initiative led by Breakthrough T1D

Phillip et al, Diabetes Care and Diabetologia 2024

ISPAD Consensus Guidelines 2024: Monitoring for early stage T1D



Haller et al, Hormone Research in Paediatrics, 2024

Currently available glycemic monitoring tools

OGTT	• Gold standard • Used to stage disease and predict progression	• Requires glucose load and 1 to 5 blood draws over 2 h	Glycemic staging risk scores for progression (DTPRS, DTPRS60, Index60, M120, PLS)
Random venous glucose	• One-off sample • Low cost	• Requires a blood draw	Similar to 2-h OGTT-derived glucose
HbA1c	• Highly specific • Can use capillary sample	• Insensitive, often normal in Stage 3a T1D • May be affected by other disease states[1]	Risk of progression to "clinical disease": HbA1c ≥5.9% (41 mmol/mol), or 10% rise over 3–12 months
CGM	• Provides real-time continuous monitoring • May enable early detection of Stage 2 diabetes	• Optimal duration and frequency of CGM wear not yet determined • Cost, access, evidence to wear continuously are needed • Data may cause anxiety and undesirable behavior change • Not currently considered superior to OGTT in the context of research trials	Risk of progression to "clinical disease": time above 7.8 mmol/L (140 mg/dL) is >10% >20% above 7.8 mmol/L (>140 mg/dL) indicates need to test for Stage 3 T1D
SMBG	• Simple • Use at home • Lower cost vs other methods	• Optimal timing and frequency have not been determined • Random result	Immediate result
Urinary glucose testing	• Simple • Use at home • Lower cost vs other methods	• Untested in this context • Less reliable than SMBG due to the altered renal threshold for glucose	Immediate result

ISPAD Consensus Guidelines, 2024

Conclusions

- Current ADA staging criteria include HbA1c and OGTT glycemic measures
- HbA1c is a specific, but not sensitive measure in children
- OGTT is highly predictive of progression, esp. if C-peptide dynamics are incorporated into risk score
- CGM based criteria are needed for the care of early stage T1D and the diagnosis of stage 3 T1D as OGTTs are not practical in clinical care
- Current data support the following CGM based criteria:
  - TA140>10% represents high risk of progression with TA140>15% consistent with stage 2 T1D
  - TA140>20% indicate needs to tests for stage 3 T1D with TA140>30% consistent with stage 3 T1D *(in the absence of T1D symptoms, diagnosis should be confirmed by another test result)*

Acknowledgments

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Type 1 Diabetes TrialNet

Autoimmunity Screening for Kids
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A SIMPLE TEST TO DETECT
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